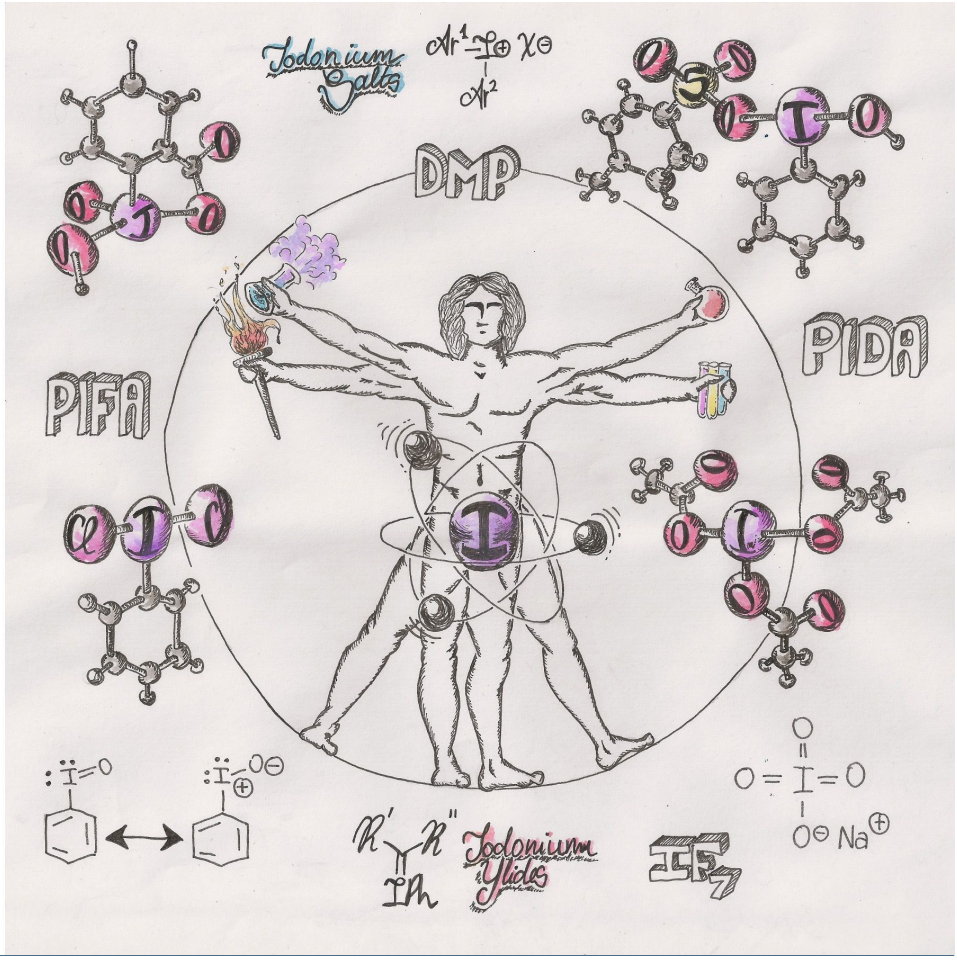
BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Hypervalent iodine chemistry in organic synthesis

Edited by Prof. Thomas Wirth



Generated on 03 November 2026, 06:31

Imprint

Beilstein Journal of Organic Chemistry
www.bjoc.org
ISSN 1860-5397
Email: journals-support@beilstein-institut.de

The *Beilstein Journal of Organic Chemistry* is published by the Beilstein-Institut zur Förderung der Chemischen Wissenschaften.

Beilstein-Institut zur Förderung der Chemischen Wissenschaften
Trakehner Straße 7–9
60487 Frankfurt am Main
Germany
www.beilstein-institut.de

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

One-pot preparation of 4-aryl-3-bromocoumarins from 4-aryl-2-propynoic acids with diaryliodonium salts, TBAB, and $Na_2S_2O_8$

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Full Research Paper

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Keywords:
3-aryl-2-propynoic acid; bromo-cyclization; coumarin; diaryliodonium triflate; O-phenylation

Beilstein J. Org. Chem. **2018,** *14,* 345–353.
doi:10.3762/bjoc.14.22

Received: 11 December 2017
Accepted: 26 January 2018
Published: 05 February 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Various 4-aryl-3-bromocoumarins were smoothly obtained in moderate yields in one pot by treating 3-aryl-2-propynoic acids with diaryliodonium triflates and K_2CO_3 in the presence of CuCl, followed by the reaction with tetrabutylammonium bromide (TBAB) and $Na_2S_2O_8$. The obtained 3-bromo-4-phenylcoumarin was transformed into 4-phenylcoumarin derivatives bearing C–H, C–S, C–N, and C–C bonds at 3-position.

Introduction

Coumarin is a benzo-α-pyrone and one of the typical heterocyclic compounds. The importance of coumarins arises from the fact that the coumarin skeleton is present in many natural products extracted from plants [1-3] and some of them show potent pharmacological activities, such as antidepressant [4], antimicrobial [5,6], antioxidants [7,8], anti-inflammatory [9,10], antinociceptive [11], antitumor [1], antiasthmatic [12], and antiviral including anti-HIV [13,14].

Comprehensive synthetic studies of coumarins and their derivatives have been carried out [15,16]. Typically, coumarins are prepared by the acid-catalyzed condensation of 2-alkynoic acids and phenols or the condensation of β-ketoesters and phenols (the Pechmann condensation) [17]. Recent studies for the metal-catalyzed reactions for the synthesis of the coumarin skeleton are as follows: the $Yb(OTf)_3$-catalyzed microwave irradiation of phenols and propynoic acids [18], the $Pd(OAc)_2$-catalyzed

oxidative cyclocarbonylation of 2-vinylphenols at 110 °C [19], the $FeCl_3$-catalyzed areneselenyl-cyclization of aryl 2-alkynoates with ArSeSeAr at rt [20], and the Rh-catalyzed annulation of arylthiocarbamates with alkynes/AgOTf/$Cu(OAc)_2$ at 120 °C [21]. As examples of the transition-metal-free construction of the coumarin skeleton, the Brønsted acid-catalyzed reaction of phenols and propynoic acids [22] and the (−)-riboflavin-catalyzed photochemical reaction of cinnamic acids [23] were reported recently. Moreover, the use of radical cyclization for the construction of the coumarin skeleton has become widespread. Examples include the radical addition–cyclization reactions of aryl 2-alkynoates with $RC(=O)CO_2H/AgNO_3$(cat.)/$K_2S_2O_8$ at 60 °C [24], with $Cu(OAc)_2$/1-trifluoromethyl-3,3-dimethyl-1,2-benziodoxole (Togni reagent) at 60 °C [25], with $R_2P(=O)H/Ag_2CO_3$(cat.)/$Mg(NO_3)_2$ at 100 °C [26], with $BrCF_2CO_2Et$/*fac*-Ir(ppy)$_3$(cat.) under irradiation at rt [27], with R-CH=O/(*n*-Bu)$_4$NBr (TBAB, cat.)/$K_2S_2O_8$ at 90 °C [28], with $ArSO_2H$/Eosin Y(cat.)/*tert*-butyl hydrogen peroxide (TBHP) at rt [29], and with $ArSO_2NHNH_2$/*n*-Bu_4NI(cat.)/TBHP at 80 °C [30].

In addition, the formation of coumarins via the bromine-radical-mediated reaction of aryl 2-alkynoates with TBAB/$K_2S_2O_8$ at 90 °C [31], the cyanomethyl-radical-mediated reaction of aryl 2-alkynoates with *tert*-butyl peroxybenzoate (TBPB)/acetonitrile at 130 °C [32], the sunlight-promoted reaction of aryl 2-alkynoates with *N*-iodosuccinimide (NIS) at rt [33], and the visible-light-mediated reaction of aryl 2-alkynoates with *N*-bromosuccinimide (NBS) at rt [34], where those reactions proceed via radical spiro-cyclization and then radical 1,2-carboxyl group migration, were reported.

On the other hand, diaryliodonium salts are very useful for the C-arylation of active CH groups, the O-arylation of OH groups, and the N-arylation of NH groups under metal-free conditions [35-39]. For example, treatment of arenecarboxylic acids and alkanecarboxylic acids with diaryliodonium salts and *t*-BuOK under toluene refluxing conditions provides the corresponding aryl carboxylates in good yields [40,41]. However, the O-arylation of 2-alkynoic acids, which are much more acidic than arenecarboxylic acids and alkanecarboxylic acids, and therefore, the conjugate bases of 2-alkynoic acids are much less nucleophilic than those of arenecarboxylic acids and alkanecarboxylic acids, was not studied. On the other hand, it is known that 4-arylcoumarins have antitumor activity [42]. Therefore, the one-pot preparation of 4-arylcoumarins from 3-aryl-2-alkynoic acids via aryl esters and cyclization is attractive and important.

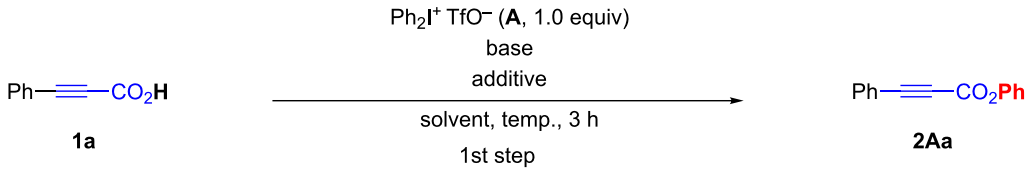
Here, as part of our ongoing investigation of the synthetic use of diaryliodonium salts for the preparation of heterocyclic compounds [43-46], we would like to report an efficient one-pot preparation of 4-aryl-3-bromocoumarins by treatment of 3-aryl-2-propynoic acids with diaryliodonium triflate in the presence of a base, followed by the reaction with tetrabutylammonium bromide (TBAB) and $Na_2S_2O_8$ in a mixture of 1,2-dichloroethane and water [31].

Results and Discussion

First, treatment of 3-phenyl-2-propynoic acid (**1a**, 0.5 mmol) with diphenyliodonium triflate (**A**, 1.0 equiv) in the presence of CuCl (5 mol %) and K_2CO_3 (1.0 equiv) in dichloromethane (3.0 mL) at 40 °C based on a previous report [46] gave phenyl 3-phenyl-2-propynoate (**2Aa**) in 46% yield, as shown in Table 1, entry 1. When the amount of the solvent was increased to 7.5 mL under the same conditions, the yield of phenyl ester **2Aa** was increased to 74% (Table 1, entry 2). Under the same conditions, the base was changed to NaH, Cs_2CO_3, *t*-BuOK, $NaNH_2$, and K_3PO_4 instead of K_2CO_3. However, the yield of phenyl ester **2Aa** was moderate to low (Table 1, entries 3–7). When the amount of K_2CO_3 was reduced to 0.5 equiv under the same conditions as those in entry 2, the yield of phenyl ester **2Aa** was increased to 80% (Table 1, entry 8). When CuCl was changed to CuI and CuBr, the difference of the yield of phenyl ester **2Aa** was small, but CuCl gave the highest yield (Table 1, entries 8–10). Then, the reaction temperature was changed to 0 °C, rt, 50 °C, and 60 °C under the same conditions as those in entry 8, and phenyl ester **2Aa** was obtained in 83% yield at 50 °C (Table 1, entries 11–14). On the other hand, when the present reaction was carried out without CuCl under the same conditions, phenyl ester **2Aa** was not obtained at all (Table 1, entry 15).

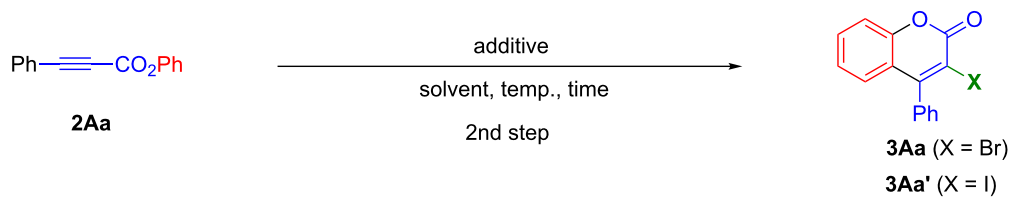
Then, the iodocyclization of phenyl ester **2Aa** to 3-iodo-4-phenylcoumarin (**3Aa'**) with *N*-iodosuccinimide (NIS, 2.0 equiv)/$BF_3{\cdot}Et_2O$ (2.0 or 1.1 equiv) was studied based on the previous reports [45,46], as shown in Table 2. However, 3-iodo-4-phenylcoumarin (**3Aa'**) was obtained in low to moderate yields (Table 2, entries 1 and 2). To improve the yield of 3-halo-4-phenylcoumarins **3Aa** or **3Aa'**, the halocyclization of **2Aa** with *N*-bromosuccinimide (NBS, 2.0 equiv)/$BF_3{\cdot}Et_2O$ (1.1 equiv), with 1,3-diiodo-5,5-dimethylhydantoin (DIH, 2.0 equiv)/$BF_3{\cdot}Et_2O$ (1.1 equiv), and with 1,3-dibromo-5,5-dimethylhydantoin (DBH, 2.0 equiv)/$BF_3{\cdot}Et_2O$ (1.1 equiv) was carried out to form 3-bromo-4-phenylcoumarin (**3Aa**), 3-iodo-4-phenylcoumarin (**3Aa'**), and 3-bromo-4-phenylcoumarin (**3Aa**) in 28, 49 and 46% yields, respectively (Table 2, entries 3–5). The treatment of phenyl ester **2Aa** with molecular iodine (2.0 equiv)/K_2CO_3 (2.0 equiv) did not generate 3-iodo-4-phenylcoumarin (**3Aa'**) at all (Table 2, entry 6). Thus, the iodonium-based or bromonium-based electrophilic cyclization of phenyl 3-phenyl-2-propynoate (**2Aa**) does not proceed effi-

Table 1: O-Phenylation of 3-phenyl-2-propynoic acid (**1a**) with diphenyliodonium triflate (**A**).



entry	base	solvent (mL)	additive (mol %)	temp. (°C)	yield (%)
1	K_2CO_3 (1.0)	CH_2Cl_2 (3.0)	CuCl (5)	40	46
2	K_2CO_3 (1.0)	CH_2Cl_2 (7.5)	CuCl (5)	40	74
3	NaH (1.0)	CH_2Cl_2 (7.5)	CuCl (5)	40	24
4	Cs_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuCl (5)	40	17
5	*t*-BuOK (1.0)	CH_2Cl_2 (7.5)	CuCl (5)	40	48
6	$NaNH_2$ (1.0)	CH_2Cl_2 (7.5)	CuCl (5)	40	9
7	K_3PO_4 (1.0)	CH_2Cl_2 (7.5)	CuCl (5)	40	30
8	K_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuCl (5)	40	80
9	K_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuI (5)	40	78
10	K_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuBr (5)	40	77
11	K_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuCl (5)	0	11
12	K_2CO_3 (0.5)	CH_2Cl_2 (7.5)	CuCl (5)	rt	71
13	**K_2CO_3 (0.5)**	**DCE (7.5)**	**CuCl (5)**	**50**	**83**
14	K_2CO_3 (0.5)	DCE (7.5)	CuCl (5)	60	75
15	K_2CO_3 (0.5)	DCE (7.5)	–	50	0

Table 2: Halocyclization of phenyl 3-phenyl-2-propynoate (**2Aa**) to 3-halo-4-phenylcoumarins **3Aa** and **3Aa'**.



entry	additive (equiv)	solvent (mL)	temp. (°C)	time (h)	yield (%)
1	NIS (2.0), $BF_3{\cdot}Et_2O$ (2.0)	CH_2Cl_2 (3.0)	40	1	36 (**3Aa'**)
2	NIS (2.0), $BF_3{\cdot}Et_2O$ (1.1)	CH_2Cl_2 (3.0)	40	1	45 (**3Aa'**)
3	NBS (2.0), $BF_3{\cdot}Et_2O$ (1.1)	CH_2Cl_2 (3.0)	40	1	28 (**3Aa**)
4	DIH (2.0), $BF_3{\cdot}Et_2O$ (1.1)	CH_2Cl_2 (3.0)	40	1	49 (**3Aa'**)
5	DBH (2.0), $BF_3{\cdot}Et_2O$ (1.1)	CH_2Cl_2 (3.0)	40	1	46 (**3Aa**)
6	I_2 (2.0), K_2CO_3 (2.0)	CH_3CN (3.0)	40	1	0
7	TBAB (2.0), $Na_2S_2O_8$ (1.5)	DCE:H_2O (1:1, 5.0)	90	19	68 (**3Aa**)
8	TBAI (2.0), $Na_2S_2O_8$ (1.5)	DCE:H_2O (1:1, 5.0)	90	19	45 (**3Aa'**)
9	**TBAB (2.0), $Na_2S_2O_8$ (1.0)**	**DCE:H_2O (1:1, 5.0)**	**90**	**19**	**79** (**3Aa**)
10	TBAB (2.0), $Na_2S_2O_8$ (2.0)	DCE:H_2O (1:1, 5.0)	90	19	51 (**3Aa**)
11	TBAB (2.5), $Na_2S_2O_8$ (1.0)	DCE:H_2O (1:1, 5.0)	90	19	69 (**3Aa**)
12	TBAB (2.0), $K_2S_2O_8$ (1.0)	DCE:H_2O (1:1, 5.0)	90	19	71 (**3Aa**)
13	TBAB (2.0), $(NH_4)_2S_2O_8$ (1.0)	DCE:H_2O (1:1, 5.0)	90	19	69 (**3Aa**)
14	TBAB (2.0), Oxone® (1.0)	DCE:H_2O (1:1, 5.0)	90	19	37 (**3Aa**)

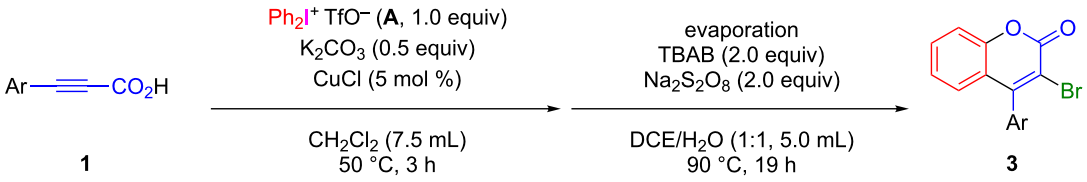
ciently. Then, the bromo-radical-based cyclization of phenyl 3-phenyl-2-propynoate (**2Aa**) with tetrabutylammonium bromide (TBAB, 2.0 equiv)/$Na_2S_2O_8$ (1.5 equiv) [31] in a mixture of 1,2-dichloroethane (DCE) and water at 90 °C was carried out to give 3-bromo-4-phenylcoumarin (**3Aa**) in 68% yield (Table 2, entry 7). When the iodocyclization of phenyl ester **2Aa** with tetrabutylammonium iodide (TBAI, 2.0 equiv)/$Na_2S_2O_8$ (1.5 equiv) was carried out, the yield of iodocyclization product **3Aa'** was decreased to 45% (Table 2, entry 8). When the bromocyclization of phenyl ester **2Aa** with TBAB (2.0 equiv)/$Na_2S_2O_8$ (1.0 equiv) in a mixture of DCE and water at 90 °C was carried out, 3-bromo-4-phenylcoumarin (**3Aa**) was obtained in 79% yield (Table 2, entry 9). When $Na_2S_2O_8$ was increased to 2.0 equivalents or TBAB was increased to 2.5 equivalents under the same conditions, the yields of 3-bromo-4-phenylcoumarin (**3Aa**) were decreased to 51 and 69%, respectively (Table 2, entries 10 and 11). Moreover, when $Na_2S_2O_8$ was changed to $K_2S_2O_8$, $(NH_4)_2S_2O_8$, and Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), the yields of 3-bromo-4-phenylcoumarin (**3Aa**) were decreased to 71, 69 and 37%, respectively (Table 2, entries 12–14). Thus, it was confirmed that the treatment of phenyl ester **2Aa** with TBAB (2.0 equiv)/$Na_2S_2O_8$ (1.0 equiv) in a mixture of DCE and water at 90 °C for 19 h was the most efficient, giving 3-bromo-4-phenylcoumarin (**3Aa**) in good yield (Table 2, entry 9).

Finally, based on the results in Table 1 and Table 2, the one-pot preparation of 4-aryl-3-bromocoumarins **3** from 3-aryl-2-propynoic acids **1** was carried out. 3-Aryl-2-propynoic acids **1**, such as 3-phenyl-2-propynoic acid (**1a**), 3-(*o*-methylphenyl)-2-propynoic acid (**1b**), 3-(*m*-methylphenyl)-2-propynoic acid (**1c**), 3-(*p*-methylphenyl)-2-propynoic acid (**1d**), 3-(*p*-methoxyphenyl)-2-propynoic acid (**1e**), 3-(*p*-fluorophenyl)-2-propynoic acid (**1f**), 3-(*p*-chlorophenyl)-2-propynoic acid (**1g**), 3-(*o*-chlorophenyl)-2-propynoic acid (**1h**), 3-(*m*-chlorophenyl)-2-propynoic acid (**1i**), 3-(*p*-bromophenyl)-2-propynoic acid (**1j**), 3-(*p*-biphenyl)-2-propynoic acid (**1k**), 3-(naphthalen-2'-yl)-2-propynoic acid (**1l**), and 3-(naphthalen-1'-yl)-2-propynoic acid (**1m**), were treated with diphenyliodonium triflate (**A**, 1.0 equiv) in the presence of CuCl and K_2CO_3 in CH_2Cl_2 for 3 h under refluxing conditions. After removal of the solvent, the second-step treatment of the reaction mixture with TBAB (2.0 equiv) and $Na_2S_2O_8$ (2.0 equiv) in a mixture of DCE and water at 90 °C for 19 h gave 4-aryl-3-bromocoumarins **3Aa**–**3Am** in moderate yields, respectively, as shown in Scheme 1. As a gram-scale experiment, treatment of 3-phenyl-2-propynoic acid (**1a**, 8 mmol) with diphenyliodonium triflate **A** in the presence of CuCl and K_2CO_3 in CH_2Cl_2 for 3 h, followed by removal of the solvent and the reaction with TBAB and $Na_2S_2O_8$ in a mixture of DCE and water at 90 °C for 19 h gave 3-bromo-4-phenylcoumarin (**3Aa**) in 52% yield. For 3-aryl-2-propynoic acids bearing heteroaromatic groups, treatment of 3-(benzothiophen-2'-yl)-2-propynoic acid (**1n**) and 3-(benzofuran-2'-yl)-2-propynoic acid (**1o**) under the same procedure and conditions gave the corresponding coumarins **3An** and **3Ao** in moderate yields, respectively. Under the present procedure and conditions, use of 2-hexynoic acid (**1p**), a 3-alkyl-2-propynoic acid, provided 3-bromo-4-propylcoumarin (**3Ap**) in 42% yield, as shown in Scheme 1.

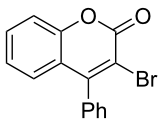
Then, other diaryliodonium triflates were used instead of diphenyliodonium triflate (**A**). Treatment of 3-phenyl-2-propynoic acid (**1a**) with diaryliodonium triflates (1.0 equiv), such as di(*p*-methylphenyl)iodonium triflate (**B**), di(*tert*-butylphenyl)iodonium triflate (**C**), di(*p*-chlorophenyl)iodonium triflate (**D**), and di(*p*-bromophenyl)iodonium triflate (**E**), in the presence of CuCl and K_2CO_3 in CH_2Cl_2 for 3 h under refluxing conditions, followed by removal of the solvent and the reaction with TBAB (2.0 equiv) and $Na_2S_2O_8$ (2.0 equiv) in a mixture of DCE and water at 90 °C for 19 h gave 3-bromo-4-phenylcoumarin derivatives **3Ba**–**3Ea** bearing methyl, *tert*-butyl, chloro, and bromo groups at 7-position in good to moderate yields, respectively, as shown in Scheme 2.

As regards the synthetic utilization of the products in the present one-pot reaction, treatment of 3-bromo-4-phenylcoumarin (**3Aa**) with Zn in ethanol under refluxing conditions gave 4-phenylcoumarin (**4Aa**) in 81% yield. Treatment of 3-bromo-4-phenylcoumarin (**3Aa**) with *p*-toluenethiol/*N,N'*-dimethylethylenediamine (DMEDA)/K_2CO_3 in the presence of CuI in toluene at refluxing temperature and with *p*-methoxybenzamide/DMEDA/K_2CO_3 in the presence of CuI in toluene at refluxing temperature generated 3-(4-methylbenzenesulfenyl)-4-phenylcoumarin (**5Aa**) and 3-(4-methoxylbenzoylamino)-4-phenylcoumarin (**6Aa**) in 62 and 51% yields, respectively. The Pd-catalyzed coupling reactions of 3-bromo-4-phenylcoumarin (**3Aa**) with 4-methylstyrene/K_2CO_3/$PdCl_2(Ph_3P)_2$, with phenylacetylene/$PdCl_2(Ph_3P)_2$/Et_3N and with $PhB(OH)_2$/K_2CO_3/$PdCl_2(Ph_3P)_2$ provided the corresponding C–C bonded coumarin derivatives **7Aa**, **8Aa**, and **9Aa** in 79, 60 and 76% yields, respectively (Scheme 3).

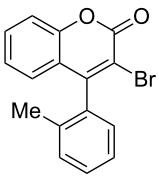
To support the present bromocyclization reaction to form 4-aryl-3-bromocoumarins with TBAB and $Na_2S_2O_8$ at the second step, the present one-pot preparation of 3-bromo-4-phenylcoumarin (**3Aa**) from 3-phenyl-2-propynoic acid (**1a**) was carried out in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl radical (TEMPO, 2.0 equiv) or 2,6-di(*tert*-butyl-*p*-cresol (BHT, 3.0 equiv) at the second step under the same procedure and conditions, but 3-bromo-4-phenylcoumarin (**3Aa**) was not obtained at all in both reactions. Thus, the present bromocyclization of the formed phenyl 3-phenyl-2-propynoate (**2Aa**)



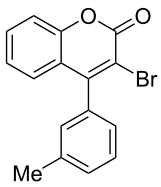
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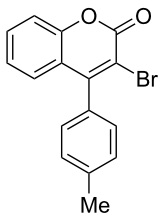
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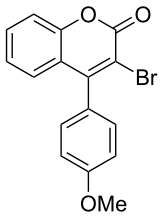
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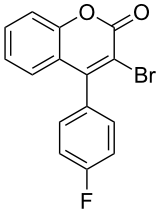
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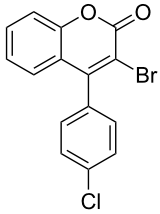
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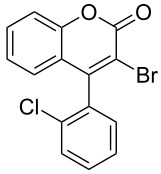
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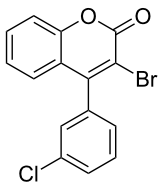
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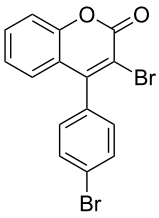
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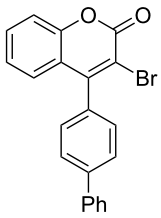
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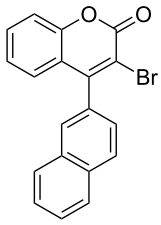
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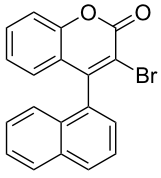
3Aj (51%)



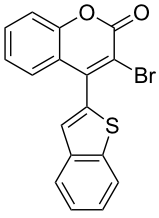
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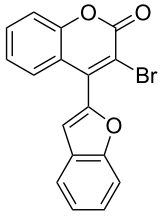
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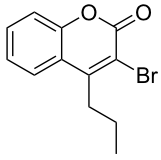
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3An (46%)

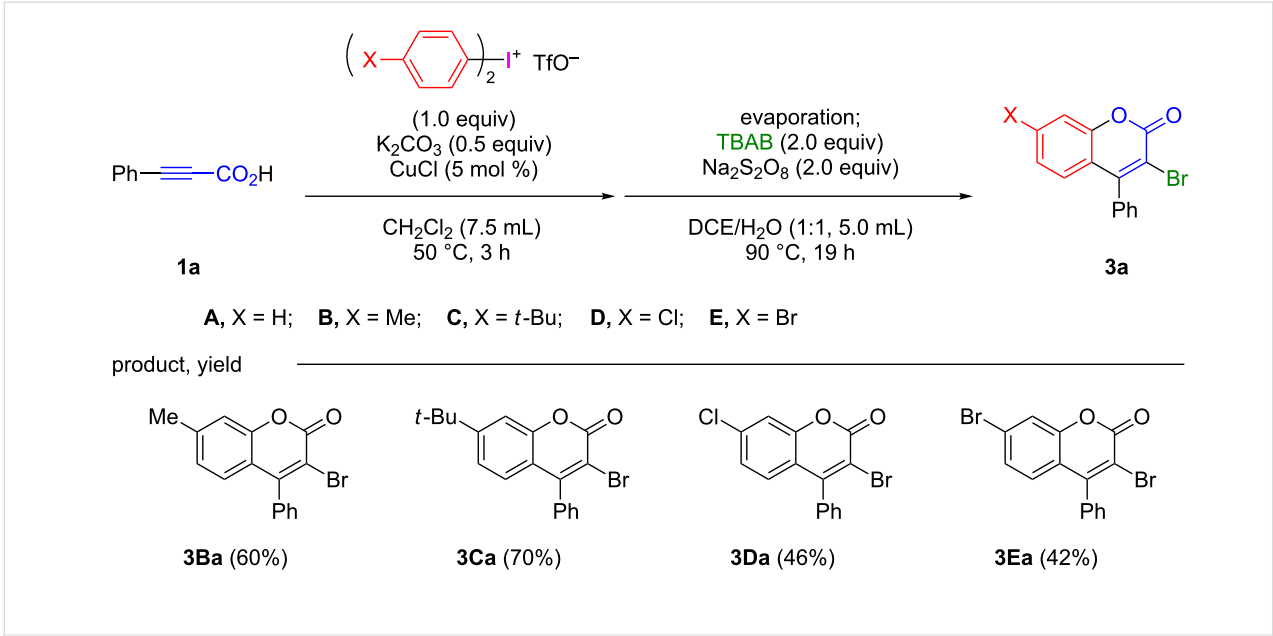


3Ao (43%)

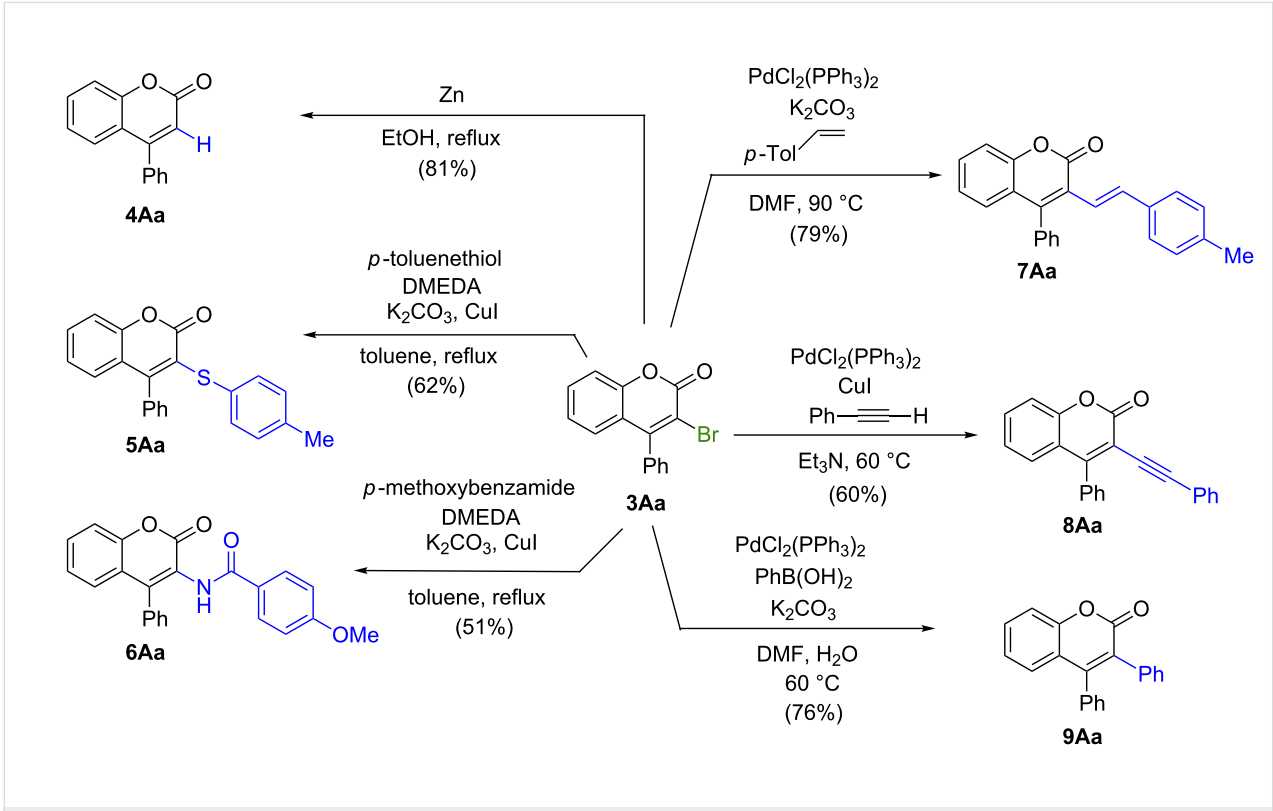


3Ap (42%)[b]

Scheme 1: One-pot preparation of 4-aryl-3-bromocoumarins **3** from 3-aryl-2-propynoic acids **1** with diphenyliodonium triflate (**A**).
[a]3-Phenyl-2-propynoic acid (**1a**, 8.0 mmol) was used. [b]The first reaction step was conducted with K_2CO_3 (1.0 equiv) under refluxing conditions.



Scheme 2: One-pot preparation of 3-bromo-4-phenylcoumarins **3a** from 3-phenyl-2-propynoic acid (**1a**) with daryliodonium triflates **B**–**E**.



Scheme 3: Derivatization of 3-bromo-4-phenylcoumarin.

with TBAB and $Na_2S_2O_8$ in a mixture of DCE and water is a radical-mediated bromocyclization reaction. X-ray crystallographic analysis of 3-bromo-7-chloro-4-phenylcoumarin (**3Da**), which was formed by the subsequent treatment of 3-phenyl-2-propynoic acid (**1a**) with di(*p*-chlorophenyl)iodonium triflate (**D**) and then with TBAB and $Na_2S_2O_8$, was carried out, as shown in Figure 1. Based on those results, the possible reaction pathway is shown in Scheme 4.

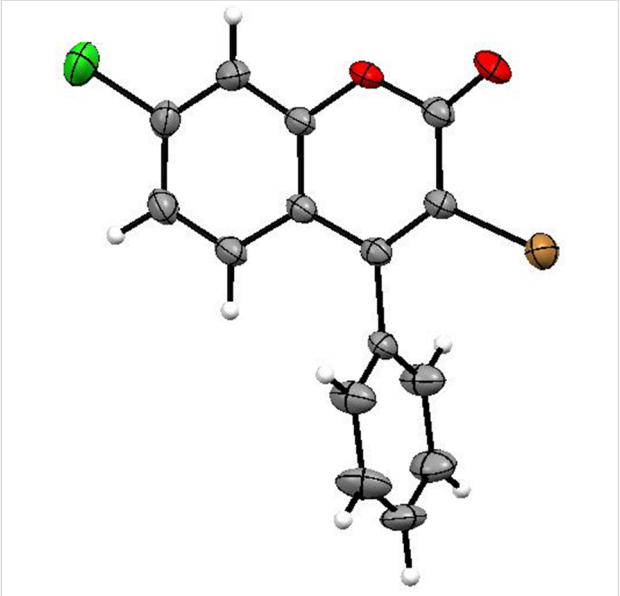
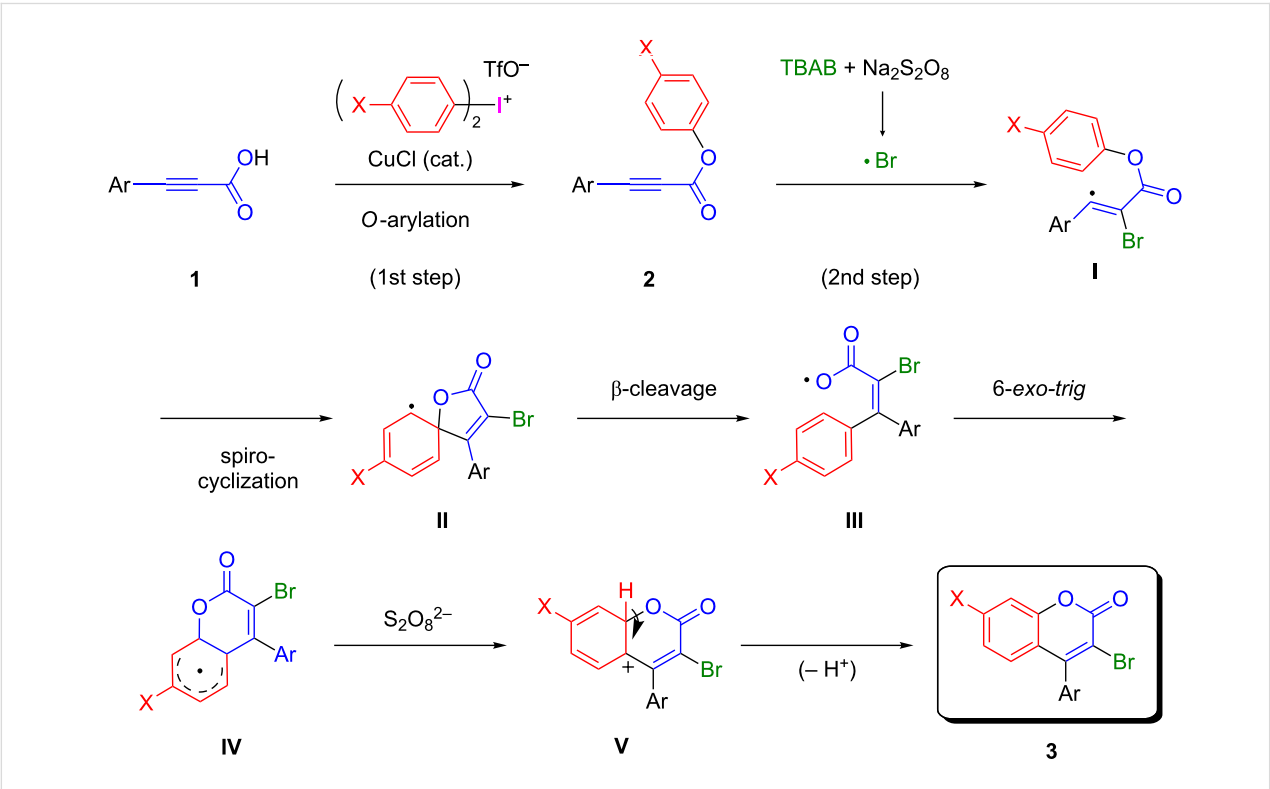


Figure 1: ORTEP of 3-bromo-7-chloro-4-phenylcoumarin (**3Da**).

The O-arylation of 3-aryl-2-propynoic acid **1** with diaryliodonium triflate in the presence of K_2CO_3 and CuCl occurs to form aryl 3-aryl-2-propynoate **2** (1st step). The bromocyclization of aryl 3-aryl-2-propynoate **2** with TBAB and $Na_2S_2O_8$ proceeds via a bromoradical addition to the triple bond to form very reactive vinyl radical **I** [47]. *Ipso*-cyclization of the vinyl radical **I** occurs to form spiro radical intermediate **II**. Then, β-cleavage of the spiro radical intermediate **II** proceeds to form carboxyl radical **III**. *6-Exo-trig* cyclization of the carboxyl radical **III** onto the aromatic ring takes place to form adduct radical **IV**, which would be rapidly oxidized by $Na_2S_2O_8$ to form cation intermediate **V**. Smooth deprotonation of cation intermediate **V** occurs to generate 4-aryl-3-bromocoumarin **3** (2nd step). The radical *ipso*-cyclization of the formed vinyl radical and its 1,2-carboxyl group migration agree with previously reported results [31-34].

Conclusion

The successive treatment of 3-aryl-2-propynoic acids with diaryliodonium triflates in the presence of K_2CO_3 and CuCl, and then with tetrabutylammonium bromide (TBAB) and $Na_2S_2O_8$ gave 4-aryl-3-bromocoumarins bearing hydrogen, methyl, *tert*-butyl, chloro, and bromo groups at 7-position in moderate yields, respectively. In one of the obtained 4-aryl-3-bromocoumarins, the C–Br bond of 3-bromo-4-phenylcoumarin was smoothly converted into 4-phenylcoumarins bearing C–H, C–S, C–N, and C–C bonds at 3-position. We believe the present method will be useful for the preparation of various 4-arylcoumarin derivatives due to its simple one-pot synthesis.



Scheme 4: Possible reaction pathway.

Supporting Information

Supporting Information File 1

NMR charts of all coumarin derivatives **3Aa**–**3Ap**, **3Ba**–**3Ea**, and **4Aa**–**9Aa**, and X-ray analytical data of **3Da**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-22-S1.pdf]

Acknowledgements

Financial support in the form of a Grant-in–Aid for Scientific Research (No. 15K05418) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan is gratefully acknowledged.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Diels–Alder cycloadditions of *N*-arylpyrroles via aryne intermediates using diaryliodonium salts

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Letter

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Keywords:
benzyne; cycloaddition; diaryliodonium salts; *N*-phenylamine; pyrrole

Beilstein J. Org. Chem. **2018,** *14,* 354–363.
doi:10.3762/bjoc.14.23

Received: 08 December 2017
Accepted: 26 January 2018
Published: 06 February 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

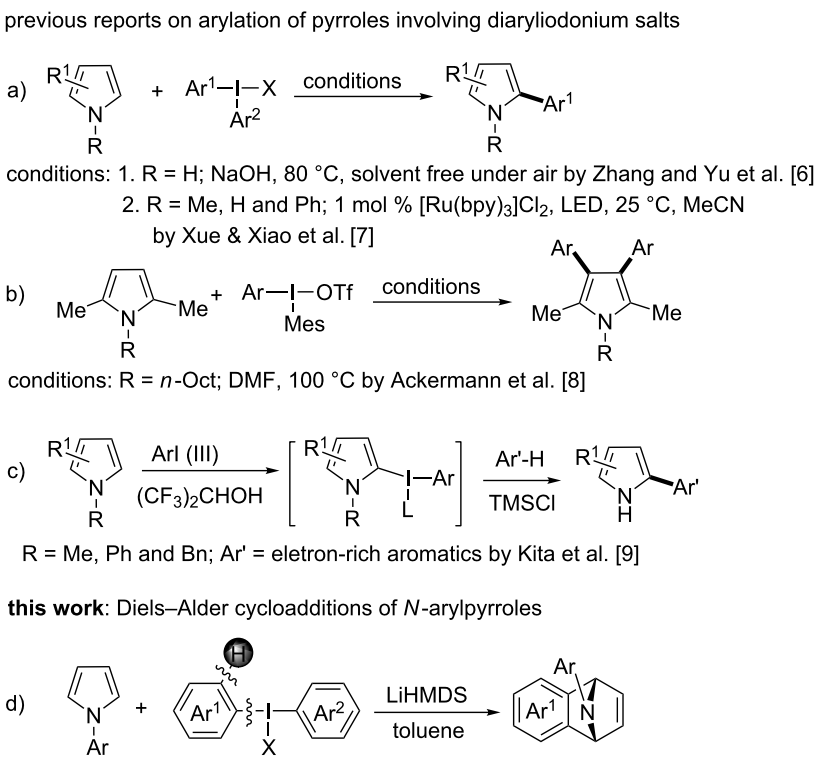
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Abstract

With a strategy of the formation of benzynes by using diaryliodonium salts, a cycloaddition reaction of *N*-arylpyrroles with benzynes was reported. A wide range of bridge-ring amines with various substituents have been synthesized in moderate to excellent yields (35–96%). Furthermore, with a catalytic amount of $TsOH·H_2O$, these amines can be converted into the corresponding *N*-phenylamine derivatives easily, which are potentially useful in photosensitive dyes.

Introduction

Pyrrole is a very useful heterocyclic substrate to produce structural attributes of valuable chemicals, functional materials and pharmaceuticals [1-5]. Recently, arylation of pyrrole derivatives with diaryliodonium salts for pyrrole–aryl coupling products is generating tremendous academic interest in organic synthesis. In 2012, the Zhang and Yu group reported that sodium hydroxide promoted direct arylation of unprotected pyrroles with diaryliodonium salts at the temperature of 80 °C, the coupling products were obtained in moderate to good yields (Scheme 1a) [6]. Later in 2013, Xue and Xiao et al. developed a method of photoredox catalysis in the presence of $[Ru(bpy)_3]^{2+}$ with visible light for the coupling reaction of arenes with unprotected or N-substituted pyrroles, pyrrole substrates were well tolerated with *N*-methyl and *N*-phenyl groups (Scheme 1a) [7]. Ackermann et al. employed a 2,5-dimethylpyrrole derivative as substrate to deliver double arylated products at 3,4-positions of the pyrrole ring (Scheme 1b) [8]. Recently, the research group of Kita documented an oxidative biaryl coupling for pyrroles



Scheme 1: Arylations of pyrrole derivatives with diaryliodonium salts.

using a hypervalent iodine reagent and a stabilizer for pyrrolyliodonium intermediates (Scheme 1c) [9]. The reactions readily provided a variety of desired coupling products in good yields. In general, the mechanism of these arylations was postulated by generating aryl radicals with diaryiodonium salts in the literature.

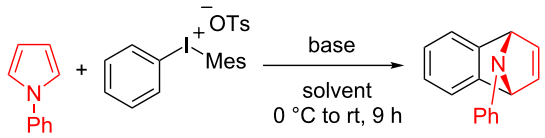
In 1995, Kitamura prepared phenyl[*o*-(trimethylsilyl)phenyl]iodonium triflate which could be used as an efficient benzyne precursor in trapping furans [10]. Surprisingly, the research groups of Stuart [11,12] and Wang [13] independently discovered in 2016 that simple diaryliodonium salts can generate benzynes under severe basic conditions, the resulted benzynes were allowed to undergo cycloaddition reaction with furan or N-arylation of secondary amides and amines. Due to the easy accessibility of the diaryliodonium salts, this kind of benzyne precursor is attracting extensive attention [14-16]. Also as a five-membered heterocyclic ring, the cycloaddition reaction of N-substituted pyrroles is much less than that of furan [17-21]. As a matter of fact, the Diels–Alder adduct formation of pyrroles with benzyne has been postulated in 1965 as transient products under thermal conditions to afford arylamines [22]. Inspired by the pioneering work of Stuart and Wang [12,13], herein we reported the usage of diaryliodonium salts as aryne precursor for Diels–Alder cycloadditions of *N*-arylpyrroles (Scheme 1d).

Results and Discussion

We initially started the cycloaddition reaction of 1-phenylpyrrole (**1a**) using phenyl(mesityl)iodonium tosylate (**2a**) as benzyne precursor. To our delight, with LiHMDS as the base in toluene, the Diels–Alder adduct **3aa** was obtained in 23% yield at room temperature (Table 1, entry 1). However, when the reaction temperature was increased to 100 °C or the solvent was changed to THF, we found a slight decrease in the yield of **3aa** (Table 1, entries 2 and 3). Interestingly, the reaction stoichiometry of **1a** and **2a** had a significant influence on the yield of **3aa**, which was similar to Stuart's work [11,12] (Table 1, entry 4–8). Further examinations of bases did not lead to better results (Table 1, entries 9–14). We then chose LiHMDS as the optimal base for the reaction. The reaction yield could be improved to 85% when an excess amount of LiHMDS was used (Table 1, entries 15–17). However, a screening of reaction temperature, solvent, and reaction time did not improve the yield of **3aa** (Table 1, entries 18–21).

With the optimal reaction conditions in hand, various aryl(mesityl)iodonium salts **2** were examined. As shown in Table 2, an extensive range of substituted aryl(mesityl)iodonium salts, bearing a wide variety of substituent groups, could react with **1a** to afford the corresponding cycloaddition adducts **3**. It was observed that the reaction gave the desired products **3ab** and **3ac** in moderate yields of 63% and 57% when iodoni-

Table 1: Optimization of reaction conditions.[a]



1a **2a** **3aa**

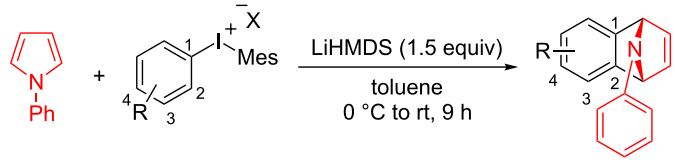
entry	**1a**/**2a** (equiv)	base (equiv)	solvent	**3aa** (%)[b]
1	1:1.2	LiHMDS (1.2)	toluene	23
2[c]	1:1.2	LiHMDS (1.2)	toluene	22
3	1:1.2	LiHMDS (1.2)	THF	20
4	1:3	LiHMDS (3)	toluene	40
5	3:1	LiHMDS (1)	toluene	59
6	4:1	LiHMDS (1)	toluene	73
7	5:1	LiHMDS (1)	toluene	80
8	6:1	LiHMDS (1)	toluene	74
9	5:1	KHMDS (1.5)	toluene	68
10	5:1	KO*t*-Bu (1)	toluene	60
11	5:1	$NaNH_2$ (1)	toluene	39
12	5:1	KO*t*-Bu (2)	toluene	65
13	5:1	NaOMe (2)	toluene	40
14	5:1	NaH (2)	toluene	n. r.
15	5:1	LiHMDS (1.2)	toluene	79
16	5:1	LiHMDS (1.5)	toluene	85
17	5:1	LiHMDS (2)	toluene	74
18[d]	5:1	LiHMDS (1.5)	toluene	70
19	5:1	LiHMDS (1.5)	THF	73
20	5:1	LiHMDS (1.5)	MeCN	n. r.
21[e]	5:1	LiHMDS (1.5)	toluene	73

[a]Reaction conditions: **1a** or **2a** (0.5 mmol, 1 equiv), base (0.5–0.75 mmol, 1–1.5 equiv), solvent (5 mL), 0 °C to rt, 9 h. [b]Isolated yield. [c]The reaction temperature was 100 °C. [d]The reaction temperature was 80 °C. [e]The reaction was quenched after 13 hours. n. r. = no reaction.

um salts **2** have electron-donating groups in the *para*-position of the aryl moiety, such as methyl groups and *tert*-butyl groups (Table 2, entries 2 and 3). For those bearing electron-withdrawing groups, such as halogens (F, Cl, Br), cyano, nitro, trifluoromethyl, and trifluoromethoxy groups, the corresponding products **3ad**–**3aj** were obtained in good to excellent yields of 67–96% (Table 2, entries 4–10). It was found that the reactions underwent smoothly to give the products **3ak**, **3al** in good yields of 89% and 82%, respectively, when there was a phenyl group on the *para*- or *ortho*-positions of the aryl moiety for diaryliodonium salts (Table 2, entries 11 and 12). Analogous to previous work [11,12], when **2m** and **2n** were employed, the cycloaddition regioselectively afforded **3am** and **3an** in good yields of 80% and 71%, respectively (Table 2, entries 13 and 14). Of note, substituents at the *ortho*-position on the aryl moiety with **2**, regardless of their electronic properties, had a negative effect on the reactivity (Table 2, entries 15–19).

To further probe the scope of this reaction, a wide range of 1-arylpyrroles **1** was employed in the reaction under the standard conditions. Generally, the conditions proved to be efficient for this Diels–Alder cycloaddition. As shown in Table 3, the electronic properties of aryl substituents had a little influence on the reaction outcome. For example, 1-phenylpyrrole with electron-donating groups (Me, *t*-Bu, OMe) gave **3ba**–**3da** in good yields of 62–83% (Table 3, entries 1–3). Meanwhile, 1-phenylpyrrole with electron-withdrawing groups (F, Cl, Br, CF_3, OCF_3, CN) also gave the corresponding products **3ea**–**3ja** in good to excellent yields of 71–93% (Table 3, entry 4–9). However, when R was biphenyl, the desired product **3ka** was only obtained in moderate yield of 35%, probably due to the poor solubility of the starting materials (Table 3, entry 10). In contrast, when N-substituents (R) were Ts, Boc, Bn or methyl, no desired product was detected by thin layer chromatography (TLC) experiments (Table 3, entries 11–13). Interestingly, the method of Lautens works with an *N*-Boc pyrrole [21].

Table 2: Scope of diaryliodonium salts **2**.[a]



1a **2** **3**

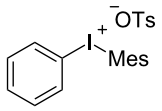
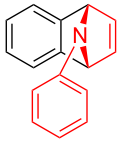
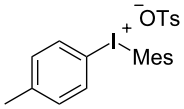
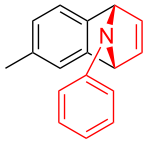
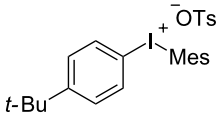
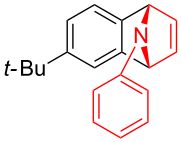
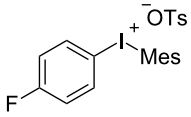
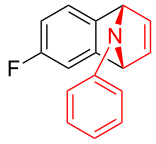
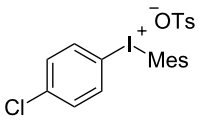
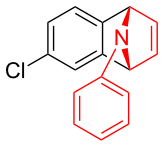
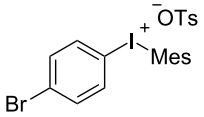
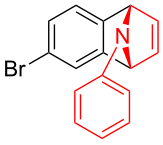
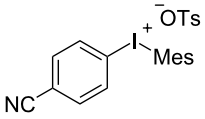
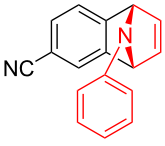
entry	aryl(mesityl)iodonium salts	product	yield (%)[b]
1	 **2a**	 **3aa**	85
2	 **2b**	 **3ab**	63
3	 **2c**	 **3ac**	57
4	 **2d**	 **3ad**	77
5	 **2e**	 **3ae**	87
6	 **2f**	 **3af**	96
7	 **2g**	 **3ag**	71

Table 2: Scope of diaryliodonium salts **2**.[a] (continued)

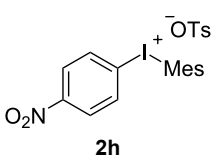
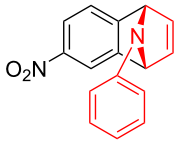
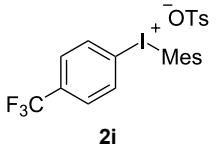
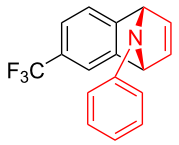
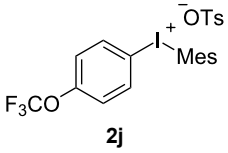
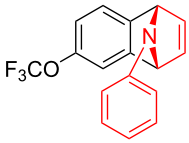
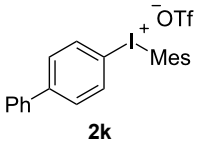
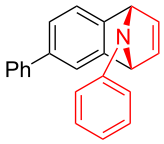
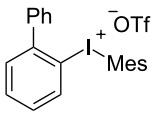
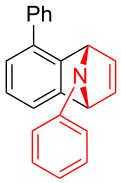
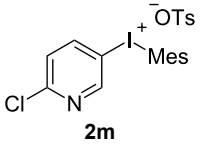
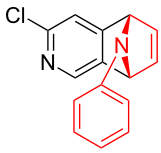
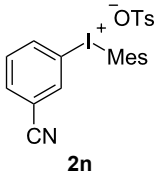
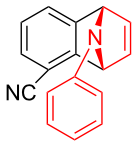
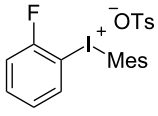
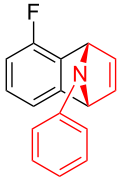
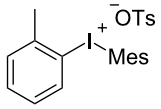
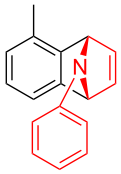
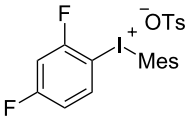
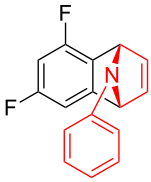
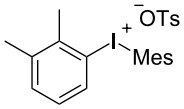
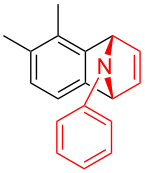
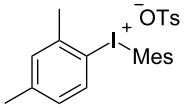
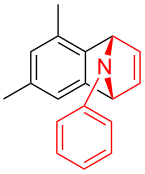
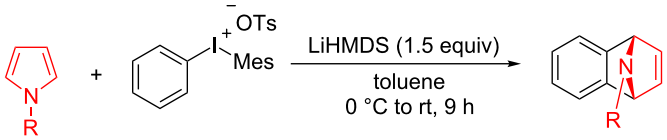
8	 **2h**	 **3ah**	67
9	 **2i**	 **3ai**	77
10	 **2j**	 **3aj**	88
11	 **2k**	 **3ak**	89
12	 **2l**	 **3al**	82
13	 **2m**	 **3am**	80
14	 **2n**	 **3an**	71
15	 **2o**	 **3ao**	78

Table 2: Scope of diaryliodonium salts **2**.[a] (continued)

16	 **2p**	 **3ap**	60
17	 **2q**	 **3aq**	48
18	 **2r**	 **3ar**	62
19	 **2s**	 **3as**	58

[a]Reaction conditions: **1a** (2.5 mmol, 5 equiv), **2** (0.5 mmol), LiHMDS (1 M in toluene, 0.75 mL, 1.5 equiv), toluene (5 mL), 0 °C to rt, 9 h. [b]Isolated yield. Mes = 2,4,6-trimethylphenyl, OTs = 4-toluenesulfonate, OTf = trifluoromethansulfonate.

Table 3: Scope of N-substituted pyrroles **1**.[a]



1 **2a** **3**

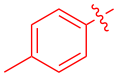
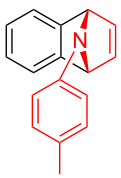
entry	R	product	yield (%)[b]
1	 **1b**	 **3ba**	77

Table 3: Scope of N-substituted pyrroles **1**.[a] (continued)

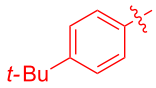
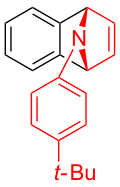
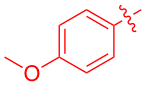
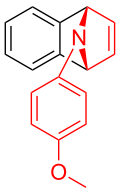
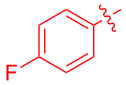
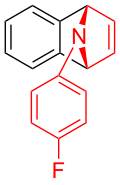
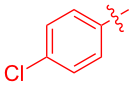
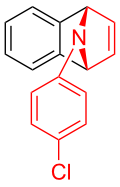
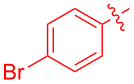
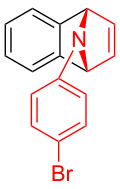
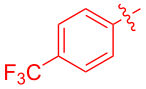
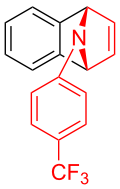
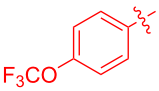
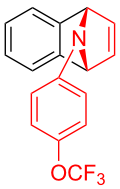
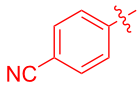
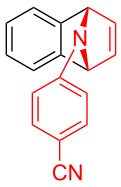
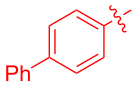
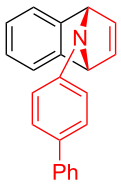
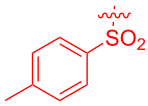
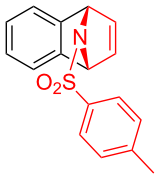
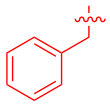
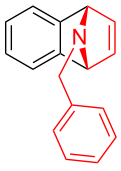
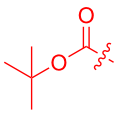
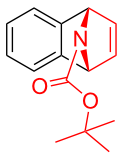
2	 **1c**	 **3ca**	83
3	 **1d**	 **3da**	62
4	 **1e**	 **3ea**	82
5	 **1f**	 **3fa**	81
6	 **1g**	 **3ga**	71
7	 **1h**	 **3ha**	90
8	 **1i**	 **3ia**	83

Table 3: Scope of N-substituted pyrroles **1**.[a] (continued)

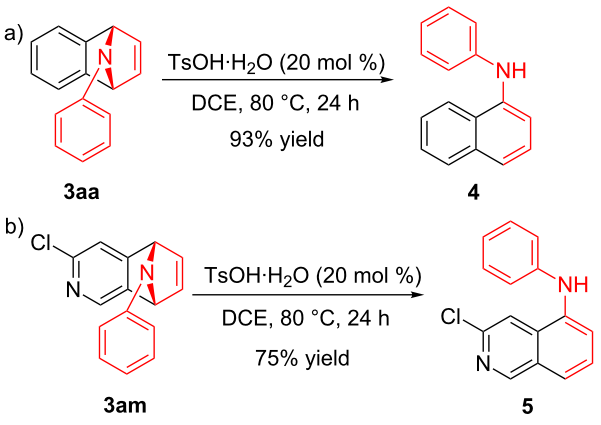
9	 **1j**	 **3ja**	93
10	 **1k**	 **3ka**	35
11	 **1l**	 **3la**	0
12	 **1m**	 **3ma**	0
13	 **1n**	 **3na**	0

[a]Reaction conditions: **1** (2.5 mmol, 5 equiv), **2a** (0.5 mmol), LiHMDS (1 M in toluene, 0.75 mL, 1.5 equiv), toluene (5 mL), 0 °C to rt, 9 h. [b]Isolated yield. Mes = 2,4,6-trimethylphenyl. OTs = 4-toluenesulfonate.

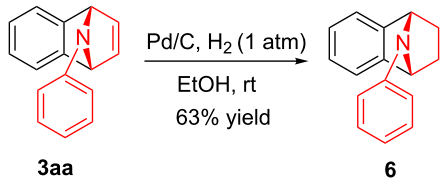
To demonstrate the practical utility of this methodology, treatment of **3aa** with 20 mol % TsOH·H_2O in DCE at 80 °C resulted in *N*-phenylnaphthalen-1-ylamine (**4**) in 93% yield [23], which was widely used in dye-sensitized solar cells [24], hole transport materials [25,26] and organic light-emitting diodes (OLEDs, Scheme 2a) [27]. In another similar reaction with **3am**, a novel *N*-phenylamine derivative **5** was synthesized in 75% yield (Scheme 2b), whose structure was determined by 2D-NMR analyses (see Supporting Information File 1). Furthermore, as a unique electron donor, the novel compound **5** may have potential applications in photosensitive dyes and OLEDs [28,29]. Interestingly, the bridged-ring compound **6** could be easily obtained in 63% yield with palladium on carbon catalyst under hydrogen atmosphere at room temperature (Scheme 3).

Conclusion

In summary, we have demonstrated a Diels–Alder cycloaddition of *N*-arylpyrroles by using diaryliodonium salts under mild conditions. The synthetic method was extended to a wide range of substrates. As such, various bridged-ring amines were prepared in moderate to excellent yields of 35–96%. Additionally, the resulting products could be easily converted to *N*-phenylamine derivatives and hydrogenated products in good yields. Further investigations on the application of this transformation are underway in our laboratory.



Scheme 2: Formation of *N*-phenylamine derivatives **4** and **5** via ring opening reactions.



Scheme 3: Preparation of product **6** by hydrogenation.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of all products, copies of ^{1}H, ^{13}C, ^{19}F NMR and HRMS spectra of all compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-23-S1.pdf]

Acknowledgements

The work was supported by the National Nature Science Foundation of China (NSFC 21472213, 21272069), National Key Program (2016YFA0200302, Study on application and preparation of aroma nanocomposites), the Fundamental Research Funds for the Central Universities and Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of fluoro-functionalized diaryl-λ^3-iodonium salts and their cytotoxicity against human lymphoma U937 cells

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Keywords:
biological activity; diaryliodonium salt; fluorine; hypervalent iodine; lymphoma; pentafluorosulfanyl

Beilstein J. Org. Chem. **2018,** *14,* 364–372.
doi:10.3762/bjoc.14.24

Received: 13 September 2017
Accepted: 24 January 2018
Published: 07 February 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Conscious of the potential bioactivity of fluorine, an investigation was conducted using various fluorine-containing diaryliodonium salts in order to study and compare their biological activity against human lymphoma U937 cells. Most of the compounds tested are well-known reagents for fluoro-functionalized arylation reactions in synthetic organic chemistry, but their biological properties are not fully understood. Herein, after initially investigating 18 fluoro-functionalized reagents, we discovered that the *ortho*-fluoro-functionalized diaryliodonium salt reagents showed remarkable cytotoxicity in vitro. These results led us to synthesize more compounds, previously unknown sterically demanding diaryliodonium salts having a pentafluorosulfanyl (SF_5) functional group at the *ortho*-position, that is, unsymmetrical *ortho*-SF_5 phenylaryl-λ^3-iodonium salts. Newly synthesized mesityl(2-(pentafluoro-λ^6-sulfanyl)phenyl)iodonium exhibited the greatest potency in vitro against U937 cells. Evaluation of the cytotoxicity of selected phenylaryl-λ^3-iodonium salts against AGLCL (a normal human B cell line) was also examined.

Introduction

There has been a surge in the number of reports about fluorine chemistry in recent decades. This is because fluorine is an extremely important element whose presence in a compound can completely change its original physical and chemical characteristics [1-3]. The chemical structures of various pharmaceuticals, agrochemicals and coatings contain fluorine or fluori-

nated functional groups [4-9]. Therefore, the development of efficient synthetic methodologies for organofluorine compounds has gained much attention [10-15]. Our research group has been actively working in this direction for decades [12,13,16-23]. Our primary goal has been to develop fluorinating and fluoro-functionalized reagents for fluorination [18,19], trifluoromethylation [13,18,19], trifluoromethylthiolation [12,21] and pentafluoroarylation [22,23]. Utilizing these reagents, we have successfully synthesized a wide variety of bioactive organofluorine compounds [24-30] including fluorinated thalidomide (antitumor) [24], fluorinated donepezil (cholinesterase inhibitor) [25], and fluorinated camptothecin (anticancer) [26]. During our research programs focused on the development of novel reagents for fluoro-functionalization [12,13,16-23], as well as the design and synthesis of biologically active fluorine-containing compounds [24-28], we noted that a series of fluoro-functionalization reagents could themselves be highly potential drug candidates. All of the reagents that we developed contain at least one fluorine atom in their structures, which may explain why they have potential biological activity [4-9]. In addition, examination of the successful records of heterocyclic compounds in the pharmaceutical history indicates that some of these reagents have a heterocyclic skeleton which makes them suitable as drug candidates [29-32]. Among these compounds, our group is interested in investigating the biological activity of hypervalent iodine-type reagents [33]. Hypervalent iodine compounds have been receiving a lot of attention lately due to their varied applications in organic synthesis [33-40]. A wide range of bioactive compounds make use of diaryliodonium reagents as a part of their synthesis [41-43]. On the other hand, there are only fragmented reports on the biological activity of diaryliodonium salts [44-49]. Goldstein et al. [45] and Doroshow et al. [46] reported that some diaryliodonium salts show effective antimicrobial and NOX inhibitor activity, respectively. Several aryliodonium salts, aryliodonium ylides, and (diacyloxyiodo)arenes were also examined for their antibacterial activities against ice nucleation active Pseudomonas syringae, and aryliodonium salts, especially those with electron-withdrawing groups, exhibit higher antibacterial activities [49]. Despite the long history of diaryliodonium salts, which exceeds 100 years, as Willgerodt's reagent [50], research on the biological effects of diaryliodonium salts is still undeveloped. Since there are iodine-containing pharmaceuticals such as a series of radiocontrast agents, levothyroxine, idoxuridine and amiodaron [51-54], we started to investigate a biological study of fluorine-containing hypervalent iodine compounds in vitro using U937 (a human histiocytic lymphoma cell line) [55-58]. The U937 cell line is maintained as replicative non-adherent cells having many of the biochemical and morphological characteristics of blood monocytes. This cell line was chosen due to the convenience with which it can be handled and its ease of growth [27]. Initially, 19 compounds [20-22,59-64] were examined for their potential cytotoxicity, and some of them showed potency, in particular *ortho*-fluoro-functionalized diaryliodonium salts. These findings led us to synthesize four more previously unknown diaryliodonium salts having a sterically demanding pentafluorosulfanyl (SF_5) functional group at the *ortho*-position, that is, unsymmetrical *ortho*-SF_5 phenylaryl-λ^3-iodonium salts. Finally, one of the new compounds, namely mesityl(2-(pentafluoro-λ^6-sulfanyl)phenyl)iodonium salt, exhibited the greatest potency in vitro against U937 cells with an IC_{50} value of 0.49 μM.

Results and Discussion

To begin our investigation related to bioactivity, we randomly selected some fluorinating reagents that we had already developed, including Shibata reagents I [20] and II [21] (trifluoromethylation reagent **1** and trifluoromethylthiolation reagent **2a,** respectively), pentafluorophenylating reagent **2b** and several hypervalent iodine reagents, i.e., diaryliodonium salts with a mesitylene ligand (**3a**–**o**) and a triisopropylphenyl ligand **4a** [20-22,59-64] (Figure 1). We used the Muse™ Annexin V and Dead Cell Assay Kit (FITC), which is a common tool to detect the ability of compounds to induce cell death. U937, a human histiocytic lymphoma cell line (DS Pharma Biomedical EC85011440; Osaka, Japan) was used to examine the ability of our synthesized compounds to induce cell death.

The investigation was initially carried out using 20 μM of several of the compounds, all of which showed strong cytotoxicity (Figure S1 in Supporting Information File 1). We therefore opted to examine this potency using lower concentrations (1 μM and 5 μM) of these compounds. The data (treated cells and untreated controls) were plotted together to compare the results (Figure 2). Shibata reagents **1** and **2a** were not very cytotoxic at 5 μM. Perfluorinated phenylthio reagent **2b** and perfluorinated phenyl reagent **3a** showed similar, but unimpressive, results at both concentrations. Pyridinyl reagent **3b**, having a pyridine-SF_5 moiety, displayed high cytotoxicity (63.0% of annexin V-positive cells) at 5 μM, as did **3d** with 58.6% cytotoxicity. However, another analogue of pyridine-SF_5 reagent **3c** showed weak (10.8%) cytotoxicity. Next, we investigated the various SF_5-phenyl aryliodonium salts **3e**–**h**. They all displayed potent cytotoxicities at 5 μM (**3e**, (86.2%); **3f** (78.6%); **3g** (94.0%); **3h** (94.1%)) and **3h** had the greatest result even at 1 μM (52.8%). Thereafter, we analysed SO_2CF_3-phenyl aryliodonium salts **3i**–**k** and CF_3-phenyl aryliodonium salts **3l**,**m**. We observed that *ortho*-substituted phenyl aryliodonium salts **3k** and **3m** seemed to provide great potency at both concentrations (60.6% and 39.8% at 1 μM and 98.6% and 88.4% at 5 μM, respectively). The *ortho*-fluorophenyl aryliodonium salt **3n** was also analysed, and its potency at 5 μM was found to be

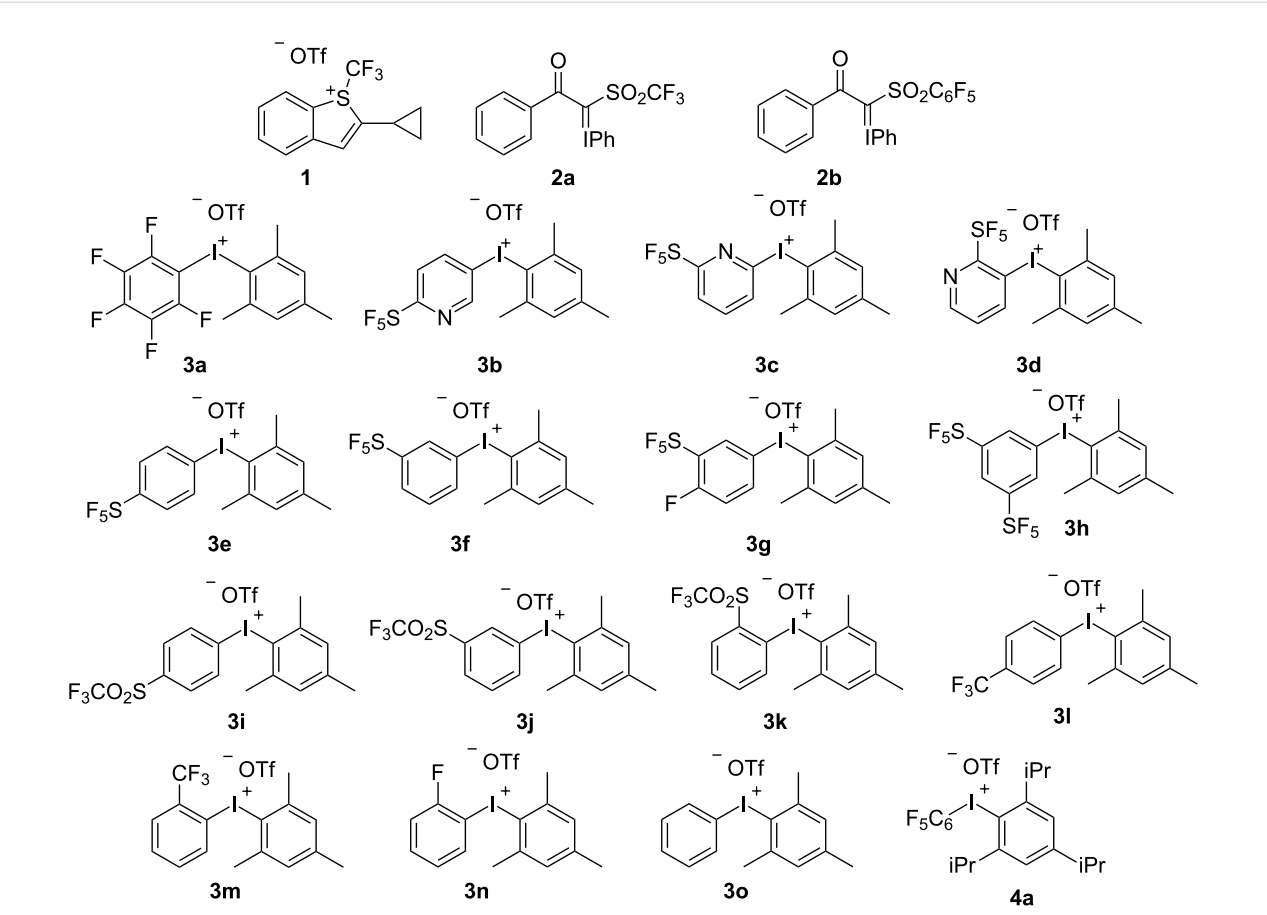


Figure 1: Compounds used for the biological study.

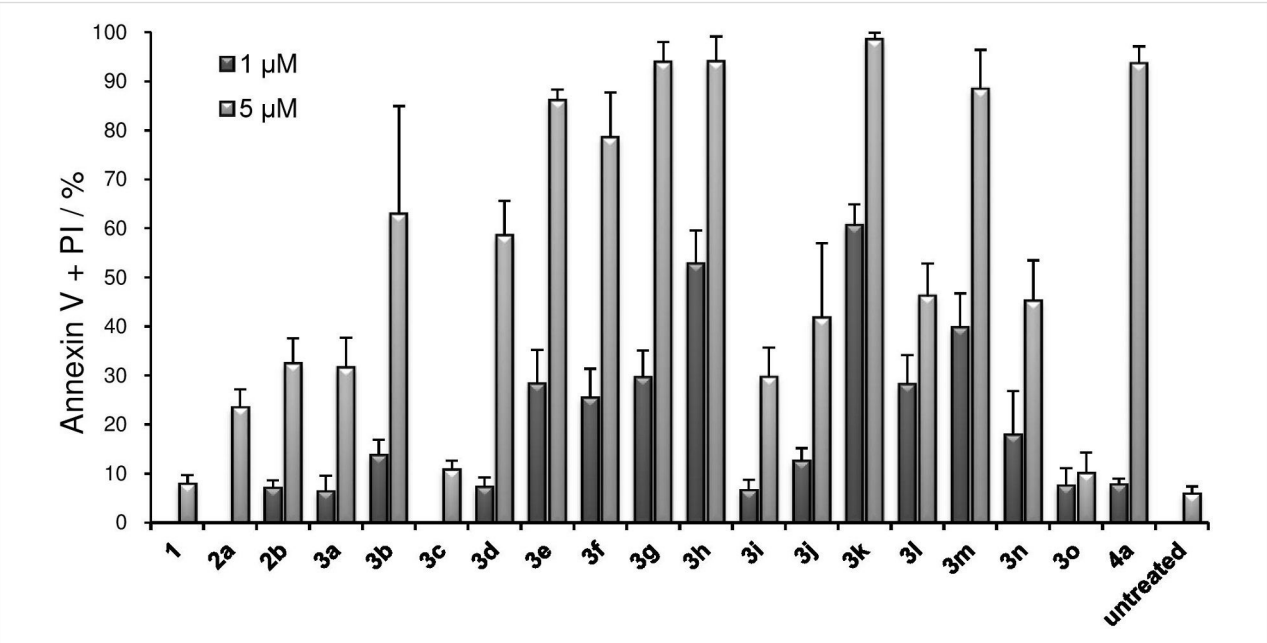
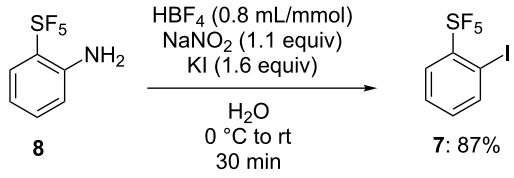


Figure 2: Compounds **1**–**4** induced cell death in U937 cells. Briefly, U937 cells (1×10^4 cells/mL) were incubated with each test compound at 1 μM and 5 μM for 24 h. Cells were stained with annexin V and propidium iodide (PI). The data shown is the mean ± SD (n = 3).

moderate (45.3%), but low at 1 μM (17.9%). The non-fluorinated diphenyl iodonium salt **3o**, on the other hand, was weakly cytotoxic at both concentrations (1 μM, 7.5%; 5 μM, 10.1%). Analysis of the perfluorinated phenyl reagent **4a** with a triisopropylphenyl ligand displayed strong cytotoxicity (93.7%) at 5 μM, but this value decreased considerably to 7.8% when used at 1 μM.

Following this investigation, we found that the *ortho*-substituted diaryliodonium salts with an *ortho*-SO_2CF_3 group **3k** and an *ortho*-CF_3 group **3m** displayed impressive results. A common feature of *ortho*-substitution on the aromatic group is steric demand, which allowed us to analyse the cell death-inducing potency of phenyl aryliodonium salts with a more sterically demanding fluoro-functional group of SF_5 at the *ortho*-position. As we did not succeed in synthesizing *ortho*-SF_5-substituted aryliodonium salts previously [59], we decided to proceed with a further investigation of the synthesis of *ortho*-SF_5 phenyl aryliodonium salts.

Four *ortho*-SF_5-substituted diaryliodonium salts were designed with different arenes as auxiliary groups, namely, electron-rich with sterically demanding mesitylene type **3p** and triisopropylphenyl type **4b**, electron-rich anisole type **5a** and simple phenyl type **6a**, which altered their electronic and steric properties [37]. First, pentafluoro-(2-iodophenyl)-λ^6-sulfane (**7**) was synthesized from commercially available 2-(pentafluoro-λ^6-sulfanyl)aniline (**8**), by completing a Sandmeyer reaction (Scheme 1). Fluoroboric acid and sodium nitrite were used to generate the diazonium ion and then KI was used to introduce iodide, providing the desired product **7** in 87% yield.



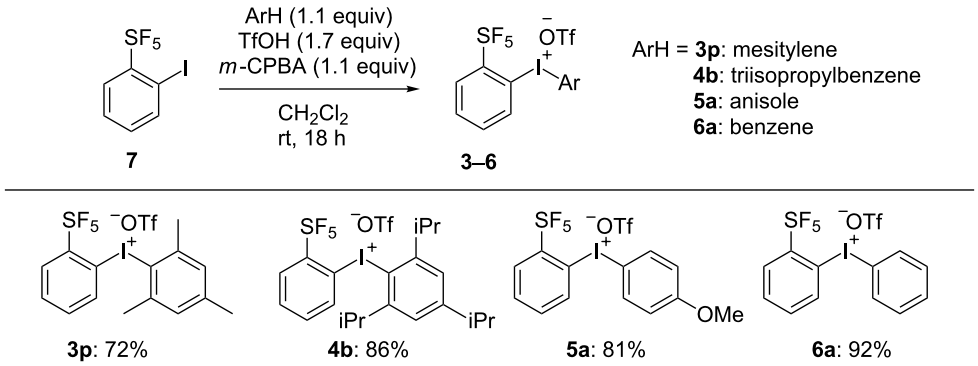
Scheme 1: Synthesis of pentafluoro-(2-iodophenyl)-λ^6-sulfane (**7**).

With **7** in hand, the synthesis of target *ortho*-SF_5 phenylaryl-λ^3-iodonium salts **3p**, **4b**, **5a** and **6a** was carried out according to a previously reported method [65,66]. This synthesis was achieved by treating iodide **7** with the respective arene, *m*-CPBA, and trifluoromethanesulfonic acid at room temperature. The desired diaryliodonium salts **3p**, **4b**, **5a** and **6a** were obtained in good yields (72%, 86%, 81% and 92%, respectively) (Scheme 2).

The newly synthesized SF_5-diaryliodonium salts **3p, 4b, 5a** and **6a** were characterized spectroscopically. The single crystal X-ray structure of **3p** was also analysed. The SF_5-diaryliodonium salt **3p** has a T-shaped geometry at the iodine centre, consistent with the general structure of diaryliodonium salts [33] (Figure 3).

Following the synthesis of the *ortho*-SF_5 phenyl aryliodonium salts, we selected salts **3p** and **5a** having mesitylene and anisole dummy ligands, respectively, and analysed their potential to induce cell death in U937 cells (Figure 4). Anisole type salt **5a** showed moderate cytotoxicity (45.2%) at 5 μM but the value decreased to 6.8% at 1 μM. Mesitylene type salt **3p**, on the other hand, displayed high potencies (98.9% and 66.9%) at 5 μM and 1 μM, respectively. To ensure that the cytotoxicity of **3p** was not due to its decomposed fragments, we analysed pentafluoro-(2-iodophenyl)-λ^6-sulfane (**7**) and pentafluoro(phenyl)-λ^6-sulfane (SF_5-C_6H_5, **9**), which did not exhibit cytotoxicity.

From the above analysis, we selected a series of *ortho*-fluorinated diaryliodonium salts SO_2CF_3 type **3k**, CF_3 type **3m** and SF_5 type **3p** and examined their IC_{50} values based on an MTT assay (Table 1). While **3k** was more potent than **3m** at both



Scheme 2: Synthesis of unsymmetrical *ortho*-SF_5 diaryliodonium salts **3p**, **4b**, **5a** and **6a**.

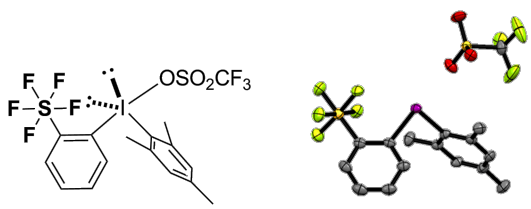


Figure 3: X-ray crystallographic structure of **3p** drawn at 50% probability (CCDC 1573953).

Table 1: Cytotoxicity of diaryliodonium salts **3k**, **3m** and **3p** against a human histiocytic lymphoma cell line (U937).[a]

diaryliodonium salt **3**	IC_{50} [μM]
3k	2.45 ± 0.24
3m	0.68 ± 0.05
3p	0.49 ± 0.05

[a]IC_{50} values were determined using an MTT assay; data represents the mean standard deviation of three independent experiments.

concentrations, i.e., 1 μM and 5 μM (Figure 2), **3m** has a lower IC_{50} value of 0.68 μM than that of **3k** (2.45 μM), as evaluated by the MTT assay. The best potency and IC_{50} value (0.49 μM) was obtained for SF_5 type **3p**, which is quite impressive when compared to the well-known antitumor drug cytosine arabinoside (ara-C), (0.16 μM) [27].

Since, **3k**, **3m** and **3p** exhibited strong cytotoxicity against U937 cells, we finally evaluated their cytotoxicity against normal cells in vitro. AGLCL, a human normal B cell line (DS Pharma Biomedical EC89120566; Osaka, Japan) was chosen for the experiments and investigations were performed at 20 μM (Figure S2 in Supporting Information File 1) and 5 μM and 1 μM concentrations (Figure 5) of the compounds. Although **3k**, **3m** and **3p** exhibited cytotoxicity even against AGLCL cells, a remarkable difference was observed. That is, moderate cytotoxicity at 5 μM (51.1%, 51.2% and 62.0%, respectively) and low cytotoxicity at 1 μM concentration (20.4%, 15.8% and 24.9%, respectively) against AGLCL cells were observed. It is noteworthy that the cytotoxicity displayed by **3k**, **3m** and **3p** against U937 cells is much higher than those against AGLCL cells at both concentrations. These results strongly suggested that antitumor drug candidates could be designed by further structural modification of these compounds **3**. Moreover, with **3p** exhibiting the greatest potency against U937 cells with comparably lower toxicity against AGLCL cells, further biological studies using **3p** including in vivo evaluation should be conducted. A mechanistic study that examines the structure–cytotoxicity relationships of a series of diaryliodonium salts **3** will also be conducted.

Conclusion

In conclusion, we have analysed a series of fluorinating reagents and diaryliodonium salts for their applicability in in-

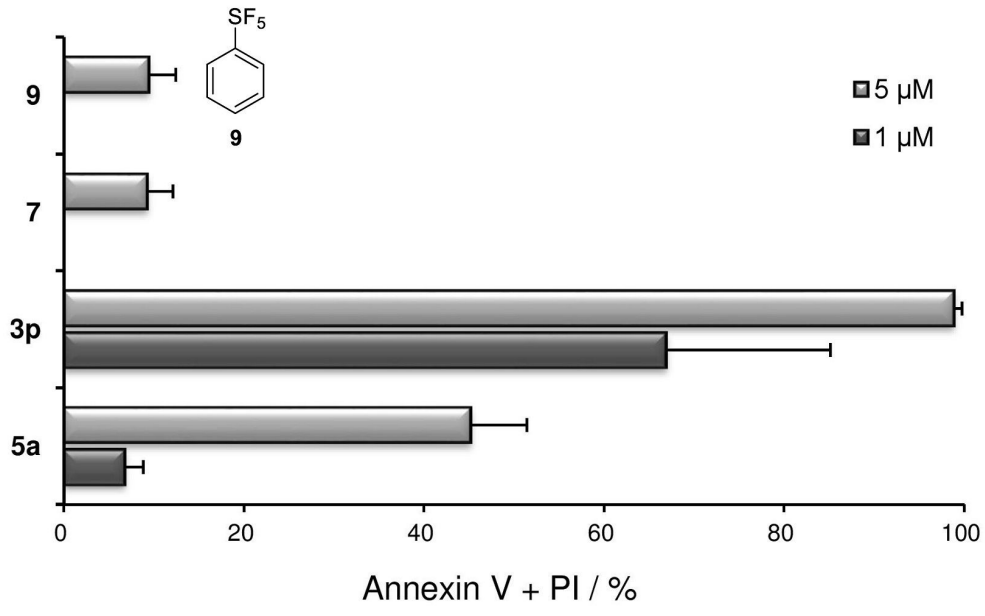


Figure 4: *Ortho*-SF_5 phenyl iodonium salts **3p** and **5a** and their structural components **7** and **9** induced cell death in U937 cells. Briefly, U937 cells (1×10^4 cells/mL) were incubated with each test compound at 1 μM and 5 μM for 24 h. Cells were stained with annexin V and propidium iodide (PI). The data shown is the mean ± SD (n = 3).

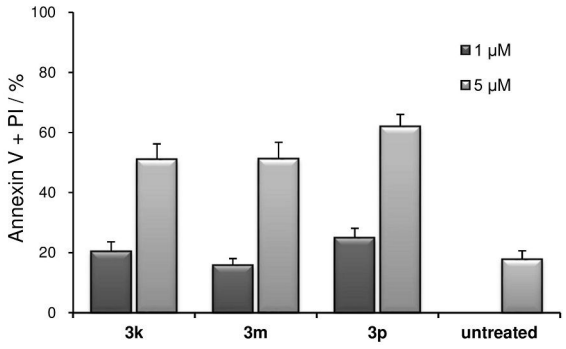


Figure 5: 3k, **3m** and **3p** induced cell death in AGLCL, a human normal B cell line. Briefly, AGLCL cells (1 × 10^4 cells/mL) were incubated with each test compound at 1 μM and 5 μM for 24 h. Cells were stained with annexin V and propidium iodide (PI). The data shown is the mean ± SD (*n* = 3).

ducing cell death based on U937 (a human histiocytic lymphoma cell line). We have also successfully synthesized novel *ortho*-SF_5 phenylaryl-λ^3-iodonium salts. As expected, several fluorinated diaryliodonium salts exhibited cytotoxicity. Among the series, the newly synthesized *ortho*-SF_5 salt **3p** displayed the greatest potency. The *ortho*-fluorinated diaryliodonium salts **3k**, **3m** and **3p** were also examined for comparison studies with AGLCL (a normal human B cell line). Although the values were rather low, selectivity was indeed observed against U937 cells. Also, even though the results are in a preliminary stage of biological evaluation, this is the first report to highlight the cytotoxicity of diaryliodonium salts against U937 cells. Since diaryliodonium salts are fundamentally oxidizing agents, there might be a stronger correlation between cytotoxicity and the oxidation potential of these salts. We will continue the biological investigation of **3** in this direction. From the view point of organic synthesis, the newly synthesized *ortho*-SF_5-substituted unsymmetrical iodonium salts **3p**, **4b**, **5a** and **6a** have potential use as electrophilic SF_5-phenylation reagents for a range of nucleophiles such as alcohols, amines, thiols, and active methylene nucleophiles [59-61]. The application of these *ortho*-SF_5-substituted diaryliodonium salts in organic synthesis, as well as their detailed bioactive behaviour, will be reported in due course.

Experimental

Biological assay

Quantification of cytotoxicity by annexin V and propidium iodide (PI): Cytotoxicity was detected with the Muse™ Annexin V and Dead Cell Assay Kit (Merck Millipore Corp., Darmstadt, Germany) and Muse Cell Analyzer (Merck Millipore Corp.) according to the manufacturer's protocols. Cells incubated in the presence or absence of the fluorinated compounds for 24 h were collected by centrifugation (2,000 rpm at 4 °C for 5 min). Cells were suspended in 100 μL of RPMI 1640 medium (Sigma-Aldrich, Steinheim, Germany), and incubated with 100 μL of annexin V reagent (in the kit) at room temperature for 20 min. These cells were measured by the Muse Cell Analyzer.

Statistical analysis: Data were analyzed using Excel software. Results are expressed as the mean ± SD of three independent replicates.

MTT assay: The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate cell viability by diaryliodonium salt compounds using the MTT cell proliferation assay kit (Cayman Chemical Company, Ann Arbor, USA). U937 cells were incubated in solutions containing the diaryliodonium salts (**3k, 3m** or **3p**). After this treatment, the U937 cells were seeded in culture medium (100 μL) in a 96-well plate (Becton and Dickinson, at a density of 2 × 10^5 cells/well) and incubated at 37 °C for 24 h. MTT reagent (10 μL) was added to each well. After mixing gently, the cells were incubated for 3 h at 37 °C in a CO_2 incubator. The culture medium was aspirated and the crystal-dissolving solution (100 μL) was added to each well and mixed. Finally, the optical density was measured (550 nm) using a microplate reader (BIO-RAD, Benchmark, Hercules, USA).

General information

All reactions were performed in oven-dried glassware under positive pressure of nitrogen or argon unless mentioned otherwise. Solvents were transferred via a syringe and were introduced into reaction vessels though a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light (254 nm). Column chromatography was carried out on columns packed with silica gel (60N spherical neutral size 63–210 μm). The ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), and ^{13}C NMR (125 MHz) spectra for solution in $CDCl_3$ or $(CD_3)_2CO$ were recorded on Varian Mercury 300 and Bruker Avance 500 spectrometers. Chemical shifts (δ) are expressed in ppm downfield from TMS (δ = 0.00) or C_6F_6 [δ = −162.2 ($CDCl_3$) or −163.5 ($(CD_3)_2CO$)] as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A (EIMS) and Shimazu LCMS-2020 (ESIMS) spectrometer. The solvent CH_2Cl_2 was dried and distilled before use.

Preparation of pentafluoro(2-iodophenyl)-λ^6-sulfane (7): The preparation of **7** was based on a modified procedure in the literature [67]. To 4 mL of HBF_4 in a round bottomed flask, 1.1 g of 2-(pentafluoro-λ^6-sulfanyl)aniline was added and

heated until a clear solution formed. The solution was cooled to 0 °C and a cold solution of $NaNO_2$ (380 mg in 2.5 mL distilled water) was added dropwise. The reaction was allowed to stir at 0 °C for 15 min after which it was added dropwise to a cold stirred solution of KI (1.33 g in 10 mL distilled water) at 0 °C. The reaction was allowed to warm to room temperature then stirred for 20 min. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with $NaHCO_3$ solution and $Na_2S_2O_3$ solution and dried over Na_2SO_4. The solvent was concentrated under reduced pressure to give a crude product which was purified using silica gel column chromatography (9:1, hexane/ethyl acetate) to give 1.4 g of **7** as a yellow oil in 87% yield. HRMS (EI–TOF) *m*/*z* $[M]^+$: calcd for $C_6H_4F_5SI$, 329.8999; found, 329.9010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (t, *J* = 9 Hz, 1H), 7.41–7.47 (m, 1H), 7.80 (dd, *J* = 9 Hz, 3 Hz, 1H), 8.14 (d, *J* = 9 Hz, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ 63.55 (d, *J* = 155.1 Hz, 4F), 83.56 (q, *J* = 155.1 Hz, 1F); ^{13}C{^{1}H}NMR ($CDCl_3$, 126 MHz) δ 88.4, 128.1, 130.3 (t, *J* = 3.75 Hz), 132.4, 144.1, 158.57 (q, *J* = 15 Hz).

General procedure A: preparation of diaryliodonium salts I

These salts were prepared according to a modified procedure in the literature [64,65]. *m*-CPBA (assume 70 wt %, 1.1 equiv) was dried in vacuo at room temperature for 1 h before the addition of **7** (1.0 equiv) and CH_2Cl_2 (6.0 mL/mmol ArI) in a round-bottomed flask. The solution was cooled to 0 °C followed by the dropwise addition of TfOH (1.7 equiv). The resulting mixture was stirred at room temperature for 2 h. It was then cooled to 0 °C and the arene (1.1 equiv) was added dropwise. The mixture was warmed to room temperature and stirred for 18 h. The solvent was then removed under reduced pressure. The resulting crude product was precipitated by the addition of Et_2O. The precipitate was filtered and dried in vacuo to give **3**–**6** as an off-white to white solid.

Mesityl(2-(pentafluoro-λ^6-sulfanyl)phenyl)iodonium trifluoromethanesulfonate (3p): Following general procedure A, **7** (330 mg, 1 mmol), *m*-CPBA (271 mg, 1.1 mmol), TfOH (0.2 mL, 1.7 mmol) and mesitylene (0.15 mL, 1.1 mmol) in CH_2Cl_2 (6 mL) were used from 0 °C to room temperature for 18 h to give **3p** as a white solid (430 mg) in 72% yield. mp: 163.7–164.7 °C; HRMS (ESI–TOF) *m*/*z* $[M - OTf]^+$: calcd for $C_{15}H_{15}F_5SI$, 448.9859; found, 448.9865; ^{1}H NMR ($(CD_3)_2CO$), 300 MHz) δ 2.44 (s, 3H), 2.69 (s, 6H), 7.42 (s, 2H), 7.64 (d, *J* = 6 Hz, 1H), 7.73 (t, *J* = 9 Hz, 1H), 7.96 (t, *J* = 9 Hz, 1H), 8.36 (dd, *J* = 9 Hz, 1.5 Hz, 1H); ^{19}F NMR ($(CD_3)_2CO$), 282 MHz) δ = −79.88 (s, 3F), 64.09 (d, *J* = 149.5 Hz, 4F), 81.34 (q, *J* = 149.5 Hz, 1F); ^{13}C{^{1}H}NMR ($(CD_3)_2CO$), 126 MHz) δ 21.2, 27.1, 106.6, 121.9 (q, *J* = 318.8 Hz), 123.0, 131.8, 132.5 (t, *J* = 5 Hz), 133.7, 135.4, 136.9, 144.5, 147.0, 154.1–154.7 (m).

(2-(Pentafluoro-λ^6-sulfanyl)phenyl)(2,4,6-triisopropylphenyl)iodonium trifluoromethanesulfonate (4b): Following general procedure A, **7** (330 mg, 1 mmol), *m*-CPBA (271 mg, 1.1 mmol), TfOH (0.2 mL, 1.7 mmol) and triisopropylbenzene (0.26 mL, 1.1 mmol) in CH_2Cl_2 (6 mL) were used from 0 °C to room temperature for 18 h to give **4b** as a white solid (604 mg) in 86% yield. mp: 106.6–107.9 °C; HRMS (ESI–TOF) *m*/*z* $[M - OTf]^+$: calcd for $C_{21}H_{27}F_5SI$, 533.0798; found, 533.0798; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 1.31 (t, *J* = 9 Hz, 18H), 3.14 (q, *J* = 9 Hz, 1H), 3.30 (q, *J* = 6 Hz, 2H), 7.45 (d, *J* = 9 Hz, 1H), 7.58 (s, 2H), 7.77 (t, *J* = 6 Hz, 1H), 7.96 (t, *J* = 9 Hz, 1H), 8.37 (dd, *J* = 9 Hz, 1.5 Hz, 1H); ^{19}F NMR ($(CD_3)_2CO$, 282 MHz) δ −79.91 (s, 3F), 64.02 (d, *J* = 149.5 Hz, 4F), 81.31 (q, *J* = 149.5 Hz, 1F); ^{13}C{^{1}H}NMR ($(CD_3)_2CO$, 126 MHz) δ 23.8, 24.2, 34.9, 40.8, 107.7, 121.9 (q, *J* = 320 Hz), 123.5, 127.1, 132.7 (t, *J* = 5 Hz), 133.7, 134.5, 136.9, 153.8, 153.9–154.2 (m), 158.1.

(4-Methoxyphenyl)(2-(pentafluoro-λ^6-sulfanyl)phenyl)iodonium trifluoromethanesulfonate (5a): Following general procedure A, **7** (416 mg, 1.26 mmol), *m*-CPBA (340 mg, 1.38 mmol), TfOH (0.24 mL, 2.14 mmol) and anisole (0.15 mL, 1.38 mmol) in CH_2Cl_2 (6 mL) were used from 0 °C to room temperature for 18 h to give **5a** as a white solid (600 mg) in 81% yield. mp: 108.7–110.4 °C; HRMS (ESI–TOF) *m*/*z* $[M - OTf]^+$: calcd for $C_{13}H_{11}OF_5SI$, 436.9495; found, 436.9499; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 3.90 (s, 3H), 7.16 (d, *J* = 9 Hz, 2H), 7.86 (t, *J* = 9 Hz, 1H), 8.03 (t, *J* = 9 Hz, 1H), 8.29 (d, *J* = 9 Hz, 3H), 8.92 (d, *J* = 6 Hz, 1H); ^{19}F NMR ($(CD_3)_2CO$, 282 MHz) δ −79.75 (s, 3F), 65.79 (d, *J* = 149.5 Hz, 4F), 81.73 (q, *J* = 152.3 Hz, 1F); ^{13}C{^{1}H}NMR ($(CD_3)_2CO$, 126 MHz) δ 56.4, 104.8, 109.8, 118.9, 131.7, 134.6, 136.9, 138.8, 142.2, 154.1–154.4 (m), 164.5.

(2-(Pentafluoro-λ^6-sulfanyl)phenyl)(phenyl)iodonium trifluoromethanesulfonate (6a): Following general procedure A, **7** (330 mg, 1 mmol), *m*-CPBA (271 mg, 1.1 mmol), TfOH (0.2 mL, 1.7 mmol) and benzene (0.1 mL, 1.1 mmol) in CH_2Cl_2 (6 mL) were used from 0 °C to room temperature for 18 h to give **6a** as a white solid (512 mg) in 92% yield. mp: 109.8–111.3 °C; HRMS (ESI–TOF) *m*/*z* $[M–OTf]^+$: calcd for $C_{12}H_9F_5SI$, 406.9390; found, 406.9385; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 7.61–7.68 (m, 2H), 7.76–7.82 (m, 1H), 7.89 (t, *J* = 9 Hz, 1H), 8.06 (t, *J* = 9 Hz, 1H), 8.31 (dd, *J* = 9 Hz, 3 Hz, 1H), 8.37 (d, *J* = 9 Hz, 2H), 9.02 (d, *J* = 6 Hz, 1H); ^{19}F NMR ($(CD_3)_2CO$, 282 MHz) δ −79.81 (s, 3F), 65.83 (d, *J* = 149.5 Hz, 4F), 81.61 (q, *J* = 152.3 Hz, 1F); ^{13}C{^{1}H}NMR ($(CD_3)_2CO$, 126 MHz) δ 109.1, 116.9, 121.9 (q, *J* = 320 Hz),

131.8, 133.2, 134.1, 134.8, 136.3, 136.9, 142.9, 154.3–154.9 (m).

Supporting Information

Supporting Information File 1

Cytotoxicity data, copies of ^{1}H, ^{19}F and ^{13}C NMR spectra of **7**, **3p**, **4b**, **5a** and **6a** and the ORTEP diagram of **3p**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-24-S1.pdf]

Acknowledgements

This research was partially supported by the Tokyo Chemical Industry Foundation, the Pesticide Science Society of Japan, and a JSPS KAKENHI Grant Number JP 16H01142 in the Middle Molecular Strategy.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Oxidative cycloaddition of hydroxamic acids with dienes or guaiacols mediated by iodine(III) reagents

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Letter

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Keywords:
acylnitroso; benzoquinone; cycloaddition; dearomatization; iodine(III)

Beilstein J. Org. Chem. **2018,** *14,* 531–536.
doi:10.3762/bjoc.14.39

Received: 25 December 2017
Accepted: 16 February 2018
Published: 28 February 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

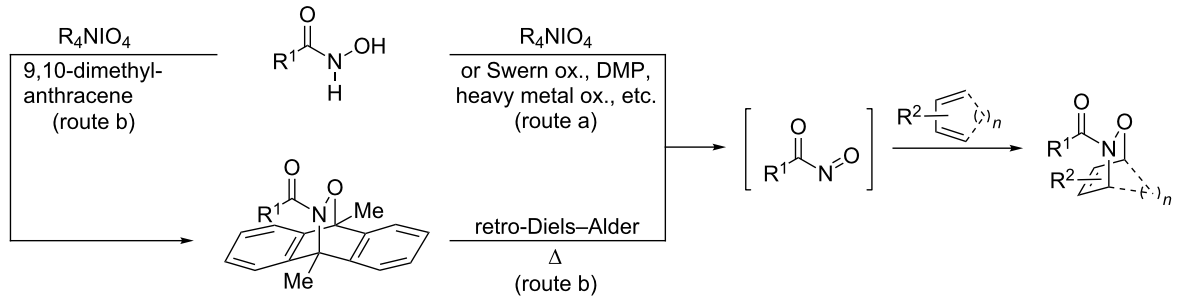
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Abstract

[Bis(trifluoroacetoxy)iodo]benzene (BTI) and (diacetoxyiodo)benzene (DIB) efficiently promote the formation of acylnitroso species from hydroxamic acids in the presence of various dienes to give the corresponding hetero-Diels–Alder (HDA) adducts in moderate to high yields. The present method could be applied to the HDA reactions of acylnitroso species with *o*-benzoquinones generated by the oxidative dearomatization of guaiacols.

Introduction

The hetero-Diels–Alder (HDA) reaction of *N*-acylnitroso species with dienes provides the facile and highly stereoselective synthesis of 1,2-oxazines, which have been widely recognized as useful synthons in the synthesis of biologically active natural products [1]. Generally, in the presence of dienes, acylnitroso species are in situ generated from hydroxamic acids with oxidants due to their instabilities (Scheme 1, route a). Among the oxidants, tetra-*n*-alkylammonium periodates are commonly employed for these HDA reactions, however, the removal of the tetra-*n*-alkylammonium salts, massively generated in these reactions, is often complicated [2-5]. Although the Swern–Moffat oxidation [6], Dess–Martin oxidation [7], and metal-mediated/catalyzed oxidation reactions [8-12] are known as alternative methods [13,14], these methods suffer from a narrow scope and/or low product yields. Furthermore, in the cases where these oxidation methods are inapplicable, a two-step procedure based on the liberation of the acylnitroso species by thermolysis of anthracenyl cycloadducts (route b) is widely used [15,16]. Therefore, there is a need to develop novel oxidation methods of hydroxamic acids for HDA reactions.



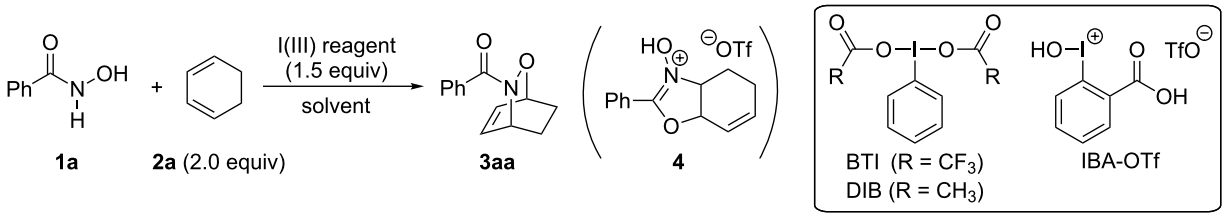
Scheme 1: Hetero-Diels–Alder (HDA) reactions of *N*-acylnitroso species.

As part of our research on the syntheses of heterocycles by iodine(III)-mediated/catalyzed oxidative cycloaddition reactions [17-19], we have found that iodine(III) reagents are effective in the oxidation of N–O bonds of oximes in the cycloaddition reaction of in situ formed nitrile oxides [20,21]. Although Adam and Bottke's group have demonstrated that (diacetoxyiodo)benzene (DIB) and iodosylbenzene are applicable to the ene reactions of acylnitroso species derived from hydroxamic acids [22], the iodine(III)-mediated oxidative cycloaddition reaction of hydroxamic acids with dienes is still unknown. Herein, we report the HDA reaction of acylnitroso species generated from hydroxamic acids by [bis(trifluoroacetoxy)iodo]benzene (BTI) or DIB. The present method could be applied to HDA reactions with not only simple dienes but also with masked *o*-benzoquinones (MOBs) generated by the oxidative dearomatization of guaiacols.

Results and Discussion

Our initial studies commenced with the screening of solvents and I(III) reagents for the oxidative cycloaddition reaction of hydroxamic acid **1a** with 1,3-cyclohexadiene (**2a,** Table 1). In the presence of BTI (1.5 equiv), in polar solvents such as methanol, tetrahydrofuran (THF), acetonitrile, and ethyl acetate (Table 1, entries 1–4), or in organochlorine solvents such as chloroform, dichloroethane (DCE), and dichloromethane (DCM, Table 1, entries 6–8), the HDA reactions smoothly

Table 1: Screening of I(III) reagents and solvents for HDA reaction of **1a** with **2a**.



entry	I(III) reagent	solvent	temp. (°C)	time (h)	**3aa** (%)[a]
1	BTI	MeOH	rt	24	78
2	BTI	THF	rt	24	85
3	BTI	MeCN	rt	24	81
4	BTI	EtOAc	rt	24	89
5	BTI	heptane	rt	24	41
6	BTI	$CHCl_3$	rt	24	89
7	BTI	DCE	rt	24	89
8	BTI	DCM	rt	1	98
9	BTI[b]	DCM	rt	1	98
10	DIB	DCM	rt	1	96
11	PhIO	DCM	rt	1	90
12	IBA-OTf	DCM	40	24	0 (**4**: 85[c])
13	IBA-OTf	DCM	−40	24	80

[a]Isolated yields. [b]1.1 equiv. [c]Yield was determined by ^{1}H NMR analysis.

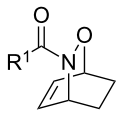
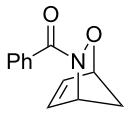
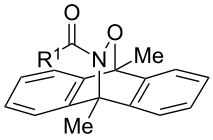
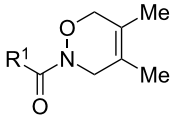
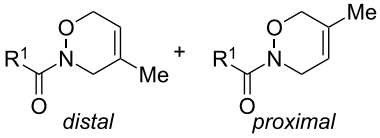
proceeded at room temperature within 24 h to give the desired *endo*-cycloadduct **3aa** in 78–98% yield. In particular, the reaction in DCM led to a full conversion to **3aa** within 1 h (Table 1, entry 8) and a reduced amount of BTI (even 1.1 equiv) brought about the similar result (**3aa**: 98%, Table 1, entry 9). Although replacing BTI with DIB or iodosylbenzene (1.5 equiv) afforded the HDA adducts **3aa** in 96 and 90% yields, respectively (Table 1, entries 10 and 11), BTI showed better results (Table 1, entries 8 and 9). On the other hand, the use of IBA-OTf, which was effective in the oxidative cycloaddition reaction of oximes [20,21], gave nitrone-trifluoromethanesulfonic acid (TfOH) complex **4** at 40 °C for 24 h in 85% yield (Table 1, entry 12). Furthermore, when IBA-OTf was employed at lower temperature (−40 °C), the HDA adduct **3aa** was obtained in 80% yield (Table 1, entry 13). These results suggest that the initially formed **3aa** is converted into **4** by TfOH derived from IBA-OTf. To test this hypothesis, the oxazine **3aa** was treated with TfOH in DCM at 40 °C for 18 h and afforded **4** quantitatively. Furthermore, the TfOH-mediated formation of nitrone from such HDA adducts has been reported [23]. It should be mentioned that the structures of **3aa** and **4** were determined by single crystal X-ray analysis [24].

Next, we investigated the oxidative cycloaddition reactions of hydroxamic acids **1a–c** with various dienes **2** under the optimal conditions (Table 2). Similarly to the benzoyl derivative **1a**, the carbamate analogues **1b** (R^1 = OBn) and **1c** (R^1 = O*t*-Bu) reacted with 1,3-cyclohexadiene (**2a**, 2 equiv) in the presence of BTI (1.5 equiv) [25] at room temperature for 1 h to give the corresponding HDA adducts **3ba** and **3ca** in 99 and 85% yields, respectively (Table 2, entries 1–3). However, in the reactions of **1a–c** with more reactive dienes such as cyclopentadiene (**2b**) and 9,10-dimethylanthracene (**2c**), DIB (1.1 equiv) showed better results, thereby affording the HDA adducts **3ab** and **3ac–3cc** in 69–82% yields (Table 2, entries 4–7). In case of less reactive dienes such as 2,3-dimethyl-1,3-butadiene (**2d**) and

Table 2: BTI or DIB-mediated oxidative HAD reactions of **1a–c** with various dienes.



1 **2** (X equiv) **3**

entry	3		X	Y	yield (%)[a]
1		**3aa** (R^1 = Ph)	2	1.1 (BTI)	98
2		**3ba** (R^1 = OBn)	2	1.5 (BTI)	99
3		**3ca** (R^1 = O*t*-Bu)	2	1.5 (BTI)	85
4		**3ab**	2	1.1 (DIB)	82
5		**3ac** (R^1 = Ph)	2	1.1 (DIB)	69
6		**3bc** (R^1 = OBn)	2	1.1 (DIB)	78
7		**3cc** (R^1 = O*t*-Bu)	2	1.1 (DIB)	76
8		**3ad** (R^1 = Ph)	5	1.1 (BTI)	61
9		**3bd** (R^1 = OBn)	5	1.5 (BTI)	73
10		**3cd** (R^1 = O*t*-Bu)	5	1.5 (BTI)	55
11	 *distal* *proximal*	**3ae** (R^1 = Ph)	5	1.1 (BTI)	49[b]
12		**3be** (R^1 = OBn)	5	1.5 (BTI)	65[b]
13		**3ce** (R^1 = O*t*-Bu)	5	1.5 (BTI)	49[c]

[a]Isolated yields. [b]Distal:proximal = 2:1. [c]Distal:proximal = 1:1.

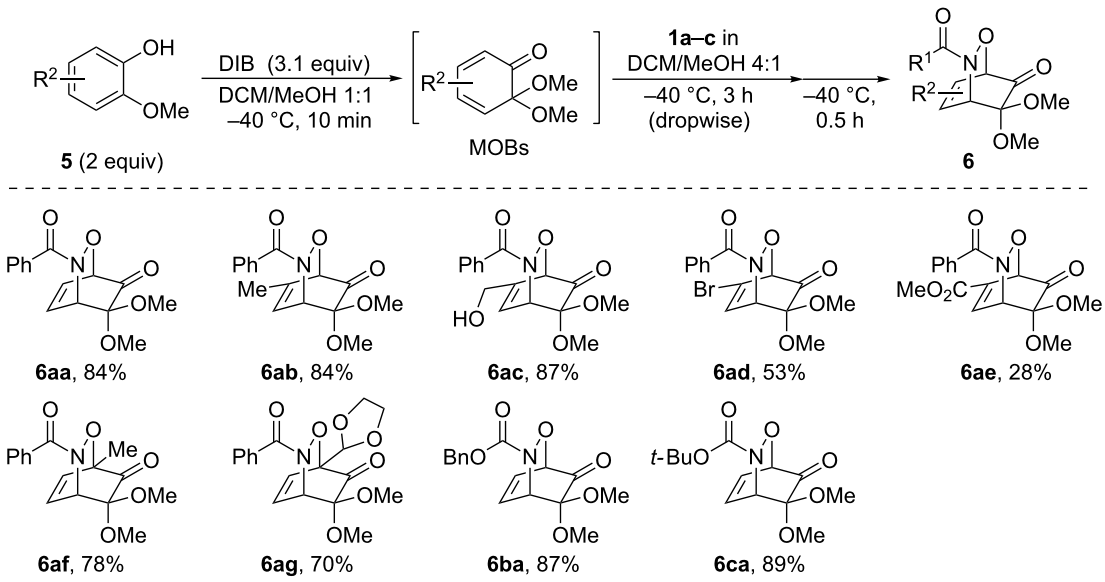
isoprene (**2e**), by the use of BTI (1.1 or 1.5 equiv) [25] along with the increase in the amount of diene to 5 equiv, the HDA adducts **3ad**–**3cd** and **3ae**–**3ce** were obtained in moderate to good yields (**3ad**–**3cd**: 55–73%, **3ae**–**3ce**: 49–65%; Table 2, entries 8–13). The HDA adducts **3ae**–**3ce** derived from **2e** were isolated as mixtures of regioisomers (distal:proximal = 2:1 or 1:1 as determined by ^{1}H NMR analysis).

As a further application of the iodine(III)-mediated oxidative cycloaddition reactions, the present method was extended to HDA reactions with masked *o*-benzoquinones (MOBs) generated by the oxidative dearomatization [26-29] of guaiacols with methanol (Scheme 2). Liao's and other groups have developed the DA reactions with MOBs as dienes [30-33], which recently were employed in the HDA reactions of acylnitroso species [34]. However, in the HDA reactions with MOBs, the oxidation of the hydroxamic acids to the acylnitroso species requires other oxidants such as tetra-*n*-alkylammonium periodates. To our delight, the sole use of DIB in a mixed solvent of DCM and methanol gave the *endo*-cycloadduct **6aa** as a single regioisomer in 84% yield starting from hydroxamic acid **1a** and guaiacol (**5a**, Scheme 2). The structure of **6aa** was determined by single crystal X-ray analysis [24]. It should be mentioned that a slow addition of **1a** to the solution of **5a** and DIB over a period of 3 h was essential for an effective formation of **6aa**. Furthermore, this procedure could be applied successfully to the oxidative cycloaddition reaction of **1a** with various guaiacols **5b**–**g** and to the reaction of hydroxamic acids **1b** and **1c** with **5a**. The corresponding products **6ab**–**6ag**, **6ba**, and **6ca** were obtained with complete regioselectivities in 70–89% yields, albeit low to moderate yields in cases of the bromo-substituted **6ad** (53%) and methoxycarbonyl-substituted **6ae** (28%).

In most cases of the attempted reactions of **1a** with simple dienes or guaiacols, benzoyl anhydride was detected as a by-product. Since benzoyl anhydride is known to be formed via the dimerization of benzoylnitroso compounds [35], these results suggest that acylnitroso species would be generated from **1a** by iodine(III) reagents. Therefore, the high *endo* selectivities of 1,2-oxadines **3aa**–**3ca**, **3ab**, and **6** would depend on the avoidance of electrostatic repulsion between the nitrogen lone pairs of acylnitroso species with π-electrons of the electron-rich dienes in the *exo* transition states (*exo*-lone-pair effect) [36]. Furthermore, the regioselectivities observed for **3ae**, **3be** [12,36], and **6** [34] are in consistency with experimental data as well as the results of FMO and DFT calculations. The decline in regioselectivity of **3ce** may be due to steric repulsion between the sterically hindered *tert*-butyloxycarbonyl group in **1c** with the 2-methyl substituent of isoprene.

Conclusion

In summary, we demonstrated that BTI and DIB promote the formation of acylnitroso species from hydroxamic acids in the presence of various simple dienes to give the corresponding HDA adducts in moderate to high yields. The present method could be applied to a one-pot reaction involving the generation of MOBs by the dearomatization of guaiacols followed by the HDA reactions of acylnitroso species with MOBs as dienes. Our findings provide an extended scope of dienes for the HDA reactions and HDA reactions of acylnitroso species with MOBs using single oxidants.



Scheme 2: DIB-mediated oxidative HDA reactions of **1a–c** with various guaiacols.

Supporting Information

Supporting Information File 1

Experimental section.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-39-S1.pdf]

Supporting Information File 2

X-ray structure of **3aa**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-39-S2.cif]

Supporting Information File 3

X-ray structure of **4**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-39-S3.cif]

Supporting Information File 4

X-ray structure of **6aa**.
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Acknowledgements

This work was partially supported by JSPS Grants-in-Aid for Scientific Research (C) (Grant No 15K07852) and by JSPS Fund for the Promotion of Joint International Research (Grant No 16KK0199). V.V.Z. and A.Y. are also thankful to Tomsk Polytechnic University (VIU-316/2017).

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Enantioselective dioxytosylation of styrenes using lactate-based chiral hypervalent iodine(III)

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Letter

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Keywords:
1,2-difunctionalization of alkenes; enantioselective synthesis; hypervalent iodine; oxidation

Beilstein J. Org. Chem. **2018,** *14,* 659–663.
doi:10.3762/bjoc.14.53

Received: 25 December 2017
Accepted: 06 March 2018
Published: 20 March 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

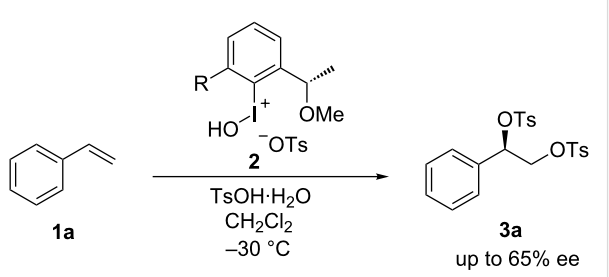
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Abstract

A series of optically active hypervalent iodine(III) reagents prepared from the corresponding (*R*)-2-(2-iodophenoxy)propanoate derivative was employed for the asymmetric dioxytosylation of styrene and its derivatives. The electrophilic addition of the hypervalent iodine(III) compound toward styrene proceeded with high enantioface selectivity to give 1-aryl-1,2-di(tosyloxy)ethane with an enantiomeric excess of 70–96% of the (*S*)-isomer.

Findings

Hypervalent aryl-λ^3-iodanes have been widely used for metal-free oxidation with high selectivity in organic synthesis [1-3]. The reactivity of an aryl-λ^3-iodane is controlled by the electronic and steric properties of the aryl group and the heteroatomic ligand coordinated to the iodine atom. Optically active hypervalent iodine compounds contain chiral ligands or chiral aryl groups. Several types of optically active hypervalent iodine reagents and catalysts have been developed for highly stereocontrolled oxidative transformations [4-14]. The enantioselective vicinal difunctionalization of alkenes constitutes one type of attractive transformation achieved by chiral hypervalent iodine compounds. As a seminal example in this field, Wirth et al. [15-17] reported the dioxytosylation of styrene (**1a**, Scheme 1). Chiral hypervalent iodine reagents **2** bearing a 1-methoxyethyl side chain were used for enantiocontrol of the dioxytosylation, and the maximum enantiomeric excess (ee) of the product **3a** reached 65%. Despite recent rapid progress in the field of asymmetric oxidation achieved by chiral hypervalent iodine compounds, there has been no subsequent examination of dioxytosylation, which can be used as a standard reaction for comparing the enantiocontrolling ability of chiral hypervalent iodine reagents.



Scheme 1: Enantioselective dioxytosylation of styrene as a seminal example.

The design of chiral hypervalent iodine reagents using a lactate motif has been employed for several types of oxidation reaction since we first reported this procedure [18]. Enantioselective oxidative transformations include the dearomatization of phenols [19-24], α-functionalization of carbonyl compounds [25-29], and vicinal difunctionalization of alkenes [18,30-50]. Here, the efficiency of the lactate-based chiral hypervalent iodine reagents **4a–e** (Figure 1) was assessed using the dioxytosylation of styrenes as a reference reaction.

A series of lactate-derived aryl-λ^3-iodanes **4a–e** was used for the oxidation of styrenes **1** in the presence of *p*-toluenesulfonic acid (TsOH) in dichloromethane. The reaction proceeded at −50 °C to give the 1,2-dioxytosylated product **3** and the rearranged product **5**. The yields of **3** and **5** were determined by ^{1}H NMR using an internal standard. The ee of **3** was determined by chiral HPLC analysis. The results for the yields and ee are summarized in Table 1.

The reaction of styrene (**1a**) with **4a** gave the 1,2-dioxytosylated product **3a** with 70% ee of the (*S*)-isomer (Table 1, entry 1). An ee of equal to or greater than 70% was also achieved in the reactions with the other lactate-based reagents **4b–e** (Table 1, entries 2–5). The reaction with the 2,6-bis(lactate)aryl reagent **4e** provided a high ee of 92%. The reactions of *p*-chlorostyrene (**1b**) gave **3b** with a similar ee, and the ratios of **3** to **5** (**3b** to **5b**) were higher than those in the reaction of **1a** (Table 1, entries 6–8). In the reactions of *o*-methylstyrene (**1c**), the ee of the 1,2-dioxytosylated product **3c** was slightly higher than those of **3a** and **3b**, but the regioselectivity for **3c** over **5c** was poor (Table 1, entries 9 and 10).

Scheme 2 illustrates possible reaction pathways that lead to **3** and the achiral byproduct **5**. The treatment of (diacetoxyiodo)benzene with TsOH readily gives Koser's reagent [PhI(OH)OTs] [51], which has a higher electrophilicity toward the carbon–carbon double bond in **1**. The dioxytosylation of alkenes with Koser's reagent was found to proceed via an S_N2 reaction of a cyclic intermediate such as $\mathbf{I_1}$, judging from the *syn* selectivity of the dioxytosylation [52,53]. The attack of the tosylate ion on $\mathbf{I_1}$ possibly takes place at the benzylic position or at the methylene carbon atom. The positive charge of $\mathbf{I_1}$ may be stabilized by the aryl group and localized at the benzylic position. This may allow the preferential formation of $\mathbf{I_3}$ from $\mathbf{I_1}$. If $\mathbf{I_2}$ was the major intermediate in the pathway leading to **3**, the stereochemical purity of **3** would have decreased owing to the facile elimination of the iodonium group [54] at the benzylic position of $\mathbf{I_2}$ (S_N1). The high enantiomeric ratio of **3** can be rationalized via a preference for the $\mathbf{I_1}\rightarrow\mathbf{I_3}\rightarrow\mathbf{3}$ pathway over the $\mathbf{I_1}\rightarrow\mathbf{I_2}\rightarrow\mathbf{3}$ pathway. The product ratio of **3** to **5** was affected by the ring substituent in styrenes **1**: the electron-withdrawing chloro substituent in **1b** increased the amount of **3**, whereas the electron-donating methyl substituent in **1c** decreased the amount of **3**. An electron-donating aryl group increases the rate of participation of the aryl group ($\mathbf{I_3}\rightarrow\mathbf{I_4}$). In other words, a reaction pathway that bifurcates from $\mathbf{I_3}$ to **3** and **5** agrees well with the regioselectivity for **3** over **5** observed for the substituted styrenes. The phenonium cation intermediate $\mathbf{I_4}$ contains two reaction sites on the ethylene bridge. Electron donation due to the lone pair on the oxygen atom of the internal tosyloxy group may weaken the bond between the tosyloxy-bonded carbon and the quaternary carbon in $\mathbf{I_4}$.

The reaction of styrene with **4a–e** preferentially gave (*S*)-**3**, which forms via an electrophilic addition of the iodane toward the *Si* face of styrene, followed by an S_N2 reaction with the

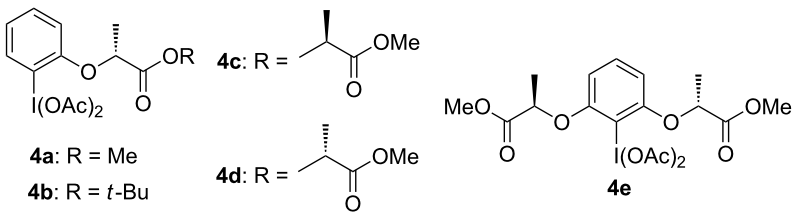
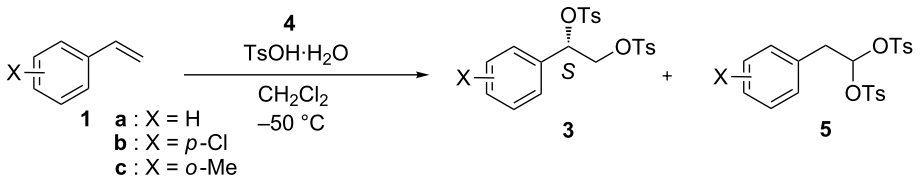


Figure 1: Series of lactate-based hypervalent iodine reagents.

Table 1: Enantioselective dioxytosylation of styrenes **1** using aryl-λ^3-iodanes **4**.[a]

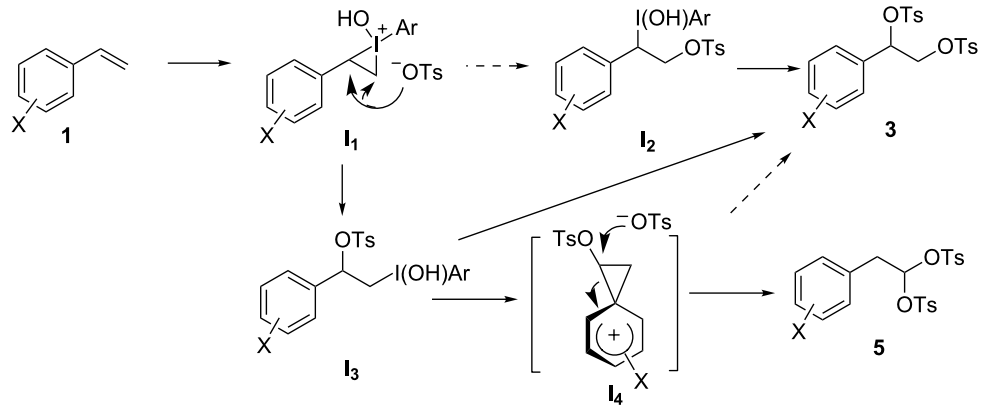


Entry	Substrate	Reagent	Yield (%)[b]		ee of **3** (%)[c,d]
			3	**5**	
1	**1a** (X = H)	**4a**	53	15	70 (*S*)
2	**1a** (X = H)	**4b**	49	16	80 (*S*)
3	**1a** (X = H)	**4c**	41	14	78 (*S*)
4	**1a** (X = H)	**4d**	41	22	70 (*S*)
5	**1a** (X = H)	**4e**	80	20	92 (*S*)
6	**1b** (X = *p*-Cl)[e]	**4a**	63	6	70
7	**1b** (X = *p*-Cl)[e]	**4b**	46	5	76
8	**1b** (X = *p*-Cl)[e]	**4e**	79	5	90
9	**1c** (X = *o*-Me)	**4a**	7	34	79
10	**1c** (X = *o*-Me)	**4e**	10	35	96

[a]The reaction was carried out at −50 °C in dichloromethane containing **4** (47 mM), TsOH (86 mM), and **1** (43 mM) for 4 h. [b]The yield was determined by ^{1}H NMR using an internal standard. [c]The ee was determined by chiral HPLC using a Daicel CHIRALPAK AD column (ø 4.6 mm × 250 mm). [d]Preferential configuration of product **3**. The absolute stereochemistry of **3b** and **3c** was not determined. [e]The reaction was carried out for 20 h.

tosylate ion. If an S_N1 mechanism were involved in the oxytosylation of $\mathbf{I_1}$, the enantiomeric ratio of **3** would decrease owing to the planar structure of the benzylic cation. Thus, the tosylate ion may act as an effective nucleophile for the S_N2 reaction of $\mathbf{I_1}$. The stereoface-differentiation in the dioxytosylation reaction using the lactate-derived aryl-λ^3-iodanes is similar to that in preceding reactions [14], which include the diacetoxylation [38,39,50] and diamination [30,49] of styrene.

In summary, the reaction of styrenes with lactate-derived aryl-λ^3-iodanes gave the dioxytosylated product with an ee of 70–96%.



Scheme 2: Plausible pathways in dioxytosylation of styrenes.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra are available.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-53-S1.pdf]

Acknowledgements

Financial support from University of Hyogo is gratefully acknowledged.

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doi:10.3762/bjoc.14.53

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Chlorination of phenylallene derivatives with 1-chloro-1,2-benziodoxol-3-one: synthesis of *vicinal*-dichlorides and chlorodienes

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Letter

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Keywords:
allene; chlorination; hypervalent iodine; synthetic methods; vinyl chloride

Beilstein J. Org. Chem. **2018,** *14,* 796–802.
doi:10.3762/bjoc.14.67

Received: 02 February 2018
Accepted: 22 March 2018
Published: 09 April 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Allyl and vinyl chlorides represent important structural motifs in organic chemistry. Herein is described the chemoselective and regioselective reaction of aryl- and α-substituted phenylallenes with the hypervalent iodine (HVI) reagent 1-chloro-1,2-benziodoxol-3-one. The reaction typically results in *vicinal* dichlorides, except with proton-containing α-alkyl substituents, which instead give chlorinated dienes as the major product. Experimental evidence suggests that a radical mechanism is involved.

Introduction

Organochlorine compounds are vital as polymer precursors [1], as pharmaceuticals [2,3] and agrochemicals [4-6] and as functional materials [7,8]. And as there is an abundance of chlorine-containing natural products, the synthesis of chlorinated functional groups, such as allyl- and vinyl chlorides, can represent challenging obstacles that practitioners of natural product synthesis must surmount [9-12]. More commonly, allyl- and vinyl chlorides are highly sought-after intermediates for effecting allylations, and for use in transition metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions [13-28]. Given the versatility of allyl chloride and β-chlorostyrene groups, installing them in close proximity (as shown in **3**) provides two handles for rapidly achieving high-density molecular complexity. Thus, the development of strategies for their synthesis is an important endeavour. We envisioned accomplishing this by developing a chemo- and regioselective *vicinal*-dichlorination of phenylallenes; however, no such chlorination reaction has yet been achieved [29-34].

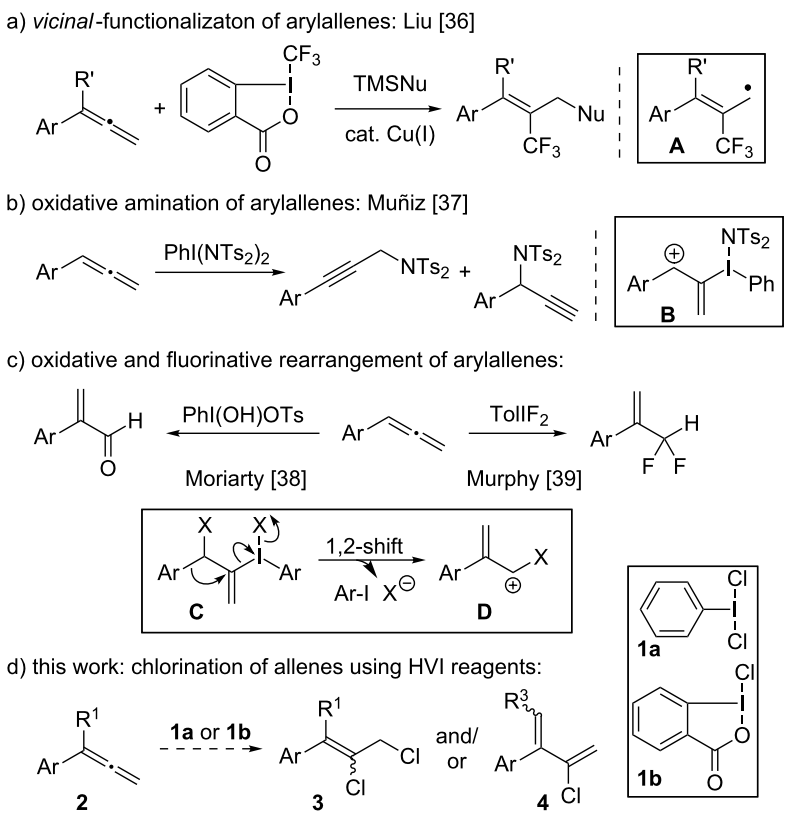
Recent reports of reactions between hypervalent iodine reagents and phenylallenes have highlighted the possible product outcomes achievable through ionic and radical reaction path-

ways. For example, Liu and co-workers used Togni's benziodoxolone reagent [35] in a radical-mediated *vicinal* 2,3-difunctionalization of allenes, which proceeded via CF_3-radical adduct **A** (Scheme 1a) [36]. In contrast, Muñiz reported that with $PhI(NTs_2)_2$, an oxidative amination occurred via cation **B**, giving regioisomeric propargylamides upon elimination of the iodanyl adduct (Scheme 1b) [37]. Moriarty and Murphy, respectively, showed how reactions of arylallenes with either PhI(OH)OTs [38] or $TolIF_2$ [39] provide α-disubstituted styrenes by sequences involving intermediates analogous to **B**, followed by a 1,2-phenyl shift (**C** to **D**, Scheme 1c). There has been no investigation of the chemistry between arylallenes and chlorinated hypervalent iodine reagents, and given the differing reactivities that might be achievable with (dichloroiodo)benzene [40] (**1a**) and chlorobenziodoxolone (**1b**) [30,41-45], there is potential for the selective generation of diverse, poly-chlorinated scaffolds. Reported here are the results of these investigations, and while indiscriminate chlorination of **2** was observed with **1a**, **1b** reacted chemo- and regioselectively to give 2,3-dichlorides (**3**) or chlorodienes (**4**).

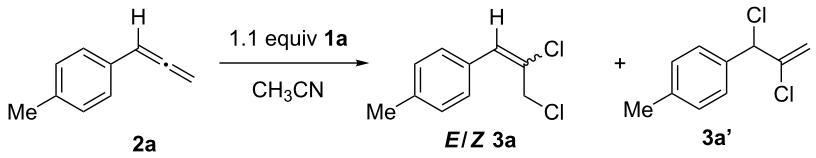
Results and Discussion

We began our investigation of allene chlorination using *p*-tolylallene (**2a**), prepared from 4-methylstyrene through Doering–Moore–Skattebøl reaction [46], and iodane **1a**. The reaction was carried out using a slight excess of **1a** in acetonitrile, at both room temperature and at reflux, and upon consumption of the allene an inseparable mixture of chlorination products **3a** and **3a'** were obtained. While the overall yield of the chlorinated products increased when under reflux conditions, very little change in chemoselectivity was observed (Scheme 2) [31]. As these results were consistent with those achievable by other allene chlorination reactions, it was not investigated further.

We next investigated the chlorination of **2a** with benziodoxolone **1b** [47-49], which proved highly regioselective. An initial reaction with 2.2 equiv of **1b** in acetonitrile at room temperature failed; however, repeating the reaction under reflux conditions gave **3a** as a mixture of *E*/*Z* alkenes in 58% yield (Table 1, entries 1 and 2). The reaction was entirely selective for the terminal alkene, with none of **3a'** being observed. Toluene, chlorobenzene, DMF and DCE were also tested as reaction solvents, but none were superior to acetonitrile (Table 1, entries 3–6). A small improvement in yield was achieved by adding **2a** dropwise over 30 minutes (Table 1, entry 7), and we ultimately found that adding **2a** dropwise over one hour was optimal, giving **3a** in 90% yield as a *E*:*Z* = 1:1.25 mixture (Table 1,



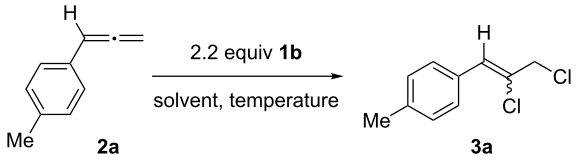
Scheme 1: Reactions of substituted allenes with HVI reagents.



Scheme 2: Chlorination of *p*-tolylallene (**2a**) with (dichloroiodo)benzene (**1a**).

entry 8). One final reaction was carried out using the related *gem*-dimethyl chlorobenziodoxole [49], but the yield of **3a** decreased to 45% (Table 1, entry 9). This result is the first example of a selective chlorination reaction of phenylallenes, and as the regiochemical outcome parallels that observed by Liu (Scheme 1a), it is likely that radical pathways are involved [50].

Table 1: Optimization of the reaction conditions.[a]



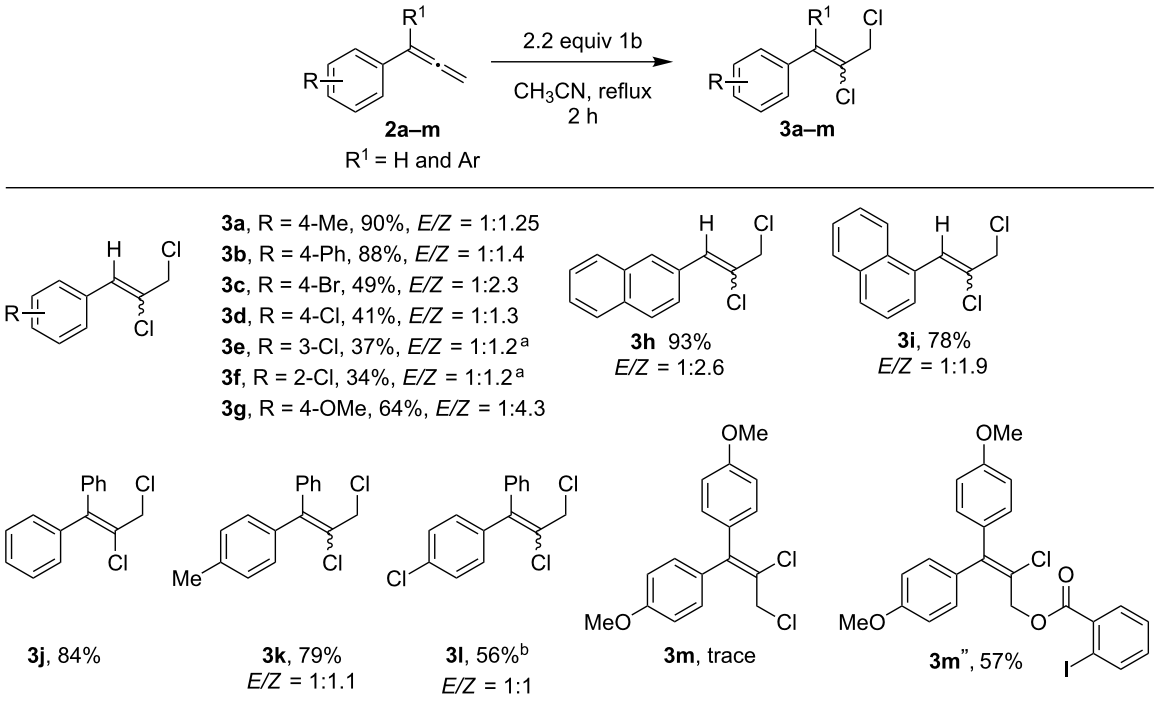
entry	solvent	temp. °C	yield (%)
1	CH_3CN	rt	trace
2	CH_3CN	85	58%
3	toluene	110	40%[b]
4	PhCl	110	trace
5	DMF	110	trace
6	DCE	85	NR
7	CH_3CN[c]	85	65%
8	CH_3CN[d]	85	90%
9	CH_3CN[e]	85	45%

[a]General conditions: Allene **2a** (0.2 mmol, 1 equiv), **1b** (0.44 mmol, 2.2 equiv) in 0.1 M solvent under reflux conditions for 2 h; isolated yield. [b] ^1H NMR yield using HMDSO (hexamethyldisiloxane) as internal standard. [c]Dropwise addition of **2a** over 30 min. [d]Dropwise addition of **2a** over 1 h. [e]3,3-Dimethyl-1-chloro-1,2-benziodoxole used instead of **1b**.

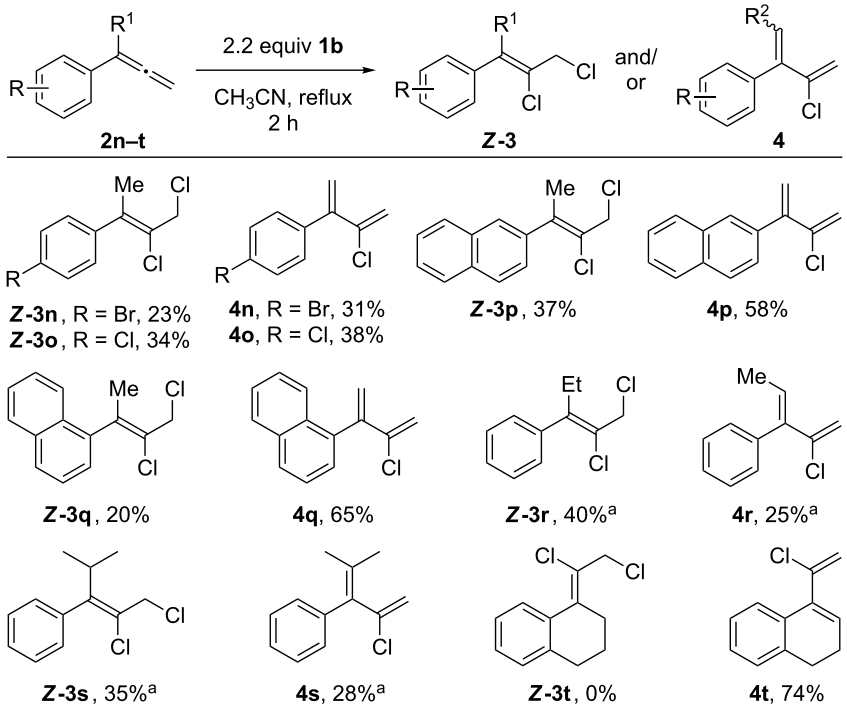
A series of aryl- and allenyl-substituted phenylallenes (**2b–v**) were then examined in the chlorination reaction. First, phenylallenes with various aryl substituents were investigated, and the *p*-tolyl and *p*-biphenyl derivatives gave the 1,2-dichlorides **3a** and **3b** in excellent yield, favouring the *Z*-alkene (Scheme 3). The 4-bromo and 2-, 3- or 4-chloro derivatives **2c–f** led to **3c–f** in only moderate yield, with the mass balance of chlorinated materials being made up by the regioisomeric *vicinal*-dichloroination products **3c'–f'** (compare with **3a'**, Scheme 2) [30]. The *p*-anisyl derivative **2g** was also viable in the reaction, giving **3g** in 64% yield, as were the 1- and 2-naphthylallenes (**2h** and **2i**), which gave the desired dichlorides **3h** and **3i** in 93% and 78% yield. In each case, preference for forming the *Z*-alkene was observed, with selectivities ranging from 1.2–4.3:1 *Z*:*E*. α-Substituents on the allenes were equally viable, as 1,1-diphenylallene gave **3j** in 84% yield, and the related mono-methyl and mono-chloro derivatives **2k** and **2l** gave dichlorides **3k** and **3l** in 79% and 56% yield, respectively, with little preference observed for formation of either the *Z* or *E* alkene. Curiously, with 1,1-di(*p*-anisyl)allene (**2m**), only a trace of **3m** was observed, and the reaction instead produced iodobenzoate **3m"** in 57% yield. Presumably, this anomalous result arose due to the increased stability offered to an electron-deficient radical intermediate by the two methoxy groups, permitting a deviation in reaction outcome.

We next subjected α-alkyl-substituted phenylallenes **2n–v** to the standard reaction conditions, which resulted in mixtures of exclusively the *Z*-dichloroalkenes (***Z*-3**) and chlorodienes **4** (Scheme 4). When the *para*-Br and *para*-Cl phenylallenes bearing α-methyl groups (**2n**, **2o**) were tested, the chlorodienes **4n** and **4o** were obtained in 31% and 38% yield, respectively, along with 23% of ***Z*-3n** and 34% of ***Z*-3o**. With α-methyl naphthylallene derivatives **2p** and **2q**, chlorodienes **4p** and **4q** were obtained in 58% and 65% yield, along with 37% and 20% of the 2,3-dichlorides. Substrates with α-ethyl (**2r**) and α-isopropyl (**2s**) substituents reacted similarly, giving chlorinated products in 63–65% yield. Lastly, vinylidene **2t** gave chlorodiene **4t** as the sole product in 74% yield.

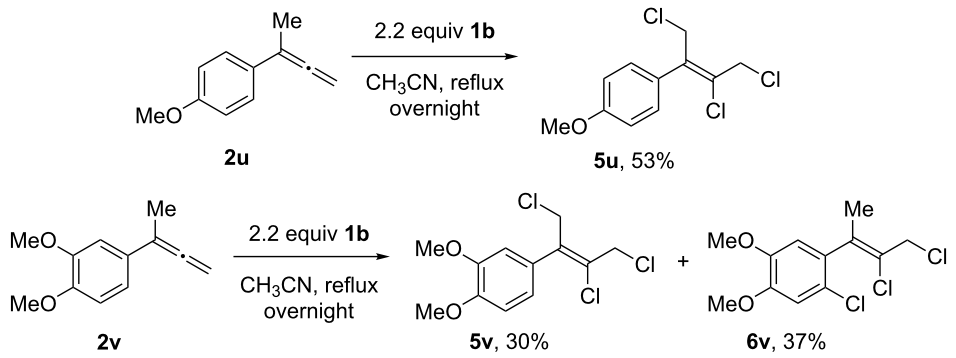
As with alkoxy substrate **2m**, the α-methylated substrates **2u** and **2v** possessing methoxy group(s) on the arene also deviated from the expected reaction course. These reactions failed to fully consume the starting materials **2u** and **2v**, even upon prolonged heating, which we discovered to be the result of **1b** being also consumed through over-chlorination. 4-Methoxy derivative **2u** gave trichloride **5u** in 53% yield, with no trace of the expected dichloride **3u** or chlorodiene **4u** products observable by NMR (Scheme 5). The 3,4-dimethoxy substrate **2v** gave trichlorides **5v** and **6v** in a combined 67% yield, or in 91% yield based on the loading of **1b** (Scheme 5). These anomalous outcomes were again rationalized as resulting from the stabi-



Scheme 3: Chlorination of various aryl-substituted allenes. General conditions: Allene **2a** (0.2 mmol, 1 equiv) was added dropwise over 1 h to a solution of **1b** (0.44 mmol, 2.2 equiv) in 0.1 M CH_3CN under reflux conditions, and the reaction stirred for 1 h; isolated yields. [a] ^1H NMR yield using HMDSO as internal standard.



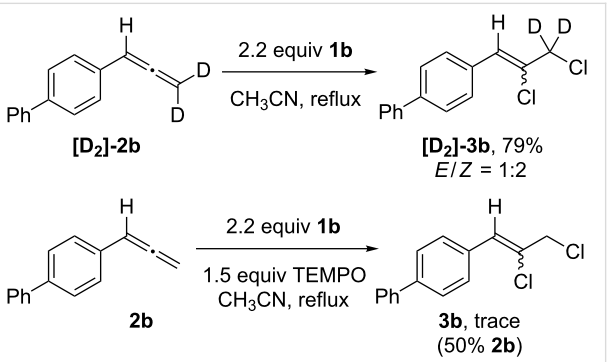
Scheme 4: Chlorination of various α-substituted phenylallene derivatives. General conditions: Allene **2a** (0.2 mmol, 1 equiv) was added dropwise over 1 h to a solution of **1b** (0.44 mmol, 2.2 equiv) in 0.1 M CH_3CN under reflux conditions, and the reaction stirred for 1 h; isolated yields. [a] ^1H NMR yield using HMDSO as internal standard.



Scheme 5: Chlorination of methoxy-substituted α-methyl phenylallenes. General conditions: Allene **2a** (0.2 mmol, 1 equiv) was added dropwise over 1 h to a solution of **1b** (0.44 mmol, 2.2 equiv) in 0.1 M CH_3CN under reflux conditions, and the reaction stirred overnight; isolated yields.

lization of radical intermediates gained upon methoxy substitution [51], which permitted further chlorination of either the methyl or arene groups.

To gain insight into the reaction mechanism we carried out two key control experiments. First, to test for rearrangement processes that might not be elucidated through product analysis alone, deuterated biphenylallene **[D_2]-2b** was subjected to the standard reaction conditions, and **[D_2]-3b** (*E*/*Z* = 1:2) was obtained in 79% yield (Scheme 6 top, also see Supporting Information File 1). As there was no indication of deuterium scrambling observable by ^{1}H or ^{2}H NMR of the product mixture, it appeared that 1,2-phenyl shifts or other rearrangement processes were not involved in the reaction. A further reaction was carried out in the presence of the radical scavenger TEMPO (1.5 equiv), from which only a trace of **3b** was recovered, along with 50% of **2b** (Scheme 6 bottom). As the chlorination reactivity was suppressed, our hypothesis that these reactions involved radical intermediates was further supported.



Scheme 6: Control reactions: (a) chlorination of deuterated biphenylallene **[D_2]-2b**; (b) reaction with TEMPO.

When allene chlorination was carried out with **1a**, the observed product distributions were consistent with the results previously obtained, suggesting that ionic processes were operative. Furthermore, since no evidence of propargyl chlorides or α-dichloromethylstyrenes were observed, it appears the chlorination of allenes with **1a** proceeded without interruption of 1,2-phenyl shifts or iodane elimination, resulting in a reactivity pattern that differs from the related reagents $TolIF_2$, PhI(OH)OTs or $PhI(NTs_2)_2$ (Scheme 1b and c). With **1b**, however, the reactions were entirely selective for 2,3-dichlorination of the allene, which was consistent with the regiochemical outcome of reactions involving a trifluoromethyl radical (Scheme 1a). This, coupled with the results of Scheme 6, led us to propose a radical mechanism that was initiated by homolytic cleavage of the I–Cl bond of **1b** at elevated temperature (Figure 1) [50]. Addition of the chlorine atom to the allene

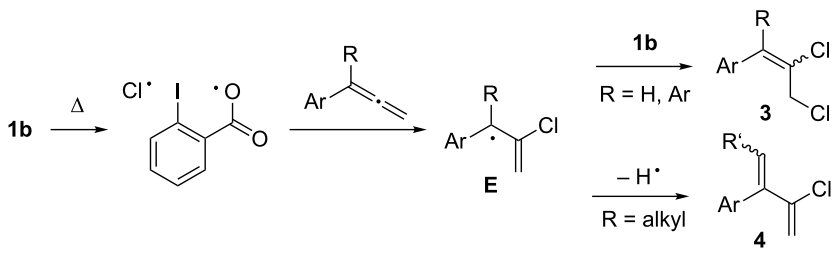


Figure 1: Proposed reaction mechanism.

central carbon resulted in the highly stabilized radical intermediate **E**, which then abstracted a chlorine atom from a second equivalent of **1b**, giving dichlorides **3**. Or, in the case of α-alkyl groups, intermediate **E** was also subject to a competing hydrogen abstraction pathway, resulting in mixtures of **3** and chlorodienes **4**.

Conclusion

In conclusion, we report here an efficient new process for the chlorination of substituted phenylallene derivatives using the hypervalent iodine reagent 1-chloro-1,2-benziodoxol-3-one (**1b**). The reactions disclosed here represent the first report of a regioselective chlorination of phenylallenes, in which the 2,3-allene olefin undergoes selective *vicinal* dichlorination. Overall, the reactions were mild and operationally-simple, tolerant to a variety of different functional groups, and provided the products in typically good yield. The selectivity of the reaction is presumably derived from it being a radical, not ionic, process, which also enabled the formation of chlorodiene products with α-alkyl substituted allenes. This reaction offers a new strategy for accessing dichlorinated functional group building blocks not readily accessible with other reagents, and our continued work in this area will be disclosed in due course.

Supporting Information

Supporting Information File 1

Experimental and characterization details, and NMR spectra of compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-67-S1.pdf]

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Waterloo. We also thank Val Goodfellow of the UWaterloo Mass Spectrometry Facility.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

One-pot synthesis of diaryliodonium salts from arenes and aryl iodides with Oxone–sulfuric acid

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Keywords:
diaryliodonium salts; iodine; iodonium; oxidation; Oxone

Beilstein J. Org. Chem. **2018,** *14,* 849–855.
doi:10.3762/bjoc.14.70

Received: 18 February 2018
Accepted: 27 March 2018
Published: 12 April 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Associate Editor: D. Y.-K. Chen

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Abstract

A facile synthesis of diaryliodonium salts utilizing Oxone as versatile and cheap oxidant has been developed. This method shows wide applicability and can be used for the preparation of iodonium salts containing electron-donating or electron-withdrawing groups in good yields. In addition, this procedure can be applied to the preparation of symmetric iodonium salts directly from arenes via a one-pot iodination–oxidation sequence.

Introduction

Diaryliodonium salts, which are also known as diaryl-λ^3-iodanes, are widely considered to be an important and practically useful class of hypervalent iodine compounds [1-4]. Diaryliodonium salts have found broad synthetic application as electrophilic arylating reagents in reactions with various nucleophiles including electron-rich carbon-centered species [5-7]. The unique arylating reactivity of diaryliodonium salts has been demonstrated in many metal-catalyzed and also metal-free transformations [8-15].

The development of novel synthetic approaches to diaryliodonium salts based on the use of inexpensive, commercially available oxidants is an important and challenging goal. A vast majority of existing procedures involve the interaction of electrophilic hypervalent iodine(III) species with suitable arenes through ligand exchange processes [16-20]. The reactive hypervalent iodine(III) species can be used as stable reagents or can be generated in situ [21-25]. In particular, Olofsson and co-workers reported procedures based on the in situ generation

of reactive λ^3-iodane species directly from arenes, which was a significant achievement in this field [26-29]. However, these now well-established processes involve oxidations using *m*CPBA in the presence of strong organic acids [30-35]. Therefore, the development of new, convenient and inexpensive methods utilizing readily available and easy-to-handle oxidants still remains a highly desirable goal.

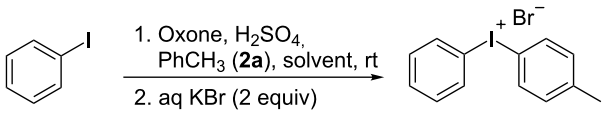
Previously, we have published the utilization of Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a readily available and effective oxidant for the preparation of various hypervalent iodine compounds [36-42]. Oxone is used as an efficient oxidant for the direct conversion of substituted 2-iodobenzoic acids to arylbenziodoxoles [37,38], 2-iodobiphenyl to dibenziodolium compounds [39], iodoarenes to iodylbenzenes and [bis(trifluoroacetoxy)iodo]arenes [40,41], and for the preparation of diaryliodonium trifluoroacetates and triflates [42]. Yakura also used Oxone® as an oxidant for the generation of iodine(III) species in the oxidation of phenols [43]. In the present work, we report the development of a reliable and convenient procedure for the preparation of diaryliodonium bromides using Oxone in the presence of sulfuric acid.

Results and Discussion

After having investigated previously described reaction conditions [37,38], initial optimization studies were performed using iodobenzene and toluene as reactants for the synthesis of diaryliodonium salt **3a** (Table 1). A simple mixing of the starting materials with finely ground Oxone and sulfuric acid leads to the formation of a very viscous and dark reaction mixture (Table 1, entry 1). Full conversion of the starting materials could not be achieved even after 24 h stirring. The addition of aqueous KBr to the reaction mixture resulted in the formation of the desired bromide salt **3a** in 30% isolated yield. The addition of KBr is necessary as the high solubility of the diaryliodonium sulfonates does not allow their isolation from the reaction mixture. Dilution of the reaction mixture with dichloromethane did not increase the yield of the target product significantly (Table 1, entry 2). Moreover, we observed the formation of 4-iodobenzenesulfonic acid in both cases, probably due to the high concentration of sulfuric acid in the reaction mixture. Mixing dichloromethane with acetonitrile resulted in an increased yield of **3a** and a decreased amount of 4-iodobenzenesulfonic acid (Table 1, entry 3). When the reaction was carried out in pure acetonitrile, the iodonium salt **3a** was formed in 75% yield (Table 1, entry 4). The addition of 2 equivalents of Oxone increased the yield to 92% (Table 1, entry 5). Surprisingly, a smaller amount of toluene did not affect the yield (Table 1, entry 6). In order to avoid the formation of undesired 4-iodobenzenesulfonic acid, the reaction was carried out using smaller amounts of acid (Table 1, entries 7 and 8). That reaction proceeds smoothly with only 7.5 equivalents of sulfuric acid producing the target compound **3a** high yields. However, the use of 3.75 equivalents of sulfuric acid resulted in a significantly lower yield.

With the optimized procedure, the synthetic utility of this method using various aryliodides and arenes was investigated (Table 2). Iodobenzene (**1a**) smoothly reacts with arenes containing electron-donating substituents to form the corresponding iodonium salts in high yields. 3-Trifluoromethyliodobenzene (**1b**) exhibited higher reactivity, and iodonium salts have

Table 1: Optimization studies.[a]

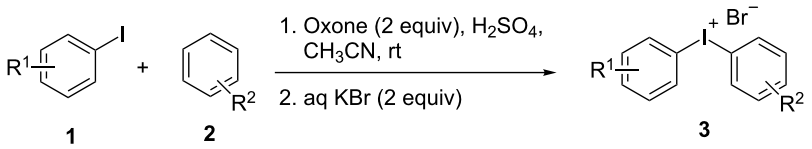


1a **3a**

entry	solvent	toluene (equiv)	Oxone (equiv)	H_2SO_4 (equiv)	yield[b] (%)
1	–	2.8	1.3	15	30[c]
2	CH_2Cl_2	2.8	1.3	15	40[c]
3	CH_2Cl_2/MeCN	2.8	1.3	15	60[c]
4	MeCN	2.8	1.3	15	75[c]
5	MeCN	2.8	2	15	92[c]
6	MeCN	1.2	2	15	88[c]
7	MeCN	1.2	2	7.5	86
8	MeCN	1.2	2	3.75	53

[a]Reaction conditions: PhI (1 mmol), overnight, rt; [b]isolated yield; [c]according to NMR data product contains up to 10% of (4-tolyl)phenyliodonium 4-iodobenzenesulfonate as an impurity.

Table 2: Synthesis of diaryliodonium bromides.[a]



1 **2** **3**

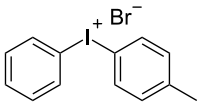
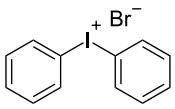
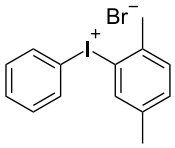
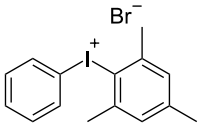
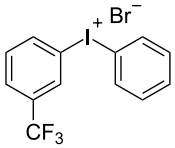
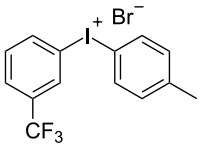
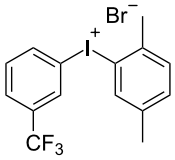
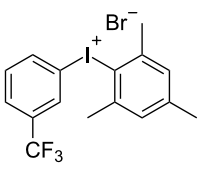
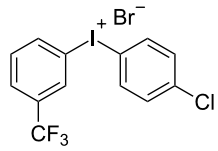
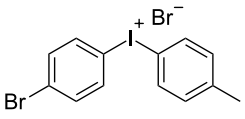
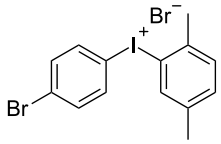
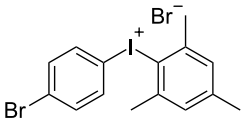
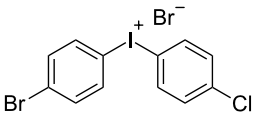
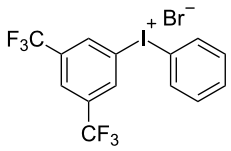
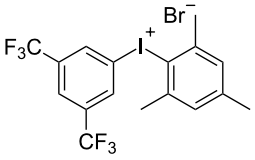
R^1 (**1**)	R^2 (**2**)	product **3**	yield[b] (%)
R^1 = H (**1a**)	R^2 = Me (**2a**)	 **3a**	86[c]
R^1 = H (**1a**)	R^2 = H (**2b**)	 **3b**	74[d,e,f]
R^1 = H (**1a**)	R^2 = 1,4-Me_2 (**2c**)	 **3c**	75
R^1 = H (**1a**)	R^2 = 1,3,5-Me_3 (**2d**)	 **3d**	75
R^1 = 3-CF_3 (**1b**)	R^2 = H (**2b**)	 **3e**	85[e,f]
R^1 = 3-CF_3 (**1b**)	R^2 = Me (**2a**)	 **3f**	76[c]
R^1 = 3-CF_3 (**1b**)	R^2 = 1,4-Me_2 (**2c**)	 **3g**	95
R^1 = 3-CF_3 (**1b**)	R^2 = 1,3,5-Me_3 (**2d**)	 **3h**	92

Table 2: Synthesis of diaryliodonium bromides.[a] (continued)

R^1 = 3-CF_3 (**1b**)	R^2 = Cl (**2e**)	 **3i**	51[g,h]
R^1 = 4-Br (**1c**)	R^2 = Me (**2a**)	 **3j**	70[c]
R^1 = 4-Br (**1c**)	R^2 = 1,4-Me_2 (**2c**)	 **3k**	32
R^1 = 4-Br (**1c**)	R^2 = 1,3,5-Me_3 (**2d**)	 **3l**	71
R^1 = 4-Br (**1c**)	R^2 = Cl (**2e**)	 **3m**	34[g,h]
R^1 = 3,5-$(CF_3)_2$ (**1d**)	R^2 = H (**2b**)	 **3n**	35[e,f]
R^1 = 3,5-$(CF_3)_2$ (**1d**)	R^2 = 1,3,5-Me_3 (**2d**)	 **3o**	62

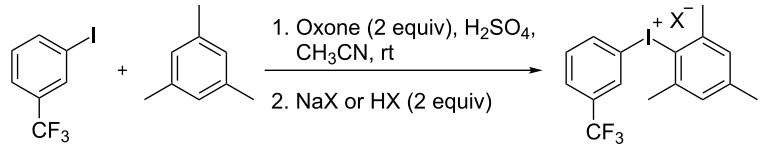
[a]Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), H_2SO_4 (7.5 mmol), MeCN (2 mL) overnight, rt; [b]isolated yield; [c]1.2 mmol of **2a** was used; [d]according to NMR data product contains an up to 1.5% of diphenyliodonium 4-iodobenzenesulfonate as impurity; [e]11.3 mmol of H_2SO_4 was used; [f]1.3 mmol of **2b** was used; [g]15 mmol of H_2SO_4 was used; [h]1.5 mmol of **2e** was used.

been isolated in higher yields. Moreover, iodoarene **1b** reacted with the moderately electron-poor chlorobenzene (**2e**) forming iodonium salt **3i** in 51% yield. In contrast, 4-bromoiodobenzene (**1c**) was less reactive and afforded iodonium salts **3j**–**m** in lower yields. Similar reactions of 3,5-bis(trifluoromethyl)iodobenzene (**1d**) with benzene and mesitylene formed the corresponding iodonium salts **3n** and **3o** in moderate yields.

With electron-deficient arenes **2** such as chlorobenzene (**2e**) and benzene, an excess of sulfuric acid and arene was used to improve the yields. Subsequently it was shown that the addition of aqueous potassium bromide can be modified and other counter anions can be introduced to prepare different diaryliodonium salts. This has been demonstrated in the preparation of diaryliodonium salts using 1-iodo-3-trifluoromethylbenzene (**1b**) and mesitylene (**2d**) as model substrates (Table 3).

The yield of the salts **3h** and **3p**–**s** do not depend on the nature of the anion and its source. Small differences in yield can be explained by different solubility of salts in aceto-

Table 3: Preparation of diaryliodonium salts with different anions.[a]



1b **2d** **3**

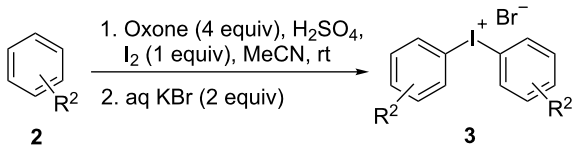
NaX / HX	product	yield[b] (%)
NaBr	**3h**	92
TsOH	**3p**	82
TfOH	**3q**	89
$NaBF_4$	**3r**	81
$NaPF_6$	**3s**	80

[a]Reaction conditions: **1b** (1 mmol), **2d** (1.1 mmol), Oxone (1 mmol), H_2SO_4 (7.5 mmol), MeCN (2 mL), NaX or HX (2 mmol) overnight, rt; [b]isolated yield.

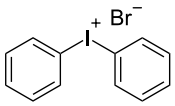
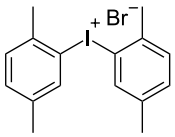
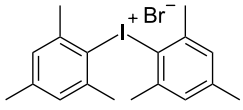
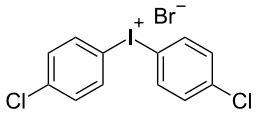
nitrile/water. Diaryliodonium bromides were isolated in higher yields because of the low solubility of these products (Table 3).

Finally, a one-step procedure for the preparation of symmetric iodonium salts directly from arenes via an in situ iodination was developed (Table 4). Arenes **2b**–**e** can be transformed to the

Table 4: Preparation of symmetric iodonium salts via a one-step iodination–oxidation procedure.[a]



2 **3**

R^2 (**2**)	product **3**	yield[b] (%)
R^2 = H (**2b**)	 **3b**	84[c,d]
R^2 = 1,4-Me_2 (**2c**)	 **3t**	80
R^2 = 1,3,5-Me_3 (**2d**)	 **3u**	77
R^2 = Cl (**2e**)	 **3v**	40[e]

[a]Reaction conditions: ArH (2.2 mmol), Oxone (2 mmol), H_2SO_4 (7.5 mmol), MeCN (2 mL) overnight, rt; [b]isolated yield; [c]according to NMR data the product contains up to 1.5% of diphenyliodonium 4-iodobenzenesulfonate as impurity; [d]11.3 mmol of H_2SO_4 and 2.6 mmol of **2b** were used; [e]15 mmol of H_2SO_4 and 3.0 mmol of **2e** were used.

symmetric iodonium salts **3b** and **3t**–**v** by the reaction with iodine, Oxone, and sulfuric acid. The attempted synthesis of the symmetric iodonium salt using toluene as substrate led to a regioisomeric mixture of products due to the low regioselectivity of iodination.

This procedure allowed the synthesis of iodonium salts with arenes containing electron-donating groups. Unfortunately, electron-poor arenes exhibited a lower reactivity and bis-(4-chlorophenyl)iodonium bromide have been isolated in only 40% yield. Nevertheless, the developed procedure is characterized by important advantages, such as simplicity, the use of inexpensive and available reagents, and typically good yields of iodonium salts. It is a versatile addition to the methodology toolbox for the preparation of diaryliodonium salts.

Conclusion

In conclusion, a new facile protocol for the preparation of diaryliodonium salts using cheap and readily available Oxone as an oxidant in the presence of sulfuric acid has been developed. The procedure allows the synthesis of a wide range of iodonium salts containing electron-donating and electron-withdrawing substituents. Particularly attractive is the possibility of the one-pot synthesis of symmetric bis-aryliodonium salts directly from arenes via an iodination–oxidation sequence.

Supporting Information

Supporting Information File 1

Experimental details and NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-70-S1.pdf]

Acknowledgements

This work was supported by the Russian Foundation for Basic Research (RFBR-mol_nr 17-33-50111), the Tomsk Polytechnic University Competitiveness Enhancement Program and the Royal Society (IE160304). We thank the EPSRC National Mass Spectrometry Facility, Swansea, for mass spectrometric data.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

2-Iodo-*N*-isopropyl-5-methoxybenzamide as a highly reactive and environmentally benign catalyst for alcohol oxidation

Takayuki Yakura*, Tomoya Fujiwara, Akihiro Yamada and Hisanori Nambu

Full Research Paper

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Keywords:
hypervalent iodine; iodobenzamide; organic catalysis; oxidation; oxone

Beilstein J. Org. Chem. **2018,** *14,* 971–978.
doi:10.3762/bjoc.14.82

Received: 13 February 2018
Accepted: 18 April 2018
Published: 30 April 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Several *N*-isopropyliodobenzamides were evaluated as catalysts for the oxidation of benzhydrol to benzophenone in the presence of Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a co-oxidant at room temperature. A study on the substituent effect of the benzene ring of *N*-isopropyl-2-iodobenzamide on the oxidation revealed that its reactivity increased in the following order of substitution: 5-NO_2 < 5-CO_2Me, 3-OMe < 5-OAc < 5-Cl < H, 4-OMe < 5-Me < 5-OMe. The oxidation of various benzylic and aliphatic alcohols using a catalytic amount of the most reactive 5-methoxy derivative successfully resulted in moderate to excellent yields of the corresponding carbonyl compounds. The high reactivity of the 5-methoxy derivative at room temperature is a result of the rapid generation of the pentavalent species from the trivalent species during the reaction. 5-Methoxy-2-iodobenzamide would be an efficient and environmentally benign catalyst for the oxidation of alcohols, especially benzylic alcohols.

Introduction

The development of an efficient and environmentally benign organic synthesis is required for minimizing material use, energy consumption, and environmental pollution in the production of both bulk and fine chemicals. Oxidation is a fundamental and frequently used transformation in organic synthesis. Heavy metal-based oxidants such as chromium(VI), lead(IV), and mercury(II) have been extensively used for this purpose for a long time. However, these oxidants are highly toxic and produce hazardous waste. Recently, hypervalent iodine oxidants have been widely employed for oxidation in organic synthesis [1-9] because they are nonmetallic, less toxic, and easy to handle, and they allow mild reaction conditions in most cases. Pentavalent iodine reagents such as Dess–Martin periodinane (DMP, **1**) [10] and 2-iodoxybenzoic acid (IBX, **2**) [11] are well known as representative environmentally benign oxidants for alcohol oxidation (Figure 1). However, despite the utility and

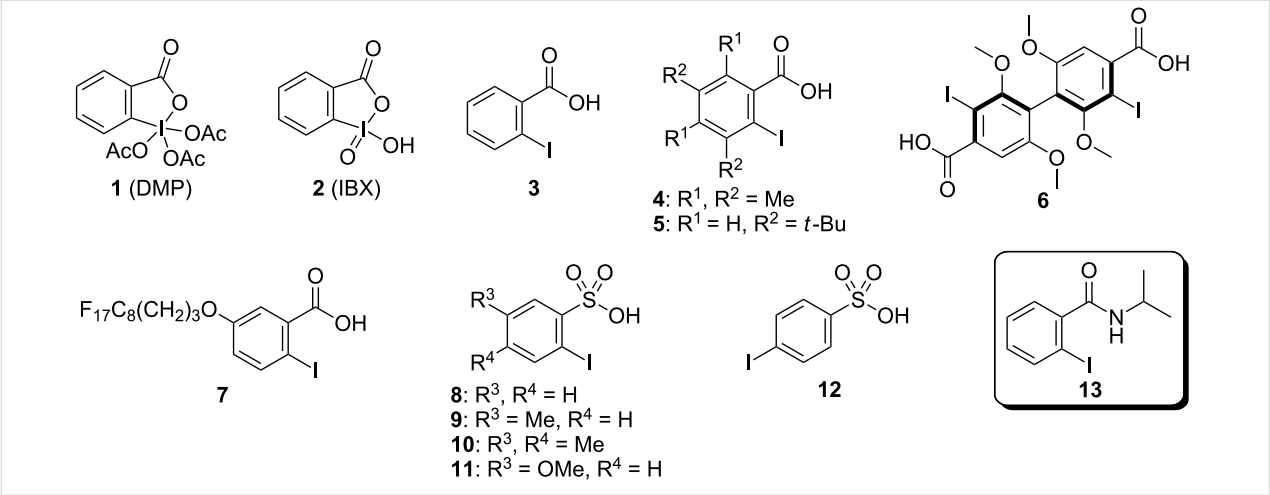


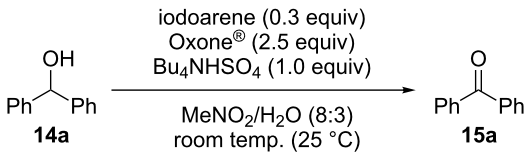
Figure 1: Structures of pentavalent iodine oxidants **1** and **2**, and iodine catalysts **3**–**13**.

versatility of these oxidants, they still have several drawbacks: both are potentially explosive, DMP is moisture-sensitive, and IBX is insoluble in common organic solvents. To overcome these drawbacks, IBX analogs [12-22] and several iodoxyarene derivatives [23-38] have been developed, and the stabilization of IBX by combining it with benzoic and isophthalic acids (SIBX) [39] has been reported. Nevertheless, from a green chemistry viewpoint, pentavalent iodine oxidants are not ideal because oxidation reactions require a stoichiometric amount of the oxidant that produces an equimolar amount of organoiodine waste. The catalytic use of pentavalent iodine species is an effective method for reducing the use of iodine compounds and the produced waste [40-44]. 2-Iodobenzoic acid (**3**) [45,46] and its derivatives such as **4**–**7** [20,47-51] and 2-iodobenzenesulfonic acid (**8**) and its derivatives **9**–**11** [52-57] have been developed as catalysts for the oxidation of alcohols in the presence of Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a co-oxidant. In these reported systems, high temperatures (40–70 °C) are often required to generate potentially explosive pentavalent iodine compounds in situ except for the reactions involving multisubstituted benzoic acids and benzenesulfonic acid (**4**–**6** and **10**) which can be performed at room temperature [20,48-51,57]. In contrast, the use of a combination of a catalytic amount of $RuCl_3$ and a stoichiometric amount of Oxone® as the co-oxidation system does not require heating despite the use of iodobenzene and 4-iodobenzenesulfonic acid (**12**) as catalysts [58,59]. As part of our study on the development of multifunctionalized organocatalysts based on hypervalent iodine chemistry [60-66], we found that *N*-isopropyl-2-iodobenzamide (**13**), when utilized as a catalyst with Oxone® at room temperature, appears to be a promising catalyst for efficient and environmentally benign alcohol oxidation reactions [67]. Herein, we report our efforts on improving the reactivity of 2-iodobenzamide catalysts.

Results and Discussion

We evaluated several 2-iodobenzoic acid derivatives including esters and amides as catalysts for alcohol oxidation in the presence of Oxone®, and we found that the simply modified derivative, *N*-isopropylamide **13**, exhibited excellent catalytic properties at room temperature [67]. Interestingly, the reactivity of **13** was much higher than that of **3** at room temperature but was lower at 70 °C. However, the reactivity of **13** itself was not so high: the oxidation of benzhydrol (**14a**) with 0.3 equiv of **13**, 2.5 equiv of Oxone®, and 1 equiv of Bu_4NHSO_4 in $MeNO_2/H_2O$ (8:3) completed in 12 h at room temperature (25 °C) to produce a 98% yield of benzophenone (**15a,** Table 1, entry 1) [67]. Therefore, enhancement of the reactivity of the catalyst was desired for practical use. To develop a more reactive catalyst, we evaluated several types of *N*-isopropyliodobenzamides (Table 1). Although most of the previously reported iodoarene catalysts based on pentavalent iodine compounds have a carboxyl or sulfoxyl group at the *ortho*-position to the iodine atom, Zhdankin and colleagues reported that both 2-iodobenzenesulfonic acid (**8**) and 4-iodobenzensulfonic acid (**12**) exhibited high reactivity in their $RuCl_3$–Oxone® co-oxidant system [58,59]. Therefore, we expected that the reactivity of 4-iodobenzamide **16** (Figure 2) would be similar to that of **13**. However, the oxidation of **14a** with **16** under the above conditions did not complete even after 24 h, and the yield of **15a** and of recovered **14a** was 30% and 67%, respectively (Table 1, entry 2). These results indicate that the reactivity of the iodobenzamides depends on the *ortho*-relationship of the iodine atom to the amide group. Therefore, we then investigated *N*-isopropyl-2-iodobenzamides that have an additional functional group on the benzene ring. Based on the results of our studies on phenol oxidation [60,62] and Ishihara's [52] and Moorthy's [20,48] studies on alcohol oxidation, an electron-donating group at the *para*-position to the iodine should be ex-

Table 1: Oxidation of benzhydrol (**14a**) to benzophenone (**15a**) catalyzed by **13** and **16**–**25**.



entry[a]	iodobenzamide	time (h)	yield (%)[b]	recovery of **14a** (%)[b]
1[c]	**13**	12	98	–
2	**16**	24	30	67
3	**17**	6	97	–
4	**18**	10	98	–
5	**19**	18	98	–
6	**20**	19	98	–
7	**21**	23	96	–
8	**22**	46	98	–
9	**23**	48	23	75
10	**24**	13	98	–
11	**25**	23	99	–

[a]All reactions were performed on a 0.5 mmol scale. [b]Isolated yield. [c]Ref. [67]

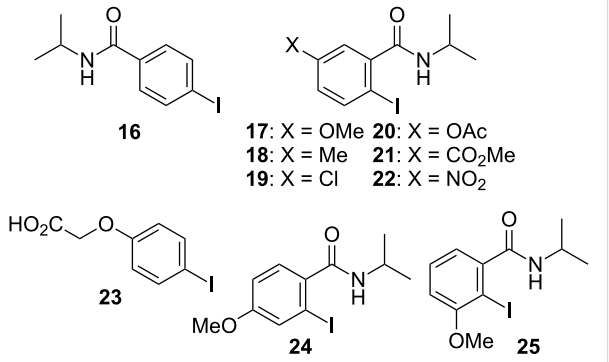
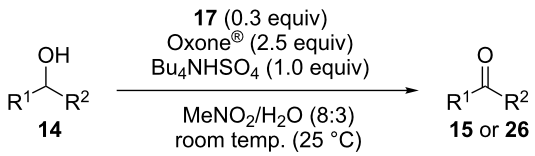


Figure 2: Structures of the catalysts **16**–**25**.

pected to enhance the reactivity of iodoarene catalysts. The investigation began with the 5-substituted 2-iodobenzamides **17**–**22** (Figure 2). Oxidation of **14a** with 5-methoxy-2-iodobenzamide **17** was much faster than that with **13** and was completed within 6 h to produce **15a** in 97% yield (Table 1, entry 3). The 5-methyl derivative **18** exhibited a slightly higher reactivity than **13** (Table 1, entry 4). The introduction of an electron-withdrawing group such as a chloro, acetoxy, methoxycarbonyl, or nitro group at the 5-position led to a decrease in reactivity (Table 1, entries 5–8). These results are in good agreement with the reported studies [20,48,52,60,62]. To confirm the importance of the electron-withdrawing carboxyamide group at the *ortho*-position, we examined the oxidation of **14a** with 4-iodophenoxyacetic acid (**23**); the results showed excellent reactivity for phenol oxidations [60-64]. When **14a** was oxidized with **23**, the reaction was very slow and yielded only 23% of **15a** and 75% of recovered **14a** even after 48 h (Table 1, entry 9) [68]. Since the 5-methoxy derivative **17** was the most reactive, we then investigated the reactivities of **24** and **25**, which have methoxy groups at the *meta*- and *ortho*-positions to the iodine atom, and found that 4-methoxyamide **24** exhibited the same reactivity as nonsubstituted **13** (Table 1, entry 10). On the other hand, oxidation with 3-methoxyamide **25** was much slower than that with **13** and needed 23 h to complete (Table 1, entry 11). Although the *ortho*- and the *para*-methoxy groups should show a similar electronic effect on the iodine atom, the lower reactivity of **25** might be explained by the steric hindrance around the iodine atom of **25**. Consequently, the reactivities of the 2-iodobenzamides **17**–**22**, **24**, and **25** decreased in the following order of substitution: 5-OMe (**17**) > 5-Me (**18**) > H (**13**), 4-OMe (**24**) > 5-Cl (**19**) > 5-OAc (**20**) > 5-CO_2Me (**21**), 3-OMe (**25**) > 5-NO_2 (**22**).

With a highly reactive catalyst in hand, we examined the oxidation of various secondary alcohols **14b**–**f** and primary alcohols **14g**–**k** with 0.3 equiv of **17** in the presence of 2.5 equiv of Oxone® and 1 equiv of Bu_4NHSO_4 in an 8:3 mixture of $MeNO_2$ and water at room temperature. These results as well as those obtained from a similar oxidation using **13** as a catalyst are summarized in Table 2. The secondary benzylic alcohols **14b**–**e** were oxidized with **17** in much shorter reaction times than those oxidized with **13** to give the corresponding ketones **15b**–**e** in good to excellent yields (Table 2, entries 1–4). Oxidation of the aliphatic secondary alcohol **14f** with **17** required a

Table 2: Oxidation of various alcohols **14b–k** with **17**.[a]



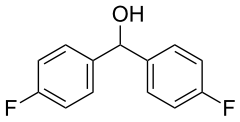
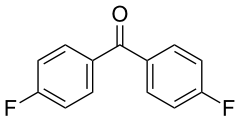
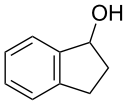
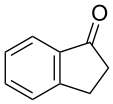
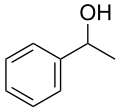
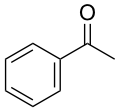
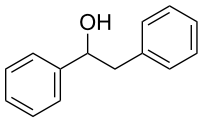
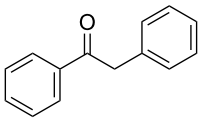
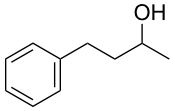
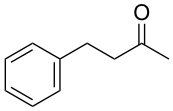
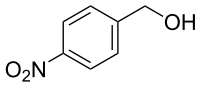
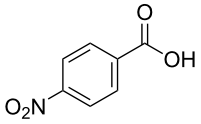
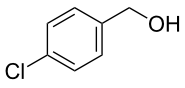
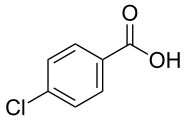
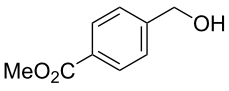
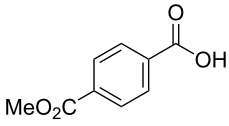
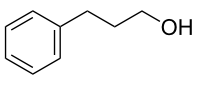
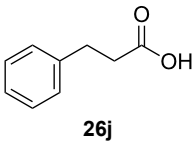
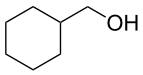
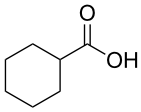
entry	alcohol	carbonyl compound	time (h)[b]	yield (%)[b,c]
1	 **14b**	 **15b**	9 (15)	95 (74)
2	 **14c**	 **15c**	7 (17)	86 (71)
3	 **14d**	 **15d**	11 (14)	62 (70)
4	 **14e**	 **15e**	10 (20)	98 (97)
5	 **14f**	 **15f**	36 (30)	64 (74)
6	 **14g**	 **26g**	10 (20)	89 (82)
7	 **14h**	 **26h**	24 (24)	83 (74)
8	 **14i**	 **26i**	16 (16)	96 (89)
9	 **14j**	 **26j**	9 (20)	85 (90)

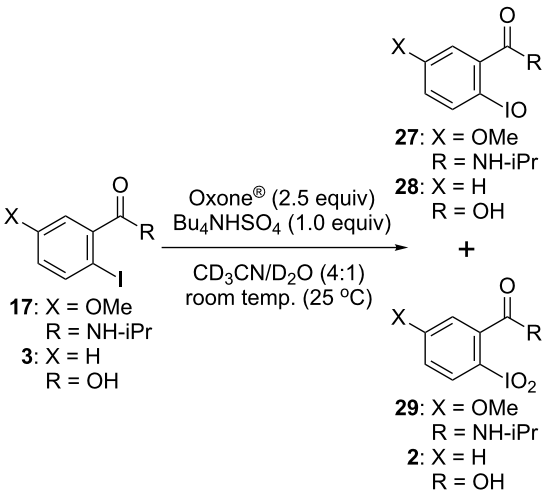
Table 2: Oxidation of various alcohols **14b–k** with **17**.[a] (continued)

10	 **14k**	 **26k**	36 (36)	59 (58)

[a]All reactions were performed on a 0.5 mmol scale. [b]The results obtained for the oxidation using **13** are shown in parentheses [67]. [c]Isolated yield.

slightly longer reaction time than that with **13** (Table 2, entry 5). The primary alcohols **14g–k** were converted into the corresponding carboxylic acids **26g–k** in moderate to excellent yields (Table 2, entries 6–10). However, the reaction times of the oxidations of **14h**, **14i,** and **14k** with **17** were similar to those involving **13**. These results may be due to the slow oxidation of the aldehydes to carboxylic acids [69]. The catalyst **17** was stable under the oxidation conditions and it was recovered in 67–92% after reductive treatment.

The next objective was to investigate the oxidation mechanism of 2-iodobenzamide catalysts. Zhdankin and colleagues reported the oxidation of alcohols to their corresponding carbonyl compounds using several 2-iodoxybenzamides [23]. Therefore, we tried to confirm the formation of 2-iodoxybenzamide **29** from 2-iodobenzamide **17** in an oxidation reaction (Scheme 1). Iodoarene **17** was treated with 2.5 equiv of Oxone® and 1 equiv of Bu_4NHSO_4 in a 4:1 mixture of acetonitrile-d_3 and D_2O at a low concentration (0.01 M) at room temperature, and the reaction was monitored by ^1H NMR spectroscopy. The reaction profiles for **17** as well as for 2-iodobenzoic acid (**3**) are summarized in Figure 3. In the reaction involving **17**, the



Scheme 1: Oxidation of the monovalent iodine derivatives **17** and **3** to the pentavalent iodine derivatives **29** and **2** using Oxone®.

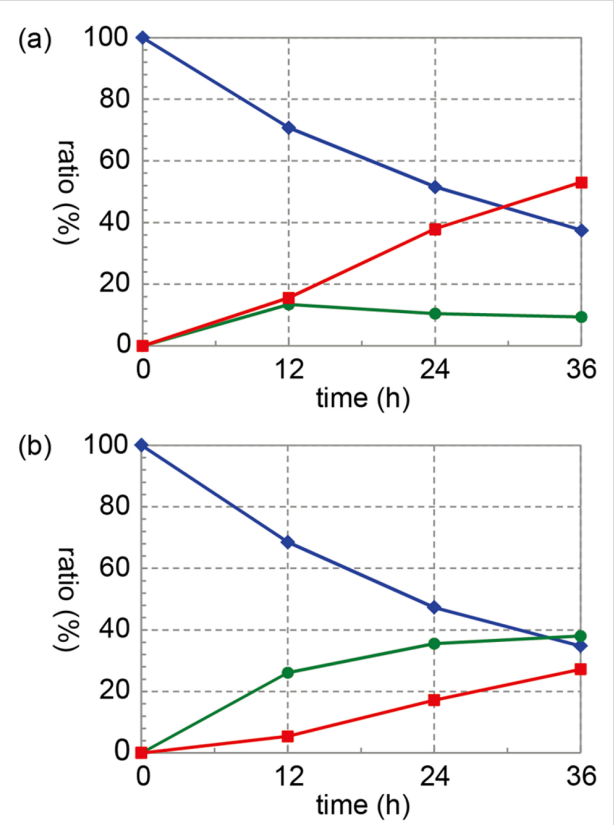
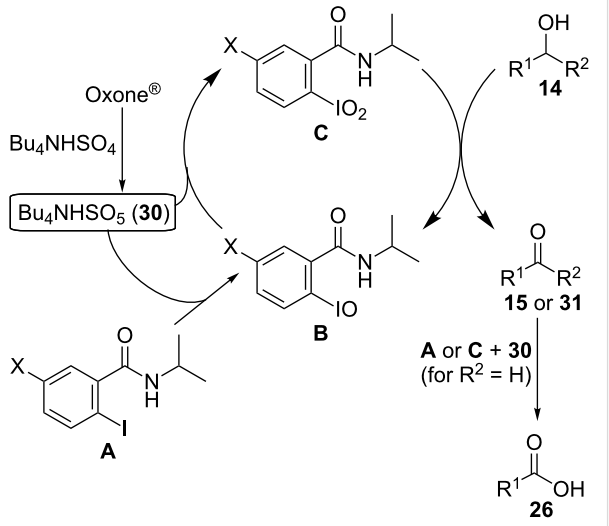


Figure 3: Reaction profile of the oxidation of (a) iodobenzamide **17** and (b) 2-iodobenzoic acid (**3**) with Oxone® in the presence of Bu_4NHSO_4 in a 4:1 mixture of CD_3CN and D_2O: monovalent iodine derivatives **17** and **3** (blue), trivalent iodine derivatives **27** and **28** (green), and pentavalent iodine derivatives **29** and **2** (red).

amount of pentavalent iodine derivative **29** gradually increased with a decrease in the amount of **17** and only a small amount of trivalent iodine derivative **27** was observed during the reaction. The ratio of **17** to trivalent **27** and pentavalent **29** was determined to be 38:9:53 after 36 h. In the oxidation of **3**, monovalent **3** was consumed at almost the same rate as the oxidation of **17**. However, the formation of pentavalent **2** was much slower than that of **29**, and a considerable amount of trivalent **28** remained during the reaction. After 36 h, the oxidation of **3** generated 27% of **2** with 35% unreacted **3** and 38% trivalent **28**. Thus, it is clear that the pentavalent iodine species **2** and **29**

were generated during the oxidation reactions of monovalent **3** and **17** and that the oxidation of trivalent **27** to pentavalent **29** is much faster than that of **28** to **2** at room temperature. These results also suggest that the formation of the pentavalent iodine species from the corresponding trivalent iodine species might be the rate-determining step in the catalytic hypervalent iodine oxidation of **17** [70].

On the basis of the above results, a plausible mechanism for the oxidation catalyzed by the 2-iodobenzamides is shown in Scheme 2. Iodobenzamide **A** is readily oxidized by tetra-*n*-butylammonium peroxymonosulfate (Bu_4NHSO_5, **30**), which is derived from Bu_4NHSO_4 and Oxone®, to pentavalent iodine species **C** at room temperature. The resultant **C** oxidizes alcohol **14** to ketone **15** or aldehyde **31** during its reduction to trivalent iodine **B**. Aldehyde **31** is further oxidized with **30** with the assistance of **A** or **C** [67] to give carboxylic acid **26**. Iodine **B** is re-oxidized with **30** to regenerate **C**. The oxidation proceeds at room temperature because of the fast oxidation of trivalent **B** to pentavalent **C**.



Scheme 2: Plausible reaction mechanism for the oxidation of alcohols catalyzed by the 2-iodobenzamides.

Conclusion

In summary, we have developed 2-iodo-*N*-isopropyl-5-methoxybenzamide (**17**) as an efficient catalyst for the oxidation of primary and secondary alcohols. The reaction of benzylic and aliphatic alcohols **14** with a catalytic amount of **17** in the presence of Oxone® and Bu_4NHSO_4 at room temperature proceeded smoothly to provide good to excellent yields of the corresponding carbonyl compounds **15** and **26**. The higher reactivity of **17** at room temperature results from the rapid oxidation of trivalent iodine compound **27** to the pentavalent compound **29**. 5-Methoxy-2-iodobenzamide **17** promises to be an efficient and environmentally benign catalyst for oxidation of alcohol, especially benzylic alcohols.

Experimental

Typical experimental procedure for the oxidation of secondary alcohols 14a–f: Secondary alcohol **14** (0.50 mmol) was added to a solution of the catalyst (0.15 mmol) and Bu_4NHSO_4 (170 mg, 0.50 mmol) in a mixture of $MeNO_2$ (1.6 mL) and water (0.6 mL), followed by Oxone® (768 mg, 1.25 mmol) at room temperature (25 °C). After **14** was completely consumed, as indicated by TLC, the resulting mixture was diluted using EtOAc and was washed with water. The organic layer was then washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give pure ketone **15** and the catalyst.

Typical experimental procedure for the oxidation of primary alcohols 14g–k: Primary alcohol **14** (0.50 mmol) was added to a solution of the catalyst (0.15 mmol) and Bu_4NHSO_4 (170 mg, 0.50 mmol) in a mixture of $MeNO_2$ (1.6 mL) and water (0.6 mL), followed by Oxone® (768 mg, 1.25 mmol) at room temperature (25 °C). After **14** was completely consumed, as indicated by TLC, the resulting mixture was diluted with EtOAc, water, and saturated aqueous $Na_2S_2O_3$. The organic layer was then washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the catalyst. The combined aqueous layers were acidified with 10% HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give pure carboxylic acid **26**.

Supporting Information

Supporting Information File 1

Experimental details and the ^1H and ^{13}C NMR spectra of the catalysts, the substrates, and the products.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-82-S1.pdf]

Acknowledgments

This research was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from the Ministry of Education, Culture, Sports, Science and Technology, Japan; JSPS Core-to-Core Program, B. Asia-Africa Science Platforms;

and Toyama Prefecture Citizens' Personal Development Foundation (TPCPDF).

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68. The oxidation of **14a** with **23** at 70 °C was also reported to be very slow [67].
69. The corresponding aldehyde remained even after the starting alcohols were completely oxidized (checked by TLC).
70. Ishihara and colleagues also suggested that the rate-determining step of their oxidations might be the regeneration of I(V) species [52].

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cross-coupling of dissimilar ketone enolates via enolonium species to afford non-symmetrical 1,4-diketones

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Full Research Paper

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Keywords:
1,4-diketones; enolates; enolonium species; hypervalent iodine; ketones; umpolung

Beilstein J. Org. Chem. **2018,** *14,* 992–997.
doi:10.3762/bjoc.14.84

Received: 10 February 2018
Accepted: 03 April 2018
Published: 03 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Due to their closely matched reactivity, the coupling of two dissimilar ketone enolates to form a 1,4-diketone remains a challenge in organic synthesis. We herein report that umpolung of a ketone trimethylsilyl enol ether (1 equiv) to form a discrete enolonium species, followed by addition of as little as 1.2–1.4 equivalents of a second trimethylsilyl enol ether, provides an attractive solution to this problem. A wide array of enolates may be used to form the 1,4-diketone products in 38 to 74% yield. Due to the use of two TMS enol ethers as precursors, an optimization of the cross-coupling should include investigating the order of addition.

Introduction

Substituted 1,4-dicarbonyl compounds are key intermediates for the preparation of numerous natural products and active pharmaceutical ingredients (APIs) with important biological activities. This is due to the facile conversion of 1,4-dicarbonyl compounds into five-membered heterocycles such as thiophenes, furans, and pyrroles. Consequently, numerous multistep approaches to unsymmetrical 1,4-dicarbonyl compounds involving, e.g., S_N2-type displacements [1] or highly functionalized substrates such as β-ketoesters [2,3] or β-ketosulfones [4] have been developed. Recently, Loh reported the palladium-catalyzed coupling of an acid chloride with premade isolable indium homoenolates ($In(CH_2CHRC{=}OR')_2$), 1.2 equiv relative to the acid chloride) to give the corresponding 1,4-diketones [5]. Yet the direct coupling of two enolates is inarguably the shortest and most direct path to 1,4-dicarbonyl compounds. However, while oxidative dimerization of enolates is fairly straightforward [6,7], the coupling of two dissimilar enolates is contrastingly highly challenging. The more similar in steric and electronic properties the two dissimilar enolates become, the more difficult it becomes to achieve a selective

cross-coupling rather than a statistical mixture of the two dimers and the desired unsymmetrical adduct. This may be overcome by using a large excess of one of the coupling partners [8-10], but this approach reduces the overall efficiency of the process. Thomson [11] and Wirth [6,7,12] both circumvented the selectivity and reactivity problem by making use of a temporary silicon connection strategy to render the reaction intramolecular. In both cases, the two ketone enolates were coupled successively to dimethyldichlorosilane. Thomson achieved the cross-coupling by using cerium(IV) as a one-electron oxidant [11]. Importantly for the discussion of the present work, Wirth's strategy relied on a hypervalent iodine [13-15] mediated oxidative cross-coupling. Although these processes add a further step to the process, carrying out the cross-coupling in an intramolecular fashion has the double advantage of avoiding homocoupling as well as helping to overcome low reactivity in hindered systems such as cyclohexanone [12].

To the best of our knowledge there are only five examples of successful intermolecular couplings of dissimilar enolates. Two of these examples involve the coupling of amide enolates with ketone enolates. Baran reported that stoichiometric Cu(2-ethylhexanoate)$_2$ or Fe(acac)$_3$ (2 equiv) are able to selectively oxidize imides, including Evan's-type chiral imides, to the corresponding radicals. The formed radical then reacts selectively with a ketone lithium enolate followed by a second SET step to complete the transformation (Scheme 1a) [16,17]. A different approach, developed by Maulide, relies on the highly efficient umpolung of amides into enolonium species using triflic anhydride, a pyridine base and pyridine *N*-oxides (Scheme 1b). These enolonium species have been shown to react intramolecularly with *N*-benzyl groups [18-24]. The same principle has also been applied to the α-oxidation of amides [25]. Recently, Maulide showed that this powerful concept provides as solution to the coupling of amides with a large variety of ketone enolates to give 1,4-dicarbonyl compounds [26]. However, the radical-based method of Baran and the umpolung method of Maulide both take advantage of the selective activation of an amide and are therefore not amenable to ketone enolates. MacMillan reported the organocatalytic oxidative enantioselective coupling of in situ formed aldehyde enamines with excess (2 equiv) trialkylsilyl enol ethers (Scheme 1c) [27]. This reaction was proposed to proceed through a mechanism involving the attack of an enamine radical on the trialkylsilyl enol ether.

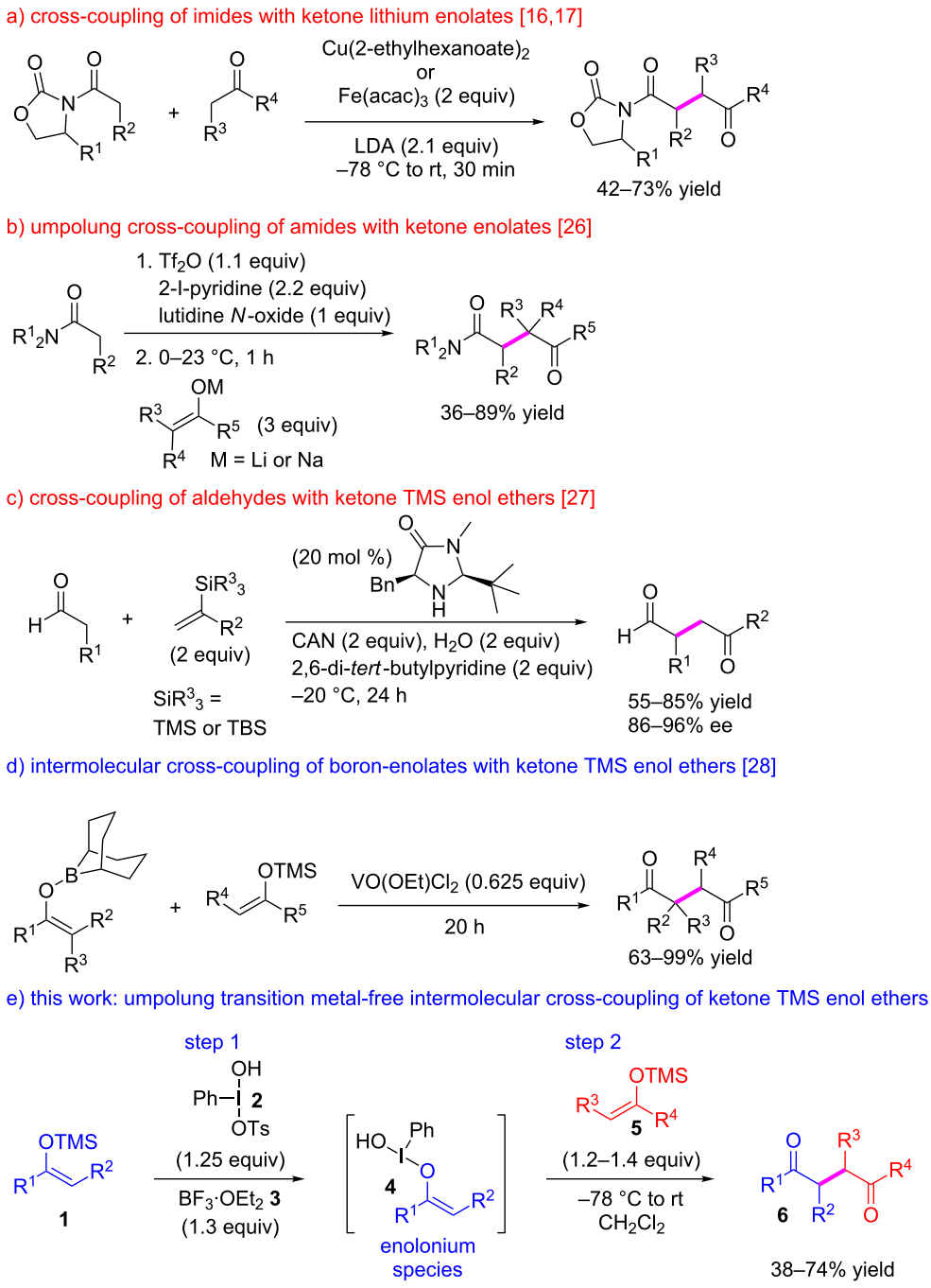
The last two examples concern the even more challenging cross-coupling of two dissimilar ketone enolates. In this context Hirao achieved the intermolecular cross-coupling by taking advantage of the different oxidation potentials of boron enolates and trimethylsilyl enol ethers to achieve selectivity with vanadium (V, 0.625 equiv) as the oxidant (Scheme 1d) [28-30]. The final example is the intermolecular cross-coupling of two dissimilar trimethylsilyl enol ethers described herein (Scheme 1e).

Results and Discussion

Previously we have established that as little as 1.25 equiv of Koser's reagent and 1.25 equiv of boron trifluoride in dichloromethane constituted an optimal recipe for preparing a variety of enolonium species. We have also shown that the enolonium species **4** (R^1 = Ph, R^2 = H) can be produced from the corresponding TMS enol ether **1** (R^1 = Ph, R^2 = H) and subsequently coupled with a second molecule of enol ether **1**/**5** ($R^{1/3}$ = Ph, $R^{2/4}$ = H) to afford the 1,4-diketone **7** in 71% yield (Scheme 2) [31]. We therefore focused on identifying the minimum amount of the second enolate that would lead to optimal yields and found that as little as 1.2–1.4 equiv provided the desired 1,4-diketones in acceptable yields without the need for a large excess of the second coupling partner (Scheme 2). Since the two coupling partners are both trimethylsilyl enol ethers, an advantage of this method is that the optimization of the coupling of a given enolate pair may be investigated by simply reversing the order of addition. In general, the major competing side reaction was the nucleophilic attack by the tosylate on the enolonium species **4**. Only in the rare cases mentioned below homocoupling did take place.

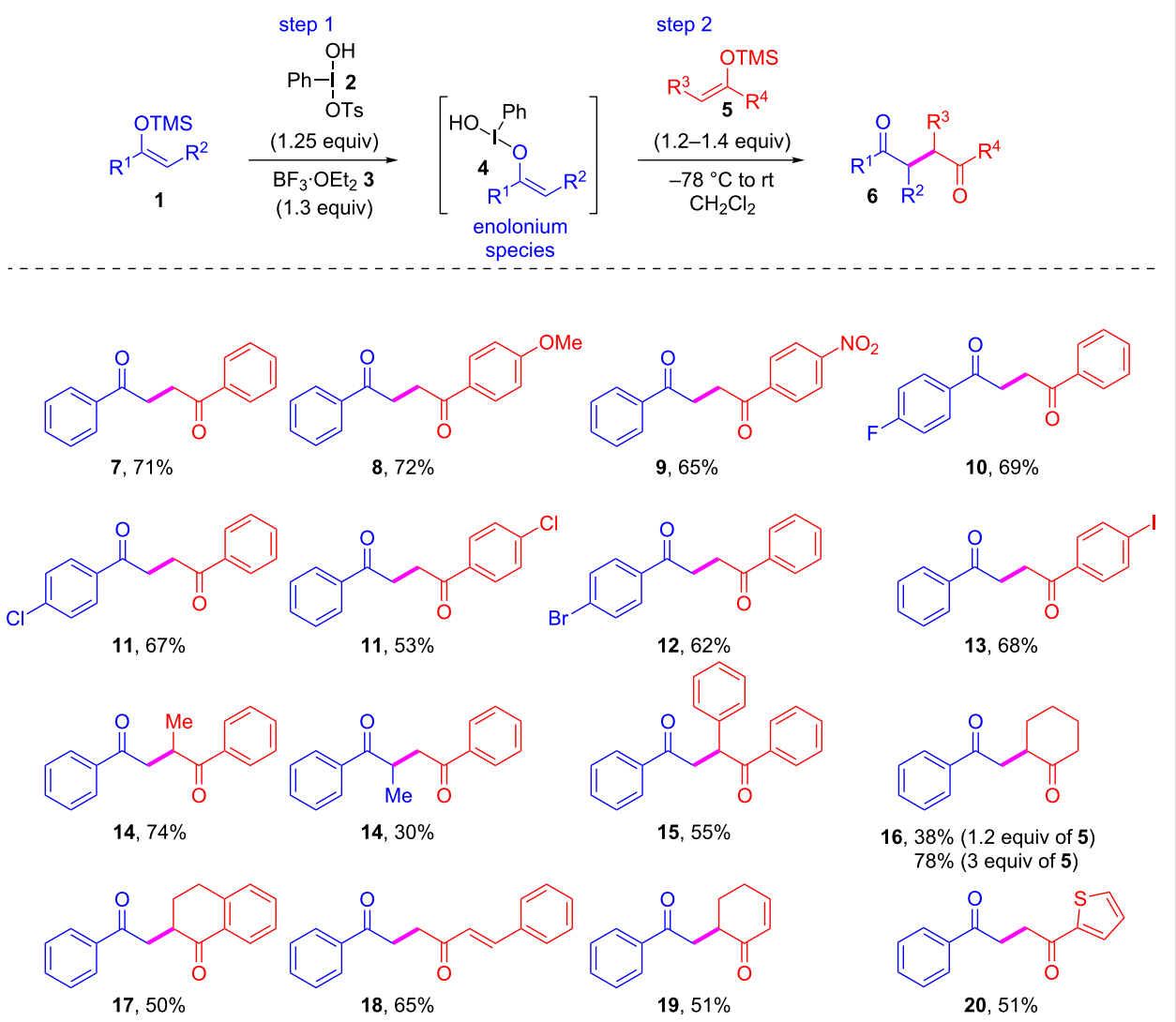
The enolonium species **4** (R^1 = Ph, R^2 = H) reacts readily with both electron-rich and electron-poor TMS enol ethers **5** (Scheme 2). Thus, the cross-coupling of **4** (R^1 = Ph, R^2 = H) with the TMS enol ether **5** (R^3 = *p*-$MeOC_6H_4$, R^4 = H) afforded compound **8** in 72% yield with no oxidation of the electron-rich aromatic ring observed. The only side product being tosyloxyacetophenone. The same enolonium species **4** (R^1 = Ph, R^2 = H) reacts with the TMS enol ether **5** (R^3 = *p*-$O_2NC_6H_4$, R^4 = H) to form **9** in 65% yield.

The method is by no means restricted to enolonium species of acetophenone as may be observed from the formation of the whole series of *para*-halogenated 1,4-diketones. Thus, the *p*-fluoro-, *p*-chloro-, and *p*-bromo-substituted enolonium species **4** (R^3 = *p*-X-C_6H_4, R^4 = H, X = F, Cl, or Br) were generated and used in the cross-coupling with TMS enol ether **5** (R^3 = Ph, R^4 = H) to give the products in 69% (**10**), 67% (**11**), and 62% (**12**) yield, respectively. In case of the reverse addition, namely reacting enolonium species **4** (R^1 = Ph, R^2 = H) with TMS enol ether **5** (R^3 = *p*-Cl-C_6H_5, R^4 = H), product **11** was isolated in 53% yield. Therefore, for non-commercially available enolates it could be advantageous to try both orders of addition to achieve an optimal result. Indeed, when the iodo-substituted enolonium species **4** (R^1 = *p*-I-C_6H_4, R^2 = H) was prepared and reacted with TMS enol ether **5** (R^3 = Ph, R^4 = H)



Scheme 1: Oxidative intermolecular cross-coupling of dissimilar enolates.

the desired product **13** is obtained in less than 10% yield accompanied with the homo-dimers and tosyloxylated ketones as byproducts. In contrast, reversing the order of addition of the TMS-enol ethers afforded **13** in 68% yield. It should be noted that we have previously used the enolonium species **4** (R^1 = *p*-I-C_6H_4, R^2 = H) successfully in the coupling with 2-methylindole and *N*-methyl-2-methylindole and obtained the products in 77% and 74% yield, respectively [32]. The low yield achieved here therefore reflects issues unique to the reaction with the second enolate and not the stability of the enolonium species itself. Based on the formation of dimers of both ketones used, we speculate that this is due to partial oxidation of the second enolate by **4** (R^1 = *p*-I-C_6H_4, R^2 = H), perhaps due to relatively slower cross-coupling. Irrespective, these issues are easily avoided simply by using the reverse addition to give the desired product **13** in good yield.



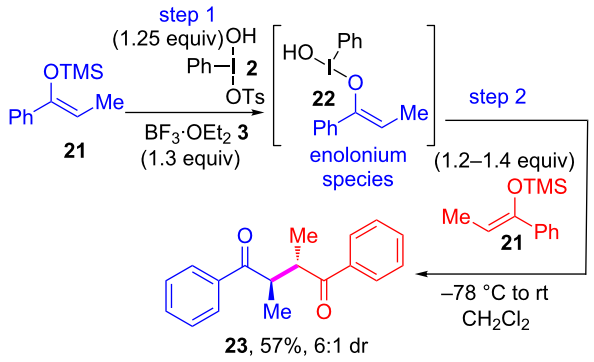
Scheme 2: Scope of the homo- and heterocoupling of enolates. The purple bond indicates the bond formed. The blue-colored fragments indicate the first TMS enol ether used to produce the electrophilic enolonium species **4** and the red fragments indicate the second TMS enol ether used as nucleophile **5**. All yields are isolated yields.

The choice of the order of addition is also of importance for substrates with more sterical hindrance. Here the trend is clear: it is advantageous to use the less sterically hindered TMS enol ether to generate the enolonium species **4** followed by the addition of the more sterically hindered TMS enol ether **5**. For example, the addition of enolonium species **4** (R^1 = Ph, R^2 = Me) to the TMS enol ether **5** (R^3 = Ph, R^4 = H) led to formation of the product **14** in 30% yield with significant formation of 1-tosyloxypropiophenone as the major byproduct. However, when the order of addition was reversed, i.e., the enolonium species **4** (R^1 = Ph, R^2 = H) was cross-coupled with TMS enol ether **5** (R^3 = Ph, R^4 = Me) the same product **14** was obtained in 74% yield. Apparently, in these cases the sterically hindered nature of the enolonium species leads it to react faster with the less-hindered tosylate despite its poor electronic nucleophilicity.

Thus, when the strategy of converting the least hindered enolate into the enolonium species **4** is used even highly hindered TMS enol ethers **5** may be used with formation of tertiary carbon centers. Thus, the enolonium species **4** (R^1 = Ph, R^2 = H) reacted with TMS enol ether **5** (R^1 = Ph, R^2 =Ph) to afford the cross-coupling product **15** in 55% yield. The same enolonium species could be cross-coupled with the TMS enol ether of cyclohexanone to afford the product **16** in 38% yield. Reversing the order of addition in this case led to only trace amounts of the desired cross-coupling product. On the other hand, using 3 equiv of cyclohexanone TMS enol ether, similarly to the conditions used by Maulide (Scheme 1b) [26] and MacMillan (Scheme 1c) [27], led to the product **16** in 78% yield. The cross-coupling of **4** (R^1 = Ph, R^2 = H) with the hindered TMS enol ether of tetralone (1.2 equiv) afforded **17** in 50% yield.

Importantly, also double-bond containing ketones may be used in the reaction. For example, **4** (R^1 = Ph, R^2 = H) reacted with the TMS enol ether of cyclohexenone to give **19** in 51% yield and the reaction with the TMS enol ether of (*E*)-4-phenylbut-3-en-2-one led to formation and isolation of **18** in 65% yield (Scheme 2). Given the ubiquity of heterocycles in natural products and modern APIs it is also of importance that cross-coupling of the easily oxidized TMS enol ether **5** (R^3 = 2-thiophenyl, R^4 = H) with **4** (R^1 = Ph, R^2 =H) afforded **20** in 51% yield.

Since both *meso*-**23** and *rac*-**23** are well-described in the literature [33], we chose to study the diastereoselectivity of the reaction using the dimerization of enol ether **21**. The geometry of the TMS enol ether **21** was established as being exclusively *Z* based on 2D-NOE NMR (Scheme 3). The enolate **21** was then converted into enolonium species **22** and cross-coupled with a second equivalent of **21** to give the two separable diastereoisomers of **23** one *meso* and one *rac* in 6:1 diastereoselectivity. This in conjunction with earlier work from our group [34] indicates that enolonium species of type **4** (Scheme 1 and Scheme 2) are mostly configurationally stable under the conditions used.



Scheme 3: Study of diastereoselectivity of the cross-coupling reaction.

Conclusion

We have shown that a two-step strategy, involving the formation of the enolonium species in the first step and attack by a nucleophilic TMS enol ether in the second step provides a powerful method for intermolecular cross-coupling of dissimilar trimethylsilyl enol ethers. Only 1.2–1.4 equiv of the second enolate is needed. Despite the low ratio between the two reacting dissimilar enolates used, the products are formed in good yield in a single operation and with good diastereoselectivity. We hope that the ease of carrying out and optimizing the procedure will make it useful for chemists interested in making unsymmetrical 1,4-diketones.

Supporting Information

Supporting Information File 1

Experimental, characterization data and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-84-S1.pdf]

Acknowledgements

This research was supported by Ariel University. AMS acknowledges support by the Israel Science Foundation (grant no. 1914/15).

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Preparation, structure, and reactivity of bicyclic benziodazole: a new hypervalent iodine heterocycle

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Keywords:
benziodazole; biheterocycles; hypervalent iodine; iodine; oxidatively assisted esterification

Beilstein J. Org. Chem. **2018,** *14,* 1016–1020.
doi:10.3762/bjoc.14.87

Received: 06 February 2018
Accepted: 20 April 2018
Published: 08 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

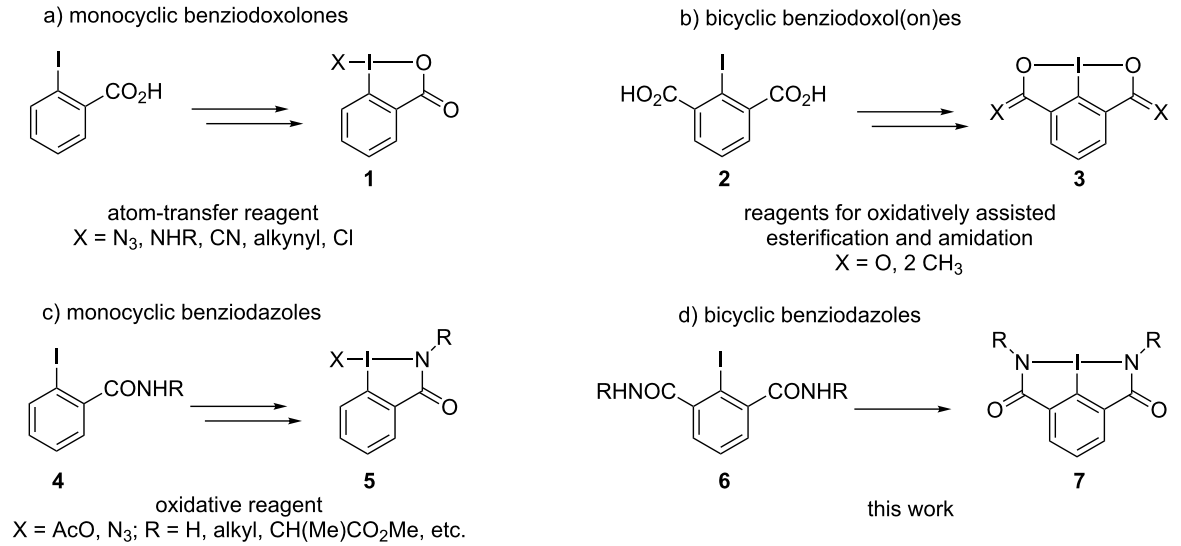
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Abstract

A new bicyclic organohypervalent iodine heterocycle derivative of benziodazole was prepared by oxidation of 2-iodo-*N,N'*-diisopropylisophthalamide with *m*-chloroperoxybenzoic acid under mild conditions. Single crystal X-ray crystallography of this compound revealed a five-membered bis-heterocyclic structure with two covalent bonds between the iodine atom and the nitrogen atoms. This novel benziodazole is a very stable compound with good solubility in common organic solvents. This compound can be used as an efficient reagent for oxidatively assisted coupling of carboxylic acids with alcohols or amines to afford the corresponding esters or amides in moderate yields.

Introduction

In recent years, the interest in heterocyclic organohypervalent iodine compounds has experienced an unprecedented growth [1-6]. A variety of new hypervalent iodine heterocycles have been prepared, and numerous reactions employing these compounds as reagents for organic synthesis have been reported. The benziodoxole-based five-membered iodine heterocycles represent a particularly important class of hypervalent iodine(III) reagents. Substituted benziodoxoles **1** (Scheme 1a) are commonly employed as efficient electrophilic atom-transfer reagents useful for conversion of various organic substrates to the corresponding products of azidation [7-11], amination [12,13], cyanation [14-17], alkynylation [18-20], or chlorination [21,22]. Recently, Zhang and co-workers reported the preparation of several bicyclic benziodoxoles **3** starting from 2-iodoisophthalic acid (**2**, Scheme 1b). These bicyclic benziodoxoles **3** can be used as efficient coupling reagents for the



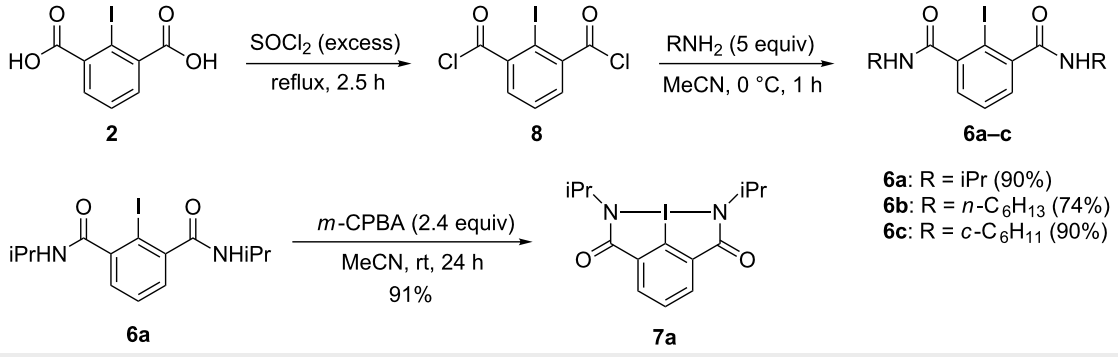
Scheme 1: Representative examples of benziodoxoles and benziodazoles.

direct condensation reaction between carboxylic acids and alcohols or amines to provide esters, macrocyclic lactones, or amides and peptides [23-25].

Numerous examples of five-membered hypervalent iodine(III) heterocycles containing other than oxygen heteroatoms, such as sulfur [26], boron [27,28], phosphorous [29], or nitrogen [30-32], have been synthesized and characterized by X-ray crystallography. In particular, several nitrogen containing heterocyclic iodine(III) compounds **5**, benziodazoles, have been reported by Gougoutas [31], Balthazor [32], and our group [33-35] (Scheme 1c). X-ray structural studies of these benziodazoles confirmed the presence of covalent bonding between iodine and nitrogen atoms in the heterocyclic ring. Benziodazoles **5** are usually prepared by the treatment of 2-iodobenzamide derivatives **4** with appropriate oxidants under mild conditions [31-35]. Derivatives of benziodazole can be used as reagents for various oxidative functionalizations of organic substrates [33,36]. For example, azidobenziodazole was used as an efficient azidation reagent with a reactivity similar to azidobenziodoxoles [33]. Recently, the Wang group reported a rhenium catalyst-mediated oxidative dehydrogenative olefination of a C(sp^3)–H bond using acetoxybenziodazole reagents [36]. To the best of our knowledge, all known benziodazoles have a mono-heterocyclic structure, and bi-heterocyclic benziodazole derivatives similar to the bicyclic benziodoxole **3** have never been reported. In this paper, we report the synthesis, structural characterization, and reactivity of a novel bicyclic benziodazole derivative **7** (Scheme 1d).

Results and Discussion

An obvious approach to the preparation of bicyclic benziodazoles **7** involves the oxidation of the corresponding 2-iodo-*N,N'*-dialkylisophthalamides **6** (Scheme 1). We have synthesized the precursors **6** in two simple steps starting from commercially available 2-iodoisophthalic acid (**2**). Firstly, 2-iodoisophthalic acid (**2**) was converted to the corresponding acyl chloride **8** by treatment with thionyl chloride (Scheme 2).



Scheme 2: Preparation of bicyclic benziodazole **7a**.

In the second step, acyl chloride **8** reacted with appropriate alkylamines to give the corresponding 2-iodo-*N,N'*-dialkylisophthalamides **6** in good yields. The oxidation of 2-iodo-*N,N'*-diisopropylisophthalamide (**6a**) with *m*-chloroperoxybenzoic acid (*m*CPBA) under mild conditions afforded the desired bicyclic benziodazole **7a** in good yield. Unfortunately, we could not obtain the corresponding pure benziodazole derivatives **7** by the oxidation of precursors **6b** or **6c** under similar conditions. According to NMR spectra of the reaction mixture of **6b** or **6c**, the desired products **7b** or **7c** were observed in the reaction as a complex mixture with other compounds. Bicyclic benziodazole **7a** is a thermally stable, white, microcrystalline compound that can be stored in a refrigerator for several weeks. Solutions of **7a** in $CDCl_3$ or CD_3CN did not show any decomposition even after storage for over one month at room temperature.

The solid state structure of compound **7a** was characterized by X-ray crystallography. A single crystal X-ray diffraction of **7a** confirmed the bicyclic benziodazole structure with two covalent bonds between the iodine atom and the nitrogen atoms I(1)–N(1) = 2.184 (4) Å, I(1)–N(2) = 2.177 (4) Å (Figure 1). These bond lengths are similar to previously reported benziodazole structures [29-32]. According to X-ray crystallography data, structure **7a** has a distorted T-shaped geometry with an N(1)–I(1)–N(2) angle of 153.90 (15)°. Compared to other reported bicyclic hypervalent iodine compounds [23,25,37], this is the most bent structure at the N(1)–I(1)–N(2) angle. An additional relatively weak intermolecular coordination between the iodine atom and the oxygen atom of a neighboring molecule (I(1)···O'(1) = 3.107 (3) Å) results in the overall pseudo-square planar geometry at the iodine center.

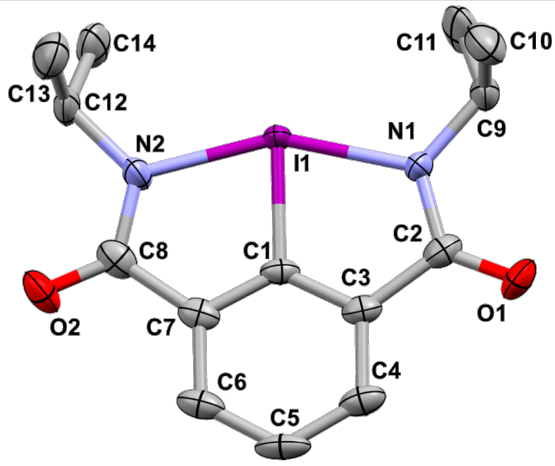
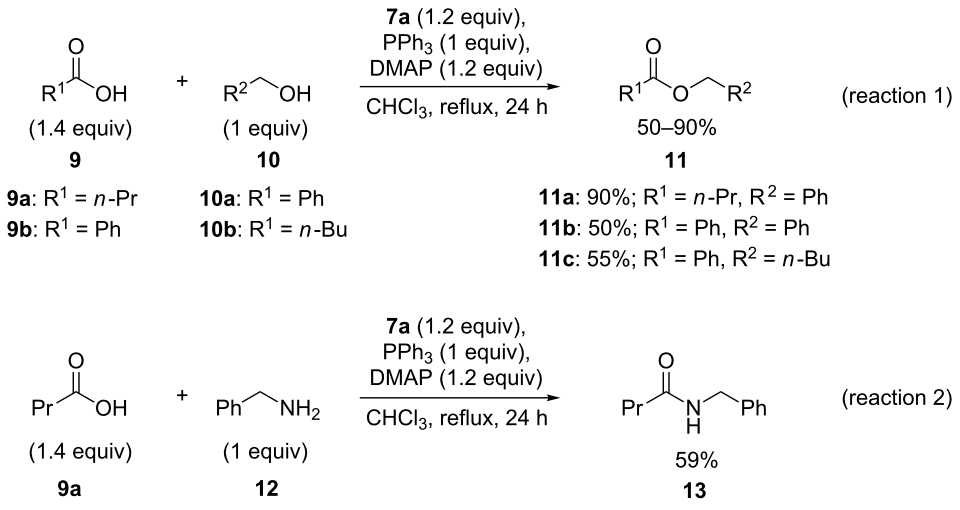


Figure 1: X-ray crystal structure of compound **7a**. Ellipsoids are drawn to the 50% probability level. Selected bond lengths and angles: I(1)–C(1) 2.040 (4) Å; I(1)–N(1) 2.184 (4) Å; I(1)–N(1) 2.177 (4) Å; N(1)–I(1)–C(1) 76.89 (18)°; N(2)–I(1)–C(1) 77.02 (18)°; N(1)–I(1)–N(2) 153.90 (15)°.

Similar to the iodosodilactone reagents [23-25], the bicyclic benziodazole **7a** could be expected to be a useful reagent for oxidatively assisted coupling reactions. Previously, Zhang and co-workers reported the reactions of carboxylic acids with alcohols or amines in the presence of stoichiometric amounts of iodosodilactones **3** forming the corresponding esters or amides in moderate to good yields via an oxidatively assisted coupling reaction [23-25]. We have investigated the analogous oxidatively assisted coupling reaction of carboxylic acids **9** with alcohols **10** or amine **12** using benziodazole **7a** under similar conditions (Scheme 3). The reaction of butyric acid (**9a**) with benzyl alcohol (**10a**) using benziodiazole **7a** in the presence of triphenylphosphine and *N*,*N*-dimethyl-4-aminopyridine (DMAP)



Scheme 3: Benziodadiazole **7a** mediated oxidatively assisted esterification and amidation reactions.

in chloroform solution under reflux conditions afforded the desired product **11a** in good yield. As expected, the reactions of benzoic acid (**9b**) with benzyl alcohol (**10a**) or 1-pentanol (**10b**) under the same conditions gave the corresponding esters **11b** or **11c** in moderate yields (Scheme 3, reaction 1). The analogous reaction of butyric acid (**9a**) with benzylamine (**12**) and benziodazole **7a** under similar conditions produced the expected amide **13** in moderate yield (Scheme 3, reaction 2). Compared to the iodosodilactone reagents **3** [23-25], benziodazole **7a** showed a comparable or better reactivity. In contrast to iodosodilactone, benziodazole **7a** has excellent solubility in chloroform allowing reactions in solution under homogeneous conditions. Similar to the reactions of iodosodilactone **3**, $Ph_3P{=}O$ and amide **6a** were observed as the byproducts in these reactions (Scheme 3), which is in agreement with the previously proposed mechanism of oxidatively assisted esterification or amidation [23,38].

Conclusion

In summary, we have prepared the new bicyclic benziodazole **7a** by the oxidation of 2-iodo-*N,N'*-diisopropylisophthalamide (**6a**) with *m*-CPBA. The solid structure of **7a** was established by X-ray crystallography. According to the X-ray data, this compound has a bis-heterocyclic structure with two covalent iodine–nitrogen bonds and distorted T-shape geometry at the hypervalent iodine center. This novel bicyclic benziodazole can be used as an efficient reagent for oxidatively assisted coupling of carboxylic acids with alcohols or amines to afford the corresponding esters or amides in moderate to good yields.

Supporting Information

Supporting Information File 1

Experimental section.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-87-S1.pdf]

Supporting Information File 2

X-ray structure of **7a**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-87-S2.cif]

Acknowledgements

This work was supported by a research grant from the Russian Science Foundation (RSF-16-13-10081). A.S. is also thankful to JSPS Grant-in-Aid for Scientific Research (C, Grant No 15K07852) and to the JSPS Fund for the Promotion of Joint International Research (Grant No 16KK0199). V.V.Z. is thankful for support from the Office of the Vice President for Research, University of Minnesota.

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38. The reaction of **7a** in the presence of DMAP did not show any shift in the NMR spectrum probably because of a weak interaction between **7a** and DMAP.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Fluorocyclisation via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines

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Full Research Paper

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Keywords:
catalysis; cyclisation; fluorination; *gauche* effect; hypervalent iodine; oxazolines

Beilstein J. Org. Chem. **2018,** *14,* 1021–1027.
doi:10.3762/bjoc.14.88

Received: 02 March 2018
Accepted: 27 April 2018
Published: 09 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Herein, we describe a catalytic fluorooxygenation of readily accessible *N*-allylcarboxamides via an I(I)/I(III) manifold to generate 2-oxazolines containing a fluoromethyl group. Catalysis is conditional on the oxidation competence of Selectfluor®, whilst HF serves as both a fluoride source and Brønsted acid activator. The C(sp^3)–F bond of the mono-fluoromethyl unit and the C(sp^3)–O bond of the ring are aligned in a *synclinal* relationship thereby engaging in stabilising hyperconjugative interactions with *vicinal*, electron-rich σ-bonds ($\sigma_{C–C}\rightarrow\sigma^*_{C–F}$ and $\sigma_{C–H}\rightarrow\sigma^*_{C–O}$). This manifestation of the stereoelectronic *gauche* effect was established by X-ray crystallographic analysis of a representative example. Given the importance of fluorine in drug discovery, its ability to modulate conformation, and the prevalence of the 2-oxazoline scaffold in Nature, this strategy provides a rapid entry into an important bioisostere class.

Introduction

Marine and terrestrial natural product bioprospecting has established a broad spectrum of structurally complex, bioactive metabolites containing the venerable 2-oxazoline unit [1,2]. This diversity is exemplified by the siderophore antibiotic D-fluviabactin, the cytotoxic agent westiellamide, the antifungal macrodiolide leupyrrin A_1 and the antitumour compound BE-70016 (Figure 1). In addition, synthetic polymers based on the 2-oxazoline building block constitute versatile platforms for a range of biomedical applications ranging from drug delivery through to tissue engineering [3,4]. Collectively, the importance of the 2-oxazoline scaffold for translational research, together with its strategic value in the design of chiral ligands and auxiliaries [5-7], has culminated in a rich and innovative arsenal of synthetic methods.

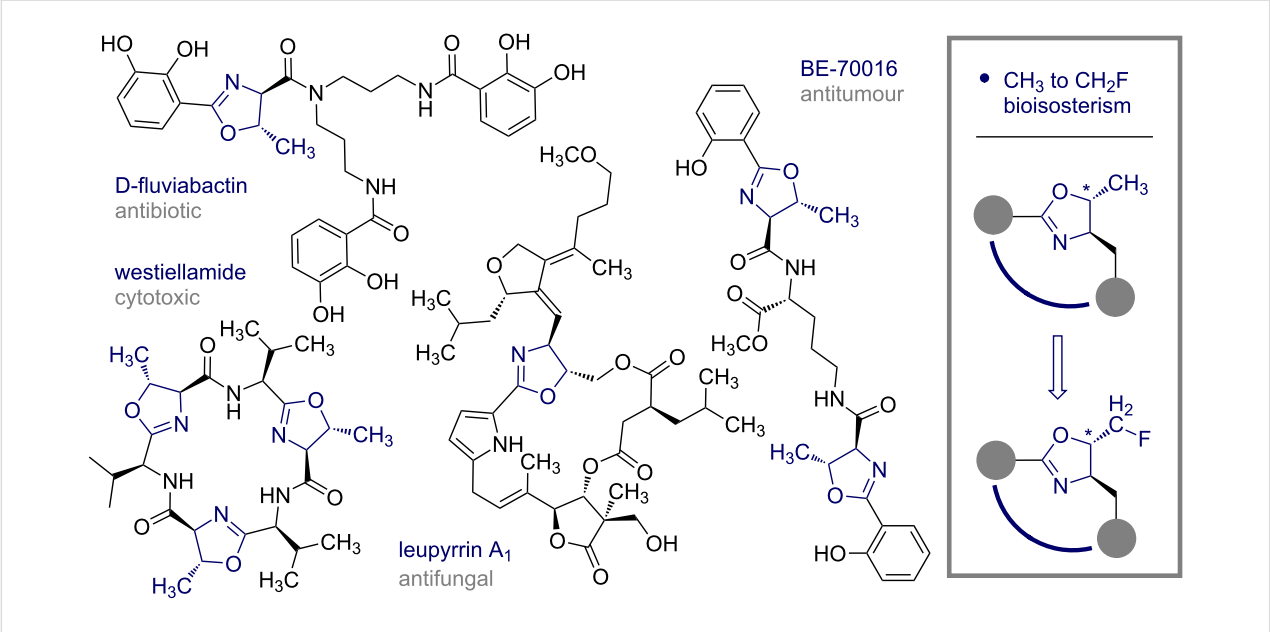


Figure 1: Selected examples of bioactive compounds containing the 2-oxazoline motif.

To contribute to the current catalysis ordnance for the preparation of 2-oxazolines, and provide a direct route to 5-fluoromethyl derivatives from simple unactivated alkenes, the fluorocyclisation of *N*-allylcarboxamides facilitated by the in situ generation of *p*-TolIF$_2$ was envisaged [8-11]. Since hydrogen and hydroxy groups are often substituted by fluorine in molecular editing processes [12], this transformation would provide facile access to a bioisostere of the parent scaffold (Figure 1, right).

In recent years, I(I)/I(III) catalysis has emerged as a powerful and expansive platform for the generation of structural complexity [13-24]. Motivated by the noticeable absence of mild, catalysis-based strategies to generate the *vicinal* difluoroethylene motif directly from simple alkenes [25-27], we recently exploited I(I)/I(III) catalysis to enable this transformation [28,29]. Employing Selectfluor® as the terminal oxidant, it was possible to generate *p*-TolIF$_2$ in situ from *p*-iodotoluene and an inexpensive HF source [30-35]. This strategy proved to be mild and general, smoothly converting terminal olefins to the corresponding 1,2-difluoroethylene unit; a substructure that may be considered a chiral, hybrid bioisostere of the Et and CF$_3$ groups (Figure 2, top) [36].

Since the success of this process is contingent on the efficient generation of *p*-TolIF$_2$ in situ, the platform lends itself to related oxidative transformations. To that end, it was envisaged that the protocol could be effectively translated to the fluorocyclisation of readily accessible *N*-allylcarboxamides (Figure 2, bottom). Whilst the initial phase of catalysis would resemble that of the catalytic difluorination, the presence of the amide would allow the original reaction path to be intercepted to generate a 2-oxazoline with an exocyclic fluoromethyl unit.

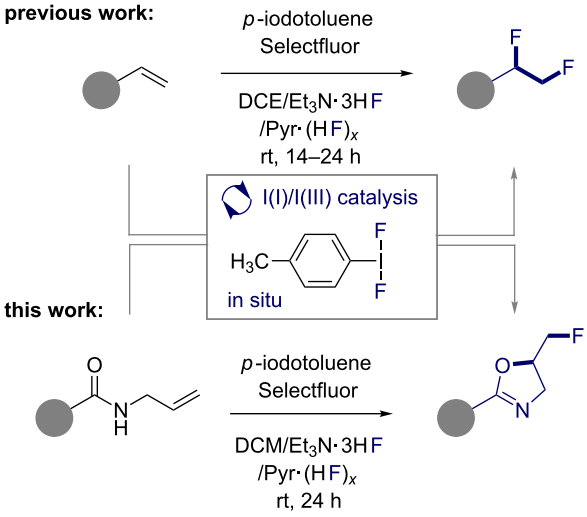
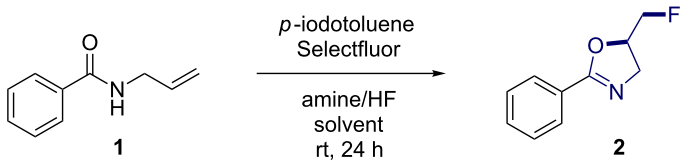


Figure 2: The catalytic difluorination of alkenes (top) and the proposed fluorocyclisation via the same I(I)/I(III) manifold (bottom).

Results and Discussion

Optimisation: As a starting point, the conversion of *N*-allylbenzamide (**1**) to the corresponding 2-phenyloxazoline **2** was investigated (Table 1). Reactions were performed in DCE (0.2 mol·L^{-1}) with 20 mol % catalyst loading, and using Selectfluor® as the oxidant. An initial reaction screen, based on the conditions reported for our *vicinal* difluorination study [9],

Table 1: Optimisation of reaction conditions for a benchmark transformation (**1**→**2**).[a]



Entry	Concentration [mol·L^{-1}]	Solvent	Catalyst loading [mol %]	Amine/HF ratio	Conversion[b] [%]	Yield [%][c]
1	0.2	DCE	20	1:4.5	>95	46
2	0.2	DCE	20	1:3	50	<5
3	0.2	DCE	20	1:7.5	>95	44
4	0.2	DCE	20	1:9.23	>95	46
5	0.2	DCE	20	Pyr·HF (6 equiv)[d]	>95	27
6	0.1	DCE	20	1:4.5	>95	81
7	0.1	toluene	20	1:4.5	>95	72
8	0.1	MeCN	20	1:4.5	78	47
9	0.1	THF	20	1:4.5	34	<5
10	0.1	DCM	20	1:4.5	>95	>95
11	**0.1**	**DCM**	**10**	**1:4.5**	**>95**	**>95 (67)[e]**
12	0.1	DCM	2.5	1:4.5	40	30
13	0.1	DCM	0	1:4.5	<5	<5

[a]Standard reaction conditions: *N*-allylbenzamide (200 μmol), catalyst *p*-iodotoluene, solvent, amine/HF source 1:1 (v/v), Selectfluor® (1.5 equiv), ambient temperature, 24 h; [b]Determined from the ^{1}H NMR spectrum using ethyl fluoroacetate (1.0 equiv) as internal standard; [c]Determined from the ^{19}F NMR spectrum using ethyl fluoroacetate (1.0 equiv) as an internal standard; [d]Reaction conducted with 1 mL of solvent; [e]Yield after column chromatography on silica gel. Reduction in yield is due to hydrolysis. DCE: 1,2-dichloroethane.

began with an exploration of the effect of amine/HF ratio. This was deemed prudent due to the perceived likelihood that HF also functions as a Brønsted acid activator in catalysis. Employing an amine/HF ratio of 1:4.5, product formation was observed (Table 1, entry 1, 46%). Reducing this ratio to 1:3 had a detrimental effect on catalysis efficiency, generating the product in <5% yield (Table 1, entry 2). Increasing the ratio to 1:7.5 and 1:9.23 (Olah's reagent) restored catalysis efficiency but did not surpass previous observations (44 and 46% yields, Table 1, entries 3 and 4, respectively). For comparison, the reaction was attempted using Pyr·HF (6 equiv) but this alteration had an adverse effect on yield (27%, Table 1, entry 5). Based on these findings, the remainder of the study was performed with an amine/HF ratio of 1:4.5. Reducing the concentration from 0.2 mol·L^{-1} to 0.1 mol·L^{-1} led to a large increase in yield (81%, Table 1, entry 6).

Whilst solvents such as toluene, acetonitrile and THF were less effective than DCE (Table 1, entries 7–9), switching to DCM led to full consumption of the starting material and a quantitative NMR yield (Table 1, entry 10). In a final optimisation round, the catalyst loading was reduced to 10 mol % with no discernable effect on performance (Table 1, entry 11). However, further decreasing the loading to 2.5 mol % demonstrates the limits of the system (30% yield, Table 1, entry 12). Finally, for completeness, the control experiment in the absence of *p*-TolI was performed and confirms the role of this species in catalysis.

Establishing scope: With a general procedure having been developed, attention was then focused on establishing the scope of the transformation (Figure 3). To explore the effect of changes to the aryl ring, compared to the parent scaffold **2a**, representative *N*-allylcarboxamides containing the *p*-OCH_3, *p*-NO_2 and *p*-CF_3 substituents were exposed to the general conditions (to generate **2b**, **2c** and **2d**, respectively). These transformations proceeded smoothly to deliver the target 2-oxazolines in good yields (up to 69%) and in the case of compound **2c**, the fluorocyclisation was performed on a 1 mmol scale with no impact on the yield. However, the aldehyde derivative **2e** proved to be more challenging and was isolated in a modest 31% yield. Systems containing *ortho*-substituents (**2f** and **2g**) were also well tolerated but in the case of **2f** it was necessary to extend the reaction time to 40 h. Disubstitution patterns such as in **2h** and **2i**, the latter of which contains a free phenol moiety, were also tolerated (69% and 65% yield, respectively), as was the highly deactivated pentafluorophenyl analogue **2j** (48%). To

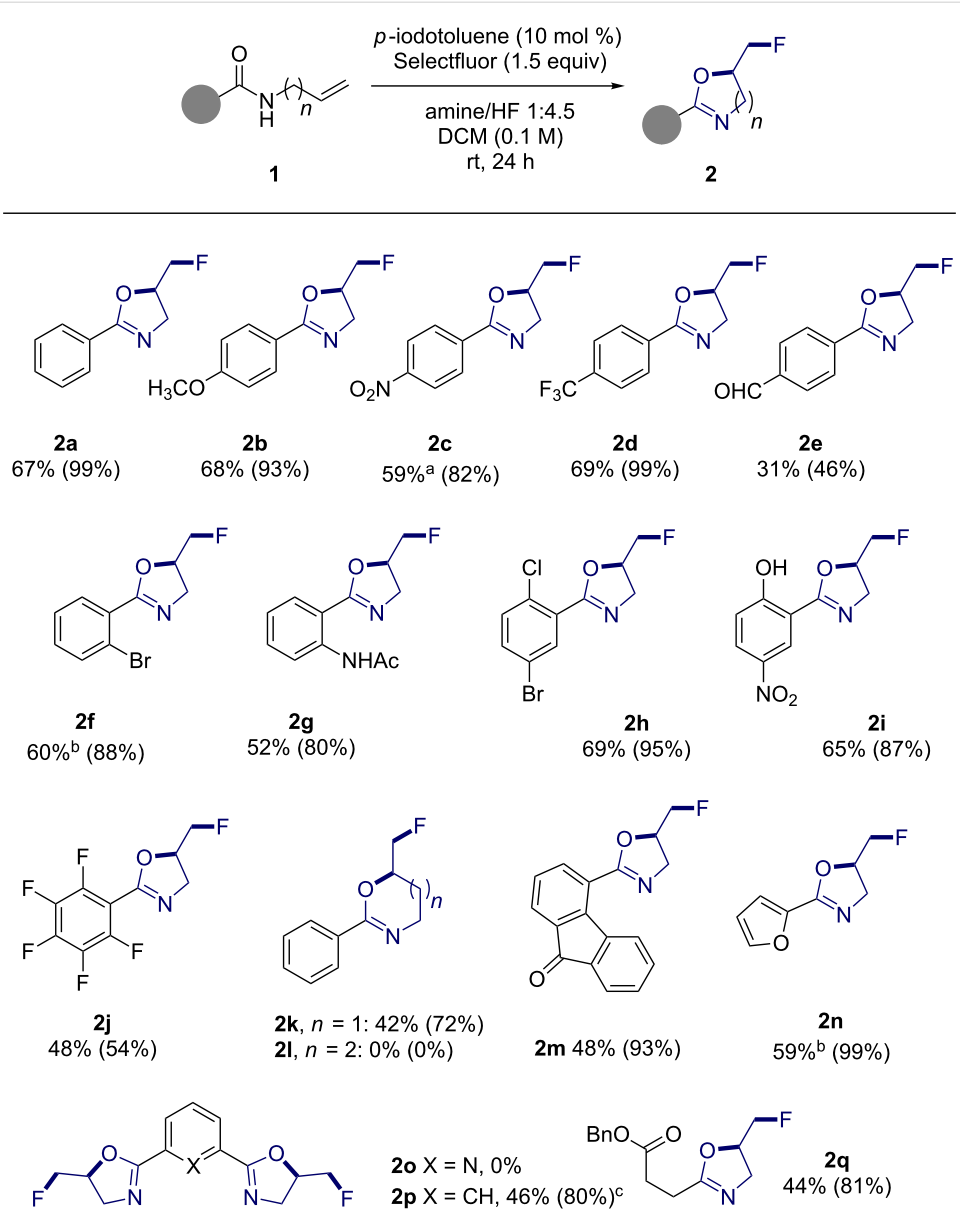
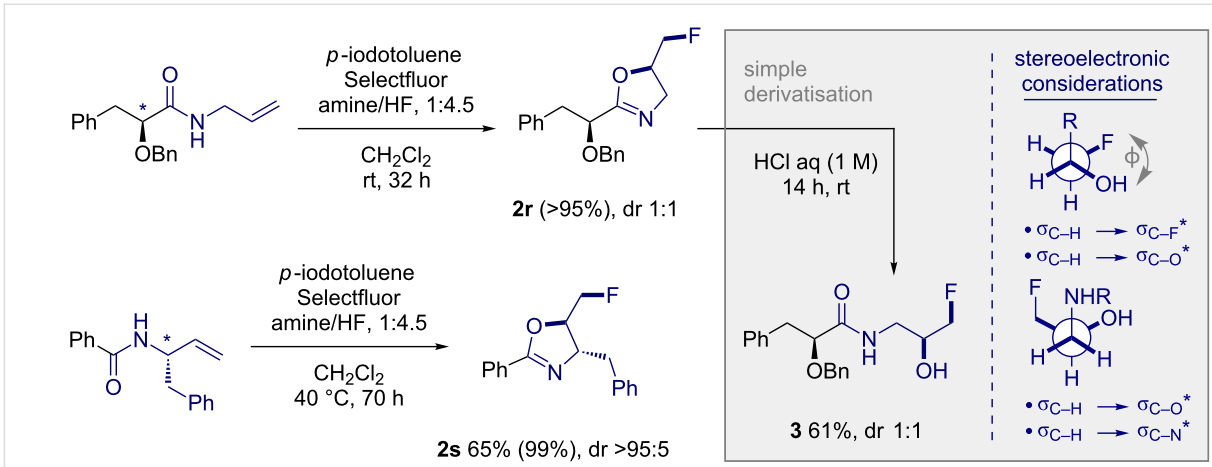


Figure 3: Substrate scope. [a]Reaction conducted on 1 mmol scale. [b]Reaction time increased to 40 hours. [c]Reaction time increased to 32 hours. Yields refer to isolated values whilst NMR yields are given in parentheses (^{19}F NMR using ethyl fluoroacetate as an internal standard).

briefly explore the effect of chain length on efficiency, the cyclisation of *N*-(but-3-en-1-yl)benzamide and *N*-(pent-4-en-1-yl)benzamide was explored (to generate **2k** and **2l**, respectively). Unsurprisingly, whilst the 6-membered ring formed in 42% yield, cyclisation to form the analogous 7-membered ring failed. It was, however, possible to generate heterocyclic species such as the 9-fluorenonyl-substituted oxazoline **2m** (48%) and the furan **2n** (59%). Whilst it was not possible to generate the bisoxazoline **2o** (X = N), the analogous carbogenic scaffold **2p** (X = CH) formed in 46% yield. Finally, although more challenging, it was also possible to generate an aliphatic 2-oxazoline (**2q**) in a modest 44% yield.

Finally, to explore possible diastereocontrol in the cyclisation event, oxazoline **2r** was generated from the corresponding α-chiral amide under standard conditions. Analysis of the crude reaction mixture by ^{19}F NMR allowed a yield of >95% to be determined and a 1:1 dr. This is to be expected given the remote nature of the stereocentre. It is important to note that attempts to separate this compound by column chromatography resulted in significant hydrolysis. Consequently, the oxazoline was exposed to acidic media and quantitatively hydrolysed to the fluorohydrin **3** in 61% yield (Scheme 1). In contrast, the cyclisation to form **2s** was highly diastereoselective on account of the proximal nature of the stereocentre (65%, dr >95:5).



Scheme 1: Exploring diastereocontrol and the synthesis of the fluorohydrin **3**. Yields in parentheses were determined by ^{19}F NMR using ethyl fluoroacetate as an internal standard. Unless otherwise stated, yields refer to isolated values.

Compound **3** is noteworthy on account of the β-amino alcohol and β-fluoro alcohol motifs that collectively preorganised the propyl chain. Stabilising hyperconjugative interactions manifest themselves in the characteristic *gauche* conformations around the two respective torsion angles [37,38]. In this case, it is also highly probable that hydrogen bonding will reinforce these conformational preferences. Whilst it was not possible to isolate crystals of **3** that were suitable for X-ray analysis, it was possible to unambiguously establish the structure of oxazoline **2c** bearing a *p*-NO_2 group (Figure 4 and Table 2) [39]. The molecular structure reveals the expected *gauche* arrangement with a dihedral angle $\phi_{FCCO} \approx -73.4°$ due to $\sigma_{C–C} \rightarrow \sigma_{C–F}^*$ and $\sigma_{C–H} \rightarrow \sigma_{C–O}^*$ interactions. This observation is in agreement with the fluorine *gauche* effect.

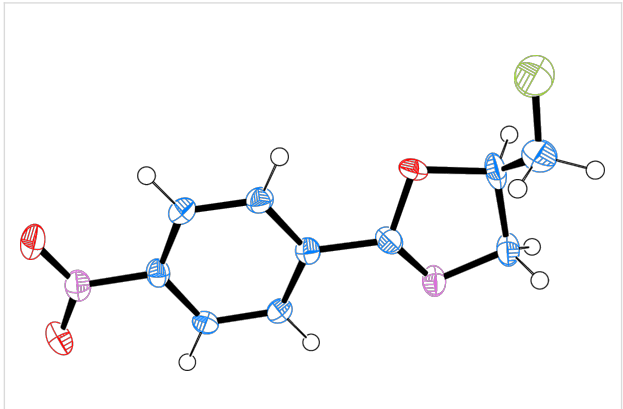


Figure 4: X-ray molecular structure of compound **2c**. Thermal ellipsoids shown at the 50% propability level. Torsion angle ($\phi_{F1–C10–C9–O1}$ −73.4°) consistent with the fluorine *gauche* effect. CCDC number 1815371.

Table 2: Crystallographic data for compound **2c**.

Entry	Data
formula	$C_{10}H_9FN_2O_3$
M_r	224.19
crystal size, mm^3	0.032 × 0.162 × 0.247
crystal system	orthorhombic
space group	*Pna*2$_1$
cell constants	
a, Å	10.0315(3)
b, Å	15.4164(5)
c, Å	6.5161(2)
V, Å^3	1007.71(5)
Z	4
D_x, Mg m^{-3}	1.48
μ, mm^{-1}	1.06
F(000), e	464
T, K	100(2)
λ, Å	1.54178
$2\theta_{max}$, deg	137
transmissions	0.78–0.97
refl. meas./indep./R_{int}	10003/1813/0.034
ref. parameters	182
restraints	118
R [*F* ≥ 4 σ(*F*)]	0.032
*w*R (*F*^{2}, all refl.)	0.086
S	1.05
$\Delta\rho_{max}$, e Å^{-3}	0.145/−0.194

Conclusion

An operationally simple route to 5-fluoromethyl-2-oxazolines from readily accessible *N*-allylcarboxamides is disclosed based

on an I(I)/I(III) catalysis manifold. This metal-free fluorocyclisation employs *p*-iodotoluene (10 mol %) as an inexpensive organocatalyst and Selectfluor® as oxidant. The optimal amine/HF ratio (1:4.5) is easily obtained by combining commercially available triethylamine tris(hydrogenfluoride) ($Et_3N{\cdot}3HF$) and Olah's reagent (Pyr·HF). Broad functional group tolerance is observed in the products, the structures of which display the stereoelectronic fluorine *gauche* effect.

Supporting Information

Supporting Information File 1

Experimental part.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-88-S1.pdf]

Acknowledgements

We acknowledge generous financial support from the WWU Münster and the Deutsche Forschungsgemeinschaft (SFB 858 and Excellence Cluster *EXC 1003 "Cells in Motion"*). We thank Dr. Nicola Lucchetti for helpful discussions.

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39. Crystallographic data: CCDC 1815371 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Hypervalent iodine-mediated Ritter-type amidation of terminal alkenes: The synthesis of isoxazoline and pyrazoline cores

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Letter

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Keywords:
amido-amidation; hypervalent iodine; isoxazoline; metal-free; oxyamidation; pyrazoline

Beilstein J. Org. Chem. **2018,** *14,* 1028–1033.
doi:10.3762/bjoc.14.89

Received: 09 February 2018
Accepted: 27 April 2018
Published: 11 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Hypervalent iodine-mediated olefin functionalization provides a rapid gateway towards accessing both various heterocyclic cores and functional groups. In this regard, we have developed a Ritter-type alkene functionalization utilizing a $PhI(OAc)_2$ ((diacetoxyiodo)benzene, PIDA)/Lewis acid combination in order to access isoxazoline and pyrazoline cores. Based on allyl ketone oximes and allyl ketone tosylhydrazones, we have developed an alkene oxyamidation and amido-amidation protocol en route to accessing both isoxazoline and pyrazoline cores. Additionally, acetonitrile serves as both the solvent and an amine source in the presence of this PIDA/Lewis acid combination. This operationally straightforward and metal-free protocol provides an easy access to isoxazoline and pyrazoline derivatives.

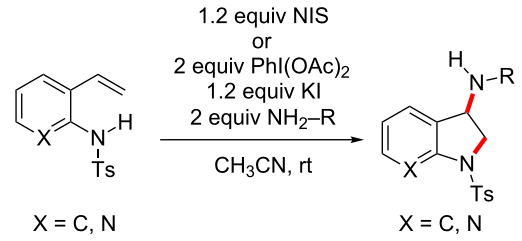
Introduction

Isoxazoline and pyrazoline-containing heterocycles are abundant in natural products and biologically active molecules [1-5]. Thus, these scaffolds are also important from the standpoint of pharmaceutical and medicinal chemistry [6-11]. Not surprisingly, the construction of diverse heterocyclic cores including isoxazolines and pyrazolines has garnered much attention from synthetic chemists [12-15]. Among precedent synthetic methods, the functionalization of unactivated olefins provides a rapid construction of different heterocycles [16,17]. More specifically, the formation of isoxazoline and pyrazoline cores via alkene heterofunctionalization of allyl ketone oximes and/or allyl ketone tosylhydrazones has been well documented [18-22].

For example, diverse halonium sources have been utilized for the synthesis of isoxazolines via halocyclization. Furthermore, transition metal-, visible light, and hypervalent iodine-mediated oxidative cyclization protocols provide isoxazoline backbones bearing diverse substituents such as –SR, -CF_3, -OH and halogens [23-27].

Results and Discussion

As depicted in Scheme 1, we have previously reported an inter-/intramolecular alkene diamination using either *N*-iodosuccinimide (NIS) or a phenyliodine diacetate (PIDA)/halide additive combination [28-30]. Vinylanilines and vinylaminopyridines in combination with electron-rich, Brønsted basic amines were converted to their corresponding indoline and azaindoline derivatives.

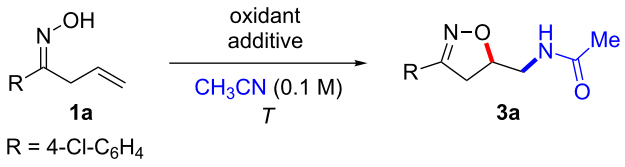


Scheme 1: Hypervalent iodine-mediated heterofunctionalization of terminal alkenes.

However, an attempted expansion of this methodology to allyl ketone oximes and allyl ketone tosylhydrazones proved unsuccessful under the previously reported reaction conditions (see Supporting Information File 1, Table S1). Upon optimization with various oxidants and additives screened, it was found that a Lewis acid additive can promote the olefin heterofunctionalization via a Ritter-type amidation using acetonitrile as both the solvent and the amine source. Interestingly, this hypervalent iodine-mediated Ritter-type oxyamidation of **1a** proved less efficient in the presence of solvent combinations with acetonitrile, despite acetonitrile being used in vast excess (see Supporting Information File 1, Table S1). Herein, we entail the first example of a hypervalent iodine(III)-mediated Ritter-type oxyamidation and amido-amidation of terminal alkenes in the presence of a Lewis acid.

Optimization studies of this Ritter-type oxyamidation commenced with oxidant screening in the presence of a Lewis acid (Table 1). Without oxidant, the Ritter-type oxyamidation still proceeded to give **3a** albeit in low yield (Table 1, entry 1). The background reaction mediated by a Lewis acid seemed plausible via an electrophilic activation of the double bond. When the reaction is performed in the presence of hypervalent iodine reagents such as PIFA ([bis(trifluoroacetoxy)iodo]benzene), $PhI(NPhth)_2$ and PIDP (bis(*tert*-butylcarbonyloxy)iodobenzene) much better yields were obtained (Table 1, entries 2–4), with $PhI(OAc)_2$ proving to be the best

Table 1: Hypervalent iodine-mediated Ritter-type alkene oxyamidation.

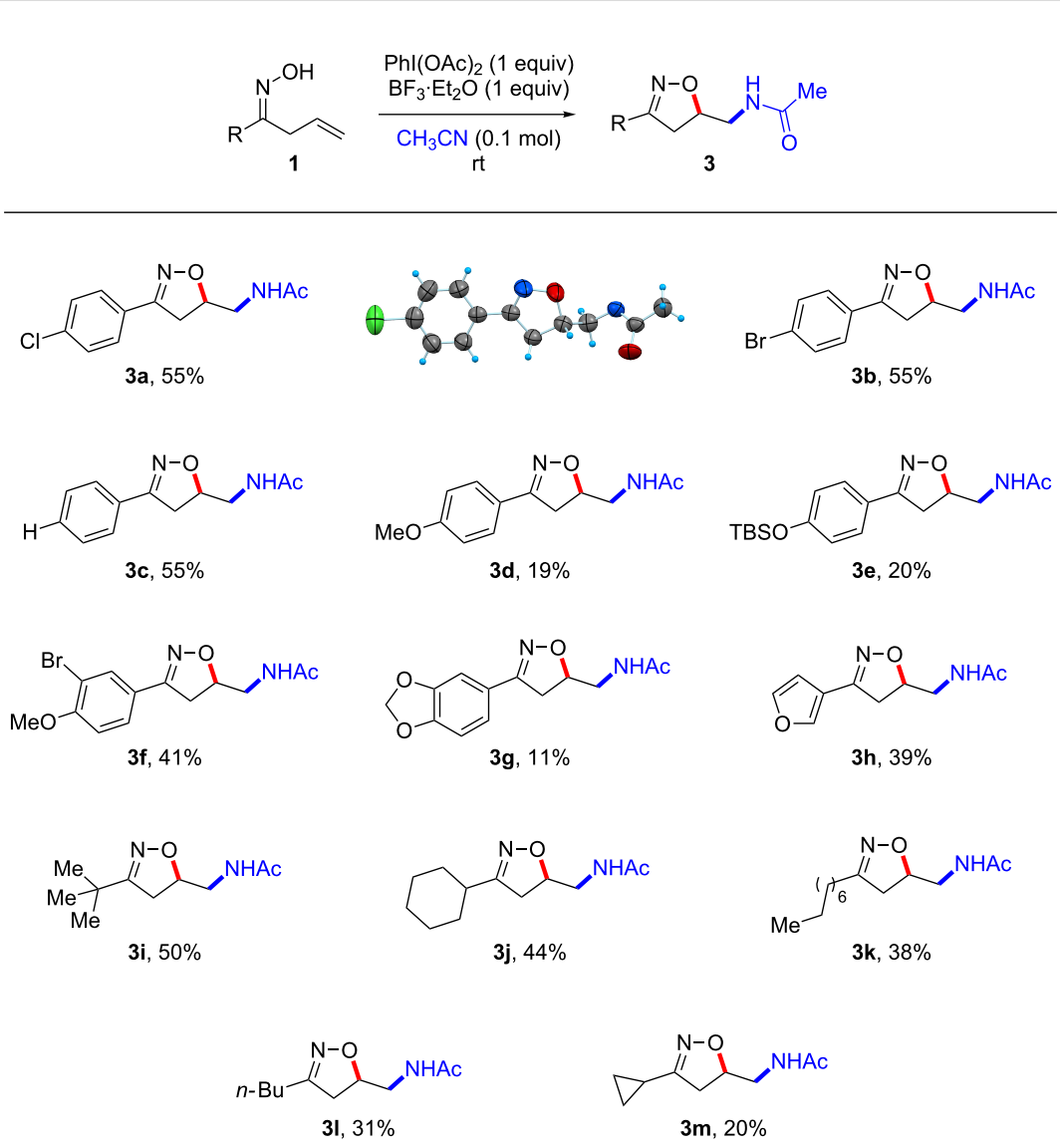


entry[a]	oxidant (equiv)	additive (equiv)	*T* (°C)	yield of **3a** (%)[b]
1	–	$BF_3{\cdot}OEt_2$ (1.0)	25	10
2	$PhI(OCOCF_3)_2$ (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	35
3	$PhI(NPhth)_2$ (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	42
4	PIDP (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	49
5	$PhI(OAc)_2$ (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	55
6	$PhI(OAc)_2$ (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	reflux	60
7	IBX (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	14
8	DMP (1.0)	$BF_3{\cdot}OEt_2$ (1.0)	25	14
9	$PhI(OAc)_2$ (1.0)	$AlCl_3$ (1.0)	25	0
10	$PhI(OAc)_2$ (1.0)	$SnCl_4$ (1.0)	25	0
11	$PhI(OAc)_2$ (1.0)	$TiCl_4$ (1.0)	25	12
12	$PhI(OAc)_2$ (1.0)	TMSOTf (1.0)	25	45
13	$PhI(OAc)_2$ (1.0)	–	25	0

[a]All reactions were performed on a 0.21 mmol scale (0.1 M) and with a standard 18 h reaction time. [b]Isolated yield.

(Table 1, entry 5). Refluxing conditions further improved the yield (Table 1, entry 6). Additionally, other cyclic hypervalent iodine oxidants such as IBX (2-iodoxybenzoic acid) and DMP (Dess–Martin periodinane) (Table 1, entries 7 and 8) gave similar yields to the background reaction. Lastly, a Lewis acid screen (Table 1, entries 9–12) was performed. Among the tested Lewis acids, $AlCl_3$, $SnCl_4$, $TiCl_4$, TMSOTf and $BF_3{\cdot}Et_2O$, the latter was found to be the best choice of additive. Remarkably, the activation of PIDA by a Lewis acid ($BF_3{\cdot}OEt_2$) seemed to be crucial for this Ritter-type oxyamidation to proceed (Table 1, entry 13). Based on these experiments, we chose the conditions outlined in Table 1, entry 5 for our further investigations due to the mild (room temperature) reaction conditions.

Next a series of allyl ketone oximes **1** were subjected to the optimized reaction conditions and the results are summarized in Scheme 2. Phenyl and electron-deficient aryl allyl ketone oximes showed robust reactivity as the corresponding products were obtained in good yields (**3a**–**c**, **3f**) [31]. However, electron-rich aryl allyl ketone oximes such as **1d**, **1e** and **1g** proved inferior. Also the furan-substituted allyl ketone oxime delivered the desired product **3h** albeit in a moderate yield. In addition, various alkyl allyl ketone oximes were investigated. While cyclopropyl allyl ketone oxime **1m** was converted to the corresponding isoxazoline **3m** in 20% yield, other alkyl allyl ketone oximes afforded higher yields of the desired products. This observation is ascribed differences in reactivity due to an in-



Scheme 2: Substrate scope of the Ritter-type oxyamidation: isoxazoline synthesis. All reactions were performed on a 0.21 mmol scale (0.1 M) and with a standard 18 h reaction time.

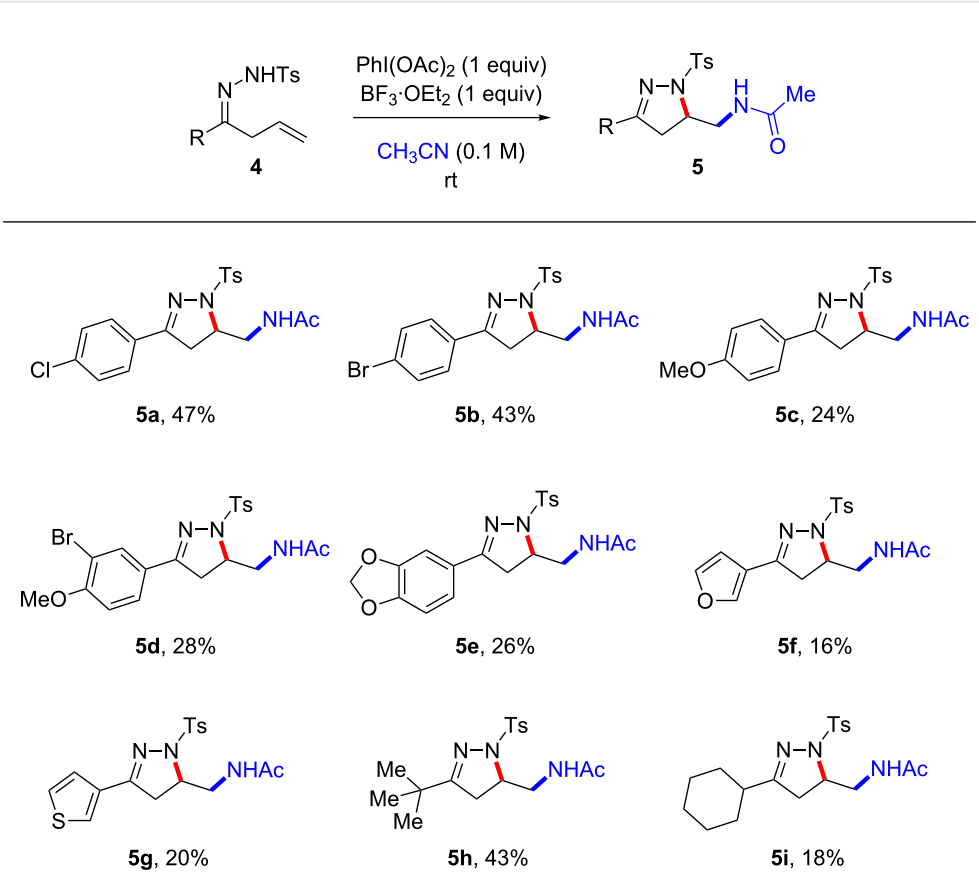
creased steric bulk at the α-position (*t*-Bu > *c*-Hex > *n*-Oct > *n*-Bu).

We next explored the hypervalent iodine-mediated Ritter-type amido-amidation reaction in the presence of a Lewis acid in order to access pyrazoline cores (Scheme 3). A series of allyl ketone tosylhydrazones **4** were subjected to the same reaction conditions. In general, the yields of the pyrazoline cores decreased marginally relative to the Ritter-type oxyamidation reaction. Monosubstituted aryl allyl ketone tosylhydrazones showed good reactivity and provided the pyrazoline heterocycles **5a**–**c** in moderate yields (24–47%). On the other hand, disubstituted aryl allyl ketone tosylhydrazones **4d** and **4e** yielded the corresponding products in 28% and 26%, respectively. The reaction of heteroaryl allyl ketone tosylhydrazones such as 3-furyl allyl ketone tosylhydrazone **4f** and 3-thiophenyl allyl ketone tosylhydrazone **4g** provided their desired products in low yields. Lastly, alkyl allyl ketone tosylhydrazones **4h** and 4**i** seemed to maintain of the trend in which increased reactivity is the result of increasing size of the alkyl side chain at the α-position (*t*-Bu > *c*-Hex).

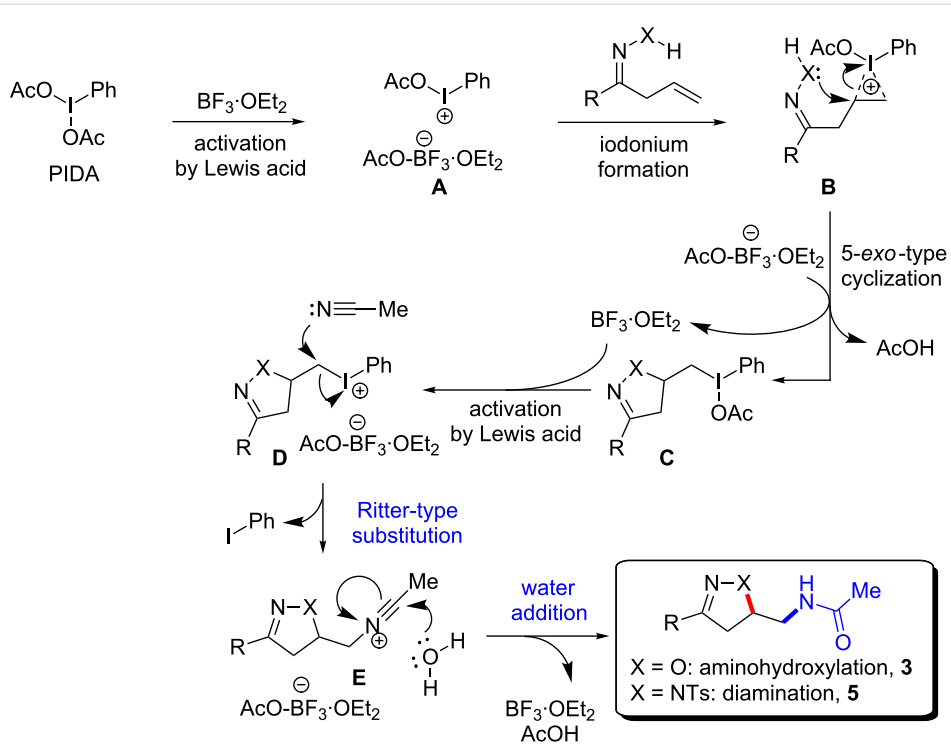
Based on these experimental data and previous reports [32,33], a plausible mechanism of the Ritter-type oxyamidation and amido-amidation is proposed in Scheme 4. First, an activation of hypervalent iodine(III) by the Lewis acid generates the active iodine(III) species **A** in situ. The resulting iodine(III) then, in turn, forms the electrophilic iodonium intermediate **B** with the terminal alkene of the allyl ketone oxime or allyl ketone tosylhydrazone. The subsequent 5-*exo*-type cyclization by nucleophilic attack on the iodonium then leads to the isoxazoline or pyrazoline cores (**C**) bearing the hypervalent iodine(III) group. Following iodine activation by the Lewis acid, the iodonium ion **D** undergoes nucleophilic substitution with excess acetonitrile to form intermediate **E**. Then water can add to the corresponding nitrilium and subsequent tautomerization delivers isoxazoline **3** (X = O) and pyrazoline **5** (X = NTs) via a Ritter-type oxyamidation and amido-amidation.

Conclusion

In summary, we have developed a hypervalent iodine(III)-mediated inter-/intramolecular Ritter-type oxyamidation and amido-amidation protocol in the presence of a Lewis acid. This trans-



Scheme 3: Substrate scope of Ritter-type amido-amidation: pyrazoline synthesis. All reactions were performed on a 0.21 mmol scale (0.1 M) and with a standard 18 h reaction time.



Scheme 4: Plausible mechanism of the hypervalent iodine(III)-mediated Ritter-type oxyamidation/amido-amidation in the presence of a Lewis acid.

formation provides direct access to diverse 5-acetaminomethyl substituted 2-isoxazoline/2-pyrazoline derivatives using acetonitrile as both the solvent and amine source.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-89-S1.pdf]

Acknowledgements

This work was supported by the research fund of Hanyang University (HY-2013-P).

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Imide arylation with aryl(TMP)iodonium tosylates

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Letter

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Keywords:
arylation; C–N coupling; diaryliodonium; hypercoordinate iodine; metal-free

Beilstein J. Org. Chem. **2018,** *14,* 1034–1038.
doi:10.3762/bjoc.14.90

Received: 23 February 2018
Accepted: 27 April 2018
Published: 11 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

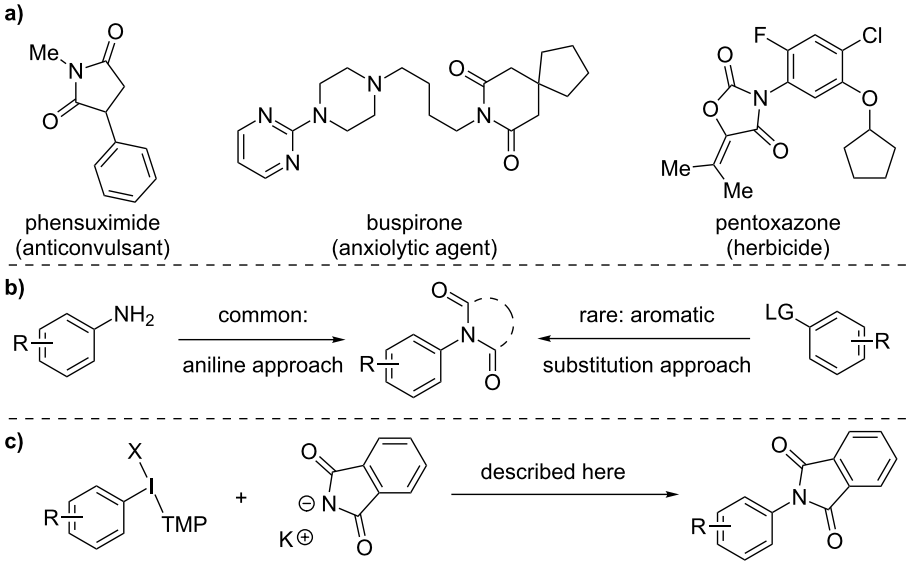
Herein, we describe the synthesis of *N*-aryl phthalimides by metal-free coupling of potassium phthalimide with unsymmetrical aryl(TMP)iodonium tosylate salts. The aryl transfer from the iodonium moiety occurs under electronic control with the electron-rich trimethoxyphenyl group acting as a competent dummy ligand. The yields of *N*-aryl phthalimides are moderate to high and the coupling reaction is compatible with electron-deficient and sterically encumbered aryl groups.

Introduction

Imides are important structural units in a range of approved pharmaceuticals and agrochemicals (Scheme 1a) [1]. Despite the general prevalence of imides, *N*-aryl imide derivatives are relatively rare in such compounds. We were surprised by this disparity, but found that a lack of methods to synthesize *N*-aryl imides may explain their scarcity; this is particularly true relative to other *N*-aryl compounds. The survey of methods revealed that the dominant approach to *N*-aryl imides is to employ aniline starting materials (Scheme 1b, left), as was done in the synthesis of pentoxazone and related herbicides [2]. The alternative aromatic substitution approach with imide anions (Scheme 1b, right) is hampered by their low nucleophilicity [3]. Therefore, transition metals feature prominently in such methods, but even recent examples employ stoichiometric metal mediators [4]. Metal-free methods by classic S_NAr are also attractive, but only possible on very electron-deficient arene substrates [5]. Diaryliodonium salts are useful reagents for metal-free aryl transfer [6-10] and Muñiz and co-workers have recently reported an elegant study on sterically controlled C–N coupling of 2,6-disubstituted aryl(phenyl)iodonium salts and imides [11]. We have been investigating the generality of electronically controlled aryl transfer from aryl(trimethoxyphenyl)iodonium salts [12-14] and describe here the development of a C–N coupling of a phthalimide anion with non-sterically biased aryl groups. The protocol is compatible with *ortho*-, *meta*-, and *para*-substitution on the aryl group and the phthalimide moiety may also provide access to anilines.

Results and Discussion

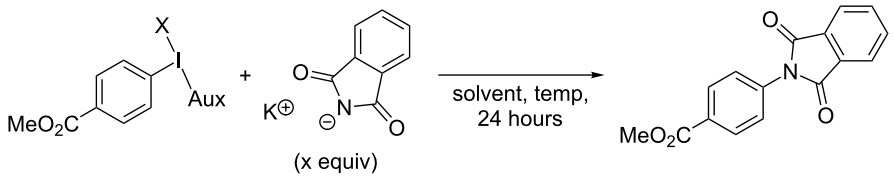
We initiated our optimization of the arylation of the potassium phthalimide nucleophile with diaryliodonium electrophiles by surveying several reaction conditions: dummy ligand (Aux),



Scheme 1: Imides as an important scaffold.

counter anion, solvent and volume, reaction temperature, and stoichiometry (Table 1). Consistent with an electronically controlled aryl transfer, the trimethoxyphenyl (TMP) auxiliary was superior to mesityl (Mes), phenyl (Ph), and anisyl (An) auxiliaries under several different reaction conditions (Table 1, entries 1–3; 11 and 12; 16 and 17). While the counter anion did

Table 1: Discovery and optimization of reaction conditions.[a]



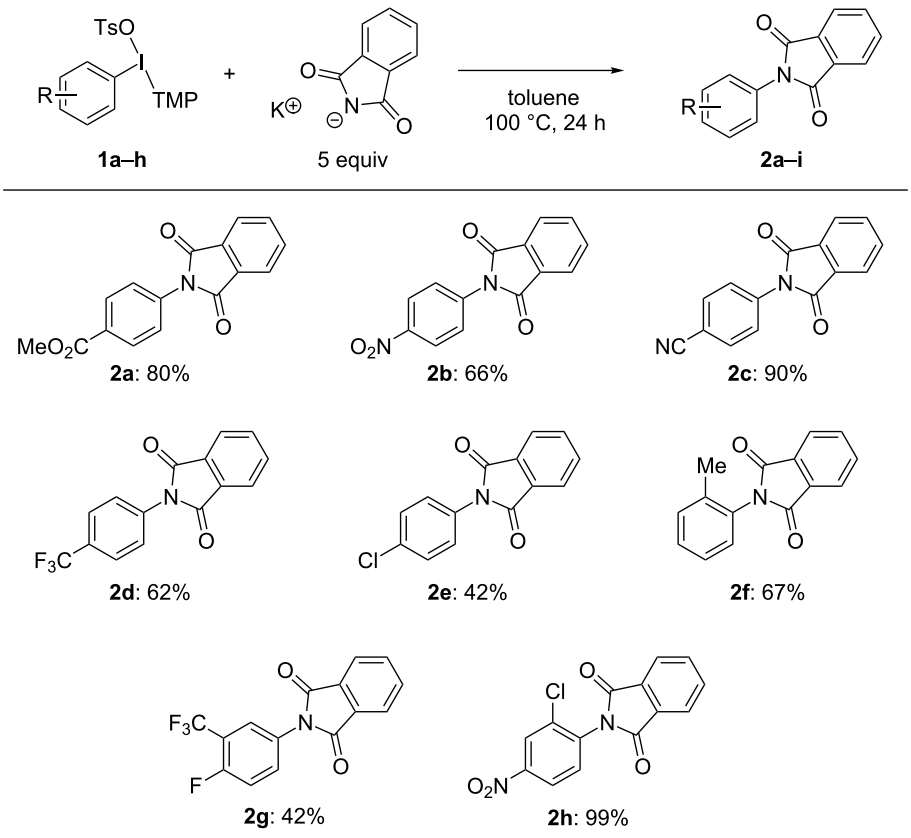
Entry	X group	Aux group	Phth. equiv	Solvent	Temp. (°C)	^{1}H NMR yield
1	TFA	Mes	2	DCE (1 mL)	70	27%
2	TFA	Ph	2	DCE (1 mL)	70	50%
3	TFA	TMP	2	DCE (1 mL)	70	52%
4	TFA	TMP	3	DCE (1 mL)	80	54%
5	OTs	TMP	3	DCE (1 mL)	80	62%
6	TFA	TMP	3	toluene (0.42 mL)	100	50%
7	OTf	TMP	3	toluene (0.42 mL)	100	56%
8	OTs	TMP	3	toluene (0.42 mL)	100	68%
9	OTs	TMP	3	toluene (0.5 mL)	90	64%
10	OTs	TMP	3	toluene (0.5 mL)	100	70%
11	OTs	Ph	3	toluene (0.5 mL)	100	23%
12	OTs	TMP	3	toluene (0.5 mL)	110	62%
13	OTs	TMP	1.1	toluene (0.5 mL)	100	39%
14	OTs	TMP	1.1	toluene (1 mL)	100	28%
15	OTs	TMP	1.1	toluene (1.5 mL)	100	16%
16	OTs	An	5	toluene (0.5 mL)	100	46%
17	OTs	TMP	5	toluene (0.5 mL)	100	75%

[a]Conditions: **1** (0.1 mmol, 1 equiv), potassium phthalimide (see table for equivalents), solvent (see table), temperature (see table), 24 hours.

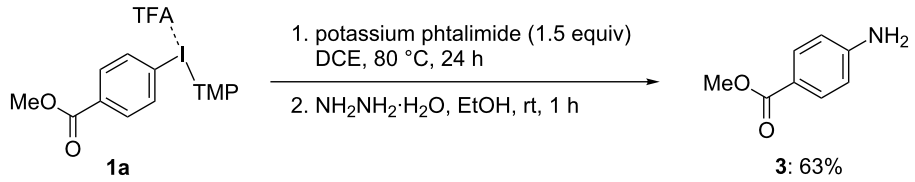
not exert a dramatic influence on the reaction yield, using tosylate (OTs) produced the highest yield in both DCE and toluene as solvent (Table 1, entries 4–8). Given our ability to readily access aryl(TMP)iodonium tosylate salts [12] we continued our optimization with these reagents. We observed a very narrow operating temperature with a maximum yield at 100 °C when toluene was used as solvent (Table 1, entries 9, 10, and 12). We also observed that the reaction yield decreases with dilution (Table 1, entries 13–15). Finally, the yield increases with increasing stoichiometry of phthalimide (Table 1, entries 10, 13, and 17). It is also important to note that under "optimal" conditions (Table 1, entry 17) we did not observe a Phth–TMP adduct. Moreover, we did observe essentially quantitative formation of TMP–I and therefore complete consumption of **1a** and high fidelity for aryl transfer selectivity. At this time we are unable to account for the remaining mass balance (≈25%) of the methyl benzoate moiety of **1a**. We have employed the conditions of entry 17 (Table 1) as our standard conditions to evaluate the scope of this reaction.

We have assessed the scope of compatible aryl groups under our optimal conditions (Scheme 2). Under electronic control, strong electron-withdrawing groups on the aryl ring lead to high yield of *N*-aryl phthalimide products (Scheme 2, **2a**–**d**, 66–90% yield). However, the TMP auxiliary also enables the coupling of phthalimide with moderately electron-deficient aryl groups. For instance the *p*-chlorophenyl moiety (**2e**) is coupled to phthalimide in moderate yield (42%). Additionally, we have observed that electronic and steric effects operate in concert to couple an *o*-tolyl (**2f**) moiety to phthalimide in high yield (67%). In this case, 2,6-disubstituted aryl groups are not required for a sterically controlled coupling. Finally, as an example two polysubstituted aryl groups are introduced in this coupling reaction, which are specifically enabled by the use of an unsymmetrical aryl(TMP)iodonium electrophile (Scheme 2, **2g** and **2h**, 42 and 99% yield, respectively).

The phthalimide moiety is well-recognized as an "NH_3" surrogate, and the products depicted in Scheme 2 may be deprotected to yield aniline derivatives. In a specific example, **1a** is reacted under modified conditions to yield **2a**. In this one-pot procedure, hydrazine in aqueous ethanol is added directly to the reaction mixture and aniline **3** is isolated in 63% yield from **1a** (Scheme 3).



Scheme 2: Scope of compatible aryl groups. Conditions: **1** (0.5 mmol, 1 equiv), potassium phthalimide (2.5 mmol, 5 equiv), toluene (2.5 mL), 100 °C, 24 hours. Isolated yields are reported.



Scheme 3: One-pot synthesis of anilines.

We have previously described the coupling of aryl(TMP)iodonium tosylates with azide nucleophiles [14]. Azide is a notably stronger nucleophile than phthalimide and it is interesting to compare the reaction of these two nucleophiles with **1a** under similar conditions (Table 2). The Mayr nucleophilicity constant of azide [15] is 20.5 and high yield (95%) is observed in a reaction with **1a** under relatively mild temperature (65 °C) and short reaction time (2 hours, Table 2, entry 1). The Mayr nucleophilicity constant for phthalimide is five-orders of magnitude lower (15.5) [3] and under similar conditions leads to trace product (Table 2, entry 2). In order to obtain a high yield of **2a**, albeit lower than given in entry 1, a higher temperature (100 °C) and a longer reaction time (24 hours) are required (Table 2, entry 3). This suggests that the contribution of nucleophilicity (via Mayr nucleophilicity constants) [16] may be useful in developing other coupling reactions with diaryliodonium electrophiles.

Conclusion

The coupling of both electron-deficient and sterically encumbered aryl groups with a phthalimide anion is achievable with aryl(TMP)iodonium tosylate salts. This is an electronically controlled coupling reaction that is enabled by the TMP auxiliary and complementary to the sterically controlled coupling previously reported. We anticipate that this reaction will find use as a starting point for the synthesis of *N*-aryl imides in a range of applications.

Supporting Information

Supporting Information File 1

General experimental details, procedures, tabulated spectroscopic data, and ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra of compounds **1g**, **2a**–**i**, and **3**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-90-S1.pdf]

Acknowledgements

We acknowledge Portland State University for financial support of this research.

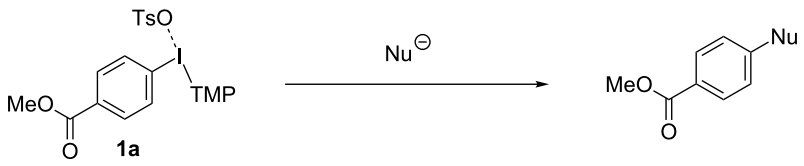
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Table 2: Comparison of nucleophilicity.



Entry	Nucleophile (Nu)	Mayr nucleophilicity	Temperature (°C)	Time	Yield
1	azide	20.5	65	2 hours	95%
2	phthalimide	15.5	65	2 hours	trace
3	phthalimide	15.5	100	24 hours	80%

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Hypervalent iodine-guided electrophilic substitution: *para*-selective substitution across aryl iodonium compounds with benzyl groups

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Full Research Paper

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Keywords:
electrophilic aromatic substitution; hypernucleofugality; hypervalent iodine; iodonio-Claisen; transmetallation

Beilstein J. Org. Chem. **2018,** *14,* 1039–1045.
doi:10.3762/bjoc.14.91

Received: 14 February 2018
Accepted: 25 April 2018
Published: 14 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

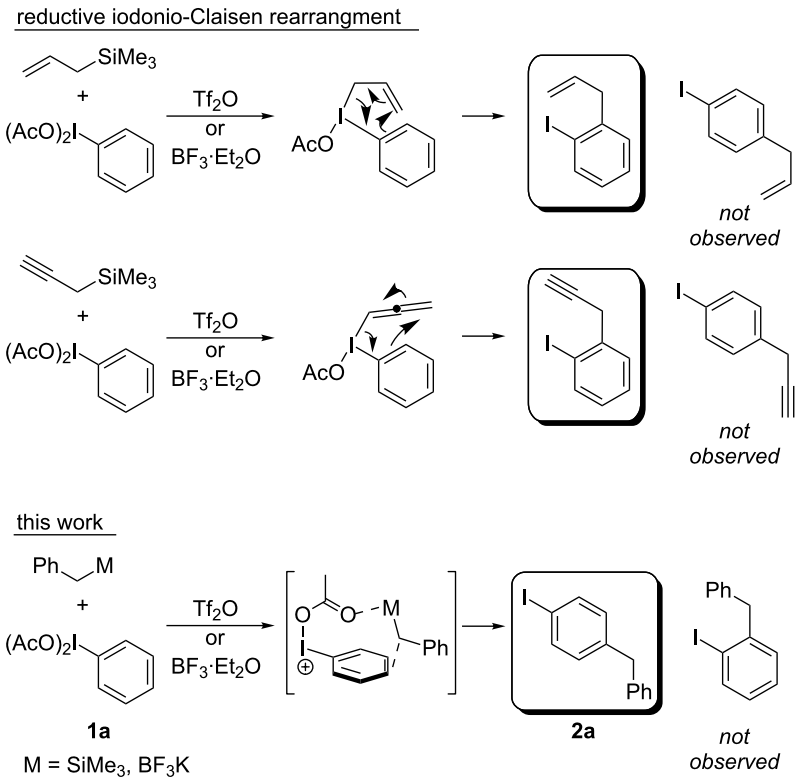
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Abstract

The reactivity of benzyl hypervalent iodine intermediates was explored in congruence with the reductive iodonio-Claisen rearrangement (RICR) to show that there may be an underlying mechanism which expands the reasoning behind the previously known C–C bond-forming reaction. By rationalizing the hypervalent iodine's metal-like properties it was concluded that a transmetallation mechanism could be occurring with metalloid groups such as silicon and boron. Hypervalent iodine reagents such as Zefirov's reagent, cyclic iodonium reagents, iodosobenzene/BF_3, and $PhI(OAc)_2/BF_3$ or triflate-based activators were tested. A desirable facet of the reported reaction is that iodine(I) is incorporated into the product thus providing greater atom economy and a valuable functional group handle for further transformations. The altering of the RICR's *ortho*-selectivity to form *para*-selective products with benzyl hypervalent iodine intermediates suggests a mechanism that involves hypervalent iodine-guided electrophilic substitution (HIGES).

Introduction

Hypervalent iodine compounds have been known for over a hundred years, but it was not until their renaissance in the 1990's that many of these useful reagents became a staple in synthetic chemistry laboratories [1,2]. Although hypervalent iodine reagents are commonly used in oxidation reactions, they have also found their own niche in useful C–C bond-formation and C–H activation reactions [3-5]. One such C–C bond formation (Scheme 1) was discovered by Oh and co-workers in 1988, and although it was based on previous work by the Ochiai group, the paper was the first to suggest a six-membered transi-



Scheme 1: Examples of the reductive iodonio-Claisen rearrangement compared to new reactivity seen with benzyl metalloids.

tion state indicative of a Claisen reaction [6,7]. In 1991, Ochiai and co-workers coined the phrase reductive iodonio-Claisen rearrangement (RICR) to describe the product selectivity they encountered [8].

More recently, exceptional progress has been made in investigating the RICR's substrate scope (electron-donating versus electron-withdrawing substituents on $PhI(OAc)_2$ (**1a**)), mechanism (deuterium labelling studies), product yields and selectivities based on appropriate solvents, temperatures, and Lewis acids [9-11]. A recent digest of RICR theorized an underlying mechanistic concept dubbed iodine-guided electrophilic aromatic substitution (IGEAS) [12]; the basis for which the work herein is titled. Other related work focused on the activation of hypervalent iodine [13], and a computational study that suggested a concerted iodination/deprotonation (CID) that is analogous to concerted metallation/deprotonation (CMD) for cationic hypervalent iodine [14]. These studies and others on the electrophilic nature and metal-like properties of iodine(III) were particularly significant in the development of the reaction reported in this communication [15,16].

A commonality in the RICR is that the proposed mechanisms involve an unstable allyl or propargyl hypervalent iodine intermediate. To the best of our knowledge, no allyl, propargyl, or alkyl hypervalent iodine species have been isolated at room temperature (besides fluorinated alkyl chains [17]), thus trapping an intermediate to validate the mechanism seemed unlikely. The process in which these hypervalent iodine intermediates form from metalloid substituted substrates has not been fully explored. It has been suggested that there may be a more all-inclusive iodine-guided mechanism that could account for a wider range of hypervalent iodine reactivity [12]. To this end, it is theorized that hypervalent iodine's metal-like properties allow it to undergo transmetallation with an appropriate metalloid substrate. This concept is counter to previous mechanisms in which the electrophilic hypervalent iodine reagent is attacked by unsaturated C–C bonds [18-22]. To show evidence for this transmetallation event, benzyl metalloid groups were used under the same reaction conditions as the RICR. The resulting diphenylmethane structure obtained after the C–C bond formation could have relevant medicinal applications since it is the core of many marketed pharmaceutical drugs with antihistaminic and anxiolytic properties [23-26].

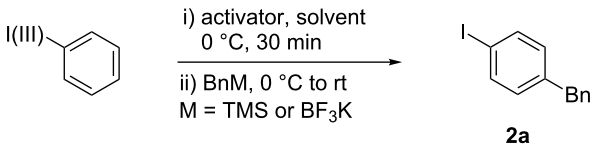
Results and Discussion

In the reaction with $PhI(OAc)_2$ (**1a**), 0.5 equiv triflic anhydride, and BnM (where M is TMS or BF_3K), a 72% yield of a coupled

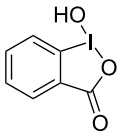
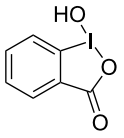
product was isolated, but the connection was unexpectedly at the *para*- not the *ortho*-position as the RICR might have predicted (Table 1). Further experiments of this hypervalent iodine-guided electrophilic substitution (HIGES) reaction were performed by varying the hypervalent iodine starting material, the activator, the solvent, and the temperature at which the activated hypervalent iodine reagent formed (Table 1). Varying the temperature at 25 °C, 0 °C, and −50 °C did not cause a substantial difference in yield, but at −50 °C the solubility of the activated hypervalent iodine species seemed poor upon visual inspection. It should be noted that the only other major products in the resultant reaction mixture were the decomposition of $PhI(OAc)_2$ (**1a**) or PhIO to PhI, and unreacted BnTMS or $BnBF_3K$. The results in Table 1 show that silyl groups seem to be superior to boron groups for the reaction to afford a good yield. The solvent choices were made based on low nucleophilicity and polarity being high enough to dissolve the hypervalent iodine starting material. Surprisingly, the protic solvent methanol worked to synthesize the product albeit in low yield. Another result is that by changing the metalloid substrate to $BnBF_3K$ (Table 1, entries 8–12), the reaction proceeds to give a product with generally lower yield. This fact is potentially explained by the partial solubility of trifluoroborates in the solvents used. The displacement of silyl and boron groups with hypervalent iodine seems to suggest that a transmetallation event from Si/B to I is occurring rather than an addition reaction to the unsaturation of the benzyl group followed by elimination of the metalloid group. The latter of which would be consistent with the mechanism currently theorized for making alkenyl and alkynyl hypervalent iodine species [18-22].

While investigating the substrate scope it was found that the substitution pattern is dependent upon the substituents on the I(III) reactant (Table 2). The trend of *para*-substitution to specific substituents appears to provide some evidence for a similar intermediate that relates to each reaction (for instance, Table 1, entry 1 compared to entry 8 or 9). Also, the optimization study showed comparable yields for activating reagents yet

Table 1: Optimization of HIGES reaction.[a]

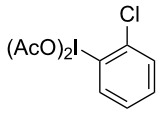
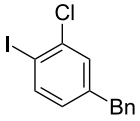
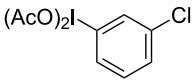
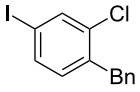
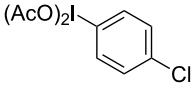
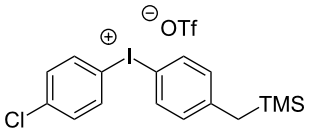
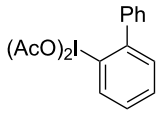
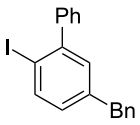
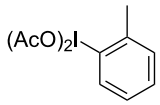
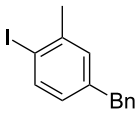
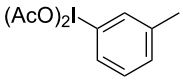
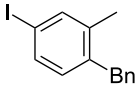
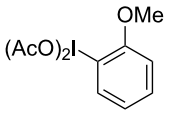
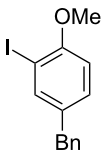
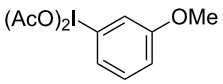
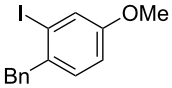
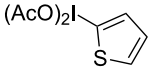
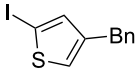
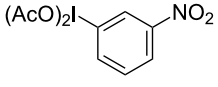
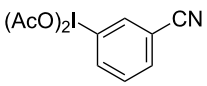


2a

Entry	Metalloid (M)	I(III) Reactant	Activator	Solvent	Yield (%)
1	TMS	$PhI(OAc)_2$	Tf_2O (0.5 equiv)	$CDCl_3$	72
2	TMS	$PhI(OAc)_2$	Tf_2O (1.0 equiv)	$CDCl_3$	73
3	TMS	$PhI(OAc)_2$	$BF_3{\cdot}Et_2O$ (1.0 equiv)	$CDCl_3$	64
4	TMS	PhIO	$BF_3{\cdot}Et_2O$ (1.0 equiv)	$CDCl_3$	80
5	TMS	PhIO	$BF_3{\cdot}Et_2O$ (1.0 equiv)	MeOH	13
6	TMS	 **3**	Tf_2O (1.0 equiv)	DCM	0
7	TMS	 **3**	Tf_2O (1.0 equiv)	CH_3CN	0
8	BF_3K	$PhI(OAc)_2$	Tf_2O (1.0 equiv)	CH_3CN	17
9	BF_3K	$PhI(OAc)_2$	Tf_2O (0.5 equiv)	CH_3CN	24
10	BF_3K	$PhI(OAc)_2$	$BF_3{\cdot}Et_2O$ (1.0 equiv)	$CDCl_3$	24
11	BF_3K	PhIO	$BF_3{\cdot}Et_2O$ (1.0 equiv)	$CDCl_3$	43
12	BF_3K	PhIO	Tf_2O (0.5 equiv)	CH_3CN	18
13	TMS	$PhI(OAc)_2$	none	$CDCl_3$	0

[a]All reactions used 0.055 M to 0.115 M I(III) reactant with the specified solvent and activator at 0 °C for 30 min followed by the addition of 1.0 equiv of BnTMS or $BnBF_3K$ and allowing the mixture to warm to room temperature. Isolated yields are reported.

Table 2: Substrate scope of substituted hypervalent iodine species.

Entry	I(III) Reactant	Product	Yield[a] (%)
1	 **1b**	 **2b**	2, 15[b,c]
2	 **1c**	 **2c**	6, 23[b,c]
3	 **1d**	 **2d**	23
4	 **1e**	 **2e**	25
5	 **1f**	 **2f**	52
6	 **1g**	 **2g**	45
7	 **1h**	 **2h**	28
8	 **1i**	 **2i**	4, 50[b]
9	 **1j**	 **2j**	76
10	 **1k**	NA	0
11	 **1l**	NA	0

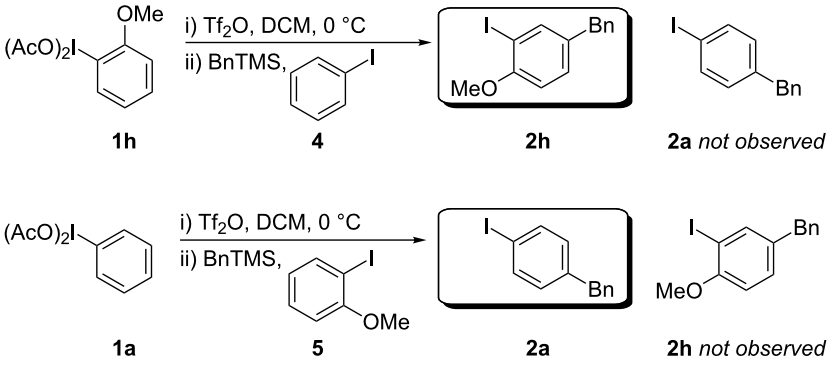
[a]All reactions used 0.055 M to 0.115 M I(III) reactant with 0.5 equiv of Tf_2O in CH_2Cl_2 or $CDCl_3$ at 0 °C for 30 minutes followed by 1.0 equiv of BnTMS unless otherwise specified. Isolated yields are reported. [b]Reaction used 1.0 equiv $BF_3{\cdot}Et_2O$ as an activator instead of Tf_2O. [c]NMR yield in $CDCl_3$.

the use of $BF_3{\cdot}Et_2O$ seemed to be superior to Tf_2O in the case of some I(III) reactants.

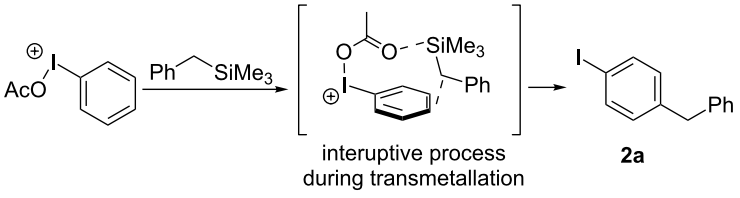
In all the reactions tested, there were no products formed with the *ortho*-substitution pattern in contrast to the RICR, however, it is clear that electron-donating groups influence the ring substitution. When weaker electron-donating and electron-withdrawing groups are used (Table 2, entries 1, 2, 4, 5 and 6), the C–C bond formation occurs *para* to the iodine, but when strong electron-donating groups are used (Table 2, entries 7 and 8) then the *para*-selectivity is dictated by that group. The effect of electron donation is also demonstrated in the thiophene (**1j**) group tested (Table 2, entry 9). In the case of electron-withdrawing groups, deactivation occurs and the only reaction is the decomposition of the I(III) to I(I) (Table 2, entries 10 and 11). The fact that no product was formed when using electron-withdrawing groups could also explain how the carbonyl of the cyclic iodonium (**3**) caused that specific reagent to fail (Table 1, entries 6 and 7). Several *para*-substituted I(III) reactants were attempted but all led to complex mixtures with the exception of the diaryliodonium triflate **2d** (Table 2, entry 3). These key features in the substitution pattern of the substrate scope led to experiments where tests were performed to better understand, if the HIGES reaction is a concerted mechanism, like RICR, or a stepwise process.

In the article and further in a footnote of Khatri and Zhu's publication [11] compelling evidence was shown by deuterium labelling studies supporting a concerted intramolecular mechanism (RICR) occurring rather than a stepwise intermolecular one. To corroborate their findings with our own, we investigated the HIGES reaction through crossover experiments which appear to conclude a concerted mechanism is occurring (Scheme 2). Two crossover reactions were performed for both iodobenzene (**4**) and 2-iodoanisole (**5**) to prevent substrate bias. One stepwise mechanism that the results in Scheme 2 eliminate is the possibility that the I(III) is decomposing to I(I) and then subsequently reacts in an electrophilic substitution on the transmetallated benzyl hypervalent iodine intermediate. If such a stepwise mechanism were to occur then one would expect to see an additional coupling product.

Based on the evidence provided by these crossover reactions it rules out such a stepwise reaction thus we propose a concerted mechanism. The mechanism speculated in Scheme 3 shows a concerted demetallation of the metalloid as the C–C bond is forming. Before the transmetallation of the metalloid group, an interruptive process could be occurring that provides an orbital overlap at the benzylic methylene and the *para*-position of the aryl iodine. In the case of entry 7 from Table 2, the methoxy group of **1h** directs the *para*-positioning in a similar manner,

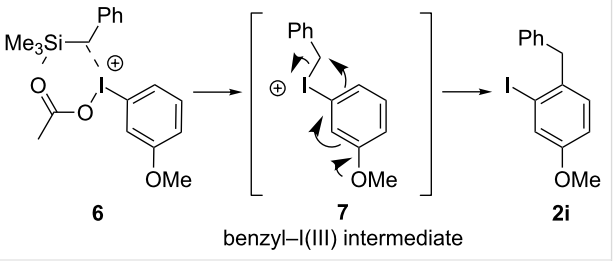


Scheme 2: Crossover reaction experiments.



Scheme 3: Suggested mechanism based on product formation and crossover experiments.

yet entry 8 from Table 2 would likely result from a different intermediate (Scheme 4).



Scheme 4: Proposed mechanism for the generation of **2i** from Table 2, entry 8.

In Scheme 4, a mechanism where a C–C bond forms by an intramolecular attack on a benzylic methylene with the hypernucleofuge attached (**6**). The mechanism in Scheme 4 shows the transmetallation occuring instead of being interrupted as in Scheme 3. The combination of both mechanisms (Scheme 3 and Scheme 4) explains how substitution *ortho* to the iodine (*para* to the methoxy group) could be generated from a benzyl–I(III) intermediate (**7**), while the products found from the interruptive transmetallation process obey the mechanism shown in Scheme 3. Another point to note is that since a product can form *ortho* to the iodine, sterics are unlikely the sole cause of the *para*-selectivity of the other reactions shown. Further investigation of in situ generated benzyl–I(III) and alkyl–I(III) intermediates is still being conducted in the research group.

Conclusion

Towards the goal of establishing a robust, novel methodology utilizing hypervalent iodine in C–C bond formation, a hypervalent iodine-guided electrophilic substitution (HIGES) reaction was discovered. The new reaction is thought to have some similarities to the reductive iodonio-Claisen rearrangement except that, with respect to the iodine, *para*-substituted instead of *ortho*-substituted products are mainly isolated. Future directions seek to elucidate the mechanism of the HIGES reaction and to develop the methodology into a reaction capable of synthesizing a variety of diphenylmethane structures.

Experimental

General procedure: The hypervalent iodine reagent (1.0 equiv) was added to the appropriate solvent. The reaction was cooled to 0 °C and the appropriate activator (0.5 or 1.0 equiv) added before allowing the reaction to stir for 30 min. The metalloid reagent, BnTMS or $BnBF_3K$ (1.0 equiv), was then added and allowed to warm to room temperature. The reaction mixtures were stirred for a period of 10 min to 2 h while monitoring the progress by TLC. The products were purified through PREP-TLC (hexane/ethyl acetate 90:10).

Supporting Information

Supporting Information File 1

Synthetic procedures, characterization data and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-91-S1.pdf]

Acknowledgements

This research was supported by Faculty Development Grants and a Frederick Bettelheim Research Award from Adelphi University to I. F. Dempsey Hyatt. We are grateful to Dr. Brian Stockman for his NMR expertise and Dr. Daniel A. Todd for acquisition of the high resolution mass spectrometry data at the Triad Mass Spectrometry Laboratory at the University of North Carolina at Greensboro.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.14.91

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Hypervalent iodine(III)-mediated decarboxylative acetoxylation at tertiary and benzylic carbon centers

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Full Research Paper

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Keywords:
acetoxylation; carboxylic acids; decarboxylation; hypervalent iodine; iodine

Beilstein J. Org. Chem. **2018,** *14,* 1046–1050.
doi:10.3762/bjoc.14.92

Received: 14 February 2018
Accepted: 27 April 2018
Published: 15 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The decarboxylative acetoxylation of carboxylic acids using a combination of $PhI(OAc)_2$ and I_2 in a CH_2Cl_2/AcOH mixed solvent is reported. The reaction was successfully applied to two types of carboxylic acids containing an α-quaternary and a benzylic carbon center under mild reaction conditions. The resulting acetates were readily converted into the corresponding alcohols by hydrolysis.

Introduction

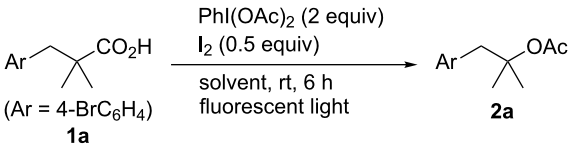
The decarboxylative functionalization of carboxylic acids and the derivatives thereof is an important transformation in organic synthesis. In recent years, increasing efforts have been devoted to the development of decarboxylative transformations [1-13], especially through radical decarboxylation processes, allowing an easy access to valuable compounds from readily available carboxylic acids. However, despite these advances, the oxidative decarboxylation coupled with C–O bond formation has received considerably less attention, even though it represents a promising strategy for the synthesis of valuable alcohol derivatives. One of the classical methods for the decarboxylative C–O bond formation of aliphatic carboxylic acids involves the use of stoichiometric amounts of heavy metal oxidants under high-temperature conditions [14,15]. Because these oxidants are typically highly toxic, their use has remained limited in organic synthesis. Barton et al. reported on the development of a practical method for the decarboxylative hydroxylation using thiohydroxamate esters as substrates [16]. Although the method was applicable to a broader range of substrates, the preparation of the activated ester is an intrinsic drawback to this procedure. While more convenient and practical methods for decarboxylative oxygenation, in which carboxylic acids are directly used as a substrate, have recently emerged, these methods have limited substrate scope [17-20].

A seminal work on decarboxylative functionalization in which a combination of $PhI(OAc)_2$ and molecular iodine (I_2) are used was reported by Suárez et al. [21]. The method features mild reaction conditions, simple operation, and the use of readily available and environmentally friendly oxidants. However, despite the great potential of this approach with respect to a decarboxylative C–O bond-forming reaction, the oxidation system was only applied to reactions of uronic acids and α-amino acids [22-24], and further applications have not been explored. We recently reported on the decarboxylative Ritter-type amination of carboxylic acids containing an α-quaternary carbon center using a combination of $PhI(OAc)_2$ and I_2 to produce the corresponding α-tertiary amine derivatives (Scheme 1) [25]. Mechanistic investigations indicated that the reaction proceeds via the formation of an alkyl iodide and the corresponding iodine(III) species as key intermediates. In this context, we concluded that the use of such an oxidation system, combined with the judicious choice of solvent, would enable a decarboxylative C–O bond forming reaction, namely acetoxylation, via the oxidative displacement of an iodine atom of the in situ generated alkyl iodide by $PhI(OAc)_2$ [26]. Herein, we report on the decarboxylative acetoxylation of carboxylic acids that contain an α-quaternary carbon center using $PhI(OAc)_2$ and I_2 in a CH_2Cl_2/AcOH mixed solvent (Scheme 1). In subsequent experiments, the method was also found to be applicable to the reaction of benzylic carboxylic acids. The acetates that were produced in the reaction were readily converted into the corresponding alcohols by hydrolysis.

Results and Discussion

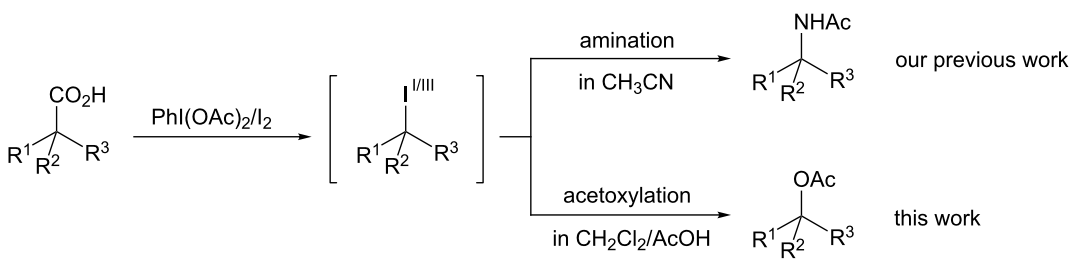
We started our investigation by examining the decarboxylative acetoxylation of 3-(4-bromophenyl)-2,2-dimethylpropanoic acid (**1a**) using $PhI(OAc)_2$ and I_2 as oxidants. When the reaction was conducted in AcOH, the corresponding acetate **2a** was obtained in low yield, and substantial amounts of the starting material were recovered, even though the use of AcOH as the solvent would be expected to promote the acetoxylation (Table 1, entry 1). Other solvents were then screened in attempts to improve the yield of the acetate **2a**. Halogenated solvents such as CH_2Cl_2, 1,2-dichloroethane, and chlorobenzene were found to be more effective in producing **2a** in moderate yields (Table 1, entries 2–4). The use of nitromethane also resulted in an improved yield of **2a** of 60% (Table 1, entry 5). Interestingly, screening of additional solvents revealed that a CH_2Cl_2/AcOH mixed solvent was suitable for this transformation, and a ratio of 1:1 (v/v) was found to be optimal, with **2a** being produced in 73% yield (Table 1, entries 6–8). When the reaction was performed at a higher concentration, the yield of product remained the same (Table 1, entry 9). Increasing the amount of oxidants used had only a slight effect on the product yield, with **2a** being

Table 1: Effect of solvents and reaction parameters on the decarboxylative acetoxylation.[a]



Entry	Solvent	Yield (%)[b]
1	AcOH	10
2	CH_2Cl_2	48
3	1,2-dichloroethane	46
4	chlorobenzene	42
5	CH_3NO_2	60
6	CH_2Cl_2/AcOH (1:1)	73
7	CH_2Cl_2/AcOH (3:1)	57
8	CH_2Cl_2/AcOH (1:3)	65
9[c]	CH_2Cl_2/AcOH (1:1)	74
10[d]	CH_2Cl_2/AcOH (1:1)	77
11[e]	CH_2Cl_2/AcOH (1:1)	75
12[f]	CH_2Cl_2/AcOH (1:1)	8
13[g]	CH_2Cl_2/AcOH (1:1)	0
14[h]	CH_2Cl_2/AcOH (1:1)	<5

[a]Reactions were conducted on a 0.2 mmol scale at a 0.2 M concentration. Unless otherwise noted, reactions were performed on the benchtop with a fluorescent light on the ceiling. [b]Determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c]The reaction was conducted at a 0.4 M concentration. [d]$PhI(OAc)_2$ (3 equiv) was used. [e]I_2 (1 equiv) was used. [f]I_2 (0.1 equiv) was used. [g]The reaction was conducted without I_2. [h]The reaction was conducted in the dark.



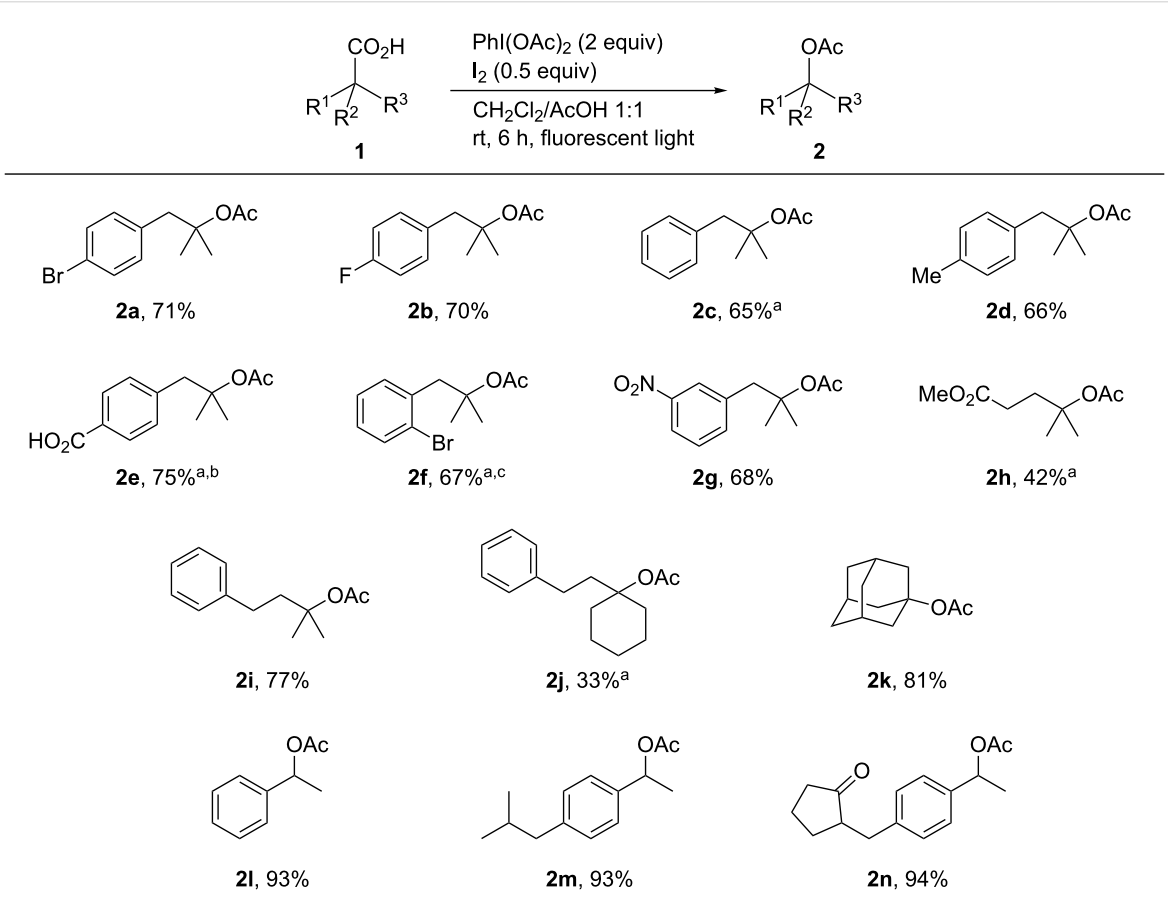
Scheme 1: Decarboxylative functionalization using $PhI(OAc)_2/I_2$ system.

produced in 77% yield, when 3 equiv of $PhI(OAc)_2$ were used (Table 1, entries 10 and 11). The reaction efficiency was significantly decreased with a catalytic amount of I_2, and no reaction was observed in the absence of I_2 (Table 1, entries 12 and 13). The reaction did not proceed in the dark, and most of the starting material was recovered (Table 1, entry 14). This result is consistent with a reaction proceeding via a light-induced radical decarboxylation process [21,25].

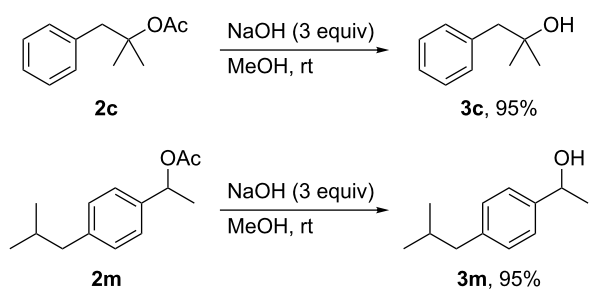
We next explored the scope of the decarboxylative acetoxylation reaction (Scheme 2). A variety of carboxylic acids containing α-quaternary carbon centers were efficiently converted into the corresponding acetates under mild reaction conditions [27]. Various functional groups, including bromo (**2a** and **2f**), fluoro (**2b**), carboxyl (**2e**), nitro (**2g**), and ester (**2h**) groups, were all well tolerated, providing the corresponding products in good yields. Notably, a carboxyl group on the phenyl ring was inert toward decarboxylation under the oxidation conditions used, allowing the acetate **2e** to be successfully synthesized. The acetoxylation of a cyclohexane framework was also achieved, but the yield of the product **2j** was somewhat lower than that of a non-cyclic **2i**. Using this protocol, 1-adamantanecarboxylic acid was smoothly transformed into the corresponding acetate **2k**. In addition to the reaction with respect to tertiary carbon centers, the present method was successfully applied to benzylic carboxylic acid derivatives. For example, commercially available arylpropanoic acids, which include ibuprofen (**1m**) and loxoprofen (**1n**), underwent decarboxylative acetoxylation in a highly efficient manner. It should be noted that, although benzylic C–H bonds are frequently incompatible with oxidative conditions, no products derived from benzylic C–H oxidation were observed in this reaction system.

Hydrolysis of the acetates **2c** and **2m** under basic conditions furnished the corresponding alcohols **3c** and **3m**, respectively, in nearly quantitative yields (Scheme 3). These results demonstrate that the present decarboxylative acetoxylation, followed by hydrolysis, offers an efficient and practical method for the synthesis of tertiary and benzylic alcohols.

The following experiments were performed in attempts to gain insights into the reaction pathway. Monitoring the reaction by

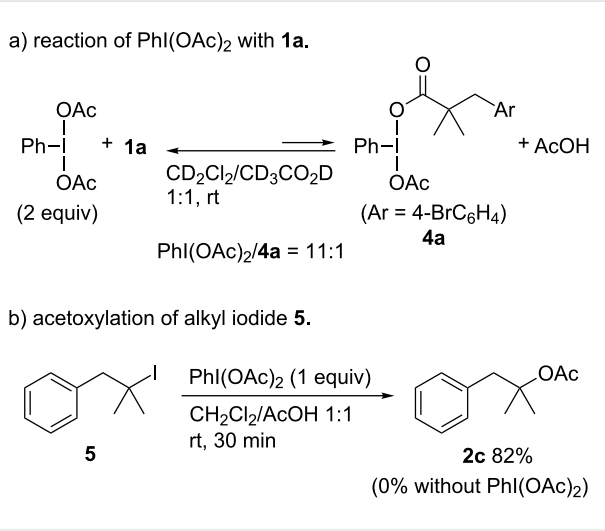


Scheme 2: Substrate scope. Reactions were conducted on a 0.5 mmol scale at a 0.2 or 0.4 M concentration on the benchtop with a fluorescent light on the ceiling. Yields are for isolated products. [a]$PhI(OAc)_2$ (3 equiv) was used. [b]I_2 (1 equiv) was used. [c]I_2 (0.75 equiv) was used.



Scheme 3: Hydrolysis of acetates.

^{1}H NMR spectroscopy showed for the reaction of a mixture of **1a** with two equimolar amounts of $PhI(OAc)_2$ in a CD_2Cl_2/CD_3CO_2D (1:1) mixed solvent the formation of a mixture of $PhI(OAc)_2$ and **4a** in a ratio of 11:1. This result indicates that ligand exchange between **1a** and $PhI(OAc)_2$ was suppressed due to the presence of an excess amount of acetic acid (Scheme 4a, see Supporting Information File 1 for details). Based on our previous work, we propose that the reaction pathway involves



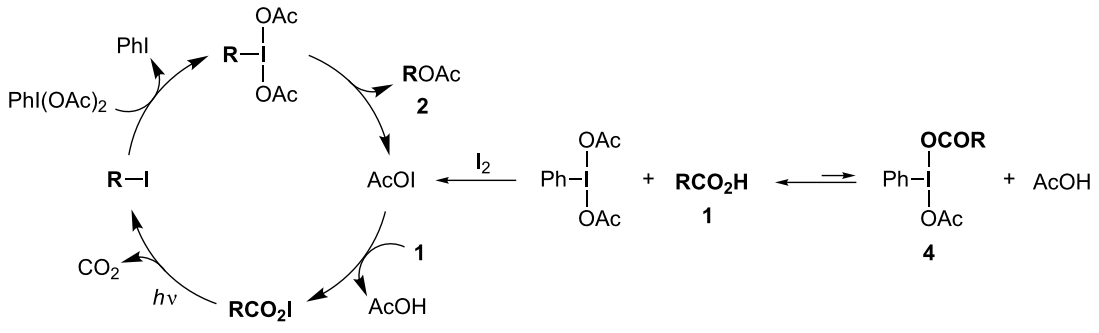
Scheme 4: Mechanistic investigations.

the formation of an alkyl iodide and the corresponding tertiary alkyl-λ^3-iodane species as intermediates [25]. To confirm the participation of these intermediates, the acetoxylation of a separately prepared sample of the tertiary alkyl iodide **5** was investigated. When **5** was treated with one equivalent of $PhI(OAc)_2$ in a CH_2Cl_2/AcOH mixed solvent at room temperature, the acetoxylation proceeded efficiently to provide **2c** (Scheme 4b). On the contrary, in the absence of $PhI(OAc)_2$, no products were formed, and the starting material was recovered. These results strongly support a reaction pathway involving the formation of an alkyl iodide, which is oxidized by $PhI(OAc)_2$ to the corresponding hypervalent iodine(III) species that then undergoes acetoxylation.

Based on the experimental results and our previous report [25], a proposed reaction pathway is depicted in Scheme 5. At the beginning of the reaction, $PhI(OAc)_2$ predominantly exists rather than **4**, as confirmed by NMR analysis. Therefore, in the initial stage, $PhI(OAc)_2$ preferentially undergoes decomposition with I_2 to provide acetyl hypoiodite (AcOI), which participates in the generation of RCO_2I by reacting with a carboxylic acid **1**. Meanwhile, RCO_2I is directly generated along with AcOI when **4** reacts with I_2. Subsequently, decarboxylative iodination of RCO_2I under irradiation with visible light affords an alkyl iodide intermediate, which is then rapidly oxidized by the remaining $PhI(OAc)_2$ to generate the corresponding alkyl-λ^3-iodane ($RI(OAc)_2$), which then undergoes the acetoxylation to afford the acetate **2** along with the regeneration of AcOI [28].

Conclusion

In conclusion, the decarboxylative acetoxylation of carboxylic acids containing α-quaternary and benzylic carbon centers was achieved by using a combination of $PhI(OAc)_2$ and I_2 in a CH_2Cl_2/AcOH mixed solvent. The key to the success of the reaction was the choice of a suitable solvent that enables an oxidative substitution of an alkyl iodide intermediate by $PhI(OAc)_2$. This operationally simple method under metal-free and mild reaction conditions can be used to produce a variety of



Scheme 5: Proposed reaction pathway.

acetates, which can be efficiently transformed into tertiary and benzylic alcohols.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-92-S1.pdf]

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP16K17868.

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26. Gallos, J.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1983,** 1999–2002. doi:10.1039/p19830001999
27. No product was observed when dodecanoic acid was used as a substrate.
28. The substitution by an acetate likely proceeds via a cationic intermediate. However, the detail of the mechanism as well as the stereochemical course of the step is not clear at this stage.

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doi:10.3762/bjoc.14.92

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Selective carboxylation of reactive benzylic C–H bonds by a hypervalent iodine(III)/inorganic bromide oxidation system

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Letter

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Keywords:
carboxylic acids; C–H activation; iodine; oxygenation; radicals

Beilstein J. Org. Chem. **2018,** *14,* 1087–1094.
doi:10.3762/bjoc.14.94

Received: 13 February 2018
Accepted: 26 April 2018
Published: 16 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

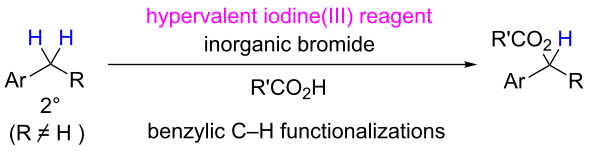
An oxidation system comprising phenyliodine(III) diacetate (PIDA) and iodosobenzene with inorganic bromide, i.e., sodium bromide, in an organic solvent led to the direct introduction of carboxylic acids into benzylic C–H bonds under mild conditions. The unique radical species, generated by the homolytic cleavage of the labile I(III)–Br bond of the in situ-formed bromo-λ^3-iodane, initiated benzylic carboxylation with a high degree of selectivity for the secondary benzylic position.

Introduction

The oxidative activation of a C(sp^3)–H bond in organic molecules to directly install various functional groups and new carbon–carbon networks is a topic of interest for researchers engaged in modern synthetic chemistry [1-8]. Benzylic oxidation is of particular interest because it is a convenient direct approach to arylcarbonyl compounds; it has a long history of research and development, and thus is included among the well-investigated C(sp^3)–H transformations [9-12]. To widen the scope, recent studies and reaction systems have been further elaborated to include elegant C–H coupling methodologies. Several important researches that provide a new benzylic C–H coupling strategy have been reported over the past few years, involving the promising catalytic activities of metal complexes [13,14]. On the other hand, reports aimed at realizing efficient and selective metal-free C(sp^3)–H transformations are rather limited; however, investigations by several research groups are still ongoing [15-30].

Hypervalent iodine reagents are now widely accepted as a safe replacement for certain heavy-metal oxidizers, such as lead, mercury, and thallium-based salts, due to their low toxicities, high stabilities, operational simplicities, and many other user-

friendly characteristics [31,32]. By virtue of their wide array of reactivity patterns, the controllable radical and single-electron-transfer (SET) reactivities [33-37] allow selective activation of the benzylic C(sp^3)–H bond for oxidative functionalization and coupling reactions. Initially, the SET oxidation ability of pentavalent iodine reagents, especially *o*-iodoxybenzoic acid (IBX), in benzylic oxidations was recognized for displaying the new reactivities of hypervalent iodine reagents toward C(sp^3)–H bonds [38,39]. By exploiting the radical behavior of trivalent iodine reagents discovered previously [40,41], the activation of trivalent iodine reagents, e.g., phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), and iodosobenzene, has since become a popular choice for benzylic oxidations, which further expanded the scope and availability of methods for direct C–H functionalization and several coupling reactions [42-50]. As such, we reported aqueous benzylic oxidations using polymeric iodosobenzene in the presence of inorganic bromide and montmorillonite-K10 [51]. In addition, a radical C–H activation strategy, using nonaqueous hypervalent iodine(III)/inorganic bromide systems that can work in organic solvents, was developed for the novel synthesis of lactones via the intramolecular oxidative cyclization of aryl carboxylic acids at the benzyl carbon under transition-metal-free conditions [52]. Based on our previous research and general interest in the unique reactivity of hypervalent iodine(III)–Br bonds [53-56], we report the results of our extensive study and optimization of our radical C–H activation strategy for the intermolecular oxidative coupling between the benzylic secondary C–H bond and the O–H group of carboxylic acids (Scheme 1).

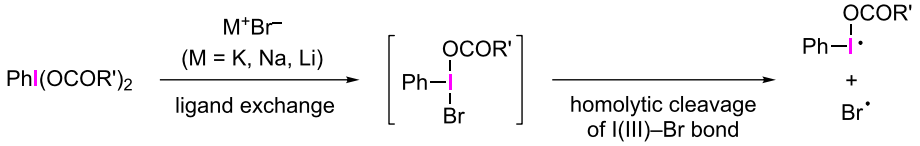


Scheme 1: Hypervalent iodine(III)-induced benzylic C–H functionalization for oxidative coupling with carboxylic acids.

Results and Discussion

Benzylic C–H carboxylation can provide a convenient route to benzyl esters from non-functionalized aromatic hydrocarbons, and thus has attracted continuous interest in the community of synthetic chemists. Significant advances for realizing such transformations have been made over the last decade, however, strategies that do not utilize a directing group to facilitate the activation of the benzylic C(sp^3)–H bond are rare [21,57-62]. Furthermore, only a limited number of transition-metal-free methods have been reported; successful examples include the Wohl–Ziegler-type conditions [21], the sodium bromate system [57] for the conversion of benzylmethyl groups, and the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [58] or catalytic tetrabutylammonium iodide with *tert*-butyl hydrogen peroxide for reactions with a large excess of aromatic hydrocarbons [59]. Other than these excellent examples of metal-free methods, two protocols using a hypervalent iodine reagent were reported, both of which include the formation of benzyl radicals during the key initial reaction step. Togo and co-workers developed a reaction system consisting of stoichiometric amounts of PIDA with catalytic amounts of molecular iodine and *p*-toluenesulfonamide for the benzylic acetoxylation and benzoyloxylation of alkylbenzenes, where an in situ-generated sulfonamidyl radical is the essential radical mediator that effectively abstracts the benzylic hydrogen [49]. More recently, Maruoka et al. succeeded in the photolytic benzylic C–H bond oxygenation of alkylbenzenes initiated by the decomposition of PIFA to form the trifluoroacetoxy radical under visible light irradiation [50].

Our approach for the generation of radical species for the benzylic carboxylation using a hypervalent iodine reagent relies on the unique reactivity of the hypervalent iodine(III)–bromine bond with the following mechanistic principles: As illustrated in Scheme 2, ligand exchange at the iodine(III) center of the phenyliodine(III) dicarboxylate with the bromide ion can gradually produce the corresponding bromo-λ^3-iodane in the first step [63,64]. This unstable hypervalent iodine(III) species subsequently decomposes by facile homolytic cleavage of the I(III)–Br bond, generating the iodanyl and bromo radicals [51,52]. It appears that these radicals can then selectively abstract the benzylic hydrogen atom of organic substrates, even in the presence of a wide variety of functional groups, such as electrophilic aromatic rings, non-acidic carbonyl groups, and suitable oxygen, nitrogen, and sulfur functionalities. Carbonyloxy radicals derived from typical hypervalent iodine(III) carboxylates by photolysis and other conditions [65-68] are



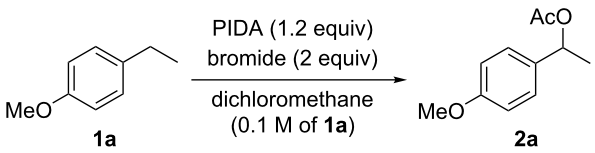
Scheme 2: Radical reactivities of the I(III)–Br bond generated from PIDA.

known to undergo irreversible decarboxylation [69,70]. Therefore, the formation of carbonyloxy radicals must be avoided to prevent non-productive side reactions and achieve the desired benzylic C–H transformations for an extended series of carboxylic acids.

Based on these considerations, we performed an optimization study using 1-ethyl-4-methoxybenzene (**1a**) as a model substrate for the oxidative C–H coupling of the benzyl group with acetic acid derived from PIDA (Table 1). Reactions using PIDA with finely powdered inorganic bromide in degassed dichloromethane containing 0.1 M of the substrate were first examined at room temperature. The use of potassium bromide [52] afforded modest yields of the carboxylation product **2a** (Table 1, entry 1). Interestingly, a dramatic influence was observed when altering the bromide source to other types; the use of lithium bromide or organic bromides, e.g., bromotrimethylsilane and tetraethylammonium bromide, instead of the potassium salt, were unsuccessful in forming the carboxylate **2a** (Table 1, entries 2–4). The reason for this behavior was thought to be because lithium bromide or organic bromides in combination with PIDA generated the electrophilic 'Br^+' species [71] and molecular bromine [72], or hypobromite and bisacetoxy bromate(I) [73], respectively, rather than the desired bromo radical. As a result, bromination at the aromatic ring of substrate **1a** occurred when LiBr was used (Table 1, entry 2), while no reaction was observed in the other two trials using organic bromides (Table 1, entries 3 and 4). At the boiling temperature of dichloromethane, ca. 40 °C, the reaction time was shorter (Table 1, entry 5). Aiming to improve the yield of the reaction, we then examined other inorganic bromides, among which sodium bromide was the most promising, and product **2a** was obtained in 76% yield (Table 1, entry 6). By adding extra acetic acid, the benzylic acetoxylation was further improved to provide an 86% yield of product **2a**. Since most of the sodium bromide was present as a precipitate in the flask, the reaction was found to work even with catalytic amounts of the bromide activator (Table 1, entry 8). Other reaction factors, such as solvent, concentration, reaction time, and reagent quantities, were screened and, eventually, the reaction conditions of entries 6 and 7, which consisted of 1.2 equiv of PIDA with 2 equiv of sodium bromide in dichloromethane (0.1 M of the reaction substrate) at 40 °C, were determined to be the best in terms of product yield. No reaction was observed in the absence of sodium bromide (Table 1, entry 9) and other representative hypervalent iodine(III) reagents, such as PIFA and PhI(OH)OTs, and pentavalent Dess–Martin periodinane and IBX, were inferior for this carboxylation when compared to PIDA.

We then examined the reactivity of different benzyl groups under the optimized reaction conditions for the radical activation system for C–H acetoxylations (Table 2). When the reactions were performed using ethylbenzene (**1b**) and its derivatives without an electron-donating group (**1c**–**e**), the corresponding benzyl bromides were mainly obtained along with a small amount of the target C–H acetoxylation product; this by-product formation might imply the intermediacy of these organic bromides before the production of benzyl acetates. Hence, the reaction system was modified to include zinc(II) acetate [74] for substrates **1b**–**d** and benzyl acetates **2b**–**d** were

Table 1: Reaction optimization of benzylic C–H acetoxylation using PIDA.

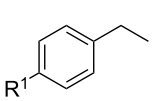
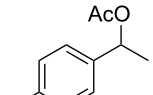
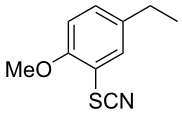
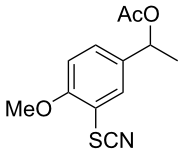
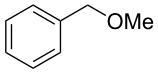
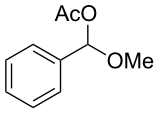
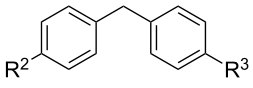
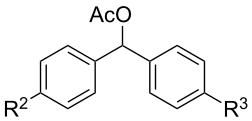
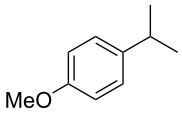
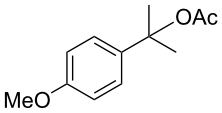


1a **2a**

entry	bromide	conditions	yield of **2a** (%)
1	potassium bromide	rt, 6 h	55
2	lithium bromide	rt, 20 h	11[a]
3	bromotrimethylsilane	rt, 20 h	nd
4	tetraethylammonium bromide	rt, 20 h	nd
5	potassium bromide	40 °C, 4 h	57
6	sodium bromide	40 °C, 4 h	76
7[b]	sodium bromide	40 °C, 3 h	86[c]
8[b]	sodium bromide[d]	40 °C, 3 h	72
9	none	40 °C, 3 h	nd

[a]Mainly bromination of the aromatic ring was observed. [b]Acetic acid (20 equiv) was added. [c]The reaction was performed on a 10 mmol scale. [d]Catalytic amounts of sodium bromide were added (0.5 equiv). nd: not determined.

Table 2: Substrate screening for benzylic C–H acetoxylation by the PIDA/NaBr system.[a]

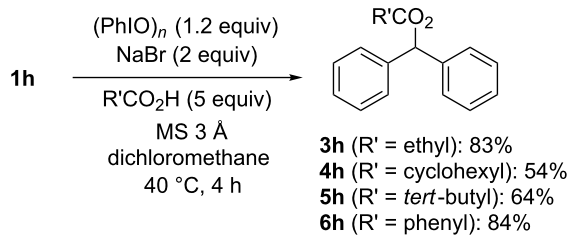
entry	substrate	product	time	yield of **2** (%)
	 **1b–e**	 **2b–e**		
1	**1b** (R^1 = H)	**2b** (R^1 = H)	20 h	55[b]
2	**1c** (R^1 = Ph)	**2c** (R^1 = Ph)	20 h	91[b]
3	**1d** (R^1 = Br)	**2d** (R^1 = Br)	20 h	65[b]
4	**1e** (R^1 = CO_2CH_3)	**2e** (R^1 = CO_2CH_3)	48 h	nd[c]
5	 **1f**	 **2f**	20 h	62
6	 **1g**	 **2g**	4 h	68
	 **1h–j**	 **2h–j**		
7	**1h** (R^2 = R^3 = H)	**2h** (R^2 = R^3 = H)	4 h	90
8	**1i** (R^2 = R^3 = F)	**2i** (R^2 = R^3 = F)	4 h	93
9	**1j** (R^2 = Ph, R^3 = H)	**2j** (R^2 = Ph, R^3 = H)	4 h	45
10	 **1k**	 **2k**	4 h	nd

[a]Conditions: PIDA (1.2 equiv), sodium bromide (2 equiv), and acetic acid (20 equiv) in dichloromethane (0.1 M of substrate **1**) at 40 °C. nd: not determined. [b]Zinc acetate (1 equiv) was added for the conversion of the benzyl bromide byproduct to the desired benzyl acetates **2b**–**d**. [c]The corresponding benzyl bromide was obtained in 60% yield.

obtained in moderate to excellent yields after prolonged reaction times (Table 2, entries 1–4). Furthermore, iterative oxidative coupling at the aromatic and benzylic C–H position using hypervalent iodine chemistry is possible, and 1-ethyl-4-methoxy-3-thiocyanatobenzene (**1f**), prepared from 1-ethyl-4-methoxybenzene (**1a**) through the hypervalent iodine(III)-induced aromatic cation radical coupling with thiocyanate [75,76], similarly acetoxylated under the standard reaction conditions without zinc(II) acetate (Table 2, entry 5). The acetoxylation at the activated benzyl carbon adjacent to an oxygen atom proceeded smoothly as shown by the formation of the *pseudo* acetal **2g** (Table 2, entry 6). Diphenylmethane and its derivatives were very good substrates for our system and were less sensitive to the electronic effects of the aromatic ring substituents than in other previously described compounds, showing higher reactivity and chemoselectivity of the benzylic position (see ref. [51]). The reactions of substrates **1h**–**j** proceeded without the use of zinc(II) acetate (see Table 2, entries 7–9 versus entry 2).

The installation of other carboxylic acids, such as propionic acid, cyclohexyl carboxylic acid, pivalic acid, and benzoic acid,

were also possible by simply replacing PIDA with iodosobenzene (Scheme 3). Here, the addition of 3 Å molecular sieves was essential for removing water derived from the iodosobenzene and to suppress the benzylic oxidation forming aryl ketones [52]. Note that the successful coupling of a range of secondary and tertiary carboxylic acids now supports the direct and selective C–H bond activation at the benzyl position by avoiding the formation of carbonyloxy radicals, which are susceptible to decarboxylation. In addition, it was revealed that more acidic benzoic acids were also suitable substrates for our method. However, even more acidic acids, such as trifluoroacetic acid and methanesulfonic acid, were not effectively introduced by our benzylic C–H carboxylation procedures.



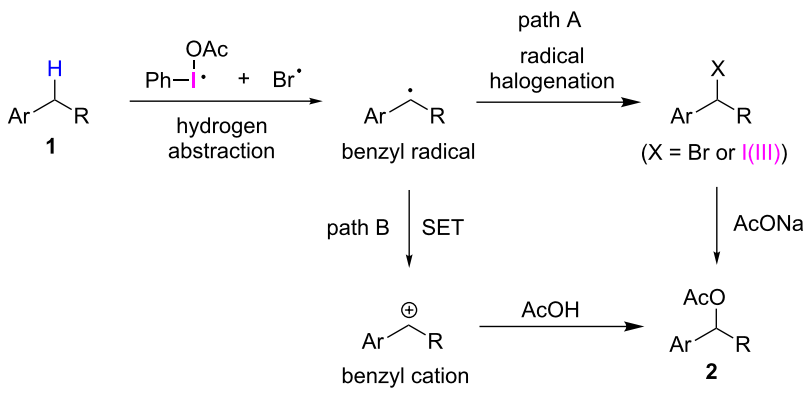
Scheme 3: Benzylic C–H carboxylations by the iodosobenzene/NaBr system.

We believe that the reaction mechanism involves a benzyl radical formation as the initiating step (Scheme 4). Either the iodanyl radical or the bromo radical may cause the H-atom abstraction generating the benzyl radical, and the resulting benzyl radical is trapped by the persistent bromo radical, giving rise to the observed benzyl bromide intermediate (path A). Alternatively, the benzyl radical formed in situ couples with the iodanyl radical to give the *pseudo* halide, benzyl-λ^3-iodane, which is more reactive to nucleophilic substitution by a carboxylic acid [77,78]. Another possible course of the reaction mechanism assumes the formation of a benzyl cation, resulting from the SET oxidation of the benzyl radical, probably by the iodanyl radicals (path B).

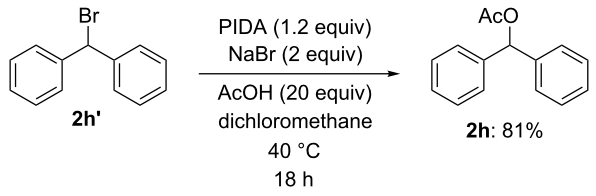
A significant point of interest in this study is understanding the relative reactivity of the iodanyl radical versus the bromo radical. To gain more information about this, we confirmed the chemoselectivity of our reaction system towards different classes of benzyl carbon atoms. To this end, the clear direction to the secondary benzylic position in substrates **1a–j** [51], and the lack of benzylic acetoxylation of the tertiary carbon in substrate **1k** (see Table 2) are noteworthy. As bromo radicals are known to readily abstract hydrogen atoms at the tertiary carbon centers [79], the results suggest a predominant participation of the iodanyl radical as the hydrogen atom abstractor for the selective secondary benzylic C–H bond activation in our reaction. It seems that the iodanyl radical is more reactive than the bromo radical and a large-size effect of the hypervalent iodine species establishes the selectivity over the electronically favored tertiary radical formation. A similar trend in the secondary-preferential hydrogen abstraction at the sp^3 carbons was recently reported by Maruoka and co-workers for the C–H oxidations of unreactive alkanes by iodanyl radicals [80]. Based on these observations, the reaction mechanism via path A that involves the formation of benzyl bromides (X = Br) seems to be more reasonable for our benzylic C–H carboxylation system based on the hypervalent iodine(III) reagent/inorganic bromide combination. This mechanistic course was also partially supported by the control experiment, whereby one of the separately prepared bromides, **2h'**, was gradually transformed into the corresponding acetate **2h** in good yield under the radical C–H acetoxylation reaction conditions (Scheme 5).

Conclusion

In conclusion, we have described the optimization and scope of an oxidation system for benzyl C–H carboxylation that utilizes



Scheme 4: Outline of the proposed reaction mechanism for the PIDA/NaBr system.



Scheme 5: Reaction of benzyl bromide **2h'** under radical C–H acetoxylation conditions.

the radical reactivity of a hypervalent iodine(III) reagent produced under suitable conditions. The mechanistic information obtained in this study indicates that iodanyl radicals, generated by the homolytic cleavage of the labile I(III)–Br bond of in situ formed bromo-λ^3-iodane, are the key initiators for this benzylic carboxylation, and they show a high degree of selectivity towards the secondary benzylic position under mild reaction conditions.

Experimental

Representative experimental procedure for the benzylic C–H acetoxylation by the PIDA/NaBr system

In a flame-dried two-necked round-bottomed flask, under nitrogen, phenyliodine(III) diacetate (PIDA, 193 mg, 0.6 mmol) and finely powdered sodium bromide (103 mg, 1.0 mmol) were subsequently added to a stirred solution of arylalkane **1** (0.50 mmol) and acetic acid (0.57 mL, ca. 10 mmol) in dry dichloromethane (5 mL). Then the mixture was vigorously stirred at 40 °C with or without zinc acetate (92 mg, 0.5 mmol). After checking the reaction completion by TLC, saturated aqueous sodium carbonate was added to the mixture and the resulting solution was stirred for an additional 5 min. The organic layer was separated, washed again with saturated aqueous sodium carbonate, then with dilute aqueous sodium thiosulfate, and was dried over anhydrous sodium sulfate. After removal of the solvents, the residue was subjected to column chromatography on silica gel (eluents: *n*-hexane/ethyl acetate) to give the benzyl acetate **2** in the indicated yield; the physical and spectral data of the reported compounds (**2a**–**d**, **g**–**j**) matched those of the authentic samples (see Supporting Information File 1).

1-(4-Methoxy-3-thiocyanatophenyl)ethyl acetate (2f). Yield 62% (156 mg). Obtained as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (d, J = 6.8 Hz, 3H), 2.05 (s, 3H), 3.89 (s, 3H), 5.80 (q, J = 6.8 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.32 (dd, J = 8.3, 1.9 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.1, 56.3, 71.3, 110.3, 111.2, 113.3, 127.6, 128.7, 135.8, 156.0, 170.2 ppm; IR (KBr): 2984, 2158, 1741, 1603, 1499, 1370, 1291, 1242, 1208, 1062, 1023 cm^{-1}; HRMS (MALDI): $[M + Na]^+$ calcd for $C_{12}H_{13}NO_3SNa$, 274.0507; found, 274.0508.

Representative experimental procedure for the benzylic C–H carboxylation by the iodosobenzene/NaBr system

In a flame-dried two-necked round-bottomed flask, under nitrogen, iodosobenzene (132 mg, 0.6 mmol) and finely powdered sodium bromide (103 mg, 1.0 mmol) were subsequently added to a stirred solution of diphenylmethane (**1h**, 84 mg, 0.50 mmol) and the carboxylic acid (ca. 2.5 mmol) with freshly-dried molecular sieves 3 Å (ca. 300 mg) in dry dichloromethane (5 mL). Then the mixture was vigorously stirred at 40 °C. After checking the reaction completion by TLC, saturated aqueous sodium carbonate was added to the mixture and the resulting solution was stirred for an additional 5 min. The organic layer was separated, washed again with saturated aqueous sodium carbonate, then with dilute aqueous sodium thiosulfate, and was dried over anhydrous sodium sulfate. After removal of the solvents, the residue was subjected to column chromatography on silica gel (eluents: *n*-hexane/ethyl acetate) to give the benzylic C–H carboxylation product in the indicated yield; the physical and spectral data of the carboxylation products (**3h, 4h, 5h, 6h**) matched those previously reported (see Supporting Information File 1).

Supporting Information

Supporting Information File 1

Starting materials and Copies of ^{1}H and ^{13}C NMR spectra of all products.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-94-S1.pdf]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (A) to Y.K. from JSPS and a Grant-in-Aid for Encouragement of Young Scientists (A) and Scientific Research (C) to T.D. from JSPS, and Ritsumeikan Global Innovation Research Organization (R-GIRO) project. T.D. thanks the research fund of the Asahi Glass Foundation.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.14.94

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Iodine(III)-mediated halogenations of acyclic monoterpenoids

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Full Research Paper

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Keywords:
halogenation; hypervalent iodine; monoterpenes

Beilstein J. Org. Chem. **2018,** *14,* 1103–1111.
doi:10.3762/bjoc.14.96

Received: 06 February 2018
Accepted: 26 April 2018
Published: 18 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Five different halofunctionalizations of acyclic monoterpenoids were performed using a combination of a hypervalent iodine(III) reagent and a halide salt. In this manner, the dibromination, the bromo(trifluoro)acetoxylation, the bromohydroxylation, the iodo(trifluoro)acetoxylation or the ene-type chlorination of the distal trisubstituted double bond occurred with excellent selectivity and moderate to good yields.

Introduction

In nature, mostly in marine environments, halogenated compounds are produced by means of various enzymes that rely on widely available halides as feedstock [1]. These halogenases can perform an extremely wide array of electrophilic halogenations on a myriad of substrates with exquisite chemo-, stereo- and enantioselectivities that remain extremely challenging to rival for the chemist. When applied to terpenic feedstock, they give birth to a variety of molecular scaffolds, from the monochlorinated linear chain of fallachromenoic acid [2], to the pentahalogenated halomon skeleton [3] and encompassing many intricate polycyclic and macrocyclic structures with complex vicinal oxygen/halogen patterns, such as bromophycolide B [4] and dichotellide B, which contains both iodine and chlorine atoms (Figure 1) [5].

This structural richness has fuelled the development of many synthetic strategies that take inspiration from these enzymatic machineries. A key aspect is to be able to mildly oxidize the halides into halenium equivalents in order to promote halogenations with increased selectivity. In this regard, hypervalent iodine reagents [6] have emerged as particularly versatile mediators [7-10]. We have shown that electrophilic halogenations [11-13], or pseudohalogenations [14] can be triggered by combining an iodine(III) derivative with a suitable halide salt. In particular, the chemoselectivity of the reaction can be finely tuned by adjusting several parameters, such as the nature of the halide as well as of the iodine(III) ligands and the halide counterion [15,16]. In the case of polyprenoids, we mostly devoted our efforts to achieve the bromocarbocyclization of aryl-geranyl

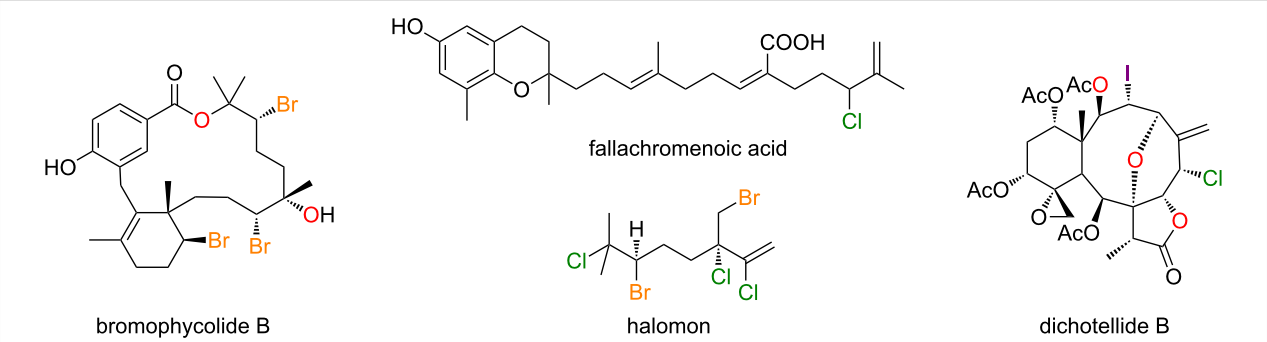


Figure 1: Halogenated terpenoids from natural sources.

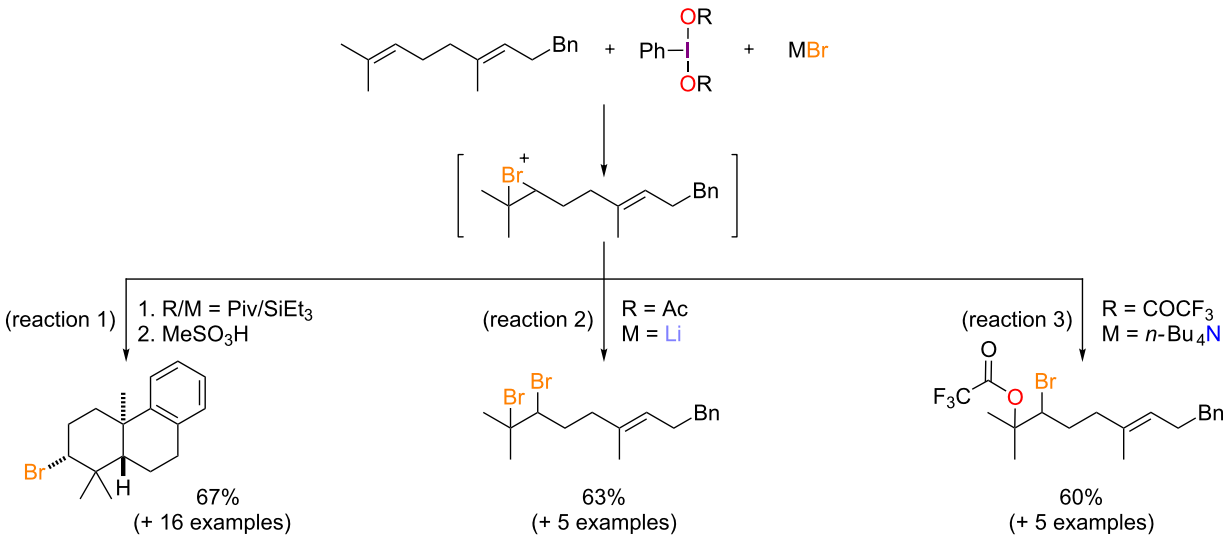
derivatives using a combination of iodine(III) oxidant and a bromide source. In this fashion, the reaction of homogeranylbenzene with bis(*tert*-butylcarbonyloxy)iodobenzene and triethylsilyl bromide, followed by acidic treatment led to a tricyclic brominated adduct (Scheme 1, reaction 1). Yet in the course of our study we also showed that the reactivity of the key bridged bromonium intermediate could also be steered towards non-cyclizing vicinal difunctionalizations using slightly different combinations of a (diacyloxyiodo)arene and a bromide salt. Indeed, (diacetoxy)iodobenzene (DIB) and lithium bromide yield a dibromo adduct (Scheme 1, reaction 2), whereas a combination of (bis(trifluoroacetoxy)iodo)benzene (PIFA) and tetra-*n*-butylammonium bromide (TBAB) gives bromo(trifluoro)acetoxylated **3a** (Scheme 1, reaction 3) [16].

We then decided to further explore the synthetic potential of the latter two vicinal difunctionalizations of terpenoids by not only expanding their substrate scope but also by trying to achieve other bromo-oxylations as well as analogous chloro- and/or iodofunctionalizations of linear terpenoids. For this purpose, five monoterpene derivatives – bearing various functional groups (protected and free alcohols, amine, *E* and *Z* olefins, diene moiety) aimed at probing potential chemo-, regio- and stereoselectivity issues – were selected: geranyl acetate (**1a**), neryl acetate (**1b**), geraniol (**1c**), *N*-tosylgeranylamine (**1d**) and myrcene (**1e**, Figure 2).

Results and Discussion

Optimizations

In order to carry out the exploration of the various halogenations that could be performed, geranyl acetate (**1a**) was chosen as the model substrate. In our study on terpenoids [16], the reaction conditions for the dibromination of the distal double bond were easily established from our previous study on the bromination of enamides [11]. Thus, using a slight excess of DIB along with a two-fold amount of lithium bromide at 0 °C in dry acetonitrile rapidly yielded dibromo adduct **2a** in 91% yield (Table 1, entry 1). Switching the reaction conditions to



Scheme 1: Previously developed bromo-functionalizations of polyprenoids using iodine(III) reagents.

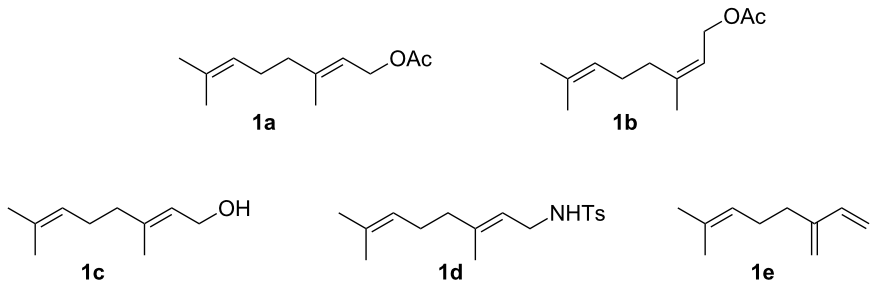
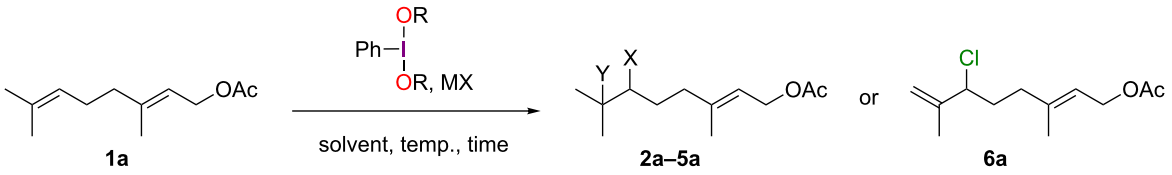


Figure 2: Selected monoterpenoids used in this study.

Table 1: Optimization of the reactions conditions.



entry	R (x equiv)	MX (y equiv)	solvent	temp.	time	N°, Y, X (yield %)[a]
1	Ac (1.2)	LiBr (2.4)	MeCN	0 °C	5 min	**2a**, Br, Br (91)
2	C(O)CF_3 (1.1)	*n*-Bu_4NBr[b] (1.2)	MeCN	0 °C	15 min[c]	**3a**, $OCOCF_3$, Br (77)
3	Ac (1.2)	LiBr (2.4)	MeCN/H_2O	rt	5 min	**4a**, OH, Br (59)[d]
4	Ac (1.2)	LiBr[e] (1.3)	MeCN/H_2O	−10 °C	15 min[c]	**4a**, OH, Br (65)[f]
5	Ac (1.4)	LiBr[e] (1.6)	MeCN/H_2O	−10 °C	15 min[c]	**4a**, OH, Br (70)
6	Ac (1.2)	LiBr (1.2)	Et**O**H	−10 °C	105 min	**4a'**, OEt, Br (68)[g]
7	C(O)CF_3 (1.5)[h]	KI (2.4)	MeCN	0 °C	20 min	**5a**, $OCOCF_3$, I (70)
8	C(O)CF_3 (1.3)[i]	*n*-Bu_4NI[b] (1.5)[i]	MeCN	0 °C	100 min	**5a**, $OCOCF_3$, I (44)
9	C(O)CF_3 (1.5)	*n*-Bu_4NI[b] (1.5)	MeCN	0 °C	20 min	**5a**, $OCOCF_3$, I (60)[j]
10	C(O)CF_3 (1.5)	*n*-Bu_4NI[b] (1.5)	CH_2Cl_2	0 °C	20 min	**5a**, $OCOCF_3$, I (63)
11	Ac (1.2)	$FeCl_3$ (0.8)	MeCN	rt	5 min	**6a** (45)
12	C(O)CF_3 (1.2)	*n*-Bu_4NCl[b] (1.5)	MeCN	0 °C	15 min[c]	**6a** (36)
13	C(O)CF_3 (1.2)	*n*-Bu_4NCl[b] (1.5)	CH_2Cl_2	0 °C	15 min[c]	**6a** (85)

[a]Isolated yields; [b]slow addition of a 0.1 M solution of the TBA salt; [c]5 min of addition followed by 10 min of stirring; [d]along with 6% of **2a**; [e]slow addition of a 0.1 M aqueous solution of LiBr; [f]full conversion was not reached; [g]along with 25% of **2a**; [h]slow addition of a 0.1 M solution of PIFA; [i]initially 1.1 equiv of PIFA and 1.2 equiv of TBAI, followed by 0.2 equiv of PIFA and 0.3 equiv of TBAI to reach completion; [j]along with 20% of **1a**.

bromo(trifluoro)acetoxylation requires the use of a PIFA/TBAB combination in a 1:1 ratio with slow addition of the latter to the reaction mixture thereby preventing the formation of **2a**. In this fashion, bromo(trifluoro)acetoxy adduct **3a** was obtained in 77% yield (Table 1, entry 2). The reaction course can also be modified by changing the solvent. For instance, the complementary hydroxybromination reaction, giving **4a** in 59% yield, was achievable if a mixture of acetonitrile and water was used as the solvent (Table 1, entry 3). In order to suppress the observed formation of minor amounts of **2a**, the reaction temperature was lowered to −10 °C and the amount of lithium bromide, which was added dropwise as an aqueous solution, was diminished to 1.3 equivalents. By doing so, both the selectivity and the yield of **4a** were improved though full conversion was not attained (Table 1, entry 4). Keeping the same procedure, complete reaction was nevertheless achieved by slightly increasing the amount of each reagent thus efficiently giving bromohydroxylated adduct **4a** in 70% yield (Table 1, entry 5). Since the use of water as the sole solvent was not possible because of solubility issues, the reaction was attempted in ethanol. In this case the analogous bromoethoxylated adduct **4a'** could be isolated in 68% yield, albeit along with 25% of **2a** (Table 1, entry 6). Turning our attention to iodination, we first used the combination of PIFA and KI that had given the best results with enam-

ides [13]. Thus, iodo(trifluoro)acetoxylated adduct **5a** was obtained in 70% yield (Table 1, entry 7). Interestingly, no traces of the diiodo compound were observed even if the hypervalent iodine(III) reagent was slowly added. Transposing the previously optimized bromo(trifluoro)acetoxylation conditions but using TBAI instead of KI did not improve the yield and reaction times and excess reagents were required to reach completion (Table 1, entry 8). Using directly 1.5 equivalents of both PIFA and TBAI did not suffice to improve the yield, whether in acetonitrile or in dichloromethane (Table 1, entries 9 and 10). When chlorination was attempted with a combination of DIB and iron(III) chloride in a 1.2:0.8 ratio (i.e., a 1:1 OAc/Cl ratio [12]) in acetonitrile, allylic chloride **6a** [17] was obtained with a moderate 45% yield (Table 1, entry 11). Switching to a combination of PIFA and TBACl (Table 1, entry 12) did not change the course of the reaction towards chloro(trifluoro)acetoxylation and, while the yield was moderate in acetonitrile, it was greatly improved in dichloromethane [18], affording **6a** in 85% yield (Table 1, entry 13).

At this stage, we chose to discard the bromoethoxylation reaction which led to mixtures of compounds, leaving five optimized transformations (dibromination, bromo(trifluoro)acetoxylation, bromohydroxylation, iodo(trifluoro)acetoxylation and ene-type chlorination) which were applied to substrates **1b–e** in order to explore their scope.

Bromination

Dibromination

Application of the dibromination protocol to neryl acetate (**1b**) proceeded smoothly and the desired compound **2b** was obtained in nearly quantitative yield without any detectable reaction on the *Z* double bond (Scheme 2). Despite the potential sensitivity of the alcohol and the amine functions, both geraniol (**1c**) and protected geranylamine **1d** gave the dibromo adduct **2c** [16] and **2d** in good yields. Finally, the reaction was performed on myrcene (**1e**), providing **2e** in 78% yield and leaving the diene moiety untouched.

Bromo(trifluoro)acetoxylation

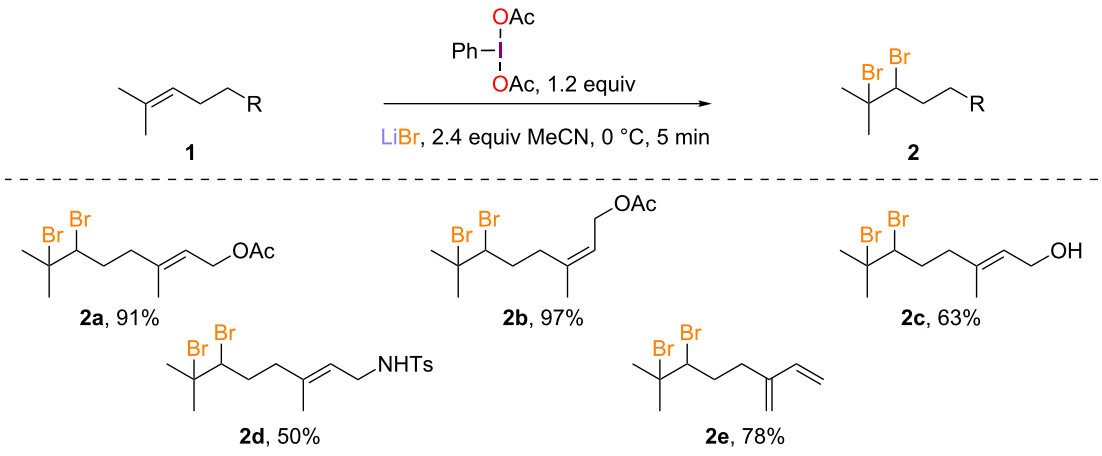
The success of the bromo(trifluoro)acetoxylation lies in the reverse addition protocol whereby the tetrabutylammonium bromide is slowly added to the suspension of the terpenoid and PIFA at 0 °C. In this manner, good to excellent yields (57–84%) were obtained for the formation of *Z*-derivative **3b**, alcohol **3c** [16], tosylamine **3d** and diene **3e** (Scheme 3). Once again, the selectivity is excellent as no reactions with the other double bonds or with the aryl ring [19] are observed and only one regioisomer is formed in all cases.

Bromohydroxylation

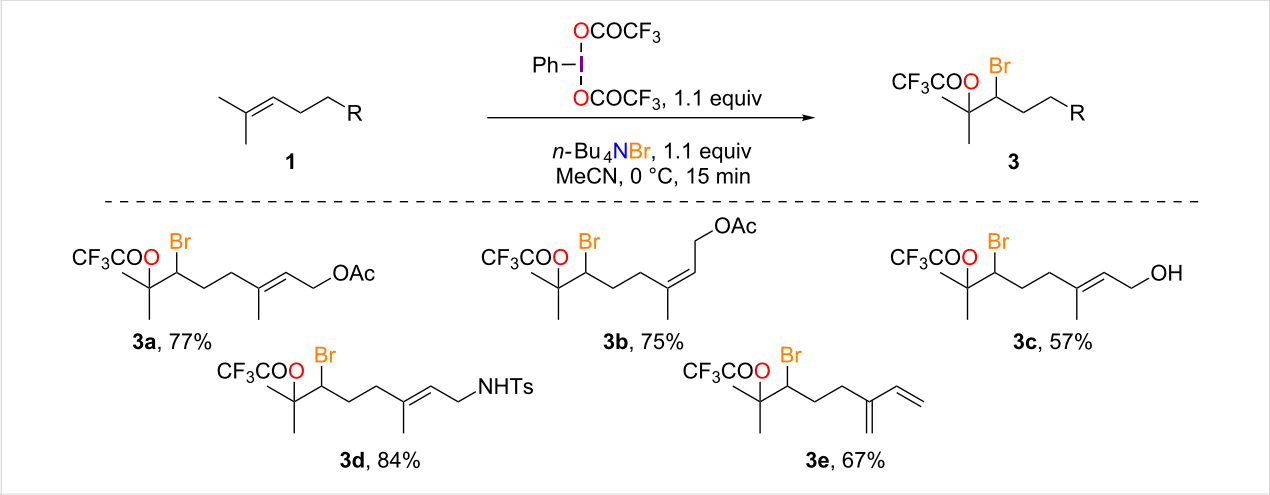
Although the trifluoroacetoxy group can be readily cleaved [16], having a direct access to the corresponding bromohydrins would still be desirable especially since selective deprotection in the presence of another ester would presumably be difficult to achieve. By using water as the co-solvent, bromohydrins **4b–e** were directly prepared from the corresponding starting material, albeit with moderate yields in the case of *N*-tosylgeranylamine (**1d**) and myrcene (**1e**, Scheme 4).

Iodo(trifluoro)acetoxylation

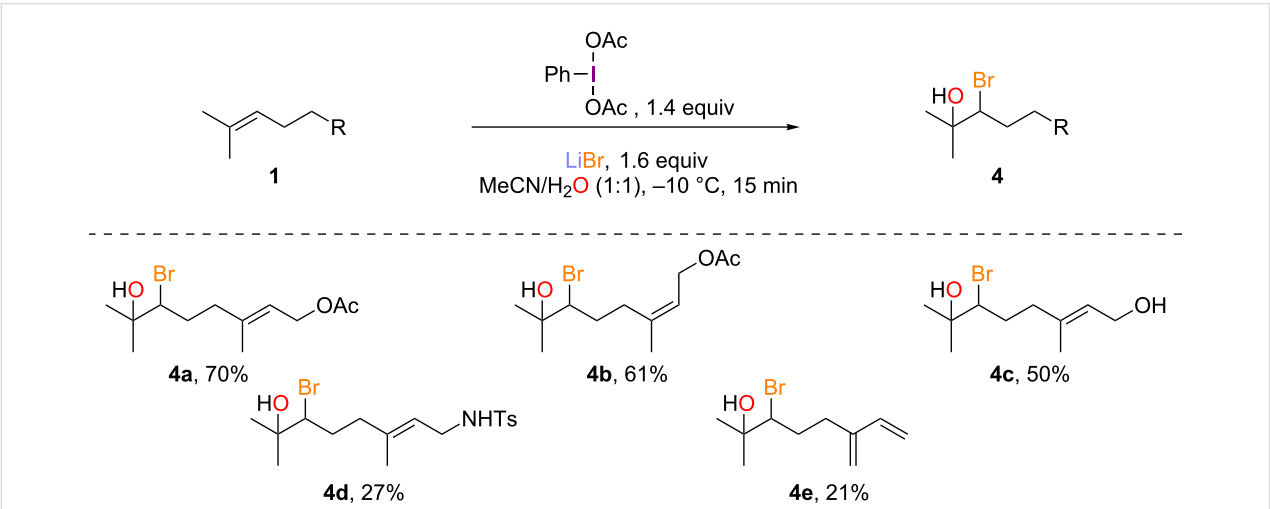
In an analogous fashion to the above-described bromo(trifluoro)acetoxylation, the iodo(trifluoro)acetoxylation proceeded with both good yields (49–70%) and chemo-selectivities for geranyl and neryl acetates (**1a**,**b**), geranylamine **1d** and myrcene (**1e**, Scheme 5). However, the adducts were quite



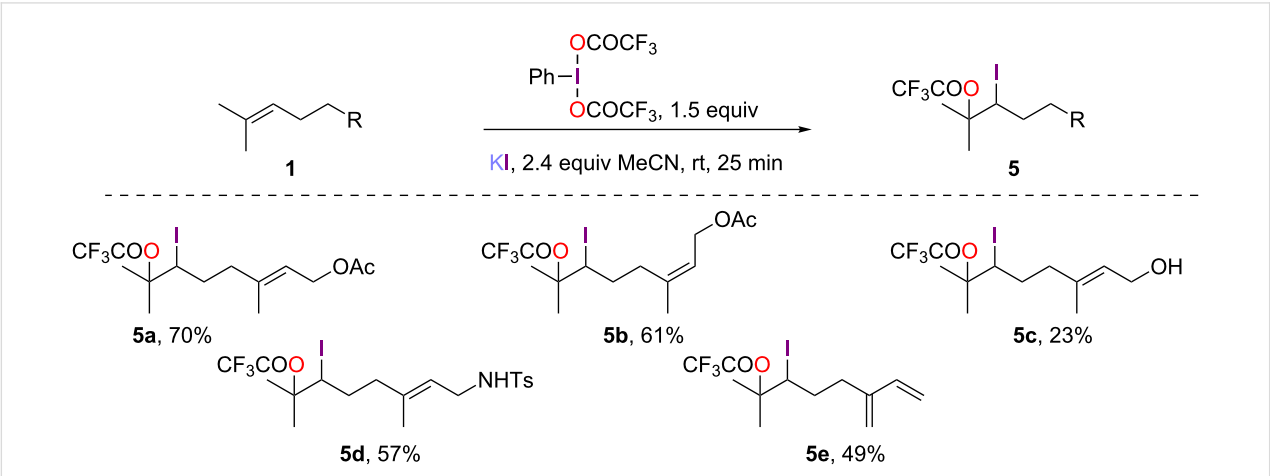
Scheme 2: Dibromination of acyclic monoterpenoids.



Scheme 3: Bromo(trifluoro)acetoxylation of acyclic monoterpenoids.



Scheme 4: Bromohydroxylation of acyclic monoterpenoids.



Scheme 5: Iodo(trifluoro)acetoxylation of acyclic monoterpenoids.

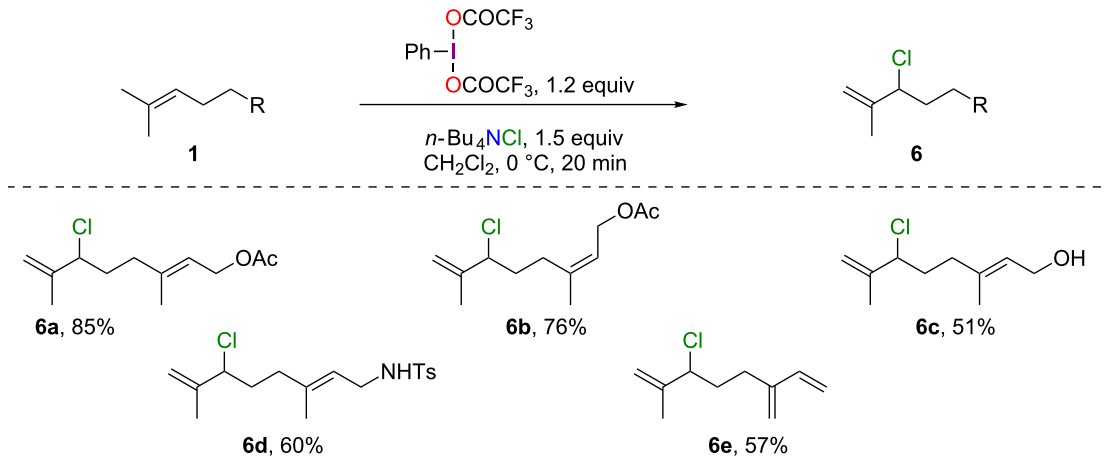
sensitive and needed to be manipulated with care (low temperature storage) to avoid rapid decomposition. Nevertheless, this was particularly the case for alcohol **5c** which could only be isolated with a 23% yield. This mild protocol offers a complementary alternative to the use of iodine monoacetate [20] or NIS [21] and does not require the use of a strong oxidant such as IBX [22]. Compared to the standard procedure for the preparation of acetoxyhypohalites that requires the use of expensive and potentially toxic silver salts [23], our method offers a more practical alternative. It also differs from the more user-friendly protocols that rely on Oxone® [20], DIB [24], or PIFA [25] since the iodide source is an iodide salt and not molecular iodine.

Chlorination

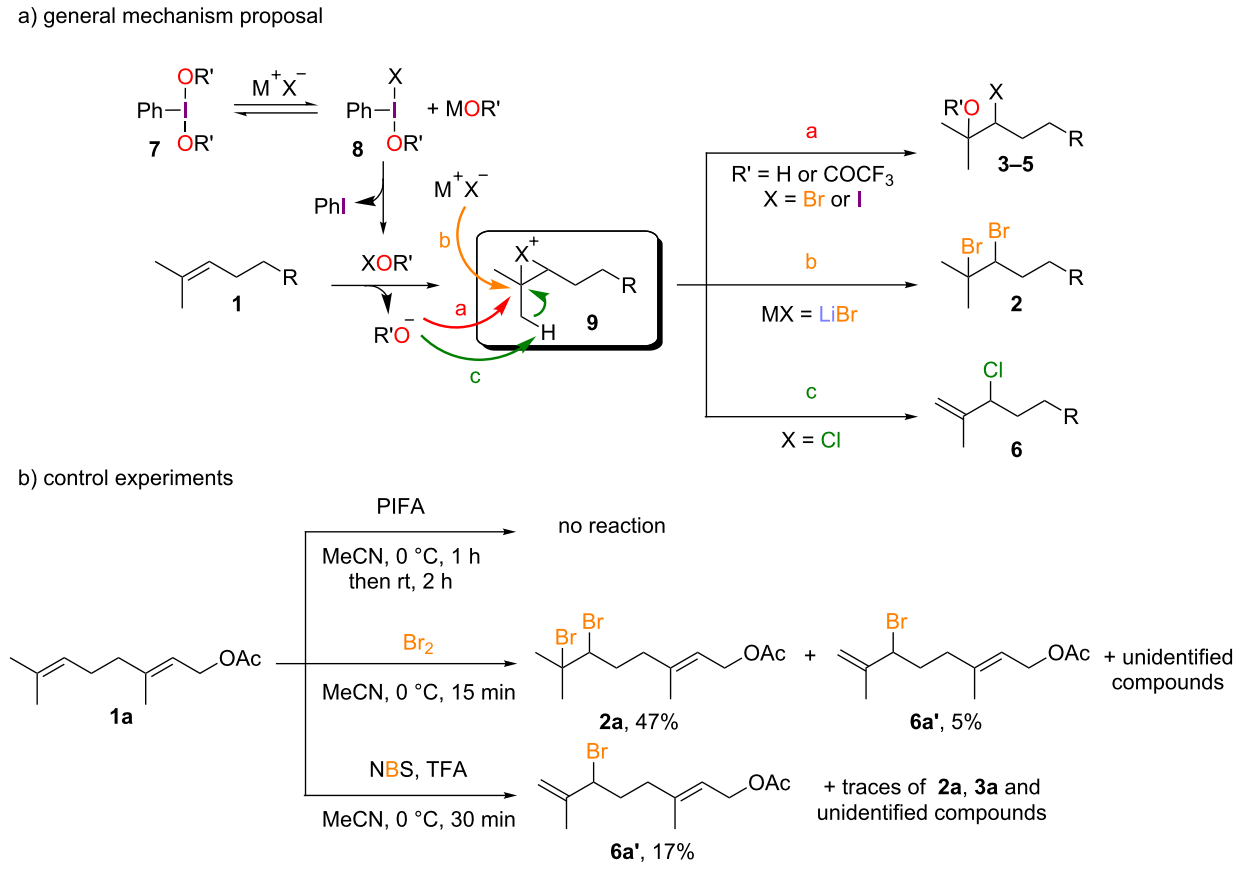
In the case of chlorination, we have yet to observe adducts arising from the vicinal difunctionalization of the double bond and, in accordance with the literature [13], ene-type products **6** were obtained (Scheme 6). The reaction performed equally well with acetates (**6a**,**b**), alcohol (**6c**), amine (**6d**) and myrcene (**6e**). Once again, excellent chemo- and regioselectivities and good yields (51–85%) were witnessed.

Mechanism proposal and control experiments

Considering the differences and similarities in the outcome of the various reaction conditions, a common mechanism with a central divergence point can be proposed. First, the diacetoxyiodobenzene reagent **7** would undergo ligand exchange with the halide to give mixed hypervalent iodine(III) **8** (Scheme 7a) [12]. We ruled out a possible direct reaction between the olefin and the hypervalent iodine(III) reagent as in the absence of any halide no reaction occurred within 1 h (Scheme 7b). A reductive elimination would then generate hypohalite R'OX which is presumably the active electrophilic species. If the reductive elimination only occurred after a second ligand exchange it would then give X_2 which is generally a less efficient electrophilic species than the corresponding acetoxyhypohalite, especially trifluoroacetoxyhypohalites [26]. Indeed, when we reacted geranyl acetate **1a** with bromine we did isolate dibromo adduct **2a** but only with 47% yield and we also observed the formation of various byproducts such as ene-bromination adduct **6a'** (Scheme 7b) [27]. Moreover, for the iodination of enamides using the PIFA/KI combination we had already shown that the observed reactivity is more akin to the one induced by acetoxyhypoiodite [13]. Alternatively, the involvement of an ammonium-complexed halogen(I) species of type n-$Bu_4N[X(O_2CCF_3)_2]$, as described by Kirschning [28] and later Muniz [29] cannot be ruled out although, to the best of our knowledge, it has yet to be characterized for X = Cl. Regardless of the actual halogenation species involved, regioselective halogenation of the terminal double bond of **1** would then give bridged halonium **9**. From there three manifolds can be at play. Pathway **a** involves the addition of an oxygenated nucleophile. For X = Br, this is the case when the bromide is the default reagent because of its slow addition (giving **3**) or because the nucleophile is the co-solvent (water giving **4** and to a lesser extent EtOH yielding **4'**). While the formation of **4** is related to the well-established NBS-mediated formation of bromohydrins in aqueous media [30], the formation of **3** is not so straightforward. For instance, submitting **1a** to NBS in the presence of trifluoroacetic acid led to a complex mixture of products, the major one being allylic bromide **6a'**. For X = I, the steric bulk would preclude the formation of the vicinal diiodide and only pathway **a** would thus be operative, yielding **5**. This is not the case for the dibromide **2**, which is readily formed



Scheme 6: Chlorination of acyclic monoterpenoids.



Scheme 7: General mechanism proposal for the formation of **2**–**6** and control experiments.

through pathway **b** when the reaction takes place in the presence of excess bromide. Finally, if X = Cl, rapid deprotonation by the acetate (or the chloride) alpha to the chloronium bridge (pathway **c**) explains the formation of allylic chloride **6**.

Conclusion

Overall, we have further extended the scope of the iodine(III)-mediated oxidative halogenation of terpenoids which now includes dibromination, bromo(trifluoro)acetoxylation, bromohydroxylation, iodo(trifluoro)acetoxylation and allylic enechlorination. The conditions are mild and selective and the reactions proceed rapidly with generally good yields. Application of this tunable strategy towards the rapid constitution of chemical libraries of biologically active molecules is now actively pursued in our laboratory.

Experimental

General procedure A: dibromination

To a solution of the geranyl derivative (1.0 equiv) in acetonitrile (0.05 M) at 0 °C, lithium bromide (2.0–2.4 equiv), 4 Å molecular sieves (1.0 mass equiv) and DIB (1.2–1.4 equiv) were added. After stirring for 5 min, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc) and concentrated under reduced pressure before purification by flash chromatography.

General procedure B: bromo(trifluoro)acetoxylation

To a solution of the geranyl derivative (1.0 equiv) in acetonitrile (0.07 M) cooled to 0 °C, PIFA (1.1 equiv) was added. A solution of tetra-*n*-butylammonium bromide (1.1 equiv) in acetonitrile (0.07 M) was then added dropwise over 5 min. After stirring for 10 min, the reaction mixture was diluted with EtOAc, saturated aqueous $Na_2S_2O_3$ solution was added and the layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by flash chromatography.

General procedure C: bromohydroxylation

To a solution of the geranyl derivative (1.0 equiv) in acetonitrile (0.1 M) cooled to −10 °C, DIB (1.4 equiv) was added. A

solution of lithium bromide (1.6 equiv) in H_2O (0.1 M) was then added dropwise over 5 min. After stirring at −10 °C for 10 min, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc) and concentrated under reduced pressure before purification by flash chromatography.

General procedure D: iodo(trifluoro)acetoxylation

To a solution of the geranyl derivative (1.0 equiv) in acetonitrile (0.1 M) at room temperature, 3 Å molecular sieves (1.0 mass equiv) and potassium iodide (2.4 equiv) were added. A solution of PIFA (1.5 equiv) in acetonitrile (0.1 M) was then added dropwise over 10 min and the reaction mixture was stirred for 15 min. The reaction mixture was diluted with EtOAc, $Na_2S_2O_3$ solution (10%) was added and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by flash chromatography.

General procedure E: allylic chlorination

To a solution of the geranyl derivative (1.0 equiv) in dichloromethane (stabilized with amylene, 0.1 M) cooled to 0 °C, PIFA (1.2 equiv) was added. A solution of tetra-*n*-butylammonium chloride (1.5 equiv) in DCM (0.1 M) was then added dropwise over 10 min and the reaction mixture was stirred for 10 min at 0 °C. The reaction mixture was diluted with EtOAc, $Na_2S_2O_3$ solution (10%) was added and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by flash chromatography.

Supporting Information

Supporting Information File 1

Full characterization data of all new compounds and copies of ^1H and ^{13}C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-96-S1.pdf]

Acknowledgements

The authors thank CNRS and ICSN for financial support. L. P. thanks MENESR for a Ph.D. fellowship and T. D. G. thanks ICSN for a Ph.D. fellowship.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recyclable hypervalent-iodine-mediated solid-phase peptide synthesis and cyclic peptide synthesis

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Full Research Paper

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Keywords:
cyclic peptide; FPID; hypervalent iodine(III) reagent; recyclable; solid-phase peptide synthesis (SPPS)

Beilstein J. Org. Chem. **2018,** *14,* 1112–1119.
doi:10.3762/bjoc.14.97

Received: 14 February 2018
Accepted: 27 April 2018
Published: 22 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The system of the hypervalent iodine(III) reagent FPID and $(4\text{-}MeOC_6H_4)_3P$ was successfully applied to solid-phase peptide synthesis and cyclic peptide synthesis. Four peptides with biological activities were synthesized through SPPS and the bioactive cyclic heptapeptide pseudostellarin D was obtained via solution-phase peptide synthesis. It is worth noting that FPID can be readily regenerated after the peptide coupling reaction.

Introduction

The amide bond is one of the most fundamental functional groups in organic chemistry, and it plays a crucial role in the elaboration and composition of biological systems. Amide bonds are widely present not only in peptides and proteins but also in pharmaceuticals and many natural products. Among the methods for amide bond formation, the direct condensation of carboxylic acids and amines in the presence of a coupling reagent is the most convenient and simplest way [1-6]. The most commonly used coupling reagents such as carbodiimide [7], phosphonium [8], and uronium salts [9] are efficient and commercially available. In spite of these merits of traditional coupling reagents, it is still far from ideal because large amounts of chemical wastes are produced during the amide bond formation reaction using these reagents and the coupling reagents cannot be regenerated [10]. Thus, methods for the peptide synthesis which are efficient and atom-economic are still needed.

Hypervalent iodine reagents have drawn researchers' considerable attentions due to their versatile reactivity, low toxicity, ready availability, environmental friendliness, and regenerability [11-27]. Our group has dedicated to the peptide synthesis mediated by hypervalent iodine(III) reagents in recent years. In 2012, for the first time, we reported that the hypervalent

iodine(III) reagent iodosodilactone (Figure 1) can serve as a condensing reagent to promote esterification, macrolactonization, amidation and peptide coupling reactions in the presence of PPh_3 [28]. In addition, the peptide coupling reaction proceeds without racemization in the absence of a racemization suppressant and iodosodilactone can be readily regenerated after the reaction. In order to further enhance the reactivity of iodosodilactone, we designed and synthesized a new derivative of iodosodilactone 6-(3,5-bis(trifluoromethyl)phenyl)-1*H*,4*H*-2aλ^3-ioda-2,3-dioxacyclopenta[*hi*]indene-1,4-dione (abbreviated as FPID, Figure 1) [29].

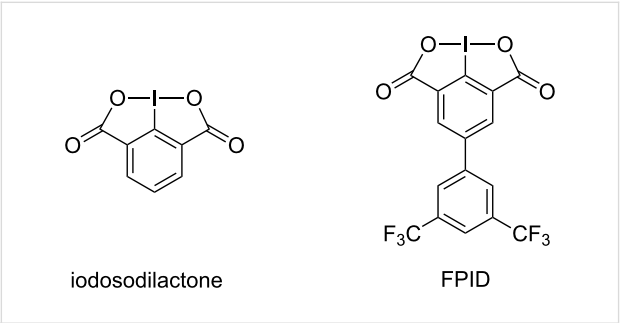
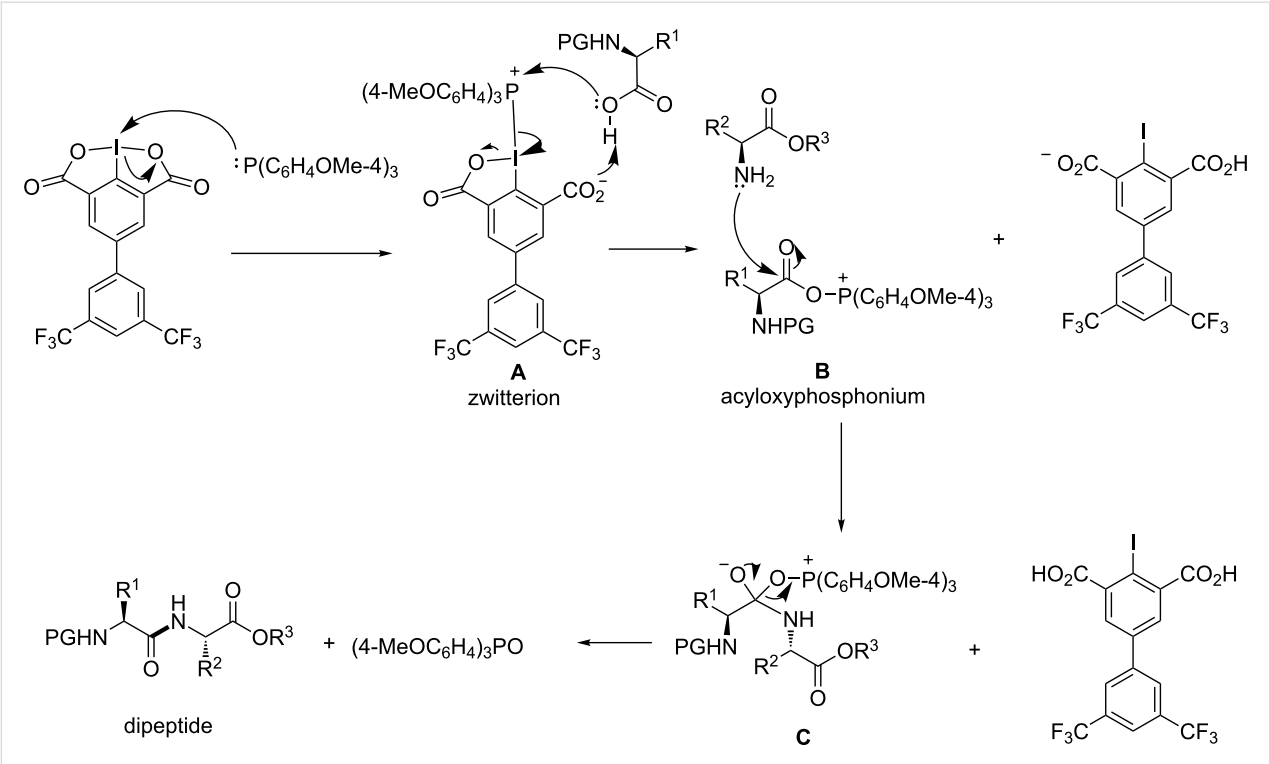


Figure 1: Iodosodilactone and FPID.

In combination with tris(4-methoxyphenyl)phosphine [(4-$MeOC_6H_4)_3P$], FPID can efficiently mediate peptide coupling reactions within 30 minutes to obtain various dipeptides from standard amino acids as well as sterically hindered amino acids. Moreover, a pentapeptide Leu-enkephalin is successfully synthesized in its protected form using this coupling system. Similar to iodosodilactone, FPID can be easily regenerated after the reaction. The mechanism for this FPID-mediated amide bond formation reaction was proposed with the acyloxyphosphonium intermediate **B** being the key intermediate (Scheme 1). Herein, as part of our continuing exploration of the application of FPID in peptide synthesis, we disclose its successful application in solid-phase peptide synthesis and cyclic peptide synthesis.

Results and Discussion

At the beginning of our study, we tried to utilize the system of FPID/(4-$MeOC_6H_4)_3P$ in the solid-phase peptide synthesis (SPPS). SPPS has been widely employed in peptide synthesis since its first report by Merrifield in 1963 [30,31]. Compared with classical solution-phase peptide synthesis, the fast development of SPPS is mainly due to its short reaction time, high efficiency, low racemization, simple work-up and automation. In recent decades, various strategies, for example, native chemical ligation (NCL) [32] and serine/threonine ligation (STL) [33], have been reported to solve the problems occurred during the development of SPPS. Peptide synthesis in solution mediated by FPID/(4-$MeOC_6H_4)_3P$ is rapid (within 30 min) and efficient, at the same time the reactions proceed without racemization.



Scheme 1: Proposed mechanism for FPID-mediated amide bond formation.

Thus, it is possible and significant to test whether the FPID/(4-$MeOC_6H_4)_3P$ system can be used in SPPS.

We selected the commercially available 2-chlorotrityl chloride resin (2-Cl-Trt-Cl resin) as the solid support and [(9-fluorenylmethyl)oxy]carbonyl (Fmoc) as the α-amino protecting group. The peptides were synthesized following the route as shown in Scheme 2. The C-terminal amino acid was immobilized onto the 2-Cl-Trt-Cl resin in the presence of 3.0 equiv of DIPEA in DCM/DMF (v:v 1:1). Subsequent peptide chain elongation was completed via Fmoc-SPPS protocol, which includes deprotection with 20% piperidine/DMF and peptide coupling with 3.0 equiv of Fmoc-protected amino acids, 3.0 equiv of FPID, 3.0 equiv of (4-$MeOC_6H_4)_3P$ and 3.0 equiv of TEA in DMF. After chain elongation and deprotection of Fmoc, the resulting resins were treated with 0.5% TFA/DCM to give the N,C-unprotected peptides as final products. The peptides were purified by reversed-phase HPLC (RP-HPLC).

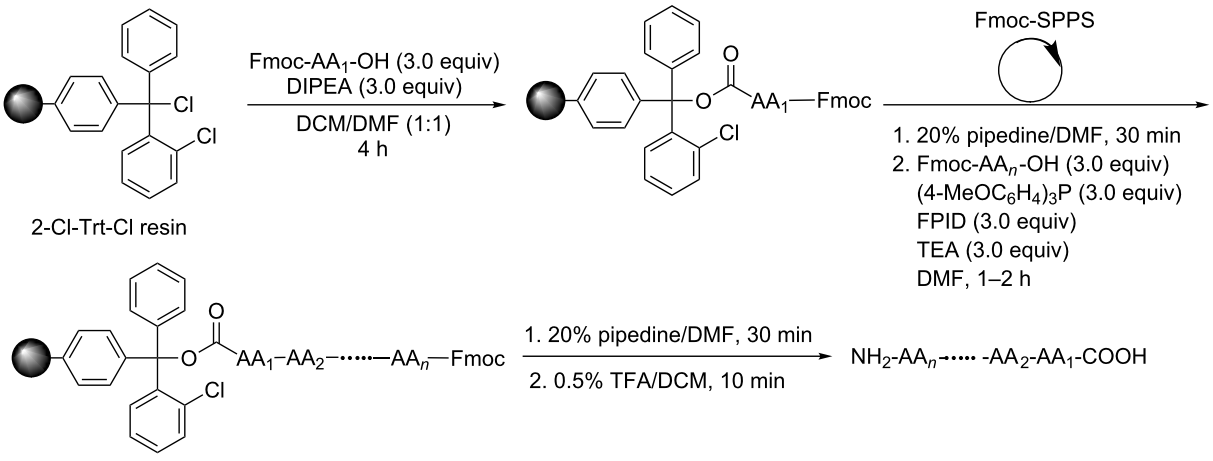
For the target peptides, we aimed at peptides with specific biological activities. Leu-enkephalin, which is isolated from pig brains, acts as an endogenous mediator at central morphine receptor sites and thus possesses potent opiate agonist activity [34-36]. Leu-enkephalin **1** (Table 1, entry 1) could be successfully synthesized following the route mentioned above (Scheme 2). Besides, the precursor **2** of a cyclic heptapeptide pseudostellarin D [37-39] was also obtained via SPPS in good yield (Table 1, entry 2), the cyclization of **2** to give pseudostellarin D using FPID/(4-$MeOC_6H_4)_3P$ will be described in the following part. Moreover, angiotensin I converting enzyme (ACE) inhibitory peptides, widely exist in plants and animals, can serve as potential antihypertensive pharmaceuticals [40-42]. The synthesis of two ACE inhibitory peptides proceeded smoothly in moderate yield (Table 1, entries 3 and 4). Notably, it is unnecessary to protect the hydroxy group of serine, threonine, or tyrosine in advance in the synthesis of these four peptides. The presence of an unprotected hydroxy group does not affect the coupling efficiency, which is consistent with peptide coupling in solution phase [29]. The HRMS spectra of these peptides are consistent with their molecular formula.

Table 1: Peptides synthesized by SPPS mediated by FPID.

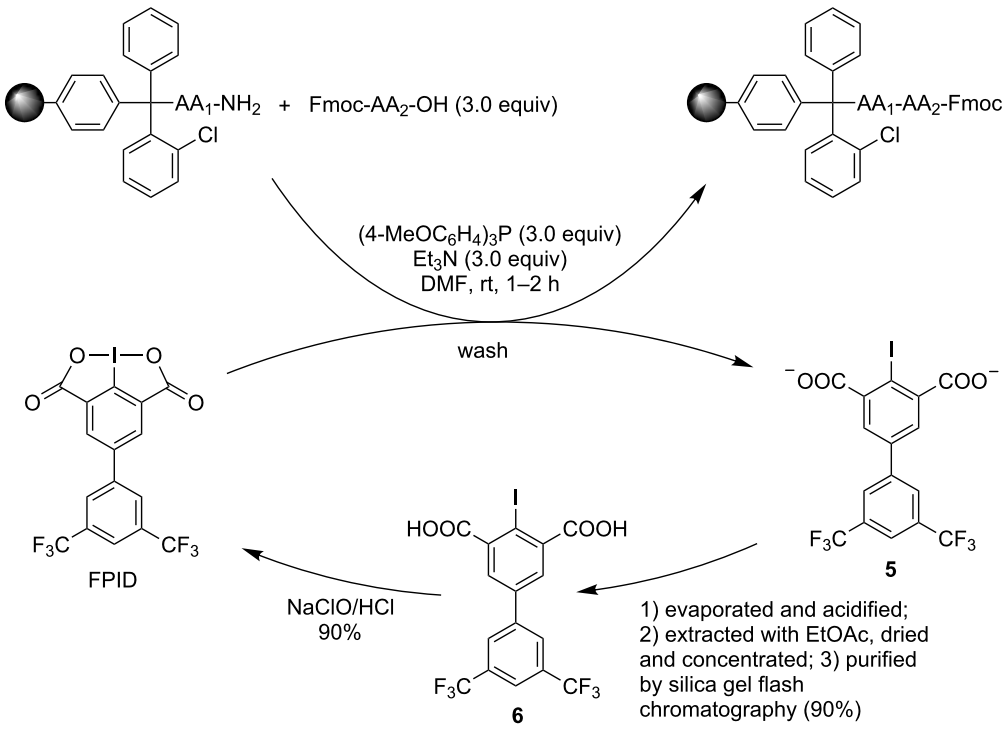
entry	peptide	yield
1	H_2N-Tyr-Gly-Gly-Phe-Leu-OH (**1**)	42%
2	H_2N-Gly-Gly-Tyr-Pro-Leu-Ile-Leu-OH (**2**)	53%
3	H_2N-Lys-Leu-Pro-Ala-Gly-Thr-Leu-Phe-OH (**3**)	30%
4	H_2N-Trp-Val-Pro-Ser-Val-Tyr-OH (**4**)	21%

Similar to the solution-phase peptide synthesis, FPID can be easily regenerated after SPPS (Scheme 3). After completion of peptide elongation, the washing solution of peptide coupling in each cycle was collected and evaporated. Then the mixture was acidified with 3 N HCl and extracted with EtOAc, dried and concentrated in vacuo. The synthetic precursor of FPID **6** could be purified by flash chromatography in order to remove excess Fmoc-protected amino acids during the peptide coupling. Compound **6** was subsequently oxidized with NaOCl/HCl to obtain FPID in 90% yield.

Cyclic peptides, an important kind of peptides, possess several favorable properties such as target selectivity, good binding affinity and low toxicity, which make them attractive candi-



Scheme 2: Solid-phase peptide synthesis mediated by FPID/(4-$MeOC_6H_4)_3P$. Conditions: The resin loading for 2-Cl-Trt-Cl resin is 0.98 mmol/g. For each peptide synthesized through SPPS, 200 mg 2-Cl-Trt-Cl resin was used. Fmoc-Ser-OH, Fmoc-Thr-OH, Fmoc-Tyr-OH, Fmoc-Trp-OH were directly used without any protecting group on OH or NH. During the synthesis of **3**, Fmoc-Lys(Boc)-OH was used.



Scheme 3: The regeneration of FPID after SPPS.

dates in the development of therapeutics [43,44]. Due to the particular significance of cyclic peptides, chemists pay considerable attention to the efficient synthesis of cyclic peptides [45]. In the second part of the investigation of the synthetic utility of the FPID/$(4\text{-MeOC}_6\text{H}_4)_3\text{P}$ system, we tested this system in the cyclic peptide synthesis.

The roots of *Pseudostellaria heterophylla* are well-known traditional Chinese medicine, which are often used as a lung and spleen tonic. There are more than 10 cyclic peptides isolated from it, for example, pseudostellarin A–H and heterophyllin A–D [37,46-49]. Cyclo(Gly-Gly-Tyr-Pro-Leu-Ile-Leu), a cyclic heptapeptide named pseudostellarin D (Figure 2), is one of these cyclic peptides. Pseudostellarin D was first isolated and identified in 1994 by Itokawa and co-workers [37]. In addition, the authors reported that pseudostellarin D showed potent tyrosinase inhibitory activities. In 1999, Belagali and co-workers further evaluated the antimicrobial, anti-inflammatory and anthelmintic activities of pseudostellarin D [38]. As for the synthesis of pseudostellarin D, the existing methods utilized the active ester method to complete the cyclization of the linear peptide precursor with the same amino acid sequence of Gly-Gly-Tyr-Pro-Leu-Ile-Leu as a result of the amide bond between "Gly-Leu" being the cyclization position. The first one was reported by Belagali in 1999, pseudostellarin D was obtained by the cyclization of the linear heptapeptide peptide-PNP ester, which is known as the *p*-nitrophenyl ester method (Scheme 4, method A). The other one was described by Agrigento and co-workers, the cyclization was completed via the *p*-chlorophenyl thioester method with peptide-thioester being the precursor (Scheme 4, method B) [39]. Herein, we realized the synthesis of pseudostellarin D following the same cyclization strategy mentioned above by direct coupling of the precursor **2** without any protecting group utilizing the system of FPID/$(4\text{-MeOC}_6\text{H}_4)_3\text{P}$ (Scheme 4, method C).

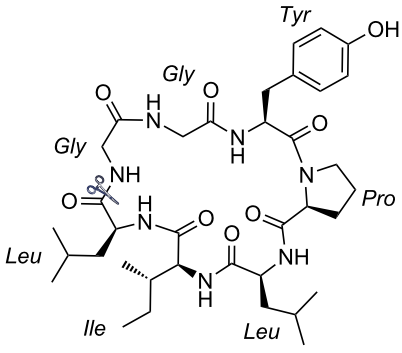
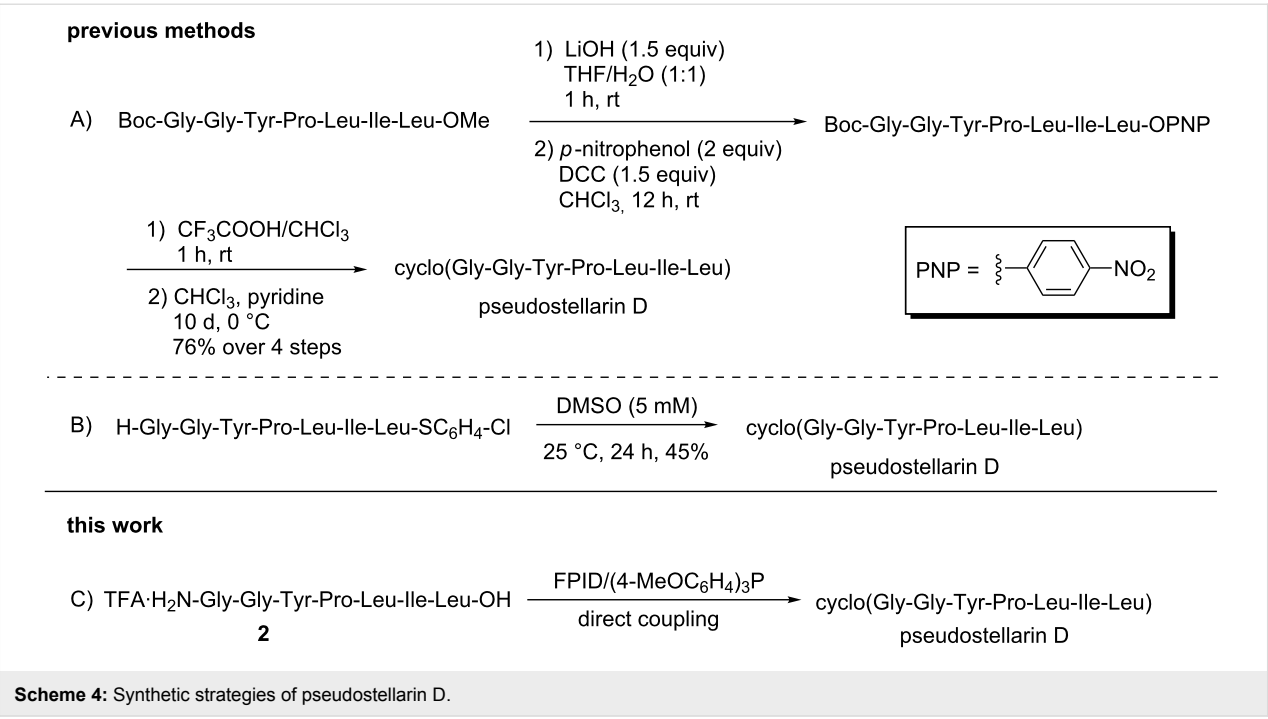


Figure 2: Structure of pseudostellarin D.

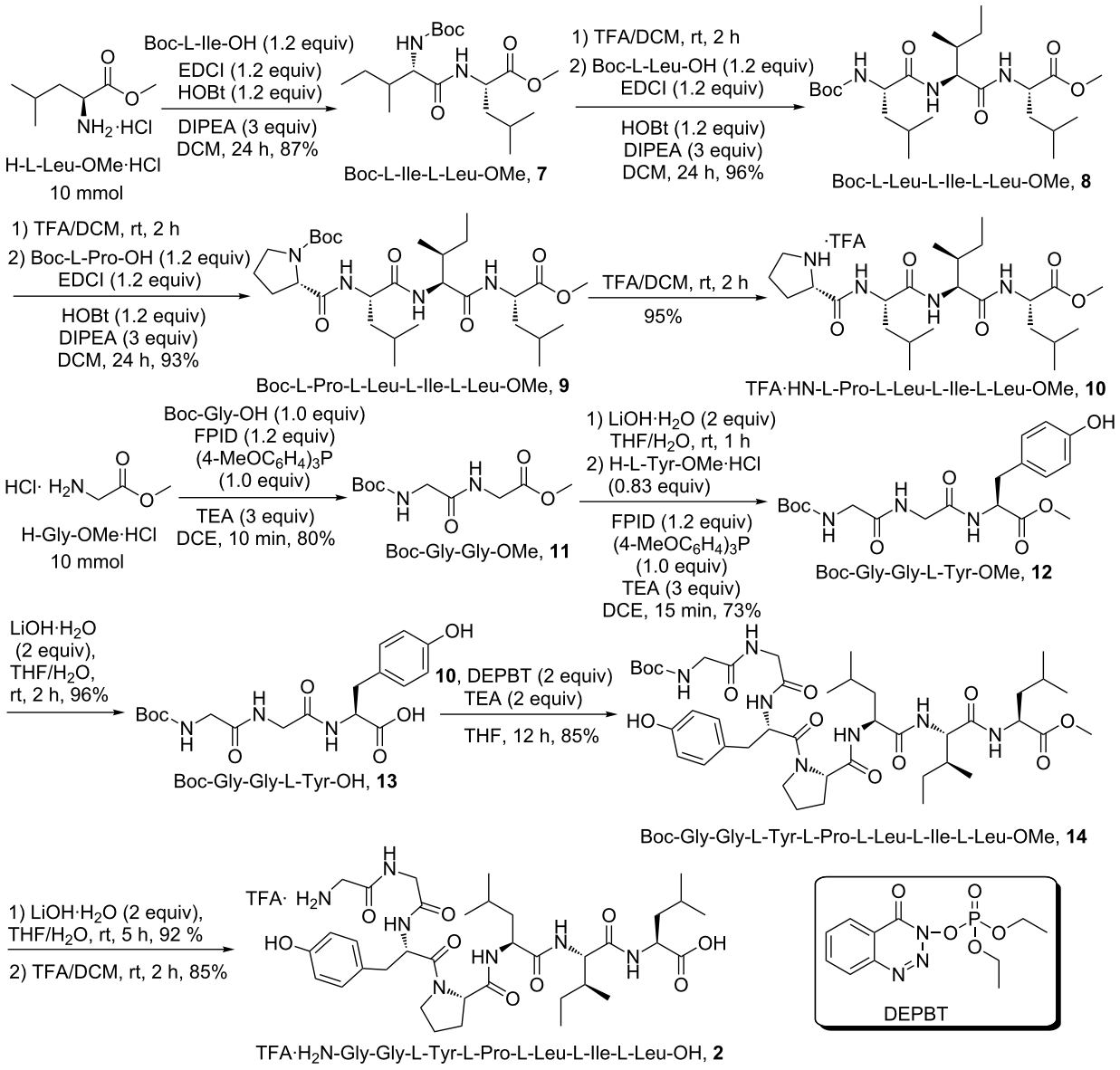


Scheme 4: Synthetic strategies of pseudostellarin D.

We have obtained the precursor **2** through SPPS mediated by FPID/(4-$MeOC_6H_4)_3P$ system (Table 1, entry 2). Firstly, the C-terminal amino acid Leu was immobilized onto 2-Cl-Trt-Cl resin. Then the chain elongation was completed by the deprotection of Fmoc and coupling with Fmoc-protected Ile, Leu, Pro, Tyr, Gly, Gly in turn. The successive deprotection of Fmoc, cleavage from the resin and purification via RP-HPLC yielded the precursor **2** (see Supporting Information File 1). Alternatively, the synthesis of the precursor **2** can be achieved through a convergent [3 + 4] segment condensation strategy in solution phase (Scheme 5). Notably, during the synthesis of tetrapeptide segment **10**, the stepwise manner was adopted in order to avoid racemization. In the synthesis of tripeptide segment **13**, our condensing system, FPID/(4-$MeOC_6H_4)_3P$ was utilized. Besides, the coupling between **10** and **13** to yield heptapeptide segment **14** was carried out using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) as coupling reagent, which was developed by Ye's group in order to reduce racemization and side reactions [50]. The precursor **2** was obtained via successive deprotection of the C-terminal and the N-terminal protecting group of **14**. The overall yield of this route is 28%.

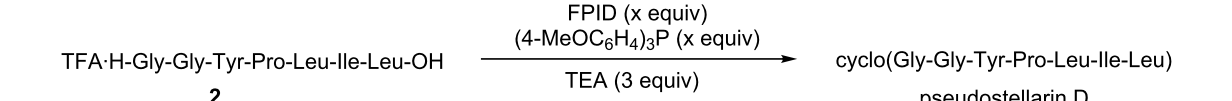
With the precursor **2** in hand, we then investigated the reaction conditions of its cyclization. Considering the solubility of **2** and FPID, we chose DMF as the solvent. At the beginning of our investigation, the reaction was carried out under air within 10 h, we tested the influence of the adding sequence of TEA, FPID and (4-$MeOC_6H_4)_3P$, and the results indicated that adding TEA first and FPID/(4-$MeOC_6H_4)_3P$ 5 minutes later performed better than the inverse sequence (Table 2, entries 1 and 2). When prolonging the reaction time to 24 h, the product was obtained in a yield of 23% and 25% according to different adding sequence of TEA and FPID/(4-$MeOC_6H_4)_3P$, and the effect of the adding sequence was the same with that mentioned above (Table 2, entries 3 and 4). Then the reaction was run under N_2 atmosphere instead of air, the cyclization yield increased to 27% (Table 2, entry 5). Increasing the equivalents of FPID and (4-$MeOC_6H_4)_3P$ to 2.0 equiv resulted in 33% NMR yield of the product (Table 2, entry 7). Ye's group disclosed that adding univalent metal ions such as Na^+, K^+ and Cs^+ to the reaction system for the synthesis of some cyclic pentapeptides and heptapeptide would not only enhance the cyclization yields but also the cyclization rates [51]. Inspired by this finding, we tried to add some metal chlorides into the reaction, such as LiCl, NaCl, KCl, CsCl (Table 2, entries 8–11). The results indicated that adding NaCl, KCl, CsCl could increase the cyclization yield, whereas LiCl decreased the yield. Among the efficient metal chlorides, adding 5 equiv of CsCl to the reaction yielded the product in 44% NMR yield. The isolated yield of pseudostellarin D under the optimized reaction conditions was 32%.

Consequently, pseudostellarin D can be successfully synthesized in 32% isolated yield (44% NMR yield) under the optimized conditions: FPID (2 equiv), (4-$MeOC_6H_4)_3P$ (2 equiv), TEA (3 equiv), CsCl (5 equiv). The ^1H NMR and HRMS spectra of pseudostellarin D are in agreement with data from the literature [37-39].



Scheme 5: Preparation of the precursor of pseudostellarin D.

Table 2: Optimization of cyclization of linear heptapeptide **2**.[a]



entry	x equiv	additive	atmosphere	time	yield (%)
1	1.2	–	air	10 h	<18
2[b]	1.2	–	air	10 h	<15
3	1.2	–	air	24 h	<23
4[b]	1.2	–	air	24 h	<20
5	1.2	–	N_2	24 h	<27

Table 2: Optimization of cyclization of linear heptapeptide **2**.[a] (continued)

6[c]	2.0	–	N_2	24 h	n.d.
7	2.0	–	N_2	24 h	33 (NMR)
8[d]	2.0	CsCl (5 equiv)	N_2	24 h	44 (NMR)
9[d]	2.0	NaCl (5 equiv)	N_2	24 h	42 (NMR)
10[d]	2.0	LiCl (5 equiv)	N_2	24 h	28 (NMR)
11[d]	2.0	KCl (5 equiv)	N_2	24 h	40 (NMR)

[a]Conditions: performed with **2** (0.05 mmol), TEA (0.15 mmol), DMF (50 mL). Unless otherwise mentioned, the adding sequence of TEA and FPID/(4-$MeOC_6H_4)_3P$ was adding TEA first and FPID/(4-$MeOC_6H_4)_3P$ 5 minutes later. "x equiv" meant the equivalents of FPID and (4-$MeOC_6H_4)_3P$. The NMR yield was calculated by adding CH_2ClBr as internal standard substance. [b]Adding FPID/(4-$MeOC_6H_4)_3P$ first and TEA 5 minutes later. [c]**2** was dissolved in 2 mL of DMF and added portionwise to the reaction system within 2 h. [d]Metal chloride was dissolved in 0.33 mL of H_2O and then added to the reaction.

Conclusion

The system of the hypervalent iodine(III) reagent FPID and (4-$MeOC_6H_4)_3P$ can be applied to the solid-phase peptide synthesis because four bioactive peptides were smoothly obtained including the precursor **2** of cyclic peptide pseudostellarin D. Moreover, we have also successfully synthesized the bioactive cyclic heptapeptide pseudostellarin D using this system. Notably, FPID can be easily regenerated after peptide coupling reaction in SPPS. These results, along with the successful use of the FPID/(4-$MeOC_6H_4)_3P$ system in the solution-phase linear peptide synthesis [29], show its potential in the practical application in peptide synthesis.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of all products, copies of ^1H, ^{13}C, HPLC, HRMS spectra of some compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-97-S1.pdf]

Acknowledgements

This work was financially supported by National Key R&D Program of China (2017YFD020030202), The National Natural Science Foundation of China (21472094, 21172110, 21421062) and The Tianjin Natural Science Foundation (17JCYBJC20300). We are grateful to MS. Bo Sun for the preliminary investigation of this project.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Rapid transformation of sulfinate salts into sulfonates promoted by a hypervalent iodine(III) reagent

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Letter

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Keywords:
hypervalent iodine; oxidation; sulfinates; sulfonation; sulfonium

Beilstein J. Org. Chem. **2018,** *14,* 1203–1207.
doi:10.3762/bjoc.14.101

Received: 13 February 2018
Accepted: 08 May 2018
Published: 24 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

An alternative method for forming sulfonates through hypervalent iodine(III) reagent-mediated oxidation of sodium sulfinates has been developed. This transformation involves trapping reactive sulfonium species using alcohols. With additional optimization of the reaction conditions, the method appears extendable to other nucleophiles such as electron-rich aromatic systems or cyclic ethers through a ring opening pathway.

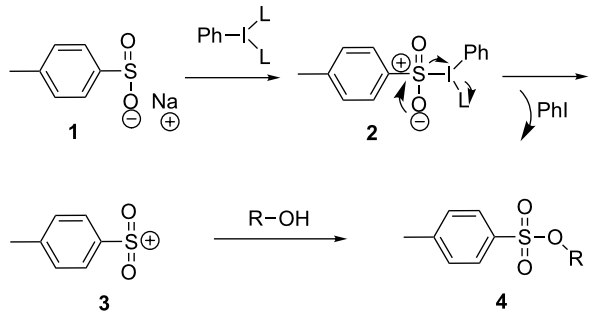
Introduction

Over the past few decades, hypervalent iodine reagents [1-4] have emerged as versatile and environmentally benign substitutes for heavy metal reagents. A number of iodanes with various oxidation states have been developed since the pioneering work of the German chemist Willgerodt, who synthesized $PhICl_2$ [5]. Iodane reagents have been extensively used in applications such as oxidation, rearrangement, cross-coupling, functionalization, decarboxylation, and fragmentation [6-27]. The sulfonate group is a useful functionality frequently employed as a leaving group in substitution reactions. Production of sulfonates [28] from alcohols generally involves reaction with a sulfonyl chloride in the presence of a base to trap the hydrochloric acid byproduct. As an alternative method involving oxidation rather than chloride substitution, we envisaged generating an electrophilic sulfonium species through oxidation of a sulfinate salt [29] that would be subsequently trapped by the alcohol. In this paper, we demonstrate that sulfonates may be produced from alcohols in the presence of sufinates through a reaction mediated by a hypervalent iodine reagent. Under these conditions, the byproduct is a weak acid such as acetic acid rather than hydrochloric acid.

Results and Discussion

Oxidative sulfonate production methods employing strong oxidizing agents such as chlorine have been previously reported [30]. More recently, a mild and efficient method

enabling the production of aromatic sulfonates using phenols and iodine was developed [31,32]. This method uses methanol as a solvent and appears to be selective for phenols; only two primary alcohol examples were produced in 63–67% yield in the presence of a strong base. A radical pathway from the alkoxide species was proposed by the authors as an explanation for the phenol selectivity under weakly basic conditions in the presence of methanol. As a complement to this interesting method, we propose extending the process to aliphatic alcohols through activation by an iodane, acting through an alternative pathway involving a sulfonium species derived from a sulfinate **1**. It should be noted that our method would not be compatible in presence of phenols. We hypothesized that the mechanism would initially involve iodane activation of the sulfur lone pair leading to **2**. Elimination of the iodane would subsequently produce the sulfonium ion **3**, which could be trapped by an alcohol nucleophile leading to sulfonate **4** (Scheme 1).

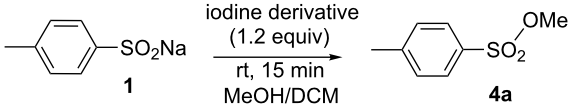


Scheme 1: Mechanistic hypothesis.

To verify our hypothesis tosyl-sulfinate **1** was treated with iodanes such as sodium periodate ($NaIO_4$), Dess-Martin periodinane (DMP) [33], 2-iodoxybenzoic acid (IBX) [34], (diacetoxyiodo)benzene (DIB), phenyliodine(III) bis(trifluoroacetate) (PIFA) in the presence of methanol. (III)-Iodanes and (V)-iodanes were both acceptable substrates, but the process was inefficient with (VII)-iodane species. We surmise that IBX and DMP are rapidly reduced to a (III)-iodane in the presence of an alcohol, and that this species is most likely the reagent promoting the formation of compound **4a**. Iodine and *N*-iodosuccinimide (NIS) were also tested; it appeared that this process was much more efficient in the presence of iodane sources (Table 1).

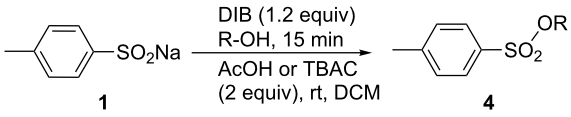
DIB was chosen as the hypervalent iodine reagent of choice since it is more compatible with alcohols than IBX or DMP. The reaction proceeded in modest to good yields depending on the structure of the alcohol. We were pleased to observe successful transformations even in the presence of poorly reactive alcohols such as trifluoroethanol (TFE, Table 2, entry c) or hexafluoroisopropanol (HFIP, Table 2, entry d). Because of the mild conditions involved, this transformation tolerates spectator functionalities such as primary halides or alkynes (Table 2).

Table 1: Oxidative sulfonylation process mediated by iodine and iodine derivatives.



entry	iodane	yield (%)
a	$NaIO_4$	–
b	IBX	89
c	DMP	98
d	DIB	98
e	PIFA	98
f	I_2	48
g	NIS	58

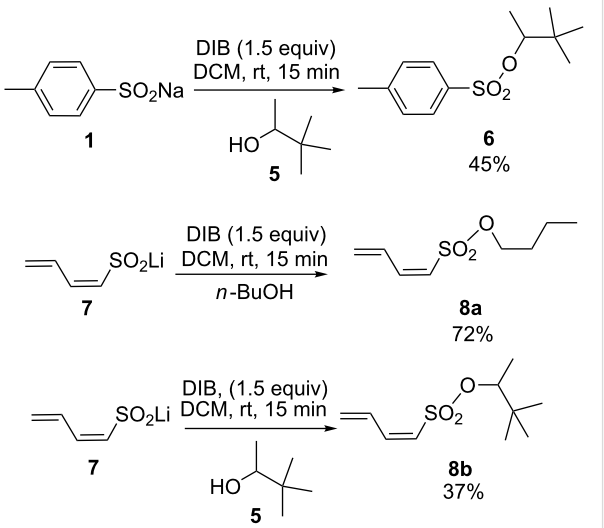
Table 2: Scope and limitations of the process.



entry	R-OH	yield (%)
a	Me-OH	99
b	Et-OH	75
c	CF_3CH_2-OH	95
d	$(CF_3)_2CH$-OH	48
e	$(CH_3)_2CH$-OH	74
f	$ClCH_2CH_2$-OH	51
g	$BrCH_2CH_2CH_2$-OH	51
h	*n*-Bu-OCH_2CH_2-OH	57
i	$HC{\equiv}CCH_2$-OH	81
j	$CH_3CHOH(CH_2)_2CH_3$	60
k	$CH_3CH_2CH(CH_3)CH_2$-OH	76
l	$ClCH_2CH(CH_3)$-OH	65
m	Ph-CH_2-CH_2-OH	50
n	*t*-Bu-OH	–
o	*n*-Bu-OH	70
p	cyclopentanol	63

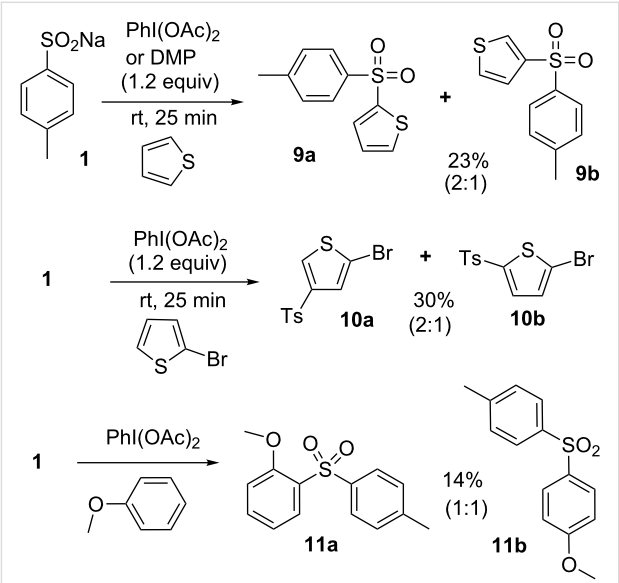
We were disappointed to observe no reaction in the presence of tertiary alcohols such as *tert*-butanol (Table 2, entry n). However, the reaction proceeded efficiently with a hindered secondary neopentylic alcohol **5** despite the presence of the neighboring *tert*-butyl group. This method could potentially be extended to other sulfinate salts, particularly aromatic or vinylic species in

which the intermediate sulfonium species would be resonance stabilized. However, most commercially available sulfinates are quite expensive. It was reported in the literature that compound **7** may be easily generated from sulfolene by treatment with *n*-butyllithium [35]. This compound is further oxidized by DIB in the presence of *n*-butanol to yield sulfonate **8a** in 72% yield. The same reaction in the presence of the hindered neopentilyc alcohol **5** led to the formation of **8b** in modest yield (Scheme 2).



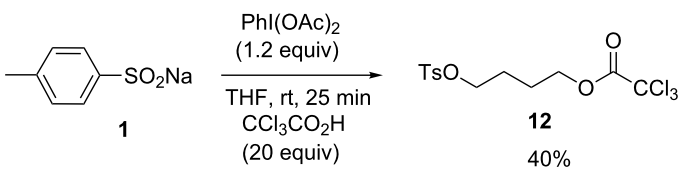
Scheme 2: Extension of the method.

As a demonstration of the potential of this novel approach, we examined the possibility of involving other nucleophiles, including carbon-based nucleophiles. For instance, the alcohol in the reaction could be replaced by an electron-rich aromatic system such as thiophene or anisole. It should be stressed that the formation of substituted aromatic systems through a Friedel–Crafts type process [36] is an argument in favor of the formation of the electrophilic sulfonium species **3** (Scheme 1). In the presence of thiophene, compounds **9** were obtained in 23% yield and in a ratio (2:1) in favour of **9a**. A similar yield was observed when DMP was substituted for DIB, demonstrating that λ^5-iodanes can also promote sulfonium activation. The reaction in the presence of 2-bromothiophene led in 30% yield to the formation of compounds **10** in a ratio (2:1) in favor of **10a**. If anisole was used instead of thiophene an expected mixture of compounds **11a** and **11b** was observed in a ratio 1:1 and in a low yield of 14%. So far, the yields observed with carbon-based nucleophiles have been low, but they clearly demonstrate the feasibility of this approach. Further investigations to extend this approach to other carbon-based nucleophiles must be developed. Presumably, the presence of an electron-donor group such as methoxy on the aromatic moiety would stabilize the sulfonium species and increase the yield obtained in these transformations (Scheme 3).



Scheme 3: Carbon-based nucleophiles.

This process may also be used to open and functionalize simple heterocycles such as THF through a ring-opening approach [37]. In the presence of trichloroacetic acid and DIB, the corresponding compound **12** was obtained in 40% yield. One advantage is that this method begins with the inexpensive compound THF and produces a diol derivative containing a linear chain in only one step. One alcohol is available as a leaving group and the second is protected by conversion into a trichloroacetate moiety (Scheme 4).



Scheme 4: THF ring opening.

Conclusion

A novel oxidative method for producing sulfonates from sulfinates using hypervalent iodine reagents has been developed. This process involves the formation of a reactive sulfonium species that is subsequently trapped by nucleophiles. As a proof of concept, we demonstrated that the method is extendable to other nucleophiles such as electron-rich aromatics or THF. Ongoing investigations of this process and potential applications will be disclosed in due course.

Experimental

General procedure for the formation of sulfonate **4**

Iodobenzene diacetate (DIB, 0.24 mmol, 1.2 equiv) was added at room temperature to a vigorously stirred solution of dichloromethane (0.5 mL), alcohol (0.5 mL), sulfinate (0.2 mmol, 1 equiv) and acetic acid (0.01 to 0.05 mL) or TBAC (55.5 mg, 0.2 mmol, 2 equiv) to dissolve the sulfonate salt. The mixture was then stirred for 15 min and filtered on silica with ethyl acetate. The residue was purified using silica gel chromatography to yield sulfonate product **4**.

Supporting Information

Supporting Information File 1

General procedures, synthesis of the products, spectroscopic data, and copies of ^{1}H, ^{13}C, NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-101-S1.pdf]

Acknowledgements

We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), and the provincial government of Quebec (FQRNT and CCVC) for their precious financial support in this research.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Rhodium-catalyzed C–H functionalization of heteroarenes using indoleBX hypervalent iodine reagents

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Letter

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Keywords:
C–H activation; hypervalent iodine; indoleBX; indoles; pyridinones; rhodium catalysis

Beilstein J. Org. Chem. **2018,** *14,* 1208–1214.
doi:10.3762/bjoc.14.102

Received: 07 March 2018
Accepted: 09 May 2018
Published: 25 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The C–H indolation of heteroarenes was realized using the benziodoxolone hypervalent iodine reagents indoleBXs. Functionalization of the C–H bond in bipyridinones and quinoline *N*-oxides catalyzed by a rhodium complex allowed to incorporate indole rings into aza-heteroaromatic compounds. These new transformations displayed complete regioselectivity for the C-6 position of bipyridinones and the C-8 position of quinoline *N*-oxides and tolerated a broad range of functionalities, such as halogens, ethers, or trifluoromethyl groups.

Introduction

Nitrogen-containing heteroaromatic compounds have valuable properties in medicinal chemistry, pharmacology and functional materials. Among those, pyridinone, sometimes called pyridone, is a key structural motif of well-known active compounds and natural products (Figure 1) [1]. For example, the 2-pyridinone ring is present in milrinone (**1**), used to treat heart failure, while a 4-pyridinone is part of mimosine (**2**), an alkaloid isolated from *Mimosa pudica*. A benzene-fused pyridinone – a quinolone – can be found in brexpiprazole (**3**), a drug used against schizophrenia. In addition, the indole core is also omnipresent in bioactive compounds [2]. It can be directly bound to other heterocycles, such as a dihydropyrazidinone in hamacanthine A (**4**) (Figure 1) [3]. Due to their occurrence in biologically active compounds, it is therefore attractive to develop new methods to functionalize pyridinones. The introduction of further heterocyclic rings, such as indoles, is particularly attractive.

Most of the methods for indolylpyridinone synthesis involve a condensation cascade process to generate the pyridinone ring [4-6]. These methods usually require an electron-withdrawing group (nitrile, nitro, carbonyl), which ends up on the pyridi-

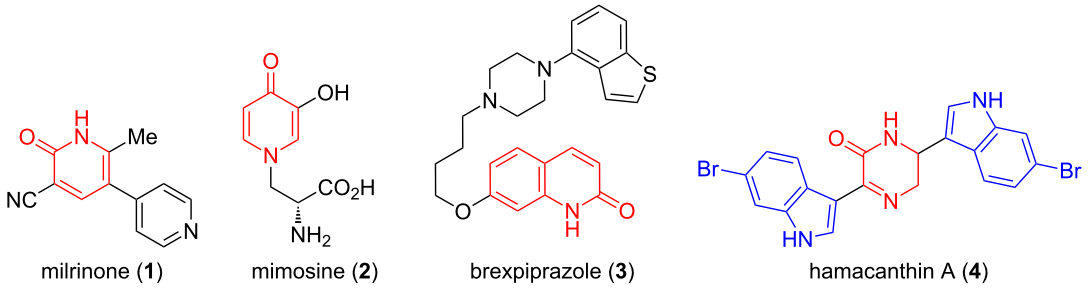
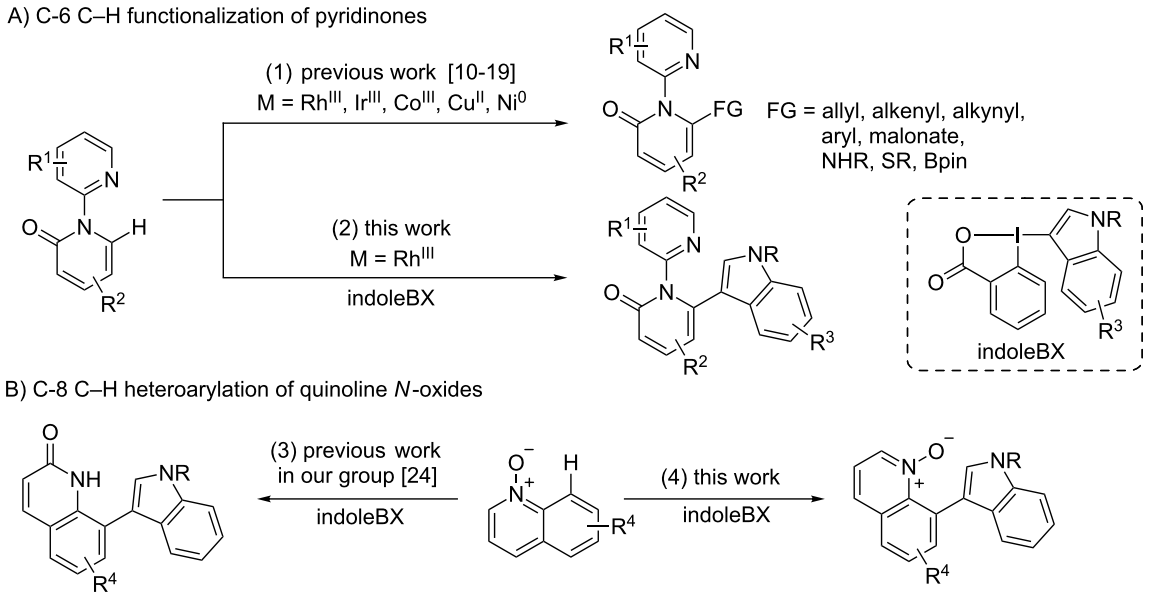


Figure 1: Bioactive compounds with pyridinone, quinolone and indole cores.

none ring. As alternative, a Suzuki–Miyaura coupling between 3-halogenoindoles and (2-methoxypyridyl)boronic acids followed by a deprotection of the methoxy group [7,8] or transition-metal-catalyzed annulation methods [9] have also been reported.

In contrast, several procedures have been described for the modification of pyridinones to introduce other substituents, especially based on highly efficient C–H functionalization methods [10]. Very recently, several research groups have selectively functionalized the C-6 C–H bond by using a 2-pyridyl directing group on the nitrogen and a transition metal catalyst (reaction 1, Scheme 1A) [11-19]. In particular, Li and co-workers have used ethynylbenziodoxolone (EBX) hypervalent iodine reagents to achieve a regiodivergent alkynylation of the pyridinone core employing either a gold(I) or a rhodium(III) catalyst for C-5 and C-6 functionalization, respectively [13]. Hypervalent iodine reagents in general [20], and benziodoxole derivatives in particular [21], have found broad application in synthetic chemistry. Aryl iodonium salts have been used successfully in transition-metal-catalyzed transformations [22], but only one application of indole iodonium salts in copper catalysis by You and co-workers had been reported until 2017 [23]. In this context, indole-based benziodoxole hypervalent iodine reagents, recently introduced by Yoshikai's and our group [24-27], appeared ideal partners to develop a new C–H heteroarylation of pyridinones.

Herein, we report the selective C–H heteroarylation of the C-6 position of bipyridinones by a rhodium-catalyzed reaction with indoleBX (reaction 2, Scheme 1A). In addition, we demonstrate that the mild conditions developed allow the heteroarylation of the C-8 position of quinoline *N*-oxides, whereas formation of the quinolinone had been observed in our previous work (Scheme 1B). The obtained products combine up to three classes of privileged heterocycles in medicinal chemistry in a



Scheme 1: C–H functionalization of pyridinones and quinoline *N*-oxides.

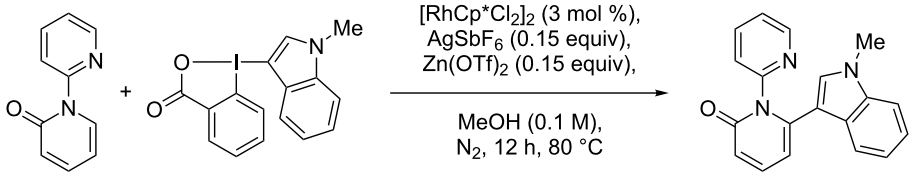
single compound, and are therefore expected to be highly useful building blocks in the search for new bioactive compounds.

Results and Discussion

We started the studies on C–H indolation with the optimization of the reactions conditions (Table 1) for the coupling of [1,2'-bipyridin]-2-one (**5a**) with Me-indoleBX **6a**, easily obtained from commercially available 1-methylindole and 2-iodobenzoic acid [24]. While the reaction conditions previously developed in our group for the C–H functionalization of 2-phenylpyridine [24] failed for the coupling of **5a** with **6a** (Table 1, entry 1), we were pleased to see that addition of 0.15 equiv $Zn(OTf)_2$ allowed a full conversion to the desired product **7a** in 86% yield (Table 1, entry 2). The Lewis acid is supposed to weaken the O–I bond by coordination of the carboxy group in **6a**. No base was required in this case. The reaction was completely selective for the C-6 position of the pyridinone ring. Control experiments pointed out that both Lewis acid (Table 1, entry 3) and $AgSbF_6$ as additive (Table 1, entry 4) were necessary for an efficient reaction. The transformation was tolerant to air (Table 1, entry 5). However, more byproducts were observed. Decreasing the temperature (Table 1, entry 6) or the catalyst loading (Table 1, entry 7) resulted in lower yields. Finally, three control experiments with 1-methylindole (**8**, Table 1, entry 8), 3-iodo-1-methylindole (**9**, Table 1, entry 9) and the poorly stable (1*H*-indol-3-yl)(phenyl)iodonium tetrafluoroborate [23] (**10**, Table 1, entry 10) did not lead to the formation of **7a**, highlighting the unique reactivity of the benziodoxolone hypervalent iodine reagent.

The scope and limitations of the reaction were then studied (Scheme 2). The diversification of the directing group was examined first. The unsubstituted pyridine group led to the formation of product **7a** in 86% yield. The electron-rich 5-methoxypyridine and the electron-poor 5-trifluoromethylpyridine directing groups gave products **7b** and **7c** in 82% and 72% yield, respectively. When a nitro group was present on the pyridine (**5d**), the product was not observed, probably due to a weaker coordination of the nitrogen on the pyridine. Pyrimidine could not be used as directing group (**5e**), confirming what has already been reported by others authors [13]. Quinoline **7f** was obtained in 79% yield. Concerning the pyridinone core, both an electron-donating methyl group and electron-withdrawing trifluoromethyl and fluoro groups (**7g–i**) were well tolerated in the C-3 position. However, the strong electron-withdrawing CF_3 group resulted in a lower 65% yield (**7h**). This observation is also true for the C-4 position. Indeed, products **7j–l** were synthesized in 78% yield for a methyl, 66% yield for a trifluoromethyl and 84% yield for a benzyloxy substituent. As previously reported [13], 5-substituted pyridinone **5m** could not

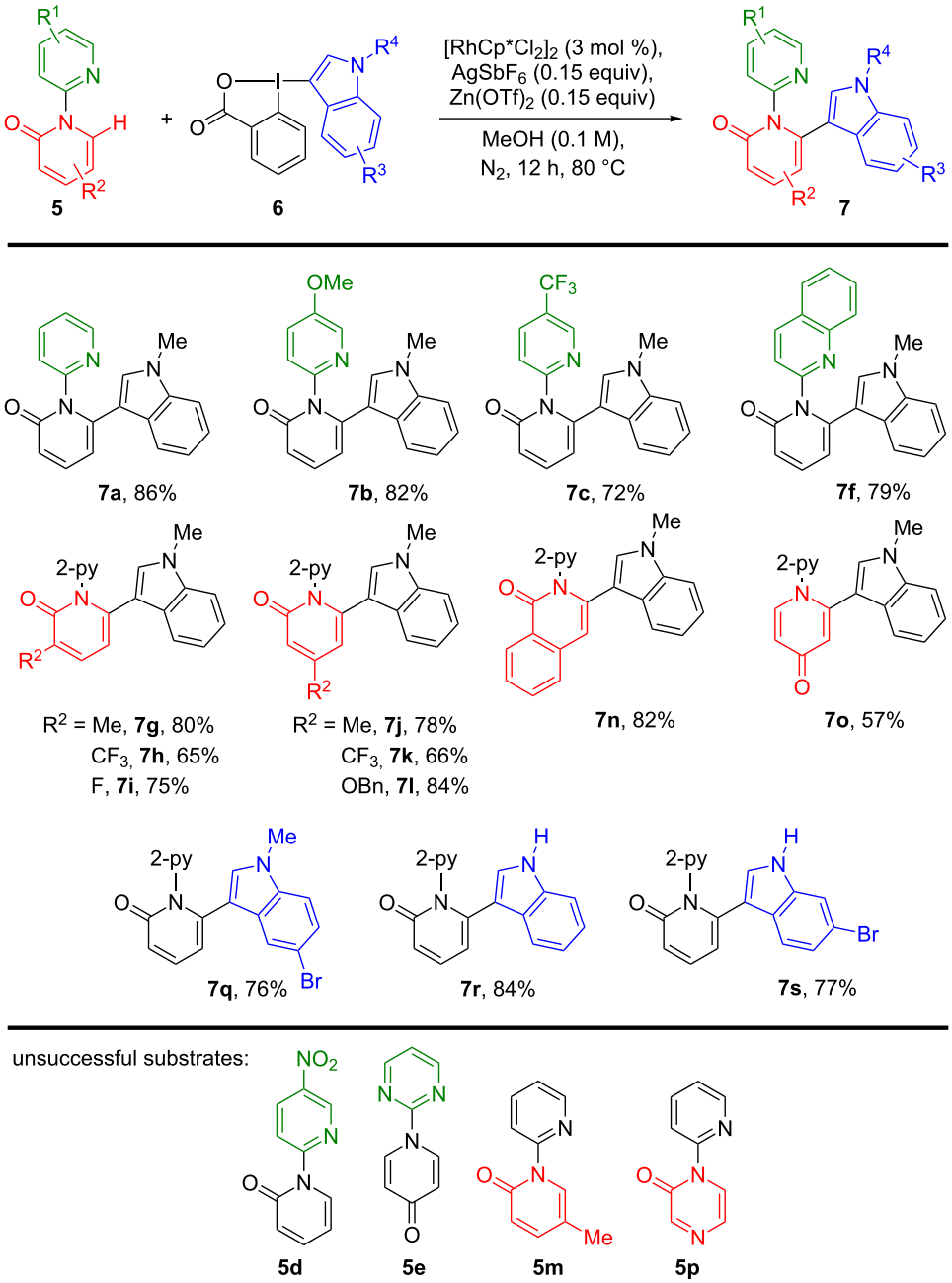
Table 1: Optimization of the C–H heteroarylation[a,b].



5a **6a** **7a**

Entry	Changes from conditions	Yield (%)
1	$[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (0.10 equiv), NaOPiv (0.10 equiv), DCE, 12 h, 50 °C	no reaction
2	–	86
3	without $Zn(OTf)_2$	no reaction
4	without $AgSbF_6$	60
5	under air atmosphere	80
6	60 °C	48
7	1 mol % of $[RhCp^*Cl_2]_2$	75
8	1-methylindole (**8**)	no reaction
9	3-iodo-1-methylindole (**9**)	0[c]
10	iodonium salt **10**	0[c]

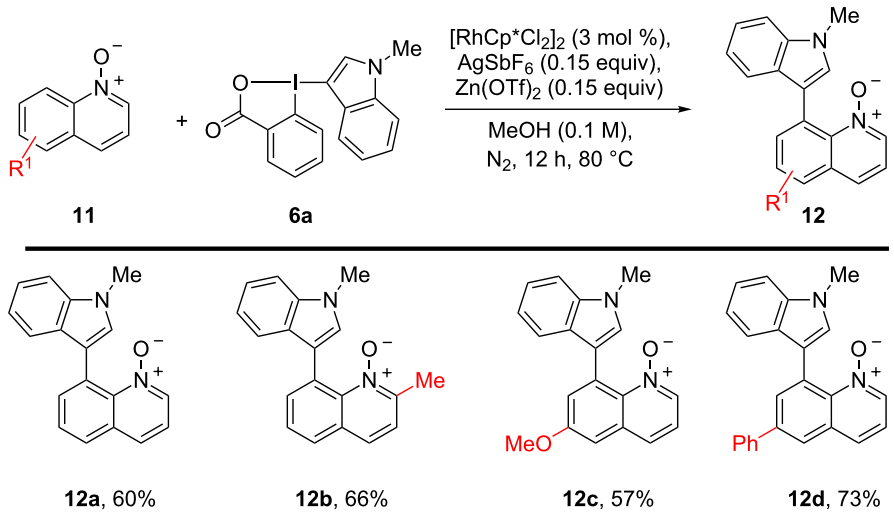
[a]Reactions conditions: **5** (0.20 mmol), **6** (0.20 mmol), $[RhCp^*Cl_2]_2$ (3.7 mg, 6.0 μmol, 3 mol %), $AgSbF_6$ (10.3 mg, 30.0 μmol, 0.15 equiv), $Zn(OTf)_2$ (10.9 mg, 30.0 μmol, 0.15 equiv), methanol (2.0 mL) at 80 °C for 12 h. [b]Isolated yield after preparative TLC. [c]Decomposition.



Scheme 2: Scope and limitations of the Rh-catalyzed C–H activation of [1,2'-bipyridin]-2-one.

be functionalized. Isoquinolone **7n** was prepared in 82% yield. The methodology could also be applied to 4-pyridone in a moderate 57% yield for product **7o**. Unfortunately, pyrazin-2-one **5p** could not be functionalized. Modification of the hypervalent iodine reagent was then investigated with three selected compounds only. A bromo substituent on the benzene ring was well tolerated (**7q**). The coupling could be also performed with N–H unprotected indoleBX reagents to afford products **7r** and **7s** in 84% and 77% yield, respectively.

We also applied these conditions to different quinoline *N*-oxides (Scheme 3). This class of substrates had also been used for C–H alkynylation using EBX reagents [28]. During our previous work, we had attempted the C8-heteroarylation of quinoline *N*-oxide with Me-indoleBX **6a**. However, the transformation required a temperature of 100 °C, leading to the formation of the corresponding isoquinolone in only 38% yield [24]. By employing the milder conditions developed for pyridinones, we were pleased to see that the *N*-oxide group could be preserved and



Scheme 3: Scope of the Rh-catalyzed *peri* C–H activation of quinoline *N*-oxides.

product **12a** was obtained in 60% yield. A methyl substitution in C-2 position gave the product **12b** in 66% yield. In C-6 position both a methoxy and a phenyl group were well tolerated giving 57% and 73% yield of products **12c** and **12d**.

The pyridine directing group could be cleaved by alkylation of the pyridine nitrogen using methyl triflate followed by reduction with sodium cyanoborohydride to deliver the N–H unprotected pyridinone **13** in 74% yield (Scheme 4) [29]. A rearrangement of the *N*-oxide furnished the corresponding isoquinolone **14** in 62% yield.

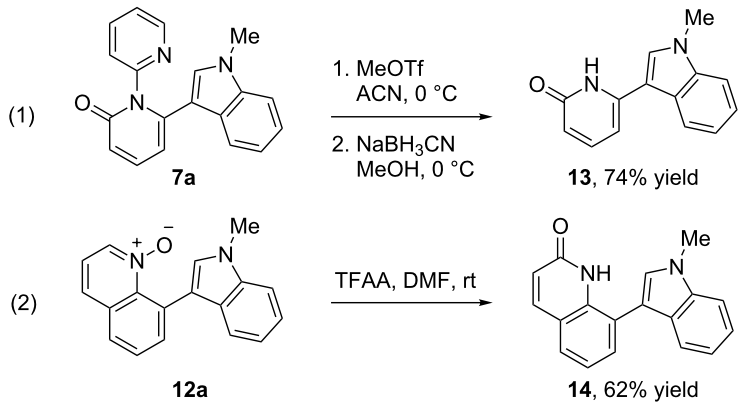
Conclusion

In summary, we have developed the C-6 selective C–H heteroarylation of pyridin-2-ones using indoleBXs as coupling partners, $[RhCp^*Cl_2]_2$ as catalyst, $AgSbF_6$ as co-catalyst and $Zn(OTf)_2$ as Lewis acid. The reaction could also be applied to functionalize one pyridin-4-one in C-6 position, one isoquinolinone in C-3 position and quinoline *N*-oxides in C-8 position. After cleavage of the directing group or rearrangement of the *N*-oxide function, we were able to access 6-(indol-3-yl)pyridinone and 8-(indol-3-yl)quinolone. The developed transformations give access to important heterocyclic building blocks for synthetic and medicinal chemistry and set the stages for the development of other C–H heteroarylation processes based on indoleBX reagents.

Experimental

General procedure for C–H heteroarylation

In a sealed tube, $[RhCp^*Cl_2]_2$ (3.7 mg, 6.0 µmol, 3 mol %), $AgSbF_6$ (10.3 mg, 30.0 µmol, 0.15 equiv), $Zn(OTf)_2$ (10.9 mg, 30.0 µmol, 0.15 equiv), the corresponding pyridinone or quino-



Scheme 4: Product modifications.

line *N*-oxide (0.20 mmol, 1.00 equiv) and the corresponding hypervalent iodine reagent (0.20 mmol, 1.00 equiv) were solubilized in dry MeOH (2.0 mL, 0.1 M) under N_2 atmosphere. The mixture was stirred at 80 °C for 12 h. The mixture was then diluted with DCM (5 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The two layers were separated and the aqueous layer was extracted twice with DCM (5 mL). The organic layers were combined, dried over magnesium sulfate dehydrate, filtered and concentrated under reduced pressure. The crude residue was purified by preparative TLC using DCM/MeOH to afford the pure desired compound.

Supporting Information

Supporting Information File 1

Detailed experimental procedures, analytical data for all compounds and copies of the NMR spectra of new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-102-S1.pdf]

Acknowledgements

This work is supported by the ERC starting grant 334840, iTools4MC, by the Swiss National Science Foundation (No. 200021_159920), the COST action CA15106 (C-H Activation in Organic Synthesis, CHAOS) and EPFL.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Investigations of alkynylbenziodoxole derivatives for radical alkynylations in photoredox catalysis

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Full Research Paper

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Keywords:
acyl radical; alkyl radical; alkynylbenziodoxoles; photoredox catalysis; radical alkynylation

Beilstein J. Org. Chem. **2018,** *14,* 1215–1221.
doi:10.3762/bjoc.14.103

Received: 12 February 2018
Accepted: 04 May 2018
Published: 28 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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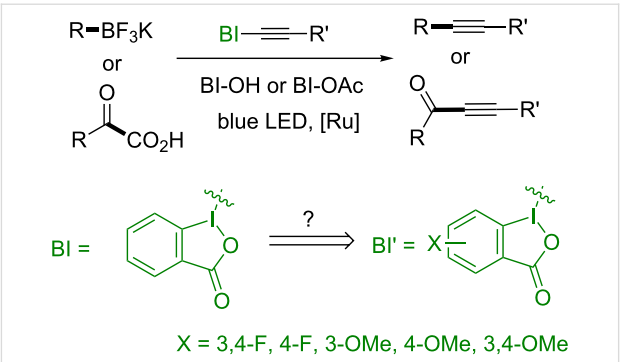
Abstract

The alkynylbenziodoxole derivatives are recently developed alkynylation reagents in organic synthesis, which demonstrate excellent radical alkynylation reactivity in photoredox catalysis reactions. Herein we report the synthesis of alkynylbenziodoxole derivatives with difluoro, monofluoro, monomethoxy, and dimethoxy substitution on the benziodoxole moiety, and investigated their radical alkynylation reactivity for the first time. A series of mechanistic experiments were conducted to study the radical acceptor and oxidative quencher reactivity of alkynylbenziodoxoles, in which unsubstituted alkynylbenziodoxoles played balancing roles in both processes, while electron-rich benziodoxole derivatives demonstrate synthetic advantages in some cases.

Introduction

The introduction of the alkynyl group to organic molecules is an important synthetic transformation in organic synthesis [1-4]. Recently, cyclic iodine(III) reagents (CIR)-substituted alkynes, alkynylbenziodoxoles, were developed with readily preparation and shelf-stableness [5-10]. The alkynylbenziodoxoles were first synthesized by the Ochiai group, and later studied by Waser and other groups for the use in electrophilic alkynylation reactions [11-18]. In 2012, the Li group first used alkynylbenziodoxoles for decarboxylative radical alkynylation under silver salt and persulfate conditions [19]. In 2014, the Chen group discovered that alkynylbenziodoxoles (BI-alkyne) readily participated in photoredox catalysis as the radical alkynylation reagent [20], after which various applications in photoredox catalysis were reported [21-27].

Currently, the use of BI-alkyne for radical alkynylation is limited to unsubstituted alkynylbenziodoxoles. While effective, its reactivity with some radical precursors was compromised [19-27]. The Waser group pioneered the study of substituted alkynylbenziodoxoles for the electrophilic alkynylation reactivity, however, no significant improvements were observed by the derivatizations [28-32]. Herein, we report the synthesis of alkynylbenziodoxole derivatives and investigate their reactivity toward alkyl radical and acyl radical additions in photoredox catalysis. The mechanistic investigations were carried out to study the derivatization of BI-alkynes in radical acceptor and oxidative quencher reactivity, and the electron-rich benziodoxole derivatives demonstrated synthetic advantages in some cases (Scheme 1).

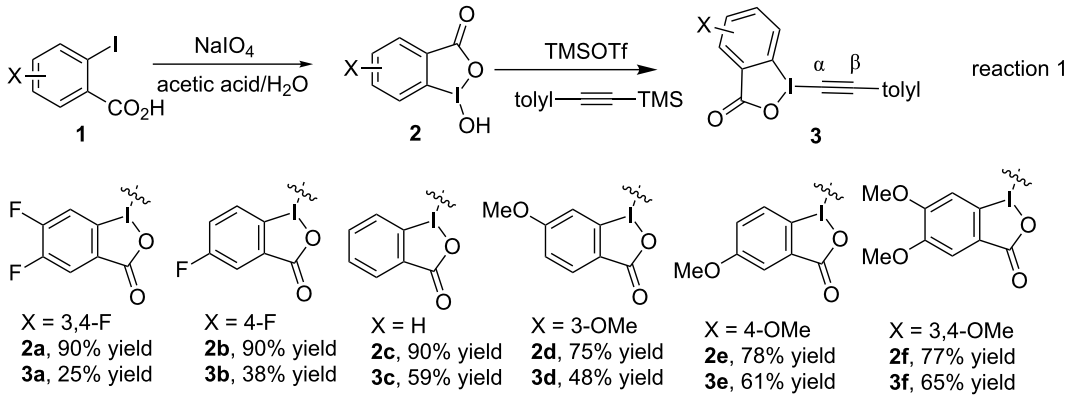


Scheme 1: Investigation of alkynylbenziodoxole derivatives for radical alkynylations.

Results and Discussion

We started the synthesis of BI-alkyne derivatives with substituted *o*-iodobenzoic acids **1** bearing 3,4-difluoro, 4-fluoro, 3-methoxy, 4-methoxy, or 3,4-dimethoxy substitutions (Scheme 2). Using a slightly modified Ochiai procedure [11], the substituted hydroxybenziodoxoles **2a**–**f** were prepared with periodate oxidation in 75–90% yield, in which the electronic effect did not have much influence on the reaction [33]. Subsequently, the treatment with trimethylsilyl *p*-tolylacetylene in the presence of trimethylsilyl trifluoromethanesulfonate afforded *p*-tolylacetylenic benziodoxoles **3a**–**f** in 25–65% yield, in which the electron-donating substitutions were beneficial for the reaction. The two-step synthesis of BI'-alkyne derivatives **3a**,**b**,**d**–**f** were in the range of 23–50% yield in gram scale, which was comparable to the synthesis of unsubstituted BI-alkyne **3c**.

The ^{13}C NMR spectra of BI-alkynes **3a**–**f** were studied with the focus on the α-carbon, which position directly underwent α-radical addition [19]. The electron density of the α-carbon was decreased in **3a** with electron-deficient 3,4-difluoro groups on the benziodoxole, and was increased for **3f** with electron-donating 3,4-dimethoxy groups. Cyclic voltammetry measurements were also carried out for BI-alkynes **3a**–**f**, in which the reduction potential (*E*p re) indicated the electron-accepting capacity of the BI-alkynes. As expected, the reduction potential of **3a** was increased with electron-deficient 3,4-difluoro substituents on the benziodoxole, and was decreased for **3f** with elec-



^{13}Cα (ppm)	110.7	105.5	107.2	105.2	105.0	104.9
^{13}Cβ (ppm)	56.6	51.0	49.3	52.9	56.4	52.5
*E*p re (V vs SCE in MeCN)	1.97	1.94	1.87	1.91	1.87	1.78
*E*p ox (V vs SCE in MeCN)	–0.95	–1.06	–1.20	–1.09	–1.20	–1.12

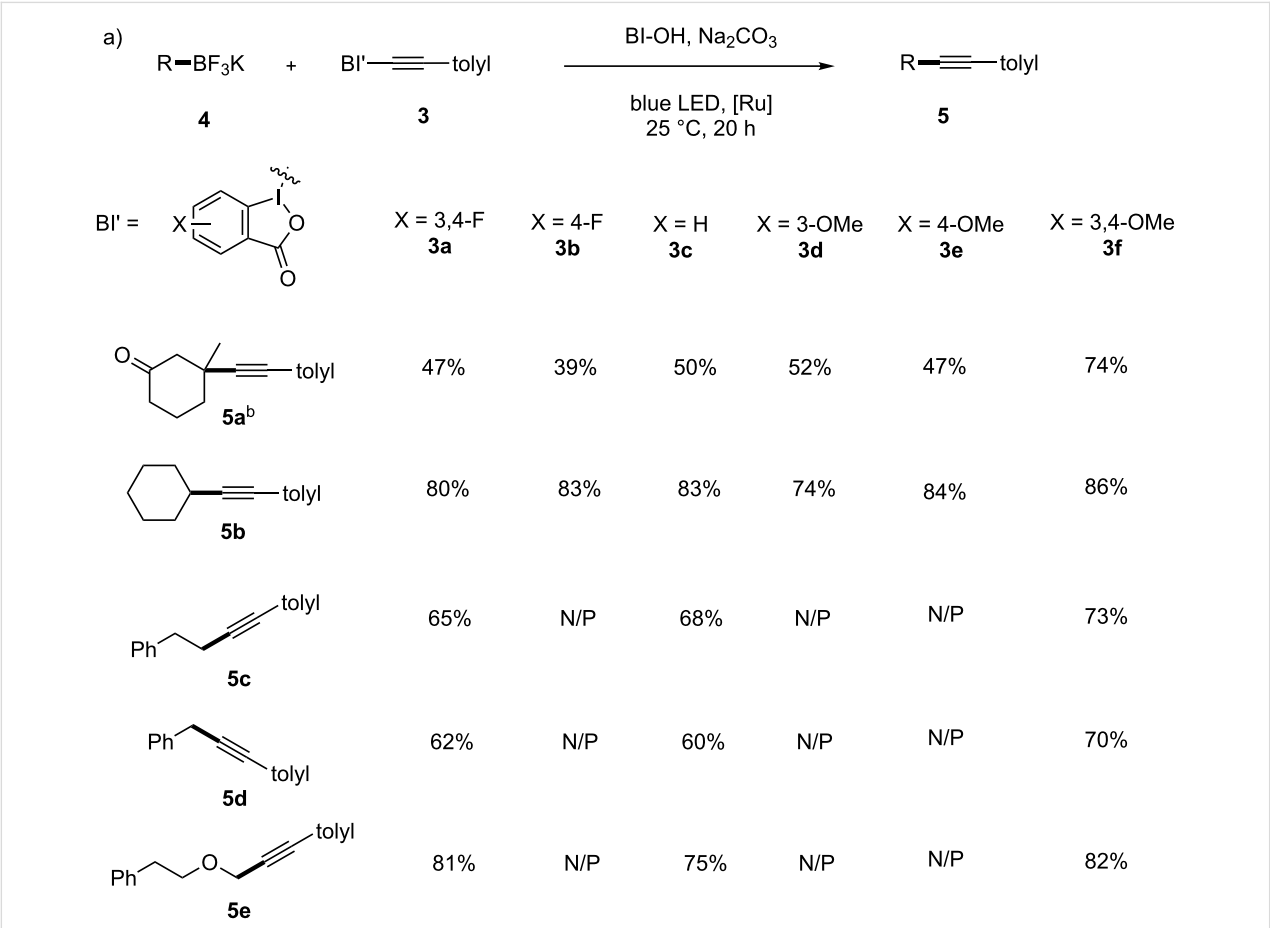
Scheme 2: Synthesis and characterization of BI-alkyne derivatives **3a**–**f**.

tron-donating 3,4-dimethoxy groups. It is interesting to note that the effect of single substitution on benziodoxoles in **3b**, **3d** and **3e** was insignificant and sporadical in both ^{13}C NMR spectroscopy and cyclic voltammetry experiments.

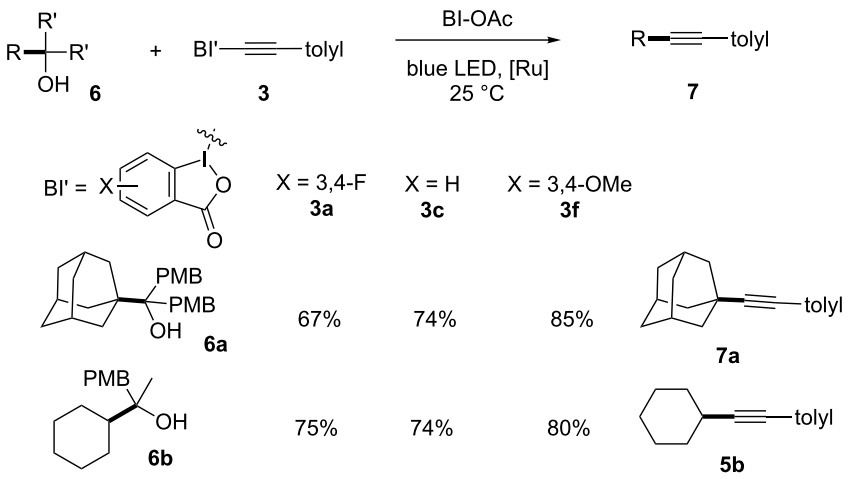
We next tested the reactivity of tolylacetylenic benziodoxole derivatives **3a**–**f** for deboronative alkynylation under photoredox catalysis conditions (Scheme 3) [20,34]. Using the tertiary alkyl trifluoroborate **4a** as the alkyl radical precursor under literature conditions, the unsubstituted BI-alkyne **3c** only results in 50% yield of alkynylation adduct **5a**, which is consistent with the literature report that tertiary alkyl trifluoroborates did not give satisfying results [20]. Using BI'-alkyne **3a** with 3,4-difluoro substitutions, the alkynylation adduct **5a** was obtained in decreased 47% yield. In contrast, 74% yield of **5a** was obtained with 3,4-dimethoxy-substituted BI'-alkyne **3f**. Being consistent with the ^{13}C NMR spectroscopy and cyclic voltammetry experiments, the effect of single substitution on the benziodoxole was insignificant and no improvement was observed.

We also tested the secondary alkyl trifluoroborate **4b** and primary alkyl trifluoroborate **4c**, in which the deboronative alkynylation with unsubstituted BI-alkynes already gave good results. The electronic effects on the benziodoxoles were less significant and fluctuated within the 5% yield range: The alkynylation adducts **5b** and **5c** were obtained in decreased 80% and 65% yields using BI'-alkyne **3a**, while 86% and 73% yields of **5b** and **5c** were obtained with BI'-alkyne **3f**. We then tested benzyl trifluoroborate **4d** and oxygen-substituted alkyl trifluoroborate **4e**, which were not reported for deboronative alkynylations before. The 3,4-dimethoxy-substituted BI'-alkyne **3f** gave the optimal 70% and 82% yields of alkynes **5d** and **5e**, which observed ≈10% yield improvement comparing to the unsubstituted BI-alkyne **3c**.

We then tested if the propensity of BI-alkyne derivatives toward alkyl radical additions was general and could extend to other alkyl radical precursors (Scheme 4). Tertiary alcohols **6** were reported to be activated by cyclic iodine(III) reagents under



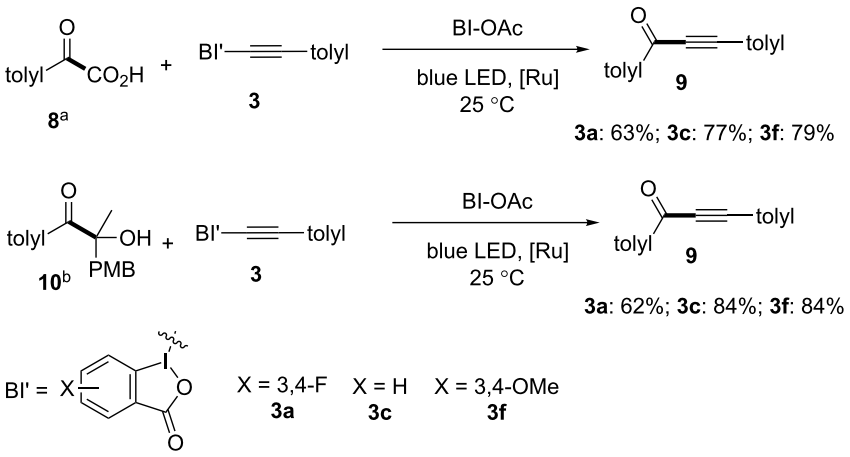
Scheme 3: Reaction of alkynylbenziodoxole derivatives for deboronative alkynylation in photoredox catalysis. Reaction conditions: a) alkyl potassium trifluoroborate **4** (0.15 mmol, 1.5 equiv), alkynylbenziodoxole **3** (0.10 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (1.7 mg, 0.002 mmol, 0.02 equiv), hydroxybenziodoxole (BI-OH, 0.05 mmol, 0.5 equiv), and Na_2CO_3 (0.2 mmol, 2.0 equiv) in 1.0 mL CH_2Cl_2 and 1.0 mL H_2O for 20 h under a nitrogen atmosphere, unless otherwise noted; b) **4** (0.3 mmol, 3.0 equiv), Na_2CO_3 (0.4 mmol, 4.0 equiv). Yields are isolated yields. N/P = not performed.



Scheme 4: Reaction of alkynylbenziodoxole derivatives for radical alkynylations in photoredox catalysis. Reaction conditions: tertiary alcohol **6** (0.25 mmol, 2.5 equiv), alkynylbenziodoxole **3** (0.10 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (0.002 mmol, 0.02 equiv), and BI-OAc (0.25 mmol, 2.5 equiv) in 2.0 mL DCE for 24 h under a nitrogen atmosphere, unless otherwise noted. Yields are isolated yields.

photoredox conditions to generate alkoxyl radicals, and subsequently underwent β-fragmentation and alkynylation to yield **7** after eliminating the arylketone [25]. With tertiary alcohol **6a** as the alkyl radical precursor, the unsubstituted BI-alkyne **3c** gave 74% yield of **7a**, which was consistent with the literature report [25]. Under otherwise identical reaction conditions, 67% yield of **7a** was obtained with 3,4-difluoro BI'-alkyne **3a**, while optimal 85% yield of **7a** was obtained with 3,4-dimethoxy BI'-alkyne **3f**. We then tested the secondary alkyl radical precursor **6b** and observed 74% yield of alkyne **5b** using unsubstituted BI-alkyne **3c**. In contrast, 3,4-dimethoxy BI'-alkyne **3f** gave improved 80% yields of **5b**.

We finally moved to test the BI-alkyne derivatives toward acyl radical additions (Scheme 5). With ketoacid **8** as the acyl radical precursor, the decarboxylative alkynylation with BI-alkyne derivatives afforded ynone **9** under the photoredox conditions [21]. Both the unsubstituted and 3,4-dimethoxy substituted BI'-alkynes **3c** and **3f** gave ynone **9** in similar 77–79% yields, while the 3,4-difluoro substituted BI'-alkyne **3a** gave a slightly lower 63% yield of **9** [21]. β-Ketone alcohols **10** were reported to be activated by cyclic iodine(III) reagents under photoredox conditions to generate alkoxyl radicals, and subsequently underwent β-fragmentation and alkynylation to yield ynone **9** [26]. The unsubstituted BI-alkyne **3c** gave 84%

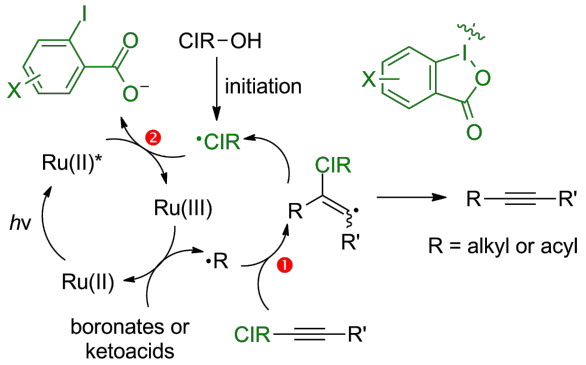


Scheme 5: Reaction of alkynylbenziodoxole derivatives for acyl radical alkynylation in photoredox catalysis. Reaction conditions: a) ketoacid **8** (0.15 mmol, 1.5 equiv), alkynylbenziodoxole **3** (0.10 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (0.002 mmol, 0.02 equiv), and BIOAc (0.10 mmol, 1.0 equiv) in 2.0 mL DCM for 5 h under a nitrogen atmosphere; b) β-ketone alcohol **10** (0.20 mmol, 2.0 equiv), alkynylbenziodoxole **3** (0.10 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (0.002 mmol, 0.02 equiv), and BI-OAc (0.20 mmol, 2.0 equiv) in 2.0 mL DCM for 24 h under a nitrogen atmosphere. Yields are isolated yields.

yield of **9** consistent with the literature report, while 62% yield of **9** was obtained with 3,4-difluoro BI'-alkyne **3a** and 84% yield of **9** was obtained with 3,4-dimethoxy BI'-alkyne **3f**.

With the preliminary hypothesis that the electron-withdrawing and electron-donating substituents on the benziodoxole have opposite effects for the radical alkynylation, we first conducted the fluorescence quenching experiments of tolylacetylenic benziodoxole derivatives **3a**–**f** and found none of them oxidatively quenched the photoexcited $Ru(bpy)_3^{2+*}$ complex (see Supporting Information File 1, Scheme S1). We next investigated if the benziodoxole radical released from the radical alkynylation of BI-alkynes affected the reaction (Scheme 6). Using the combination of substituted hydroxybenziodoxoles (BI'-OH) and substituted BI'-alkynes, we found the 3,4-difluoro electron-withdrawing substituents either on BI'-OH or BI'-alkyne decreased the reaction yields, while the use of both further decreased the formation of **5a** to 39% yield. In contrast, the use of electron-donating 3,4-dimethoxy group either BI'-OH or BI'-alkyne increased the yields of **5a** to 74% and 72% yields, while the use of both increased the formation of **5a** to optimal 80% yield.

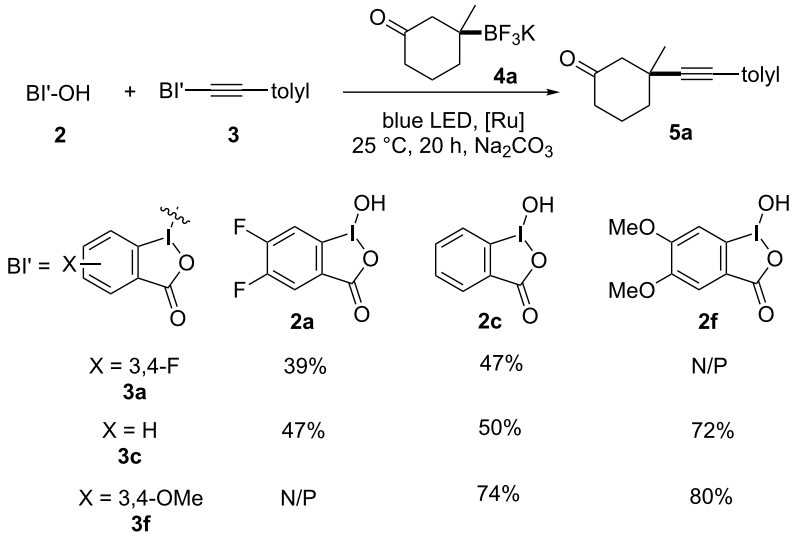
Based on mechanistic investigations above, we propose that the electronic effect on benziodoxoles affected both the radical acceptor and oxidative quencher reactivity of BI-alkyne derivatives (Scheme 7). In the alkyl or acyl radical addition step to BI'-alkyne (step 1) and the oxidative quenching step by benziodoxole radical (step 2), the electron-donating substituents on BI'-alkynes are both beneficial, while the electron-withdrawing substituents have opposite effects.



Scheme 7: The role of alkynylbenziodoxole derivatives for radical alkynylation in photoredox catalysis.

Conclusion

In conclusion, we have developed and investigated novel alkynylbenziodoxole derivatives as radical alkynylation reagents in photoredox catalysis reactions. Alkynylbenziodoxole derivatives with electron-rich benziodoxoles demonstrate synthetic advantages in some situations. The mechanistic investigations suggested both the radical acceptor (step 1) and oxidative quencher reactivity (step 2) were affected by BI-alkyne derivatization. We envision these alkynylbenz-



Scheme 6: Mechanistic investigations of alkynylbenziodoxole for radical acceptor and oxidative quenching reactivity. Yields are isolated yields. N/P = not performed.

iodoxole derivatives will provide alternative radical alkynylation reagents in photoredox catalysis and other synthetic applications.

Supporting Information

Supporting Information File 1

Experimental details, and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-103-S1.pdf]

Acknowledgements

Financial support was provided by National Natural Science Foundation of China 21472230, 21622207, 91753126, National Basic Research Program of China 2014CB910304, and Strategic Priority Research Program of the Chinese Academy of Sciences XDB20020200.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

A survey of chiral hypervalent iodine reagents in asymmetric synthesis

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Review

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Keywords:
alkene functionalization; asymmetric synthesis; hypervalent iodine; organocatalysis; oxidation

Beilstein J. Org. Chem. **2018,** *14,* 1244–1262.
doi:10.3762/bjoc.14.107

Received: 12 February 2018
Accepted: 02 May 2018
Published: 30 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The recent years have witnessed a remarkable growth in the area of chiral hypervalent iodine chemistry. These environmentally friendly, mild and economic reagents have been used in catalytic or stoichiometric amounts as an alternative to transition metals for delivering enantioenriched molecules. Varieties of different chiral reagents and their use for demanding asymmetric transformations have been documented over the last 25 years. This review highlights the contribution of different chiral hypervalent iodine reagents in diverse asymmetric conversions.

Introduction

It is more than one century ago since the discovery of the first hypervalent iodine reagent (HIR) [1] and hypervalent iodine chemistry has started to flourish as one of the important and leading areas in organic synthesis. In recent years many excellent reviews have detailed the bonding, reactivity, synthesis, and uses of hypervalent iodine reagents [2-14]. These compounds feature a unique three-centered four-electron bond [15-20] that renders them valuable and important alternatives to transition-metal chemistry. Over the last 25 years hypervalent iodine reagents have gained growing application due to their reduced toxicity, ready availability and lower costs as replacement for transition metals leading to several “metal-free” like chemical transformations.

The ongoing demand of modern synthetic chemistry for the development of catalytic enantioselective C–C bond formation reactions turned the attention of the scientific community towards the evolution of new chiral hypervalent iodine reagents. In recent years, many complex synthetic challenges have been successfully addressed by applying these reagents [21,22]. The superior advantage of these reagents lies in their strong electrophilicity and appreciable oxidizing properties. The transformat-

ions associated with asymmetric induction mainly focused on the asymmetric oxidation and oxidative dearomatization chemistry. Asymmetric difunctionalization of alkenes, α-functionalization of carbonyls and also some typical 1,2-aryl rearrangement reactions add further value to this chemistry.

The strategies used for the synthesis of chiral hypervalent iodine reagents include either the introduction of chirality through the attachment of chiral acids or chiral alcohols to the iodine centers by ligand exchange or are achieved by the introduction of axial chirality through the iodoarene backbone. A series of chiral iodine reagents are documented below (Scheme 1). In many cases chiral I(I) reagents get oxidized in situ to the hypervalent I(III) reagents and/or these chiral I(III)/I(V) reagents are used in a catalytic amount in the presence of an external oxidant. The use of catalytic chiral hypervalent iodine reagents in asymmetric catalysis is one of the most challenging ongoing topics and this review will focus on the development of various chiral hypervalent iodine reagents and their application in typical organic transformations.

Review

Asymmetric oxidation of sulfides

Pribam was the first to use chiral iodine reagents [23]. After a long time without further developments in this direction, Imamoto et al. introduced a new class of chiral hypervalent iodine reagents **1** obtained by the reaction of iodosylbenzene with various derivatives of L-tartaric acid anhydrides in 1986. A promising asymmetric induction was achieved for the oxidation of sulfides **23** to sulfoxides **24**. This marked the beginning of an era of asymmetric oxidation of sulfides. However, the presence of C_2 symmetry in the chiral unit is essential to obtain decent enantioselectivity [24]. Later, Kita et al. used chiral tartaric acid derivatives to synthesize chiral I(V) reagents **2** from $PhIO_2$. This represented the first example of the catalytic use of chiral hypervalent reagents in the oxidation of sulfides to sulfoxides with decent enantioselectivities (ees, Scheme 2a). The asymmetric oxidations were examined in 20 mol % cetyltrimethylammonium bromide (CTAB) reversed micelles [25]. Interestingly, Varvoglis et al. synthesized another new class of a chiral reagent **3** using (+)-camphor sulfonic acids as the source of chirality [26] which was used by Chen et al. for the oxidation of sulfides to sulfoxides with good yields but with poor enantioselectivity (Scheme 2b) [27]. Later, Zhdankin et al. synthesized different classes of chiral I(V) reagents **4** based on various amino acids as sources of chirality. The oxidation of the readily available 2-iodobenzamides (synthesized from amino acid derivatives) with potassium bromate or Oxone ($2KHSO_5/KHSO_4/K_2SO_4$) efficiently delivered the I(V) reagents **4** (Scheme 2c) [28,29]. Although good product yields were obtained for the oxidation of sulfides, the ees were very low.

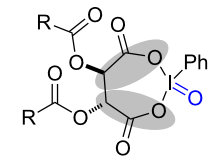
New classes of chiral hypervalent iodine reagents were obtained by the introduction of chiral alcohols directly to the iodine reagent through ligand exchange. Koser et al. used (+)- or (−)-menthol as a source of chirality during their synthesis of the new chiral iodine reagent **5** [30]. Chiral sulfoxides **24** (having R^1 = *p*-Tol, *t*-Bu, Bn and R^2 = Me) were obtained for the first time with excellent enantioselectivity (Scheme 2d). Another class of chiral I(V) reagents **6** was synthesized by Wirth et al. who synthesized the desired compounds through esterification between chiral alcohols and the I(I)-substituted aromatic acids followed by oxidation with dimethyldioxirane (Scheme 2e) [31]. A summary of chiral hypervalent iodine reagents used in the asymmetric oxidation of sulfides is sketched below (Scheme 2).

Asymmetric oxidative dearomatization, alkene functionalization and rearrangement strategy

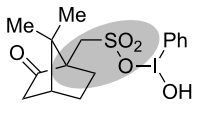
Oxidative dearomatization

Asymmetric oxidative dearomatizations and the use of dearomatized products to generate chiral complex molecular scaffolds in a short and efficient way is one of the attractive strategies used in chiral hypervalent iodine chemistry. Kita et al. for the first time developed a new chiral I(III) catalyst **7** having a rigid spirocyclic backbone. They applied it for the enantioselective oxidative dearomatization of phenolic derivatives **25** (spirolactonization) which is known as Kita oxidation to yield spirocyclic compounds **26** with good enantioselectivity [32]. The indication of an associative mechanism was also confirmed due to an increased enantioselectivity observed in polar solvents. Further, they were able to improve the enantioselectivity by implying steric effects at the *ortho*/*ortho′* (R = Et in **7**) positions of the aromatics (Scheme 3) [33]. The regeneration of the catalyst was achieved by *m*-CPBA converting iodine compound **7′** to chiral catalyst **7**. The authors predicted a plausible mechanism and transition-state model **27** for the formation of the major isomer through the attack of the carboxylic acid group to the *ipso* position of the naphthol ring from the less sterically hindered *Re*-face of the substrate **25**. It is worth mentioning that very recently they have introduced a new kind of binaphthyl-based chiral I(III) prereagent **19** with the 8 and 8′ positions of the naphthalene substituents being occupied by iodide. Here they have observed that this chiral hypervalent iodine reagent **19** in the presence of co-oxidant *m*-CBPA is very useful for the dearomatizing spirocyclization of naphthol carboxylic acid [34].

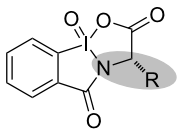
Later Birman et al. reported a new variation of a chiral I(V) reagent, namely 2-(*o*-iodoxyphenyl)oxazoline derivative **28** [35]. The reagent was applied to an asymmetric [4 + 2] Diels–Alder dimerization of phenolic derivatives **29** to construct tricyclic derivatives **30** with moderate enantiose-



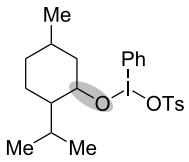
I(III) **1** (R = Me, *t*-Bu, Ph)
I(V) **2** (R = 2-OMeC$_6$H$_4$)



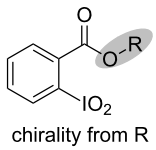
I(III) **3**



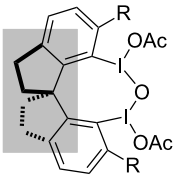
R = alkyl
I(V) **4**



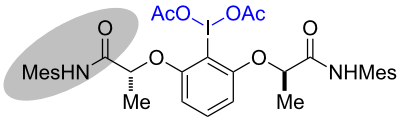
I(III) **5**



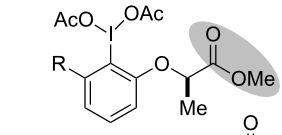
chirality from R
R = alkyl, aryl
I(V) **6**



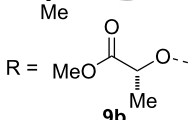
R = H, Et
I(III) **7**



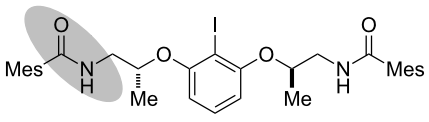
Mes = mesityl
I(III) prereagent **8a**
I(III) **8b**



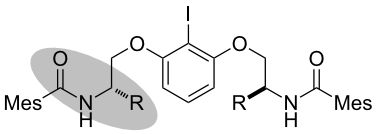
R = H, alkyl
9a



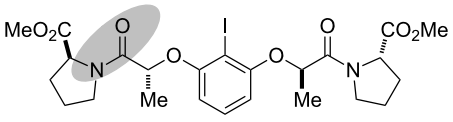
I(III) **9**
9b



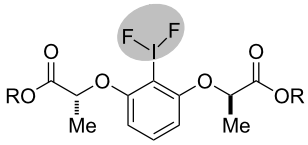
Mes = mesityl
I(III) prereagent **10**



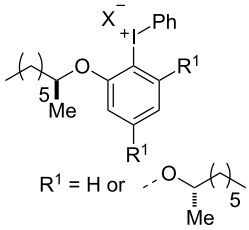
R = iPr, *t*-Bu
I(III) prereagent **11**



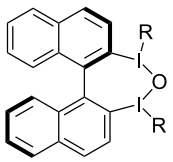
I(III) prereagent **12**



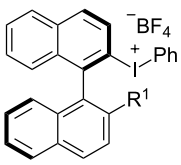
R = *t*-Bu
I(III) **13**



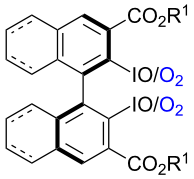
iodonium salt **14**



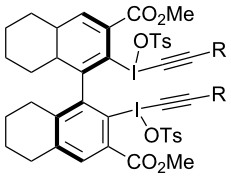
R = OCOMe, OCOCF$_3$
I(III) **15**



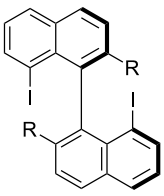
R^1 = H, Bn
iodonium salt **16**



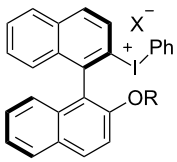
R^1 = H or Me
I(III) **17a** and I(V) **17b**



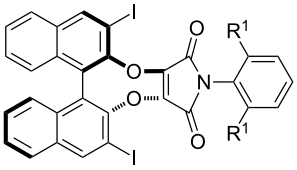
R = *t*-Bu, TBS
I(III) **18**



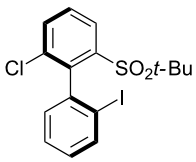
R = H, Me, iPr
I(III) prereagent **19**



R = Me, Ph
X = BF$_4$, BPh$_4$
iodonium salt **20**

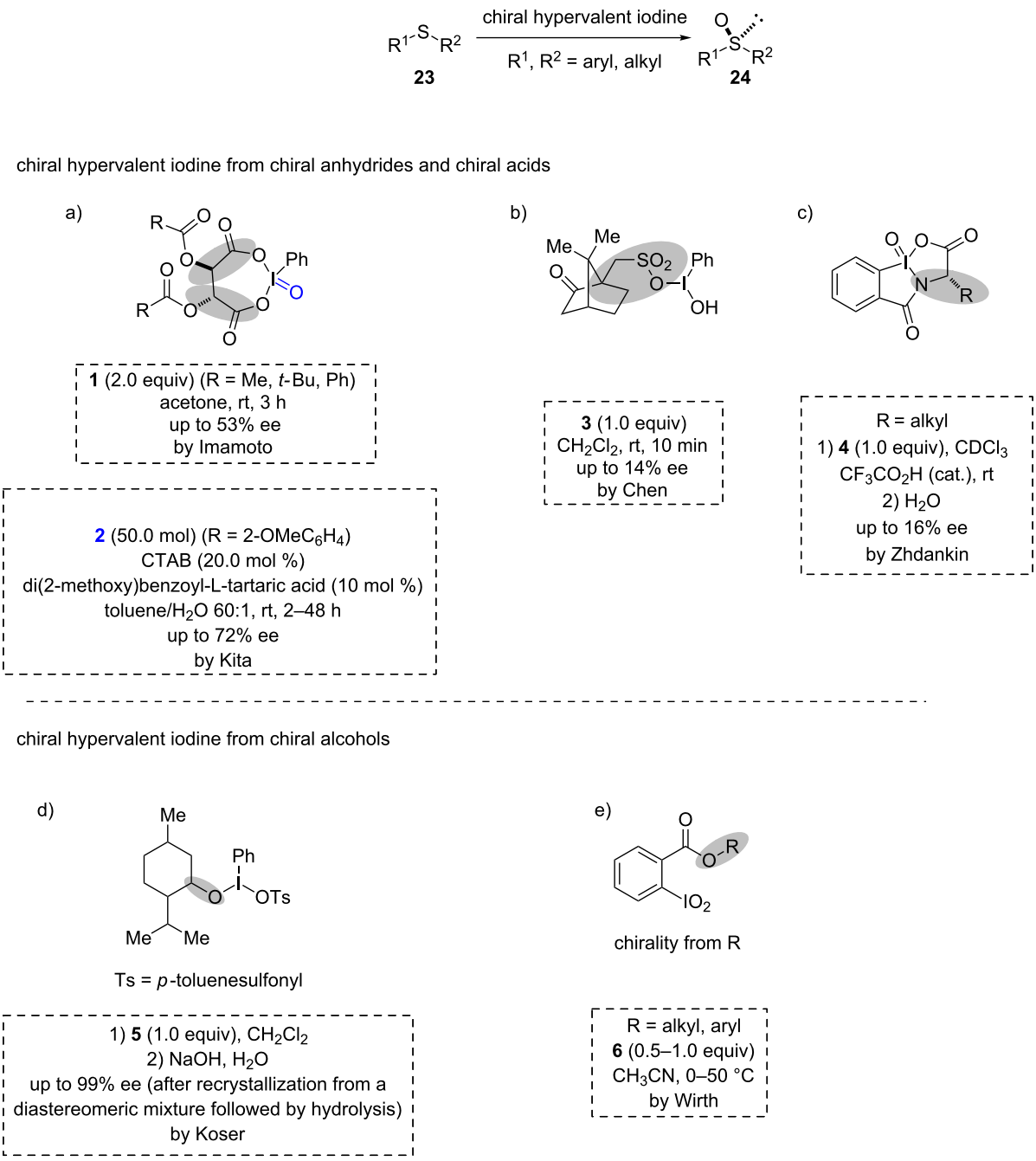


R^1 = alkyl, Br, aryl, benzyl alcohol, benzyl ester
I(III) prereagent **21**



I(III) prereagent **22**

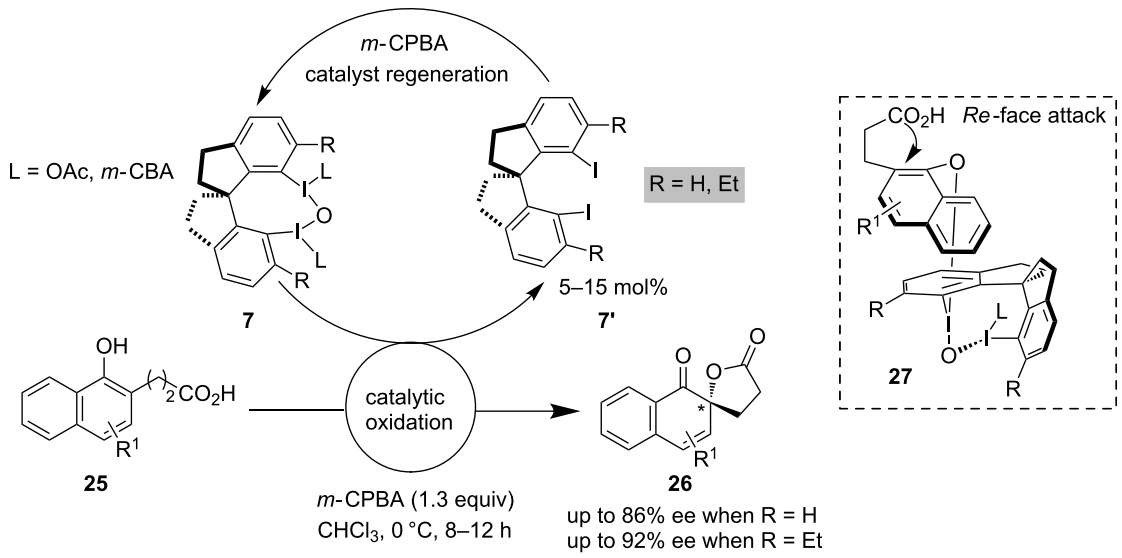
Scheme 1: An overview of different chiral iodine reagents or precursors thereof.



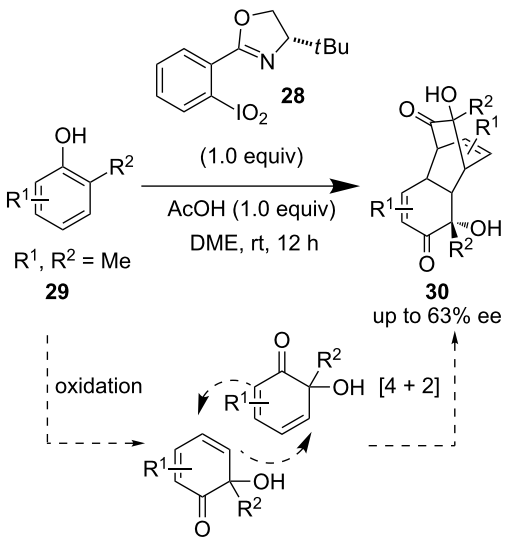
Scheme 2: Asymmetric oxidation of sulfides by chiral hypervalent iodine reagents.

lectivity (Scheme 4). Although modest ees were obtained, this chiral oxazoline-based compound demonstrated encouraging potential as a new class of chiral hypervalent iodine reagent.

Fujita et al. synthesized non C_2-symmetric chiral iodoarene reagents **9a** derived from lactic acid derivatives and utilized them in stoichiometric fashion for the synthesis of chiral tetrahydrofuran derivatives [36]. A major breakthrough was achieved in this field by the discovery of a family of conformationally flexible C_2-symmetric chiral iodoarene reagents. Ishihara et al. thoughtfully designed a new class of C_2-symmetric chiral iodoarene precatalyst **8a** using (−)-ethyl lactate as a chiral linker with the aromatics attached followed by its successful conversion to the amide derivative to generate precatalyst **8a** [37,38]. Application of this precatalyst **8a** was employed for the Kita oxidation [32] with a high level of enantioselectivity. Naphthol derivatives **31** were converted to spirocyclic lactones



Scheme 3: Oxidative dearomatization of naphthol derivatives by Kita et al.

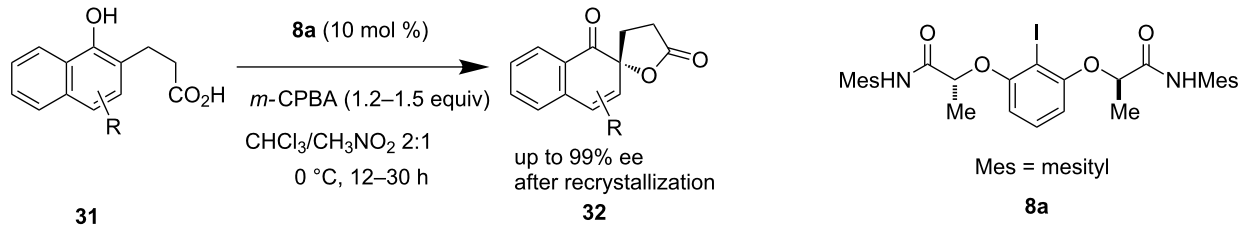


Scheme 4: [4 + 2] Diels–Alder dimerization reported by Birman et al.

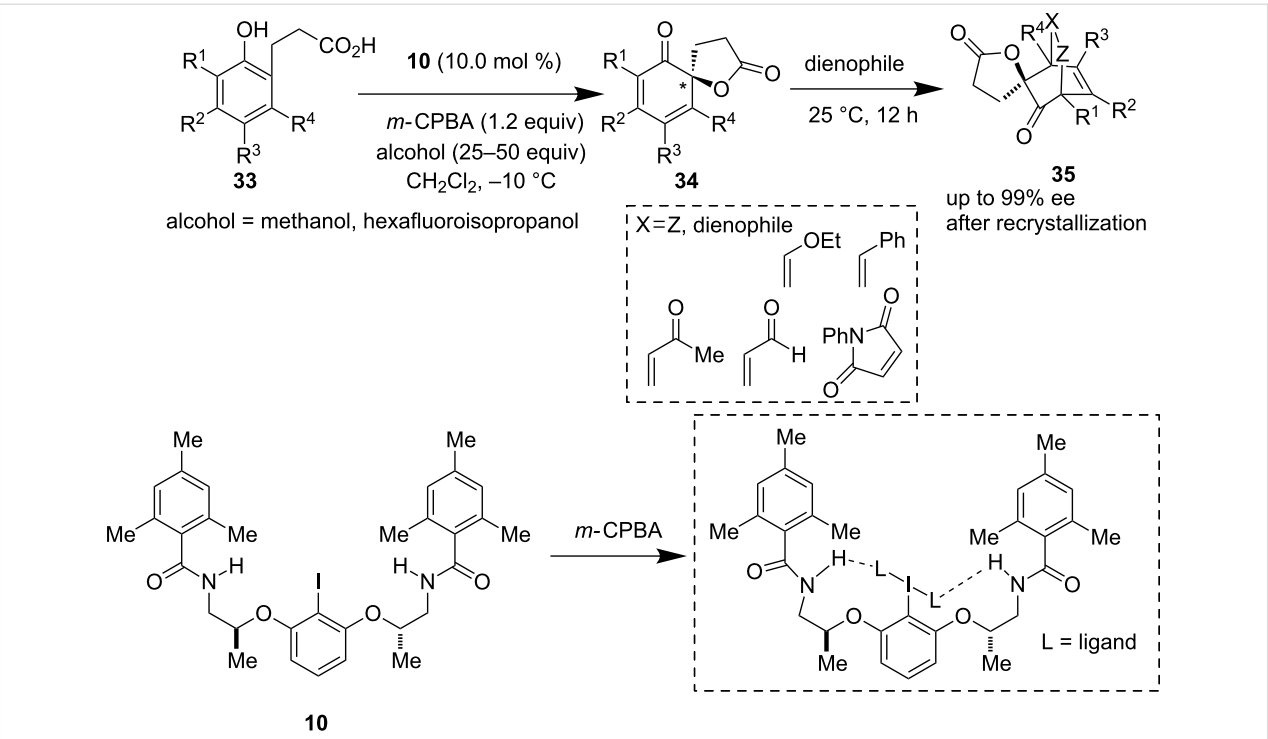
32 in the presence of *m*-CPBA as co-oxidant for the in situ generation of the I(III) catalyst. Secondary n–π* and/or hydrogen-bonding interactions of the catalyst ensured remarkable enantioselectivities (Scheme 5).

Later, this dearomatization strategy was further reinvestigated by the Ishihara group using a new chiral iodine precatalyst **10** derived from a chiral 2-aminoalcohol [39]. Its application in the oxidative dearomatization of phenol **33** and the subsequent reaction of the so-obtained dienes **34** with different dienophiles furnished Diels–Alder adducts **35** with excellent enantioselectivity. Intramolecular H-bonding and the presence of an achiral alcohol as additive helped them to achieve outstanding enantioselectivity (up to 99%) even when using very low catalyst loadings (1–10 mol %, Scheme 6)

Ciufolini et al. further carefully modified precatalyst **10** to generate a new chiral iodine precatalyst **11** [40]. They critically altered the chiral center next to the amide NH group to achieve



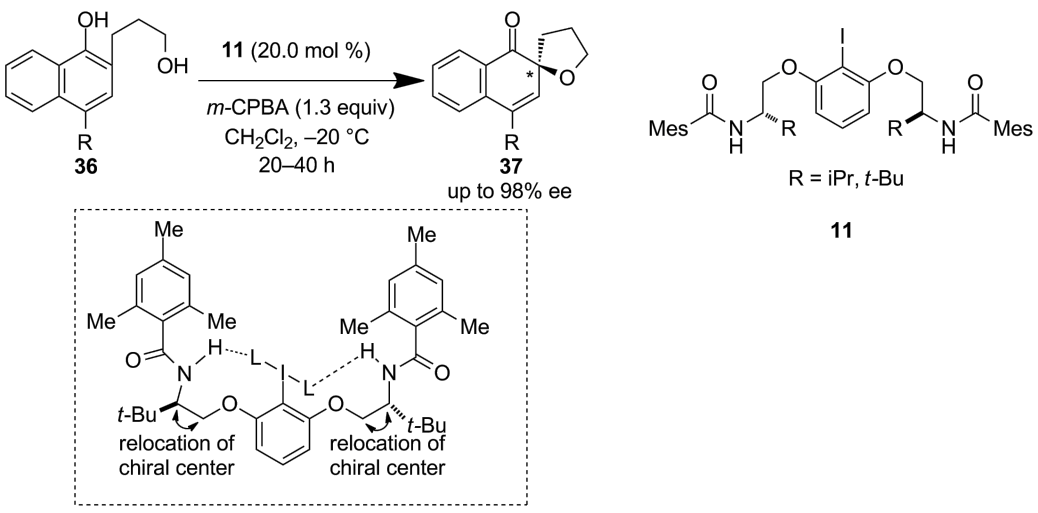
Scheme 5: *m*-CPBA guided catalytic oxidative naphthol dearomatization.



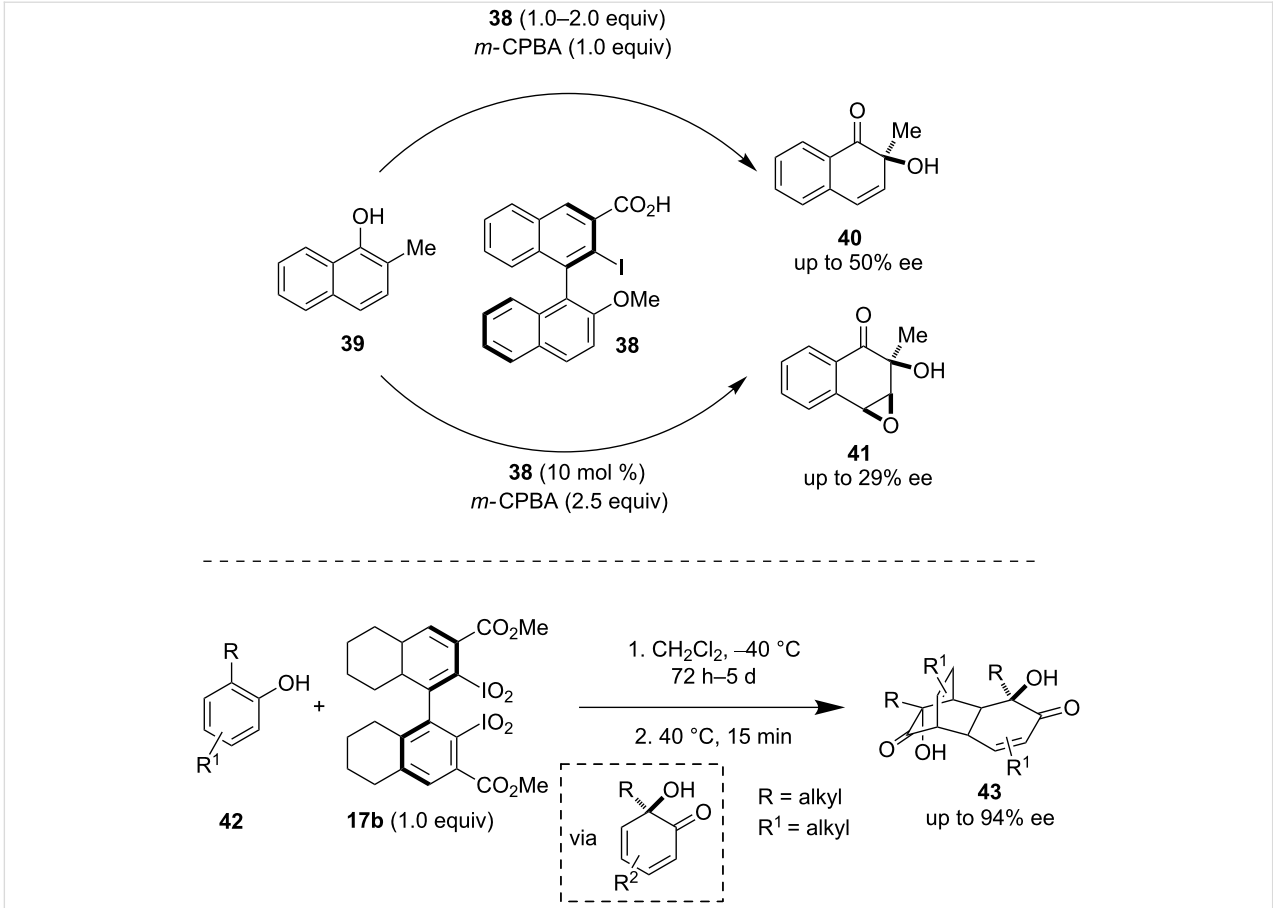
Scheme 6: Oxidative dearomatization of phenolic derivatives by Ishihara et al.

a high catalyst efficiency (Scheme 7). The crucial point is the better hydrogen-bonded conformation of **11** which imparted superior reactivity compared to Ishihara's system without the need of achiral alcohols as an additive. Profitable results were obtained regarding the oxidative cyclization of phenolic derivatives **36** to spirocyclic compounds **37**.

Chiral hypervalent iodine reagents having binaphthyl backbones were used by Quideau et al. for the α-hydroxylation of phenolic derivatives via oxygenative dearomatization. Quideau et al. showed that iodobiarene **38** was oxidized in situ by *m*-CPBA to generate the I(III) reagent which is responsible for the hydroxylative naphthol dearomatization affording the product in moderate enantioselectivity (Scheme 8 upper part). By this method naphthol **39** could be oxidized to chiral *o*-quinol **40** with 50% ee [41]. Varying the catalyst loading could alter the reaction outcome to afford either *o*-quinol **40** or epoxy *o*-quinol **41**.



Scheme 7: Oxidative spirocyclization applying precatalyst **11** developed by Ciufolini et al.



Scheme 8: Asymmetric hydroxylative dearomatization.

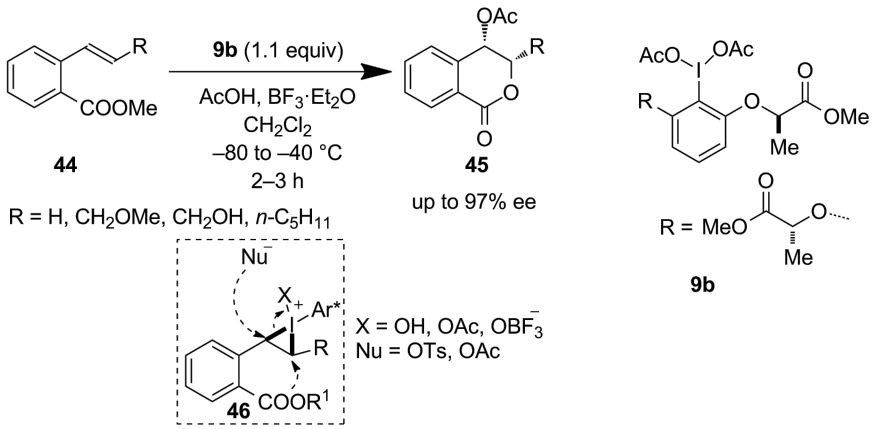
Recently, Pouységu and Quideau et al. modified their iodobiarenes to synthesize a new class of I(III) and I(V) reagents **17**. These were applied for the hydroxylative dearomatization of phenolic derivatives **42** followed by the successive use of the hydroxylated products as dienes in [4 + 2] cycloaddition reactions [42]. This new reagent promoted oxygen transfer in phenol dearomatization, leading to the formation of cyclodimerization products **43** with high enantioselectivity (up to 94% ee, Scheme 8 lower part).

Alkene functionalization

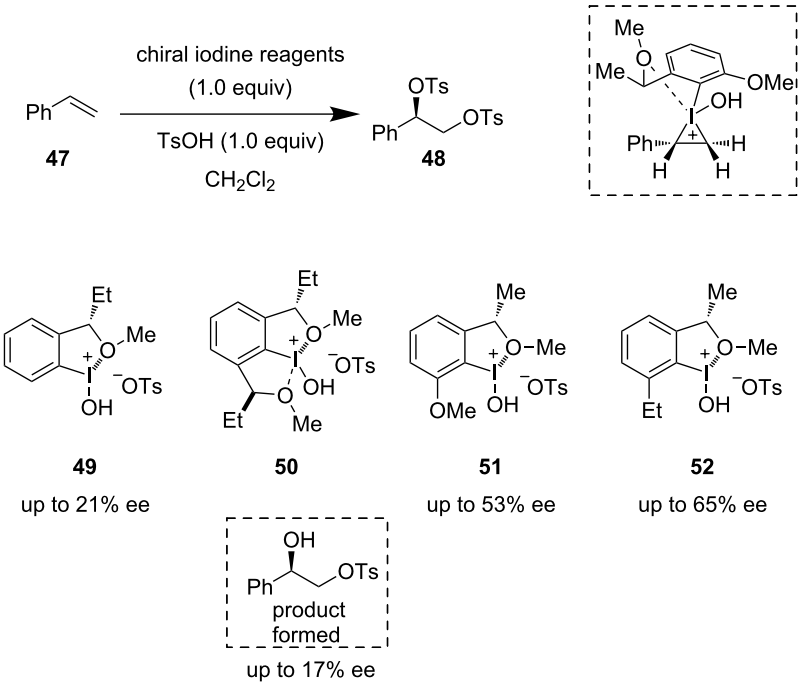
Nearly simultaneously to Ishihara's work, Fujita et al. reported on the modification of their previously synthesized non C_2-symmetric reagent **9a** to obtain a C_2-symmetric chiral iodoarene reagent **9b** having an ester end group instead of an amide (as in case of Ishihara's work). The enantioselective oxylactonization was achieved efficiently using stoichiometric amounts of chiral reagent **9b** (Scheme 9). This lactate-derived I(III) reagent **9b** was used successively for the synthesis of δ-lactones **45** in a highly stereoselective manner starting from **44** [43]. The formation of cyclic iodonium **46** is the vital part of this difunctionalization process.

Wirth et al. were the first to introduce asymmetric dioxytosylation of styrene (**47**) using a new class of chiral hypervalent iodine reagents **49**–**52** to furnish **48** with moderate enantioselectivity (Scheme 10) [44-47]. Their constant efforts towards alkene dioxygenation helped them to discover new chiral hypervalent iodine reagents and also to reach up to 65% enantioselectivity using **52**.

Fujita et al. further explored the difunctionalization strategy for the development of diacetoxylation of alkenes following a Prevost and Woodward reaction [48]. Recently, the same group used chiral iodine reagent **55** together with acid co-reagent for the intramolecular oxyarylation and aminoarylation of alkenes **53** to produce **54** (Scheme 11). The presence of a silyloxy group is essential to achieve high enantioselectivity in case of the oxyarylation [49]. The Lewis acid activates the hypervalent chiral iodine reagent and then adds to the alkene system. The nucleophilic addition of the internal oxy/amino group followed by the nucleophilic addition of the aryl group delivers the desired products **54**. The key to success also lies on the enantiotopic face discrimination of the alkene by the lactate-based chiral iodine reagent.



Scheme 9: Enantioselective oxylactonization reported by Fujita et al.

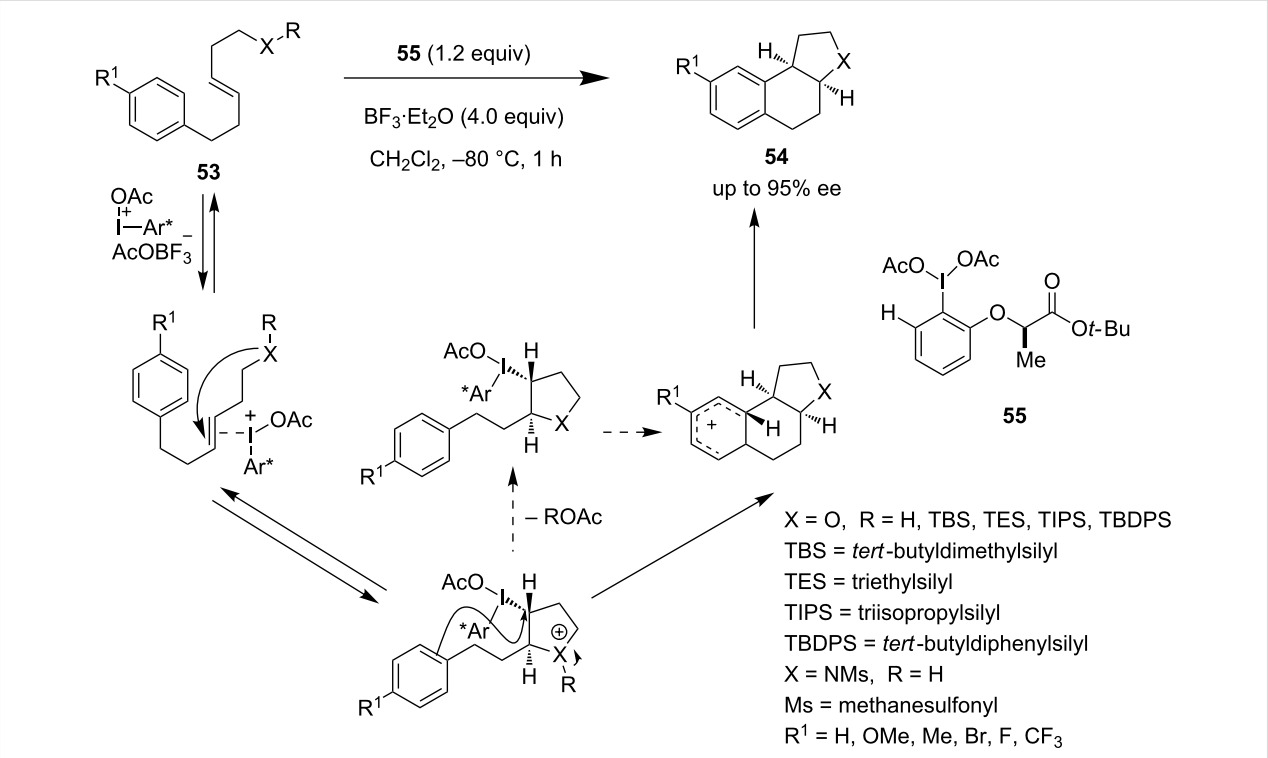


Scheme 10: Dioxytosylation of styrene (**47**) by Wirth et al.

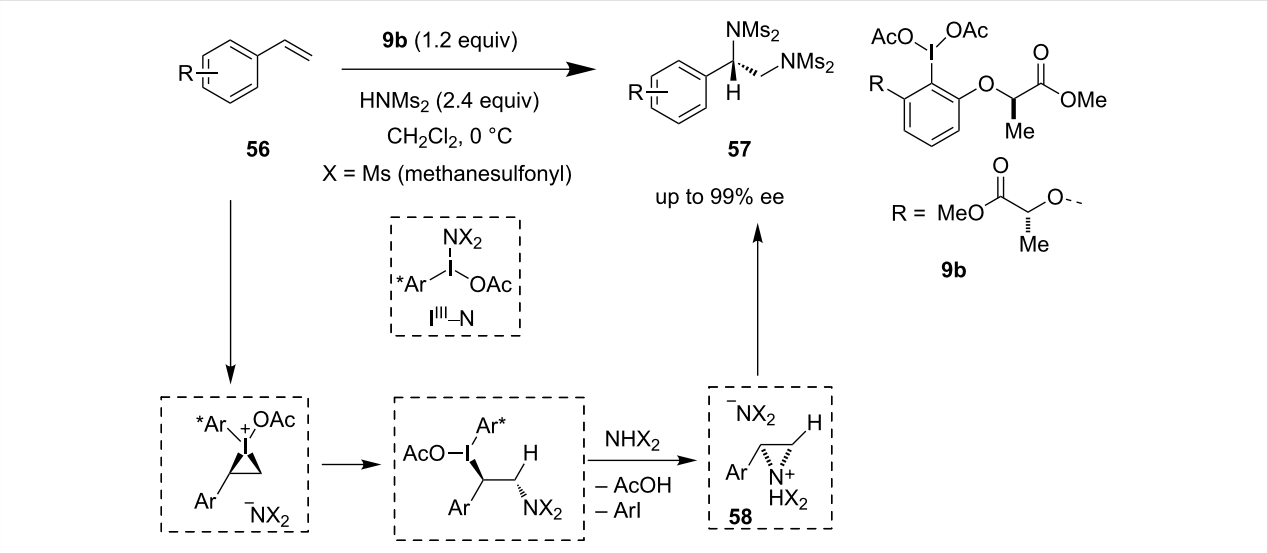
This difunctionalization strategy was further showcased by Muñiz et al. as intermolecular diamination protocol of alkenes **56** using **9b** (Scheme 12) [50]. This represented the first example of an asymmetric diamination of simple nonfunctionalized alkenes to acquire diaminated products **57**. The existence of an I(III)–N bond under ligand exchange conditions and the formation and ring opening of aziridinium intermediate **58** elucidate the product formation in this transformation [51].

Wirth et al. successfully employed I(III) reagent **8b** in combination with trimethylsilyltriflate (TMSOTf) for the stereoselective oxyamination of **59** to furnish isourea **60** with >99% ee (Scheme 13) [52]. Both the Lewis acid and solvent used play an important role in this transformation. This method was applied to the synthesis of other isourea derivatives **62**–**64** with moderate enantioselectivity. The reactions were triggered by the activation of olefins followed by the formation of C–N bonds. The subsequent intramolecular substitution reaction of intermediate **61** having hypervalent iodine as a good leaving group yielded the required heterocycles.

After Wirth's report, Nevado et al. discovered a newly modified chiral iodine reagent **13** analogous to lactate-based chiral iodoarenes [53]. They have utilized this chiral difluoroiodo-



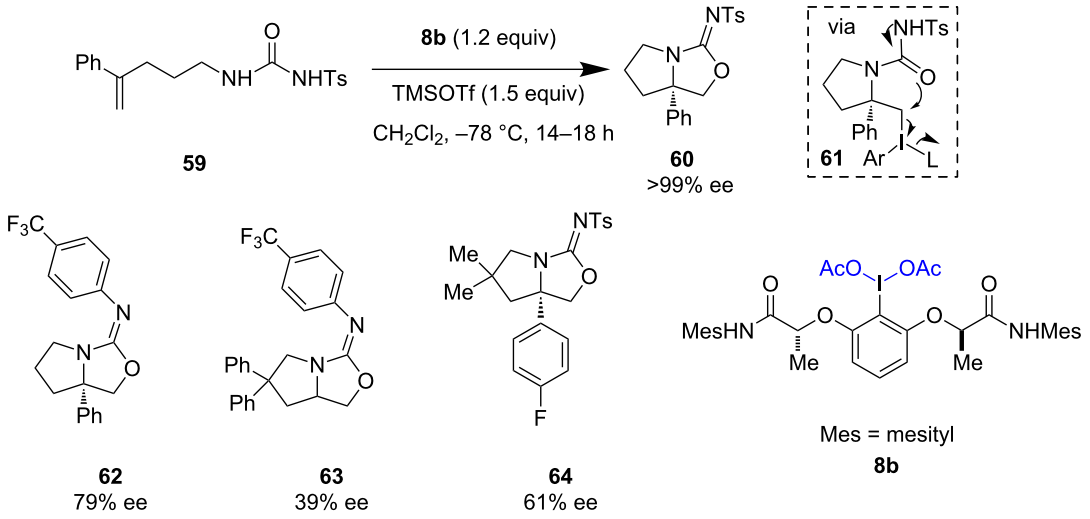
Scheme 11: Oxyarylation and aminoarylation of alkenes.



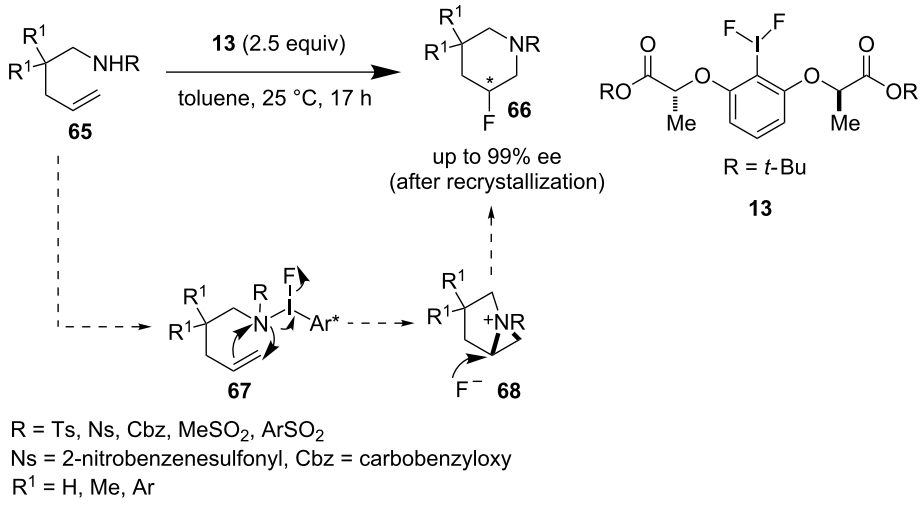
Scheme 12: Asymmetric diamination of alkenes.

nium salt **13** for the asymmetric synthesis of aminofluorinated compounds **66** from **65** (Scheme 14). In addition to this, they extended this methodology for the regioselective intermolecular aminofluorination of styrenes with a racemic catalyst. The nucleophilic attack of the nitrogen atom onto the alkene (intermediate **67**) to generate aziridinium ion **68** is the crucial step in this transformation.

Recently, Jacobsen et al. developed a highly stereoselective difunctionalization method for the synthesis of chiral fluorine-containing molecules and the 1,2-difluorination, 1,1-difluorination and fluorolactonization protocols appeared almost simultaneously (Scheme 15). The lactate-based C_2-symmetric chiral iodine precatalysts **73**, **76**, and **79** were used to deliver chiral fluorinated scaffolds from alkene starting materials **69** in the



Scheme 13: Stereoselective oxyamination of alkenes reported by Wirth et al.

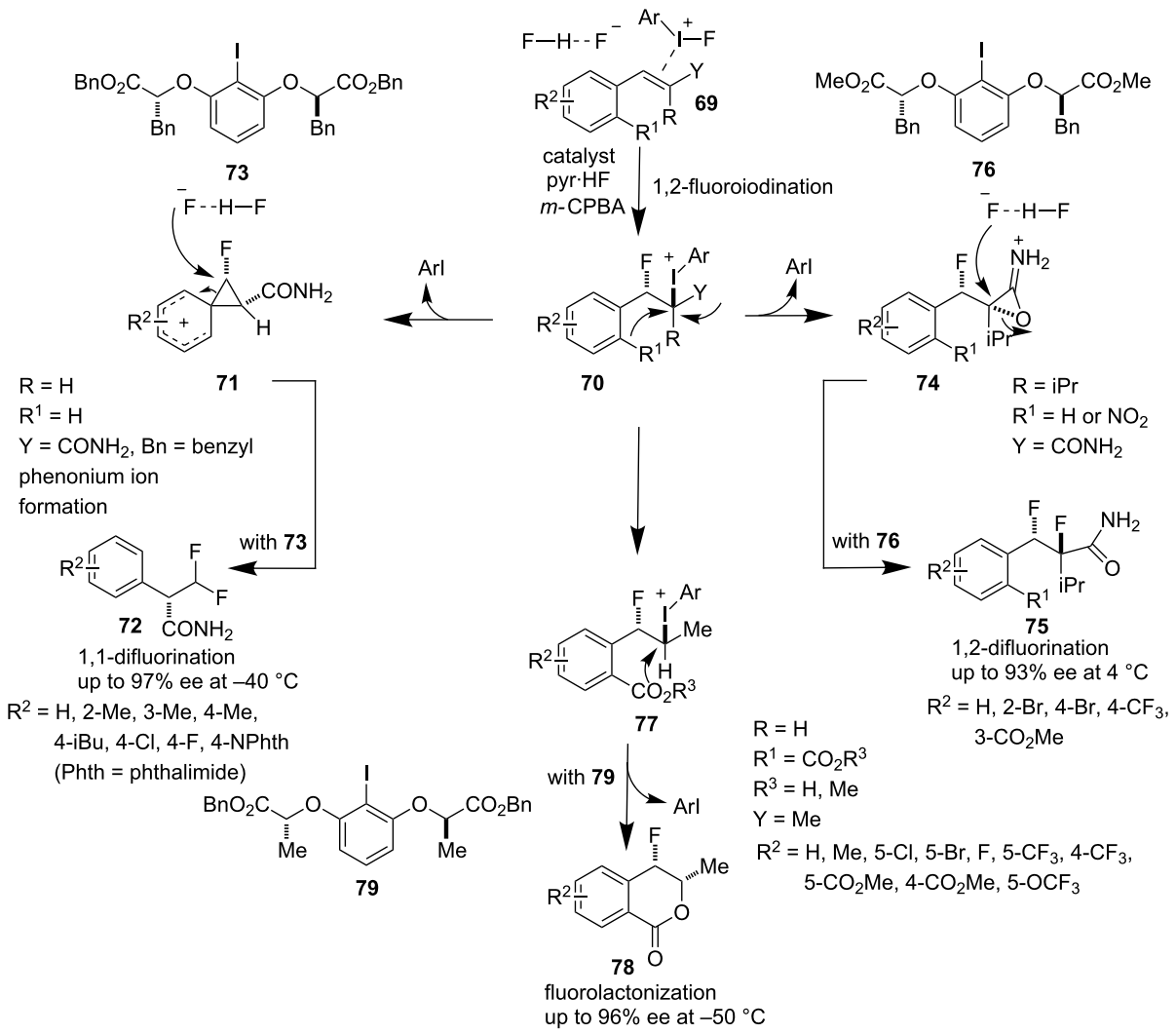


Scheme 14: Enantioselective and regioselective aminofluorination by Nevado et al.

presence of pyr·HF as a nucleophilic fluoride source. The reactions were guided by the formation of intermediate **70**. Anchimeric assistance via the phenonium ion intermediate **71** and subsequent ring-opening rearrangement delivered the 1,1-difluorinated products **72** in the presence of catalyst **73** [54]. On the other hand the anchimeric assistance via participation of the amide carbonyl group (intermediate **74**) dictated the formation of 1,2-difluorinated products **75** and catalyst **76** was identified as the optimal catalyst for this transformation. The 1,2-difluorinated products **75** can also be obtained with high diastereoselectivity by an anchimeric assistance of an *o*-NO_2 group present in the aryl ring [55]. The authors cleverly replaced the *o*-NO_2-substituent with a CO_2R group (R = H or Me). With this modification they were able to obtain fluorolactonization products with high enantioselectivity using **79** as a catalyst, via the intramolecular displacement of the aryl iodide by the CO_2R group in **77** leading to chiral lactones of type **78** [56].

Rearrangement strategy

Wirth et al. used I(III) reagent **8b** for the development of a stereoselective oxidative rearrangement method to synthesize α-arylated carbonyls **81** from α,β-unsaturated carbonyls **80** (Scheme 16, upper part) [57,58]. The reaction proceeds via the formation of the phenyliodinate intermediate **82** followed by a stereoselective 1,2-aryl migration. Elegantly, they utilized the 1,2-aryl migration approach to develop an enantioselective oxidative rearrangement of 1,1-disubstituted olefins **83** leading to the formation of valuable α-arylated ketones **84**. In this reaction



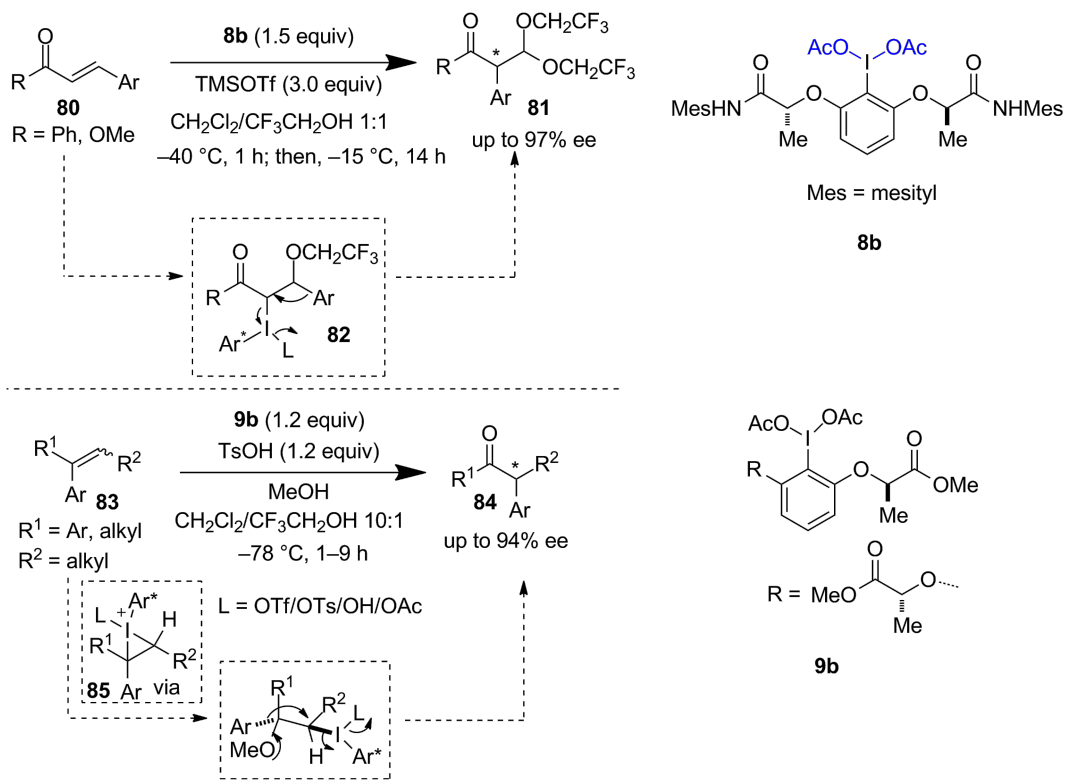
Scheme 15: Fluorinated difunctionalization reported by Jacobsen et al.

I(III) reagent **9b** gave the best reaction outcome. Key to the success of the reaction is the formation of the cyclic iodonium ion intermediate **85** (Scheme 16, below part) [59,60].

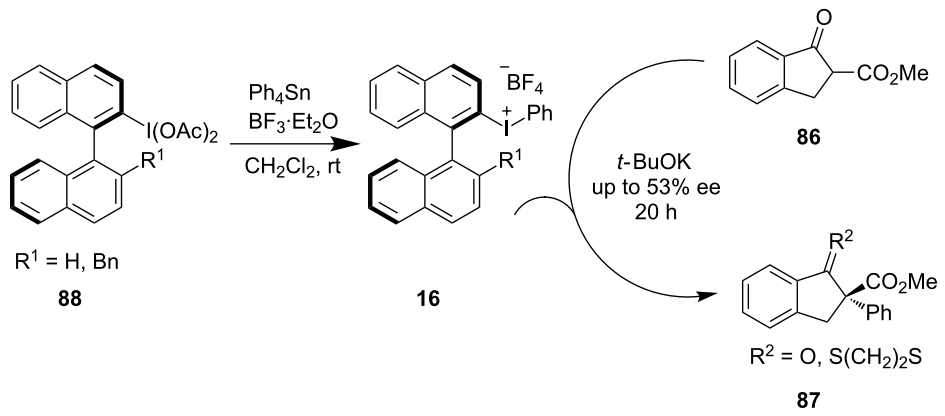
Asymmetric α-functionalization strategy

Methods for carbonyl α-functionalizations are still considered as highly demandable in synthetic organic chemistry. In this regard transition metals have been successfully applied and even allow accomplishing such transformations asymmetrically. On the other hand, diaryliodonium salts are known to transfer aryl groups ultimately leading to α-arylated products. This part of the review focuses on the development of α-functionalization strategies based on chiral diaryliodonium reagents having either an axially chiral backbone or that can be considered analogous to the C_2-symmetric iodoarene moiety. For this purpose various chiral iodine reagents were synthesized having an axially chiral biaryl backbone. In this part, we mainly focused on the transformations using chiral iodine reagents instead of achiral iodine reagents in a combination with other chiral sources [61].

More than one century after Pribam discovered diphenyliodonium tartrate [23], Ochiai et al. realized the introduction of chirality through incorporation of binaphthyl backbones [62] and they synthesized new classes of chiral hypervalent iodine reagents **15**. Later, to ensure asymmetric transformations, the same group developed the synthesis of more effective chiral iodonium salts **16** which were used for the α-arylation of β-ketoester **86** to deliver α-arylated β-ketoesters **87** with moderate enantioselectivity (Scheme 17) [63]. This was the first example of an asymmetric α-arylation of β-ketoesters using hypervalent iodine reagents. A more reactive organostannane derived Sn–I(III) exchange in the presence of $BF_3{\cdot}Et_2O$ was the crucial step in the synthesis of the chiral iodonium salts from **88**.



Scheme 16: Aryl rearrangement reported by Wirth et al.

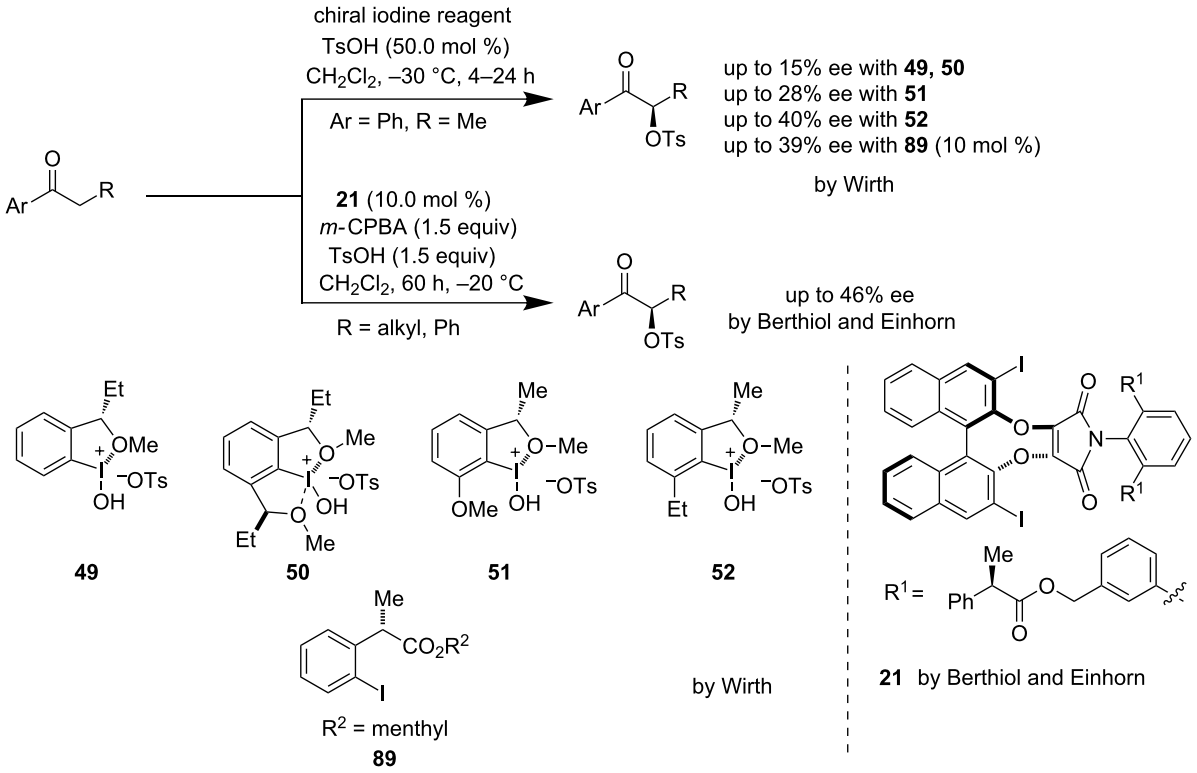


Scheme 17: α-Arylation of β-ketoesters.

In view of developing asymmetric α-arylations of carbonyls, Olofsson et al. has independently synthesized a new class of diaryliodonium salts **14** with different stereoelectronic properties by using aliphatic alcohols as a sole source of chirality [64]. Olofsson and Wirth et al. also jointly reported the synthesis of new structurally distinct chiral reagents **20** considering their interest towards asymmetric metal-free arylation [65].

In 1997, Wirth et al. for the first time reported an asymmetric α-oxytosylation of propiophenone using hypervalent iodine reagents **49**/**50** [45]. Later they improved the enantioselectivity by a structurally modified catalyst **51** to obtain up to 28% ee [46]. After a further few years, in 2001, they came up with a modified catalyst **52** which allowed them to reach up to 40% ee [47]. A catalytic variant of this methodology was developed by the same group using *m*-CPBA as co-oxidant together with catalyst **89** to get up to 39% ee [66] (Scheme 18).

In 2013, Berthiol and Einhorn et al. demonstrated an intermolecular asymmetric α-oxytosylation of ketones by using a new



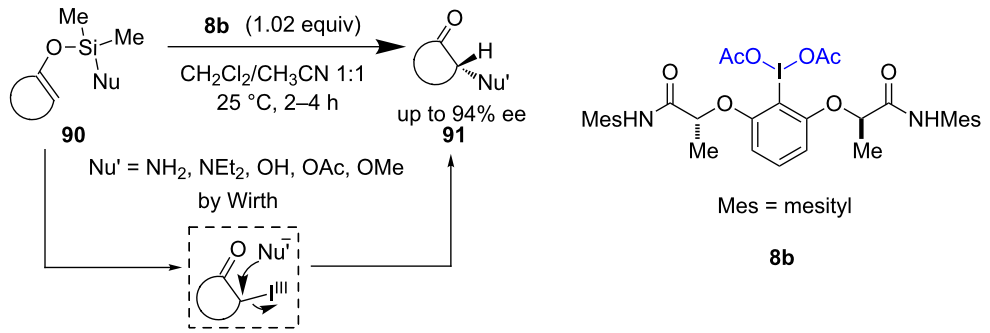
Scheme 18: Asymmetric α-oxytosylation of carbonyls.

family of chiral hypervalent iodine catalyst **21** with up to 46% ee [67]. The investigation of the reaction mechanisms revealed that the steric crowding around the iodine center improves the enantioselectivity (Scheme 18).

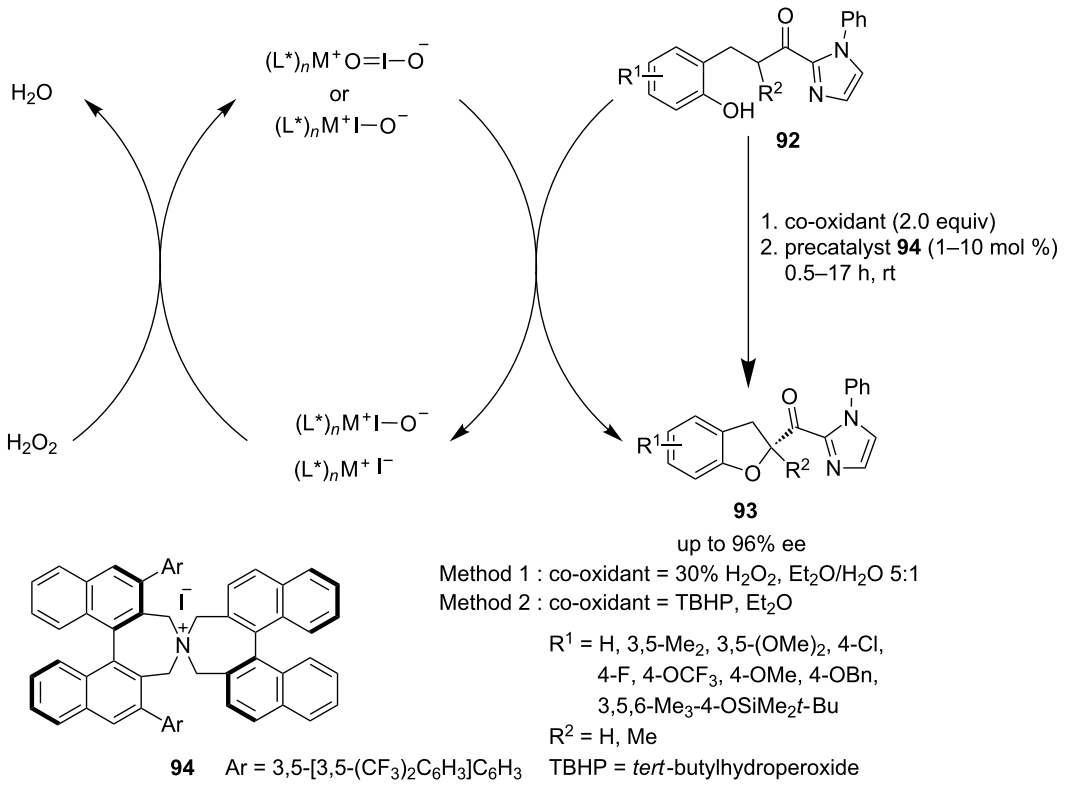
Asymmetric oxygenation and nitrogenation reactions of carbonyls were established by Wirth et al. Nucleophile transfer from silyl enol ethers **90** delivered α-functionalized carbonyls **91** with good enantioselectivity [68]. "Umpolung" reactivity and silyl-tethered enol ethers allowed the delicate synthesis of α-functionalized carbonyls (Scheme 19). C_2-symmetric I(III) reagent **8b** was used to obtain high enantioselectivity.

Ishihara et al. appealingly reported an oxidative cycloetherification of ketophenols **92** in the presence of an in situ generated chiral quaternary ammonium (hypo)iodite salt **94**, with hydrogen peroxide as an oxidant to deliver chiral dihydrobenzofuran derivatives **93** as α-functionalized products of ketophenols **92** (Scheme 20) [69]. The substituents at the 3,3′-position of the binaphthyl moiety of the salt **94** played a crucial role to achieve high enantioselectivities up to 96%.

Very recently, Gong et al. developed an asymmetric oxidative intramolecular cross-coupling of C−H bonds in **95** using catalytic chiral iodine **12** for the synthesis of a diverse array of

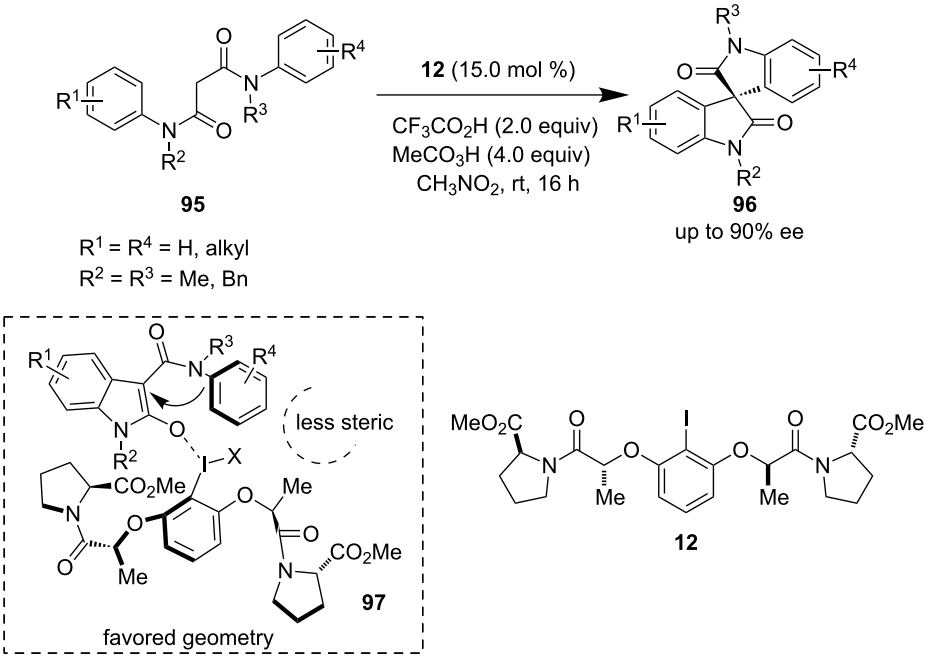


Scheme 19: Asymmetric α-oxygenation and α-amination of carbonyls reported by Wirth et al.



Scheme 20: Asymmetric α-functionalization of ketophenols using chiral quaternary ammonium (hypo)iodite salt reported by Ishihara et al.

spirooxindoles **96**. Ishihara's catalyst was modified by using an (*S*)-proline derivative to achieve a high level of enantioselectivity in the presence of peracetic acid (Scheme 21) [70]. They postulated the formation of possible intermediate **97** which favored the nucleophilic attack of the aryl ring from the less sterically hindered side. Later, Du et al. used this same precata-



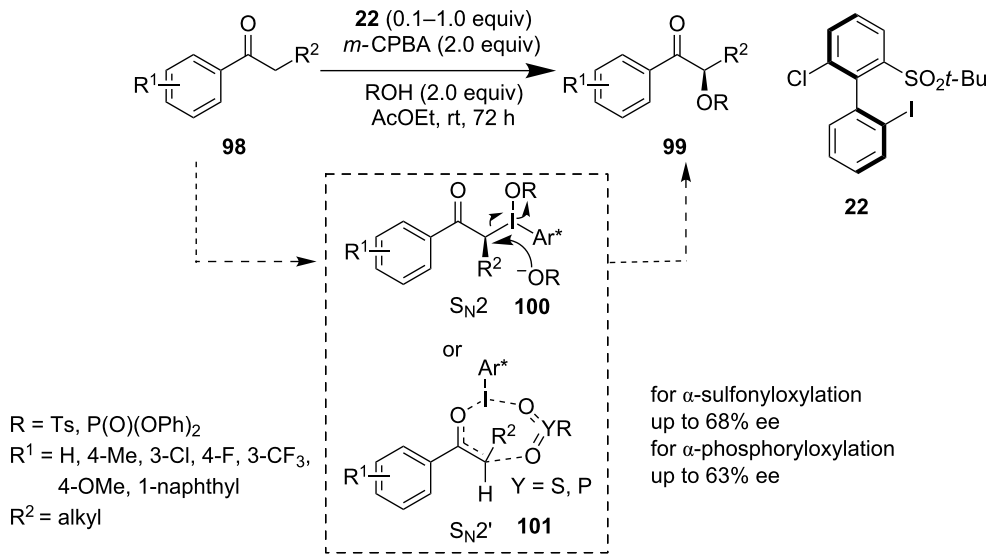
Scheme 21: Oxidative Intramolecular coupling by Gong et al.

lyst **12** to obtain spirofurooxindole derivatives with high enantioselectivity through cascade cross-coupling sequences [71].

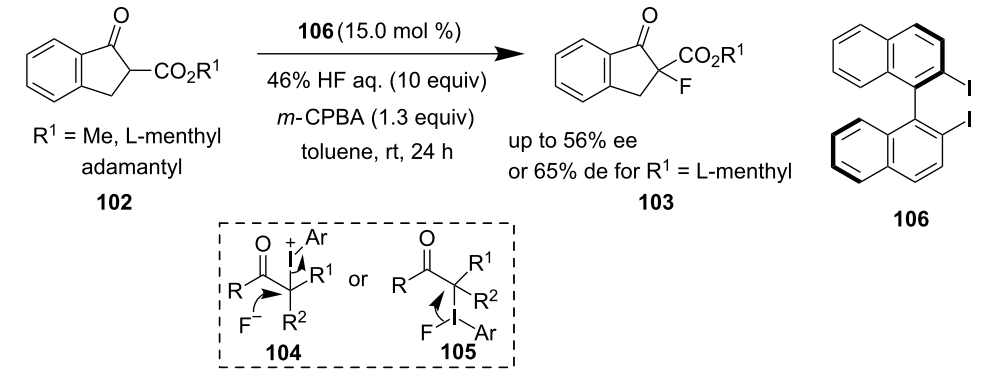
Latterly, Masson et al. reported a new chiral iodoarene pre-reagent **22** which they have used for the direct oxygenation of carbonyls **98**. They were able to get α-sulfonyls and α-phosphoryl oxyketones **99** with moderate ees (Scheme 22) [72]. A new type of non C_2-symmetric chiral hypervalent reagent was utilized for the asymmetric α-oxygenation of carbonyls. Nucleophilic attack of the oxygen nucleophile to the intermediate **100** or alternatively a reaction pathway through *O*-enolate intermediate **101** can explain the desired product formation.

In 2014, Kita and Shibata reported a catalytic, enantioselective, nucleophilic fluorinating technique of β-keto esters **102** using **106**/HF/*m*-CPBA as a catalytic system to access fluorinated β-keto esters **103** with moderate enantioselectivity [73]. β-Keto esters having sterically hindered adamantyl or menthyl groups lead to good selectivity. However, no further enhancement of ee could be achieved even by using a 50 mol % catalyst loading. A nucleophilic attack of the fluoride ion to the intermediate **104** or a possible ligand coupling pathway via **105** could justify the product formation (Scheme 23).

Waser et al. developed an asymmetric alkynylation of β-ketoesters and amides **107** catalyzed by a phase-transfer catalyst [74]. Their previous findings on the same reaction using a Cinchona-based phase-transfer catalyst [75] was further improved by using Maruoka's binaphthyl-derived ammonium salt **110**. The formation of intermediate **112** (chiral catalyst still attached to the substrate) from the enolate intermediate **111** followed by the generation of a C–C bond via conjugate addition



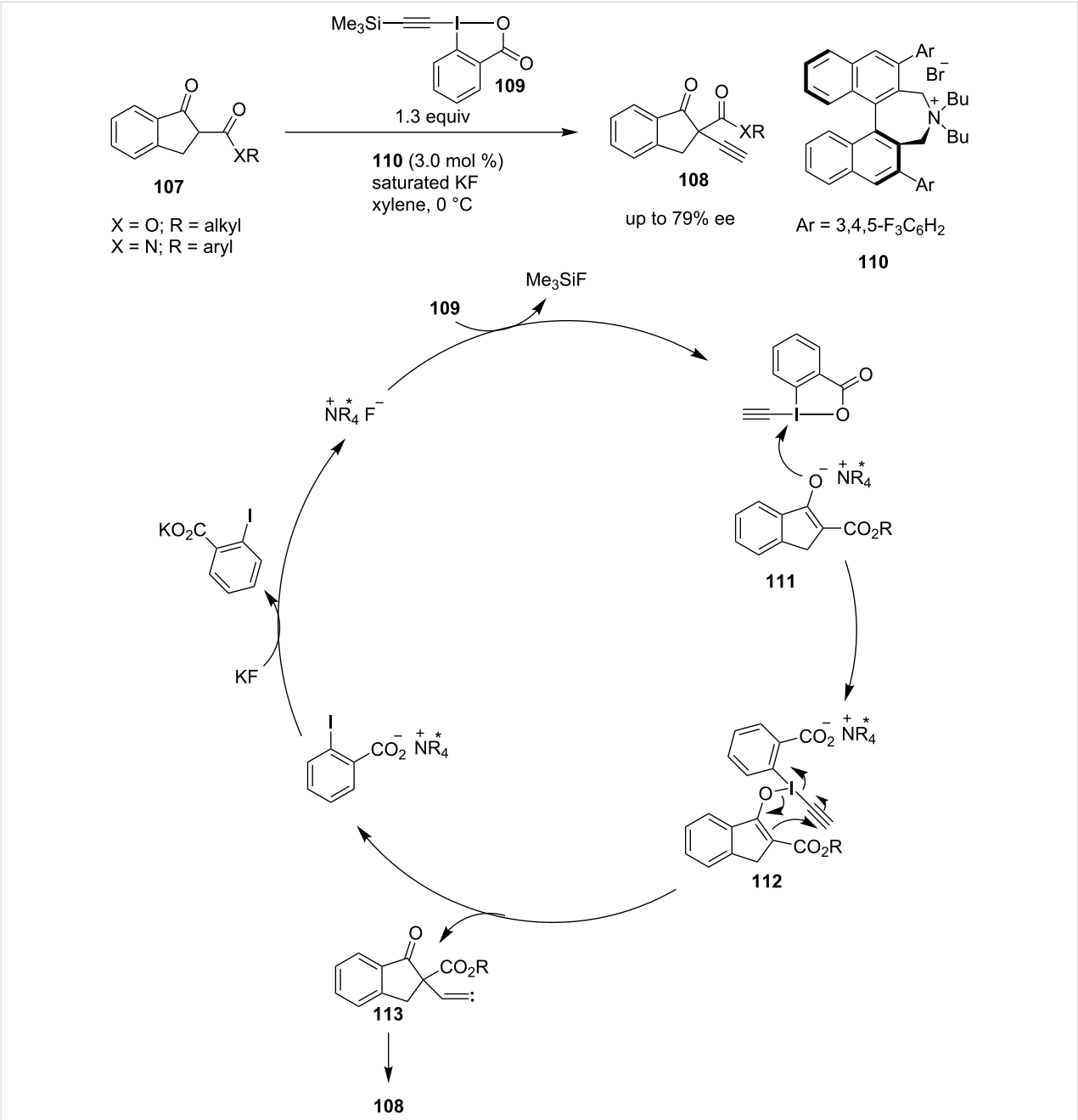
Scheme 22: α-Sulfonyl and α-phosphoryl oxylation of ketones reported by Masson et al.



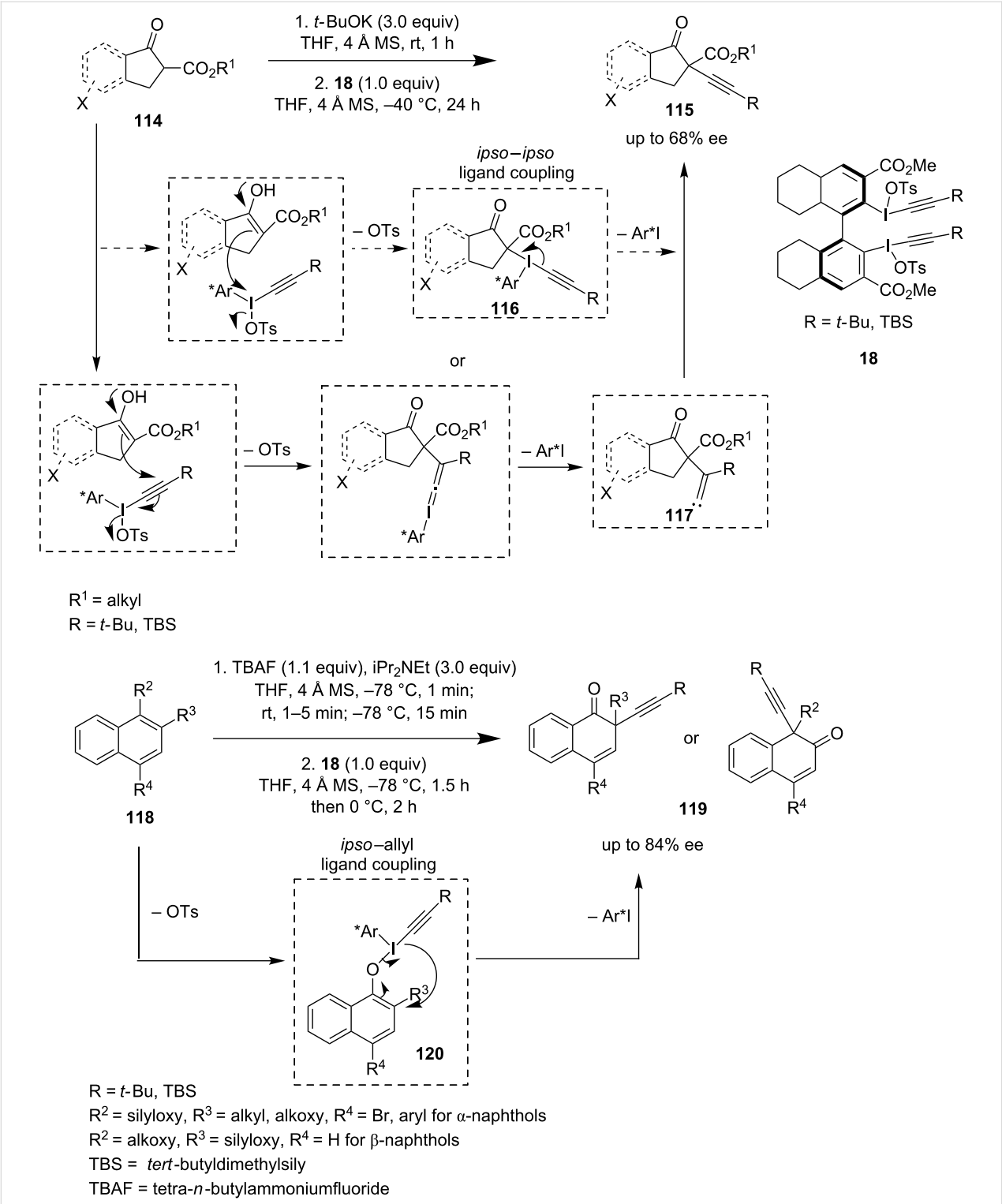
Scheme 23: α-Fluorination of β-keto esters.

delivered intermediate carbene **113**. A 1,2-hydrogen shift led to the formation of products **108** with enantioselectivities up to 79% (Scheme 24). Later, Maruoka et al. improved the enantioselectivity up to 95% ee for the alkynylation of β-ketoesters [76].

Pouységu and Quideau et al. prepared new axially chiral biaryl I(III) reagents **18** assembled with alkynyl ligands. They were able to achieve alkynylation of β-ketoesters **114** as well as dearomative alkynylation of phenolic derivatives **118** to obtain derivatives **115** and **119**, respectively, with decent enantioselectivity (Scheme 25) [77]. The formation of an alkylidene carbene **117** and its rapid rearrangement via 1,2-silyl shift (in case of R = silyl group) into the alkylated β-ketoesters **115** can fairly explain the reaction outcome. On the other hand, the ligand exchange/coupling sequence through the iodosyl intermediate **116** can be an alternative pathway for the formation of **115**. Likewise, a C–C *ipso*–allyl ligand coupling via intermediate **120** from *O*-naphtholate **118** explains the formation of product **119**.



Scheme 24: Alkynylation of β-ketoesters and amides catalyzed by phase-transfer catalyst.



Scheme 25: Alkynylation of β-ketoesters and dearomative alkynylation of phenols.

Conclusion

To conclude, throughout this review we have seen substantial growth in the field of chiral hypervalent iodine reagents. This review points a number of striking chiral hypervalent iodine reagents used in stoichiometric or in catalytic fashion for quite a number of useful organic transformations. Most importantly the oxidative chemistry can be done using catalytic amounts of chiral hypervalent iodine reagents in the presence of an external

oxidant. For convenient reading, we have only highlighted the optimized chiral catalysts or reagents used in the mentioned transformations. We hope that these new classes of reagents can achieve synthetically more challenging and application-oriented conversions that can be applied for the total synthesis of natural products as well as in industry related to pharmaceutical and medicinal chemistry.

These environmentally friendly, cheap and readily available reagents will surely attract the attention of scientists towards a sustainable replacement of transition metals. The application of chiral hypervalent iodine reagents is expected to pave the way for new reactions and reagent design in the field of asymmetric synthesis and catalysis.

Acknowledgements

The authors highly acknowledge the financial assistance received from the Indian Institute of Technology, Ropar. S. G. and. S. P. thank UGC, New Delhi and IIT Ropar, respectively, for their research fellowships. We thank Prof. Rano Ringo for proofreading the manuscript and valuable suggestions. We kindly acknowledge http://www.pexels.com/ from where we adapted our graphical abstract.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Atom-economical group-transfer reactions with hypervalent iodine compounds

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Review

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Keywords:
atom economy; benziodoxolones; homogeneous catalysis; hypervalent iodine; iodonium salts

Beilstein J. Org. Chem. **2018,** *14,* 1263–1280.
doi:10.3762/bjoc.14.108

Received: 22 February 2018
Accepted: 02 May 2018
Published: 30 May 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Hypervalent iodine compounds, in particular aryl-λ^3-iodanes, have been used extensively as electrophilic group-transfer reagents. Even though these compounds are superior substrates in terms of reactivity and stability, their utilization is accompanied by stoichiometric amounts of an aryl iodide as waste. This highly nonpolar side product can be tedious to separate from the desired target molecules and significantly reduces the overall atom efficiency of these transformations. In this short review, we want to give a brief summary of recently developed methods, in which this arising former waste is used as an additional reagent in cascade transformations to generate multiple substituted products in one step and with high atom efficiency.

Introduction

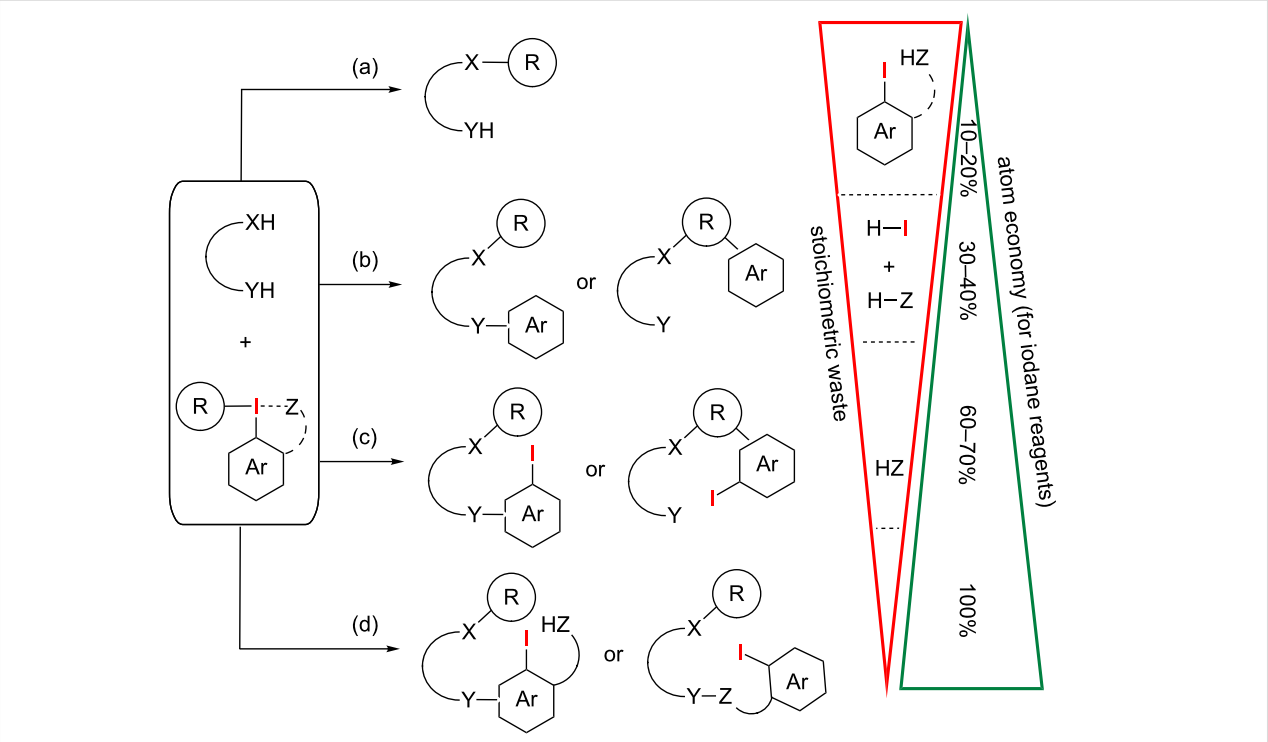
Atom economy (AE) is an important parameter which helps to evaluate the overall efficiency of a chemical reaction or a chemical process [1,2]. It is defined as the quotient between the molecular mass of the desired reaction product(s) and the molecular mass of all reactants (Equation 1):

$$\text{atom economy}(\%) = \frac{\text{molecular mass of the desired reaction product}}{\text{molecular mass of all reactants}} \times 100 \quad (1)$$

In an ideal reaction with 100% atom economy, every atom of the reactants is becoming part of the desired product. In this short review, we want to discuss recent advances in atom-economical transformations using hypervalent iodine reagents (iodanes) as electrophilic group-transfer reagents. Iodanes, in particular iodonium salts, are well-balanced reagents in terms of stability, reactivity and synthetic and/or commercial availability and therefore it is not surprising to see these compounds as key reagents in a great number of recently developed transformations [3-15]. However, in terms of atom economy, they have an intrinsic problem: their high reactivity is based on the emergence of aryl iodides as supernucleofuges. λ^3-Iodanes are the

generally preferred hypervalent iodine compounds for electrophilic group transfer reactions, during which the central iodine atom is transformed from a high energy hypervalent state into a normal valent state by a two-electron reduction. The high stability of the newly formed aryl iodide is the thermodynamic driving force for all λ^3-iodane-mediated oxidative transformations. Even though this process guarantees the high reactivity of these reagents, it has one major obstacle: after the oxidation process, stoichiometric amounts of the aryl iodide are produced as waste. Aryl iodides, as nonpolar organic waste, are oftentimes hard to separate from the desired reaction products since they cannot be simply washed out with aqueous solutions. Instead, they must be separated by column chromatography. In terms of AE, the high atomic mass of iodine (126.9 u) leads to a dramatic negative impact of iodanes on this "green" reaction parameter. To overcome this obstacle, promising approaches are the use of iodoarenes as precatalysts in combination with external co-oxidants and the utilization of specific hypervalent iodine compounds (polymer-supported as well as non-polymeric species), whose reduced forms are easy to recycle [3,4,16,17]. On the other hand, the additional incorporation of the former iodoarene waste into the reaction product via a cascade reaction does not only improve the overall AE of a chemical reaction but also directly leads to highly functionalized target molecules. A rough estimate about the impact of the incorporation efficiency of the iodane on the AE is depicted in Scheme 1. Here, only the molecular mass of the corresponding iodane substrates is taken into account for AE estimation.

The transfer of only one functional group, for instance in iodane-mediated electrophilic monoarylations, produces not only the aryl iodide, but also stoichiometric amounts of salt side-products, limiting the AE of these transformations to roughly 10–20% (Scheme 1, reaction (a)). In the second case, both organic residues (one carbon or heteroatom ligand plus the arene of the former aryl-λ^3-iodane or aryliodonium salt) are transferred to the substrate (Scheme 1, reaction (b)). The loss of iodine and the counterion still limits the overall AE to 30–40%. A dramatic increase in AE arises, if the iodine atom is incorporated in the desired reaction product as well (Scheme 1, reaction (c)). This does not only lead to an overall AE of up to 70% but also produces synthetically versatile intermediates for subsequent transformations, in particular metal-catalyzed cross-coupling reactions. If benziodoxolones or benziodoxoles are used as group-transfer reagents, nearly 100% AE is possible since the counterion (the carboxylate or alcoholate) is covalently attached to the aryl iodide and hence does not get lost during the reaction cascade (Scheme 1, reaction (d)). This is very effective, if this *ortho*-functionality is a desired part of the final reaction product or if it can be readily transformed into synthetically useful functional groups.



Scheme 1: Overview of different types of iodane-based group-transfer reactions and their atom economy based on the molecular mass of the corresponding λ^3-iodane.

In this short review, we will give a brief summary of very recent efforts toward the atom-economical use of aryl-λ^3-iodanes, in particular aryliodonium salts in group-transfer reactions. In our definition, this includes transformations in which at least two of the three ligands attached to the iodane are part of the target molecule or in which the iodane acts as an oxidant and a group-transfer reagent in a consecutive reaction sequence. The chapters are divided by the structure of the transferred functional groups, starting from simple diarylations and oxidative arylations with moderate AE to highly atom efficient transformations using alkynyl and azide-substituted benziodoxolones. The given AE values are simplified and were calculated on the basis of the key substrates, whereas the required equivalents of all starting materials (iodane and usually its reaction partner) are taken into account. Other additives, such as additional bases, acids or catalysts were neglected.

Review

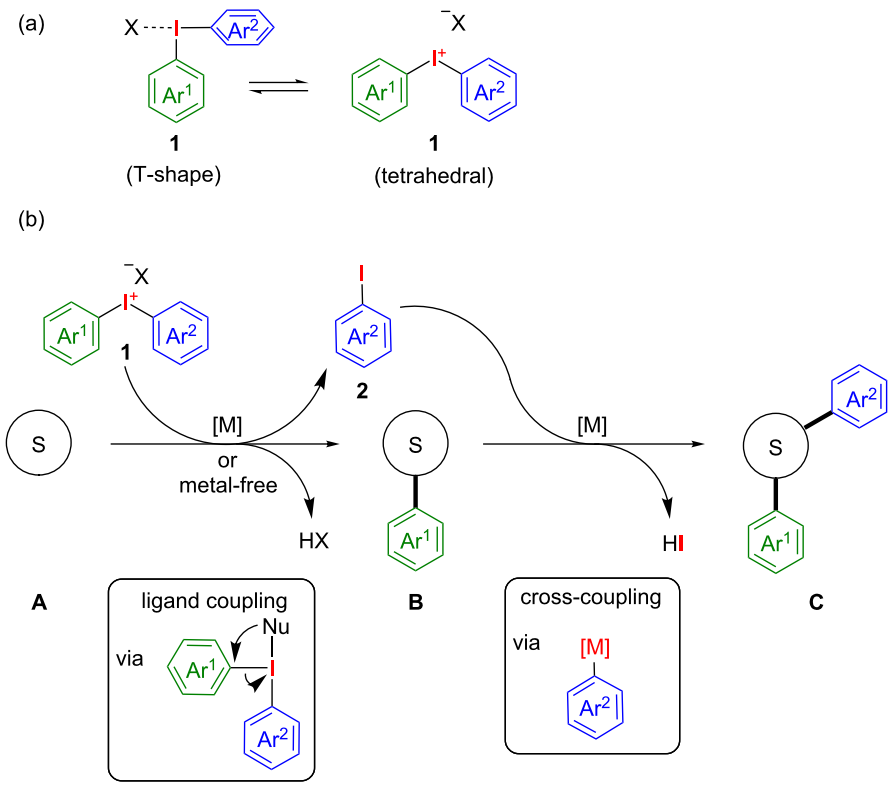
1. Diaryliodonium salts

1.1. Acyclic diaryliodonium salts

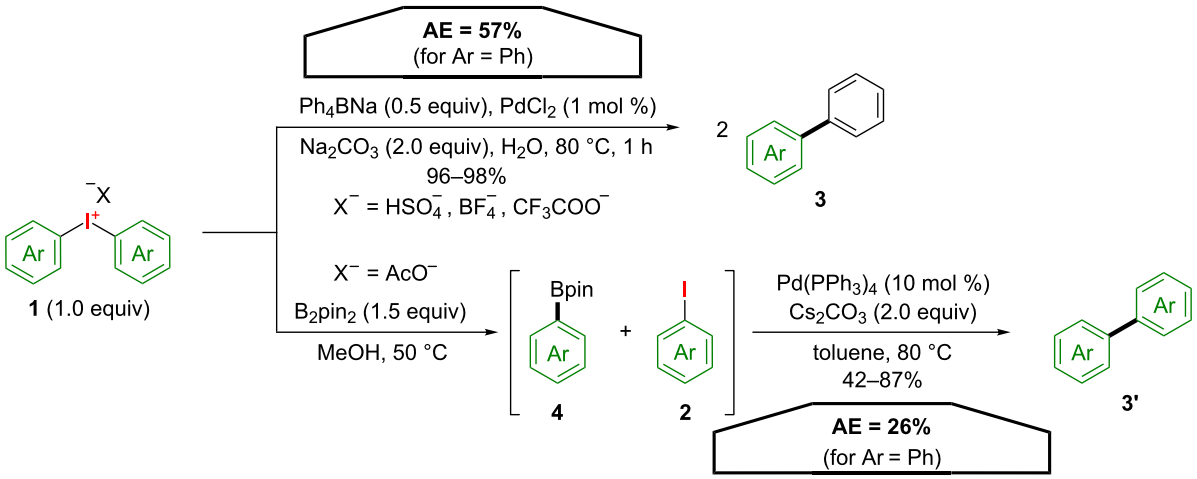
Acyclic diaryliodonium salts **1** find widespread application in numerous metal-free and transition metal-mediated electrophilic arylation protocols [18-22]. While in solid state they clearly have a T-shaped pseudotrigonal bipyramid structure, the common structural motif for λ^3-iodanes, recent theoretical investigations revealed a potential role of the cationic, normal valent tetrahedral form, in atom transfer processes (Scheme 2a) [23]. Throughout this review, iodonium salts will be shown consequently in the latter structure due to clarity and due to literature habits.

Typically, only one of the two aryl ligands is transferred to the substrate, yielding a monoarylated reaction product and aryl iodide as stoichiometric waste. Examples for their atom-economical utilization, in which at least both aryl ligands are transferred, are still rare. A general approach would involve at first a metal-catalysed or metal-free arylation step of a suitable substrate **A** with the diaryliodonium salt **1** to give monoarylated intermediate **B**. Subsequently, a metal-catalysed cross-coupling initiated by an oxidative addition of the metal catalyst into the C–I bond of the emerging iodoarene **2** affords the diarylated product **C** (Scheme 2b).

A first report utilizing this strategy was published by Bumagin and co-workers as early as 1995 [24]. Here, symmetrical diaryliodonium salts **1** were used in a palladium-catalysed cross-coupling reaction with sodium tetraphenylborate (Scheme 3). This reaction not only provides excellent yields of



Scheme 2: (a) Structure of diaryliodonium salts **1**. (b) Diarylation of a suitable substrate **A** with one equivalent of diaryliodonium salt **1**.

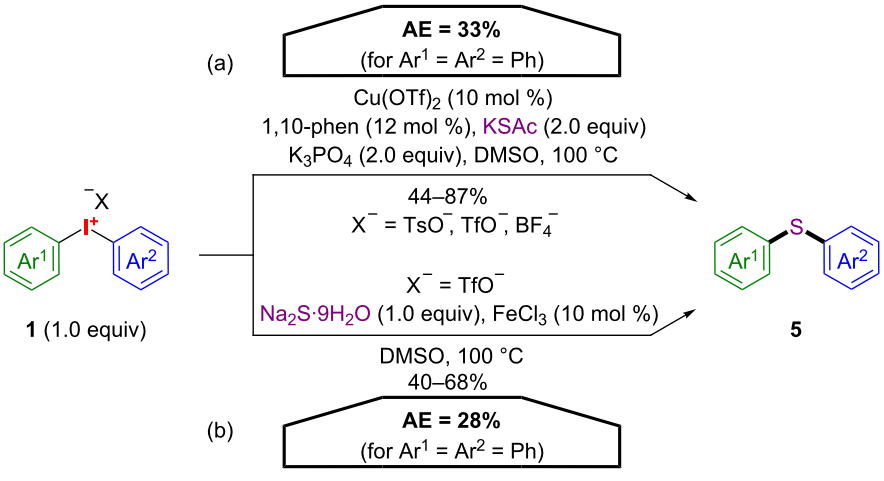


Scheme 3: Synthesis of biphenyls **3** and **3'** with symmetrical diaryliodonium salts **1**.

the respective biphenyls **3** but also exhibits a high AE (57% for Ar = Ph). However, its general synthetic utility is limited since it requires highly reactive boron compounds as nucleophiles.

Symmetrical biphenyls **3'** can be generated from the corresponding symmetrically substituted diaryliodonium salts **1** and bis(pinacolato)diboron as demonstrated by Muñiz and co-workers [25]. In the first step, a mild carbon–boron bond formation gives one equivalent of arylboronic ester **4** and an iodoarene **2** through a metal-free boron arylation. Subsequent cross coupling under Suzuki conditions affords symmetrical biphenyls **3'** in good yields. Due to the temporary introduction and cleavage of the boron moiety the formal atom economy for this transformation is rather low (26% for Ar = Ph). However, 45% of the molecular weight of the starting iodonium salt **1** is present in the product **3'**.

Diaryl thioethers **5** can be synthesized using either cyclic iodonium salts (will be discussed briefly in section 1.2) or their acyclic counterparts **1** (Scheme 4) [26,27]. Jiang and co-workers developed a Cu(II)-catalysed methodology for the conversion of acyclic diaryliodonium salts **1** and potassium thioacetate to the corresponding thioethers **5** (pathway (a)) and later applied the optimized reaction conditions towards cyclic iodonium salts. In an independent work, Li and co-workers successfully utilized a catalytic system based on $FeCl_3$ with comparable results (pathway (b)). However, both procedures have only moderate AE values (28–33% for $Ar^1 = Ar^2$ = Ph),

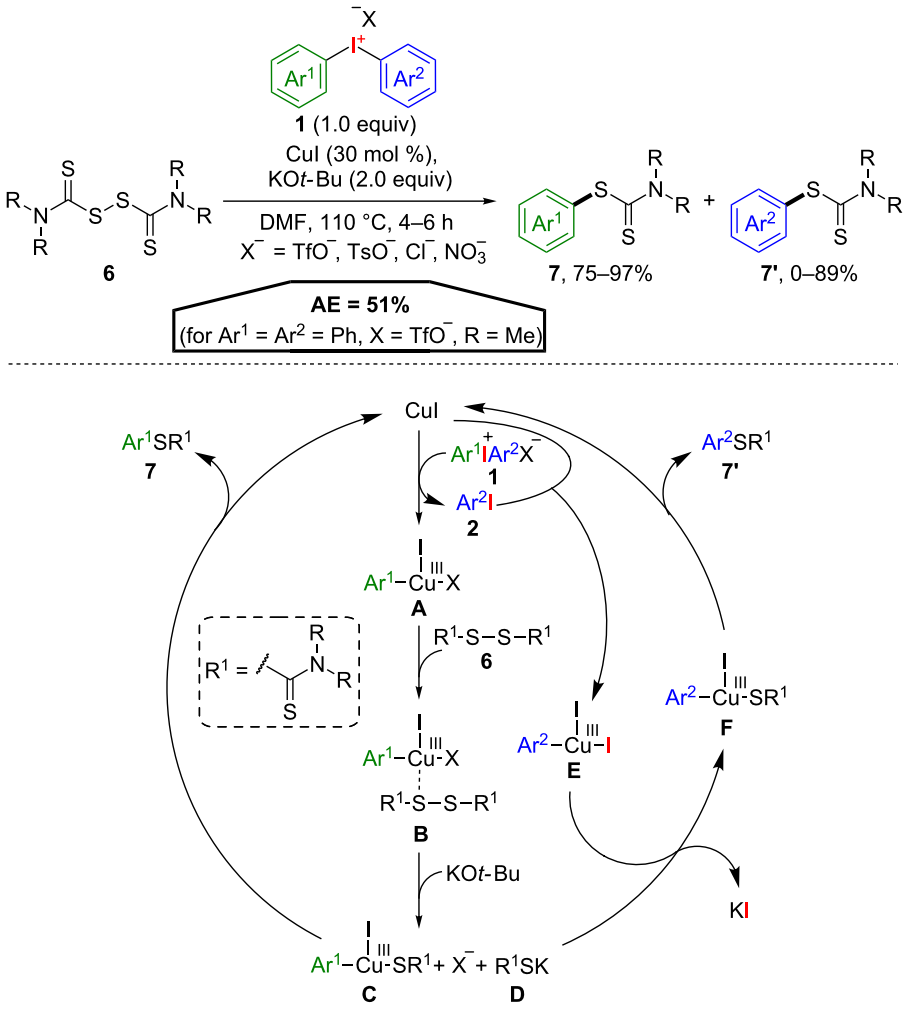


Scheme 4: Synthesis of diaryl thioethers **5**.

since the transferred aryl groups account for only about 35% to the mass of the respective diaryliodonium salts **1**.

An atom efficient *S*-arylation of tetraalkylthiuram disulfides **6** was developed by Dong and co-workers under Cu(I)-catalysis (Scheme 5) [28]. This reaction yields two equivalents of *S*-aryl dithiocarbamates **7** and **7'** in typically high yields applying only one equivalent of a diaryliodonium salt **1**. It is worth to mention, that the AE of 51% (for $Ar^1 = Ar^2$ = Ph, X = TfO^-, R = Me) is only valid if both dithiocarbamates **7** and **7'** are defined as desired reaction products. If symmetrical diaryliodonium salts are used, as also demonstrated, only one arylation product is formed. The proposed reaction mechanism starts with the oxidative addition of the diaryliodonium salt **1** to copper(I) iodide affording the Cu(III) species **A**, releasing aryl iodide **2**. Coordination of the disulfide **6** to the metal centre leads to complex **B**, followed by the base-induced formation of arylcopper sulfide complex **C** and potassium salt **D** upon treatment with KO*t*-Bu. Reductive elimination from **C** produces the product **7**, under regeneration of the Cu(I) species. The released aryl iodide **2** on the other hand then undergoes oxidative addition forming the Cu(III) species **E**, which can provide intermediate **F** upon reaction with the potassium salt **D** and the release of potassium iodide. Reductive elimination then affords the second *S*-aryl dithiocarbamate **7'**.

If both aryl groups are not transferred to the same reaction centre in metal-mediated diarylations when unsymmetrical diaryliodonium salts are used as aryl-transfer reagents, poor chemoselectivities are often observed. Since electronic differences in many cases exhibit only unsatisfactory levels of selectivity [29,30], sterically demanding groups, such as mesityl moieties, are mostly used to solve this issue. However, the high steric demand can be of disadvantage if the development of an atom-economical transformation is intended through a subsequent functionalization of the emerging, now less reactive,

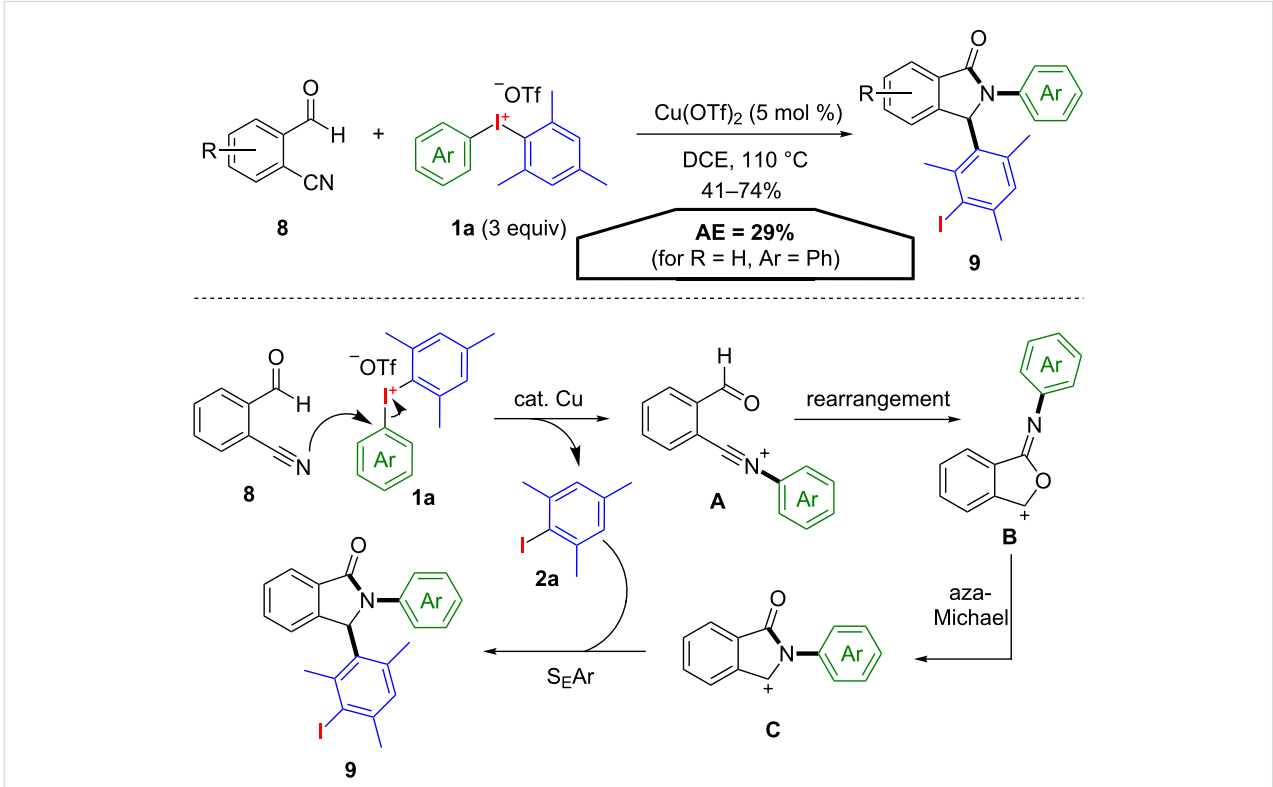


Scheme 5: Synthesis of two distinct *S*-aryl dithiocarbamates **7** and **7'** from one equivalent of diaryliodonium salt **1**.

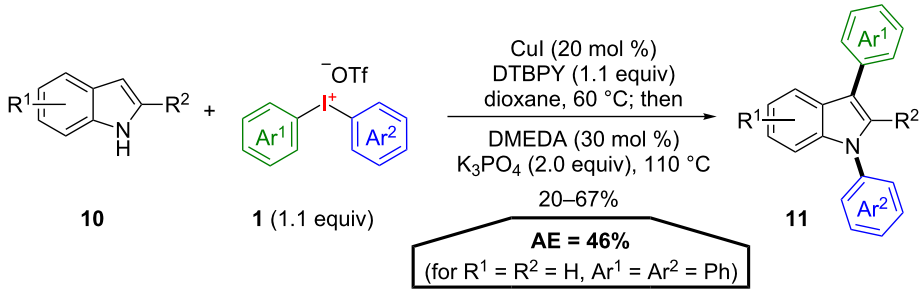
mesityl iodide. A procedure which impressively combines the selectivity of mesityl(aryl)iodonium salts **1a** with this difficult second arylation step was developed by Li and co-workers [31]. Under copper-catalysis diarylated isoindolin-1-ones **9** were formed starting from 2-formylbenzonitriles **8** upon treatment with mesityl(aryl)iodonium salts **1a** (Scheme 6). A plausible reaction mechanism starts with the selective terminal arylation of the nitrile, forming the arylnitrilium cation **A** and 2-iodomesitylene (**2a**). Intramolecular cyclization leads to the iminofuranylium intermediate **B** which affords the cationic isoindolin-1-one structure **C** via subsequent intramolecular aza-Michael type rearrangement. This intermediate reacts in the final step with the electron-rich 2-iodomesitylene (**2a**) in an S_EAr reaction to give the diarylated isoindolin-1-one **9**. A drawback of these reaction conditions is the use of excess (3 equiv) mesityl(aryl)iodonium salt **1a** to achieve satisfying yields. This dramatically lowers the atom-economy to only 29% (for R = H, Ar = Ph), instead of theoretical 75%, if only one equivalent of the iodane **1a** would have been sufficient.

In recent years a variety of domino C–H and/or N–H arylations as powerful tools towards selective diarylations of (hetero)arenes was employed by Greaney and co-workers, who were among the first to establish more atom-economical procedures with λ^3-iodanes. These methods commonly exhibit good AE for (di)arylation procedures, since only small excesses of diaryliodonium salts are necessary. In an initial study, the selective diarylation of indoles **10** using symmetrical and unsymmetrical diaryliodonium salts **1** was demonstrated (Scheme 7) [32]. A selective C–H arylation at C3 of the indole was realised under copper catalysis before the addition of a ligand and an inorganic base initiated the N-arylation with the in situ formed iodoarene. The desired diarylated indoles **11** are obtained with an AE of 46% (for $R^1 = R^2 = H$, $Ar^1 = Ar^2 = Ph$). The scope of this transformation is broad, only C2-substituted indoles show poor reactivity. Furthermore, this is a rare example for good chemoselectivities in atom-efficient reaction cascades even if unsymmetrical substituted diaryliodonium salts are applied.

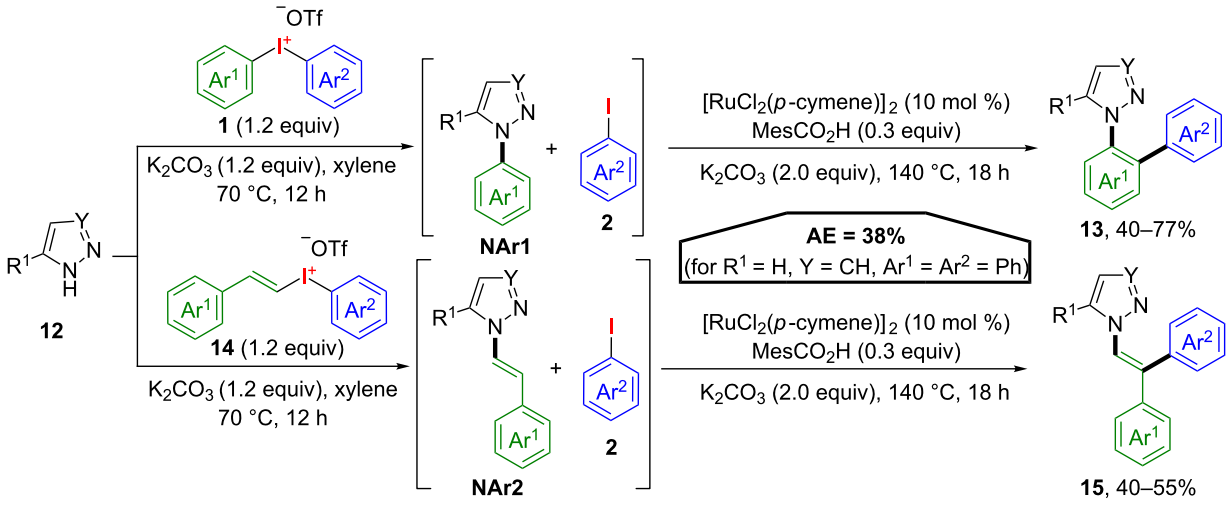
Based on this initial procedure, an impressive atom-economical biphenylation of N-heterocycles was developed [33]. This method involved a direct N-arylation of pyrazoles or triazoles **12** under basic conditions, followed by a ruthenium-catalysed C–H arylation with the emerging aryl iodide (Scheme 8). Due to the fact that the first step of this reaction sequence proceeds under metal-free conditions, the selective transfer of the more electron-deficient aryl group of the unsymmetrical iodonium salts **1** is achieved. The N-arylated heterocycle **NAr1** then serves as the directing group in the following *ortho*-C–H functionalisation with the iodoarene as coupling reagent to yield



Scheme 6: Synthesis of substituted isoindolin-1-ones **9** from 2-formylbenzonitrile **8** and the postulated reaction mechanism.



Scheme 7: Domino C-/N-arylation of indoles **10**.

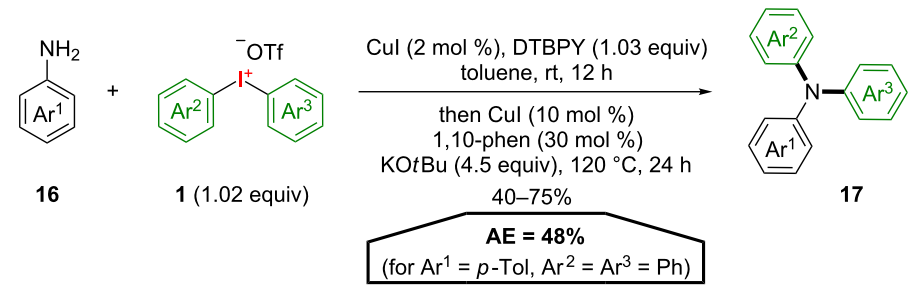


Scheme 8: Domino modification of N-heterocycles **12** via in situ-generated directing groups.

biphenyls **13**. The optimized reaction conditions are also applicable to alkenyl(aryl)iodonium salts **14** making arylated benzylidenes **15** accessible through the N-alkenylated intermediate **NAr2**.

The AE for this transformation is 38% (for R^1 = H, Y = CH, Ar^1 = Ar^2 = Ph), a typical value for iodane-mediated double functionalisations with aryl iodonium salts.

Another achievement of Greaney and co-workers is the atom-economical double arylation of anilines **16** with symmetrical diaryliodonium salts **1** (Scheme 9) [34]. The corresponding triarylamines **17** are important structural motifs for organic electronics and can be obtained in good yields and an AE of 48% (Ar^1 = *p*-Tol, Ar^2 = Ar^3 = Ph) using this Cu(I)-catalysed domino approach. The formation of an intermediately found diarylaniline supposedly follows a Cu(I)/Cu(III) cycle, whereas



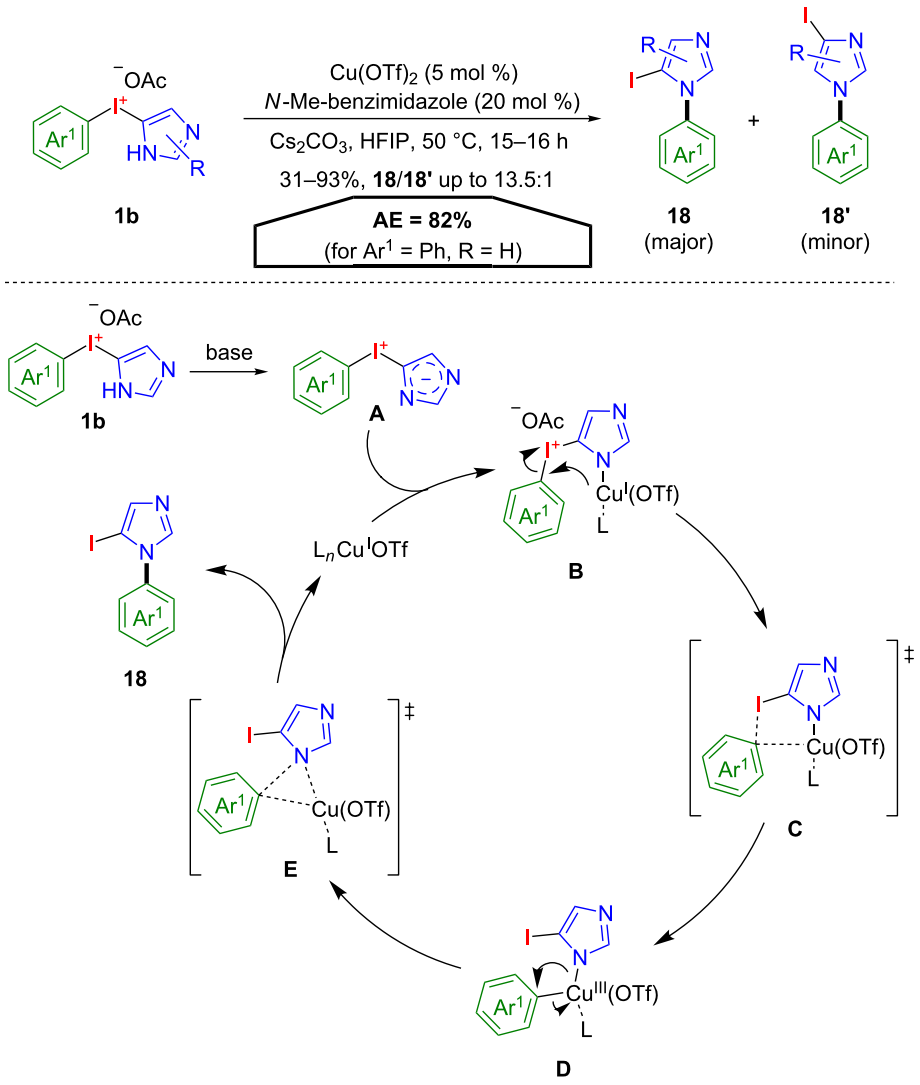
Scheme 9: Synthesis of triarylamines **17** through a double arylation of anilines.

a radical mechanism is proposed for the second arylation. Unfortunately, a selective aryl transfer using unsymmetrical diaryliodonium salts was not successful under the reaction conditions, giving only mixtures of mono N-arylated anilines in low yields after the first step.

A different approach towards the functionalisation of heterocycles was taken by Shafir, Lledós, and co-workers, who investigated the intrinsic conversion of novel N-heterocyclic aryliodonium salts **1b** [35]. Under the influence of base, copper catalyst and *N*-Me-benzimidazole as a ligand, the heterocyclic aryliodonium salt **1b** was converted into the *N*1-aryl-5-iodoimidazole **18** as the major isomer (Scheme 10). Compound **18** is a valuable intermediate for a variety of coupling reactions to yield 1,5-disubstituted imidazoles – structural motifs which are generally difficult to obtain – in a selective fashion. The proposed reaction mechanism based on DFT calculations starts with the deprotonation of the imidazolyl group to give betain **A**, which binds to a Cu(I)-OTf fragment leading to complex **B**. Next, the aryl group is transferred from the iodine to the copper atom leading to the Cu(III) complex **D** via a five-membered transition state **C**. Reductive elimination through transition state **E** provides **18** and restores the active Cu(I) species. Since this reaction follows an intramolecular pathway, it is featured by a remarkable high atom economy of 82% (for Ar^1 = Ph, R = H), lowered only by the loss of one formal equivalent of acetic acid.

1.2. Cyclic diaryliodonium salts

Within the vast scope of hypervalent iodine compounds the class of cyclic diaryliodonium salts **19** is predestined to undergo atom-efficient transformations. Owing to their unique structure in which both carbon ligands attached to the central iodine atom



Scheme 10: Selective conversion of novel aryl(imidazolyl)iodonium salts **1b** to 1,5-disubstituted imidazoles **18**.

are connected to one another, no iodoarene "waste" can be formed in the reaction process. Depending on the reaction conditions the selective functionalisation of just one aryl iodine moiety or the modification of both carbon ligands in either a symmetrical or unsymmetrical transformation is possible leading to a plethora of useful carbo- and heterocycles (Scheme 11).

The chemistry of cyclic diaryliodonium salts has been reviewed by Grushin in 2000 [36] and more recently by Goswami and co-worker [37]. Therefore, this topic will not be discussed in further detail in this article. However, since iodine and the counterion are inevitable stoichiometric side products, it is worth mentioning that the theoretical AE for these particular transformations is usually limited to 30–40%.

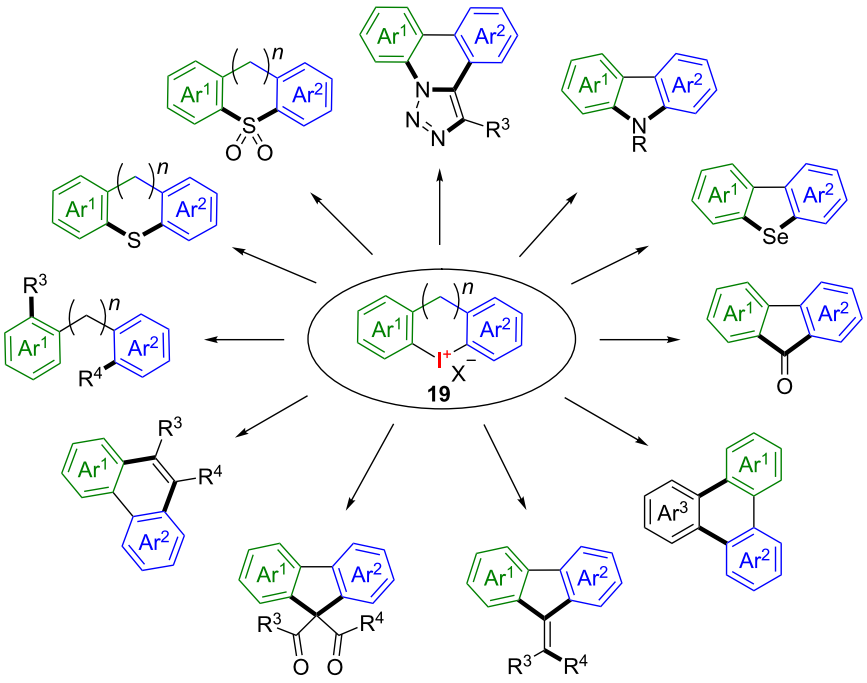
2. (Dicarboxyiodo)benzenes

From a synthetic point of view, (dicarboxyiodo)benzenes **20** are probably one of the most popular hypervalent iodine compounds in organic synthesis [3,9,38-41]. They have been widely applied in C–H oxygenations, nitrene generations, oxidative dearomatisations and dehydrogenative couplings by transferring one of their two carboxyl ligands or external oxygen nucleophiles to a substrate. In all these "classical" reactions aryl iodides are produced as stoichiometric waste products once again. The further utilization of this side product in a subsequent reaction step would dramatically increase the AE for such oxidative transformations.

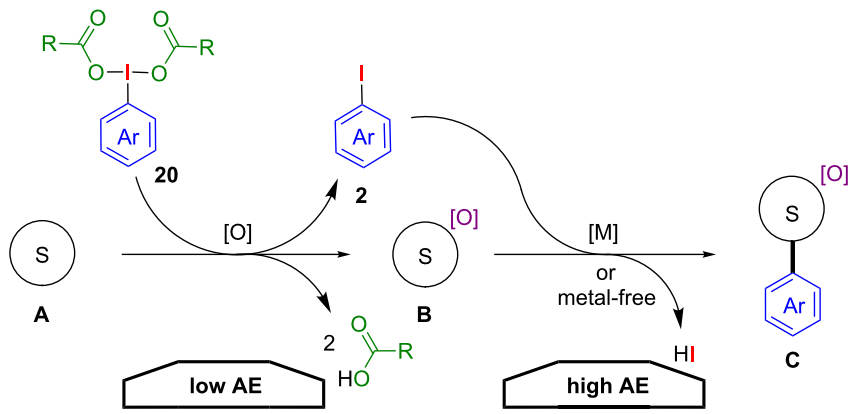
A general procedure for such a tandem sequence would involve an initial oxidation step of a substrate **A** followed by a coupling of the formed iodoarene **2** with the oxidised substrate **B** either under metal-free or metal-catalysed conditions to form the product **C** (Scheme 12).

The first examples for an oxidation–arylation cascade using (dicarboxyiodo)benzenes were reported by Shafir and co-workers [42,43]. Herein, the authors describe an efficient α-arylation of a variety of 1,3-dicarbonyl derivatives **21** using [bis(trifluoroacetoxy)iodo]benzene (**20a**, PIFA). In this metal-free approach the target structures **22** are efficiently synthesised even without any initial prefunctionalisation of the arene moiety (Scheme 13). Remarkably, the intact 2-iodoaryl group is transferred via presumed transition state **TS1**, which leads to a good AE (50% for **22a**) and allows the further transformation of the α-arylation product **22** via cross coupling reactions. In addition, the in situ generation of the PIFA reagent proved viable, in order to temporary generate potentially unstable λ^3-iodane derivatives and immediately convert them under the established α-arylation conditions.

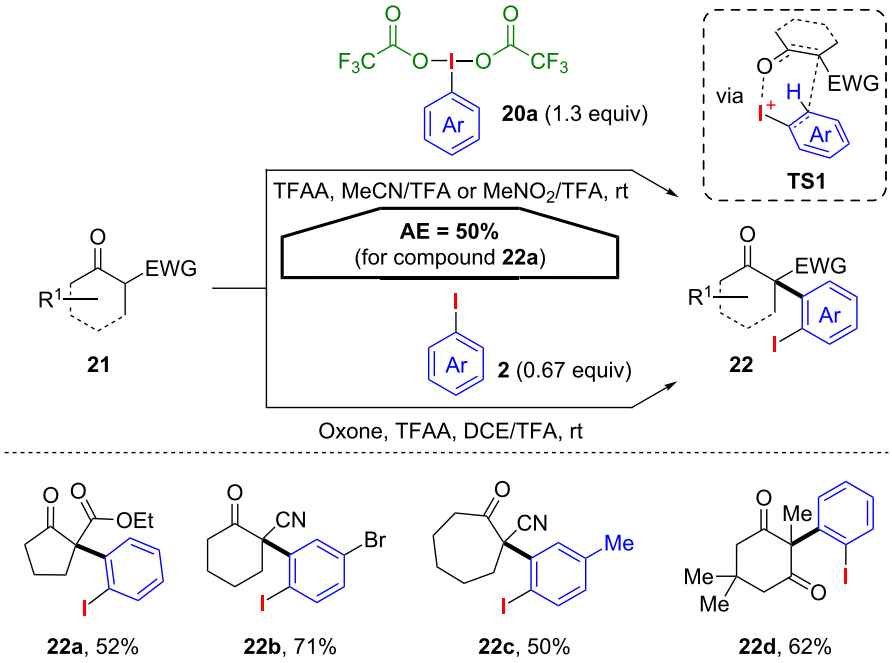
A PIDA ((diacetoxyiodo)benzene)-mediated *ortho*-iodination/O-arylation cascade was developed by Panda and co-workers using diversely functionalised phenols **23** (Scheme 14) [44]. The reaction presumably proceeds via an *ortho*-addition of the λ^3-iodane **20b**, followed by an iodine-to-oxygen 1,3-aryl migration via a concerted mechanism through the five-membered



Scheme 11: Selected examples for the application of cyclic diaryliodonium salts **19**.



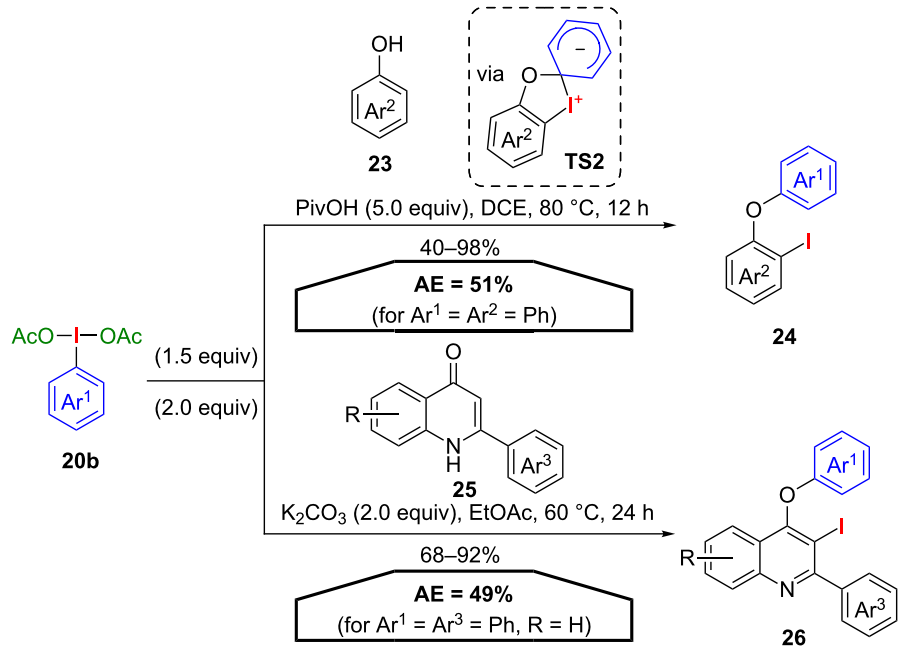
Scheme 12: Tandem oxidation–arylation sequence with (dicarboxyiodo)benzenes **20**.



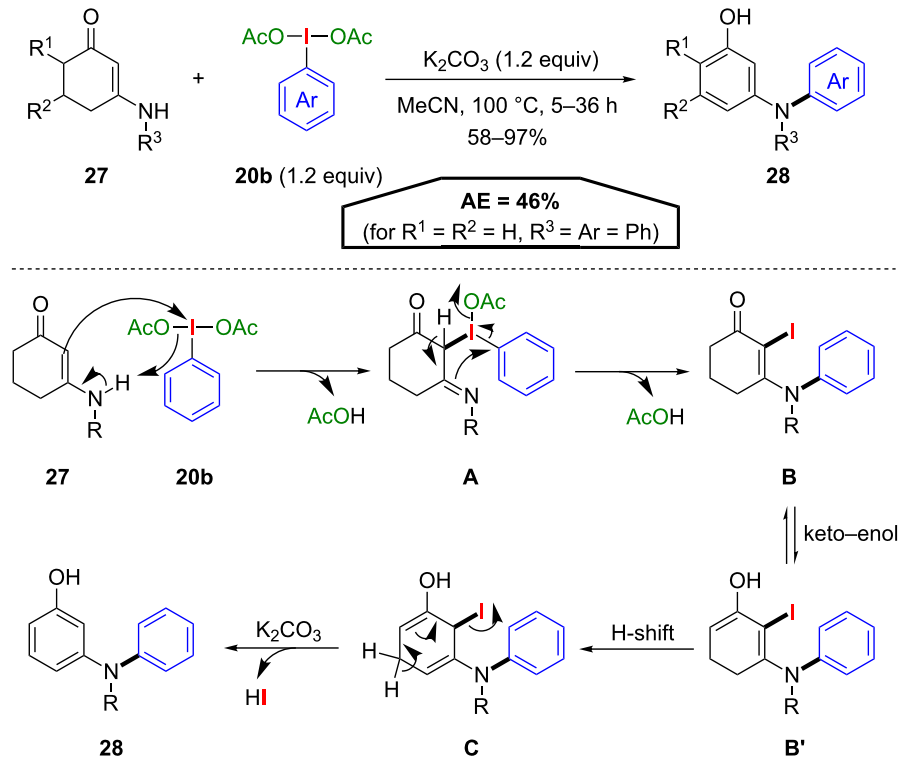
Scheme 13: Oxidative α-arylation via the transfer of an intact 2-iodoaryl group.

intermediate **TS2** to afford the corresponding diaryl ether **24**. A mechanistically similar *ortho*-iodination/O-arylation cascade for the modification of 2-arylquinolones **25** was developed by Xie and co-workers, providing the respective products **26** in a one pot sequence [45]. Both methods are characterised by a good AE (49–51% for Ar = Ph) due to the incorporation of both, the aryl group and the iodine atom. However, the usage of 1.5 to 2.0 equivalents of the hypervalent iodine reagent **20b** lowers the conclusive atom efficiencies.

In another closely related procedure, Das and co-workers employed PIDA derivatives **20b** for an aromatization–arylation cascade of exocyclic β-enaminones **27** [46]. Under basic reaction conditions *meta*-*N*,*N*-diarylaminophenols **28** were obtained in good to excellent yields using **20b** both as the aromatization and arylation agent (Scheme 15). In the first step of the postulated mechanism, a ligand exchange of the starting material **27** and PIDA **20b** forms intermediate **A**, which leads to the formation of the stable N-arylated intermediate **B** via an iodine-to-nitrogen 1,3-phenyl migration. An equilibrium with its enol form **B'** is proposed, which affords the aromatization product **28** via H-shift to intermediate **C** and subsequent dehydroiodination under basic conditions. Although the iodine atom is not incorporated into the final product, the calculated AE (46% for $R^1 = R^2 = H$, $R^3 = Ar = Ph$) is close to the procedures of Panda and Xie due to lower PIDA loadings.

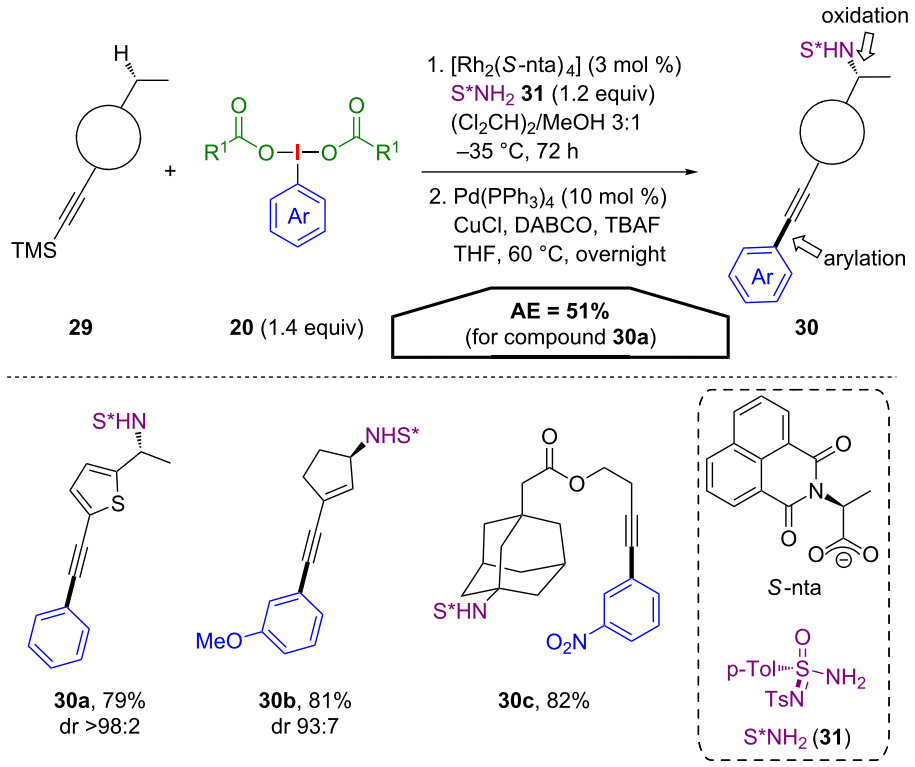


Scheme 14: Tandem *ortho*-iodination/O-arylation cascade with PIDA derivatives **20b**.



Scheme 15: Synthesis of *meta*-*N*,*N*-diarylaminophenols **28** and the postulated mechanism.

A metal-catalysed procedure for the atom-economical utilization of (dicarboxyiodo)benzenes **20** in a tandem C(sp^3)–H amination/sila-Sonogashira–Hagihara reaction was developed by Dauban and co-workers (Scheme 16) [47]. The first step of this sequence includes an iodine(III)-mediated rhodium-catalysed enantioselective amination of an unactivated C(sp^3)–H bond with a chiral sulfonimidamide **31**. Afterwards, the iodoarene byproduct of the first step is coupled with the alkyne



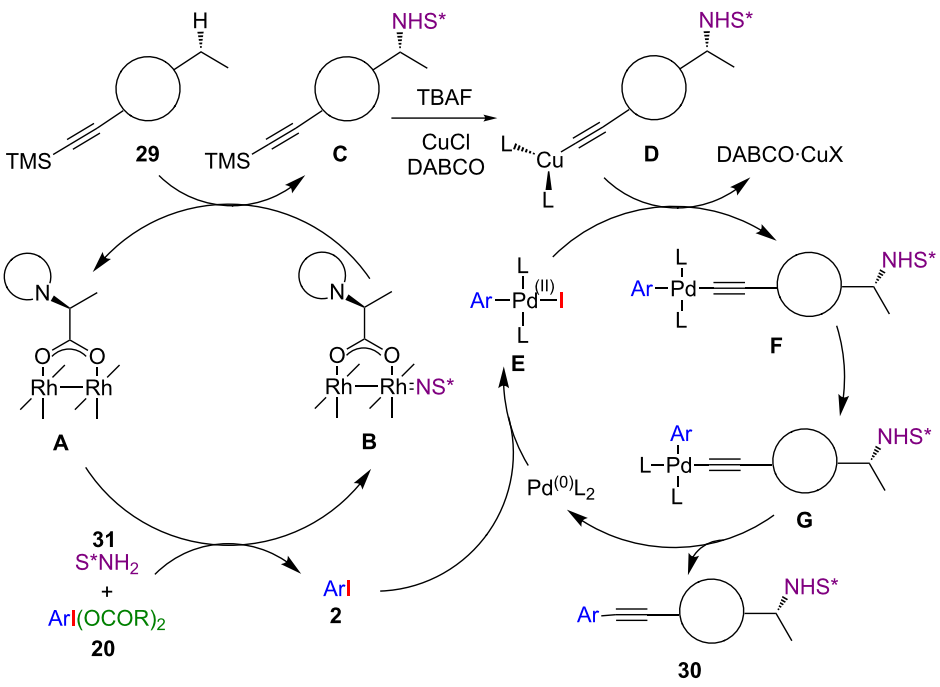
Scheme 16: (Dicarboxyiodo)benzene-mediated metal-catalysed C–H amination and arylation.

under palladium catalysis. A broad range of TMS-substituted acetylenes **29** was converted efficiently under the optimized reaction conditions, forming the desired arylacetylenes **30** in good yields with high stereoselectivity. The applicable substrate scope is rather broad including thiophene, cyclopentene and adamantyl derivatives **30a–c** with good AE values (51% for **30a**).

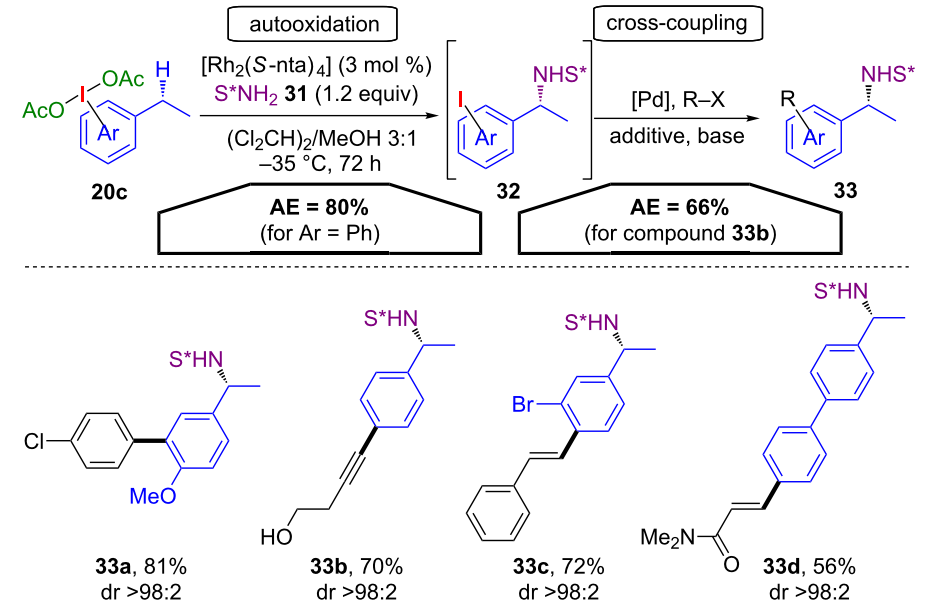
The proposed mechanism involves two distinct catalytic cycles for the amination and the arylation reaction step (Scheme 17). First, a metallanitrene **B** is formed via the reaction of the (dicarboxyiodo)benzene **20** with the sulfonimidamide **31** in the presence of the chiral rhodium(II) catalyst **A**. Hereby, one equivalent of iodoarene **2** is released. The insertion of the nitrene species into the C(sp^3)–H bond affords the amination product **C**, which is the final product of the first reaction step. In the following step, **C** is subsequently desilylated with TBAF in the presence of CuCl and DABCO to obtain the alkynylcopper species **D**. In the meantime oxidative addition of the previously released iodoarene **2** to the Pd(0) species occurs and the resulting palladium(II) complex **E** then undergoes transmetallation with the copper species **D** to provide complex **F**. Isomerisation to the *cis*-palladium complex **G** and subsequent reductive elimination finally delivers **30**.

In such sequences, the iodane can also be prone to autooxidation processes, as demonstrated by Dauban and co-workers. Alkyl-substituted PIDA derivatives **20c** are the substrates for both the chiral C(sp^3)–H amination and for the following cross-coupling reaction (Scheme 18) [48]. In the first step, the C(sp^3)–H bonds of PIDA derivatives were efficiently converted via an auto-amination with the external sulfonimidamide **31** to form the corresponding aminated iodoarenes **32**. These species smoothly underwent subsequent Suzuki–Miyaura, Sonogashira and Mirozoki–Heck couplings. The respective arylated, alkynylated and alkenylated products **33a–d** were obtained in high yields with excellent stereoselectivity. Due to the intramolecular pathway of the first step, high AE values (66% for **33b**) are obtained.

In another tandem procedure, a metal-free C(sp^3)–H olefination of amidines **34** with DMSO and PIDA derivatives **20b** was developed by Namitharan and co-workers [49]. A Pd(II)-catalysed Heck reaction of the formed exocyclic double bond with the emerging iodoarene yields substituted acrylamidines **35** (Scheme 19). The proposed reaction mechanism starts with the activation of DMSO (**A**) via the iodine(III) species **20b**. Iodosoarene **C** is released under basic conditions, forming the sulfonium intermediate **D**. This intermediate reacts with the



Scheme 17: Postulated mechanism for the amination–arylation sequence.

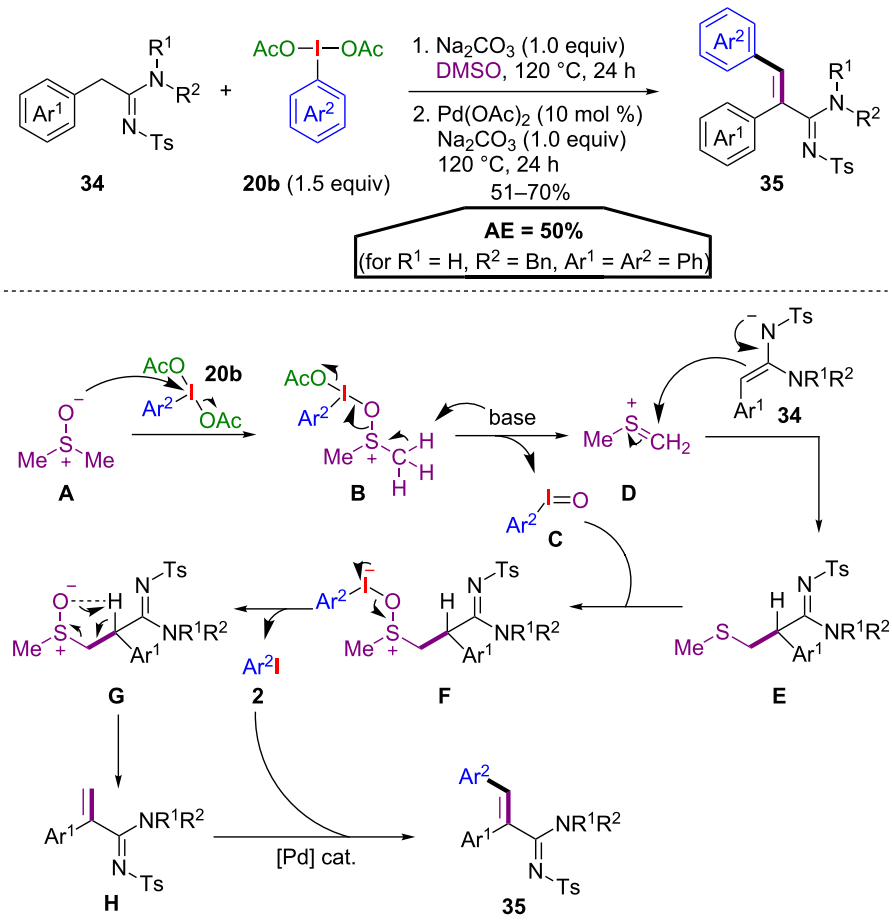


Scheme 18: Auto-amination and cross-coupling of PIDA derivatives **20c**.

amidine **34** to give the sulfide **E**, which is then oxidized to the sulfoxide **G** by iodosoarene **C** via the postulated activated sulfoxide **F**, releasing one equivalent of aryl iodide **2**. A Chugaev-type elimination yields the olefin **H**, which finally affords acrylamidine **35** via Heck coupling with the iodoarene **2** with 50% AE (for R^1 = H, R^2 = Bn, Ar^1 = Ar^2 = Ph).

3. Benziodoxolones

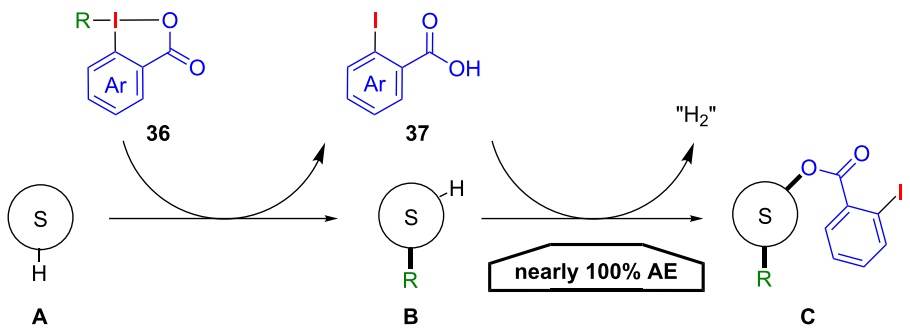
Iodine(III) compounds with a benziodoxolone or a benziodoxole structure are privileged reagents for electrophilic group transfer reactions, in particular in electrophilic alkynylations, azidations, cyanations and trifluoromethylations [3,50-54]. Here, 2-iodobenzoic acid is formed as a quantitative waste



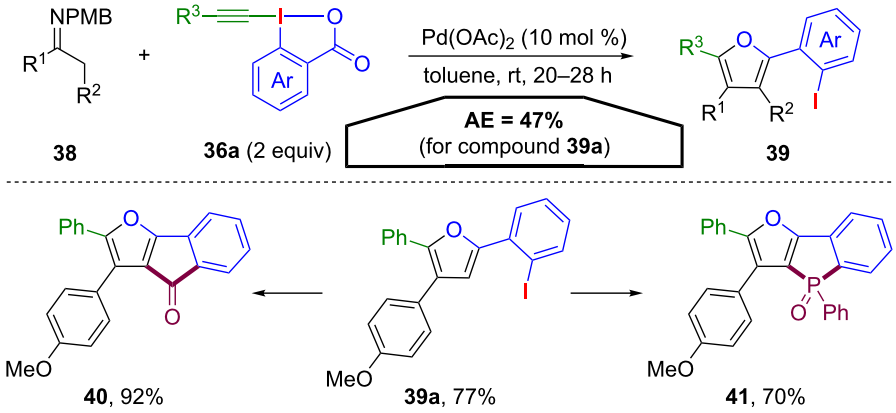
Scheme 19: Tandem C(sp^3)–H olefination/C(sp^2)–H arylation.

product, thus lowering the atom efficiency of these transformations. An atom-economical application of benziodoxolones **36** would involve the utilization of the nucleophilic properties of the released benzoic acid **37**, after the initial electrophilic group transfer to form **B** from substrate **A**. This would give target structures **C** that fully include the 2-iodobenzoic acid with a theoretical AE of nearly 100% (Scheme 20). Only molecular hydrogen is produced as formal waste in this process.

The first report for an atom-economical application of benziodoxolones was a reaction of *N*-arylimines **38** with ethynylbenziodoxolones **36a** (EBX), under the influence of a palladium catalyst, developed by Yoshikai and co-workers [55]. Instead of the expected α-alkynylated product, highly substituted furans **39** were observed (Scheme 21). Both, the electrophilic alkyne and the nucleophilic 2-iodobenzoate group took part in this transformation in a complex putative reaction mech-



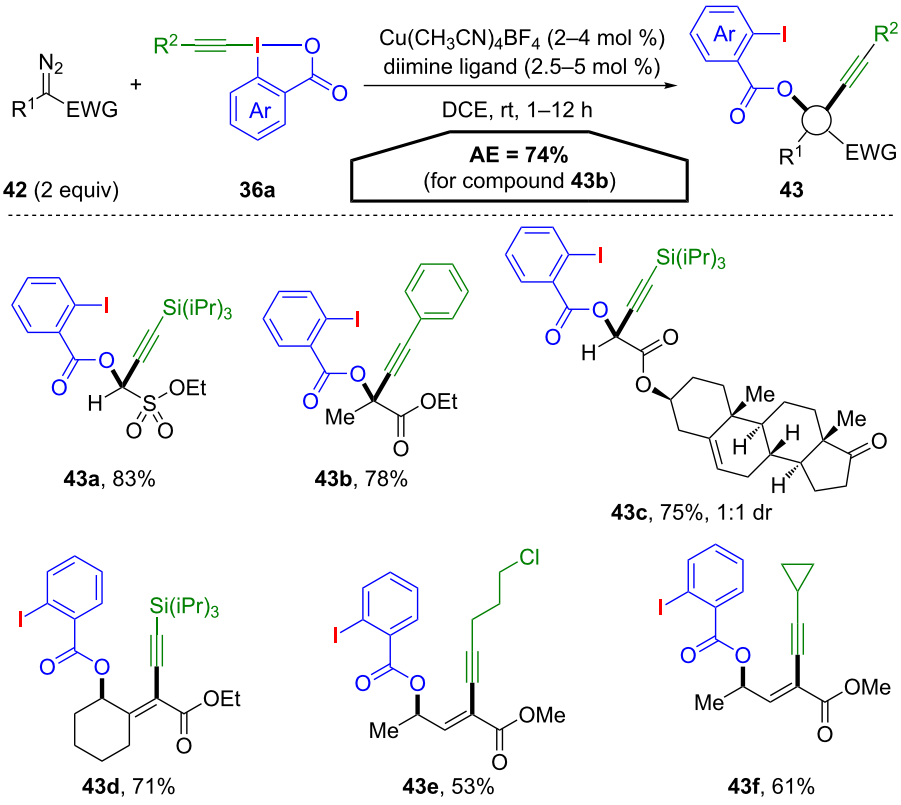
Scheme 20: Atom efficient functionalisations with benziodoxolones **36**.



Scheme 21: Atom-efficient synthesis of furans **39** from benziodoxolones **36a** and their further derivatisations.

anism. However, since two equivalents of EBX (**36a**) are used, the AE for this transformation is rather low (47% for **39a**). The obtained furans **39** are highly useful synthetic intermediates, since the 2-iodoaryl group can be successfully employed in further derivatisations. In example, indenones **40** and phospholes **41** could smoothly be generated.

In contrary to this unexpected reaction pathway, Waser and co-workers particularly aimed for an atom-economical application of EBX reagents **36a** utilizing a copper-catalysed reaction with diazo compounds **42** (Scheme 22) [56]. This strategy is not only atom economic regarding the applied hypervalent iodine reagent but also with regard to the chosen substrate. The metal carbene species generated from the diazo compounds displays nucleophilic as well as electrophilic reactivity at the same carbon atom and only gaseous dinitrogen is produced as stoichiometric waste. The reaction provides oxyalkynylated products **43** in high yields and addresses a broad scope of diazo derivatives **42** and EBX compounds **36a**. For diazo compounds bearing hydrogen, alkyl or aryl groups (R^1), propargyl esters **43a–c** are



Scheme 22: Oxyalkynylation of diazo compounds **42**.

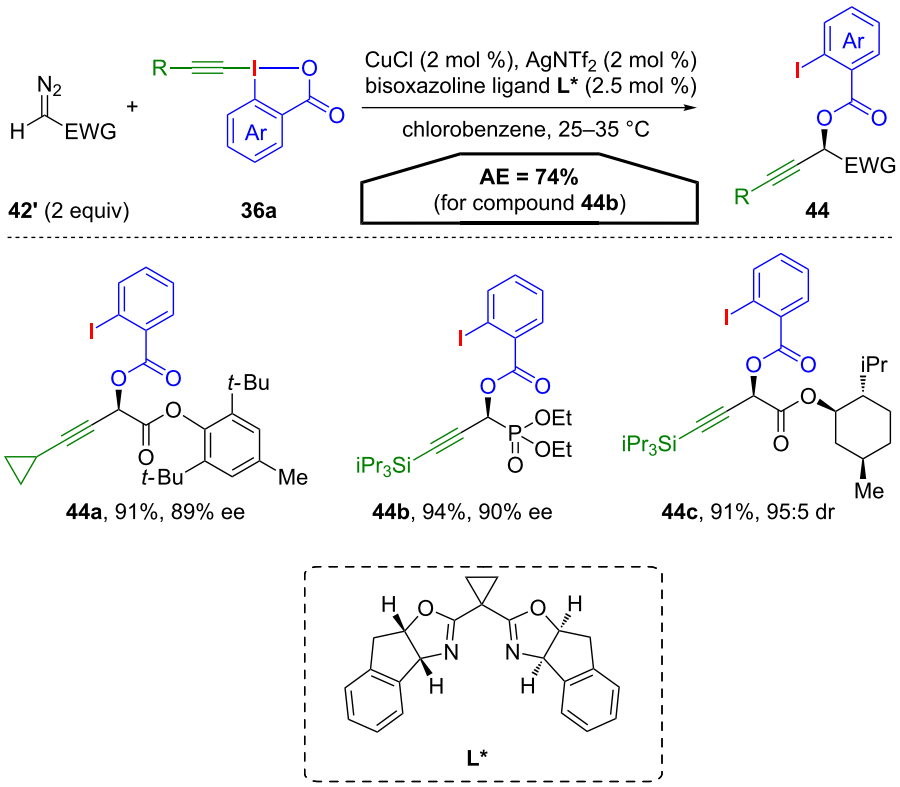
obtained. In contrast, vinyldiazo compounds yielded the corresponding 1,3-enynes **43d–f** in good yields. The oxyalkynylation shows an excellent AE regarding the iodine(III) species **36a**. Every atom of the benziodoxolone **36a** is present in the final product **43** and only one equivalent of elemental nitrogen is lost over the course of the reaction. The overall AE is only diminished by the necessity to use two equivalents of the diazo compound (AE = 74% for **43b**).

Furthermore, an enantioselective version of this oxyalkynylation (for R^1 = H) was developed [57]. Employing a chiral bisoxazoline ligand, diazo compounds **42'** with various electron-withdrawing groups were efficiently oxyalkynylated affording highly enantioenriched propargyl esters **44** (Scheme 23).

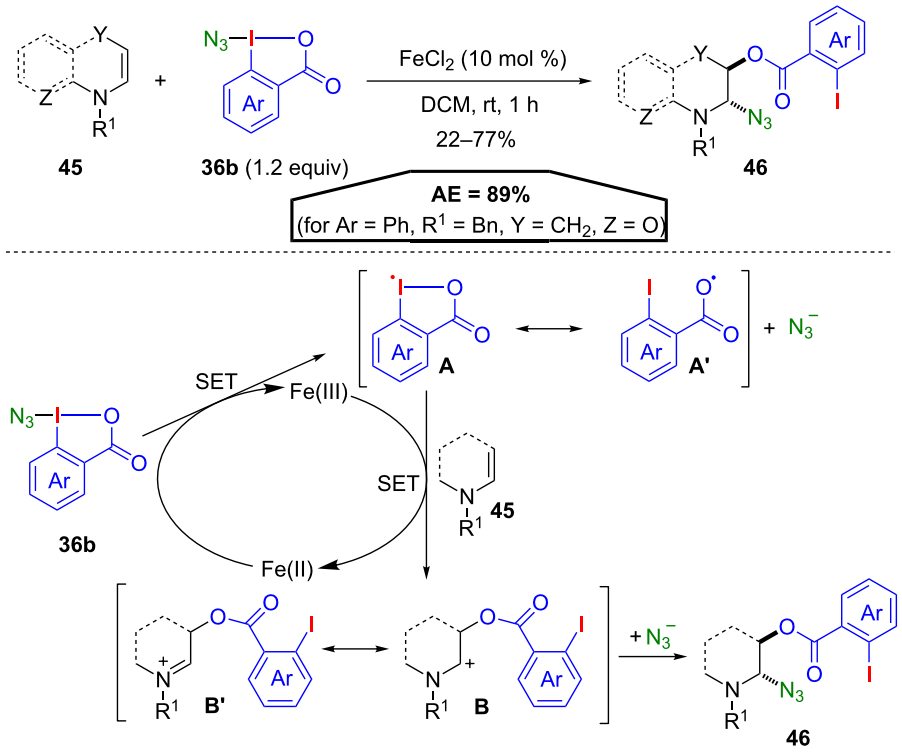
Subsequent reductive cleavage of the ester gave direct access to enantiopure propargyl alcohols. Besides EBX reagents, azidobenziodoxolones **36b** (ABX), could be utilized for atom-economical reactions. Gillaizeau and co-workers developed an iron-catalysed oxyazidation of enamides **45** using ABX derivatives **36b** (Scheme 24) [58]. The reaction proceeds with complete regio- and stereoselectivity introducing the azide group in C2 and the ester moiety in C3 position, affording the *trans*-isomer **46** exclusively. The reaction mechanism presumably follows a radical pathway, which begins with a single electron transfer (SET) from Fe(II) to **36b** generating a Fe(III) species as well as benziodoxolonyl radical **A** or benzoyloxy radical **A'** and an azide anion. Next, a SET from the enamide **45** to Fe(III) affords again Fe(II) and a further reaction with the radical **A** or **A'** leads to the formation of carbocation **B** or iminium ion **B'**, respectively. Recombination of these positively charged intermediates with the azide anion finally affords the oxyazidated product **46**. Overall this oxyazidation exhibits the highest AE so far observed for iodane-mediated group transfer reactions with 89% (for Ar = Ph, R^1 = Bn, Y = CH_2, Z = O).

Conclusion

In summary, we hope that we could demonstrate in this short focused overview, that aryl-λ^3-iodanes are not only stable and highly reactive reagents for electrophilic group-transfer reagents, but that their utilization can be highly atom efficient if the emerging aryl iodides are constructively used in further transformations by cascade processes through a smart reaction design. The small number of discussable transformations, in which at least two of the three ligands attached to the central hypervalent iodine atom are transferred to a given substrate,



Scheme 23: Enantioselective oxyalkynylation of diazo compounds **42'**.



Scheme 24: Iron-catalysed oxyazidation of enamides **45**.

exemplifies, that this field of research is still in its infancy. Nonetheless, this comparative article should give new impulses to researchers working in the field of iodane-mediated coupling reactions and hopefully will lead to new atom-efficient reaction methods utilizing these highly useful substrates, also in large-scale synthetic applications.

Acknowledgements

A.B. is thankful for a scholarship from the Fonds der Chemischen Industrie. P.F. is thankful for a postdoctoral scholarship from the German Academic Exchange Service (DAAD).

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of trifluoromethylated 2*H*-azirines through Togni reagent-mediated trifluoromethylation followed by PhIO-mediated azirination

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Full Research Paper

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Keywords:
azirination; 2*H*-azirine; iodosobenzene; Togni reagent; β-trifluoromethylation

Beilstein J. Org. Chem. **2018,** *14,* 1452–1458.
doi:10.3762/bjoc.14.123

Received: 10 March 2018
Accepted: 18 May 2018
Published: 15 June 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The reaction of enamine compounds with the Togni reagent in the presence of CuI afforded β-trifluoromethylated enamine intermediates, which were converted directly to biologically interesting trifluoromethylated 2*H*-azirines by an iodosobenzene (PhIO)-mediated intramolecular azirination in a one-pot process.

Introduction

The trifluoromethyl group is a striking structural motif, which can be widely found in the fields of pharmaceutical and agrochemical sciences. The introduction of this functional group in drug molecules can enhance their chemical and metabolic stability, improve their lipophilicity and bioavailability, and increase protein-binding affinity [1-6]. In this regard, the CF_3 group has been introduced into many pharmaceutical agents [7-16]. For example, fluoxetine hydrochloride (Figure 1, **A**) [4,9,10] (Prozac®, an antidepressant and a selective serotonin reuptake inhibitor for the treatment of major depressive disorders, obsessive–compulsive disorders, etc.), teriflunomide (Figure 1, **B**) [11-13] (Aubagio®, the active metabolite of leflunomide for the treatment of multiple sclerosis), and pleconaril (Figure 1, **C**) [14-16] (an antiviral drug), all possess this privileged substituent. Although many useful synthetic methods [17-21] have been established for introducing the CF_3

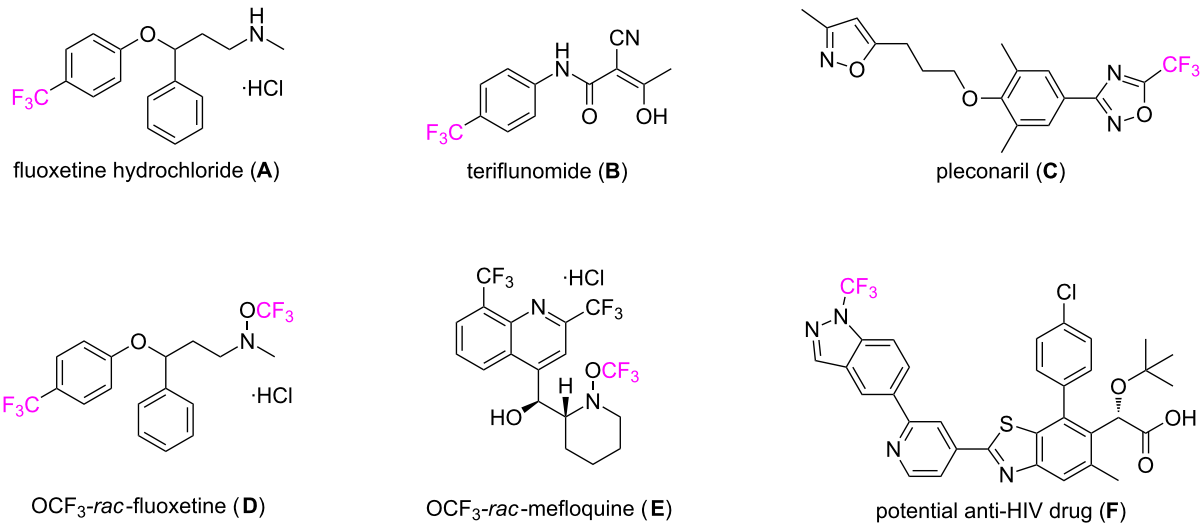


Figure 1: Representative pharmaceutical agents bearing the CF_3 group.

group into various organic molecules, the further development of novel routes for the selective trifluoromethylation is of continuing interest for synthetic and medicinal chemists.

Togni reagents, including 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (**1**) and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**1'**, Figure 2), are effective and efficient hypervalent iodine reagents for trifluoromethylation reactions of a variety of substrates [22,23]. These reagents have found wide applications in the area of organofluorine chemistry, synthetic method development as well as medicinal chemistry [24-40]. For example, the Togni reagents have been successfully applied to introduce the CF_3 group into pharmaceutical agents such as the fluoxetine derivative **D** (Figure 1), the mefloquine derivative **E** [41] and compound **F** [42] – a potential anti-HIV drug bearing a NCF_3 moiety.

2*H*-Azirines are a class of highly strained and reactive molecules containing a C–N double bond. The exclusive framework can be found in some natural products [43-47], which were shown to possess antibiotic activities [43,44]. Furthermore, compounds with this structural motif are also useful building

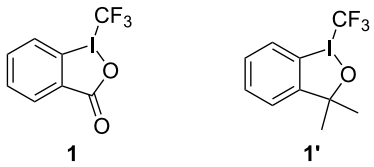
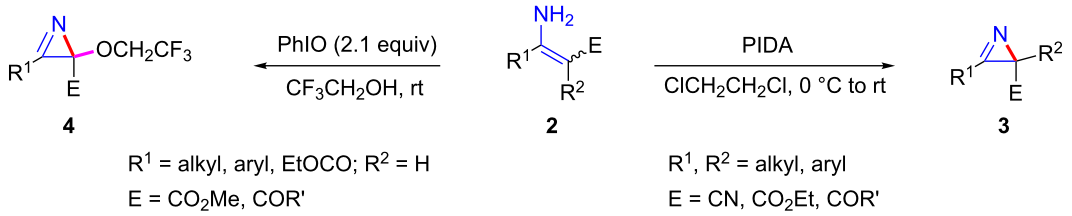


Figure 2: The structures of the Togni reagents 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (**1**) and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**1'**).

blocks for the synthesis of functionalized amino derivatives and N-containing heterocyclic derivatives [48-51]. Thus, this class of compounds has gained considerable attention from synthetic chemists and many useful synthetic approaches [52-55] have been developed for accessing this exclusive class of heterocycles. In our previous works, we have realized the application of hypervalent iodine reagents for the construction of the 2*H*-azirine skeleton starting from enamines **2** via intramolecular oxidative cyclization (Scheme 1) [56,57]. When the R^2 substituent is alkyl or aryl, the corresponding substrates **2** were converted to a series of alkylated or arylated 2*H*-azirines **3** in the presence of phenyliodine diacetate (PIDA) in 1,2-dichloro-



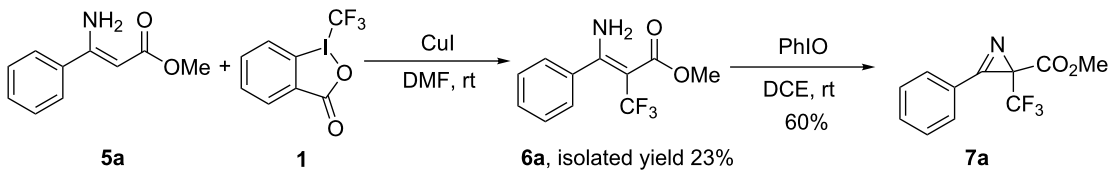
Scheme 1: Our previous hypervalent iodine-mediated synthesis of 2*H*-azirine compounds.

ethane (DCE) [56]. Alternatively, the treatment of β-unsubstituted enamine substrates (**2**, R^2 = H) with PhIO in 2,2,2-trifluoroethanol (TFE) afforded 2-trifluoroethoxy-2*H*-azirines **4** [57]. The latter process involves an intermolecular oxidative trifluoroethoxylation and the subsequent oxidative intramolecular azirination. In continuation of our interest in the construction of the 2*H*-azirine skeleton bearing versatile substituents, we herein report that the biologically interesting CF_3 group can be incorporated into the privileged 2*H*-azirine framework through the Togni reagent **1**-mediated trifluoromethylation followed by PhIO-mediated azirination in a one-pot process.

Results and Discussion

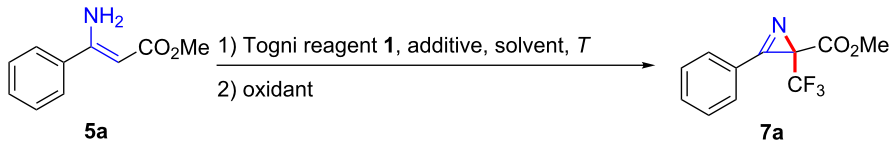
It is well documented that Togni reagents can realize the direct trifluoromethylation of alkenes [58-60] and electron-rich enamides [61]. Inspired by this, we envisaged that Togni reagent **1** could also enable the introduction of a CF_3 group to the β-position of enamine substrates, and the so-obtained trifluoromethylated enamines could undergo a hypervalent iodine-mediated intramolecular azirination to give the corresponding trifluoromethylated 2*H*-azirines [56,57]. To test this conversion, the readily available enamine **5a** was used as a model substrate. The treatment of **5a** with Togni reagent **1** in the presence of CuI in *N*,*N*-dimethylformamide (DMF) [62] at room temperature for two hours afforded the β-trifluoromethylated enamine **6a** in a 23% yield. Subjecting enamine **6a** to PhIO in 1,2-dichloroethane (DCE) for 12 hours at room temperature led to the formation of the desired β-trifluoromethylated 2*H*-azirine **7a** in a yield of 60% (Scheme 2).

In order to make the synthesis of β-trifluoromethylated 2*H*-azirine more concise and convenient, we were keen to probe whether the two-step synthesis could be combined into a one-pot process. For this purpose, we first carried out the reaction of Togni reagent **1** and **5a** in the presence of CuI in DMF at room temperature, followed by an addition of PhIO. However, only trace amounts of the expected product **7a** were obtained (Table 1, entry 1). We next screened various solvents to



Scheme 2: Study on the presumed Togni reagent **1**-mediated trifluoromethylation followed by PhIO-mediated azirination.

Table 1: Optimization of reaction conditions.[a]

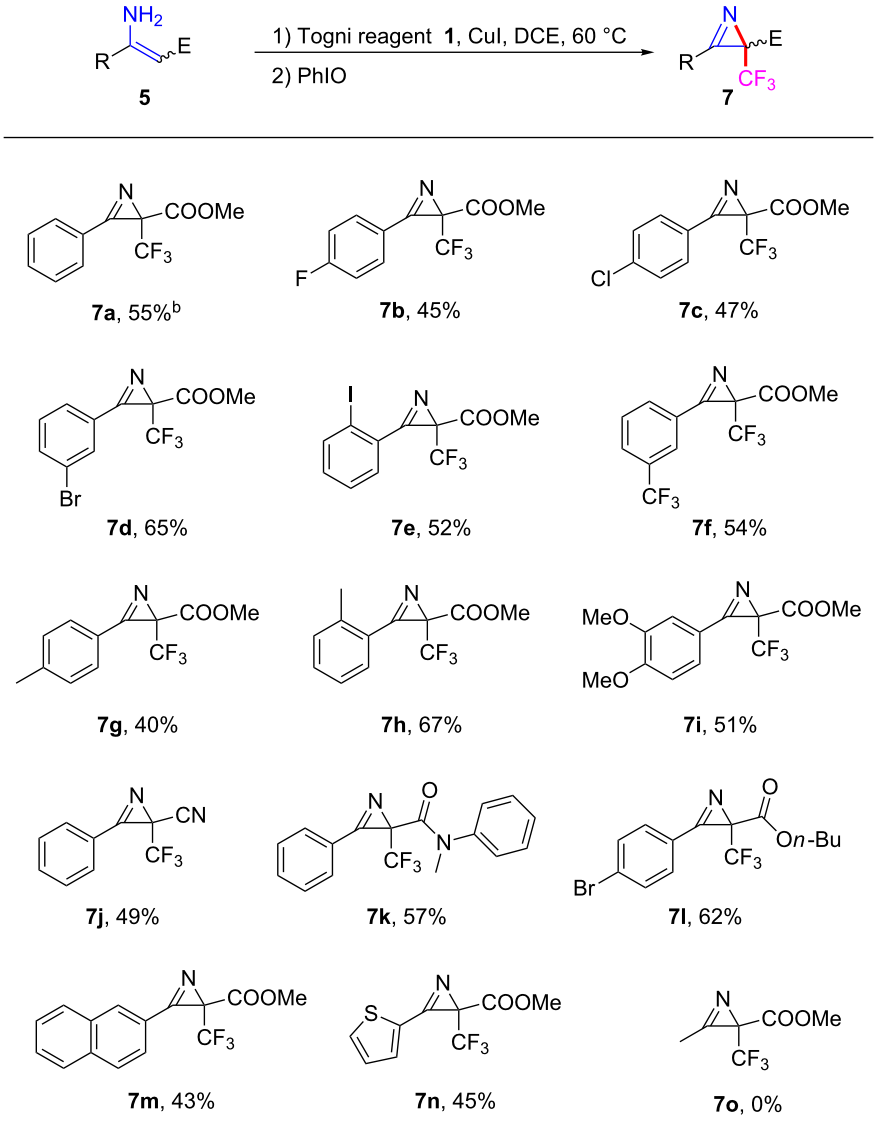


Entry	Catalyst	Oxidant[b]	Solvent	Temp. (°C)	Yield[c] (%)
1	CuI	PhIO	DMF	rt	trace
2	CuI	PhIO	CH_3CN	rt	13
3	CuI	PhIO	DCE	rt	24
4	CuI	PhIO	toluene	rt	12
5	CuI	PhIO	DCE	40	35
6	CuI	PhIO	DCE	60	55
7	CuI	PhIO	DCE	reflux	48
8	CuCl	PhIO	DCE	60	49
9	CuBr	PhIO	DCE	60	50
10	CuOAc	PhIO	DCE	60	38
11	CuI	PIDA	DCE	60	46
12	CuI	PIFA	DCE	60	30

[a]Reaction conditions: Togni reagent **1** (1.2 mmol), **5a** (1.0 mmol), catalyst (0.2 mmol), oxidant (1.5 mmol) in solvent (10 mL) unless otherwise stated. [b]The oxidant was added to the reaction mixture after the substrate **5a** was completely consumed (TLC analysis). [c]Isolated yield.

increase the reaction outcome (Table 1, entries 1–4). Judging by the yield of the desired product, it was concluded that DCE was the best solvent (Table 1, entry 3). By increasing the reaction temperature from rt to 60 °C, the yields significantly increased to 55% (Table 1, entries 3, 5 and 6). However, an attempt to improve the product yield by operating the reaction at a higher temperature was unsuccessful (Table 1, entry 7). Replacing the catalyst CuI with other commonly used copper catalysts including CuCl, CuBr and CuOAc led to a decreased yield in each case (Table 1, entries 8–10). In addition the other commonly employed hypervalent iodine(III) reagents, namely, PIDA and phenyliodine bis(trifluoroacetate) (PIFA) were tested, but the results indicated that they were ineffective to further improve the yields (Table 1, entries 11 and 12).

With the optimized conditions in hand, we next explored the substrate scope for this newly established one-pot oxidative trifluoromethylation and azirination reaction. As shown in Scheme 3, a variety of substrates bearing halogen substituents at the *ortho*, *meta* and *para*-positions of the phenyl ring in the substrates were converted to the expected 2*H*-azirines **7b**–**e** in 45–65% one-pot yield. Notably, the substrate having a trifluoromethyl group at the *meta*-position in the phenyl ring also afforded the desired 2*H*-azirine product **7f** bearing two CF_3 sub-

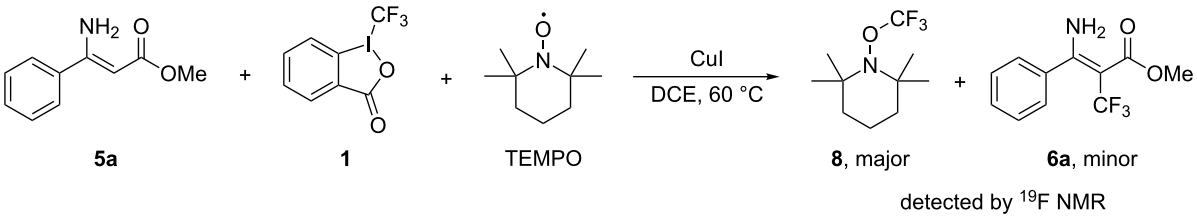


Scheme 3: Togni reagent/PhIO-mediated one-pot synthesis of β-trifluoromethyl 2*H*-azirines. Reaction conditions: **1** (1.2 mmol), **5** (1.0 mmol), CuI (0.2 mmol), PhIO (1.5 mmol) in DCE (10 mL) unless otherwise stated. PhIO was added to the reaction mixture after the substrate **5** was completely consumed (TLC analysis). Yields refer to isolated yields.

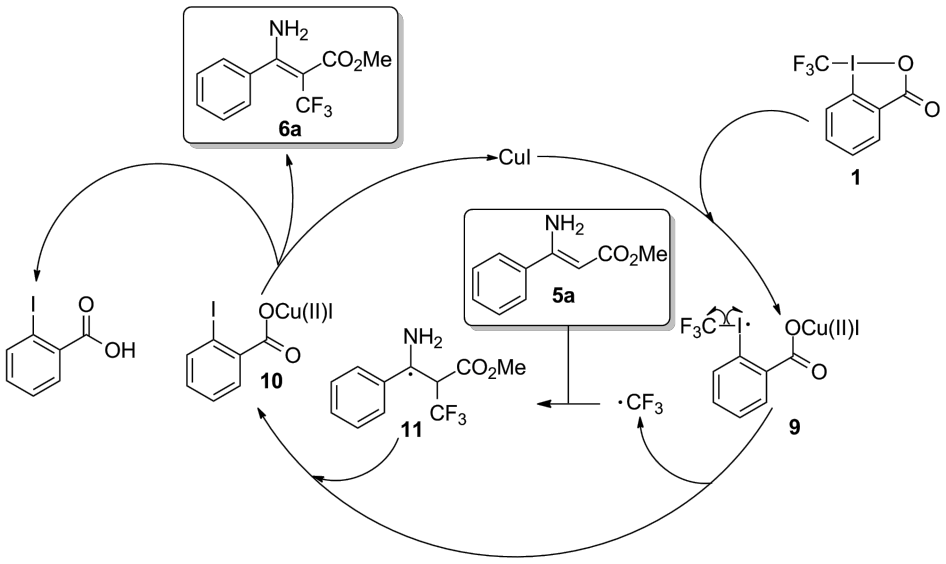
stituents in a satisfactory one-pot yield. Various enamine substrates with electron-donating groups (*p*-Me, *o*-Me and 3,4-di-OMe) in the aryl ring, also reacted efficiently under the conditions of the one-pot process to afford the corresponding products **7g–i** in a yield of 40–67%. Furthermore, when replacing the methoxycarbonyl group in **5a** with a cyano or *N*-methyl-*N*-phenylformyl group, the corresponding substrates **5j** and **5k** were converted to the desired products **7j** and **7k** in a yield of 49% and 57%, respectively. The methoxy group in the ester moiety could also be replaced by the *n*-butoxy group, with the desired product **7l** being isolated in a yield of 62%. In addition, this method was also applicable to substrates bearing naphthyl or thienyl groups at R substitution to give the desired products **7m** and **7n** in a yield of 43% and 45%, respectively. However, the method was not applicable to the substrate bearing an alkyl group, as the reaction of **5o**, even at lower temperatures (−20 °C, 0 °C, 20 °C and 40 °C) gave a complex mixture after adding PhIO.

To gain further insights into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, was introduced to the model reaction (Scheme 4) following the method previously reported in the literature [63]. It was found that the trifluoromethylation was hampered and the TEMPO-CF_3 adduct **8** was formed as a major product based on the analysis of its ^{19}F NMR (δ −55.67).

The above results from the experiment provided supportive evidence that the CF_3 radical was likely involved as a reactive species in the reaction process. Based on this and previous reports [62-68], a possible reaction pathway has been proposed and is outlined in Scheme 5. Initially, CuI catalytically activates the Togni reagent **1**, leading to the formation of the CF_3-containing radical intermediate **9**. Decomposition of the intermediate **9** produces (2-iodobenzoyloxy)copper(II) iodide (**10**) [65,66] with the simultaneous release of a CF_3 radical. Then, the reaction of enamine **5a** with the CF_3 radical affords the car-



Scheme 4: Control study with TEMPO.



Scheme 5: Proposed mechanism for the Togni reagent-mediated trifluoromethylation of enamines.

bon-centered radical **11**. Next, the reaction of **10** and **11**, possibly through an electron-transfer process, along with the conversion of intermediate **10** to 2-iodobenzoic acid enables the conversion of intermediate **11** to **6a** (possibly tautomerized from its imine isomer) [69]. Finally, the β-trifluoromethylated enamine **6a** undergoes intramolecular azirination affording the corresponding β-trifluoromethylated 2*H*-azirine via a known pathway [56,57].

Conclusion

In summary, we have reported an efficient hypervalent iodine-mediated trifluoromethylation and azirination process. In this transformation, the introduction of the CF_3 group to the β-position of enamines followed by the intramolecular azirination was realized in a one-pot process, providing a general and straightforward access to biologically interesting trifluoromethylated 2*H*-azirine compounds. This method features mild reaction conditions, a simple operation, and metal-free characteristics. The presence of both, the biologically interesting CF_3 group and the 2*H*-azirine skeleton in the products obtained might making them interesting for further applications in biological studies.

Supporting Information

Supporting Information File 1

Synthetic details and characterization data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-123-S1.pdf]

Acknowledgements

We acknowledge the National Natural Science Foundation of China (No. 21472136) and Tianjin Research Program of Application Foundation and Advanced Technology (15JCZDJC32900) for their financial support. We also thank Ms Jeanette Mar [School of Health Science Platform, Tianjin University] for editing the English version in this paper.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Metal-free formal synthesis of phenoxazine

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Letter

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Keywords:
arylation; cyclization; diaryl ether; diaryliodonium salt; phenol

Beilstein J. Org. Chem. **2018,** *14,* 1491–1497.
doi:10.3762/bjoc.14.126

Received: 30 March 2018
Accepted: 06 June 2018
Published: 20 June 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

A transition metal-free formal synthesis of phenoxazine is presented. The key step of the sequence is a high-yielding *O*-arylation of a phenol with an unsymmetrical diaryliodonium salt to provide an *ortho*-disubstituted diaryl ether. This species was cyclized to acetylphenoxazine in moderate yield. The overall yield in the three-step sequence is 72% based on recovered diaryl ether. An interesting, unusually stable iodine(III) intermediate in the *O*-arylation was observed by NMR and could be converted to the product upon longer reaction time.

Introduction

Phenoxazine (**1**) is a tricyclic compound consisting of an oxazine ring fused between two benzene rings. A range of compounds with interesting biological or photophysical properties contain the phenoxazine core, where the amine moiety is either functionalized or oxidized to the corresponding imine [1-4]. Phenoxazine derivatives can display antitumor activity [5-8], are present in a variety of dyes [9], and can be applied in chemosensors and dye-sensitized solar cells (Figure 1) [10-12]. *N*-Arylphenoxazines were recently employed as photoredox catalysts in metal-free polymerizations [13].

The first synthesis of phenoxazine dates back more than 100 years [14], and a range of synthetic routes to this target has since been developed [1]. Transition metal-free routes include the synthesis from 2-aminophenols and 3,4-dihaloarenes decorated with electron-withdrawing substituents, which proceed through a Smiles rearrangement (Scheme 1a) [15-17]. More recently, Bolm and co-workers reported a metal-free cyclization of iodo-substituted diaryl ethers with a broad scope (Scheme 1b) [18]. Transition metal-catalyzed cross couplings have also been employed to form the required C–O and C–N bonds, e.g., by Cu-catalyzed cyclization of 2-(2-bromophenoxy)anilines [17,19,20]. A Pd-catalyzed double *N*-arylation using di(2-bromoaryl) ethers and primary amines was recently developed (Scheme 1c) [21]. Furthermore, *N*-functionalization of the phenoxazine core can be performed under metal-free conditions [22].

Our research group has reported highly efficient *O*-arylations of phenols using diaryliodonium salts [23-25], which are reactive

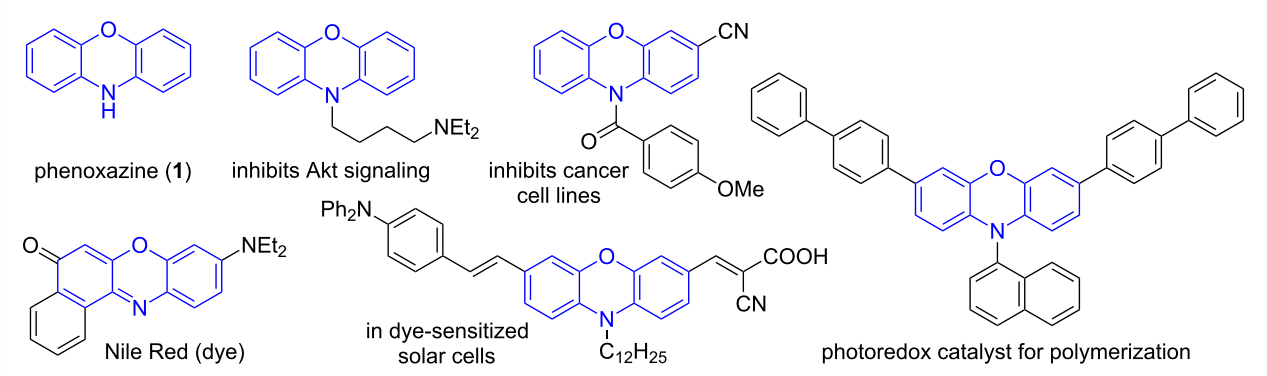
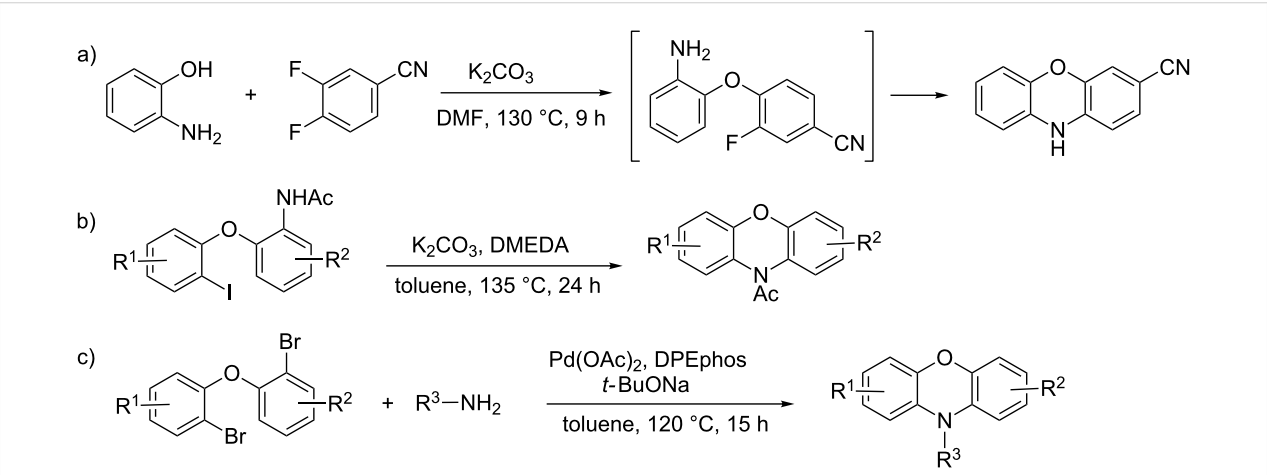


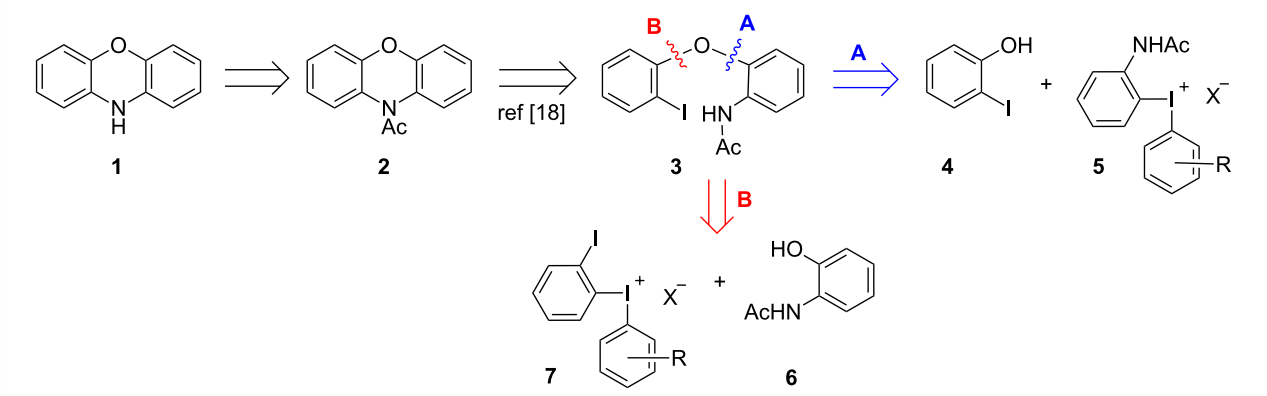
Figure 1: Compounds containing a phenoxazine moiety.



Scheme 1: Reported syntheses of phenoxazine derivatives.

electrophilic arylation reagents [26-28]. As diaryliodonium salts can be easily synthesized in a one-pot manner [28], we envisioned that phenoxazines could be obtained in a straightforward and efficient manner from commercially available starting materials.

According to the retrosynthesis depicted in Scheme 2, target **1** would be formed from acetyl derivative **2**, which can be derived from the functionalized diaryl ether **3** using Bolm's *N*-arylation (see Scheme 1c) [18]. The synthesis of diaryl ether **3** is the key step of the sequence, proceeding via arylation of phenols with



Scheme 2: Retrosynthesis of phenoxazine.

diaryliodonium salts using our reported methodology [23-25]. In reactions with unsymmetrical iodonium salts, this type of *O*-arylation is known to have an *ortho*-effect, i.e., chemoselective transfer of the *ortho*-substituted aryl moiety [29,30]. The use of unsymmetrical iodonium salts facilitates the synthesis of the reagents and avoids waste of an expensive iodoarene, and we hence envisioned chemoselective transfer of the desired aryl moiety from an unsymmetrical salt with a suitable "dummy" aryl group.

Two different approaches to reach **3** are illustrated, either employing 2-iodophenol (**4**) and 2-acetamido-substituted salt **5** (route A) or *N*-functionalized phenol **6** with 2-iodophenyl salt **7** (route B). In route A, the chemoselective transfer of the 2-amido aryl group over the other aryl group would require a quite electron-rich dummy group or the use of a symmetric iodonium salt (R = 2-NHAc). In route B, the challenge would instead be the synthesis of iodonium salt **7**, as the iodo substituent might be prone to oxidation. Furthermore, selective *O*-arylation in the presence of an amide moiety could be challenging, as *N*-arylation of amides with diaryliodonium salts proceeds at room temperature [31,32].

Results and Discussion

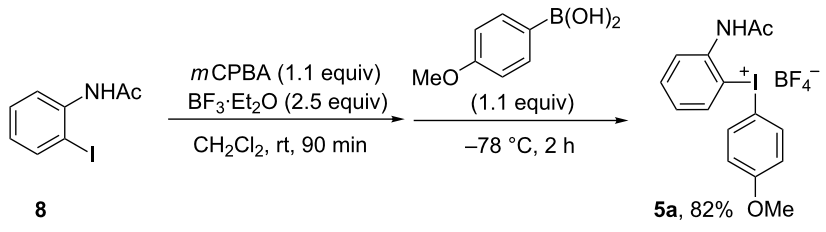
We initially focused on route A and decided to explore an anisyl moiety as dummy group in iodonium salt **5**. The electronic difference between the aryl groups in the formed salt should be sufficient to allow chemoselective transfer of the desired aryl moiety, and the *ortho*-effect exerted by the 2-amido substituent was expected to improve the chemoselectivity further. Salt **5a** was synthesized in good yield using our reported arylboronic acid methodology [33] (Scheme 3). Attempts to form the corresponding tosylate salt, either from iodoarene **8** with anisole and *m*CPBA/TsOH [34] or via anion exchange of **5a** were in vain.

The *O*-arylation of 2-iodophenol (**4**) with salt **5a** was investigated using our previously reported methodology [24,25]. As expected, the reaction proceeded well, both in THF and toluene, of which the latter was most appealing as it might allow a tandem arylation and cyclization to reach *N*-acetylphenoxazine (**2**) in one pot. The arylations were analyzed by crude ^{1}H NMR yields using an internal standard and revealed that a minor amount of a byproduct was formed along with the expected diaryl ether **3** (Table 1, entry 1). This was initially believed to be 2-iodophenyl 4-anisyl ether, i.e., the diaryl ether that would form upon transfer of the anisyl moiety to the nucleophile. The reaction was thus further investigated to find conditions that would allow high yield of **3** with complete chemoselectivity.

The amount of byproduct remained approximately constant when solvents and bases were screened (Table 1, entries 1–4, see also Supporting Information File 1), whereas certain changes in stoichiometry influenced the yield (Table 1, entries 5–7). Diaryl ether **3** was efficiently formed using the conditions in entry 7, and could be easily isolated by flash chromatography in 91% yield. A shortening of the reaction time to 1 h profoundly increased the amount of byproduct to 52% (Table 1, entry 8). Surprisingly, the desired product **3** could be isolated in 58% yield from this experiment after prolonged storage of the neat crude product at rt, along with 52% of 4-iodoanisol (see Supporting Information File 1).

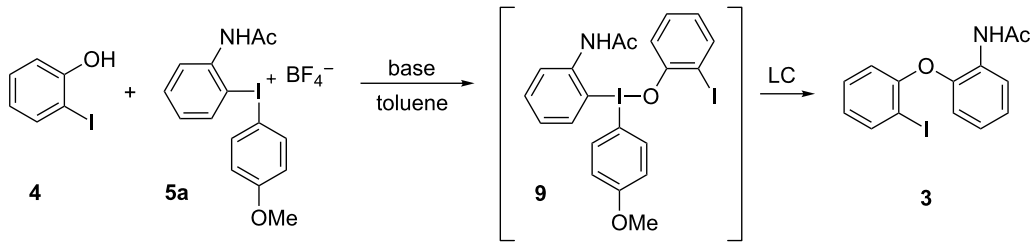
This observation is in line with a ligand-coupling (LC) mechanism [30,35,36] where the observed byproduct could be the T-shaped intermediate **9** or the corresponding 4-coordinated species with two phenoxide units [37]. This type of intermediate is expected in LC reactions but can rarely be detected. The groups of Quideau and Muñiz have reported such compounds using an *ortho*-nitro substituted phenol and tetrafluorophthalimide as nucleophiles, respectively [38,39]. Those compounds were isolable at room temperature and could be converted to the arylated products upon heating. The reactivity of **9** is unusual, as it proved stable to neutral work-up with brine, formed product **3** upon longer reaction time or rt storage in $CDCl_3$ or neat, but decomposed to starting materials upon work-up with sat. ammonium chloride solution (Table 1, entry 11).

Due to the successful outcome of route A, pathway B was only briefly explored. Several dummy groups were considered for



Scheme 3: Synthesis of iodonium salt **5a**.

Table 1: Optimization of the *O*-arylation of route A.[a]



entry	phenol **4** (equiv)	salt **5a** (equiv)	base (equiv)	*T* (°C)	time (h)	yield **3** (%)[b]	yield byproduct (%)[c]
1	1	1.1	*t*-BuOK (1.1)	rt	18	80	3
2[d]	1	1.1	*t*-BuOK (1.1)	rt	18	67	2
3	1	1.1	NaH (1.1)	rt	18	14	2
4	1	1.1	K_2CO_3 (1.1)	rt	18	65	2
5	1	1.5	*t*-BuOK (1.1)	rt	18	77	4
6	1	1.5	*t*-BuOK (1.5)	rt	18	74	14
7	**1.5**	**1**	***t*-BuOK (1.5)**	**rt**	**18**	**89 (91)**	**5**
8	1.5	1	*t*-BuOK (1.5)	rt	1	9 (58)	52
9	1	1	*t*-BuOK (1.5)	40	1	49	38
10	1.5	1	*t*-BuOK (1.5)	80	1	79	4
11[e]	1.5	1	*t*-BuOK (1.5)	rt	1	7	trace

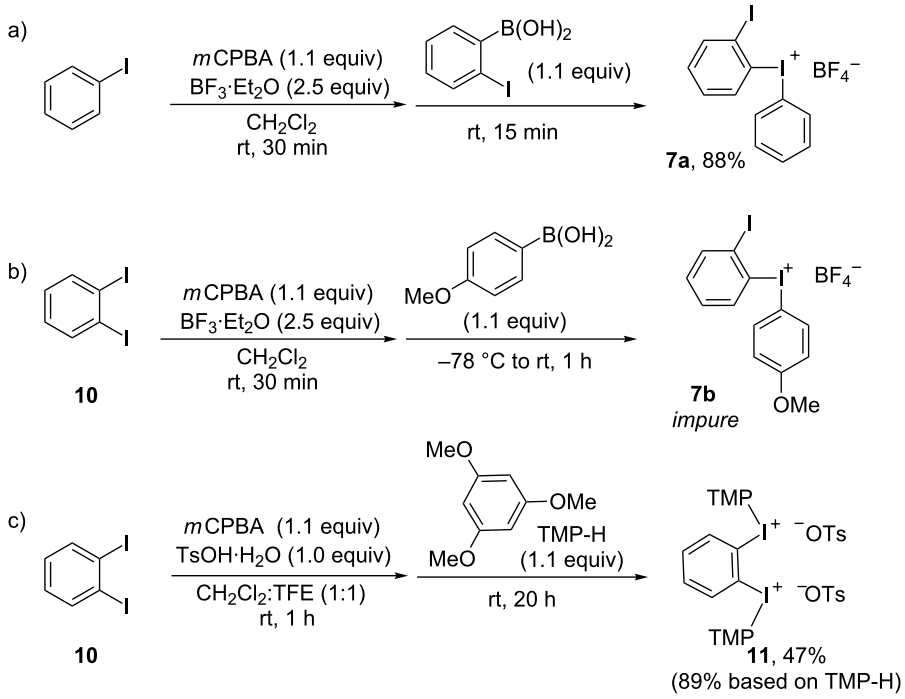
[a]Phenol **4** (0.2 mmol) and base were stirred in anhydrous toluene (1 mL) for 30 min at rt before addition of **5a**. The reaction was stirred at the tabulated temperature and time and quenched with brine (see Supporting Information File 1 for details). [b]^{1}H NMR yield using dibromomethane as internal standard (isolated yield in parenthesis). [c]^{1}H NMR yield based on the assumption of one OMe group in byproduct, see Supporting Information File 1. [d]0.5 mL DME as co-solvent. [e]Quenched with sat. ammonium chloride solution instead of brine.

the iodonium salt **7**. A phenyl dummy might give sufficient chemoselectivity due to the *ortho*-effect, and the synthesis of salt **7a** was straightforward using 2-iodophenylboronic acid (Scheme 4a). The use of an anisyl dummy proved more difficult, and tetrafluoroborate **7b** was isolated with impurities using the arylboronic acid methodology [33] (Scheme 4b). The *m*CPBA/TsOH methodology [34] with 1,2-diiodobenzene (**10**) and anisole or trimethoxybenzene (TMP-H) as dummy surprisingly delivered the corresponding bisiodonium ditosylates [40-42] instead of the desired **7** (Scheme 4c, see also Supporting Information File 1). The stoichiometry of the reaction did not allow complete formation of **11**, but the yield based on TMP-H was 89%.

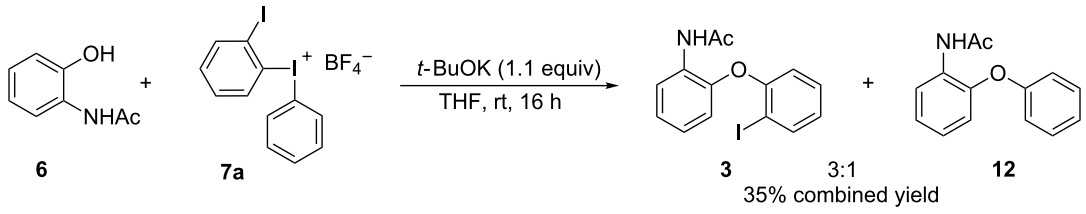
The arylation of phenol **6** with unsymmetrical diaryliodonium salt **7a** provided the desired diaryl ether **3** in modest yield and limited chemoselectivity (Scheme 5). Competitive *N*-arylation of the amide moiety [31,32] was not observed. Preliminary attempts to employ the bisiodonium salt **11** in the arylation of **6** were fruitless (see Supporting Information File 1), and we hence concluded that route A was most suitable for further investigations.

With high-yielding conditions for the *O*-arylation step at hand (Table 1, entry 7), the literature-reported [18] cyclization of **3** to *N*-acetylphenoxazine (**2**) was performed (Scheme 6a). In our hands, however, product **2** could only be isolated in 49% yield as the cyclization did not reach completion. The ratio of product **2** to starting material **3** remained 1:1 also upon modified conditions (see Supporting Information File 1). Still, the reaction was clean and the yield based on recovered starting material was 96%. The limited conversion into product **2** complicated our aim to perform the arylation and cyclization in one pot. The tandem reaction set up depicted in Scheme 6b delivered the *O*-arylated **3** in 87% yield, rather than product **2**, further illustrating the sensitivity of the cyclization step. Attempts to perform the cyclization with *t*-BuOK and DMEDA only resulted in byproduct formation.

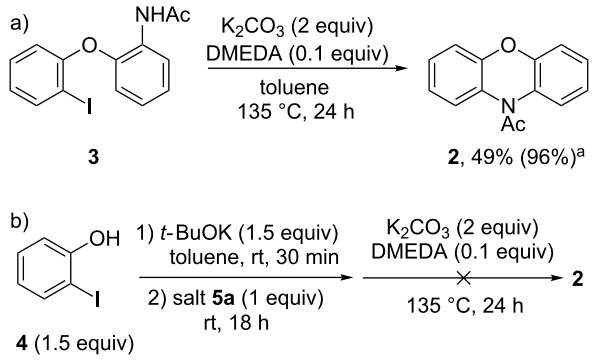
The deprotection of **2** is reported to proceed in high yield [18], and the synthesis of **2** hence constitutes a metal-free formal synthesis of phenoxazine (**1**). The complete route is depicted in Scheme 7 and delivered *N*-acetylphenoxazine (**2**) in 72% overall yield over 3 steps. Combined with the literature yield for the deprotection, this would provide the target **1** in 65% overall



Scheme 4: Synthesis of iodonium salt **7**.



Scheme 5: *O*-Arylation via route B.

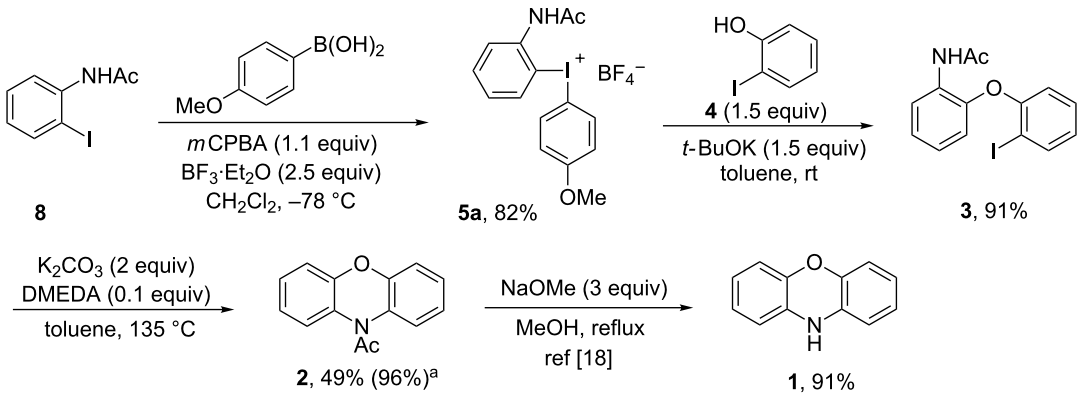


Scheme 6: a) Cyclization of diaryl ether **3**. b) Attempted one pot-synthesis of **2**. [a]Based on recovered **3**.

yield based on recovered **3**. The required starting materials in this route can easily be further substituted; hence we expect the methodology to be applicable also for phenoxazine derivatives.

Conclusion

A transition metal-free formal synthesis of phenoxazine is presented, relying on the *O*-arylation of phenol **4** with unsymmetrical diaryliodonium salt **5a** to provide substituted diaryl ether **3** as the key step. This species underwent an intramolecular *N*-arylation to provide the cyclized product **2**. The overall yield in this three-step sequence is 72% based on recovered diaryl ether. Interestingly, an unusually stable iodine(III) intermediate was formed in the *O*-arylation. This species survived neutral work-up and could be converted to product upon longer reaction time.



Scheme 7: Formal synthesis of phenoxazine (**1**). [a]Based on recovered **3**.

Supporting Information

Supporting Information File 1

Experimental details for the synthesis of starting materials and products, analytical data for products **2**, **3**, **5a**, **7a, 9** and **11**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-126-S1.pdf]

Supporting Information File 2

NMR spectra for products **2**, **3**, **5a**, **7a** and **11**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-126-S2.pdf]

Acknowledgements

The Swedish Research Council (2015-04404) is kindly acknowledged for financial support. Carl Trygger Foundation (CTS 14:359) is acknowledged for a postdoctoral scholarship to C. Dey.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Hypervalent organoiodine compounds: from reagents to valuable building blocks in synthesis

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Review

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Keywords:
atom-economy; couplings; hypervalent iodine; oxidation; tandem reactions

Beilstein J. Org. Chem. **2018,** *14,* 1508–1528.
doi:10.3762/bjoc.14.128

Received: 20 February 2018
Accepted: 25 May 2018
Published: 21 June 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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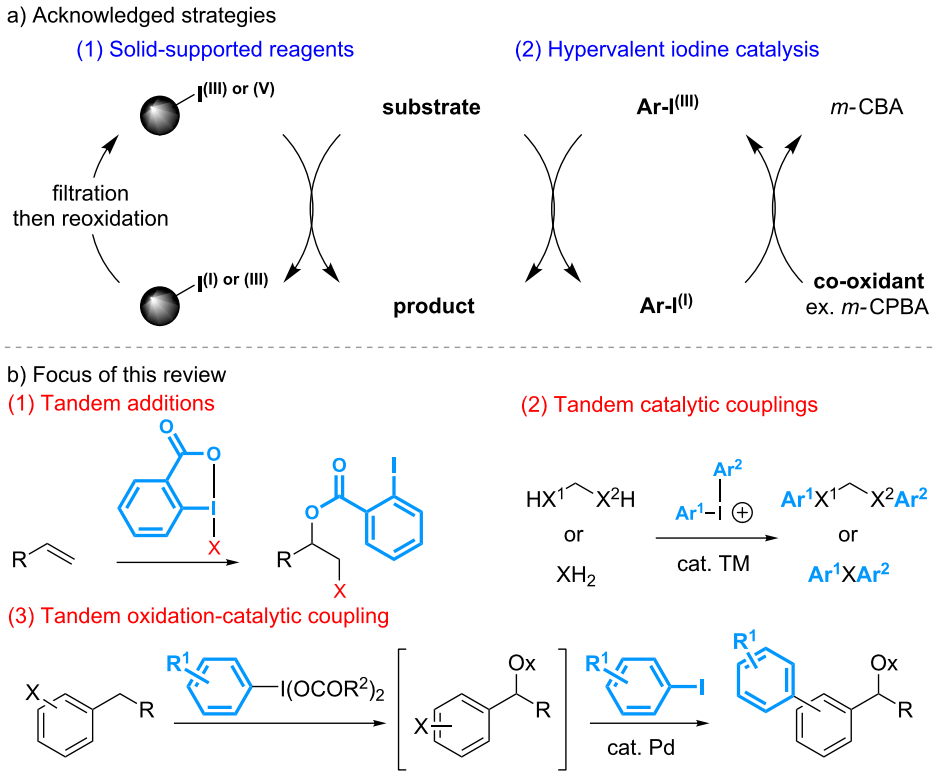
Abstract

Most of the polyvalent organoiodine compounds derive from iodoarenes, which are released in stoichiometric amounts in any reaction mediated by λ^3- or λ^5-iodanes. In parallel to the development of solid-supported reagents or reactions catalytic in iodine, a third strategy has emerged to address this issue in terms of sustainability. The atom-economy of transformations involving stoichiometric amounts of λ^3- or λ^5-iodanes, thus, has been improved by designing tandem reactions that allows for incorporating the aryl motif into the products through a subsequent one-pot nucleophilic addition or catalytic coupling reaction. This review summarizes the main achievements reported in this area.

Introduction

Synthetic applications of the hypervalent iodine chemistry have grown exponentially in the last four decades as highlighted by several books and comprehensive reviews dedicated to this topic [1-13]. A still growing number of λ^3- and λ^5-iodanes are now available as non-toxic and environmentally benign reagents that allow for performing a wide range of transformations under mild conditions. The oxidation of functional groups, halogenations, C–C, C–O, or C–N couplings, dearomatization of phenols, rearrangements, to name but a few, have been reported using these compounds thereby reflecting their versatility.

A survey of the general structure of polyvalent organoiodine compounds reveals that they are prepared mostly from iodoarene starting materials. Accordingly, any transformation relying on stoichiometric amounts of these reagents will inevitably produce the same quantity of iodoarene derivatives, which can be considered as a waste in the context of sustainable chemistry. Various strategies, thus, have been described to address this issue. A first solution has arisen from the development of polystyrene-supported reagents, which allows their recycling following simple filtration and re-oxidation (reaction 1 in Scheme 1a) [14,15]. More recently, the design of



Scheme 1: Strategies to address the issue of sustainability with polyvalent organoiodine reagents.

processes catalytic in iodine compounds has been extensively investigated and significant achievements have been reported making iodine compounds now useful organocatalysts in asymmetric synthesis (reaction 2 in Scheme 1a) [15-24].

In parallel to these investigations, a third strategy has been envisaged with the development of tandem reactions involving a step that enables the introduction of the iodoarene side-compound into the products. Various sequences combining oxidation reactions, nucleophilic additions, or aromatic couplings, thus, have been reported (Scheme 1b). In addition to address the issue of sustainability, this complementary solution has provided opportunities to explore a new chemical space. This review aims to highlight the main achievements reported in this context since the first study described in 1995 on the palladium-catalyzed cross couplings of symmetrical diphenyl-λ^3-iodanes with sodium tetraphenylborate [25].

Review

Tandem additions

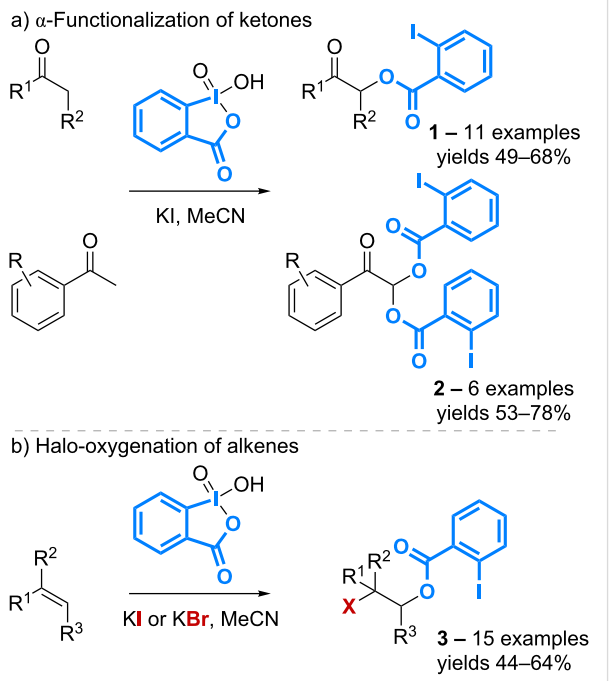
λ^5-Iodanes such as the Dess–Martin periodinane or IBX [26], and λ^3-iodanes such as benziodoxolones [27], are versatile reagents in organic synthesis. These are often used, respectively, for the oxidation of alcohols or carbonyl compounds, and in atom-transfer reactions. These transformations always lead to the release of 2-iodobenzoic acid in the reaction mixture. Thus, with the aim to value this side product, a variety of tandem reactions including an oxidation and an addition step have been designed to incorporate the nucleophilic acid into the final product.

λ^5-Iodane reagents

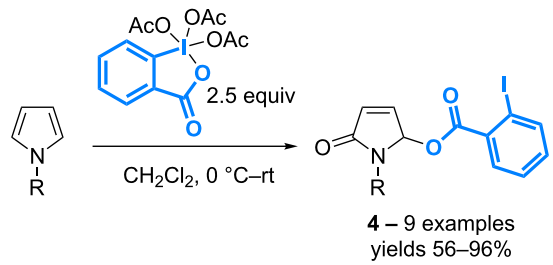
One of the first studies documenting the use of the iodoarene moiety as a building block in synthesis has been reported in 2004. The λ^5-iodane reagent IBX has been shown to promote the α-functionalization of ketones following the introduction of the 2-iodobenzoic acid motif (Scheme 2a) [28].

Mono- and disubstituted products **1** and **2** are obtained respectively from aliphatic ketones and methyl aryl ketones. The reaction conditions have then been extended to the functionalization of alkenes to afford 1,2-halo-oxygenated compounds **3** (Scheme 2b) [29]. This transformation has recently been used for the stereoselective *trans* iodo-benzoylation of glycals using a combination of IBX and molecular iodine, that is considered as a source of I^+ formed from the in situ generated hypoiodite species [30].

The controlled oxidation of various *N*-(alkyl)- and *N*-(aryl)pyrroles with Dess–Martin periodinane also leads to



Scheme 2: Functionalization of ketones and alkenes with IBX.



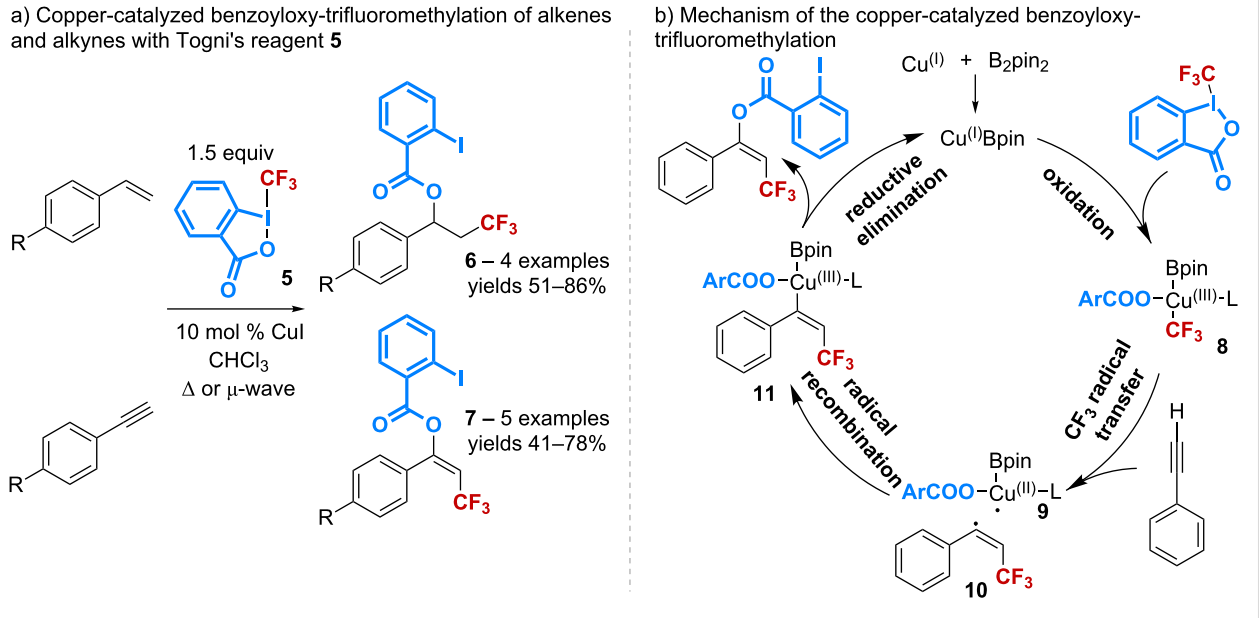
Scheme 3: Functionalization of pyrroles with DMP.

introduction of the iodobenzoic acid motif onto the pyrrole ring. 5-Aroyloxy-γ-lactams **4** can be isolated with yields in the 56–96% range, however, the reaction requires 2.5 equivalents of the λ^5-iodane reagent, a result that supports its limited efficiency in terms of atom economy (Scheme 3) [31].

λ^3-Iodane reagents: CF_3-benziodoxolone (Togni's reagent)

The ability to introduce the 2-iodobenzoic acid motif released from benziodoxolones has first been noticed by Ochiai in an isolated example of radical benzoyloxylation of THF [32], and by Gouverneur in the study of trifluoromethylation of allylsilanes [33]. The use of this acid as an oxygen nucleophile, then, has been more fully investigated by the groups of Szabó and Sodeoka who have simultaneously described the copper-catalyzed benzoyloxy-trifluoromethylation of alkenes and alkynes using Togni's reagent **5**.

The group of Szabó has first reported the use of copper(I) iodide as a catalyst for the regioselective difunctionalization of aromatic alkynes and alkenes with an optimal atom-economy (Scheme 4a) [34,35]. The transformation proceeds efficiently, particularly in the presence of an electron-donating substituent



Scheme 4: Catalytic benzoyloxy-trifluoromethylation reported by Szabó.

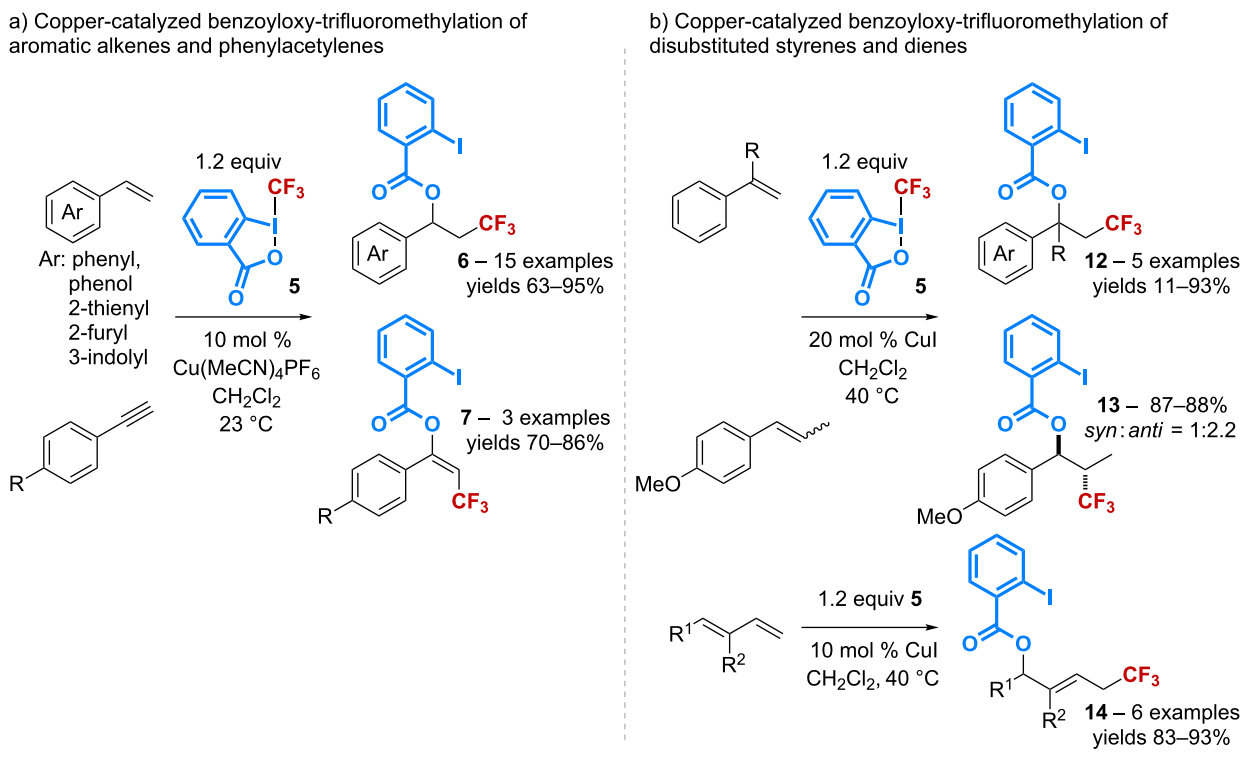
on the aromatic ring. The same reaction has been later found to be mediated by copper(I) cyanide starting from *p*-methoxystyrene [36]. However, under these conditions, other styrene derivatives bearing a phenyl, a *tert*-butyl, or an electron-withdrawing substituent have been shown to afford products resulting from a cyanotrifluoromethylation reaction.

The mechanistic study of the oxy-trifluoromethylation of phenylacetylene has then led to demonstrate that the reaction is accelerated in the presence of additives such as B_2pin_2 [35]. A mechanism involving an initial step of transmetallation of B_2pin_2 with the Cu(I) catalyst was proposed (Scheme 4b). The intermediate Cu–Bpin, then, could undergo an oxidative addition into the CF_3–I bond to give **8** that, after a CF_3 radical transfer, would afford the radicals **9** and **10**. Radical recombination followed by reductive elimination would finally lead to the *E*-product and regenerate the Cu–Bpin complex.

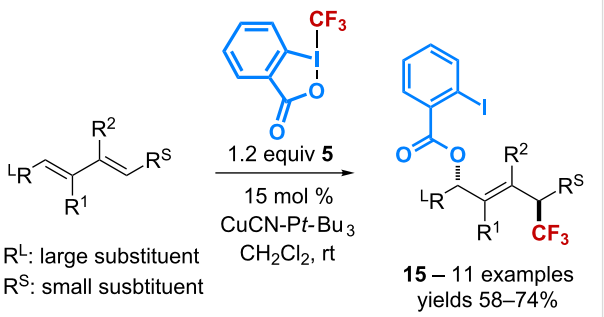
The group of Sodeoka, in parallel, has described the same 1,2-difunctionalization reaction of alkenes and alkynes with **5** in the presence of $[Cu(MeCN)_4]PF_6$ as the catalyst (Scheme 5a) [37]. It should be pointed out that this copper(I) complex was previously described by Szabó as a poor catalyst in his process. The reaction applies to phenylacetylenes and various types of aromatic alkenes, however, its scope has been extended to dienes and disubstituted styrenes by using the less Lewis acidic CuI complex (Scheme 5b) [38]. Interestingly, *cis* and *trans* β-methyl-styrenes lead to product **14** with the same *syn*:*anti* ratio while 1,4-addition products containing an (*E*)-olefin are selectively obtained from dienes. The authors have also shown that the reaction performed in the presence of a stoichiometric amount of *p*-TsOH gives β-trifluoromethylstyrene derivatives instead of the expected oxy-trifluoromethyl compound.

The benzoyloxy-trifluoromethylation of dienes has also been reported with CuCN as the catalyst. The reaction, again, is selective with respect to the olefin geometry – (*E*)-alkenes are exclusively obtained – and the regioselectivity – products resulting from a sterically-controlled 1,4-*anti*-addition are selectively isolated (Scheme 6) [39]. The proposed radical mechanism, which takes into account the beneficial effect of the bulky monophosphine P(*t*-Bu)$_3$ on the reaction rate, is consistent with that reported by Szabó (Scheme 4b).

The scope of the copper-catalyzed benzoyloxy-trifluoromethylation has been extended to several other substrates. Starting from *N*-(aryl)- and *N*-(benzyl)allylamines **16**, the reaction affords β-benzoyloxy-β'-trifluoromethylamines **17** through the formation of an aziridine intermediate (Scheme 7) [40]. The latter was further utilized to give access to a variety of β-trifluo-

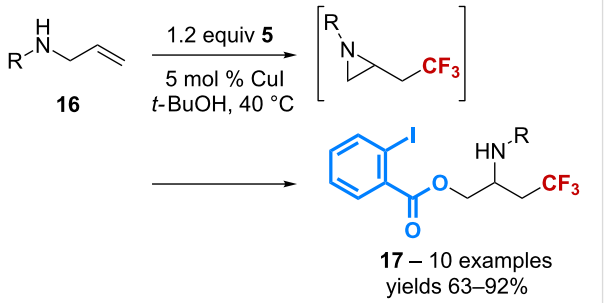


Scheme 5: Catalytic benzoyloxy-trifluoromethylation reported by Mideoka.



Scheme 6: Catalytic 1,4-benzoyloxy-trifluoromethylation of dienes.

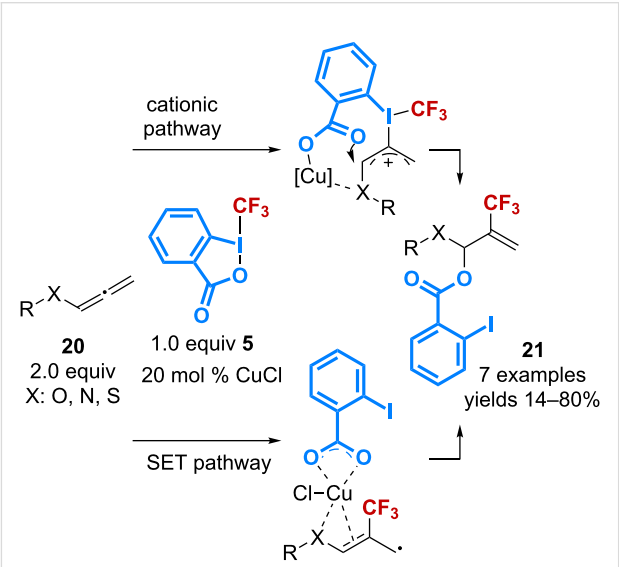
romethylamines after reaction with several *O*-, *N*-, *S*-, and *C*-nucleophiles.



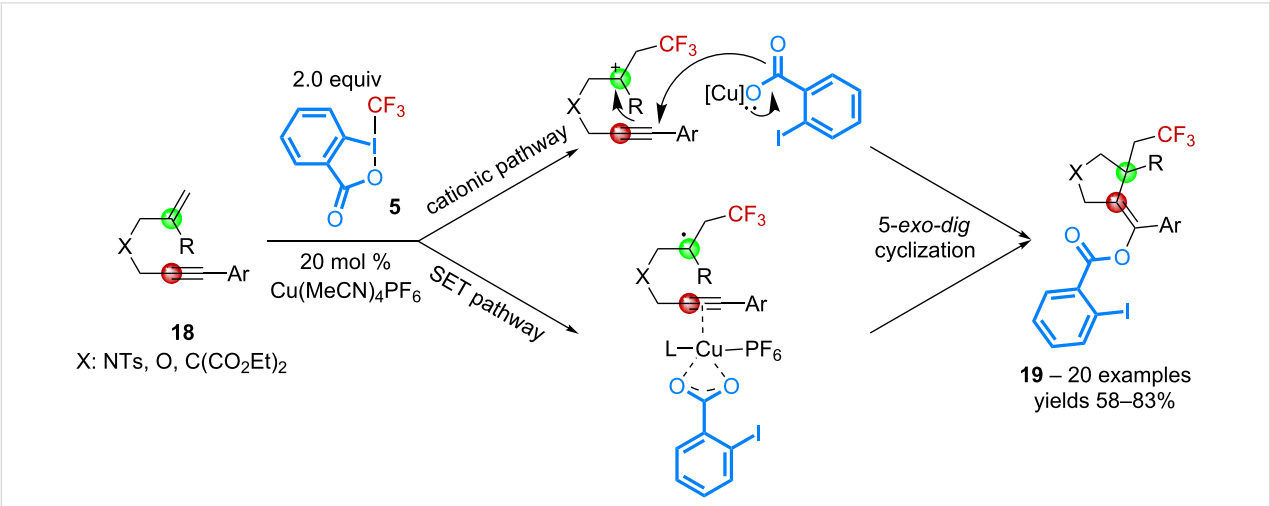
Scheme 7: Catalytic benzoyloxy-trifluoromethylation of allylamines.

Application of the same reaction conditions to enynes **18** has led to the discovery of an elegant cascade that gives access to a wide range of trifluoromethylated five-membered carbo- and heterocycles **19** (Scheme 8) [41]. Six-membered heterocycles can also be obtained in good yields. The reaction is believed to involve either a tertiary radical intermediate or a carbocationic species, both being able to undergo a 5-*exo*-*dig* type cyclization to afford compounds **19**.

The copper-catalyzed benzoyloxy-trifluoromethylation has also been applied to the conversion of allenes **20**. A regioselective 1,2-addition on the internal π-bond was observed to afford the products **21**, because of the presence of a heteroatom substituent that can stabilize the radical or cationic intermediate by coordination with the copper complex (Scheme 9) [42]. However, the efficiency of the reaction is limited by the need to use 2 equivalents of allenes **20** to obtain good yields.



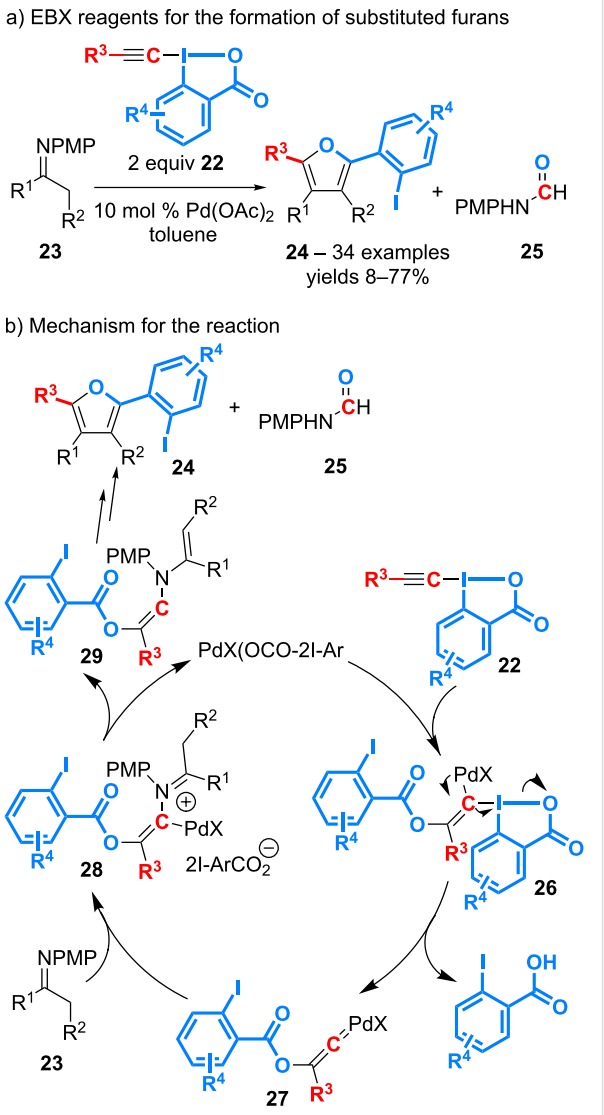
Scheme 9: Catalytic benzoyloxy-trifluoromethylation of allenes.



Scheme 8: Catalytic benzoyloxy-trifluoromethylation of enynes.

λ3-Iodane reagents: alkynylbenziodoxolone

Ethynylbenziodoxolone (EBX) is a powerful reagent to perform the electrophilic alkynylation of various functional groups such as carbonyl derivatives, thiols, arenes and heteroarenes [43,44]. A first solution to value the 2-iodobenzoic moiety released from EBX has arisen from the reaction of derivatives **22** with *N*-(aryl)imines **23** in the presence of 10 mol % of $Pd(OAc)_2$, which gives access to tri- or tetrasubstituted furans **24** and *N*-(aryl)formamides **25** (Scheme 10a) [45]. The scope of the overall transformation is wide both in terms of imines and EBX reagents.



Scheme 10: Alkynylation of *N*-(aryl)imines with EBX for the formation of furans.

Several isotope-labelling experiments have allowed for proposing a mechanism for this complex transformation (Scheme 10b). The latter would first involve the addition of a Pd(II)-2-iodobenzoate species to the triple bond of **22** to give the intermediate **26**, followed by the reductive elimination of the trivalent iodine motif to afford the palladium-vinylidene **27**. This would undergo a nucleophilic addition of the imine and a subsequent proto-demetallation to give enamine **29**. A series of rearrangements including the cleavage of the triple bond and the fragmentation of the carboxylate unit, would finally lead to the furans **24** and the formamide **25**.

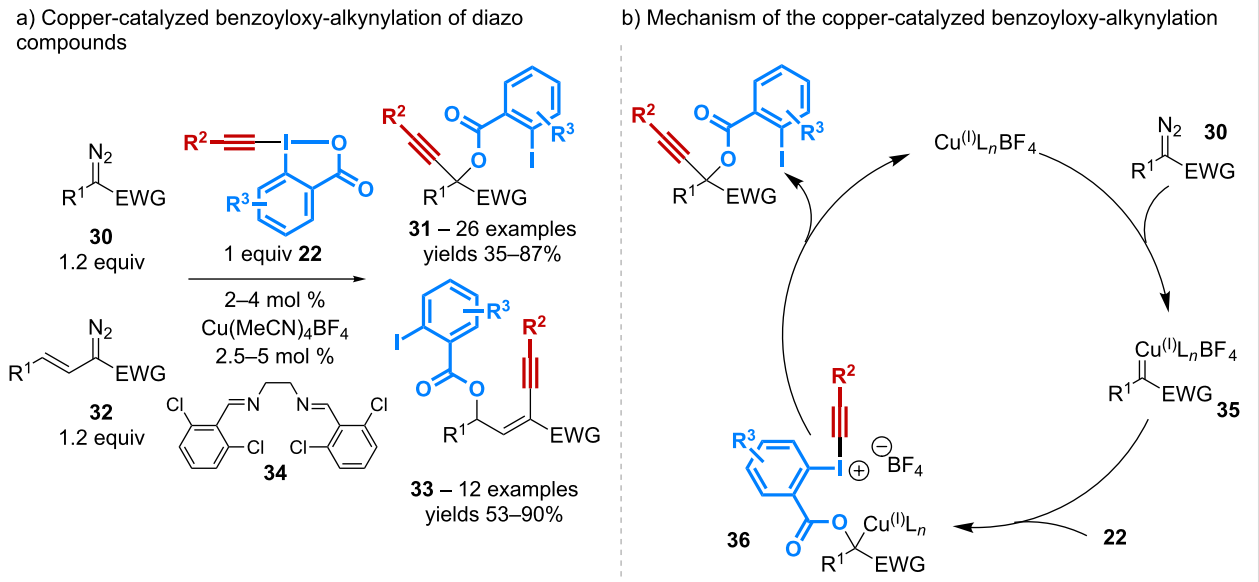
The group of Waser has discovered an atom-economical multicomponent process between alkynylbenziodoxolones **22** and diazo compounds, which is catalyzed by the copper(I) complex $[Cu(MeCN)_4]BF_4$. The reaction gives access to versatile building blocks while generating only N_2 as side-product (Scheme 11a) [46]. Worth of mention is the use of a 1,2-diimine ligand **34** that is crucial to obtain good conversions.

Compounds **31** resulting from the *gem*-addition of the benzoate motif and the alkynyl group are obtained from various acceptor or donor–acceptor diazo compounds **30**, while the use of vinyldiazo derivatives **32** leads to enynes **33** arising from the vinylogous addition of the carboxylate. Significantly, the benzoyloxyalkynylation reaction can be applied to the late-stage modification of complex products such as steroids. On the other hand, both the alkyne and the iodoarene moiety can be modified through post-transformation reactions thereby increasing the molecular diversity accessible with this process. The mechanism of the reaction (Scheme 11b) would first involve the formation of the copper-carbene species **35**, to which the carboxylate of alkynylbenziodoxolone could add to afford the intermediate **36**. Final alkynyl transfer would give rise to the products **31** and **33**, however, the nature of this alkynylation step remains to be elucidated.

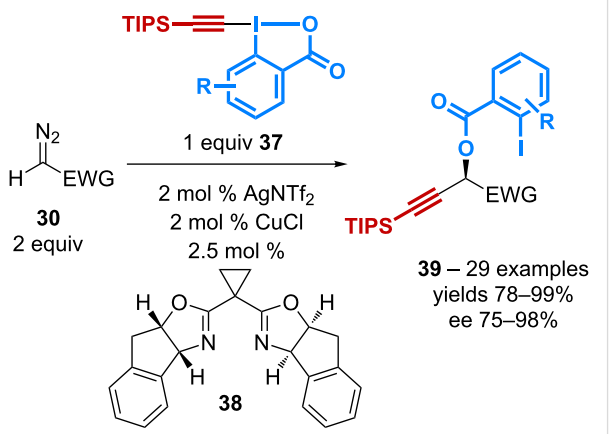
In a subsequent study, the same group has demonstrated the ability to perform the reaction with TIPS-EBX **37** in an enantioselective manner using the cyclopropylbisoxazoline ligand **38** (Scheme 12) [47]. Starting from various acceptor diazo compounds, the *gem*-addition of the carboxylate and the alkyne proceeds with ees of up to 98% to afford α-benzoyloxy propargylic derivatives **39**. Again the strategy can be applied to the late-stage modification of steroids with high levels of diastereoselectivity.

λ3-Iodane reagents: azidobenziodoxolone (ABX) and chlorobenziodoxolone

In a similar manner to the previously described catalytic benzoyloxy-trifluoromethylation using Togni's reagent **5** (Scheme 4 and Scheme 5), the 1,2-benzoyloxy-azidation of alkenes can be performed in the presence of a copper catalyst with the



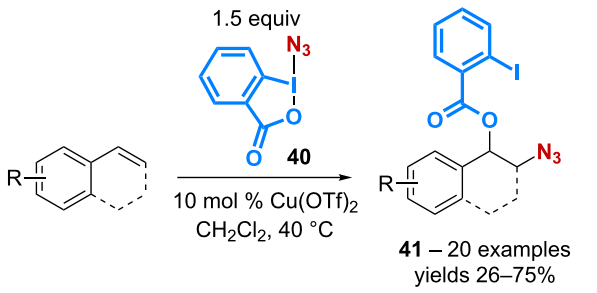
Scheme 11: Catalytic benzoyloxy-alkynylation of diazo compounds.



Scheme 12: Catalytic asymmetric benzoyloxy-alkynylation of diazo compounds.

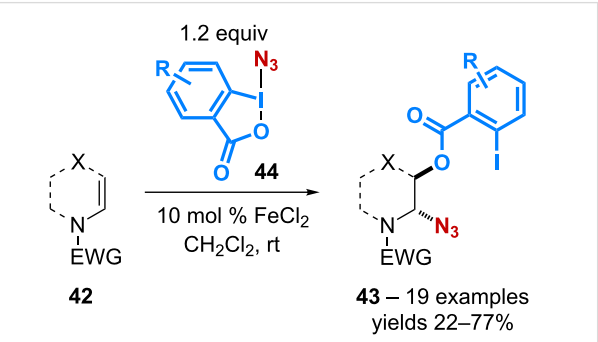
azidobenziodoxolone ABX **40**. The reaction takes place in dichloromethane using the copper(II) complex $Cu(OTf)_2$ as the catalyst thereby leading to the expected products **41** with yields in the 26–75% range (Scheme 13) [48]. Interestingly, an alkene diazidation reaction is observed by simply performing the transformation in DMSO and replacing $Cu(OTf)_2$ by CuI as the catalyst.

Enamides **42** are also relevant substrates for the 1,2-benzoyloxy-azidation reaction. Based on a preliminary observation made during their study on catalytic trifluoromethylation of enamides [49], the group of Gillaizeau has reported the catalytic conversion of enamides with various ABX derivatives **44**



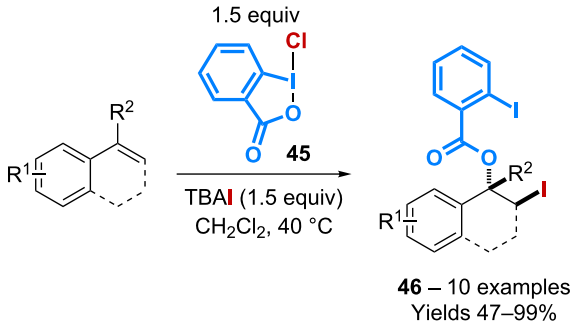
Scheme 13: Catalytic 1,2-benzoyloxy-azidation of alkenes.

[50]. A screening of various metal complexes has led the authors to demonstrate the superior ability of cheap $FeCl_2$ to mediate the 1,2-addition thereby allowing the formation of the *trans*-products **43** with complete regio- and diastereocontrol (Scheme 14).



Scheme 14: Catalytic 1,2-benzoyloxy-azidation of enamides.

The group of Hamashima has reported that various 1,2-difunctionalizations of alkenes can occur with chlorobenziodoxolone **45** [51]. Oxychlorinated, dichlorinated, azidochlorinated and chlorothiocyanated products can thus be isolated mostly from styrenyl substrates. However, the treatment of **45** with tetrabutylammonium iodide followed by the addition of an alkene leads to the formation of products **46** resulting from a 1,2-benzoyloxyiodination and isolated with moderate to excellent yields (Scheme 15). The reaction is believed to take place through the formation of a hypoiodous species that activates the olefin via an iodonium intermediate.



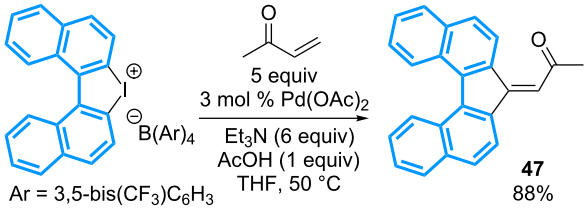
Scheme 15: Catalytic 1,2-benzoyloxy-iodination of alkenes.

Tandem catalytic couplings

Diaryliodonium compounds, also named diaryl-λ^3-iodanes, are stable, easy-to-handle crystalline solids, which have found numerous applications as arylating agents since their first use in the α-phenylation of 1,3-diones reported in the 60s [52-54]. Because of the hypernucleofuge nature of the Ar–I moiety in λ^3-iodanes, their reactivity is higher than that of the corresponding aryl halides, a property that has been widely exploited to develop efficient transition-metal-catalyzed cross coupling reactions [55]. The latter, however, allow for transferring only one of the two aromatic motifs of the iodonium reagents. Several elegant catalytic domino reactions, accordingly, have been recently designed to incorporate both aryl groups into the products.

Cyclic diaryl-λ^3-iodanes

Cyclic diaryl-λ^3-iodanes have been extensively studied for the preparation of complex polycyclic structures following the application of catalytic domino reactions. The group of Hayashi has reported in 2004 the first example of the transformation of a cyclic diaryl-λ^3-iodane, for which both Ar–I bonds are used in a palladium cross-coupling reaction [56]. It relies on a double Heck reaction performed with methyl vinyl ketone in the presence of $Pd(OAc)_2$ in THF, and affords the dibenzoalkylidenefluorene **47** in an excellent 88% yield (Scheme 16).



Scheme 16: Seminal study with cyclic diaryl-λ^3-iodane.

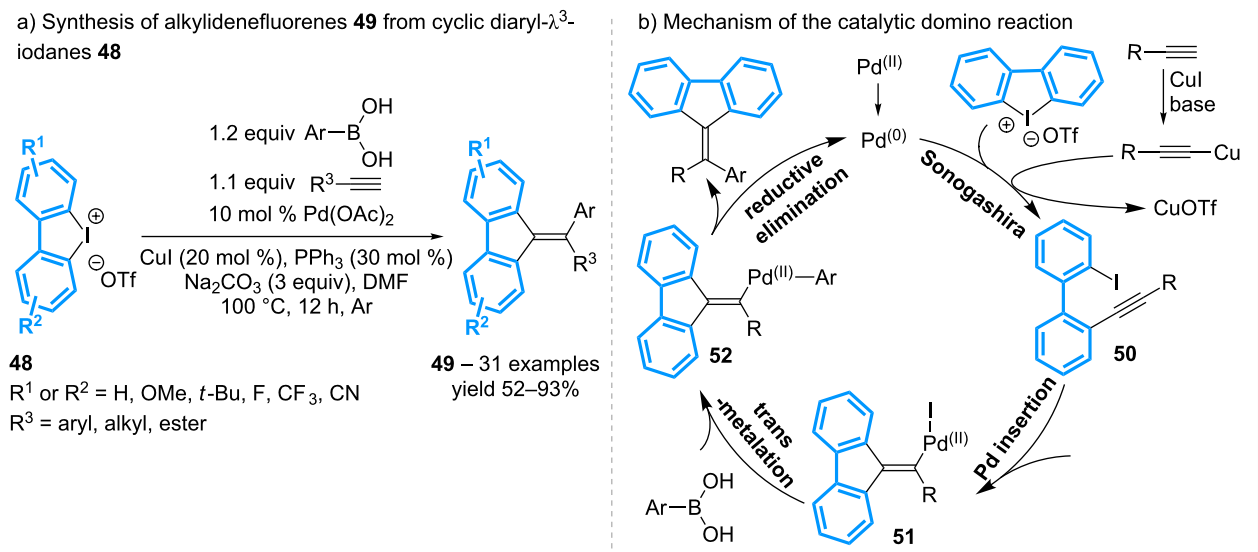
Ten years later, Huang, Wen and co-workers have demonstrated that, in the presence of both a terminal alkyne and a boronic acid, various cyclic diaryl-λ^3-iodanes undergo a transition-metal catalyzed cascade reaction to afford alkylidenefluorenes **49** (Scheme 17) [57]. In terms of mechanism, a Pd(0)/Cu(I)-catalyzed Sonogashira coupling reaction from the iodonium salt **48** delivers a 2-alkynyl-2'-iodoarene **50** that, then, cyclizes to **51** via insertion of the Pd(0) species into the iodoarene moiety and migratory addition into the proximal alkyne. Transmetalation of the vinylpalladium with the boronic acid and reductive elimination finally leads to alkylidenefluorenes **49**. This multicomponent strategy allows the variation of the alkyne, the boronic acid and the diaryliodonium salts, but the use of non-symmetrical diaryl-λ^3-iodanes raises the issue of regioselectivity.

This strategy has been then extended to the preparation of alkyne-substituted alkylidenefluorenes **53** by replacing the arylboronic acid with a second equivalent of the terminal alkyne and performing the reaction at 35 °C (Scheme 18) [58].

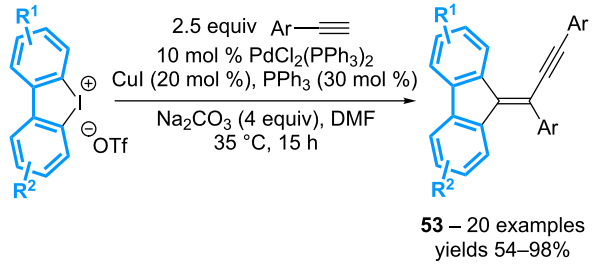
Importantly, the reaction with non-symmetrical diaryl-λ^3-iodanes gives the corresponding products with high regioselectivities, when an *o*-methyl substituent is present on one aromatic ring. The reaction can also be performed sequentially with the isolation of the iodoaryl intermediate, which can be resubmitted to the cyclization conditions in the presence of a different terminal alkyne, or an activated alkene.

The same authors have then showed that the reaction of cyclic diaryl-λ^3-iodanes in the presence of internal alkynes and the catalytic system $Pd(OAc)_2$-PCy_3 affords functionalized phenanthrenes **54** in moderate to good yields (Scheme 19) [59].

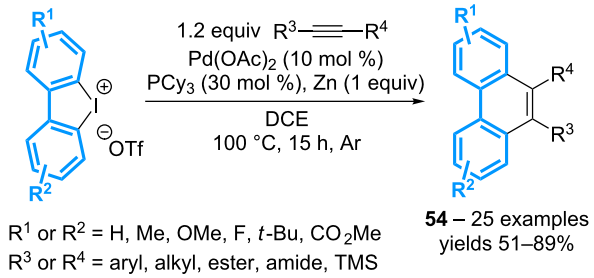
Indoles also are relevant substrates for the tandem arylation with cyclic diaryl-λ^3-iodanes, allowing the preparation of dibenzocarbazoles **55** in moderate yields (Scheme 20) [60]. The reaction is catalyzed simply by $Pd(OAc)_2$ in the absence of any ligands, and tolerates a variety of substituents on both the indole and the iodonium salt. However, the atom-economy of the reac-



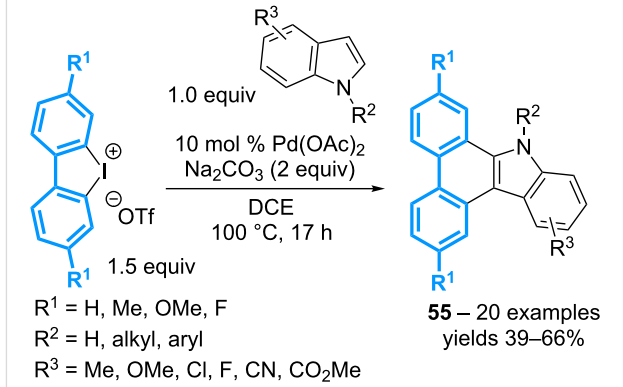
Scheme 17: Synthesis of alkylidenefluorenes from cyclic diaryl-λ3-iodanes.



Scheme 18: Synthesis of alkyne-substituted alkylidenefluorenes.



Scheme 19: Synthesis of phenanthrenes from cyclic diaryl-λ3-iodanes.

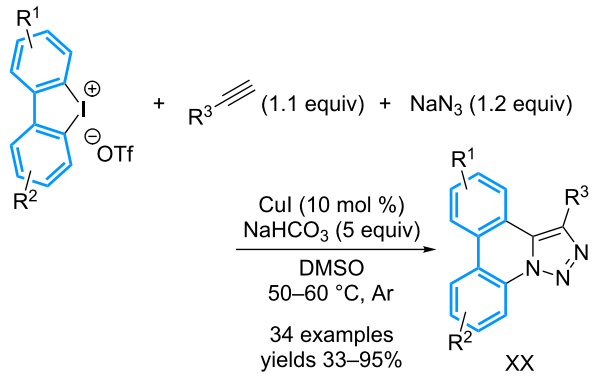


Scheme 20: Synthesis of dibenzocarbazoles from cyclic diaryl-λ3-iodanes.

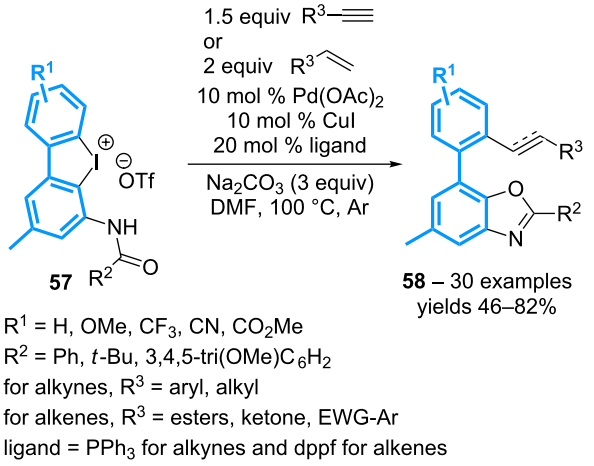
tion is limited by the need to use the iodonium salts in slight excess (1.5 equivalents).

Another multicomponent reaction has been designed for the preparation of triazolophenanthridines **56** that are obtained in a one-pot manner by combination of a cyclic diaryl-λ3-iodane with sodium azide and a terminal alkyne, in the presence of 10 mol % of CuI (Scheme 21) [61]. The expected triazolophenanthridines were generally isolated in good to excellent yields, but the presence of strong electron-donating or withdrawing groups on the phenylacetylene moiety proved to be detrimental to the conversion. In addition, mixtures of regioisomeric products are generally obtained starting from non-symmetrical diaryl-λ3-iodanes. A series of reactions has been performed to gain insight into the mechanism that first involves the formation of a 2'-iodobiphenyl-2-azide promoted by the copper complex. The latter then catalyzes an intermolecular [3 + 2] cycloaddition with the alkyne. Finally, the copper-triazole moiety inserts intramolecularly into the second Ar–I bond, allowing a ring closure after reductive elimination.

Starting from the *ortho*-*N*-(acyl)diaryl-λ3-iodanes **57**, a combination of copper and palladium catalysis, in the presence of a phosphine ligand, induces the internal *O*-arylation of the proximal amide moiety, followed by a subsequent metal-catalyzed coupling-reaction with the resulting Ar–I motif (Scheme 22)



Scheme 21: Synthesis of triazolophenantridines from cyclic diaryl-λ^3-iodanes.

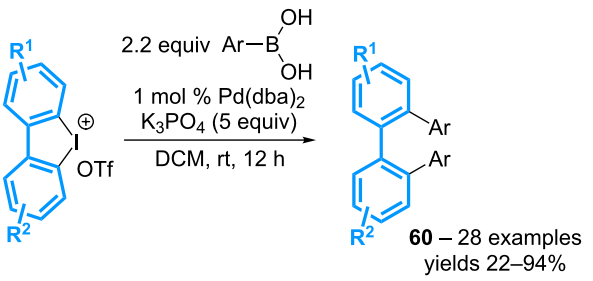


Scheme 22: Synthesis of functionalized benzoxazoles from cyclic diaryl-λ^3-iodanes.

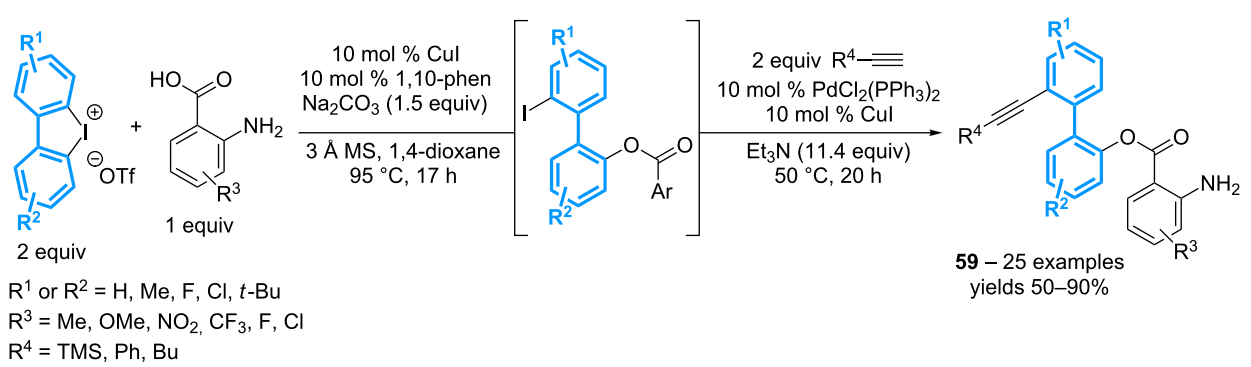
[62]. Hence aryl- and alkyl-substituted terminal alkynes can be coupled via a Sonogashira reaction when PPh_3 is used as ligand, while the use of diphenylphosphinoferrocenyl ligand (dppf) allows the Heck-type coupling of acrylates, vinyl ketones and electron-poor styrene derivatives. This relayed strategy can therefore be applied to non-symmetrical cyclic diaryliodonium species, thereby affording a library of functionalized benzoxazoles **58** with complete regiocontrol.

The group of Zhang has developed a one-pot procedure for the sequential difunctionalization of cyclic diaryl-λ^3-iodanes (Scheme 23) [63]. The first step relies on the copper-catalyzed coupling between an anthranilic acid derivative and the biphenyl moiety. The resulting iodoarene product is then submitted to a Sonogashira coupling reaction, allowing the one-pot preparation of a library of biphenyl products **59** in moderate to good yields. Nevertheless, a two-fold excess of the iodonium triflate is needed to secure a good conversion, a point that limits again the atom-economy of the overall process.

Similarly, the group of Liu has described the double Suzuki–Miyaura coupling reaction of cyclic diaryl-λ^3-iodanes with various aryl- and heteroarylboronic acids for the formation of *o*-tetraaryls **60** (Scheme 24) [64]. The reaction generally requires only 1 mol % of $Pd(dba)_2$ to afford the expected products in good to high yields. It is worth mentioning that a comparative test starting from a 2,2'-diiodobiaryl has led to a much



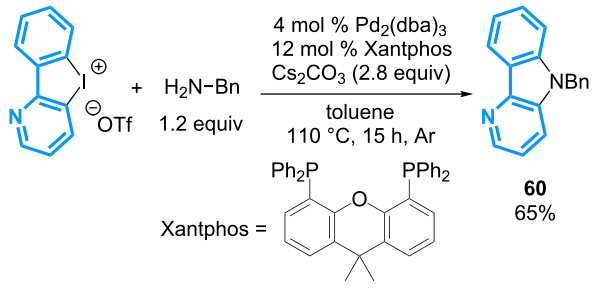
Scheme 24: Double Suzuki–Miyaura coupling reaction of cyclic diaryl-λ^3-iodanes.



Scheme 23: Sequential difunctionalization of cyclic diaryl-λ^3-iodanes.

lower yield when compared to that obtained from the corresponding diaryl-λ^3-iodane.

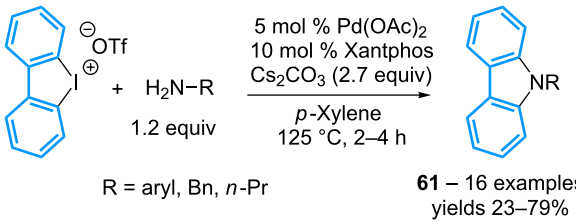
In 2011, the group of Detert has reported the first example of a palladium-catalyzed double C–N bond formation starting from the cyclic (phenyl)(pyrido)-λ^3-iodane **61** (Scheme 25) [65]. The reaction requires the use of 4 mol % of $Pd_2(dba)_3$, 12 mol % of Xantphos, 2.8 equivalents of Cs_2CO_3 and 1.2 equivalents of benzylamine to afford the corresponding δ-carboline in a 65% yield.



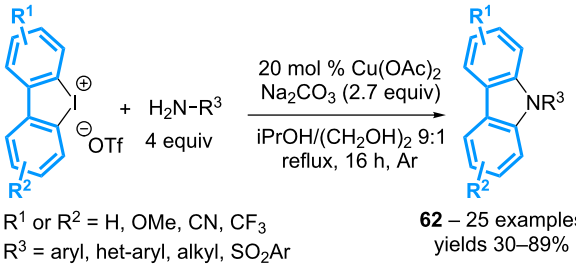
Scheme 25: Synthesis of a δ-carboline from cyclic diaryl-λ^3-iodane.

Two years later, the group of Nachtsheim has designed a similar strategy for the preparation of *N*-(aryl)carbazoles **61** from cyclic diaryl-λ^3-iodanes (Scheme 26) [66]. The palladium phosphine ligand plays a crucial role as a bidentate ligand with a bite angle greater than 100° such as DPEphos (104°) or Xantphos (108°) significantly improves the yields. The reaction applies to a series of anilines and aliphatic amines, but electron-poor anilines afford better results than their electron-rich congeners, while a hindered amine (*t*-BuNH$_2$) completely inhibits the reaction.

Shortly after, a similar synthesis of carbazoles involving $Cu(OAc)_2$ as the catalyst in the presence of ethylene glycol both as a ligand and the co-solvent has been reported (Scheme 27) [67]. A variety of amines such as anilines, sulfonamides and aliphatic amines has been utilized though in large excess. But in contrast to the previous method, electron-rich anilines proved to be better candidates for this reaction than the electron-poor analogs.



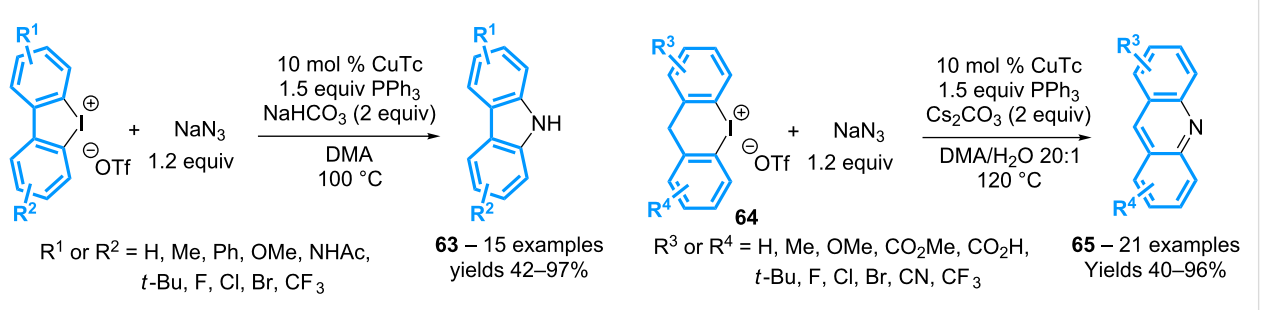
Scheme 26: Synthesis of *N*-(aryl)carbazoles from cyclic diaryl-λ^3-iodanes.



Scheme 27: Synthesis of carbazoles from cyclic diaryl-λ^3-iodanes.

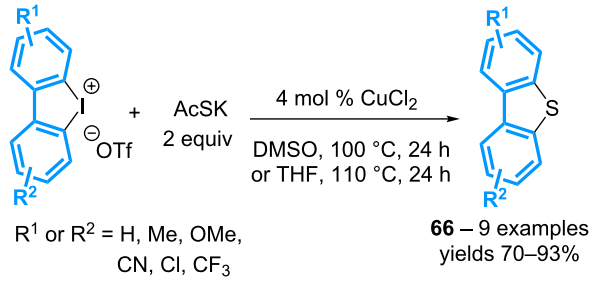
The group of Jiang has very recently described a complementary method for the synthesis of carbazoles by combining cyclic diaryl-λ^3-iodanes with sodium azide in the presence of copper(I) thiophene-2-carboxylate (CuTc) and triphenylphosphine. The reaction affords the expected of N–H free derivatives **63** in moderate to high yields, irrespective of the nature of the substituents (Scheme 28) [68]. The scope of the reaction has been extended to 6-membered ring cyclic diaryl-λ^3-iodanes **64**. The acridines **65**, hence, have been obtained with similar yields.

The group of Shimizu has reported the formation of dibenzothiophenes **66** following the reaction of cyclic diaryl-λ^3-iodanes



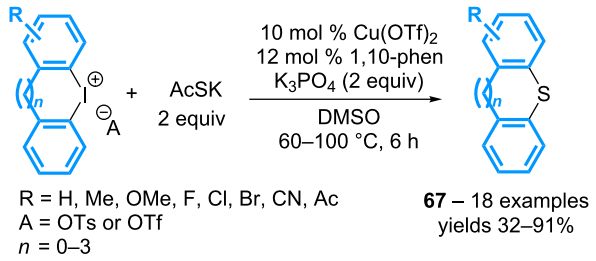
Scheme 28: Synthesis of carbazoles and acridines from cyclic diaryl-λ^3-iodanes.

with potassium thioacetate as the sulfur donor, and $CuCl_2$ as the catalyst (Scheme 29) [69]. The reaction can be performed either in THF or DMSO, affording both symmetrical and non-symmetrical products in good to excellent yields.



Scheme 29: Synthesis of dibenzothiophenes from cyclic diaryl-λ^3-iodanes.

The scope of the reaction has been extended by using a combination of 10 mol % of $Cu(OTf)_2$, 12 mol % of 1,10-phenanthroline, and 2 equivalents of potassium phosphate, as reported by the group of Jiang (Scheme 30) [70]. Six- to eight-membered sulfur heterocycles **67** can thus be isolated from cyclic diaryl-λ^3-iodanes. More significantly, the reaction can be applied to acyclic diaryl-λ^3-iodanes (vide infra).

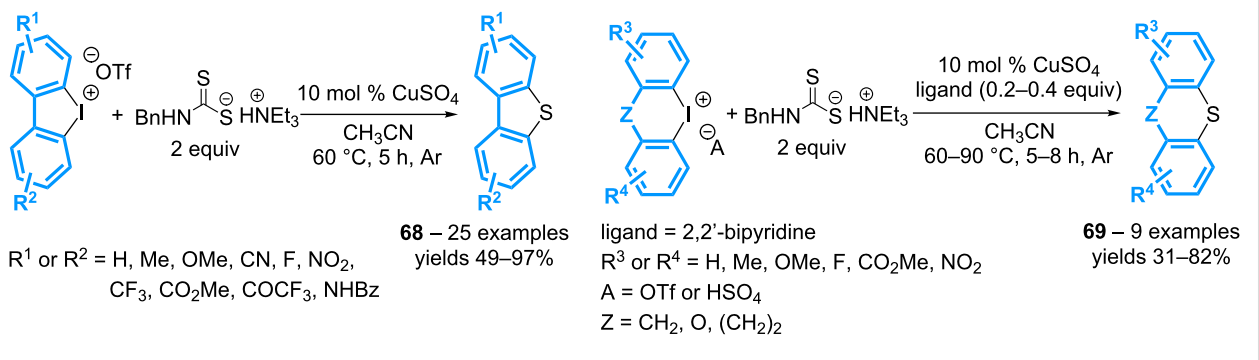


Scheme 30: Synthesis of various sulfur heterocycles from cyclic diaryl-λ^3-iodanes.

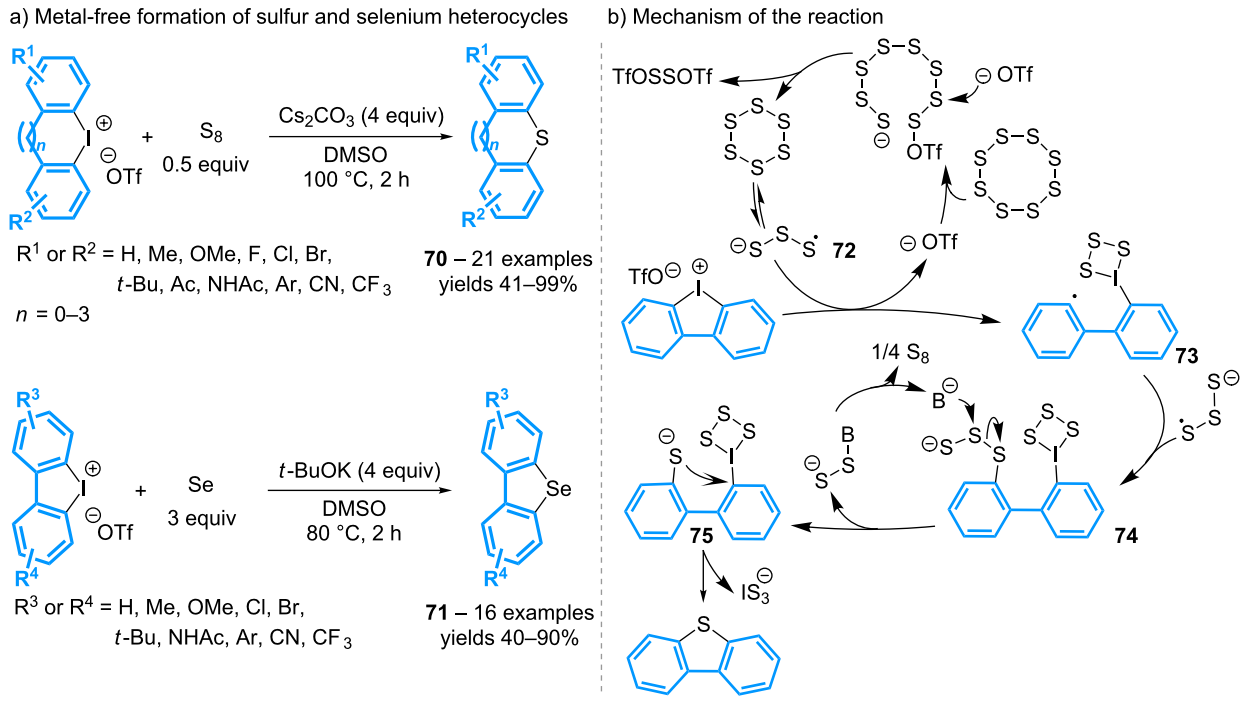
A similar approach involving the *N*-benzyldithiocarbamate-triethylamine salt as the sulfur source and copper sulfate as the catalyst also provides dibenzothiophenes isolated generally in good to excellent yields, irrespective of the nature of the substituents (Scheme 31) [71]. The transformation has been extended to other cyclic diaryl-λ^3-iodanes by using 2,2'-bipyridine as the copper ligand, allowing the preparation of the corresponding thioxanthenes, phenoxathiines and dibenzothiepines in moderate to good yields.

A metal-free alternative to the previous methods of formation of sulfur heterocycles **70** has been reported by using elemental sulfur in the presence of cesium carbonate (Scheme 32) [72]. The strategy can be extended to the synthesis of the cyclic selenium analogs **71** by utilizing elemental selenium and potassium *tert*-butoxide. Several substituted 5- to 8-membered ring π-conjugated systems are isolated in moderate to high yields. Mechanistic investigations for the iodine/sulfur exchange have led to propose the initial formation of the trisulfur radical anion $S_3^{\bullet-}$ **72**, which adds to the diaryliodonium moiety thereby inducing the formation of the aryl radical **73**. The latter then couples with another trisulfur radical anion to give the intermediate **74**. After the base-promoted formation of the corresponding thiophenol anion **75**, a cyclization delivers the expected product **70** by displacement of the iodine moiety.

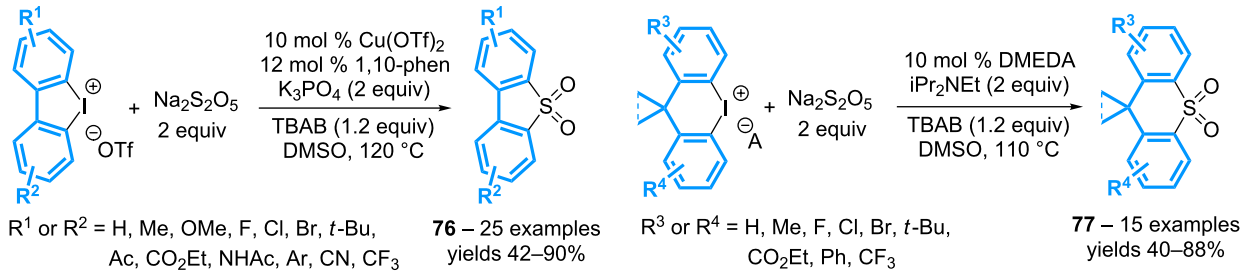
The same group has then developed a radical method to access the corresponding sulfones from cyclic diaryl-λ^3-iodanes (Scheme 33) [73]. The reaction is catalyzed by a 1,10-phenanthroline-copper complex and affords the dibenzothiophene-5,5-dioxides **76** in moderate to high yields. The transformation has been further extended to the synthesis of a new series of molecules **77**, where the central thiophene moiety is replaced by a 6-membered heterocycle, which is substituted by a *gem*-dimethyl or a cyclopropyl group. In this case, the reaction can be performed under metal-free conditions in the presence of a catalytic amount of dimethylethylenediamine.



Scheme 31: Synthesis of dibenzothioheterocycles from cyclic diaryl-λ^3-iodanes.



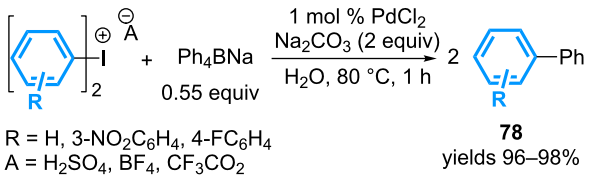
Scheme 32: Synthesis of dibenzosulfides and dibenzoselenides from cyclic diaryl-λ^3-iodanes.



Scheme 33: Synthesis of dibenzosulfones from cyclic diaryl-λ^3-iodanes.

Linear diaryl-λ^3-iodanes

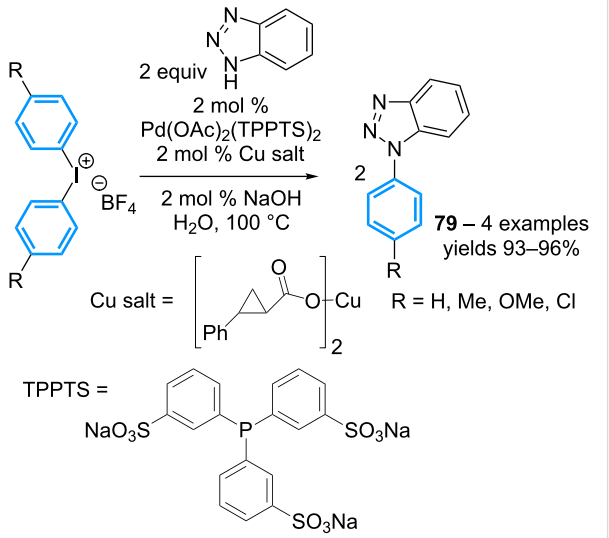
When compared to cyclic diaryl-λ^3-iodanes, the linear analogues inherently raise a more challenging issue to address in terms of sustainability, particularly in the case of non-symmetrical reagents. As mentioned in the introduction, the first study documenting the coupling of both aromatic groups of a diaryl-λ^3-iodane has been reported in 1995 by Bumagin and co-workers [25]. One equivalent of symmetrical diaryl-λ^3-iodanes could be engaged in palladium-catalyzed cross-coupling reactions with 0.55 equivalent of sodium tetraphenylborate to afford 2 equivalents of the corresponding biphenyl products in nearly quantitative yields (Scheme 34). It is assumed that the first cross coupling reaction with the iodonium salt liberates an aryl iodide moiety, available for the second palladium-catalyzed coupling reaction.



Scheme 34: Seminal study with linear diaryl-λ^3-iodanes.

Three years later, the high yielding *N*-arylation of 1*H*-1,2,3-benzotriazole (BTA), utilizing symmetrical diaryl-λ^3-iodanes as two-fold aryl donors has been reported in the presence of $Pd(OAc)_2$ and TPPTS as a water-soluble ligand, and copper(II) phenylcyclopropylcarboxylate (Scheme 35) [74]. Noteworthy, it is mentioned that Ar–I fails to furnish the *N*-arylation products

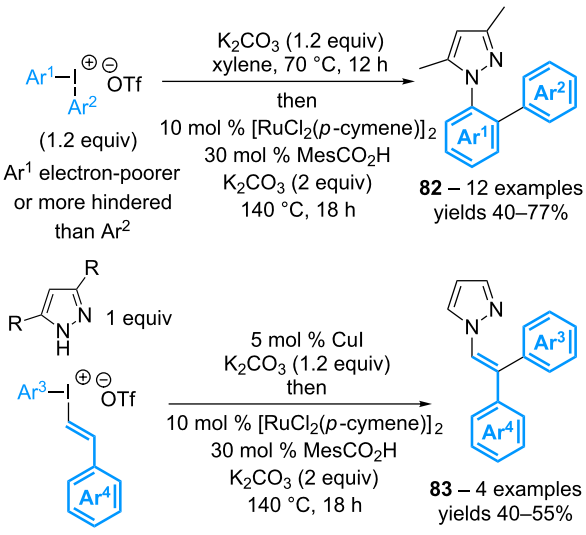
under the same reaction conditions, leading the authors to conclude that this suggested intermediate remains in the coordination sphere of the palladium catalyst.



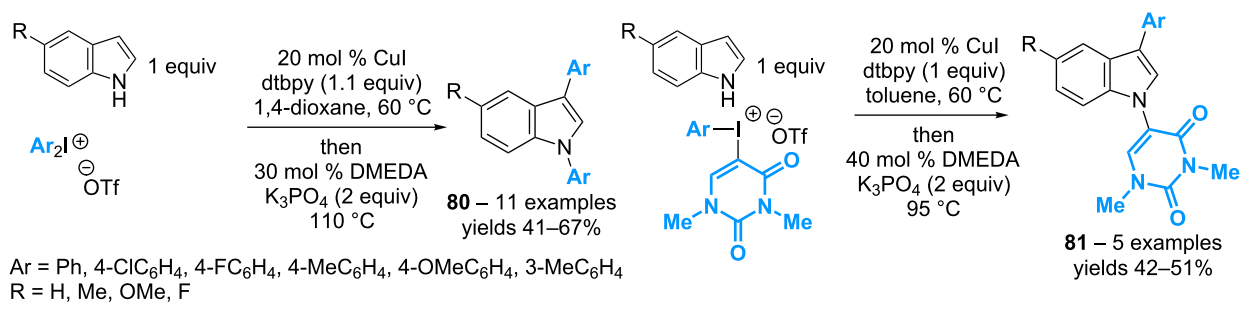
Scheme 35: *N*-Arylation of benzotriazole with symmetrical diaryl-λ^3-iodanes.

In 2015, the group of Greaney has described a tandem copper-catalyzed C_3–H/N–H arylation of indoles with diaryl-λ^3-iodanes (Scheme 36) [75]. The reaction first involves the use of 20 mol % of CuI and 1.1 equivalents of di-*tert*-butylpyridine (dtbpy) to convert the indole to the C_3–H arylated product. The released Ar–I building block, then, can be engaged in the subsequent step of N–H arylation by adding 30 mol % of dimethylethylenediamine (DMEDA) and potassium phosphate to the same pot. Symmetrical diaryl-λ^3-iodanes afford the diarylated indoles **80** with yields ranging from 41% to 67%. More significantly, whereas non-symmetrical diaryl-λ^3-iodanes based on electron poor/rich aryl moieties do not provide good levels of regiocontrol in the tandem process, the use of (aryl)(dimethyluracyl)-λ^3-iodanes allows for obtaining difunctionalized indoles of type **81** resulting from the regioselective introduction of the dimethyluracyl group at the N–H position.

The same group has then reported a remarkable domino process for the introduction of both aromatic rings of diaryl-λ^3-iodanes, though a small excess of this reagent is needed to obtain good yields. An initial *N*-arylation reaction of 3,5-dimethylpyrazole is performed in the presence of potassium carbonate, in xylene at 70 °C, releasing 1 equivalent of aryl iodide. The latter is then used for a sequential ruthenium-catalyzed *ortho*-C–H functionalization directed by the pyrazole group (Scheme 37) [76]. Starting from non-symmetrical diaryl-λ^3-iodanes, the electron-poorest or more sterically hindered aromatic group is first transferred to the 3,5-dimethylpyrazole. The reaction has been extended to 1,2,3-triazoles, benzotriazole, and pyrazole. In the latter case, the use of (styryl)(aryl)-λ^3-iodanes has also proved to be possible, with the styryl moiety being selectively transferred in the first step. The following step of C–H activation



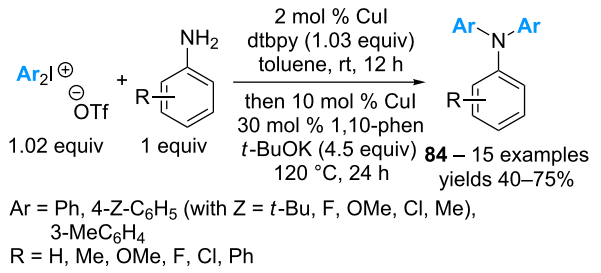
Scheme 37: Tandem *N*-arylation/C(sp^2)–H arylation with diaryl-λ^3-iodanes.



Scheme 36: Tandem catalytic C–H/N–H arylation of indoles with diaryl-λ^3-iodanes.

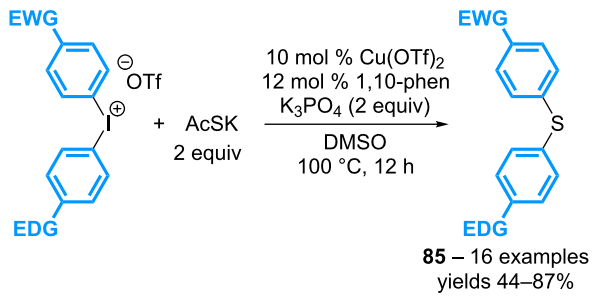
then gives access to 2,2-diarylated enamines **83** isolated as a single isomer with respect to the alkene geometry.

While the diarylation of anilines with cyclic diaryl-λ^3-iodanes for the formation of *N*-arylated carbazoles has been described in 2013 [66,67], the truly intermolecular diarylation of anilines with linear reagents has been described only in 2017 by the group Greaney [77]. Except for anilines bearing strong electron-withdrawing substituents (*p*-NO_2), the triarylated amines **84** can be obtained in moderate to good yields, irrespective of the substitution of the aniline and the diaryl-λ^3-iodane (Scheme 38). However, the scope of the reaction is limited to symmetrical diaryl-λ^3-iodanes as non-symmetrical reagents afford mixtures of *N*-arylated products in the first step of the tandem process.



Scheme 38: Catalytic intermolecular diarylation of anilines with diaryl-λ^3-iodanes.

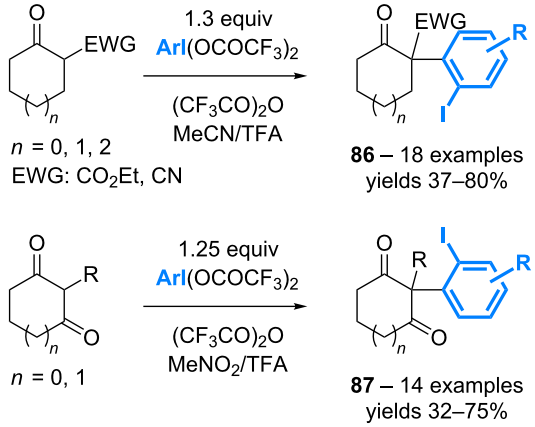
As mentioned in the Scheme 30, the group of Jiang has reported the formation of cyclic diarylsulfides from the corresponding cyclic diaryl-λ^3-iodanes, utilizing potassium thioacetate as the sulfur source, in the presence of 10 mol % of $Cu(OTf)_2$, and 12 mol % of 1,10-phenanthroline [70]. This transformation has been successfully applied to linear diaryl-λ^3-iodanes (Scheme 39). Interestingly, symmetrical and non-symmetrical reagents bearing two electronically different aryl groups can be transferred to provide the corresponding diarylsulfide products **85**, a result that stands in contrast to the observation made by Greaney in his study with anilines described in Scheme 38.



Scheme 39: Catalytic synthesis of diarylsulfides with diaryl-λ^3-iodanes.

Alternative to diaryl-λ^3-iodanes for the α-arylation of carbonyl compounds

In addition to their role as aryl donors in numerous metal-catalyzed couplings, diaryl-λ^3-iodanes are also relevant reagents to perform the α-arylation of enolates. However, the reaction is again limited to the transfer of a single aryl group. As an alternative to address this issue of atom-economy, the group of Shafir has reported the metal- and base-free arylation of keto-esters and cyanoketones using [bis(trifluoroacetoxy)iodo]arenes $ArI(OCOCF_3)_2$ (Scheme 40) [78]. The reaction can also be applied to cyclic 1,3-diones with equal efficiency [79].

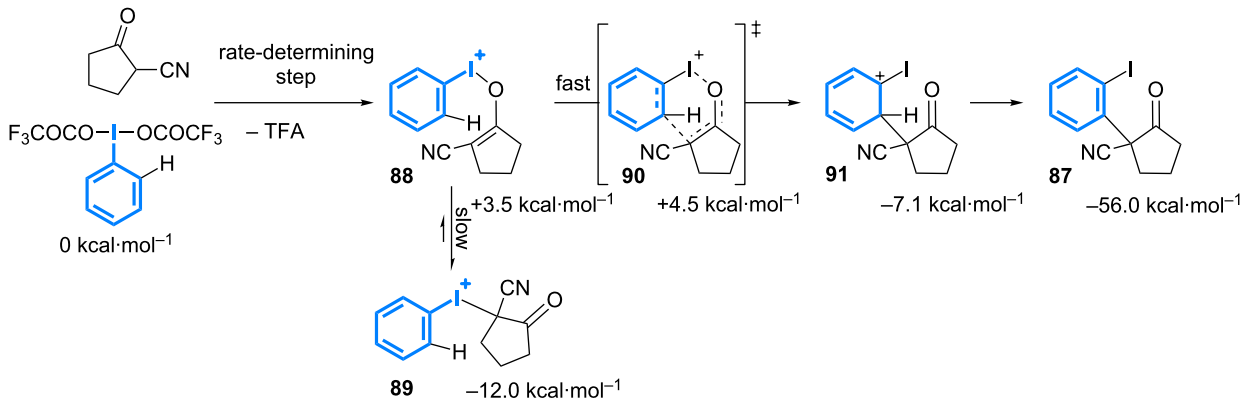


Scheme 40: α-Arylation of enolates using [bis(trifluoroacetoxy)iodo]arenes.

Mechanistic studies supported by DFT calculation have led to propose that the rate-determining step of the process would be the ligand exchange between TFA and the *O*-enolate (Scheme 41) [79]. The resulting cationic intermediate **88** could rapidly evolve through a [3,3] rearrangement. Even though the *C*-enolate **89** is more stable than its *O*-tautomer **88**, the rearrangement step seems to be much faster. The use of the radical scavenger TEMPO had no effect on the reaction outcome suggesting that the initial hypothesis is correct. By screening additives, it was shown that the hypervalent iodine could be quickly generated in situ by using Oxone as a terminal oxidant, thereby allowing for extending the scope of the reaction in terms of iodoarenes.

Tandem oxidation–catalytic couplings

A large range of oxidation reactions can be performed with [bis(acyloxy)iodo]arenes best represented by the commercially available reagents $PhI(OAc)_2$ and $PhI(OCOt\text{-}Bu)_2$. These λ^3-iodanes have been widely used in atom-transfer reactions, particularly for the generation of metal-bound nitrenes that are highly active species for the aziridination of alkenes and the direct amination of benzylic, allylic or tertiary C(sp^3)–H bonds

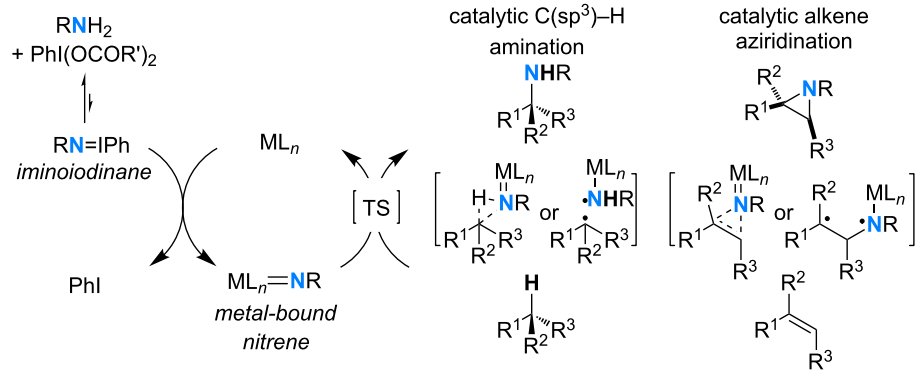


Scheme 41: Mechanism of the α-arylation using [bis(trifluoroacetoxy)iodo]arene.

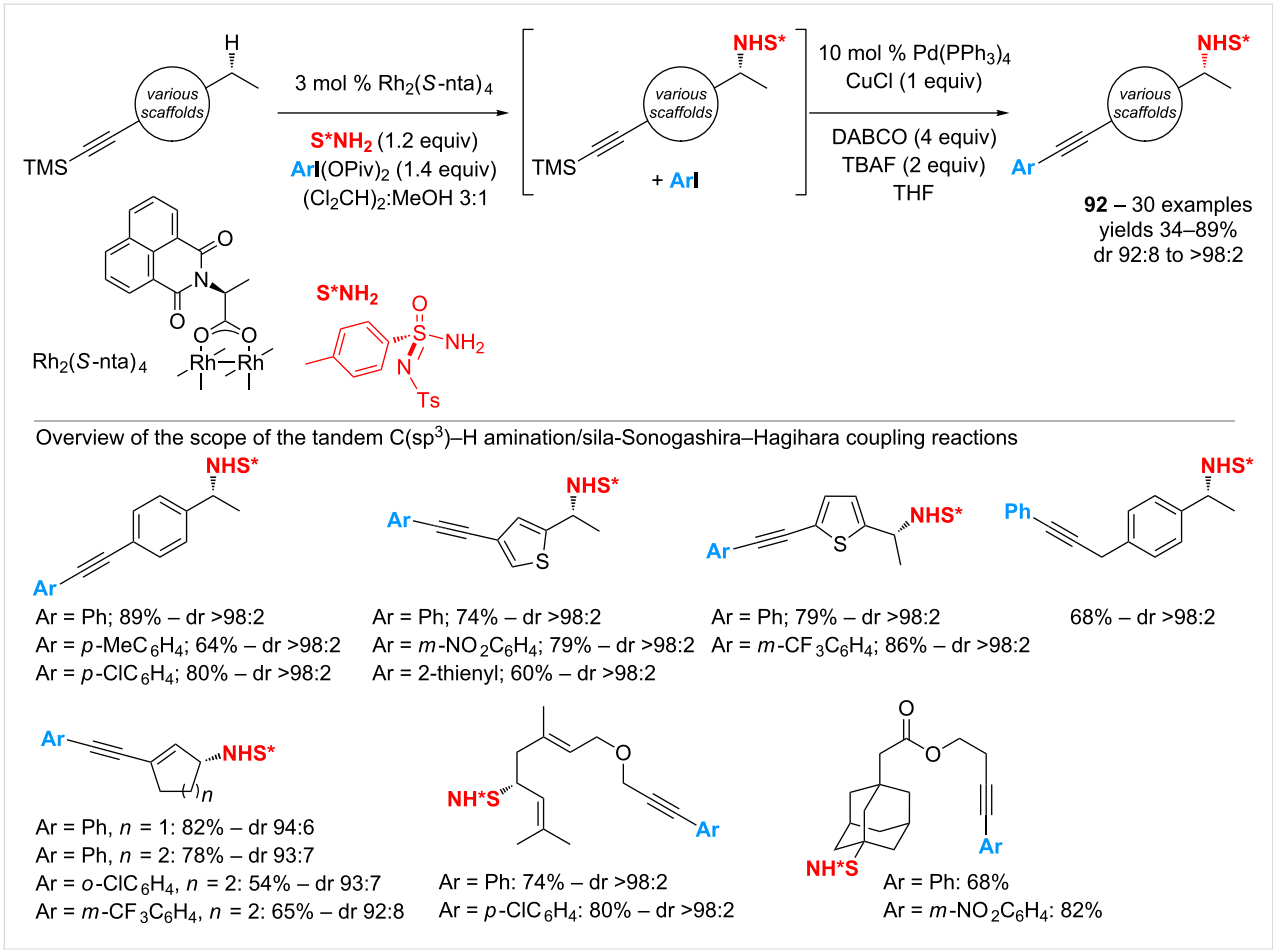
[80-85]. Seminal catalytic nitrene transfers mediated by λ^3-iodanes [86-89] were described from iminoiodinanes of general formula PhI=NR that can be prepared mainly from sulfonamides [90]. However, the scope of catalytic C(sp^3)–H amination and alkene aziridination reactions has been greatly enhanced following the discovery of practical procedures for the in situ generation of iminoiodinanes, a synthesis which is known to be troublesome [91-93]. According to these protocols and following the design of dirhodium(II) complexes, highly efficient catalytic nitrene transfers have been reported from carbamates [92], sulfamates [94-97], ureas and guanidines [98], sulfamides [99], hydroxylamine-derived sulfamates [100], carbamimidates [101], and sulfonimidamides [102-107]. These reactions involve the formation of a metal-bound nitrene that can insert into a C(sp^3)–H bond or a π-bond via the asynchronous concerted addition of a singlet species or a stepwise radical pathway (Scheme 42) [83,84].

While these transformations cannot be performed under conditions catalytic in iodine, recent investigations have revealed the possibility to value the iodoarene side-product in a subsequent one-pot palladium-catalyzed cross-coupling reaction. The use of a sulfonimidamide (S*NH_2), as a chiral nitrene precursor, in combination with the chiral dirhodium(II) complex Rh_2(*S*-nta)$_4$ has led to the discovery of intermolecular C(sp^3)–H amination reactions that proceed from hydrocarbons used as the limiting components, with nearly quantitative yields and complete diastereoselectivity [102-105]. Such a highly efficient atom-transfer process has provided the opportunity to design a tandem of C–N and C–C bond-forming reactions that relies on an initial step of catalytic nitrene addition. The latter would release the iodoarene that could be coupled to a suitable functionality previously introduced on the starting material. The strategy has been first validated from TMS-protected alkyne derivatives via a tandem of C(sp^3)–H amination/sila-Sonogashira–Hagihara coupling (Scheme 43) [108].

The overall process affords complex nitrogen-containing compounds **92** with very good yields and complete stereocontrol starting from benzylic, allylic and adamantyl substrates. In addition, the preparation of substituted [bis(acyloxy)iodo]arenes following the reaction of iodoarenes with sodium perborate



Scheme 42: Catalytic nitrene additions mediated by [bis(acyloxy)iodo]arenes.



Scheme 43: Tandem of C(sp^3)–H amination/sila-Sonogashira–Hagihara coupling.

enables the introduction of various aryl groups on the alkyne moiety.

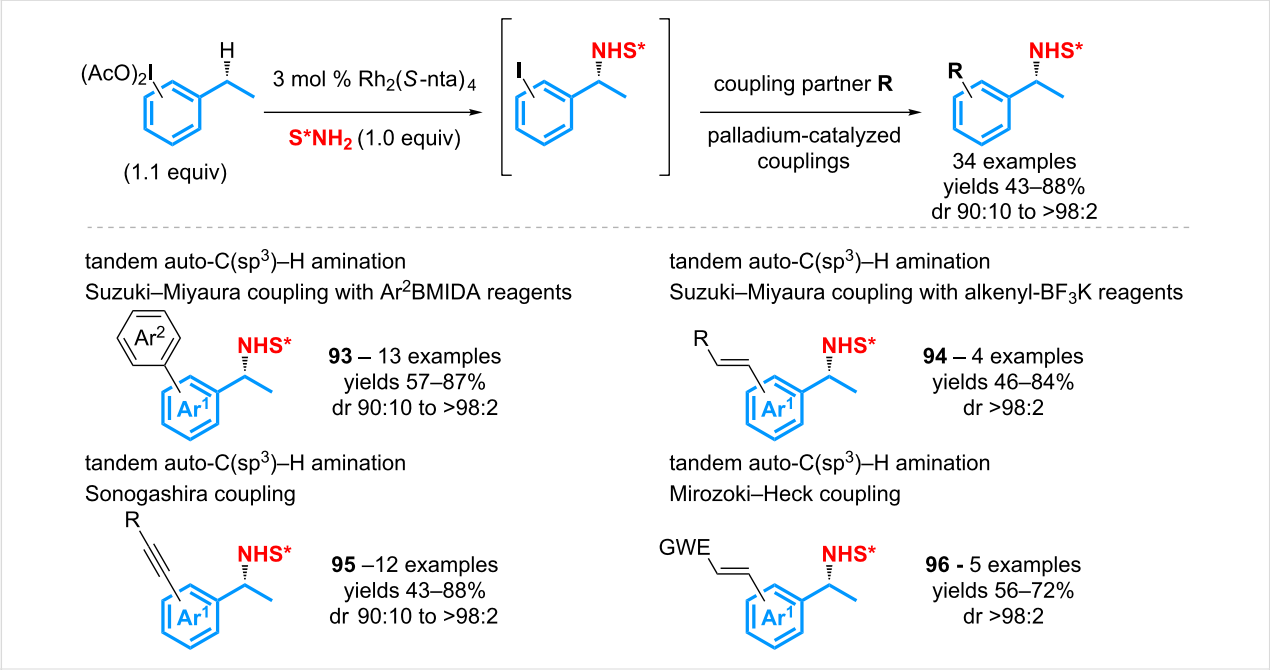
However, as a limitation of this study, the reaction allows for recycling at best 1 equivalent of the iodoarene while it involves the use of 1.4 equivalents of the λ^3-iodane. Moreover, it requires the design of specific alkynyl substrates that reduces its scope. With the aim to address these issues, it has been demonstrated that, in addition to its role of oxidant and coupling partner, the λ^3-iodane can simultaneously be used as the substrate for the C(sp^3)–H amination reaction (Scheme 44) [109]. The catalytic auto-amination, thus, gives access to various iodoaminated intermediates that can be subsequently engaged in palladium-catalyzed Suzuki–Miyaura, Sonogashira, or Mizoroki–Heck cross-coupling reactions. Various aryl, alkenyl, or alkynyl substituents can thus be introduced in good to very good yields.

When compared to the previous strategy, not only this process enables to increase the molecular diversity, but it also displays a higher atom-efficiency as only 1.1 equivalents of the λ^3-iodane are required to achieve good to excellent conversions. In addition, it should be pointed out that the tandem reactions based on the auto-amination process enables to address the issue of chemoselectivity in some cases. For example, the Suzuki–Miyaura coupling allows for introducing a pyridinyl or a furyl ring that are not compatible with the rhodium-catalyzed oxidizing amination reactions.

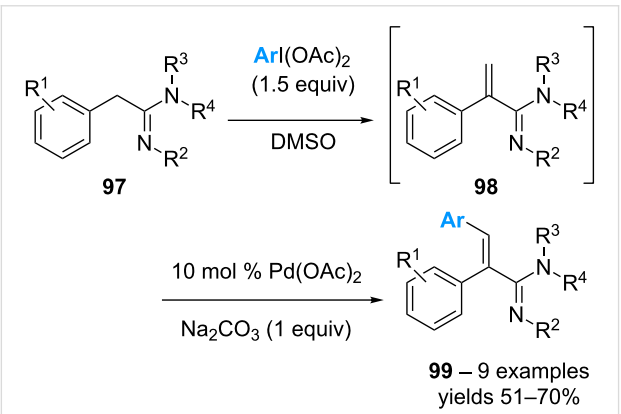
In a similar manner, the group of Namitharan has very recently demonstrated that a one-pot palladium-catalyzed Heck coupling allows for transferring the aryl group of (diacetoxyiodo)arenes released after a metal-free methylenation reaction (Scheme 45) [110]. The latter that is performed by reacting PhI(OAc)$_2$ with DMSO, applies to amidines **97** to afford the methylene intermediates **98** The following coupling leads to 1,2-diarylated acrylamidines **99** in good yields, but only starting from iodoarenes substituted by electron-donating groups.

Conclusion

With the aim to reduce the formation of iodo-containing side-products, the design of tandem reactions that enable the incor-



Scheme 44: Tandem reaction using a λ3-iodane as an oxidant, a substrate and a coupling partner.



Scheme 45: Synthesis of 1,2-diarylated acrylamidines with $ArI(OAc)_2$.

poration of the aryl groups of λ3- or λ5-iodanes into the products, has emerged as a relevant versatile alternative to the solid-supported reagents and the iodine-catalyzed transformations. Most of the achievements reported in this context have been made through the application of modern transition-metal-catalyzed methods. Simple hypervalent iodine reagents can now be considered as valuable building blocks in the synthesis of both polyfunctionalized compounds and complex polycyclic skeletons. We believe that the application of this strategy could be a source of inspiration for the conception of new multicatalytic cascades that receive increasing attention in organic synthesis [111,112]. Extending their scope in terms of molecular diversity and complexity is expected from their application starting from other classes of λ3- or λ5-iodanes.

Acknowledgements

We wish to thank the French National Research Agency (program n° ANR-11-IDEX-0003-02, CHARMMMAT ANR-11-LABX-0039), the Ministère de l'Enseignement Supérieur et de la Recherche (fellowship to G. G.), and the Institut de Chimie des Substances Naturelles for their support.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Glycosylation reactions mediated by hypervalent iodine: application to the synthesis of nucleosides and carbohydrates

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Review

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Keywords:
glycosylation; hypervalent iodine; Lewis acid; nucleoside; oligosaccharide

Beilstein J. Org. Chem. **2018,** *14,* 1595–1618.
doi:10.3762/bjoc.14.137

Received: 02 February 2018
Accepted: 15 June 2018
Published: 28 June 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

To synthesize nucleoside and oligosaccharide derivatives, we often use a glycosylation reaction to form a glycoside bond. Coupling reactions between a nucleobase and a sugar donor in the former case, and the reaction between an acceptor and a sugar donor of in the latter are carried out in the presence of an appropriate activator. As an activator of the glycosylation, a combination of a Lewis acid catalyst and a hypervalent iodine was developed for synthesizing 4'-thionucleosides, which could be applied for the synthesis of 4'-selenonucleosides as well. The extension of hypervalent iodine-mediated glycosylation allowed us to couple a nucleobase with cyclic allylsilanes and glycal derivatives to yield carbocyclic nucleosides and 2',3'-unsaturated nucleosides, respectively. In addition, the combination of hypervalent iodine and Lewis acid could be used for the glycosylation of glycals and thioglycosides to produce disaccharides. In this paper, we review the use of hypervalent iodine-mediated glycosylation reactions for the synthesis of nucleosides and oligosaccharide derivatives.

Introduction

Nucleic acids and oligosaccharides are both mandatory polymers for the maintenance of life and cell growth. The former exists in nuclei and codes genetic information, which is transformed into proteins through a transcription process known as the "central dogma" (i.e., DNA makes RNA makes proteins). The latter make up the cell walls of microorganisms and also play a role in transmitting information on the cell surface, whose interactions with proteins are a starting point for signal transduction into cells [1]. Since both types of polymers are essential for cell viability, their biological synthesis, including

the synthesis of their monomer units, e.g., nucleotides, is highly regulated. Damage to these vital molecules often results in congenital disease with ultimately fatal consequences [2,3]. Accordingly, the study of polymers and their biosynthesis is quite important, and informs the development of new drugs for diseases including cancers and infectious diseases caused by viruses [4-7]. Indeed, many drugs related to nucleic acids and oligosaccharides have been developed and used in clinical fields. Synthetic chemists have contributed to the studies by supplying biological tools for the analyses of these polymers, as well as by synthesizing effective drug candidates for the diseases mentioned above [4,8-14].

To synthesize nucleoside and oligosaccharide derivatives, glycosylation reactions are often used to form a glycoside bond. In the case of nucleoside synthesis, a coupling reaction between a persilylated nucleobase and a sugar donor is typically used [15-17]. On the other hand, the reaction between an acceptor and sugar donor is carried out in the presence of an appropriate activator for oligosaccharide synthesis [18,19]. In both cases, a Lewis acid is generally used as an activator for sugar donors. Our previous review focused on the development of glycosylation reactions and their application to the synthesis of nucleoside derivatives [17]. In this review, we showed our glycosylation reactions under oxidative conditions. These were quite useful and the conceptually similar reactions were widely used for synthesizing nucleoside derivatives. Recently, a combination of a Lewis acid catalyst and hypervalent iodine was developed for synthesizing 4’-thionucleosides, which was based on a Pummerer-type reaction coupled with oxidation. The concept of the oxidative glycosylation reaction was successfully applied to the synthesis of other nucleoside derivatives, including 4’-selenonucleosides and carbocyclic nucleosides. The hypervalent iodine-mediated glycosylation has also been used for oligosaccharide synthesis employing glycals and thioglycosides as sugar donors. In this review, we survey the synthesis of nucleoside and disaccharide derivatives under oxidative conditions mostly based on the hypervalent iodine-mediated glycosylation reactions.

Review

Synthesis of 4’-thionucleosides

Over the last decade, we have steadily pursued the identification of novel antitumor and antiviral nucleoside derivatives [17,20-22]. Matsuda and co-workers reported a 2’-substituted cytidine derivative, DMDC (**1**), with potent antitumor activity [23,24]. In other reports, Walker [25] and Secrist [26] independently described the potent antiherpesvirus activity of 2’-deoxy-4’-thionucleoside **2**, in which sulfur was introduced in place of the sugar ring oxygen of 2’-deoxynucleoside. The results for 2’-substituted nucleosides and 2’-deoxy-4’-thionucleosides strongly suggested that 2’-substituted 4’-thionucleosides would be promising candidates for novel antitumor agents. Thus, we designed a novel 2’-substituted 4’-thiocytidine, 4’-thioDMDC (**3**), as our target molecule for potential antitumor agents [27,28] (Figure 1).

At the time we started our project, there had been no reports regarding the synthesis of even 2-substituted 4-thiosugar derivatives. We thus developed the first synthetic route accessing the 4-thiosugar derivative by way of bicyclic intermediate **8** from diacetoneglucose (**5**). Construction of the bicyclic ring of **8** was achieved by consecutive inter-/intramolecular S_N2 reactions of the dimesylate derivative **7** obtained by manipulations of **5**. After acetal hydrolysis and the subsequent hydride reduction, 4-thioarabinose derivative **9** was obtained in good yield. Introduction of a TBDPS group at the primary hydroxy group of **9**, oxidation and Wittig reaction, followed by deprotection of the benzyl group, gave allyl alcohol **11**.

The most popular method to form a glycosyl bond between the sugar moiety and the base of a nucleoside is a Vorbrüggen reaction [15,16], in which a silylated base and sugar donor, e.g., 1-acetoxy sugar, are condensed by a Lewis acid catalyst. It was clear that this reaction could also be used in the synthesis of 4’-thionucleosides as well as normal “4’-oxy” nucleosides. However, for reasons which will be described later, we decided to develop an alternative method to build the glycosyl bond of 4’-thionucleosides by using a direct coupling of a 4-thiosugar

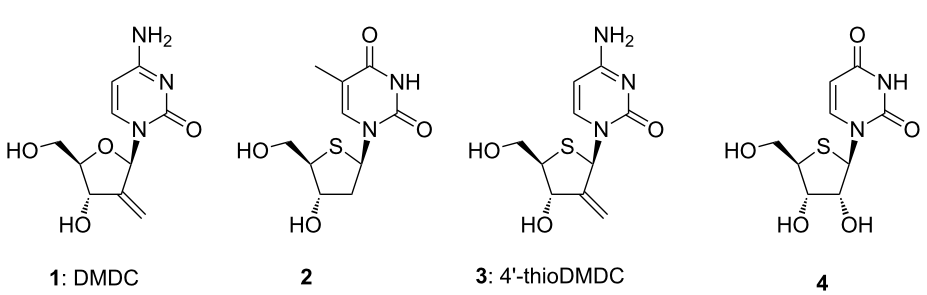


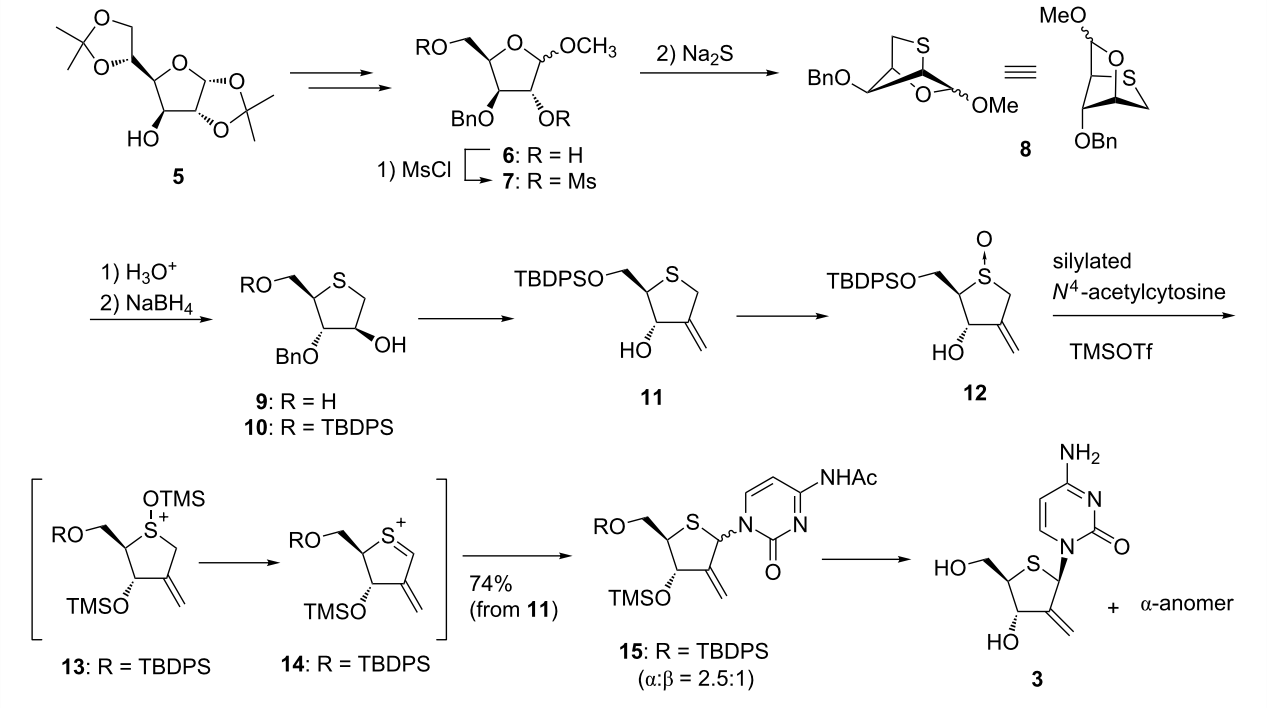
Figure 1: Design of potential antineoplastic nucleosides.

sulfoxide and a silylated base under sila-Pummerer conditions [29,30]. We found that treatment of **12**, obtained by oxidation of **11**, with excess persilylated N^4-acetylcytosine in the presence of TMSOTf as a Lewis acid gave an inseparable mixture of α- and β-anomers of 4'-thioDMDC derivatives **15** in good yield. Based on the study of the sila-Pummerer reaction by Kita, it was plausible that the reaction proceeded via the formation of sulfenium ion **14** which was formed by β-elimination of silylated sulfoxide **13**. The 4'-thioDMDC derivative **15** was deprotected and the resulting anomeric mixture was separated to furnish 4'-thioDMDC (**3**) and its α-anomer [27,28] (Scheme 1).

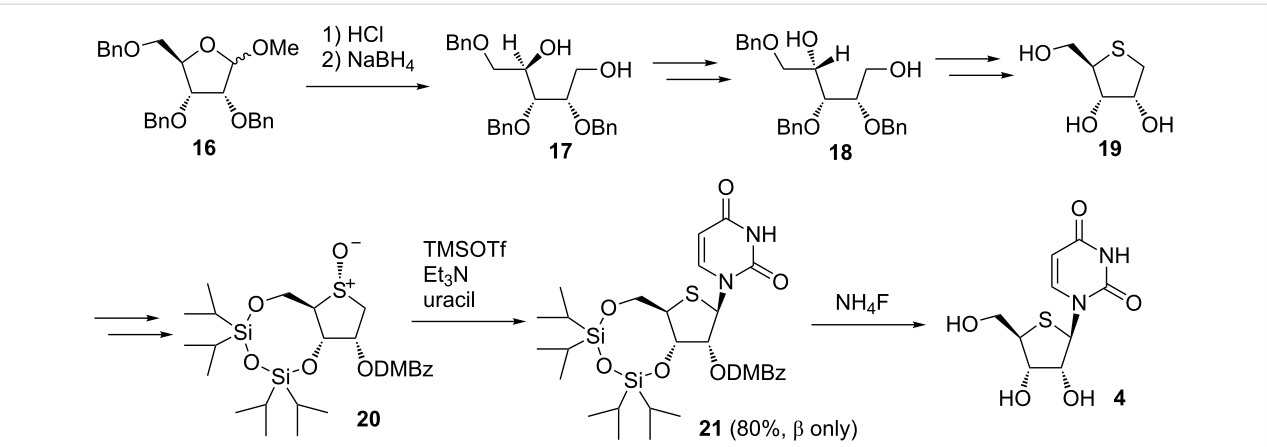
After we reported the synthesis of 4'-thioDMDC using a Pummerer-type glycosylation reaction, Minakawa and Matsuda applied the reaction to the syntheses of 4'-thioribonucleosides. Applying the synthetic scheme of 2'-deoxy-4'-thionucleoside by Walker to a ribo derivative, 2-dimethoxybenzoate **20** was prepared from tribenzylated ribose **16**. Introduction of a dimethoxybenzoyl (DMBz) group at the 2-position and diastereoselective formation of sulfoxide **20**, favored in Pummerer-type glycosylation reactions and cases where the approach of the nucleophile is restricted, were the key strategies for their synthesis of 4'-thioribonucleosides. Under optimized conditions, the desired 4'-thiouridine derivative **21** was the sole product and it was obtained in excellent yield (Scheme 2). Using the method developed, they succeeded in preparing all four kinds of 4'-thioribonucleosides [31].

We also synthesized 4'-thioribonucleosides constructing the skeleton of the 4-thioribose via a ring-contraction reaction under reductive conditions [32] from 2-mesylate **23**, which was obtained from **22**. As shown in Scheme 3, the reaction first started to form an episulfonium ion **24** triggered by intramolecular S_N2 reaction at the 5-position by sulfur atom. Secondary, ring contraction from thiopyranose to thiofuranose occurred to produce 5-aldehyde **26**. Finally, hydride reduction of **26** gave the 4-thiofuranose derivative **27**. The Pummerer-type glycosylation reaction of 5-*O*-silylated sulfoxide **28**, by treating with 2,4-bis(trimethylsilyl)uracil (**29**) and excess diisopropylethylamine (DIPEA) in the presence of TMSOTf, gave 4'-thiouridine derivative **30** in a good yield. The reaction stereoselectively proceeded and resulted the predominant formation of the β-anomer due to steric hindrance of the 2,3-di-*O*-isopropylidene group.

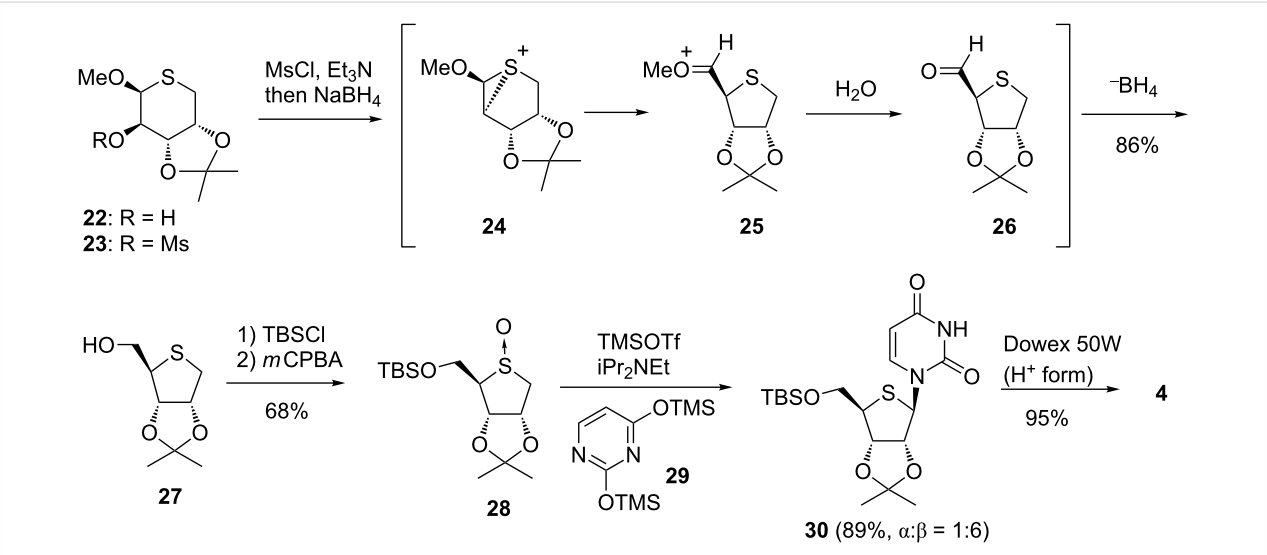
Before our reports regarding the Pummerer-type glycosylation, the synthesis of 4'-thionucleosides was based on the known chemistry: typically, a 1-acetoxy-4-thiosugar or its synthetic equivalent was obtained from natural sugars and subjected to the Vorbrüggen reaction as in the case of 2'-deoxy-4'-thionucleosides [25,26]. When synthesizing 4'-thionucleosides by the way of a sulfide derivative **31**, the known chemistry should lead us to use a classical Pummerer reaction to produce 1-acetoxy derivative **33** after converting **31** to the corresponding sulfoxide **32**. Even though this scheme should be promising



Scheme 1: Synthesis of 4'-thioDMDC.



Scheme 2: Synthesis of 4'-thioribonucleosides by Minakawa and Matsuda.



Scheme 3: Synthesis of 4'-thioribonucleosides by Yoshimura.

enough, we intended to introduce an additional synthetic idea based on the fact that both of the reaction intermediate of the Vorbrüggen reaction [15,16] of **33** and the sila-Pummerer reaction developed by Kita [29,30] involving sulfoxide **32** would be the same sulfenium ion **34**. This new glycosylation reaction was unique and attractive since it was capable of skipping a step. In other words, the reaction could directly access sulfenium ion **34** from sulfoxide **32**. Thus we developed the Pummerer-type glycosylation as mentioned above. From these results it can be deduced that the expected sulfenium ion had formed and that the concept of the Pummerer-type glycosylation was actually effective for the formation of the glycosyl bond of 4'-thionucleosides. After we had reported our synthesis of 4'-thioDMDC, the method was widely adopted for the synthesis of 4'-thionucleoside derivatives by other groups and became a standard approach for the glycosylation [33-37]. On the other hand, the conversion from the sulfide to 4'-thionucleoside using the Pummerer-type glycosylation included an oxidation step. If the oxidation of sulfide **31** and the Pummerer-type glycosylation of the sulfoxide **32** could be performed in the same flask, the reaction could bypass two of the reaction steps and would directly produce 4'-thionucleoside **35** from **31**. Indeed, the utilization of hypervalent iodine would have enabled this short-cut reaction (Figure 2).

Hypervalent iodine reagents have been widely used in organic synthesis [38]. Although originally used as oxidative agents, their use has spread to coupling reactions, including those for the formation of C–C bonds [39-43]. In the case of C–N bond formation, introduction of an azido group using PhI=O and $TMSN_3$ was reported by Kita and co-workers [44]. Their paper prompted Nishizono et al. to study the glycosylation reaction

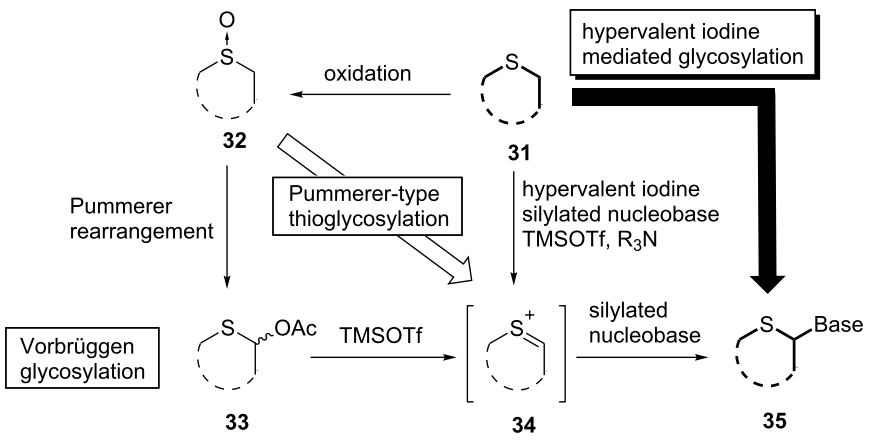


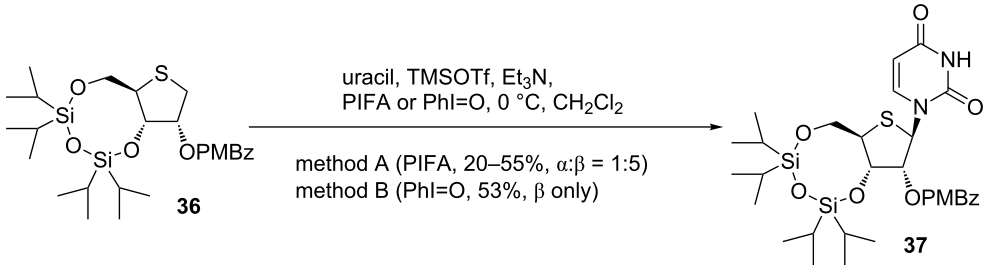
Figure 2: Concept of the Pummerer-type glycosylation and hypervalent iodine-mediated glycosylation.

for 4'-thionucleosides using hypervalent iodine reagents. As a 4-thiosugar donor, 2-*p*-methoxybenzoate derivative **36** was prepared following Matsuda's method as shown in Scheme 2, and then was subjected to the Pummerer-type glycosylation mediated by hypervalent iodine. Treatment of **36** with bis(trifluoroacetoxy)iodobenzene (PIFA) and uracil in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine gave a 5:1 mixture of 4'-thiouridine derivative **37** in 55% yield. The reaction of **36** with iodosylbenzene (PhI=O) proceeded stereoselectively and gave only the β-anomer of **37** in 53% yield [45] (Scheme 4).

The mechanism of hypervalent iodine-mediated glycosylation can be expressed as shown in Figure 3. The activated hypervalent iodine reagents in the presence of TMSOTf reacted a sulfur atom of **36** to give **38**, in which elimination of iodobenzene and HX might subsequently occur to generate a sulfenium ion **40** (path a). The nucleophilic attack of the silylated base to the sulfenium ion **40** favored approaching from the β-face to give only the β-anomer **37** as in the case of Minakawa and Matsuda's synthesis described above.

Nishizono considered that the difference between the stereoselectivities of the coupling reactions in methods A and B was caused by the existence of another reaction path of the sulfonium salt (**38** or **39**). In path b, the 4-thiosugar **41** was generated and reacted with a nucleobase, giving a mixture of α- and β-anomers since the reaction might occur by the simple S_N2 reaction. Thus, the reaction proceeded through both paths a and b in method A, but path a was predominant in the reaction of method B [45] (Figure 3).

Nishizono et al. applied the hypervalent iodine-mediated glycosylation to purine 4'-thionucleosides [46]. However, the reaction of **36** with 6-chloropurine resulted in the formation of a regioisomer reacting at the 4-position without any formation of the desired purine 4'-thionucleoside. The result should relate to the acidity of the α hydrogen adjacent to a sulfur atom, which affects the regioselectivity of the reaction. To study the effects of a protecting group on the reaction, the regioselectivity of the reaction was examined using **42** and **43**, which were obtained from **27**. When the 5-hydroxy group was protected with a benzoyl group, the coupling reaction of **42** occurred at the 4-po-



Scheme 4: Oxidative glycosylation of 4-thioribose mediated by hypervalent iodine.

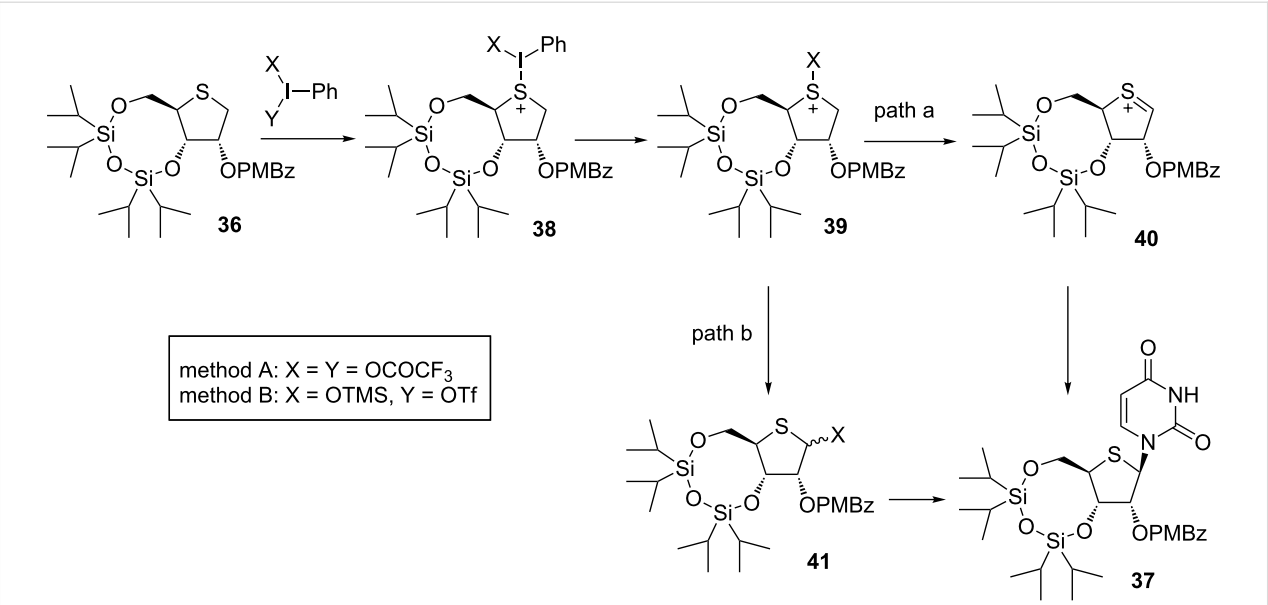
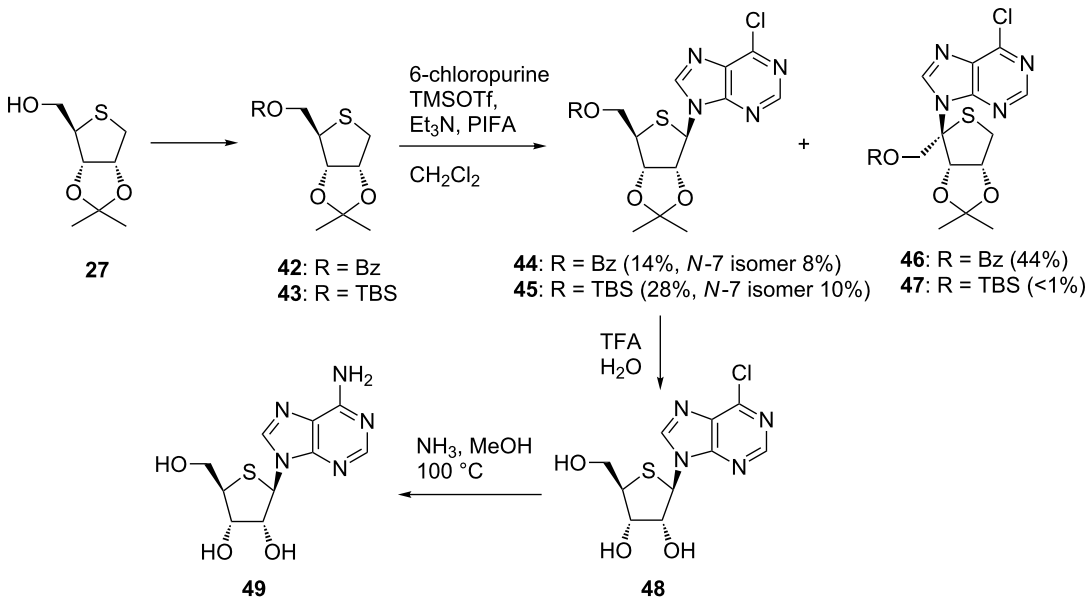


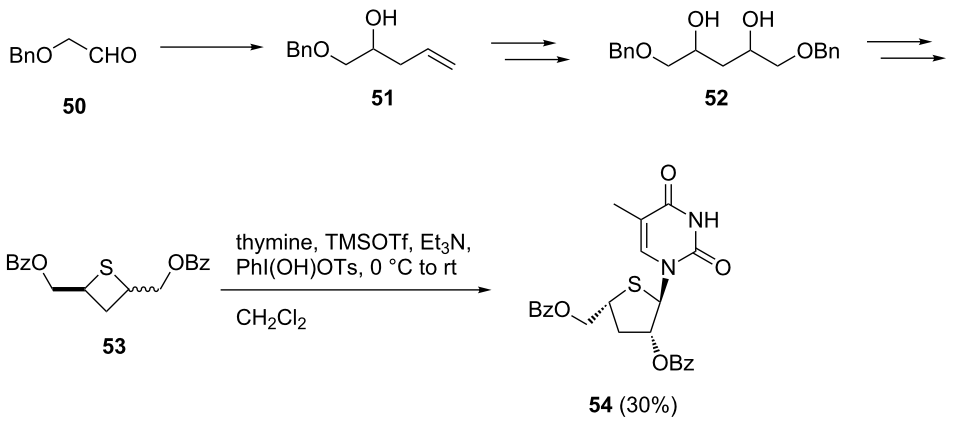
Figure 3: Speculated mechanism of oxidative glycosylation mediated by hypervalent iodine.

sition, as in the case mentioned above, to give **46** in 44% yield along with the desired product and its N7 isomer. In contrast, switching the protecting group of **27** at the 5-position to TBS resulted in the exclusive formation of **45** reacted at the 1-position (28%) along with the N7 stereoisomer (10%). These results support the above-mentioned hypothesis. Finally, 4'-thioadenosine (**49**) was synthesized by treating **45** with TFA followed by methanolic ammonia [46] (Scheme 5).

The same group attempted to apply the oxidative coupling reaction to the synthesis of thietane nucleosides [47]. The substrate of the coupling reaction was prepared as shown in Scheme 6 starting from benzyloxyacetaldehyde (**50**). When a hypervalent iodine reagent was used for glycosylation with a diastereomeric mixture of sulfide **53**, the reaction stereoselectively gave the ring-expanded nucleoside **54** in 30% yield, but did not give the desired thietane nucleoside at all (Scheme 6).



Scheme 5: Synthesis of purine 4'-thioribonucleosides using hypervalent iodine-mediated glycosylation.



Scheme 6: Unexpected glycosylation of a thietanose derivative.

Considered that the ring-expansion occurred in the absence of the hypervalent iodine reagent, the Nishizono and co-workers speculated that the reaction mechanism was as shown in Scheme 7. First, the Lewis acid catalyzed the intramolecular S_N2 reaction of sulfur to form the epi-sulfonium ion **55**, which proceeded only from the *cis*-isomer due to the steric requirement. The subsequent nucleophilic attack leaving the benzoate anion resulted in the formation of a ring-expanded product **56**, which became a substrate of the hypervalent iodine-mediated glycosylation. As a result, 4'-thiofurano nucleoside **54** was stereoselectively obtained with the assistance of the neighboring benzoyl group as in **58**.

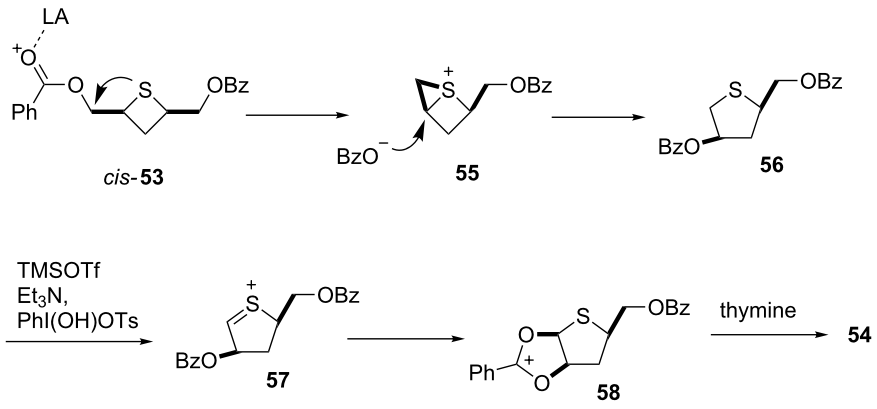
The desired thietanonucleosides **62** and **63** with an anomeric hydroxymethyl group were synthesized by the Pummerer-type glycosylation reaction of *trans*-cyclobutane sulfoxide **59**. The authors concluded that the stereochemistry of the sulfoxide and the nature of the protecting groups had no significant effect on the yield of the Pummerer-type glycosylation [47] (Scheme 8).

Pummerer-type glycosylation, which was developed by our group, improved the synthesis of 4'-thionucleosides. It greatly contributed to search new biological active nucleoside derivatives. The use of hypervalent iodine reagents helped to further improve their synthesis by saving reaction steps to improve synthetic efficiency.

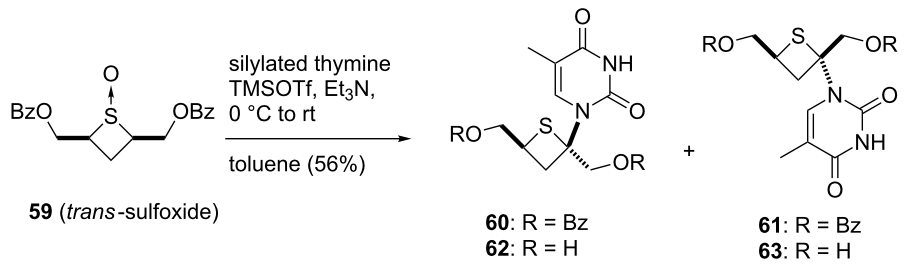
Synthesis of 4'-selenonucleosides

The unique biological activity of 4'-thionucleosides triggered the synthesis of their chalcogen isosters, 4'-selenonucleosides, the activity of which were reported. The first synthesis of 4'-selenonucleosides was reported by Jeong and co-workers in 2008 [48,49].

As in the case of the 4'-thioribonucleoside described in Scheme 3, Jeong et al. chose a 2,3-di-*O*-isopropylidene-protected intermediate as a donor of glycosylation, which was synthesized based on their method developed for 4'-thionucleosides. Starting from compound **64**, which was obtained from



Scheme 7: Speculated mechanism of the ring expansion of a thietanose derivative.

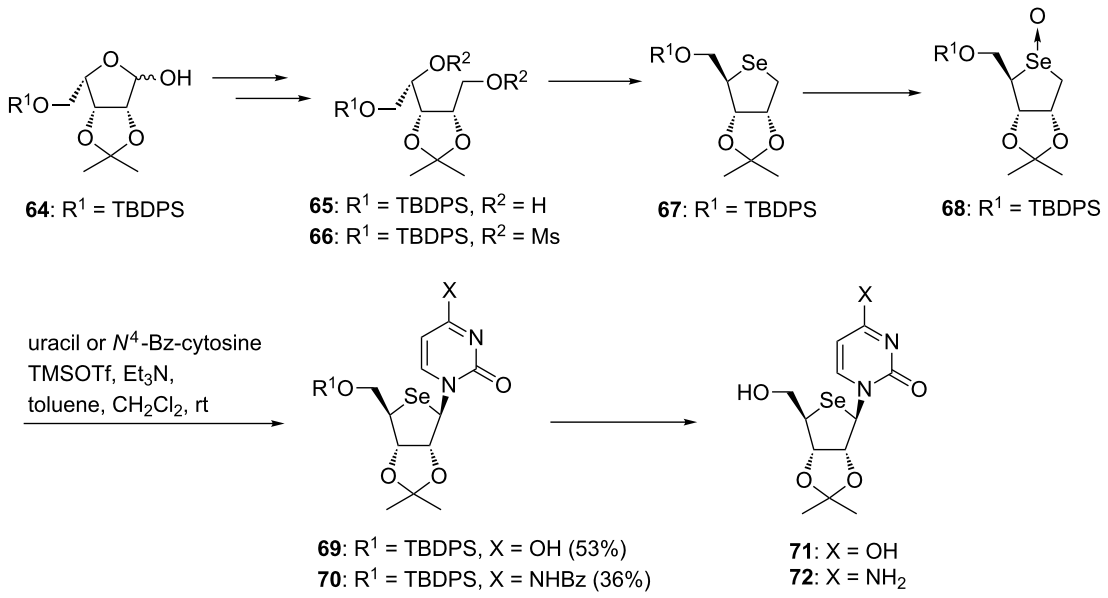


Scheme 8: Synthesis of thietanonucleosides using the Pummerer-type glycosylation.

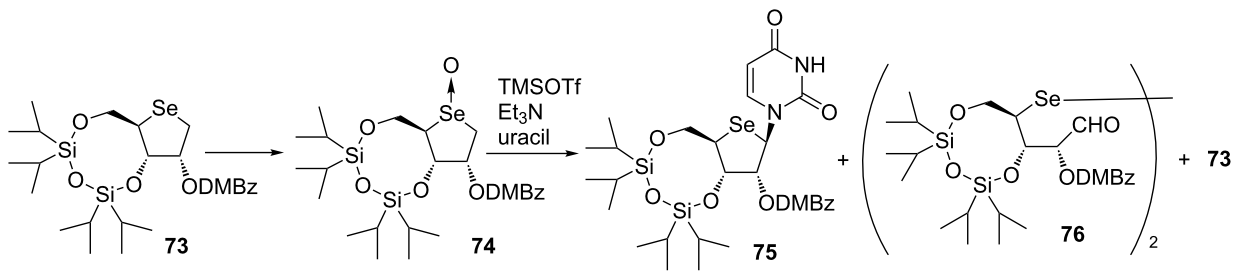
D-gulonic γ-lactone, dimesylate **66** was prepared. The consecutive inter-/intramolecular S_N2 reactions of **66** by selenide anion gave a 4-seleno sugar **67** in an excellent yield. After converting **67** to the corresponding selenoxide, the resulting **68** was immediately treated with uracil or N^4-benzoylcytosine under the same conditions for Pummerer-type glycosylation to give the desired 4'-selenouridine and 4'-selenocytidine derivatives in moderate yields. Deprotection of the nucleoside derivatives afforded 4'-selenouridine and 4'-selenocytidine, respectively [48] (Scheme 9). In the year in which the first synthesis of 4'-selenonucleoside was reported, Jayakanthan et al. used the same strategy to synthesize 4'-selenonucleosides, including 4'-selenoadenosine [50].

After successful application of the Pummerer-type glycosylation to the synthesis of 4'-selenonucleosides, Jeong's group reported various 4'-selenonucleoside derivatives by using the same method [51-58]. Minakawa and his group attempted to synthesize 4'-selenonucleosides based on their method described in Scheme 2 [59]. However, the Pummerer-type glycosylation of selenoxide **74** obtained from **73** gave the desired 4'-selenonucleoside in low yield along with the formation of diselenide **76** and deoxygenated **73** (Scheme 10). One of the reasons for the unsatisfactory result was the instability of selenoxide **74**. Jeong et al. faced the same problem and suppressed decomposition by the immediate reaction after synthesizing the corresponding selenoxide [48].

To overcome these problems, Minakawa decided to use hypervalent iodine for the glycosylation reaction [59] as in Nishizono's synthesis of 4'-thionucleosides [45]. First, they optimized the reaction conditions by examining the reaction of **73** with uracil in the presence of hypervalent iodine reagents. None of the desired pyrimidine nucleoside **75** was formed when the reaction was performed by treatment with iodosylbenzene, TMSOTf and triethylamine in the presence of the silylated uracil (Table 1, entry 1). Instead of trimethylamine, 2,6-lutidine was employed to give **75** in 48% yield together with selenoxide



Scheme 9: First synthesis of 4'-selenonucleosides.



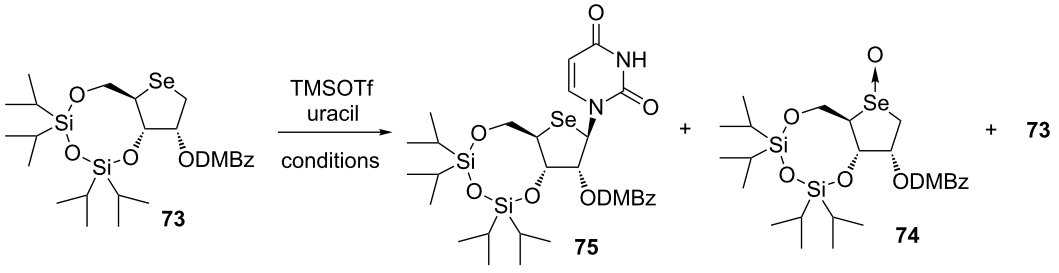
Scheme 10: The Pummerer-type glycosylation of 4-selenoxide **74**.

74 (20%) and starting **73** (8%) (Table 1, entry 2). The use of more reactive hypervalent iodine agents (PIFA and diacetoxyiodobenzene) did not improve the chemical yield of **75** (Table 1, entries 3 and 4). When **73** was treated with iodosylbenzene, TMSOTf, 2,6-lutidine and the silylated uracil in dichloroethane at 50 °C, the reaction gave **75** in 64% yield while suppressing the formation of **74** (Table 1, entry 5).

Minakawa's group attempted to apply the aforementioned reaction to the synthesis of purine derivatives [60]. Based on the reports by Jeong et al., who synthesized 4'-selenoadenosine using the Vorbrüggen reaction [53], they conceived that the hypervalent iodine-mediated reaction of "disarmed" sugar donor **73** bearing an electron-withdrawing group at the 2-position would not readily yield the desired purine derivative. Therefore, they decided to use "armed" seleno sugar **67** as a donor for the hypervalent iodine-mediated glycosylation reaction as in Jeong's synthesis.

The reaction of **67** was performed by treating with silylated 6-chloropurine, iodosylbenzene, TMSOTf and 2,6-lutidine in dichloroethane at 85 °C for 2.5 h to give the desired N9-isomer **78** in 39% yield along with the formation of the N7-isomer **77** (31%) and the α-isomer (8%, N7/N9 mixture). On the other hand, consumption of **67** required longer times and subsequent isomerization to **78** was insufficient at 50 °C, giving **78** in 31% yield with the predominant formation of **77** (40%). The separated N7 isomer **77** was successfully isomerized to the desired N9 isomer **78** in 53% yield upon treatment with TMSOTf in toluene at 90 °C. Under similar conditions, the hypervalent iodine-mediated glycosylation reaction of **67** in the presence of 2,6-dichloropurine was conducted. The coupling reaction proceeded to give an inseparable mixture of N7-isomer **80** and N9-isomer **81** in 64% yield (**80**:**81** = 1:1). To isomerize the undesired N7-isomer to the desired product as in the case of 2,6-dichloropurine, the subsequent treatment of the resulting mixture with TMSOTf in toluene at 90 °C gave rise to exclusive formation of

Table 1: The Pummerer-like glycosylation reaction mediated by hypervalent iodine.



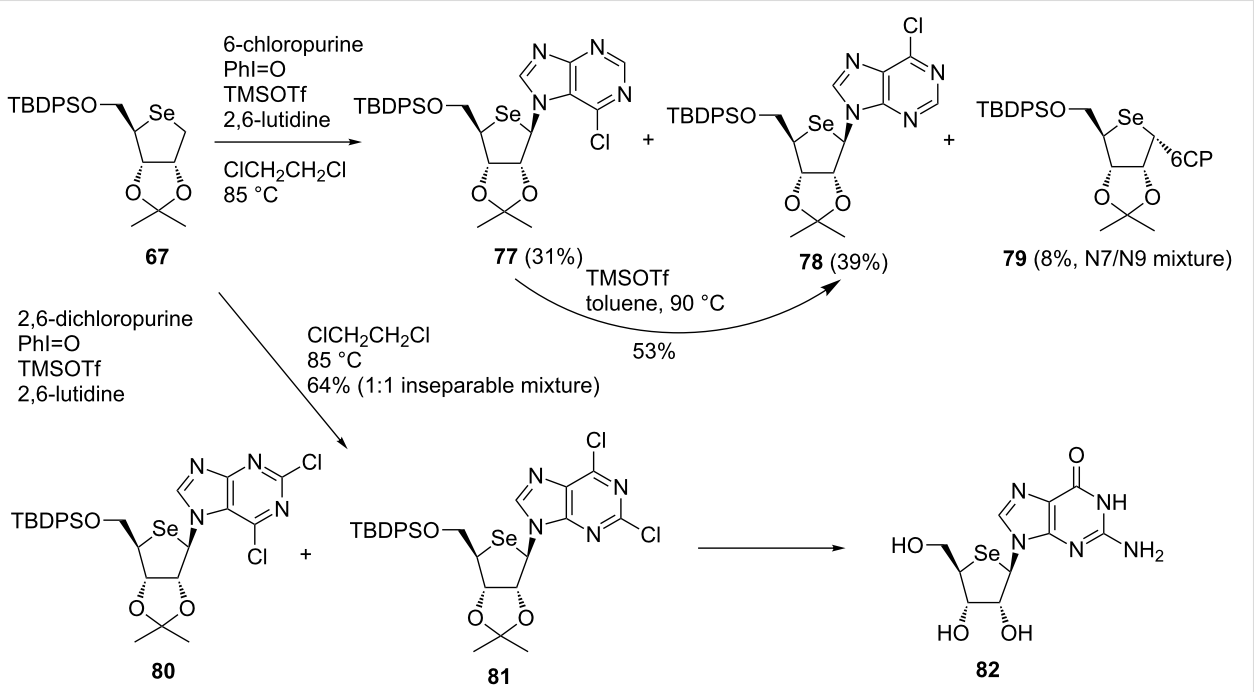
		Conditions				Yield (%)		
Entry	Hypervalent iodine (1.2 equiv)	Base (8 equiv)	Solvent	Temp (°C)	Time (h)	**75**	**74**	**73**
1	PhIO	Et_3N	CH_2Cl_2	0	4.5	0	0	33
2	PhIO	2,6-lutidine	CH_2Cl_2	rt	17	48	20	8
3	$PhI(OCOCF_3)_2$	2,6-lutidine	CH_2Cl_2	rt	3	38	0	40
4	$PhI(OAc)_2$	2,6-lutidine	CH_2Cl_2	rt	5	25	0	20
5	PhIO	2,6-lutidine	$ClCH_2CH_2Cl$	50	1.5	64	0	13

the desired N9-isomer **81** in 62% yield. Finally, **81** was converted to the desired guanosine derivative **82** [60] (Scheme 11).

As in the case of 4'-thionucleosides, the use of hypervalent iodine greatly improved the glycosylation reaction with 4-seleosugars by skipping the preparation of unstable selenoxide derivatives.

Synthesis of carbocyclic nucleosides

As described above, in the hypervalent iodine-mediated glycosylation, a thiosugar donor **83** was oxidized to a cationic intermediate **84** with the assistance of a Lewis acid (TMSOTf) and a base and the subsequent nucleophilic attack of silylated base to **84** gave the desired nucleoside **85**. The success of the hypervalent iodine-mediated glycosylation led us to apply the reaction to the synthesis of carbocyclic nucleosides. In addition, we were also encouraged by the study of Ochiai, who developed the Friedel–Crafts reaction via umpolung of allylsilanes using hypervalent-iodine reagents [61] and the pioneering work on C–N bond formation using hypervalent iodine by Kita [62]. Thus, we envisioned the use of allylsilanes as a pseudosugar donor for the synthesis of carbocyclic nucleosides. We expected to couple a cyclic allylsilane **86**, which could act as a pseudosugar donor for carbocyclic nucleosides **88**, with a persilylated nucleobase by using a combination of hypervalent iodine and an appropriate Lewis acid (Figure 4).



Scheme 11: Synthesis of purine 4'-selenonucleosides using hypervalent iodine-mediated glycosylation.

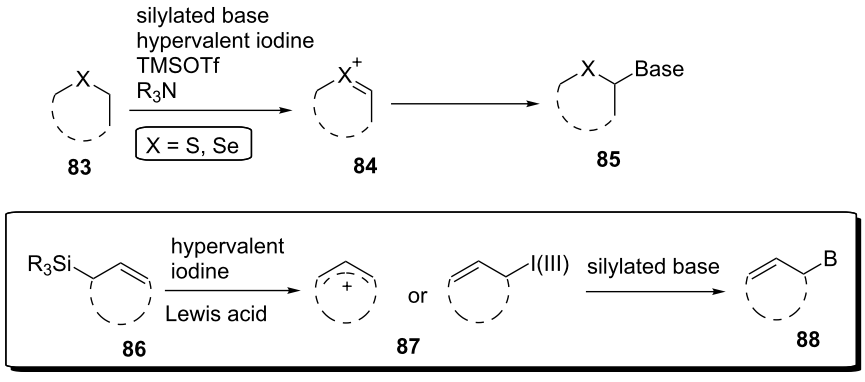
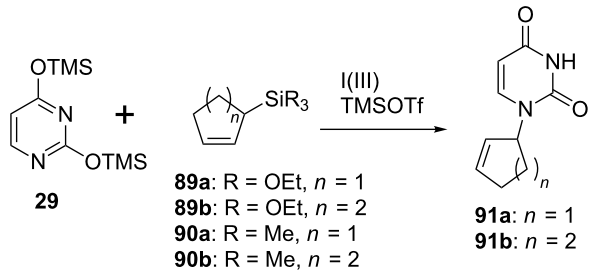


Figure 4: Concept of the oxidative coupling reaction applicable to the synthesis of carbocyclic nucleosides.

As shown in Scheme 12, an oxidative coupling reaction was examined using a model reaction [63]. Cycloalkenylsilanes **89a**,**b** and **90a**,**b** were prepared by hydrosilylation of cyclopentadiene and cyclohexadiene. Using TMSOTf as a Lewis acid, the hypervalent iodine-mediated coupling reaction of **89a**,**b** and **90a**,**b** with silylated uracil **29** was examined and the results are summarized in Table 2. Our first attempt to couple triethoxysilanes **89a**,**b** with **29** in the presence of diacetoxyiodobenzene gave cycloalkenyluracil **91a** and **91b** in 45% and 49% yields respectively (Table 2, entries 1 and 2). On the other hand, the use of trialkylsilanes **90a** and **90b** successfully improved the chemical yield of **91a** and **91b** (Table 2, entries 3 and 4). In contrast, the reactions using PIFA, iodosylbenzene, and [hydroxyl(tosyloxy)iodo]benzene (PhI(OH)OTs) resulted in a decrease of the reaction yield (Table 2, entries 5–7).



Scheme 12: Oxidative coupling reaction mediated by hypervalent iodine.

Table 2: Summary of the oxidative coupling reaction using hypervalent iodine.

entry	comp	I(III)	Time (h)	yield (%)
1	**89a**	$PhI(OAc)_2$	15	**91a**: 45
2	**89b**	$PhI(OAc)_2$	15	**91b**: 49
3	**90a**	$PhI(OAc)_2$	1	**91a**: 65
4	**90b**	$PhI(OAc)_2$	1	**91b**: 65
5	**90b**	$PhI(O_2CCF_3)_2$	1	**91b**: 55
6	**90b**	PhIO	1	**91b**: 57
7	**90b**	PhI(OH)OTs	1	**91b**: 29

To prove the usefulness of the oxidative coupling reaction mediated by hypervalent iodine, the reaction was applied to the synthesis of a carbocyclic nucleoside derivative designed as a potential anti-HIV agent.

As a target, cyclohexenylcytosine **99** was designed and was planned to synthesize using the oxidative coupling reaction. To prepare the substrate of the coupling reaction, cyclohexenylsilane **96** was synthesized using the Diels–Alder reaction of trimethylsilylbutadiene **92** and dimethyl fumarate (**93**), which gave cyclohexene diester **94** (1:1 mixture of diastereomers) [64]. Reduction and subsequent separation by silica gel column chromatography gave diols **95a** and **95b**, the hydroxy groups of which were protected to give di-TBDPS derivatives **96a** and **96b**. The resulting cyclohexenylsilanes **96a** and **96b** were subjected to the oxidative coupling reaction with 2,4-bis(trimethylsilyl)uracil (**29**) using diacetoxyiodobenzene, respectively, and the results are shown in Table 3. The reaction of **96a** gave an inseparable mixture containing 4 stereoisomers of **97a–d** with a ratio of 6:10:2:1.5, which was determined based on the analysis of its ^{1}H NMR spectrum. The reaction of **96b** also gave a similar result. In both reactions, the formation of cyclohexadiene **98** was observed. These results strongly supported that the reaction proceeded through the carbocation intermediate, as expected and depicted in Figure 4, since **98** was considered to be formed by E1 elimination of the allyl cation intermediate. The fact that **96a** and **96b** showed different reactivities could be explained by the steric interaction between the substituents on the cyclohexene ring and the nucleobase approaching. Compounds **97a–d** were converted to the corresponding cytosine analogues [63]. During the course of conversion, all the stereoisomers were separated. Among them, only the cytosine derivative **99** showed weak anti-HIV activity (Scheme 13 and Table 3).

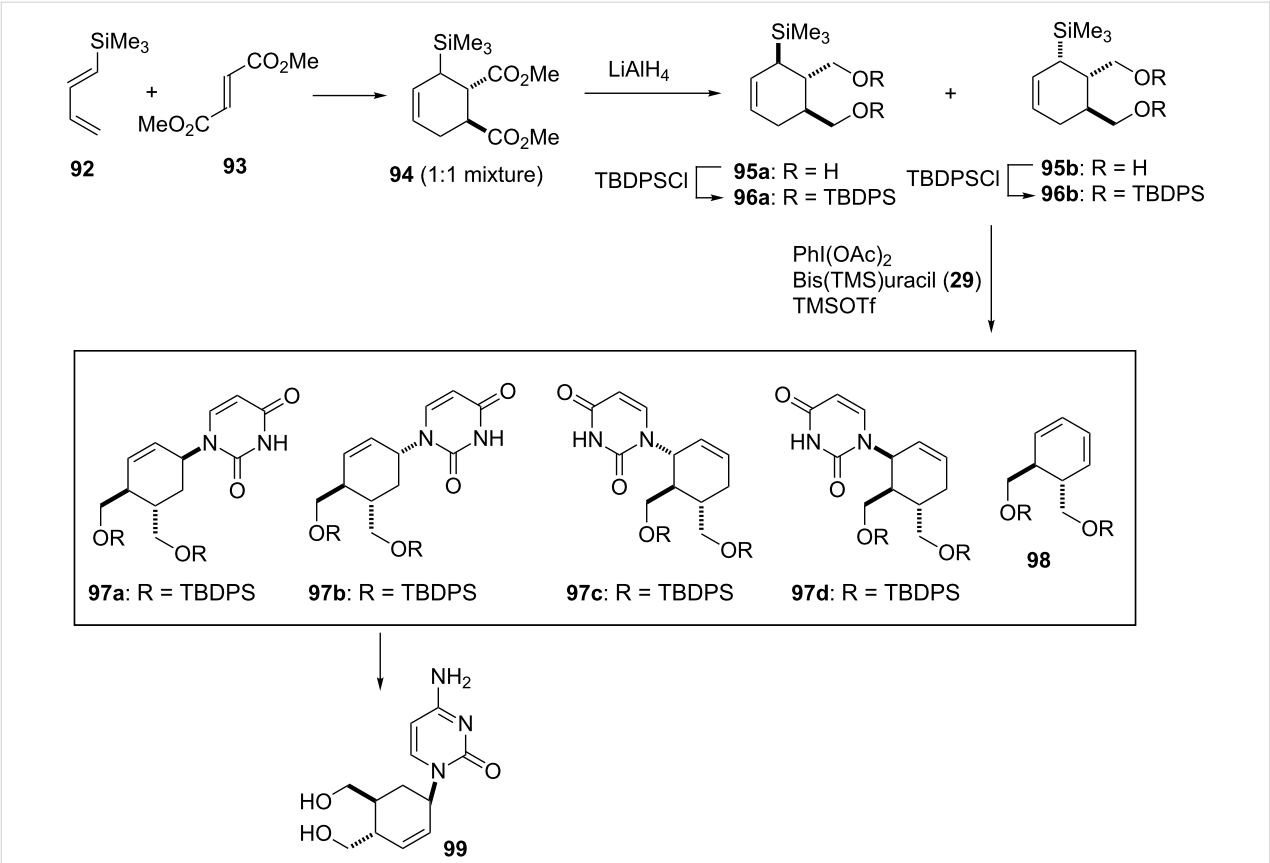
Table 3: Summary of the oxidative coupling reactions of **96a** and **96b**.

comp	time	yield (%)			ratio
		97a–d	**98**	recov.	**97a**:**97b**:**97c**:**97d**
96a	1 h	60	18	0	6:10:2.0:1.5
96b	24 h	50	11	20	3:10:2.5:0.5

An oxidative coupling reaction for synthesizing carbocyclic nucleosides mediated by hypervalent iodine was developed. Since the Friedel–Crafts type reaction involved carbocation intermediate, the reaction always gave a mixture of products. Unfortunately, the reaction was not efficient. However, it is worthy that the oxidative coupling reaction contains a novel type of C–N bond formation and would help to synthesize new carbocyclic nucleosides.

Synthesis of dihydropyranonucleosides

The success of the oxidative coupling reaction for constructing a carbocyclic nucleoside skeleton led us to develop a glycosylation reaction applicable to glycal derivatives. Since an electron-rich enol ether unit of glycal could react with oxidative agents, it was expected to form a cationic intermediate as in the case of allylsilanes described above. A direct coupling of glycals with nucleobases is challenging, since it is formally a C–N bond-



Scheme 13: Synthesis of cyclohexenyl nucleosides using an oxidative coupling reaction.

forming reaction with cleaving of the inactive C–H bond at the γ-position. Actually, the C–N bond-forming reactions using hypervalent iodine agents have attracted much attention [62,65-68]. In the case of the hypervalent iodine-catalyzed coupling reaction with allylsilanes (Figure 5), the reaction involves the following 2 steps: 1) the generation of allyl cation **87** by the oxidation of an allylsilane **86** with $PhI(OAc)_2$ and TMSOTf, and 2) the subsequent nucleophilic attack of the persilylated base to **87** as shown in Figure 5. Therefore, we expected that subjecting

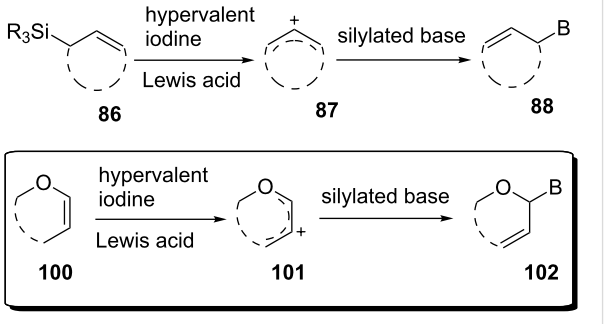
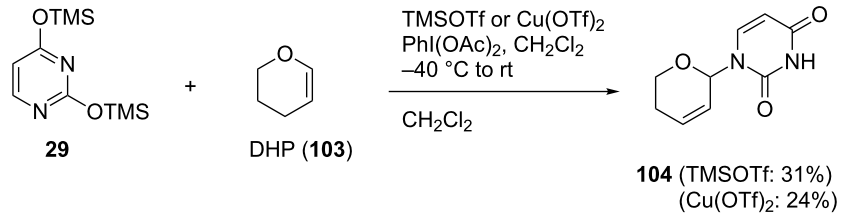


Figure 5: Concept of the oxidative coupling reaction of glycal derivatives.

the electron-rich glycal **100** to the hypervalent iodine-mediated reaction described above would generate an oxocarbenium ion **101** to serve as an intermediate, giving a nucleoside **102**.

First, we attempted model reactions of the oxidative coupling to enol ether using a TMSOTf/$PhI(OAc)_2$ system. After several attempts, we found that the reaction of 3,4-dihydro-2*H*-pyran (DHP, **103**) with $PhI(OAc)_2$ and TMSOTf, starting at −40 °C and then gradually raised to room temperature, gave a dihydropyranyluracil derivative **104** in 31% yield [69]. We also found that when $Cu(OTf)_2$ was used as a catalyst in place of TMSOTf, the reaction gave **104** in 24% yield (Scheme 14).

We speculated that the mechanism of the oxidative coupling reaction was as shown in Scheme 15. DHP (**103**) was reacted with $PhI(OAc)_2$ to produce an acetoxyiodobenzene derivative **105** with the assistance of TMSOTf. With respect to the pathway from the intermediate **105** to the N1-substituted uracil **104**, there were two plausible routes. In path a, a nucleophilic attack of 2,4-bis(trimethylsilyl)uracil (**29**) occurs prior to an elimination. In path b, on the other hand, an allylic carbocation **110** formed from **108** reacts with **29**. From the result that the reaction of 2,3-dihydrofuran gave side products generated from an

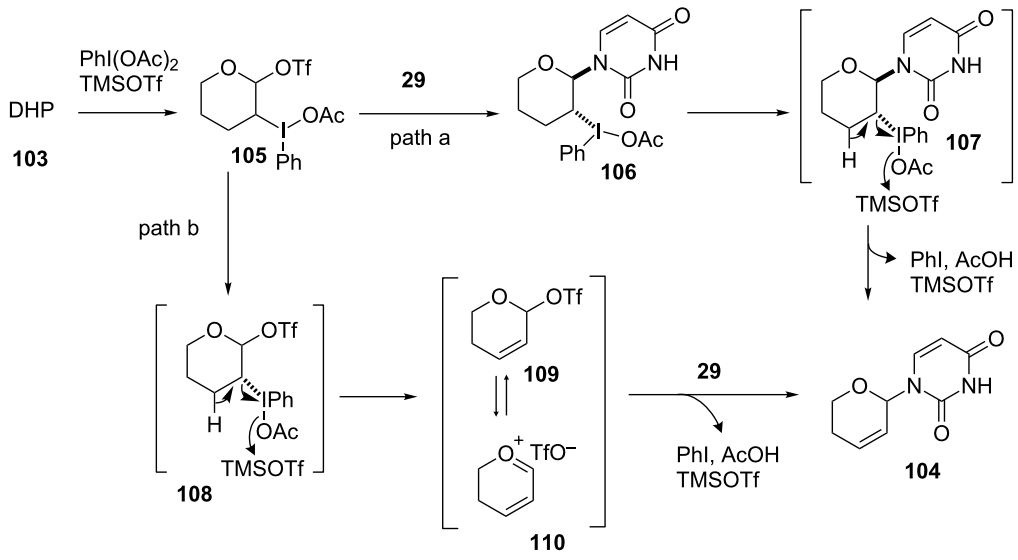


Scheme 14: Oxidative coupling reaction of silylated uracil and DHP using hypervalent iodine.

intermediate resembling **107** (data not shown), it was strongly suggested that the oxidative coupling reaction preferred path a rather than path b (Scheme 15).

Because further optimization of the oxidative coupling reaction was not successful, we decided to examine the effect of adding a co-catalyst. The speculated reaction mechanism depicted in Scheme 15 suggested that the instability of the intermediates **105** and **106** might have caused the low yield of the oxidative coupling. Based on this idea, we intended to use $(PhSe)_2$ as a co-catalyst, since it might prevent the formation of unstable **105** and **106** and yield **102** in one step (Figure 6).

We examined the effect of $(PhSe)_2$ as an additive by the reaction of various glycals and their chemical equivalents [69] and the results are summarized in Table 4. The reaction of **103** and **29** was performed by treatment with $PhI(OAc)_2$ and $(PhSe)_2$ in the presence of catalytic amounts of TMSOTf to selectively yield a *trans*-isomer of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil (**116**) in 73% yield (Table 4, entry 1). Although this result was unexpected, it was important, since the reaction appeared to be applicable to access various nucleoside derivatives, including 2'-deoxynucleosides. More importantly, we could avoid the use of unstable reagents such as PhSeBr. In other words, the reaction using hypervalent iodine and stable



Scheme 15: Proposed mechanism of the oxidative coupling reaction mediated by hypervalent iodine.

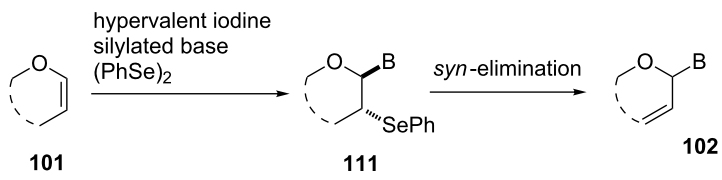
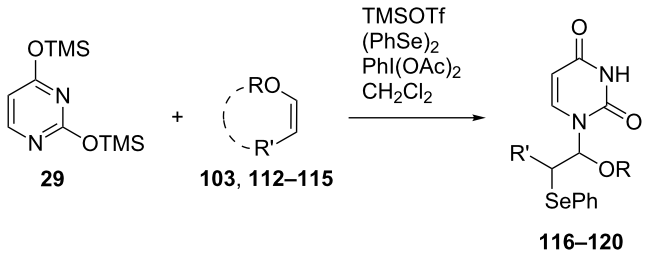


Figure 6: Synthesis of 2',3'-unsaturated nucleosides using hypervalent iodine and a co-catalyst.

$(PhSe)_2$ in the presence of a Lewis acid would be expected to yield the same products as the reaction using PhSeBr. The reaction with dihydrofuran (**112**) furnished 1-(3-phenylselanyltetrahydrofuran-2-yl)uracil (**117**) in 31% yield (Table 4, entry 2). The reaction of **113** with **29** at −5 °C afforded **118** in 69% yield (Table 4, entry 3). The reaction of **114** gave an anomeric mixture of **119** in 80% yield with the predominant formation of the β-nucleoside (Table 4, entry 4). In contrast, the oxidative glycosylation reaction of D-glucal **115** gave a 1:1 mixture of α-**120** and β-**120** in 64% yield (Table 4, entry 5). From these data, the oxidative coupling reaction mediated by hypervalent iodine of glycal derivatives can clearly be regarded as a new glycosylation reaction that is applicable to the synthesis of 2'-deoxy- and 2',3'-dideoxydidehydronucleosides, some of which are known to have anti-HIV activity (Table 4).

To reveal the scope of this reaction, we designed a new dihydropyranonucleoside as a potential anti-HIV agent and attempted to synthesize it by using the oxidative coupling reaction [70]. First, the PMB-protected epoxide **121** was converted to diene **122**. The dihydropyran ring of **123** was constructed by RCM of **122** catalyzed by a Grubbs 1st generation catalyst. The

Table 4: Summary of the oxidative coupling reaction of bis(trimethylsilyl)uracil **29** with enol ethers using the TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system.



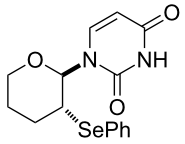
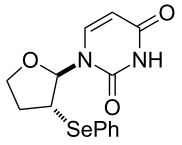
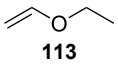
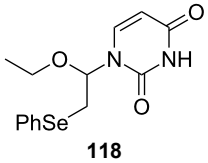
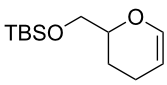
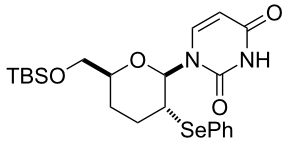
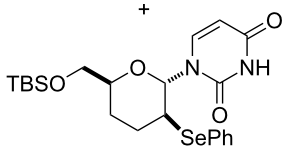
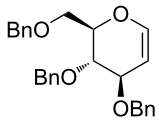
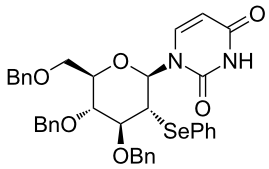
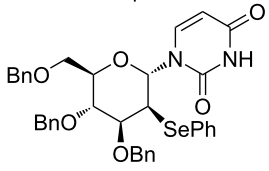
entry	enol ether	product	yield (%)
1	 **103**	 **116**	73
2	 **112**	 **117**	31
3	 **113**	 **118**	69
4	 **114**	 β-**119** +  α-**119**	80 (α:β=1:2)

Table 4: Summary of the oxidative coupling reaction of bis(trimethylsilyl)uracil **29** with enol ethers using the TMSOTf/PhI(OAc)$_2$/(PhSe)$_2$ system. (continued)

5	 **115**	 β-**120** +  α-**120**		64 (α:β=1:1)

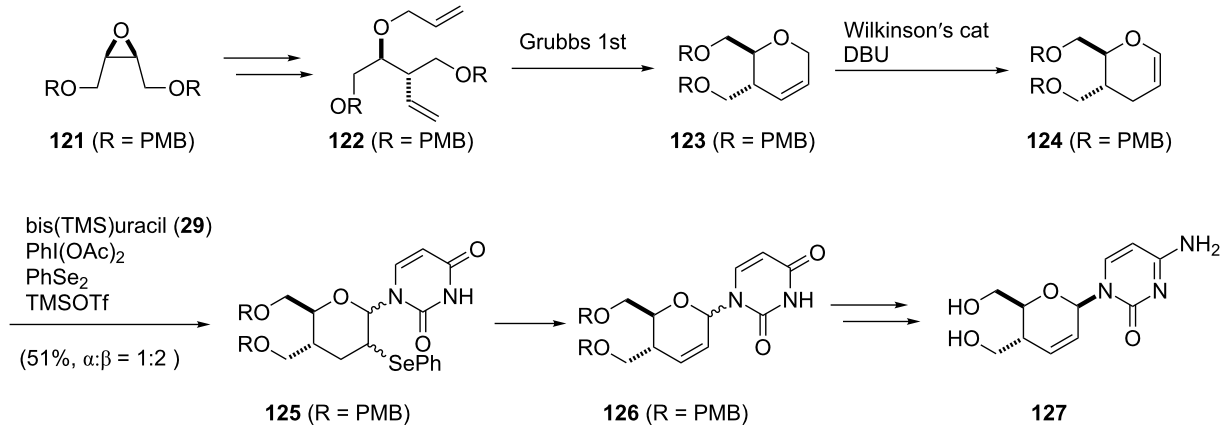
isomerization of the double bond in **123** by treatment with a Wilkinson catalyst under basic conditions afforded glycal **124** (Scheme 16).

The hypervalent iodine-mediated glycosylation of 2,4-bis(trimethylsilyl)uracil (**29**) with glycal **124** gave an inseparable mixture of α- and β-anomers **125** (α:β = 1:2) in 51% yield as we expected. Compound **125** was then oxidized by treatment with mCPBA, followed by elimination of the resulting selenoxide to give **126**. After the separation of anomers, the major β-anomer was converted into a cytosine derivative **127** [70]. However, **127** did not show any activity against HIV whereas its 5'-thio counterpart did show anti-HIV activity (Scheme 16).

The reaction mediated by hypervalent iodine provides an alternative method for constructing glycosidic bonds of nucleoside derivatives by using a glycal as sugar donor. Its usefulness was proved by applying the reaction to synthesize new nucleoside derivatives as mentioned above.

Synthesis of acyclic nucleosides

It is known that the oxidative C–C bond cleavage of glycols, epoxides, and olefins takes place by the action of hypervalent iodine [38,71,72]. For example, Havare and Plattner reported the oxidative cleavage of α-aryl aldehydes using iodosylbenzene to give chain-shortened carbonyl compounds and formaldehyde [71]. In the field of carbohydrate chemistry, similar deformylation by action of hypervalent iodine has also been demonstrated: the β-fragmentation reaction of an anomeric alkoxy radical of carbohydrates was mediated by a hypervalent iodine reagent [73]. The reaction results in the formation of carbohydrates with a reduction of one carbon. From the viewpoint of the synthetic method, the reaction would be useful for dehomologation of aldoses and preparation of chiral synthons



Scheme 16: Synthesis of dihydropyranonucleoside.

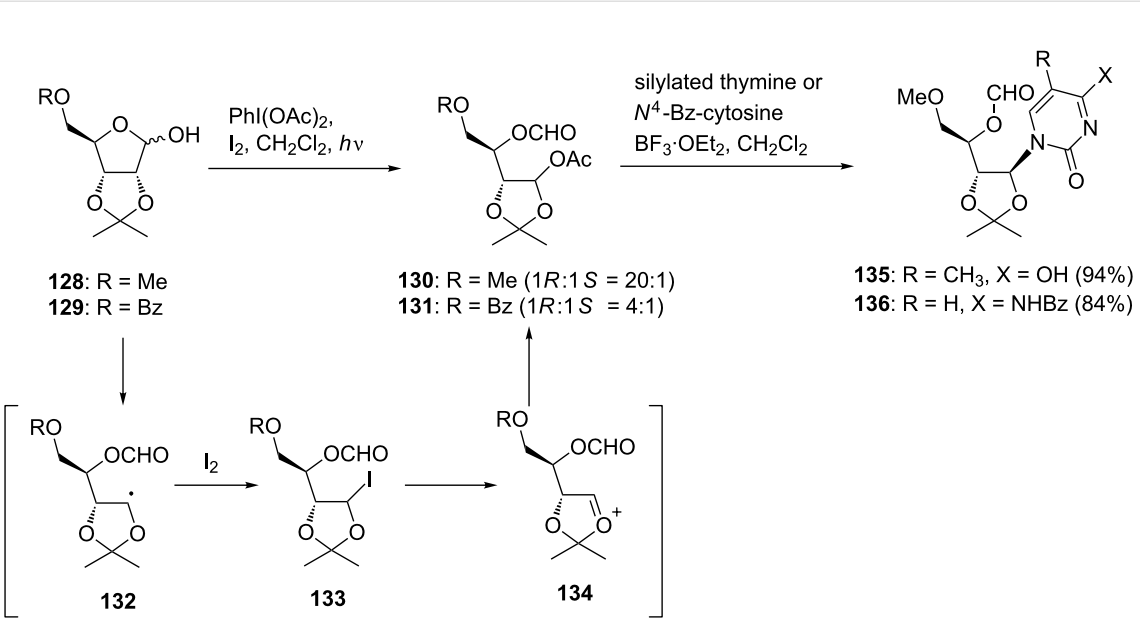
deriving from sugars. The reaction procedure involves the initial formation of an alkoxy anomeric radical by a hypervalent iodine reagent in the presence of iodine, which triggers the β-fragmentation of the C1–C2 bond. As a result, a C2 radical is generated and is further oxidized to a carbocation that is reacted with nucleophilic agents to give the desired products.

Boto et al. applied the reaction to the one-pot synthesis of acyclic nucleosides that belong to an important class of nucleosides with antiviral activity [74]. First, they tried to synthesize acyclic nucleosides in a stepwise manner. The substrates **128** and **129** for the fragmentation reaction were synthesized from ribose in a few steps by the conventional method. The oxidative scission of **128** and **129** was carried out by treatment with diacetoxyiodobenzene and iodine under irradiation with visible light to give acetoxy acetals **130** and **131** in good yields with high stereoselectivities. As shown in Scheme 17, the reaction was expected to proceed via the formation of anomeric alkoxyl radicals, which underwent fragmentation to produce radical **132**. The radical **132** could be trapped with iodine, giving iodide **133**. The oxycarbenium ion **134** generated by the extrusion of iodide from **133** reacted with the acetoxy ion to furnish the resulting acetate derivatives. The acetates **130** and **131** were then treated with silylated thymine or N^4-benzoylcytosine in the presence of a Lewis acid to give the desired acyclic nucleosides **135** and **136** in excellent yields. The results revealed that the nucleophilic attack of the nucleobase selectively occurred from the less hindered side of the oxycarbenium ion intermediates, giving 1',2'-*trans* isomers as major products (Scheme 17).

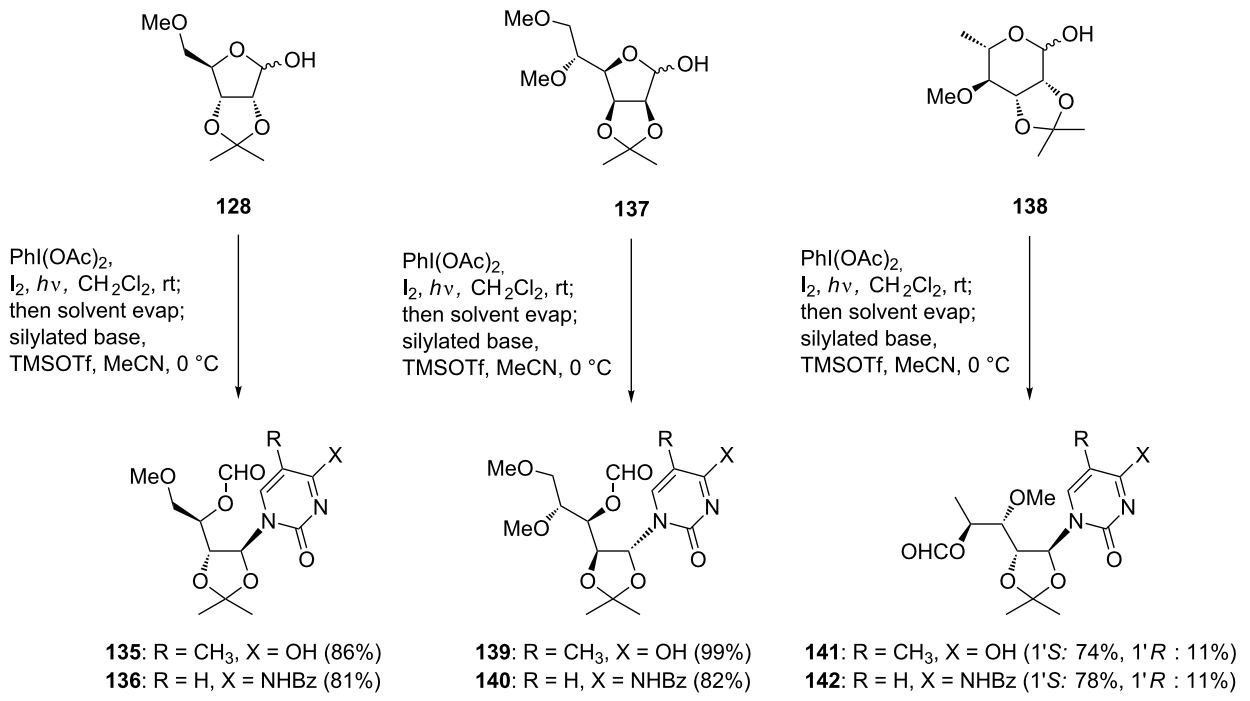
Based on the conditions for the stepwise fragmentation and glycosylation procedure, Boto et al. explored the one-pot version of the reaction [74]. When the β-fragmentation, the first step of oxidative glycosylation, was carried out in CH_2Cl_2 and then the Lewis acid and the silylated base were added, the acyclic nucleosides were obtained in low yields. Boto and co-workers overcame this problem by replacing the solvent before glycosylation. After the fragmentation reaction was finished, the solvent (CH_2Cl_2) was removed and replaced with acetonitrile. The resulting mixture was treated with TMSOTf and the silylated base. Under the optimized conditions, the reactions of ribose derivative **128**, mannose derivative **137**, and rhamnose derivative **138** gave the desired acyclic nucleosides in excellent yields as shown in Scheme 18. It is worth noting that the overall yields for the one-pot process are comparable or superior to those obtained with the two-step procedure (Scheme 18).

Synthesis of disaccharides

Classically, carbohydrates have been considered primarily an energy source for life – as in the cases of glucose, fructose and their oligosaccharides, e.g., starch. However, more recently it has been revealed that oligosaccharides and glycoconjugates also play important roles in various biological processes, as mentioned earlier. As a result, the increasing significance of oligosaccharides in biological events has led to a strong demand for synthetic routes towards oligosaccharides, which would also contribute to the identification and development of drug candidates. For example, cancer immunotherapy based on vaccines



Scheme 17: Synthesis of acetoxyacetals using hypervalent iodine and addition of silylated base.



Scheme 18: One-pot fragmentation-nucleophilic additions mediated by hypervalent iodine.

derived from carbohydrate antigen–adjuvant combinations has received much attention in recent years [75-77]. However, the difficulties associated with the isolation of tumor-associated carbohydrate antigens from natural sources have impeded extensive research. Thus, the most promising approach to the supply of these antigens is to develop a suitable method for their chemical synthesis.

To date, various glycosylation reactions capable of constructing oligosaccharides with high stereoselectivities have been reported [18,19]. Thioglycosides are often used as a sugar donor in these reactions due to their stability under various conditions and specific activation with thiophilic agents. For example, one of the typical conditions used for the construction of oligosaccharides is the combination of Lewis acids and iodine or its chemical equivalents. Fukase and co-workers reported a glycosylation reaction with thioglycoside using hypervalent iodine reagents in the 1990s [78,79]. The outline and postulated mechanism of the reaction are shown in Figure 7. The reaction of iodosylbenzene and electrophiles, e.g., triflic anhydride or Lewis acids, should generate a potent thiophile **143** that reacts with thioglycoside **144** to form an oxocarbenium ion **145**. The resulting oxocarbenium ion **145** should in turn react with a sugar acceptor to give the glycosylated product **147** (Figure 7).

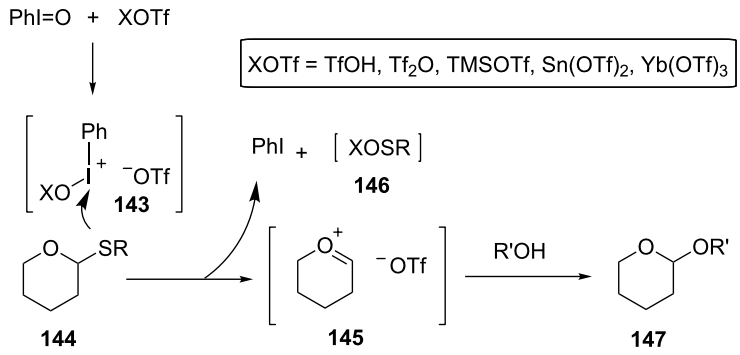


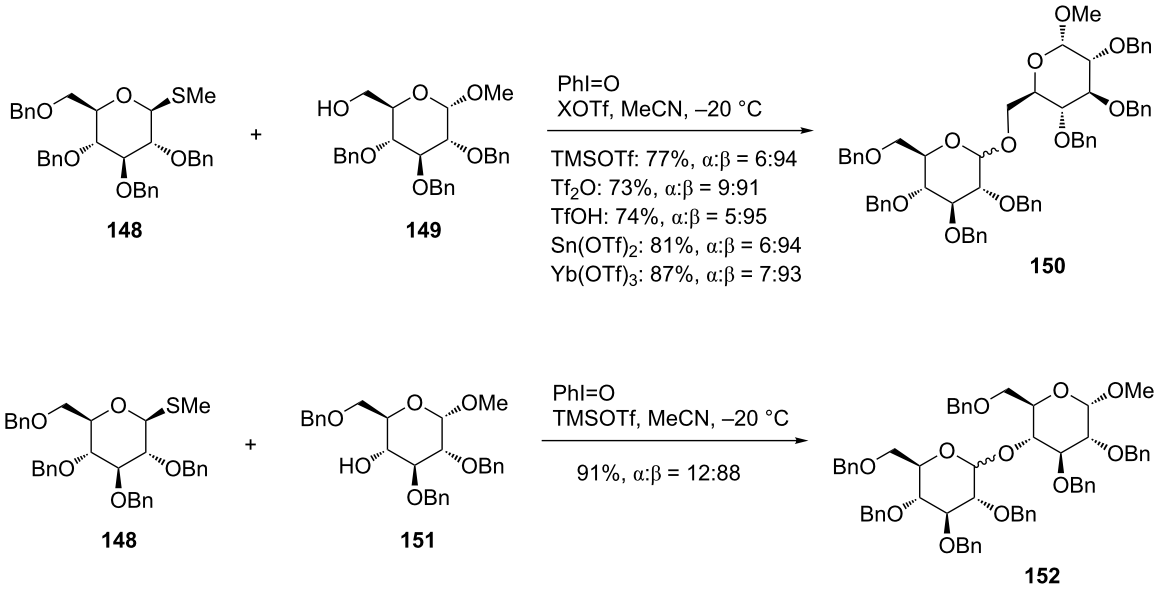
Figure 7: The reaction of thioglycoside with hypervalent iodine in the presence of Lewis acids.

By this reaction, Fukase et al. reported the glycosylation of methyl thioglycoside **148** as a sugar donor to give disaccharides **150** and **152** in high chemical yields as depicted in Scheme 19. As mentioned above, not only triflic anhydride, but various Lewis acids (TMSOTf, $Sn(OTf)_2$, $Yb(OTf)_3$) and a Brønsted acid (TfOH) were proven useful as activators, by which the reaction finished in a short time and gave the products with high stereoselectivity [79].

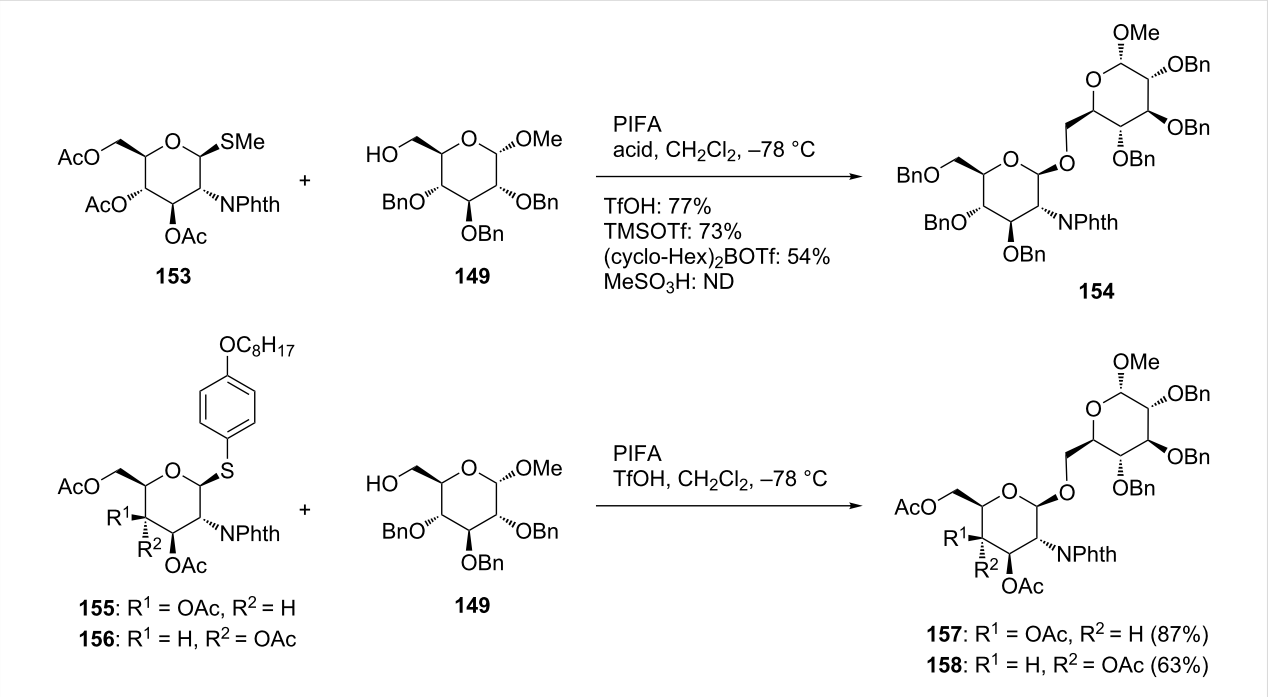
Recently, the reaction was revisited by Kajimoto et al., who sought a glycosylation reaction that could be applied to disarmed thioglycosides using hypervalent iodine reagents [80,81]. One of the reactions they examined was the glycosylation reaction of methyl 2-phthalimidothioglucopyranoside **153** with methyl tribenzylglucopyranoside **149** by PIFA in the presence of various acid catalysts. The results showed that the reaction with PIFA and TfOH afforded the best result, giving disaccharide **154** in 77% yield. On the other hand, the use of bis[cyclohexyl]trifluoromethanesulfonylborane [$(cyclo\text{-}Hex)_2BOTf$] and methanesulfonic acid resulted in a poor yield. The synthesis of disaccharides under the optimized conditions was performed using "odorless" thioglycoside **155** and **149** as the donor and the acceptor [81]. Even with the combination of "disarmed" **155** and "armed" **149**, the reaction gave rise to the desired disaccharide **157** in 87% yield. The same reaction of the corresponding 3-epimer **156** proceeded smoothly to give the disaccharide **158** in good yield (Scheme 20).

Randolph and Danishefsky reported a glycal assembly strategy to the synthesis of a branched oligosaccharide [82]. Bennett and co-workers reported that phenyl(trifluoroethyl)iodonium triflimide was a stable promoter for glycosylation reactions using thioglycoside donors [83]. Since the reactions often were unselective in the absence of C2 acetate-directing groups, Bennett et al. investigated the compatibility of the above-mentioned reaction in nitrile solvents documented to have a β-directing effect, with the aim of developing a glycosylation that can be selectively achieved in the absence of directing groups. After preliminary screens, they found that the reaction in the presence of phenyl(trifluoroethyl)iodonium triflimide **160** and the non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) at 0 °C with the solvent combination of 2:1 CH_2Cl_2/pivalonitrile provided the optimal reaction outcome. However, they also encountered a problem: the reduced solubility of substrate in the solvent system resulted in lower yields. They therefore examined mixed nitrile solvents again, and eventually found that a quaternary solvent mixture composed of 6:1:1:1 CH_2Cl_2/acetonitrile/isobutyronitrile/pivalonitrile greatly improved both the chemical yields and stereoselectivity, as shown in Scheme 21. The results suggested that both the solvent system and iodonium salt promoter are required for selectivity.

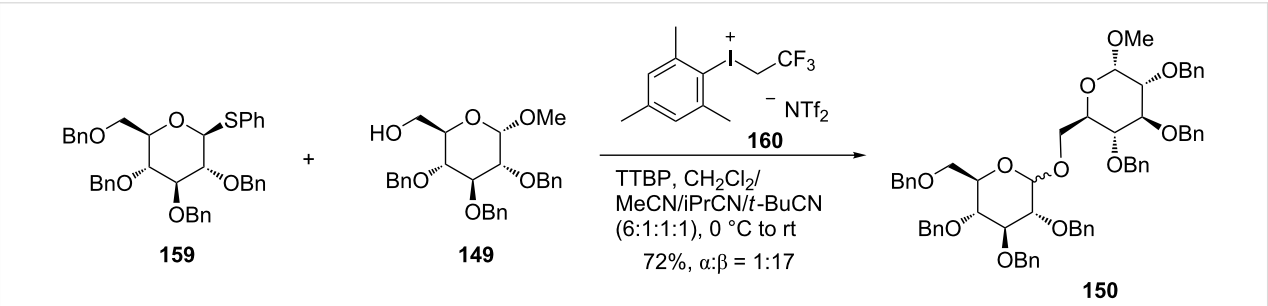
Even though glycals have a π-electron-rich enol ether unit, reports regarding transformations involving glycal oxidation as well as installation of heteroatom substituents at the C2 position were limited. In 2001, Gin's group reported the C2-acycloxyglycosylation procedure based on hypervalent iodine chemistry [84]. In this reaction, the use of a combination of hypervalent iodine and Lewis acid was key, as in the reactions described above. In this procedure, a solution of the glycal



Scheme 19: Synthesis of disaccharides employing thioglycosides under an oxidative coupling reaction mediated by hypervalent iodine.



Scheme 20: Synthesis of disaccharides using disarmed thioglycosides by hypervalent iodine-mediated glycosylation.



Scheme 21: Glycosylation using aryl(trifluoroethyl)iodium triflimide.

donor and a (diacyloxyiodo)benzene reagent was first treated with $BF_3{\cdot}OEt_2$. Then, the glycosyl acceptor (R"OH) and a catalytic amount of TfOH were added to the mixture, giving the 1,2-*trans* disubstituted C2-acyloxylglycoside. A plausible mechanism of the reaction is shown in Figure 8. The first step of the reaction between glycal **161** and (diacyloxyiodo)benzene formed the glycosyl ester intermediate **162** bearing a phenyl iodonium(III) functionality at C2, which was transformed to a diacyloxylated product **163**. As evidence in support of this mechanism, they reported that **163** was indeed isolated when the reaction was finished at the first step. In the second step, the resulting diacyloxylated product **163** could effectively glycosylate the appropriate acceptor by the action of TfOH to give the C2-acyloxyglycoside **164** with good selectivity at the anomeric position as a consequence of participation by the neighboring C2 acyloxy group (Figure 8).

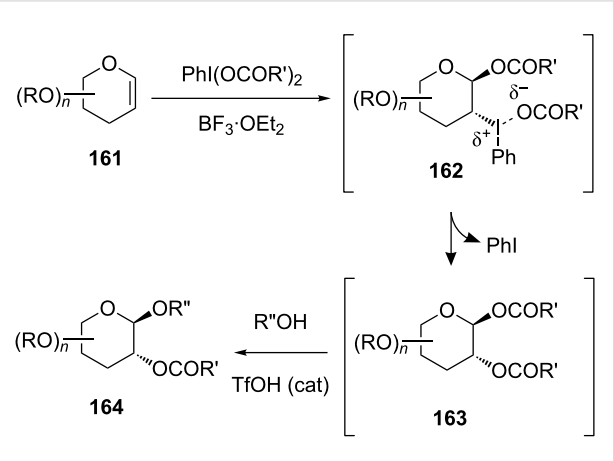
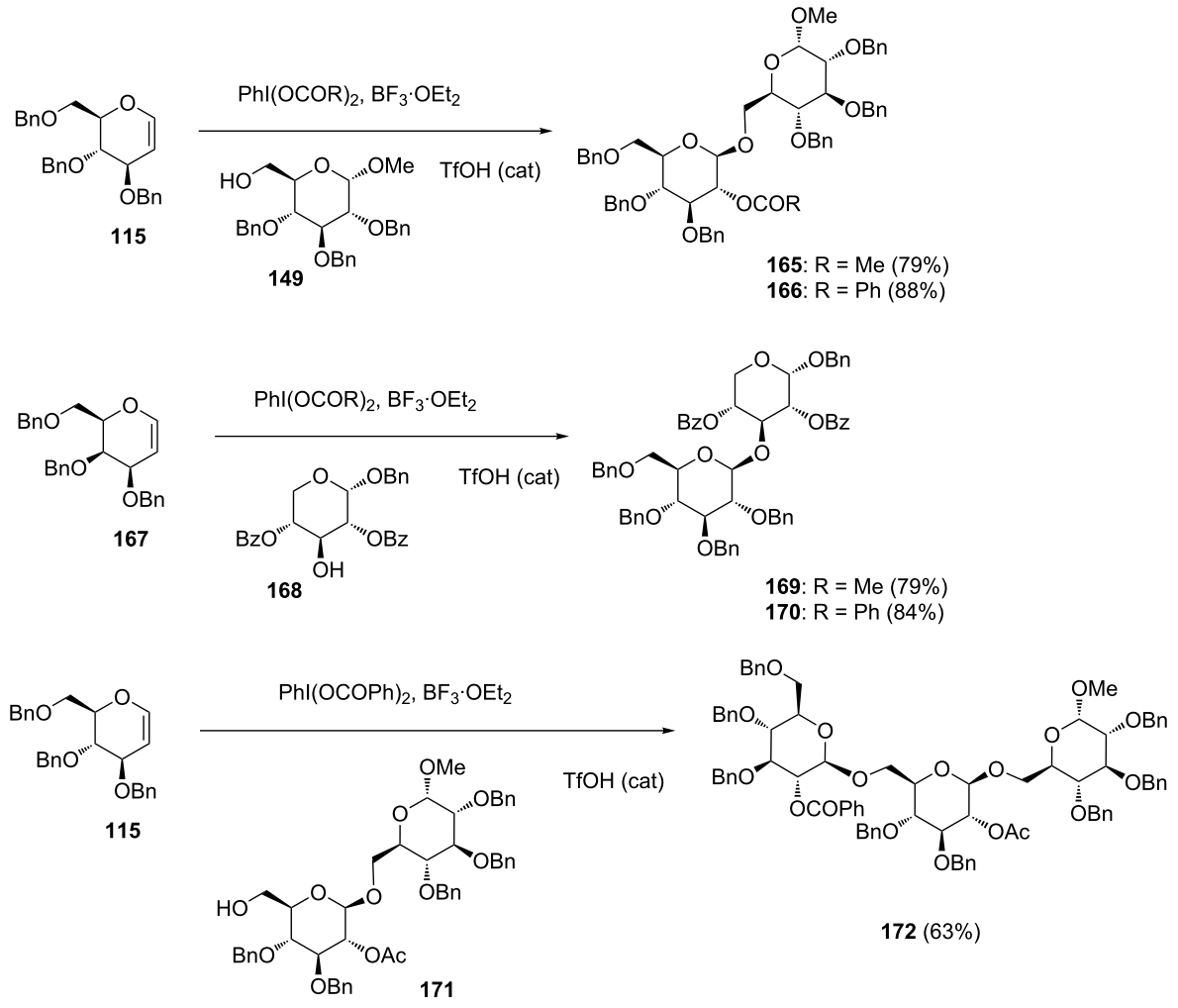


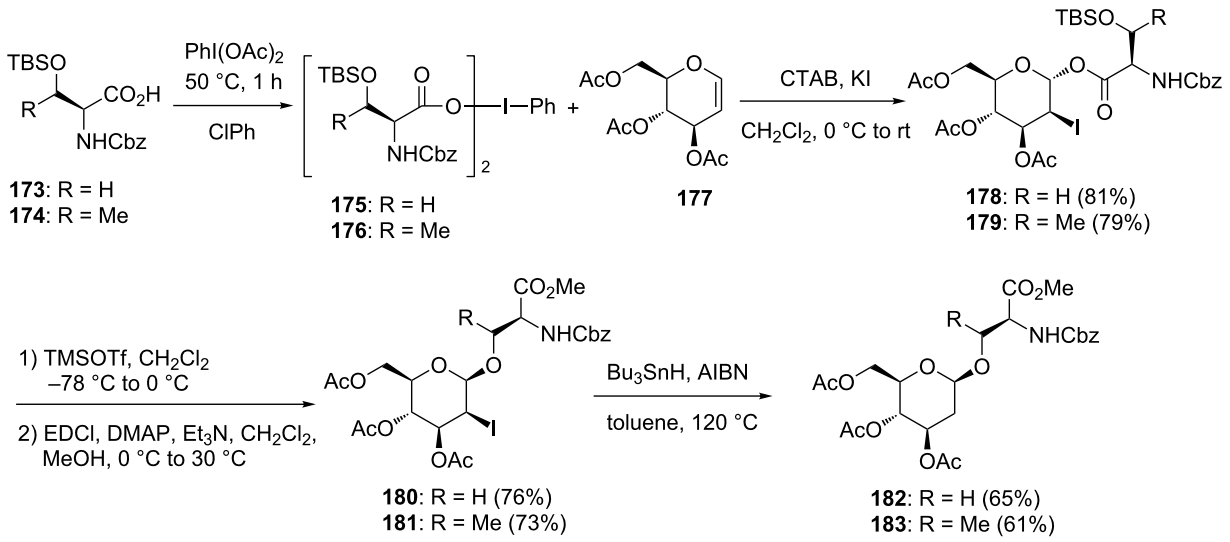
Figure 8: Expected mechanism of hypervalent iodine-mediated glycosylation with glycals.

They prepared C2-acyloxy glycosides **165**, **166**, **169**, **170** and **172** using hypervalent iodine-mediated coupling reactions with glycals, and the results are shown in Scheme 22. Either (diacetoxyiodo)benzene or (dibenzoyloxyiodo)benzene could serve as an efficient oxidant, and the reactions utilizing them gave the products installing either the acetate or benzoate functionality, respectively, at the C2-position. Both glucal **115** and galactal **167** were amenable to the oxidative glycosylation reaction to stereoselectively give C2-acyloxylated β-glycosides in good yields [84] (Scheme 22).

Hotha and co-workers utilized the reaction of glycals with hypervalent iodine reagents for the stereoselective synthesis of C2 deoxyglycosides and amino acid glycoconjugates [85]. In their work, they also utilized an important chemical attribute of cetylammonium bromide (CTAB) – namely, CTAB forms surfactant-assembled lipophilic nanoreactors stable in organic solvents, which could be used for regioselective functionalization of indenes. Therefore, they investigated the regioselective iodination of glycals by using CTAB and hypervalent iodine reagents for the synthesis of 2-deoxy-2-iodoacetates. In the preliminary experiments, the reaction between per-*O*-acetylglucal (**177**) and $PhI(OAc)_2$ in CTAB and KI gave *trans*-2-iodo α-acetate and its corresponding bromo acetate in a 94:5 ratio. The latter was expected to be formed by halide counter ion exchange between CTAB and KI. Since the reaction occurred as expected, it was applied to the synthesis of amino acid conjugates. Acetyl groups of the (diacetoxyiodo)benzene were exchanged with N- and O-protected amino acids by slow evaporation of a mixture of $PhI(OAc)_2$ and amino acid **173** and **174** in chlorobenzene to give $PhI(OCOR)_2$ compounds **175** and **176**. The formation of iodo ester glycosides **178** and **179** from **175** and **176** was achieved in very good yields under the conditions shown in Scheme 23.



Scheme 22: Synthesis of oligosaccharides by hypervalent iodine-mediated glycosylation with glycals.



Scheme 23: Synthesis of 2-deoxy amino acid glycosides.

Notably, the resulting iodo ester glycosides **178** and **179** were considered to have self-assembled structures versatile for the synthesis of serenylated and threonylated glycosides by intramolecular glycosylation. In addition, the access to 2-deoxyglycosides should be easily achievable by subsequent radical deiodination of the products. After several experiments, treatment with a catalytic amount of TMSOTf was found to be suitable for the intramolecular glycosylation, giving the corresponding acid, which was easily converted to the corresponding methyl ester **180** under EDCI/DMAP/MeOH conditions [85]. Similarly, the reaction of the threonine derivative **179** afforded **181** in good yield. Radical deiodination of **180** and **181** using Bu_3SnH and AIBN successfully gave 2-deoxy-β-glycosides **182** and **183**, which were difficult to synthesize from the corresponding 2-deoxy sugar derivative in a stereoselective manner (Scheme 23).

As mentioned above, the iodo ester glycosides were considered to have self-assembled structures suitable for intramolecular glycosylation. As depicted in Figure 9, treatment of **184** with TMSOTf first cleaved the silyl ether to form **185**, which was correctly positioned to undergo intramolecular glycosidation. As a result, the Lewis acid could also facilitate the departure of the anomeric ester and the resulting **185** gave rise to the intramolecular nucleophilic attack to furnish the corresponding acid **186**.

Glycals and thioglycosides were often used as sugar donors for the glycosylation of oligosaccharides. It is interesting that the hypervalent iodine-mediated oxidative reactions with theses derivatives provide a different method to build glycosidic bonds. Diversity in glycoside bond forming reactions would contribute to improve the oligosaccharide synthesis.

Conclusion

The Pummerer-type glycosylation includes oxidation of a sulfide to the corresponding sulfoxide followed by the TMSOTf-mediated coupling reaction. The reaction utilizing hypervalent iodine reagents could bypass one step of the Pummerer-type glycosylation and directly give 4'-thionucleosides from the corresponding sulfide derivative. The reaction could be efficiently applied to the synthesis of 4'-selenonucleosides as well as 4'-thionucleosides. Based on the concept of hypervalent iodine-mediated glycosylation, a reaction applic-

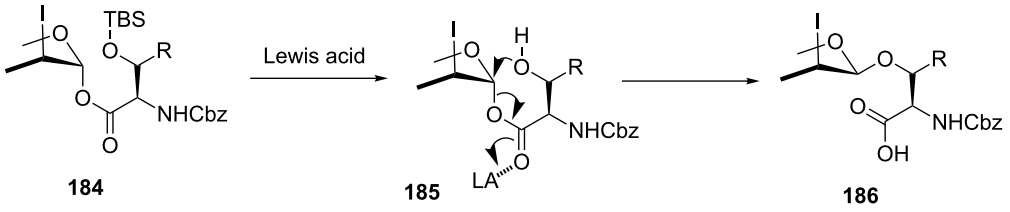


Figure 9: Rationale for the intramolecular migration of the amino acid unit.

able to the synthesis of carbocyclic nucleosides and a coupling reaction between nucleobase and glycal derivatives were developed. The latter reaction was employed to synthesize dihydropyranonucleosides. Oxidative scission is a characteristic reaction mediated by hypervalent iodine reagents and is typically used for dehomologation of sugars. A one-pot glycosylation using this reaction was also developed for the synthesis of acyclic nucleoside derivatives. In addition to nucleoside synthesis, hypervalent iodine-mediated glycosylation could also be applied to the synthesis of oligosaccharides and glycoconjugates when thioglycosides and glycals were used as sugar donors. There is no doubt that the use of hypervalent iodine reagents greatly improved the efficiency of the synthesis of nucleosides and oligosaccharides. The results of these syntheses demonstrate the power of glycoside bond-forming reactions, and should assist in the future identification or synthesis of biologically active nucleoside and glycoconjugate derivatives.

Acknowledgements

Our work described in this review article was supported in part by a Grant-in-Aid for Scientific Research from JSPS and by a grant from the Strategic Research Foundation Grant-aided Project for Private Universities from the Ministry of Education, Culture, Sport, Science, and Technology, Japan (MEXT).

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.14.137

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

DFT calculations on the mechanism of copper-catalysed tandem arylation–cyclisation reactions of alkynes and diaryliodonium salts

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Full Research Paper

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Keywords:
catalysis; DFT calculation; iodonium salts; reaction mechanism; tandem arylation–cyclisation

Beilstein J. Org. Chem. **2018,** *14,* 1743–1749.
doi:10.3762/bjoc.14.148

Received: 12 April 2018
Accepted: 20 June 2018
Published: 12 July 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

We present a computational mechanistic study on the copper(III)-catalysed carboarylation–ring closure reactions leading to the formation of functionalised heterocycles. We have performed DFT calculations along selected routes and compared their free energy profiles. The calculations considered two viable options for the underlying mechanism which differ in the order of the oxazoline ring formation and the aryl transfer steps. In our model transformation, it was found that the reaction generally features the aryl transfer–ring closing sequence and this sequence shows very limited sensitivity to the variation of the substituent of the reactants. On the basis of the mechanism the origin of the stereoselectivity is ascribed to the interaction of the Cu ion with the oxazoline oxygen driving the ring-closure step selectively.

Introduction

Recently a very efficient synthetic strategy has been developed where diaryl iodonium salt **1** [1-8] and copper(I) catalyst **2** are employed together to produce in situ Ar–Cu(III) species **3** for the carbofunctionalisation of appropriate substrates **4** [9-28]. In particular, the arylation–cyclisation reactions promoted by the highly electrophilic Cu(III)–aryl intermediates **3** can allow access to aryl-functionalised carbocyclic and heterocyclic molecules **8** with valuable functionalities [9,29-44]. The mechanistic

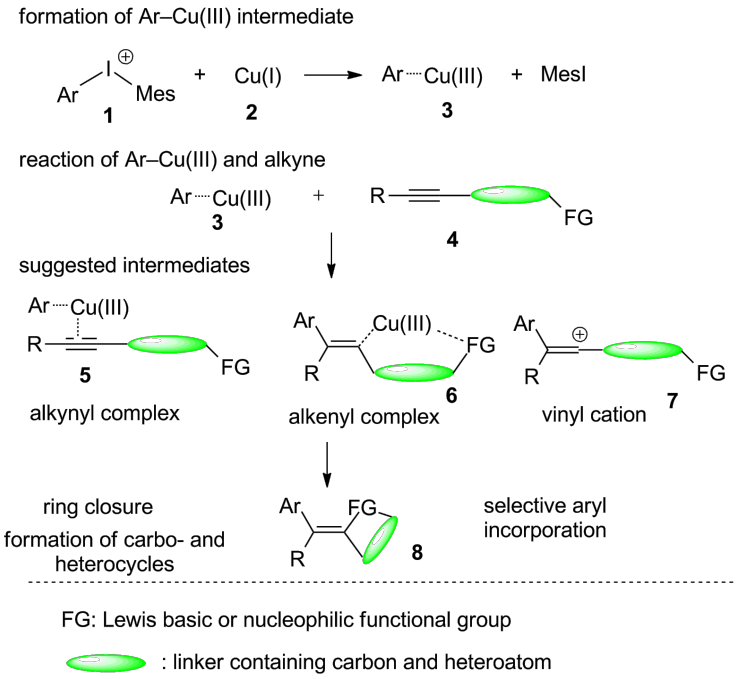
details of these cascade reactions are not clear as evidenced by the different mechanistic proposals (see, e.g., [18,30,40,44]). These mechanisms suggest the presence and existence of vinyl cation **7**, alkynyl–Cu(III) **5**, or alkenyl–Cu(III) complexes **6** before the C–O bond formation in the ring closing step (see Scheme 1).

As an example of the catalytic arylation–cyclisation strategy, an efficient procedure to form substituted oxazoline derivatives from alkyl and aryl propargylamides has been developed. The process involves a 5-*exo*-dig cyclisation and an aryl group transfer step affording a wide range of oxazoline derivatives [44]. An intriguing issue is the order of the arylation and ring-closure steps and whether this sequence can be affected by the electronic or steric properties of the ligands. Although these mechanistic variations have been postulated in the literature, the exact sequence remained unclear. In this article we report our theoretical studies addressing the mechanism of this reaction, which could provide valuable information for other, analogous copper-catalysed arylation–cyclisation reactions.

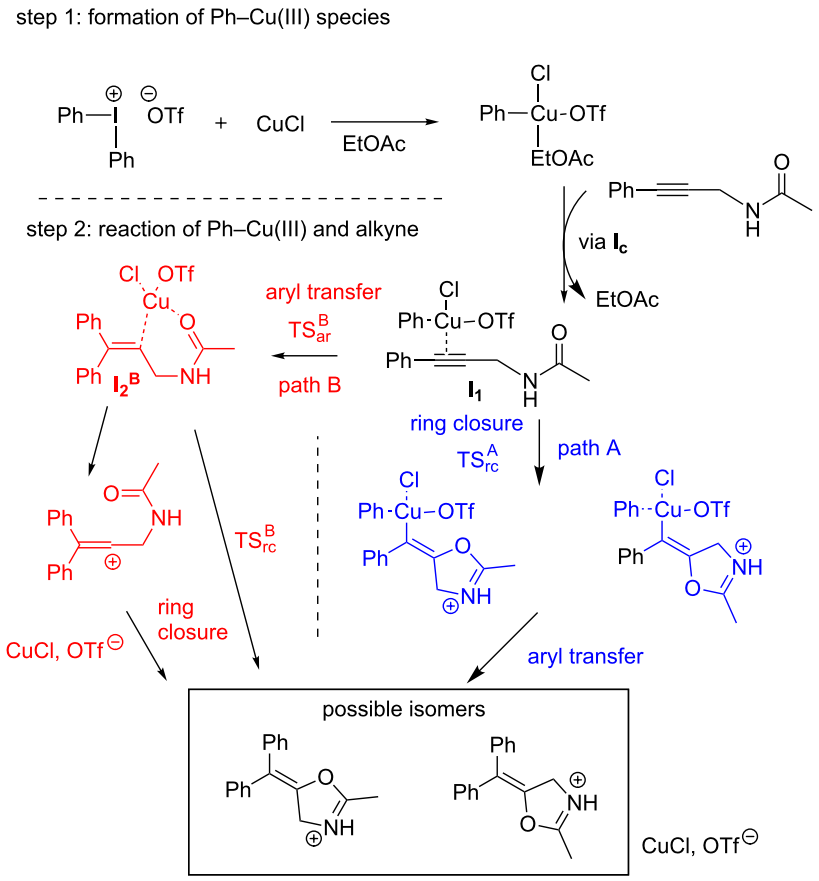
Results and Discussion

First, we explain our computational strategy and discuss the possible reaction paths leading to the formation of 5-(diphenylmethylene)-4,5-dihydrooxazole in the reaction of propargylic amides and diaryliodonium salts in the presence of a Cu(I) catalyst. This is a simplified model of the original reaction scheme [44] and allows the exploration of the possible reaction routes of the carboarylation–ring-closure reactions in a computationally efficient manner. As the first step of the reaction we considered the formation of the key Ar–Cu(III) species, followed by the interaction of this intermediate with the alkyne (Scheme 2, step 1). In the next step we compared the energetics of two different paths (paths A and B), to get insight into the order of the arylation and cyclisation steps. Additionally, the relevance of vinyl cation formation and the stereoselectivity were examined.

The energy profiles start with the interaction of the reactant with the catalyst complex formed in the EtOAc medium. In this process the complexing EtOAc ligand leaves and the reactant *N*-(3-phenylprop-2-yn-1-yl)acetamide binds to the Cu(III) ion in an η^2 mode with its triple bond yielding $\mathbf{I_1}$. The process occurs via an associative substitution route often observed for the 16 electron metal complexes. We could locate a crucial structure ($\mathbf{I_c}$) where the incoming reactant and the leaving solvent molecule occupy the equatorial position of the trigonal bipyramid formed by the five ligands of the Cu(III) ion. We decided to characterise this step by the free energy level of the intermediate: 17.6 kcal/mol. There are two reasons behind this choice: i) the preceding and subsequent barriers were computed to be very close in energy to that of this structure; ii) one of the participants of this step is the solvent EtOAc molecule, i.e., the solvent plays a two-fold role: it is a reactant and a solvating agent; as it is known, such situations are difficult to describe by



Scheme 1: Possible intermediates of the interaction of alkynyl compounds with Ar–Cu(III) species.



Scheme 2: Two possible reaction routes for the oxazoline formation explored by computations. The schemes indicate the possible stereochemical outcomes. For the definition of the labels of intermediates and transition states see Scheme 3.

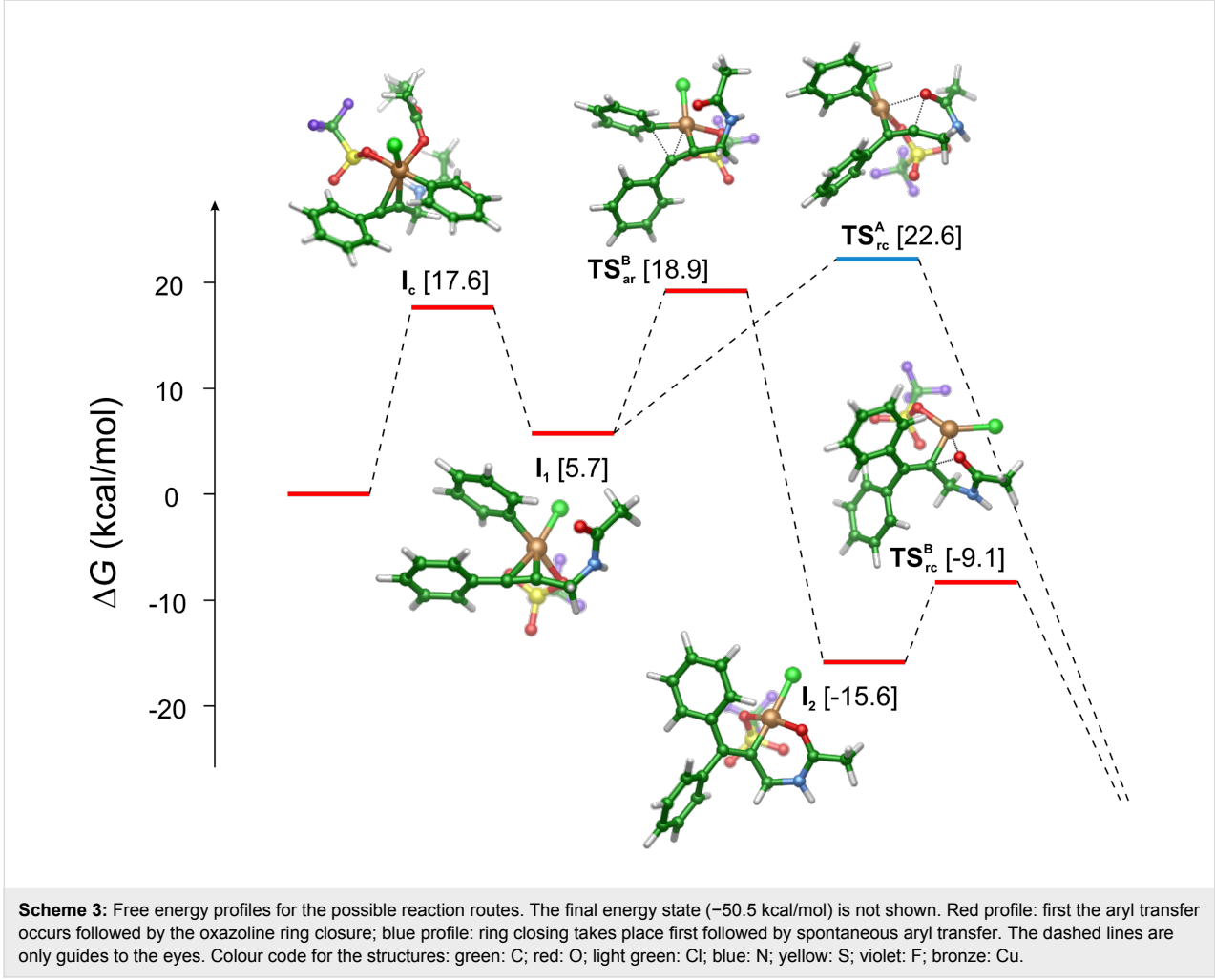
implicit solvent models [45]. The intermediate formed in this step ($\mathbf{I_1}$) is stabilised at 5.7 kcal/mol.

From this intermediate, the two reaction paths diverge. On path A (blue in Scheme 2 and Scheme 3) the ring formation takes place with an activation free barrier of 22.6 kcal/mol (TS_{rc}^{A}). Along this path this is the rate determining step. The calculations revealed that once the ring is formed, the aryl transfer spontaneously occurs and a significant amount of free energy is released (more than 70 kcal/mol) by the formation of the adduct of the protonated product and the catalyst (free energy level of −50.5 kcal/mol, not shown in Scheme 3).

In contrast the route starting with the aryl transfer from Cu(III) to the activated reactant features a two-step mechanism (red in Scheme 2 and Scheme 3): the aryl-transfer leads to the formation of a quite stable intermediate $\mathbf{I_2}^{\mathbf{B}}$ with a ca. −20 kcal/mol exergonicity with respect to the first intermediate ($\mathbf{I_1}$). We can also notice that this step requires a smaller, 18.9 kcal/mol activation free energy (TS_{ar}^{B}) as compared to TS_{rc}^{A}. The aryl transfer is followed by the O–C bond formation which results in the oxazoline ring. This step requires a moderate 6.5 kcal/mol activation energy (TS_{rc}^{B}) which indicates that this step is very fast under the reaction conditions. After the ring is formed the system is stabilised by releasing a large amount free energy to arrive at the same state as postulated for path A.

Comparison of the two free energy profiles indicates that the preferred route is the one where the aryl transfer precedes the oxazoline ring formation. On the other hand, the calculated activation free energy barriers are compatible for both routes with the experimental conditions and indicate that both mechanisms can operate at the relatively low, 50 °C temperature.

As the reaction profiles indicate the final state is highly stable. Further stabilisation is expected when the product is formed by deprotonation (presumably at the work-up stage). However, deprotonation may occur earlier if this is thermodynamically favourable in the presence of a suitable base. In the reaction mixture such potential bases are the triflate anion and the reactant. As they are very weak bases we can expect that deprotonation does not take place before the final product formation.



Scheme 3: Free energy profiles for the possible reaction routes. The final energy state (−50.5 kcal/mol) is not shown. Red profile: first the aryl transfer occurs followed by the oxazoline ring closure; blue profile: ring closing takes place first followed by spontaneous aryl transfer. The dashed lines are only guides to the eyes. Colour code for the structures: green: C; red: O; light green: Cl; blue: N; yellow: S; violet: F; bronze: Cu.

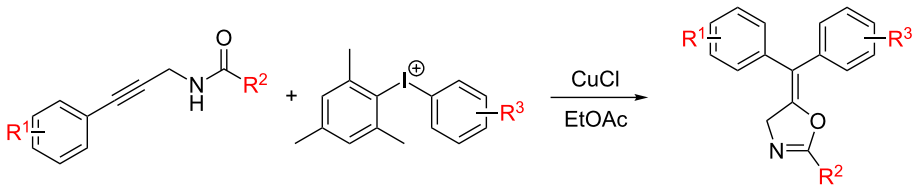
Indeed, the calculations show that none of the reactants and intermediates is strong enough acids to deprotonate: +55 kcal/mol, +18 kcal/mol and +25 kcal/mol of free energy are required to deprotonate the reactant and intermediates $\mathbf{I_1}$ and $\mathbf{I_2^B}$, respectively.

As Scheme 2 indicates the products oxazoline can be *cis*- or *trans*-isomers regarding the relative positions of the oxazoline oxygen and the incoming aryl group at the double bond. Formation of a vinyl cation would imply a non-stereospecific oxazoline formation. The calculations, however, revealed that its formation requires ca. 3 kcal/mol more free energy investment than the barrier toward the intramolecular ring closure (TS_{rc}^B). Therefore, we can exclude that the reaction path goes through a vinyl cation intermediate. In contrast, the mechanism obtained from the calculations shows that the catalyst steadily interacts with the substrate via Cu–C bonds along the full path. Further inspection reveals a crucial interaction between the carbonyl oxygen and the catalyst Cu ion (see, e.g., $\mathbf{I_2^B}$ in Scheme 3 where the Cu–O bond length is 1.87 Å). In fact, this cooperation drives selectively the reaction toward the formation of the *cis*-isomer, which is consistent with the experimental results.

Although the above 3 kcal/mol energy difference is large enough to guide the reaction toward the intermolecular ring closure, it is important to note that this also indicates an opportunity to influence the reaction mechanism: stabilisation of the vinyl cation [17,42] may induce a deviation toward a path with less efficient stereocontrol.

To obtain further insight into the mechanism we have calculated these paths for a large number of reactions where the R^1, R^2 and R^3 substituents of the reactants are varied (see reaction scheme in Table 1). A selection of these routes is summarised in Table 1 whereas the data of the full set of reactions are given in Supporting Information File 1. The reactions collected in Table 1 represent the scope of the methodology [44]. Inspection of Table 1 shows that the aryl transfer route is always preferred to the one where the oxazoline ring formation occurs first (the barriers of the ring closure are consistently higher than

Table 1: Effect of the substituents on the barrier heights (kcal/mol). Selection of the substituents is based on [44].



			barrier of (kcal/mol)		
R^1	R^2	R^3	complex formation	aryl transfer first	ring closure first
Ph	*t*-Bu	Ph	16.9	17.6	19.8
o-Me-Ph	*t*-Bu	Ph	19.4	18.8	21.3
p-Me-Ph	*t*-Bu	Ph	15.4	17.5	20.9
p-OMe-Ph	*t*-Bu	Ph	15.8	17.7	20.3
p-COOEt-Ph	*t*-Bu	Ph	18.5	18.8	21.7
p-Ac-Ph	*t*-Bu	Ph	18.6	18.9	20.3
p-Cl-Ph	*t*-Bu	Ph	16.6	17.8	19.1
m-Br-Ph	*t*-Bu	Ph	17.0	18.7	20.3
Ph	Ph	Ph	16.5	18.5	21.9
Ph	*p*-MeO-Ph	Ph	12.3	11.8	16.1
Ph	*p*-NO_2-Ph	Ph	17.0	19.5	23.9
Ph	*t*-Bu	*m*-Br-Ph	18.8	17.1	19.4
Ph	*t*-Bu	*p*-Ac-Ph	18.1	17.6	18.8
2-thiophene	*t*-Bu	Ph	16.9	18.5	18.5
Ph	Et	Ph	18.0	18.6	21.0
Et	*t*-Bu	Ph	17.9	17.2	19.5

those of the aryl transfers). It is also interesting to note that in some cases the initial complex formation is the rate determining step along the aryl-transfer path although in most cases the differences in the two barrier heights are very small.

The full set of reactions also shows that the aryl transfer as the first step after the complex formation with the catalyst is preferred over the route where the ring closure precedes the aryl transfer. Only three cases from the calculated ca. fifty reactions show a reverse trend. We could not identify a common motif behind this discrepancy; instead we attribute these exceptions to the limitations of the methodology.

Conclusion

In summary, we have shown with the selected model reaction that the above copper-catalysed carboarylation–ring closure reaction of alkynyl substrates with diaryliodonium salts can be depicted as follows: first the Cu(III)–aryl electrophile forms an intermediate with the triple bond of the reactant, then the aryl moiety migrates to the activated triple bond which is followed by a fast ring-closing step. The calculations provided several new chemical insights: deprotonation can take place only after the tandem arylation–cyclisation sequence; the mechanism shows a very limited sensitivity in a wide range of substituents installed on the reactants; a crucial copper–oxygen interaction is responsible for the very high stereoselectivity of the reaction and it also excludes the formation of vinyl-cation intermediates. The obtained results could serve as a useful and more general description of the mechanism of the carboarylation–ring closure strategy based on the utilisation of alkynes and diaryliodonium salts, beyond the selected and studied oxazoline synthesis.

Experimental

The calculations have been performed using the Gaussian 09 program package [46]. The M06 exchange–correlation functionals have been employed to solve the Kohn–Sham equations [47]. For the geometry optimisations, transition state searches and vibrational calculations the 6 31G* basis set was used. All the stationary structures obtained by the optimisation procedures were further recalculated using the 6 311++G(3df,3pd) basis set and the SMD implicit solvent model [48] employing ethyl acetate as solvent. The equilibrium structures of the reactant, product and intermediate states had only positive frequencies. The transition states have been verified having a single imaginary frequency and connecting the corresponding intermediate structures. The discussions are based on Gibbs free ener-

gies obtained within the ideal-gas model using the rigid-rotor harmonic-oscillator model for 323.15 K (experimental condition). The present methodology and its close variants have been successfully applied to explore the mechanisms of Cu-catalysed organic reactions [49-51].

Supporting Information

Supporting Information File 1

Full version of Table 1, total energies and Cartesian coordinates of all stationary points.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-148-S1.pdf]

Acknowledgements

This work was supported by NKFI (Grant No. K116034 and K125120). This project was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences. COST-CHAOS (CA15106) Action is also acknowledged.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of spirocyclic scaffolds using hypervalent iodine reagents

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Review

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Keywords:
hypervalent iodine reagents; iodoarenes; natural products; oxidative cyclization; spirocyclic compounds

Beilstein J. Org. Chem. **2018,** *14,* 1778–1805.
doi:10.3762/bjoc.14.152

Received: 23 March 2018
Accepted: 18 June 2018
Published: 17 July 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Hypervalent iodine reagents have been developed as highly valuable reagents in synthetic organic chemistry during the past few decades. These reagents have been identified as key replacements of various toxic heavy metals in organic synthesis. Various synthetically and biologically important scaffolds have been developed using hypervalent iodine reagents either in stoichiometric or catalytic amounts. In addition, hypervalent iodine reagents have been employed for the synthesis of spirocyclic scaffolds via dearomatization processes. In this review, various approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents are covered including their stereoselective synthesis. Additionally, the applications of these reagents in natural product synthesis are also covered.

Review

1. Introduction

The chemistry of spirocyclic compounds is a well established research area of organic and medicinal chemistry [1-5]. These scaffolds are common structural motifs found in various classes of naturally occurring systems [6-8]. More importantly, various natural and synthetic products containing a spirocyclic ring are currently used as commercial drugs for the treatment of several health problems [9,10]. Annosqualine (**1**) is an isoquinoline-cored alkaloid and it was isolated in 2004 from the stem of *Annona squamosa* [11] (Figure 1).

Griseofulvin (**2**) is a spirobenzofuranone-based naturally occurring compound which was isolated from *Penicillium griseofulvum* in 1939 [12]. In 1959, it was launched in the market as antifungal agent for the treatment of ringworm in human beings and animals [4,13]. Stepharine (**3**) is a member of the proaporphine alkaloid family and isolated from an angiosperm *Stephania glabra* [14]. Tofogliflozin (**4**) is a synthetic spirocyclic glycoside that was launched as antidiabetic agent in 2012 in Japan [15]. Rolapitant (**5**) is a marketed drug that was ap-

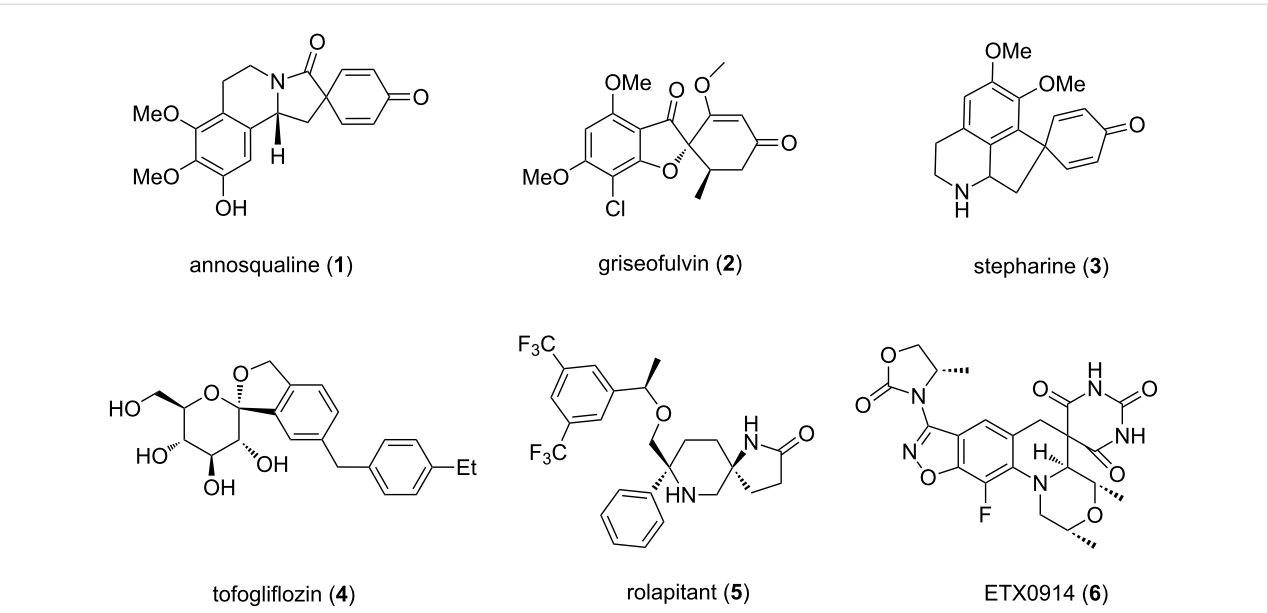


Figure 1: The structures of biologically active natural and synthetic products having spirocyclic moiety.

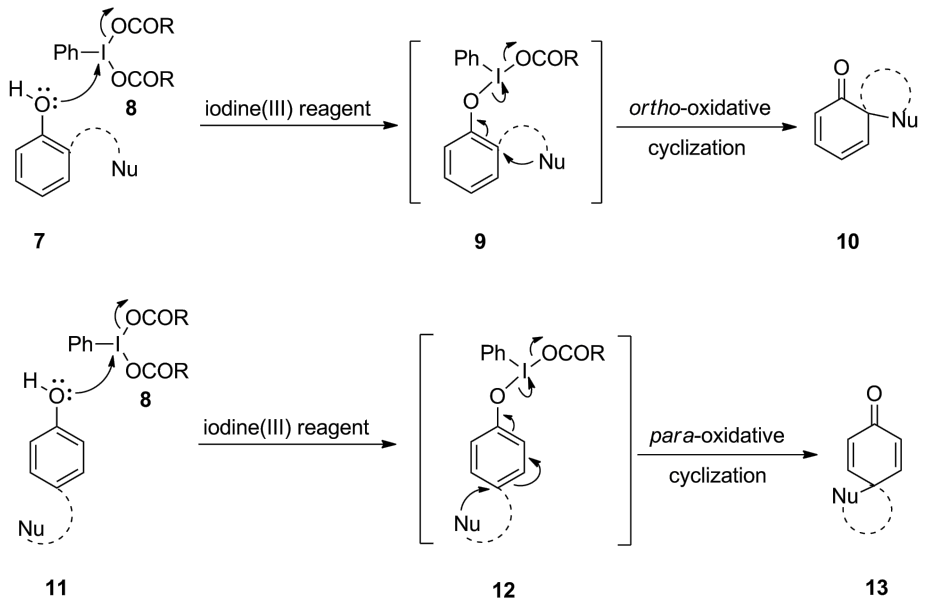
proved in 2015 for the treatment of nausea and vomiting [16]. Compound **6** is a spiropyrimidinetrione analogue which is currently in clinical trials for the treatment of gonorrhea [17]. There are several ways available in literature for the synthesis of spirocyclic compounds but most of them are associated either with transition metals or hypervalent iodine reagents [1-3].

Hypervalent iodine reagents provide various functional group transformation opportunities in organic chemistry. Their environment-friendly nature and mild reaction conditions makes them more attractive candidates for the replacements of various toxic metals in organic synthesis [18-31]. These reagents are more popular for their oxidizing properties [32-38] and electrophilic nature of different iodine(III) reagents has been explored to developed various synthetic transformation including rearrangements [39-62]. Hypervalent iodine chemistry has now become a well-established research area and various book chapters [19,20,27] and review articles [21-24,31-35,60,63,64] appeared to explain the chemistry of these reagents. In the past two decades, a number of organic chemists used these reagents for the construction of a variety of spirocyclic scaffolds. In 2008, Quideau and co-workers published a nice review article where they have described various spirocyclization reactions using hypervalent iodine reagents via dearomatizations of aromatic phenolic species [32]. This review article is quite useful for readers who want to know the chemistry involved during the dearomatization of phenols and to find the relevant literature available until 2008. In this review article, various approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents are covered including stereoselective reactions. Hypervalent iodine reagents are mainly popular for their oxidative properties but various iodine(III) reagents have been used as electrophiles. Numerous iodine(III) reagents have been successfully used to achieve diverse spirocyclic scaffolds. Phenols **7** or **11** having an internal nucleophile at *ortho*- or *para*-position can be used as starting material for the synthesis of *ortho*- and *para*-spirocyclic compounds in the presence of iodine(III)-based electrophiles (Scheme 1). Phenolic oxygen of compound **7** attacks to the iodine of **8** to form intermediate **9**. Furthermore, on nucleophilic attack of the internal nucleophile to the *ortho*-position intermediate **9** converts to *ortho*-spirocyclic compound **10** with the elimination of the hypervalent iodine moiety. Similarly, *para*-spirocyclic compounds **13** can be achieved starting from compounds **11** and iodine(III) reagent **8** (Scheme 1). The synthesis of spirocyclic compounds can be achieved using stoichiometric or catalytic amounts of iodine(III) reagents. According to literature reports, both heterocyclic and carbocyclic spirocyclic compounds can be achieved using these reagents [27,32].

2. Synthesis of spirolactones

2.1. Using stoichiometric amounts of iodine(III) reagents

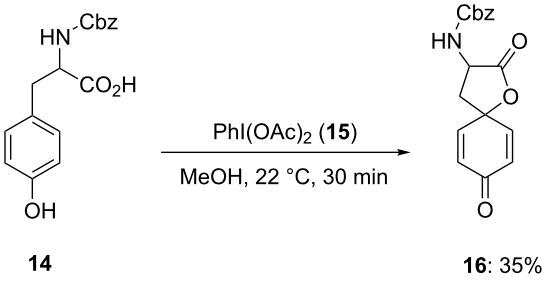
The history of the utility of hypervalent iodine reagents in the synthesis of spirocyclic compounds is going to become quite old now. Initially, iodine(III) reagents were applied for synthesis of spirocyclic in 1990s [65,66]. In 1991, Kita and co-workers [67] established the synthesis of spirohexadiones from *N*-acyltyramines using iodine(III) reagent. After these reports, numerous hypervalent iodine-mediated spirocyclizations were investigated and phenolic oxidations of substrates



Scheme 1: Iodine(III)-mediated spirocyclization of substituted phenols **7** and **11** to **10** and **13**, respectively.

have been explored for the construction of spirodienone motifs [21,64].

In 1993, Wipf and Kim [68] employed PIDA (**15**) for spirocyclization of N-protected tyrosine **14** to spirolactone **16**. The spirocyclization reaction was carried out in methanol using stoichiometric amounts of PIDA (**15**) and spirolactone **16** was isolated in 35% yield (Scheme 2). Probably, the cyclization reaction proceeded via dearomatizaion of phenolic substrate **14** followed by nucleophilic attack of the carbonyl moiety of carboxylic group.



Scheme 2: PIDA-mediated spirolactonization of N-protected tyrosine **14** to spirolactone **16**.

Furthermore, Giannis and co-workers [69] reported the synthesis of novel aminomethylpolystyrene-supported (diacetoxyiodo)benzene (PSDIB) reagents **17a** and **17b** starting from aminomethylated polystyrene with 4-iodobenzoic acid and 4-iodophenylacetic acid in two steps (Figure 2).

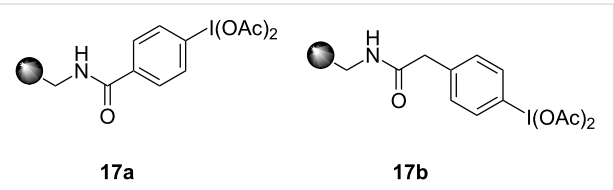
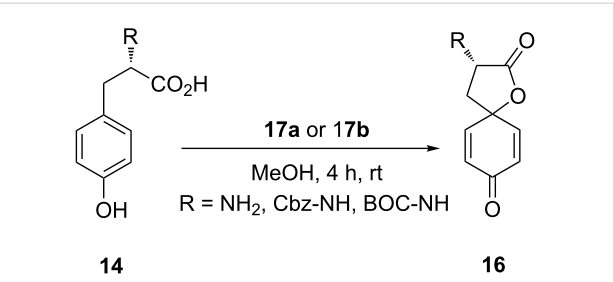


Figure 2: The structures of polymer-supported iodine(III) reagents **17a** and **17b**.

Both polymer-supported reagents **17a** and **17b** were used in similar spirocyclizations of tyrosine **14**. Both tyrosine **14a** and N-protected tyrosine derivatives **14b**,**c** were used as starting material and results of their spirolactonization are summarized in Table 1 (Scheme 3).



Scheme 3: Spirolactonization of substrates **14** to spirolactones **16** using polymer-supported reagents **17a** and **17b**.

The spirolactonization products **16** were isolated in excellent yields when reactions were performed with substrates **14**

Table 1: Spirolactonization of substrates **14** to spirolactones **16** using polymer-supported reagents **17a** and **17b**.

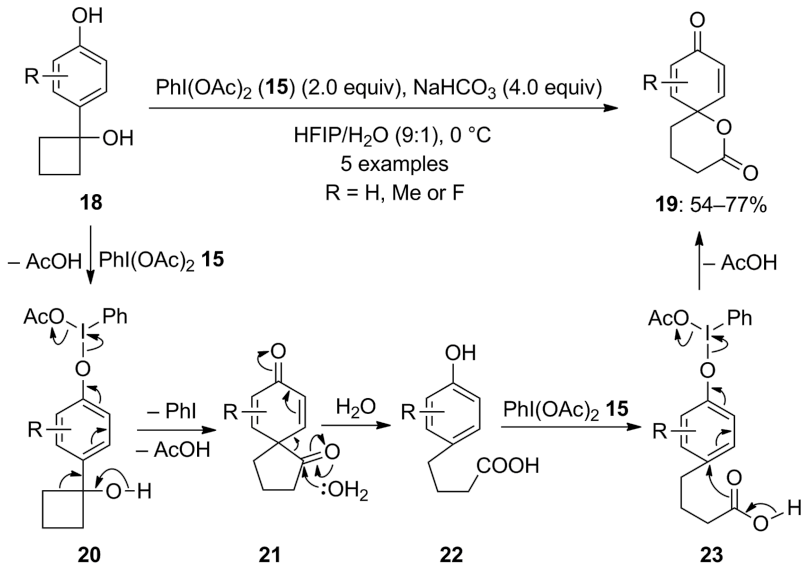
entry	substrate **14**	PS-iodine(III) reagent	**16** yields (%)
1	**14a**: R = NH_2	**17a**	82
2	**14a**: R = NH_2	**17b**	80
3	**14b**: R = Cbz-NH	**17a**	25
4	**14b**: R = Cbz-NH	**17b**	26
5	**14c**: R = Boc-NH	**17a**	24
6	**14c**: R = Boc-NH	**17b**	25

(R = NH_2) having free amino group (Table 1, entries 1 and 2). Notably, the poor yields were observed during the spirolactonization of N-protected tyrosine derivatives **14b** and **14c** (Table 1, entries 3–6). The advantage of this reaction is that the polymer-supported reagent can be regenerated and reused without loss of any significant activity [69].

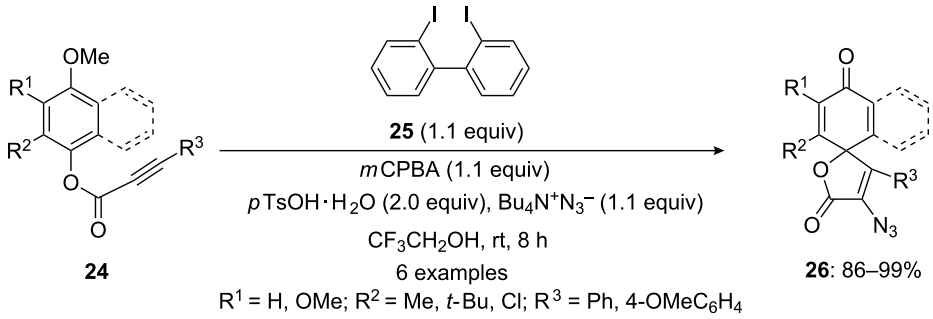
In 2010, Kita and co-workers [70] developed another approach for PIDA-mediated spirolactonization of 1-(*p*-hydroxyaryl)-cyclobutanols **18** to spirolactones **19** in good yields (Scheme 4). The reaction was initiated with formation of an intermediate **20** by the oxidation of the phenolic hydroxy group of **18**, which rearranged to compound **21**. Furthermore, water attacks the ketone moiety of **21** to form *para*-substituted phenol **22**. The phenolic intermediate **22** is further oxidized with another molecule of PIDA (**15**) to form intermediate **23**, which yielded the final product **19** on intramolecular cyclization [70].

Furthermore, Kita and his research group [71] reported an iodine(III)-mediated cyclization of arylalkynes **24** to spirocyclic products **26** by in situ-generated active hypervalent iodine species. In this report, *para*-substituted esters **24** were cyclized to corresponding spirolactones **26** using stoichiometric amount of bis(iodoarene) **25** with terminal oxidant *m*CPBA in the presence of $TsOH{\cdot}H_2O$ in TFE (Scheme 5). In this reaction, active hypervalent iodine species was generated in situ by the oxidation of bis(iodoarene) **25** using *m*CPBA as terminal oxidant.

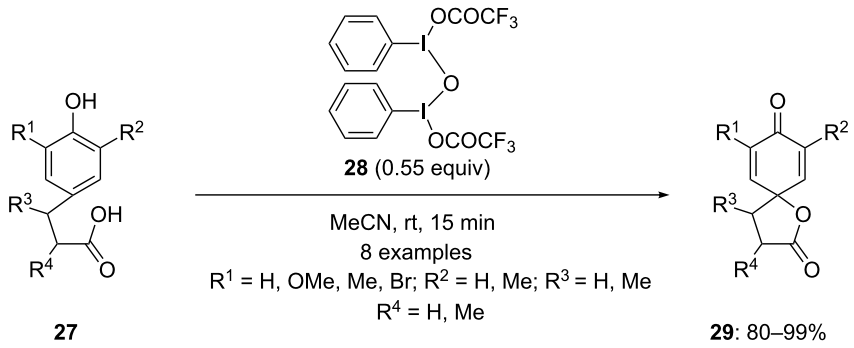
In 2011, Kita and co-workers [72] investigated a more reactive μ-oxo bridged hypervalent iodine(III) reagent used in the spirocyclization of phenolic substrates **27** to spirolactones **29**. The reaction products were obtained in excellent yields using 0.55 equivalents of bridged iodine(III) reagent **28** in acetonitrile at room temperature (Scheme 6). Furthermore, a comparative study was done between bridged iodine(III) reagent **28** with PIFA. It was found that the reaction products **29** were obtained in higher yield using the bridged iodine(III) reagent compared to that using PIFA. Probably, the iodine-$OCOCF_3$ bond of the bridged compound **28** has a significant ionic character as



Scheme 4: PIDA-mediated spirolactonization of 1-(*p*-hydroxyaryl)cyclobutanols **18** to spirolactones **19**.



Scheme 5: Iodine(III)-mediated spirocyclization of aryl alkynes **24** to spirolactones **26** by the reaction with bis(iodoarene) **25** in the presence of *m*CPBA.



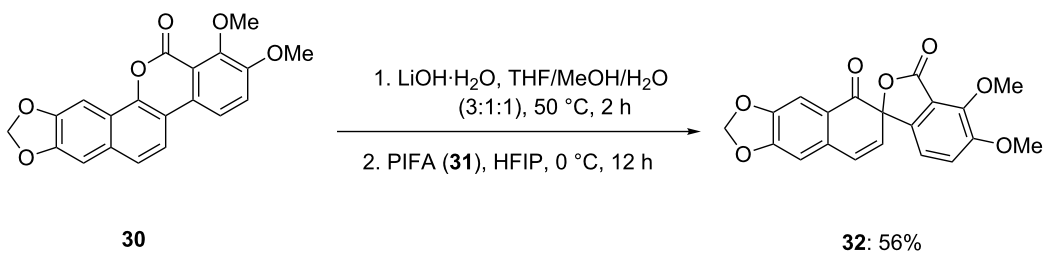
Scheme 6: Bridged iodine(III)-mediated spirocyclization of phenols **27** to spirodienones **29**.

the iodine–oxygen bond distance is larger than in PIFA which intends to make it more reactive than PIFA.

PIFA (**31**) is a more electrophilic iodine(III) reagent than PIDA (**15**) due to the presence of two trifluoroacetoxy groups. There are some approaches for the synthesis of spirocyclic compounds where PIFA (**31**) is used as electrophile.

Recently, Lewis and co-workers [73] reported the conversion of arnottin I (**30**) to its spirocyclic analogue arnottin II (**32**) by reaction with LiOH followed by PIFA (**31**). The spirocyclic product arnottin II (**32**) was isolated in 56% yield (Scheme 7). This approach is based on a tandem oxidative dearomatization process and will be quite useful for the conversion of functionalized benzocoumarins to spirocyclic lactones.

In 2015, Du and co-workers [74] reported a spirocyclization of diarylacetylenes to fused spiro polycyclic compounds through a hypervalent iodine-mediated cascade annulation reaction. In this reaction, the Lewis acid $BF_3{\cdot}Et_2O$ acts as catalyst which activates the substrate. A further treatment with PIDA **(15)** forms the spirocyclic products through intramolecular cyclization.



Scheme 7: Iodine(III)-mediated spirocyclization of arnottin I (**30**) to its spirocyclic analogue arnottin II (**32**) using stoichiometric amount of PIFA (**31**).

2.2. Using hypervalent iodine reagents as catalyst

The hypervalent iodine-catalyzed synthesis of spirocylic compounds can be achieved either by using catalytic amounts of a hypervalent iodine species or by generation of a similar active catalytic species in situ by the oxidation of iodoarene using a terminal oxidant. More commonly, *m*-chloroperbenzoic acid (*m*CPBA) and oxone are used as oxidant to generate the hypervalent iodine species in situ via oxidation of iodoarenes. In 2014, Singh and Wirth have compiled a review article where they have covered various aspects of hypervalent iodine catalyzed reactions [75].

In 2005, Kita and his research group investigated a hypervalent iodine-catalyzed spirocyclization reaction by generating the catalytic hypervalent iodine species via in situ oxidation of iodoarene using *m*CPBA as terminal oxidant [76]. In this report, *p*-substituted phenols **27** were cyclized to the corresponding spirolactones **29** using iodotoluene **33** as precatalyst, *m*CPBA as oxidant and TFA as an additive. The spirolactones **29** were isolated as reaction products in excellent yields (Scheme 8). Probably, the iodine(III) species was generated in situ as the active catalytic species that was playing the key role for the dearomatization of phenol. In addition, a similar reaction was also achieved by using various PIFA analogues as catalyst directly in the presence of 1.5 equivalents of *m*CPBA. Since this report, several iodine(III)-catalyzed oxidative spirocyclization reactions have been successfully developed.

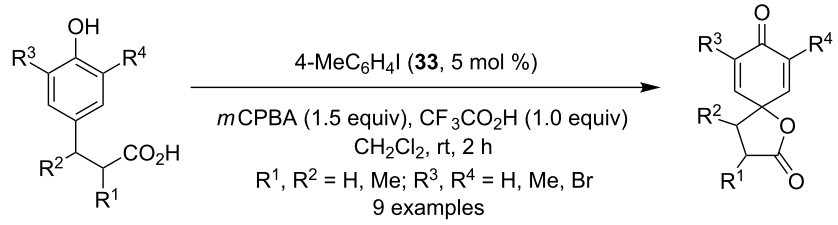
In 2009, Ishihara and co-workers [77] developed an oxylactonization of ketocarboxylic acid **34** to spirolactone **36** using 10 mol % of iodobenzene (**35**) as precatalyst, 20 mol % of $TsOH·H_2O$ as additive and 1.8 equivalents of *m*CPBA as oxidant. The catalytic reaction was carried out in nitromethane at 50 °C for 23 h and spirolactone **36** was isolated in 74% yield (Scheme 9). It was noted that 20 mol % of additive was essential to initiate the reaction efficiently. The reaction was quite slow when 10 mol % of additive was used. Once again, iodine(III) species was generated in situ which was probably working as active catalytic species.

2.3. Stereoselective synthesis of spirolactones

Recently, Kita and co-workers [78] reported a new type of binaphthyl-based chiral iodine(III) species **38** and its efficient utilization in the spirocyclization of naphthols containing carboxylic acids. 1-Naphthol-2-propionic acids **37** were cyclized to corresponding spirolactone derivatives **39** using chiral-8,8'-diiodonaphthyl reagent **38** as precatalyst, *m*CPBA as an oxidant in chloroform at low temperature. The reaction products **39** were isolated in good yields with more than 78% enantiomeric excess (Scheme 10). The active catalytic hypervalent iodine species was generated in situ by oxidation of optically active iodoarene **38** using *m*CPBA as an oxidant.

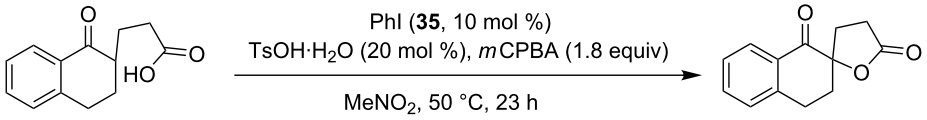
2.4. Application of spirolactones in natural products synthesis

In 2005, Wipf and Spencer [79] reported the first total synthesis of the *Stemona* alkaloid (−)-tuberostemonine (**40**). In this report, PIDA (**15**) was used as an electrophile for the synthesis of spirolactone **16** in 35% yield by the cyclization of L-tyrosine **14** in nitromethane at room temperature for 2.5 h (Scheme 11).



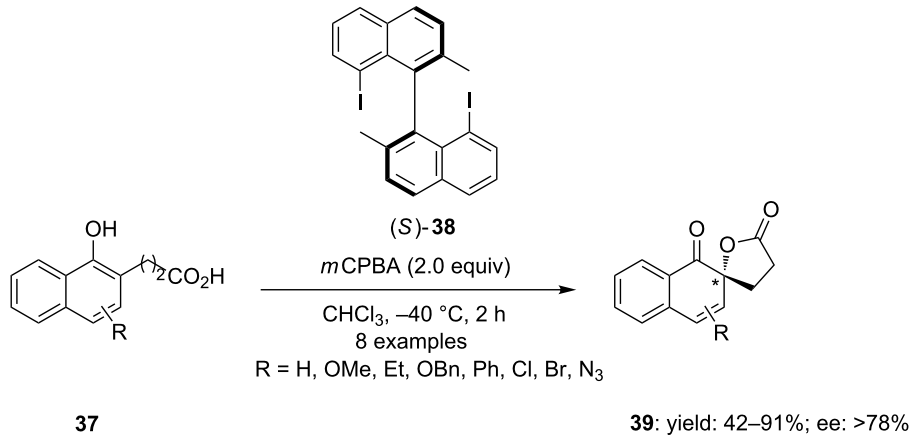
27 **29**: 66–91%

Scheme 8: Iodine(III)-catalyzed spirolactonization of *p*-substituted phenols **27** to spirolactones **29** using iodotoluene **33** as a precatalyst and *m*CPBA as an oxidant.

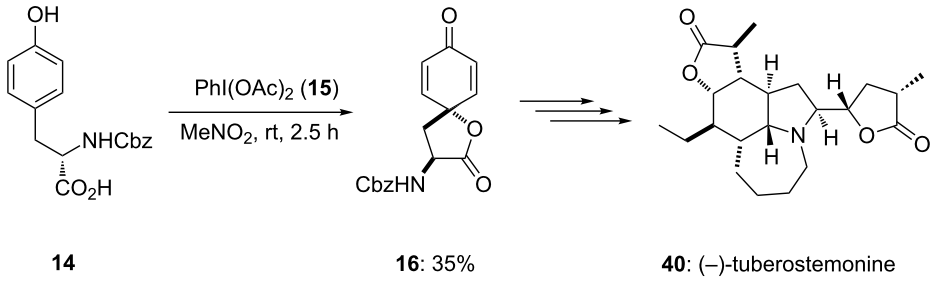


34 **36**: 74%

Scheme 9: Iodine(III)-catalyzed oxylactonization of ketocarboxylic acid **34** to spirolactone **36** using iodobenzene **35** as precatalyst in the presence of *m*CPBA.



Scheme 10: Iodine(III)-mediated asymmetric oxidative spirocyclization of naphthyl acids **37** to naphthyl spirolactones **39** using chiral iodoarene **38** as precatalyst.



Scheme 11: Oxidative cyclization of L-tyrosine **14** to spirocyclic lactone **16** using PIDA (**15**).

Additionally, the synthesized spirocyclic precursor **16** was transfered to (−)-tuberostemonine (**40**) in three chemical steps.

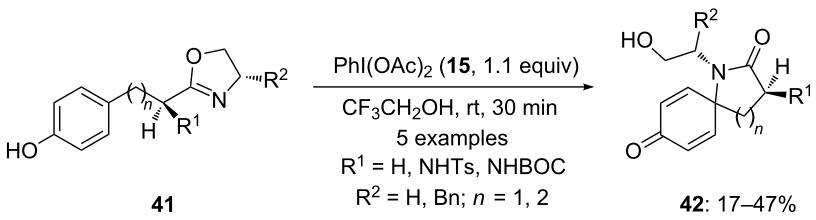
3. Synthesis of spirolactams

3.1. Using stoichiometric amounts of iodine(III) reagents

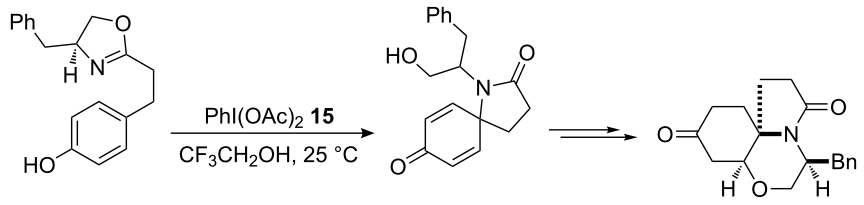
In 1998, Ciufolini and co-workers [80] reported the oxidative cyclization of tyrosine derivatives to spirolactams using iodine(III) reagents. In this reaction, oxazoline derivatives **41** were cyclized to spirocyclic products **42** using PIDA (**15**) as an electrophile in trifluoroethanol at room temperature for 30 minutes. The desired products **42** were isolated in moderate yields (Scheme 12).

Additionally, the same research group [81] reported the oxidative cyclization of a phenolic substrate to a spirolactam using PIDA as electrophile. In this methodology, oxazoline **43** was cyclized to spirolactam **44** in 50% yield using PIDA (**15**) in trifluoroethanol at room temperature (Scheme 13). Furthermore, spirolactam was used as intermediate in the synthesis of tricyclic compound **43** possessing a similar structure like that of the naturally occurring heterocyclic compound FR901483 [82].

Wardrop and co-workers [83] developed a new method for the preparation of 1-azaspiranes **47** by treatment of α- and β-substituted 3-(methoxyphenyl)-*N*-methoxypropionamides **46** with [bis(trifluoroacetoxy)iodo]benzene (PIFA, **31**) in dichloro-



Scheme 12: Oxidative cyclization of oxazoline derivatives **41** to spirolactams **42** using PIDA (**15**).



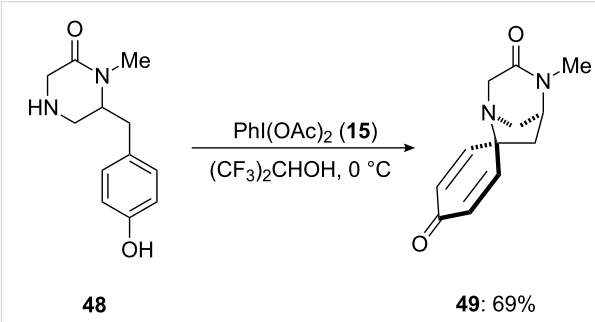
Scheme 13: Oxidative cyclization of oxazoline **43** to spirolactam **44** using PIDA **15** as oxidant.

methane (Scheme 14). The reactions were carried out at low temperature and spirolactams **47** were achieved in high yields with up to 96% enantiomeric excess. Furthermore, these compounds have been employed as important synthetic intermediates for the construction of biologically active molecules such as histrionicotoxins and the cytotoxic marine alkaloid fasicularin [84].

In 2010, Honda [85] reported the synthesis of isoquinoline alkaloids possessing spirocyclic framework using PIDA (**15**) as an electrophile in hexafluroisopropanol solvent. The *p*-substituted phenolic compound **48** was used as starting material for the construction of spirolactam **49** in 69% yield (Scheme 15). This is an important intermediate in the synthesis of various naturally occurring alkaloids such as TAN1251A, TAN1251C and TAN1251D [86].

Wardrop and Burge [87] reported a iodine(III)-mediated oxidative spirocyclization of hydroxamates **50**. The azaspirans **51** containing quaternary carbon centers were synthesized in good to excellent yields on treating substrates **50** with PIFA (**31**) in dichloromethane/methanol (1:1, Scheme 16). The reaction products (spirolactams **51**) were obtained as inseparable mixture of *anti*- and *syn*-diastereomers.

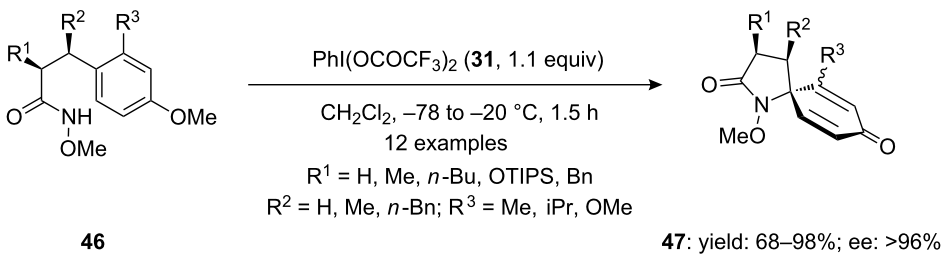
Haroutounian and co-workers [88] investigated a PIFA-mediated synthesis of spirocyclic lactam **54** as side product by treating substrate **52** with 1.5 equivalents of PIFA (**31**) in presence of 3.0 equivalents of TFA as an additive in dichloro-



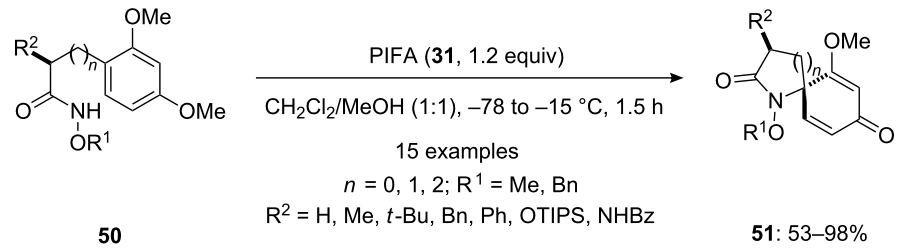
Scheme 15: Synthesis of spirolactam **49** from phenolic enamide **48** using PIDA (**15**).

methane (Scheme 17). The fused tricyclic compound **53** was obtained as major product in 55% yield along with the spiro compound **54** as a minor product in 8% yield.

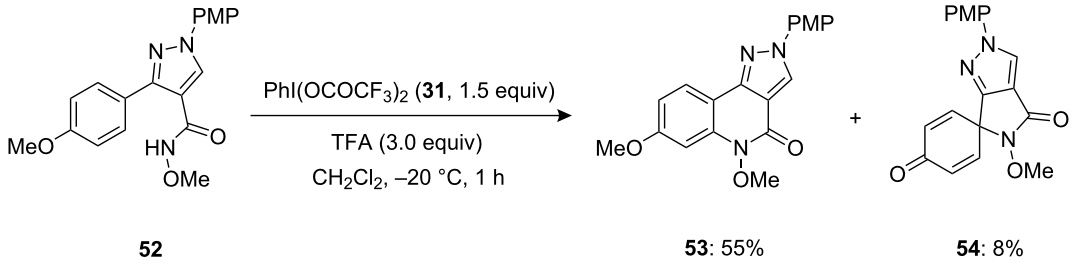
In 2009, Zhang and co-workers [89] reported an efficient method for the synthesis of spiro β-lactams via oxidative dearomatization reactions. In this report, the synthesis of spiro β-lactams **56** were achieved successfully by the oxidative cyclization of *p*-substituted phenols **55** using PIDA (**15**) as an electrophile and copper(II) sulfate pentahydrate as an additive in the presence of DMAP base. The spirocyclization reactions were performed in MeOH for 2 h at 0 °C and spirocyclic products **56** were isolated in good yields (Scheme 18). Additionally, fused bicyclic compounds **57** were also observed in few reactions in traces. The structure of the spiro β-lactam was confirmed by single crystal X-ray crystallography.



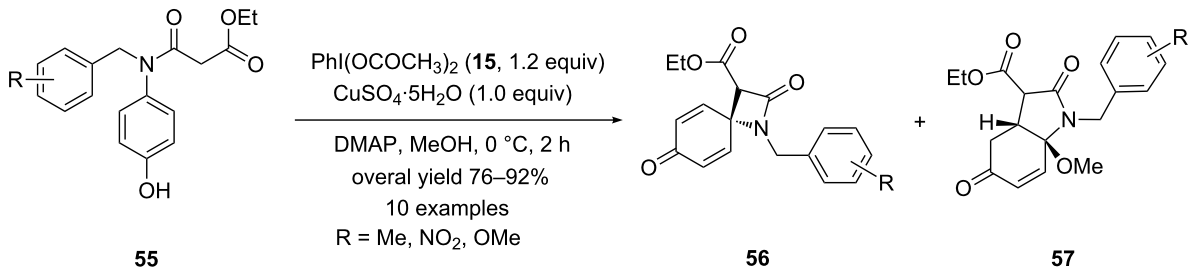
Scheme 14: PIFA-mediated spirocyclization of amides **46** to *N*-spirolactams **47** using PIFA (**31**) as an electrophile.



Scheme 16: Iodine(III)-mediated spirocyclization of alkyl hydroxamates **50** to spirolactams **51** using stoichiometric amount of PIFA (**31**).



Scheme 17: PIFA-mediated cyclization of substrate **52** to spirocyclic product **54**.



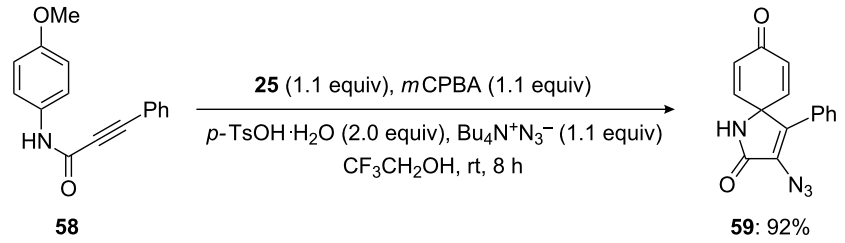
Scheme 18: Synthesis of spiro β-lactams **56** by oxidative coupling reaction of *p*-substituted phenols **55** using PIDA (**15**) and $CuSO_4·5H_2O$ in the presence of base in methanol.

Dong and co-workers [90] developed a novel way for the synthesis of five membered spiro pyrazolin-5-ones using amide and amine-containing precursors. Herein, five-membered azaheterocyclic derivatives were synthesized efficiently in presence of PIFA and with TFA as an additive.

Furthermore, Kita and his research group [71] displayed a method for the cyclization of alkyne derivative **58** to spirolactam **59** by an in situ-generated active hypervalent iodine species. In this method, *para*-substituted amide **58** was cyclized to the corresponding spirolactam **59** in 92% yield using a stoichiometric amount of bis(iodoarene) **25** with the terminal oxidant *m*CPBA in the presence of $TsOH·H_2O$ in TFE (Scheme 19).

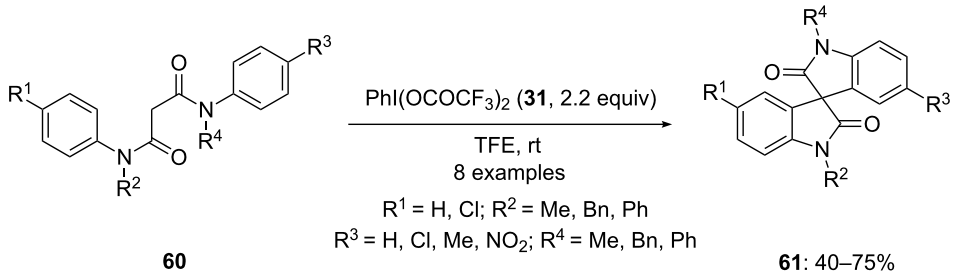
In 2012, Zhao and co-workers [91] developed a new approach for the construction of spirooxindoles **61** through tandem cascade oxidation of substituted anilides **60**. In this methodology, anilide derivatives **60** were reacted with [bis(trifluoroacetoxy)iodo]benzene (**31**, PIFA) in TFE at room temperature to afford functionalized lactams **61** in good yields (Scheme 20). Various electron-donating and withdrawing groups at the phenyl ring in anilides were successfully tolerated.

Furthermore, Sunoj and Sreenithya [92] developed a metal-free approach for the synthesis of 1,1'-dimethyl-3,3'-spirobi[indoline]-2,2'-dione (**61**) from N^1,N^3-dimethyl-N^1,N^3-diphenylmalonamide (**60**) using PIFA (**31**) in trifluoroethanol at room temperature. The spirolactam **61** was isolated in 75% yield



58 59: 92%

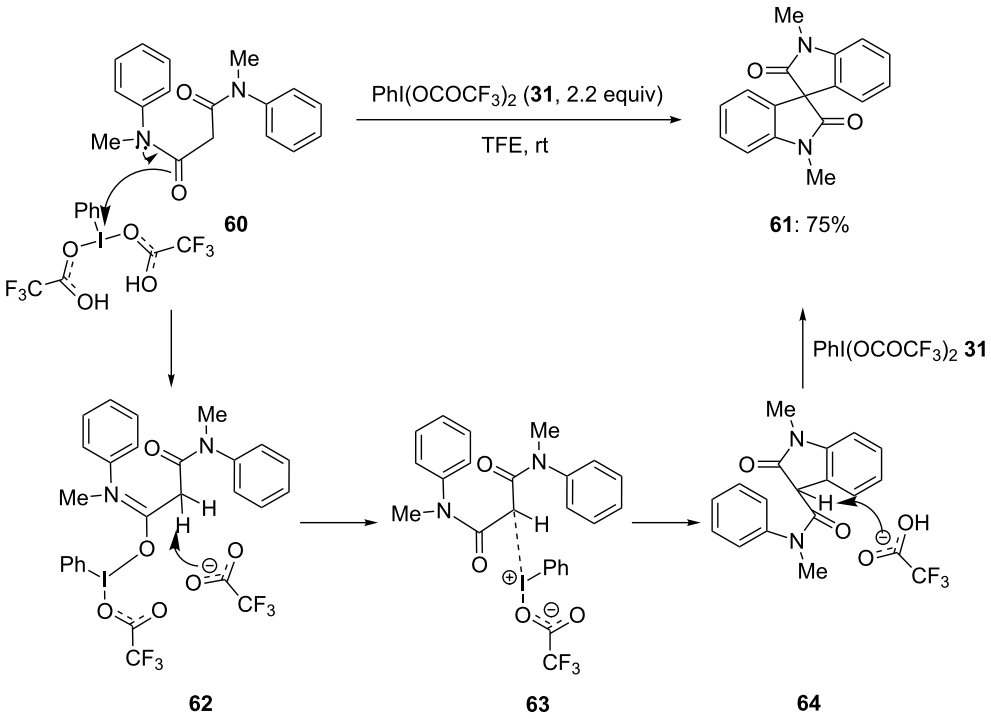
Scheme 19: Iodine(III)-mediated spirocyclization of *para*-substituted amide **58** to spirolactam **59** by the reaction with bis(iodoarene) **25** in the presence of *m*CPBA.



60 61: 40–75%

Scheme 20: Iodine(III)-mediated synthesis of spirolactams **61** from anilide derivatives **60**.

(Scheme 21). According to the proposed mechanistic pathway, the reaction was initiated with formation of an intermediate **63** by the attack of the carbonyl oxygen to electrophilic iodine(III) reagent **31** which could be rearranged to compound **64**. Finally, the acetate anion attacks the β-hydrogen of **64** to form spirolactam product **61**.



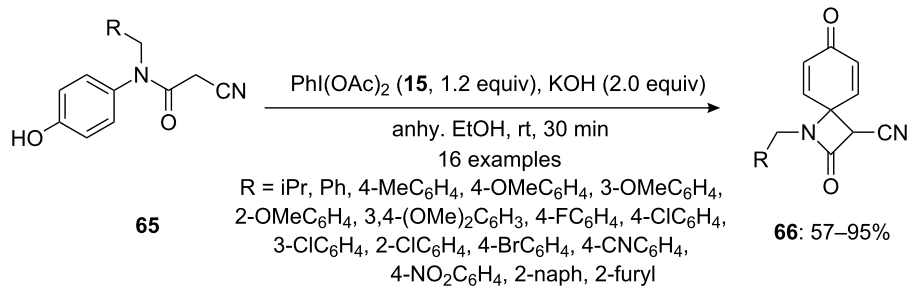
Scheme 21: PIFA-mediated oxidative cyclization of anilide **60** to bis-spirobisoxindole **61**.

In 2014, Xu and Abdellaoui [93] reported a nucleophilic intramolecular cyclization of phenylacetamides **65** to spirocyclic lactams **66** via iodine(III)-mediated spirocarbocyclizations. In literature, there are limited methods available for the synthesis of spiro-β-lactam-3-carbonitrile which is widely used as an antibiotic [94]. In this methodology, *N*-(*p*-hydroxyphenyl)cyanoacetamides **65** were cyclized to corresponding 4-spiro-β-lactam-3-carbonitriles **66** in useful yields using PIDA (**15**) as an electrophile in the presence of KOH as base in anhydrous ethanol at room temperature (Scheme 22).

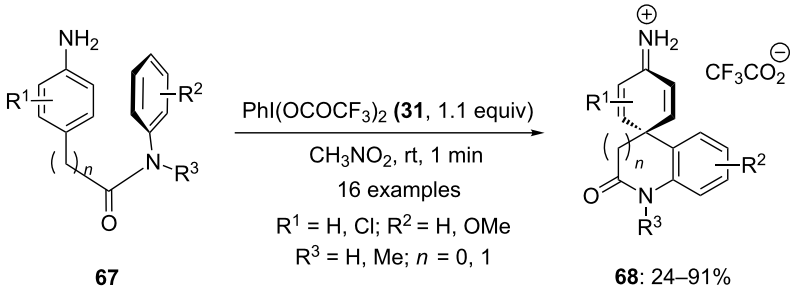
In 2014, Fan and co-workers [95] investigated an efficient approach for the synthesis of a spirocyclic-skeleton-containing dieniminium moiety. Herein, arylamines **67** were cyclized to spirocyclic dieniminium salts **68** using PIFA (**31**) as an electrophilic species in nitromethane (Scheme 23). All the reactions were completed within a minute and desired lactams were isolated in good yields. The presence of electron-withdrawing groups at the aromatic ring shows a negative effect on the yield while the presence of electron-enriched groups afforded the products **68** in high yields.

In addition, Zhu and co-workers [96] developed another hypervalent iodine-mediated intermolecular spirocarbocyclization approach for synthesis of spirolactam. In this approach, *N*-methoxybenzamide **69** and diphenylacetylene (**70**) were treated in presence of PIFA (**31**) in dichloromethane to corresponding spirodienone compound **71** in 48% yield (Scheme 24). Additionally, trifluoroacetic acid (TFA) was used as an additive in the reaction.

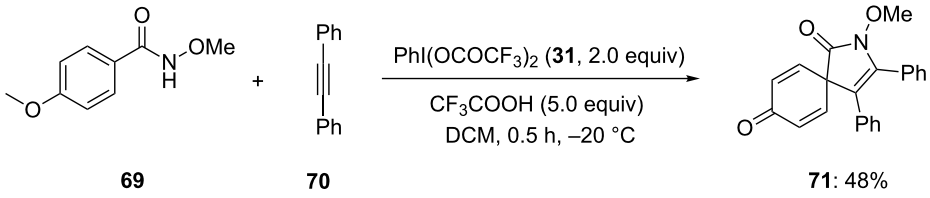
In 2015, Wang's group [97] reported an iodine(III)-mediated approach for the intermolecular spirocyclization of amides **72** with sulfonylhydrazides **73** to spirolactams **75**. In this method,



Scheme 22: PIDA-mediated spirocyclization of phenylacetamides **65** to spirocyclic lactams **66**.



Scheme 23: Oxidative dearomatization of arylamines **67** with PIFA (**31**) to give dieniminium salts **68**.



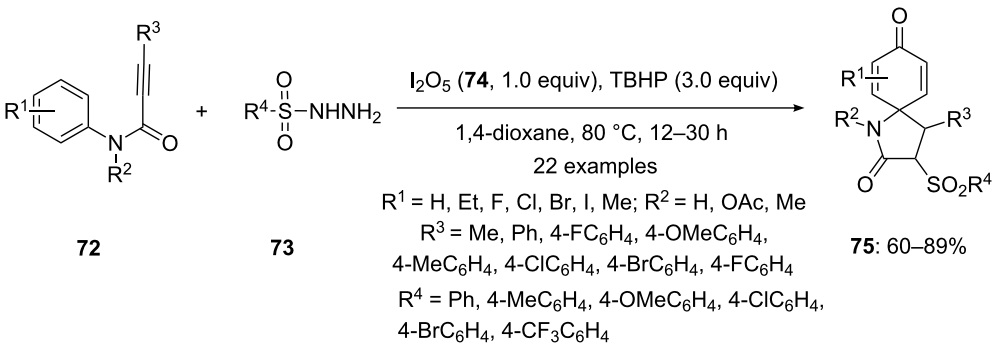
Scheme 24: PIFA-mediated oxidative spirocarbocyclization of 4-methoxybenzamide **69** with diphenylacetylene (**70**) to spirolactam **71**.

functionalized amides **72** containing an alkyne moiety and sulfonylhydrazides **73** undergo intermolecular spirocyclization in presence of I_2O_5/TBHP oxidative system to give the sulfonated spirolactams **75** in high yields (Scheme 25). This oxidative system found to be more efficient and could sustain the presence of diverse functional groups. The structure of **75** was confirmed by single crystal X-ray crystallography.

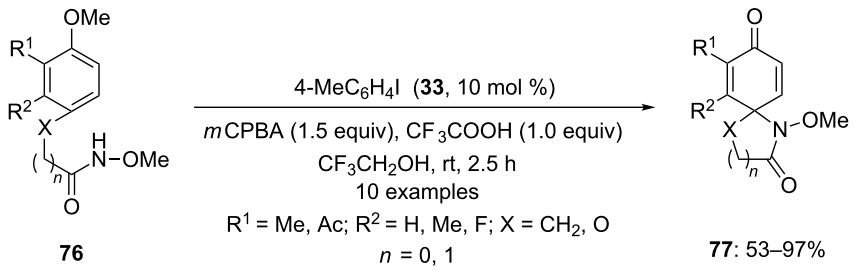
3.2. Using hypervalent iodine reagents as catalysts

In 2007, Kita and co-workers [98] investigated the first iodoarene-catalyzed spirocyclization of functionalized amides **76** to spirocyclic systems **77** by carbon–nitrogen bond formation using 10 mol % of iodotoluene **33** as precatalyst, 1.0 equivalent of CF_3COOH as an additive and *m*CPBA as terminal oxidant in trifluoroethanol (Scheme 26). The spirocyclic compounds **77** were isolated in high yields. The cyclization reaction was probably initiated by in situ generated active iodine(III) species by the oxidation of iodotoluene **33** in the presence of *m*CPBA.

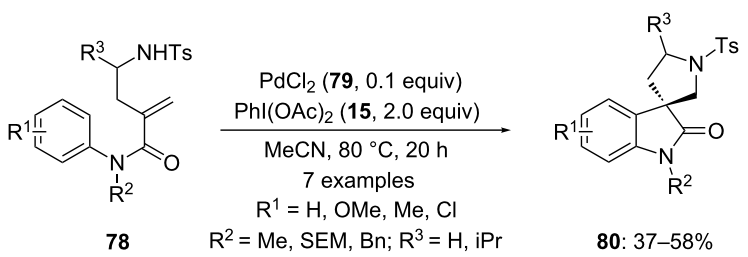
In 2010, Zhu's research group [99] achieved a Pd-catalyzed synthesis of spirolactams **80** by the cyclization of functionalized amides **78** using 10 mol % $PdCl_2$ (**79**) in presence of $PhI(OAc)_2$ (**15**) in acetonitrile solvent at 80 °C. The spirocyclic products **80** were obtained in moderate yields (Scheme 27). It was observed that the introduction of electron-donating group at *para*-position in substrates **78** gave the desired products in good yields whereas introduction of strong electron with-



Scheme 25: Synthesis of spiroxyindole **75** using I_2O_5/TBHP oxidative system.



Scheme 26: Iodine(III)-catalyzed spirolactonization of functionalized amides **76** to spirolactones **77** using iodotoluene **33** as a precatalyst and *m*CPBA as an oxidant.



Scheme 27: Intramolecular cyclization of alkenes **78** to spirolactams **80** using Pd(II) **79** and PIDA (**15**) as the oxidative system in acetonitrile.

drawing groups resulted in a decrease in the yield of spirocyclic products.

Kita and co-workers [100] developed another catalytic approach for the cyclization of amides **76** to spirolactams **77**. In this approach, 2 mol % of bis(iodoarene) **81** was used as precatalyst and peracetic acid (PAA) as an oxidant instead of *m*CPBA, which plays an important role in generation of active iodine(III) species. The bis(iodoarene) **81** was oxidized to a unique μ-oxo-bridged hypervalent iodine(III) species in situ, wherein PAA is used as extremely green oxidant which releases non-toxic co-products (Scheme 28).

In 2011, Yu and co-workers [101] developed an intramolecular lactonization of *p*-substituted phenols **82** to spirooxindoles **83** using 10 mol % of iodobenzene (**35**) as precatalyst, *m*CPBA as an external oxidant and TFA as additive. All the catalytic reactions were performed in dichloromethane and spirolactams **83** were isolated in good to excellent yields (Scheme 29). It was noted that *m*CPBA/TFA combination did not work well for some transformations and it was replaced with oxidant urea·H_2O_2 and TFAA as an additive.

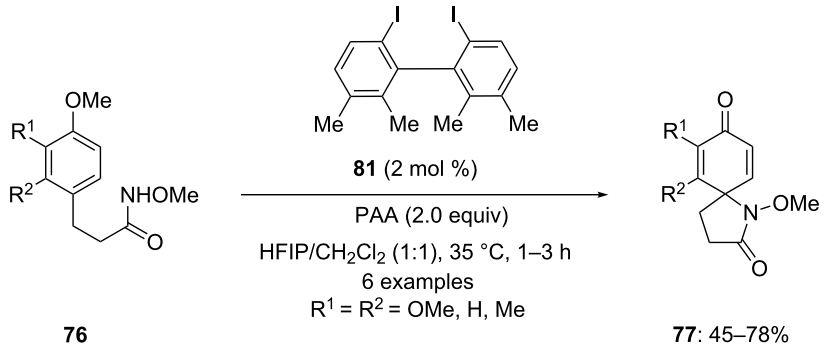
3.3. Stereoselective synthesis of spirolactams

Gong and co-workers [102] efficiently cyclized 1-hydroxy-*N*-aryl-2-naphthamides **84** to corresponding spirolactam derivatives **86** using chiral iodoarene **85** as precatalyst, *m*CPBA as an oxidant and TFE as an additive. The presence of 10.0 equivalents of H_2O was required to get the reaction products in high yields with up to 92% ee (Scheme 30). The chiral hypervalent-λ^3-iodanes were generated in situ by the oxidation of the chiral C_2-symmetric iodoarene **85** that was playing the key role for the oxidative spirocyclization of phenols.

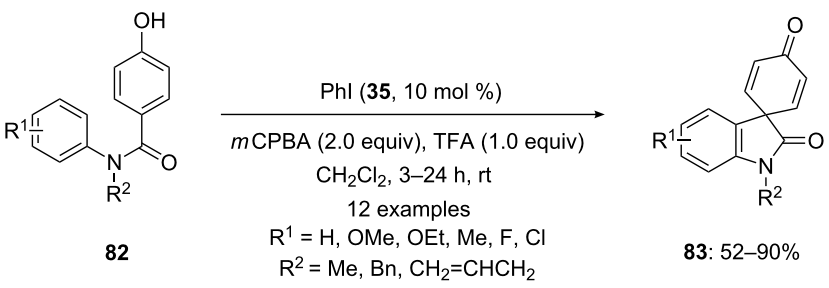
In addition, *N*-methyl-*N*-(2-naphthyl)-2-naphthamides **87** were also cyclized to corresponding spiro compounds **88** in high yields and with upto 84% enantiomeric excess (Scheme 31). Furthermore, the absolute configuration of **88** was assigned by its single crystal X-ray analysis.

3.3. Application of spirolactams in natural product synthesis

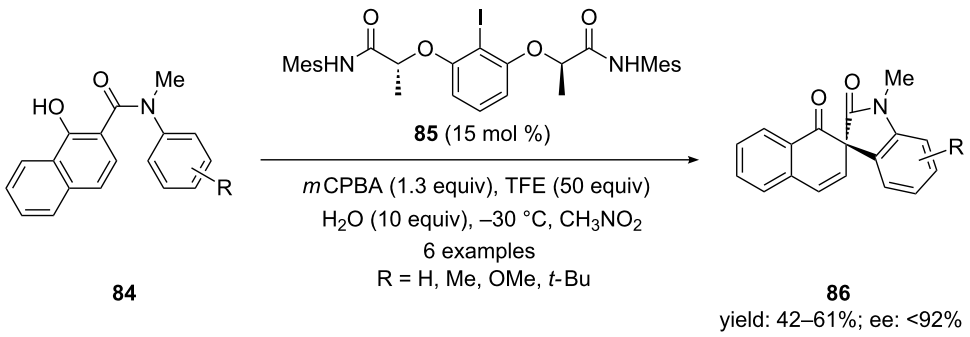
In 2001, Ciufolini and co-workers [103] employed PIDA (**15**) as an electrophile during the synthesis of naturally occurring tricyclic azaspirane derivative TAN1251C. In this report,



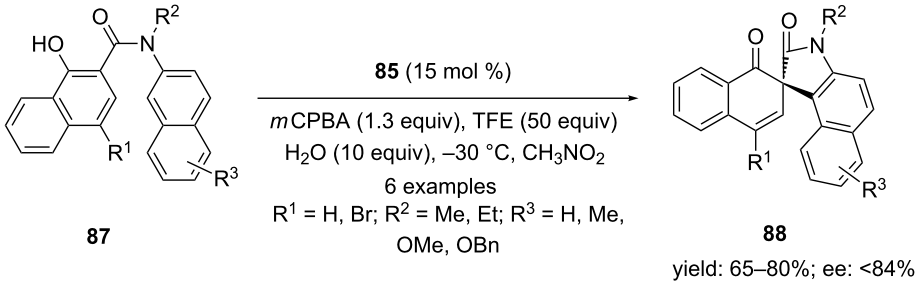
Scheme 28: Iodine(III)-catalyzed spiroaminocyclization of amides **76** to spirolactam **77** using bis(iodoarene) **81** as a precatalyst in the presence of PAA.



Scheme 29: Iodine(III)-catalyzed spirolactonization of *N*-phenyl benzamides **82** to spirolactams **83** using iodobenzene **35** as a precatalyst.

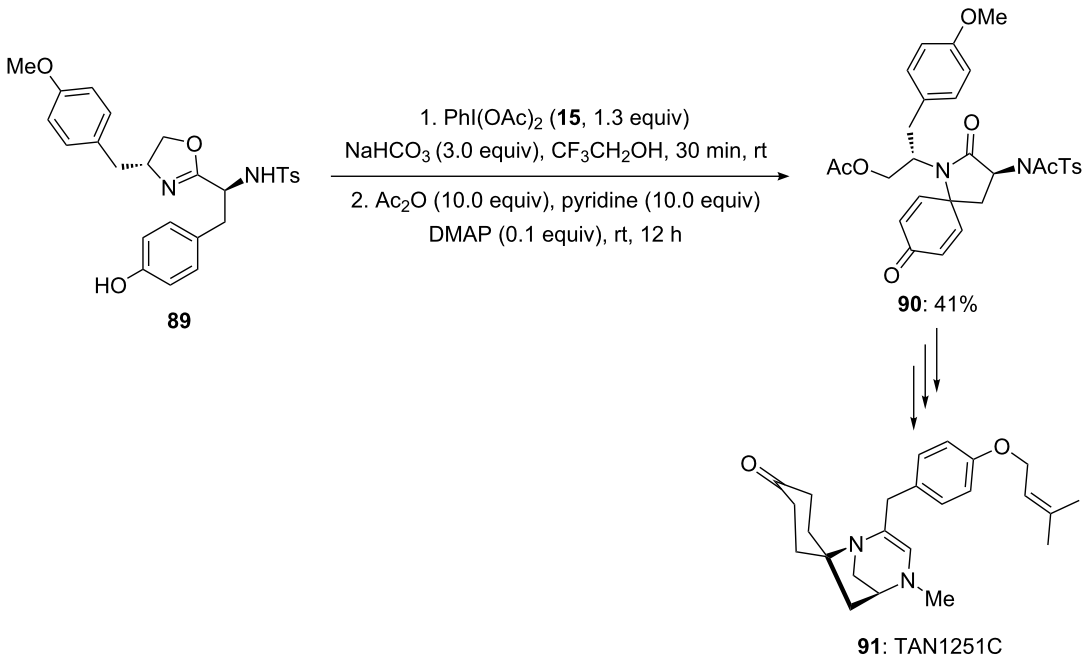


Scheme 30: Iodine(III)-mediated asymmetric oxidative spirocyclization of phenols **84** to spirolactams **86** using chiral iodoarene **85** as precatalyst.



Scheme 31: Iodine(III)-catalyzed asymmetric oxidative spirocyclization of *N*-aryl naphthamides **87** to spirocyclic compounds **88** using chiral iodoarene **85** as precatalyst.

phenolic 3-arylpropionamide **89** was cyclized to spirolactam **90** in 41% yield using PIDA (**15**) as an electrophile in the presence of $NaHCO_3$ in trifluoroethanol (TFE) at room temperature followed by addition of acetic anhydride and pyridine in the presence of 10 mol % DMAP (Scheme 32). In addition, spirocyclic product **90** was used as key precursor in the synthesis of naturally occurring tricyclic azaspirane derivative TAN1251C **91** in a sequence of steps.



Scheme 32: Cyclization of *p*-substituted phenolic compound **89** to spirolactam **90** using PIDA (**15**) in TFE.

Furthermore, PIDA (**15**) was used as an electrophile during the synthesis of biologically active molecule FR901483 by the same research group [104]. In this report, spirocyclic oxazoline **93** was prepared by starting from *para*-substituted phenolic compound **92** under the reaction conditions mentioned in Scheme 32 (Scheme 33).

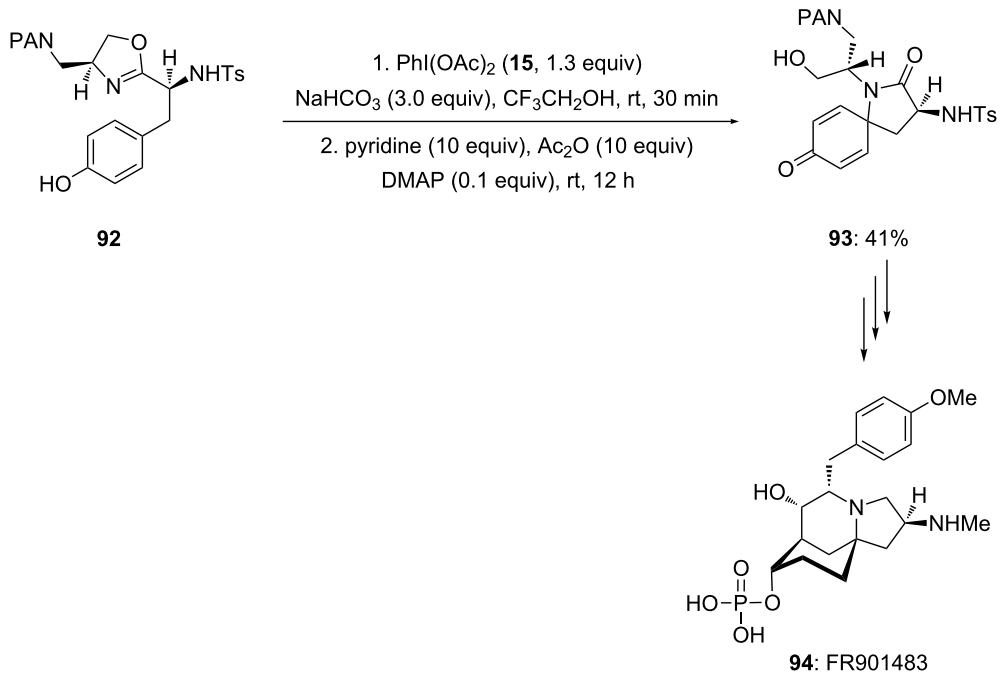
In 2002, Honda and co-workers [105] reported the synthesis of naturally occurring (−)-TAN1251A (**95**) employing an oxidation of phenols via an dearomatization process. In this report, *para*-substituted phenolic compound **48** was cyclized to spirocyclic lactam **49** using PIDA (**15**) as an electrophile. The spirocyclic compound **49** was achieved in 69% yield (Scheme 34). Additionally, synthesized spirocyclic compound **49** was converted to natural product **95** in few chemical steps.

4. Synthesis of spirocarbocycles

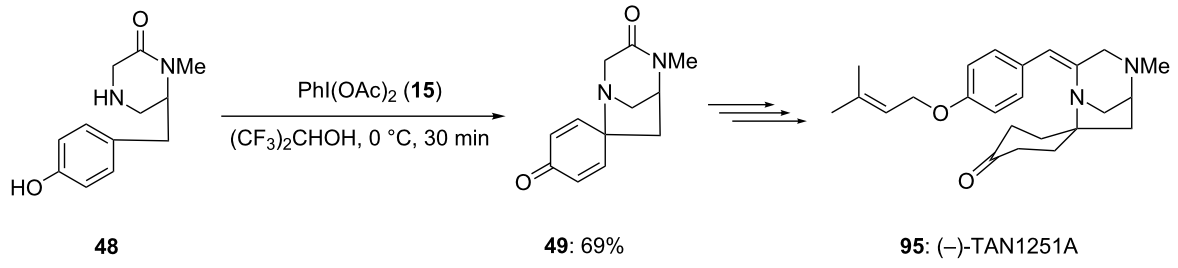
4.1. Using stoichiometric amounts of iodine(III) reagents

Furthermore, *O*-silylated phenolic compound **96** was spirocyclized to spirocarbocyclic compound **97** in 95% yield using bridged iodine(III) reagent **28** as an electrophile and trifluoroethanol (TFE) as the solvent at room temperature (Scheme 35). Compound **97** was further used as substrate for the synthesis of discorhabdin alkaloids [106,107].

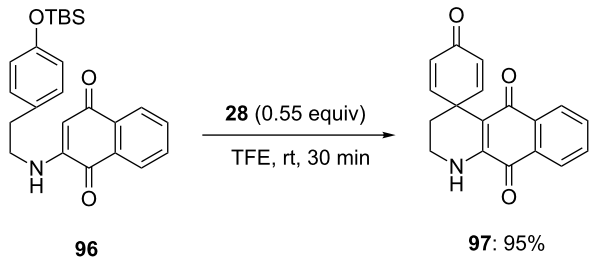
In 1996, Kita and co-workers [108] developed an intramolecular cyclization of *ortho*-substituted phenols **98** to aza-spirocarbocyclic compounds **101** via hypervalent iodine-mediated spirocarbocyclization reactions using **31** as an electrophile. In this methodology, *ortho*-substituted phenolic derivatives **98** were



Scheme 33: Iodine(III)-mediated synthesis of spirocyclic compound **93** from substrates **92** using PIDA (**15**) as an electrophile.



Scheme 34: Iodine(III)-mediated spirocyclization of *p*-substituted phenol **48** to spirocyclic compound **49** using PIDA (**15**) as an electrophile.

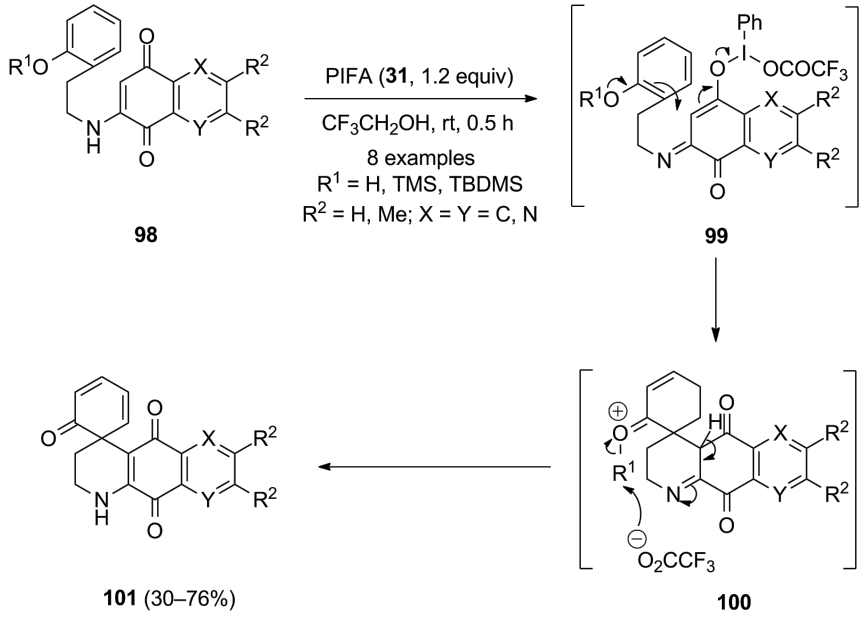


Scheme 35: Bridged iodine(III)-mediated spirocyclization of *O*-silylated phenolic compound **96** in the synthesis of spirodienone **97**.

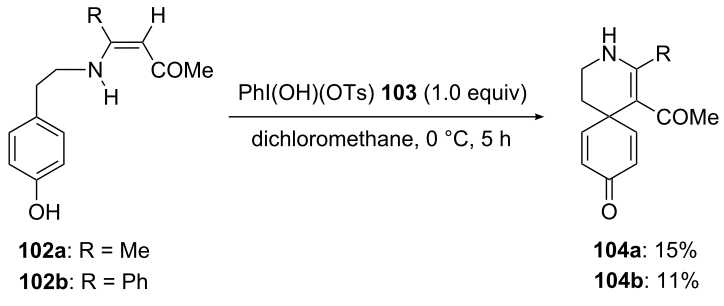
treated with stoichiometric amounts of PIFA (**31**) in trifluoroethanol at room temperature for 0.5 h to afford spirocyclic compounds **101** in good yields (Scheme 36).

Like PIDA and PIFA, Koser reagents are other iodine(III) reagents known to behave as electrophiles. In 2000, Spyroudis and co-workers [109] reported the spirocyclization of *para*-substituted phenols **102** to corresponding spirocarbocyclic derivatives **104** via dearomatization process using Koser reagent. In this reaction, substrates **102** were reacted with a stoichiometric amount of [(hydroxy)(tosyloxy)iodo]benzene (**103**) in dichloromethane at 0 °C. The spirocyclic products **104** were obtained in poor yields (Scheme 37).

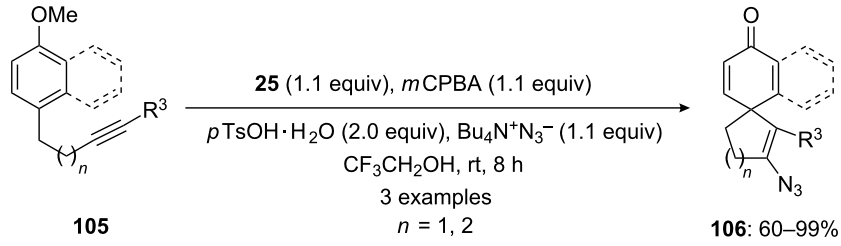
Furthermore, Kita and his research group [71] reported the synthesis of spirocarbocyclic compounds **106** from arylalkynes **105** using a hypervalent iodine reagent generated in situ by the oxidation of bis(iodoarene) **25** in the presence of *m*CPBA as an terminal oxidant (Scheme 38).



Scheme 36: PIFA-mediated approach for the spirocyclization of *ortho*-substituted phenols **98** to aza-spirocarbocyclic products **101**.



Scheme 37: Oxidative cyclization of *para*-substituted phenols **102** to spirocarbocyclic compounds **104** using Koser reagent **103**.



Scheme 38: Iodine(III)-mediated spirocyclization of aryl alkynes **105** to spirocarbocyclic compound **106** by the reaction with bis(iodoarene) **25** in the presence of *m*CPBA.

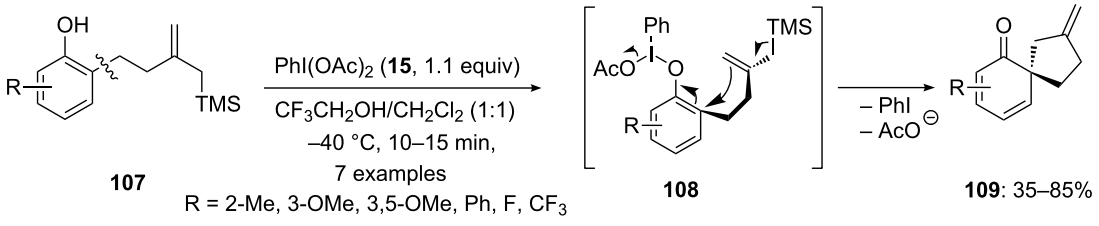
Wang and co-workers [110] developed a hypervalent iodine-mediated synthesis of *ortho*-spirocarbocyclic compounds via dearomatization of *ortho*-substituted phenols. In this reaction, *ortho*-substituted phenols **107** were cyclized to form spirocarbocyclic compounds **109** in useful yields. All the reactions were performed in a CF_3CH_2OH/CH_2Cl_2 (1:1) solvent combination using PIDA (**15**) as an electrophile at −40 °C for 10–15 minutes (Scheme 39). This is an example of an *ortho*-oxidative phenol dearomatization reaction wherein there is the formation of the steriogenic center at the spiro-ring junction. This approach provides an easy and direct method for the construction of *ortho*-spirocarbocyclic compounds which is broadly found to originate in most of bioactive natural products [111,112].

4.3. Application of spirocarbocyclic compounds in natural product synthesis

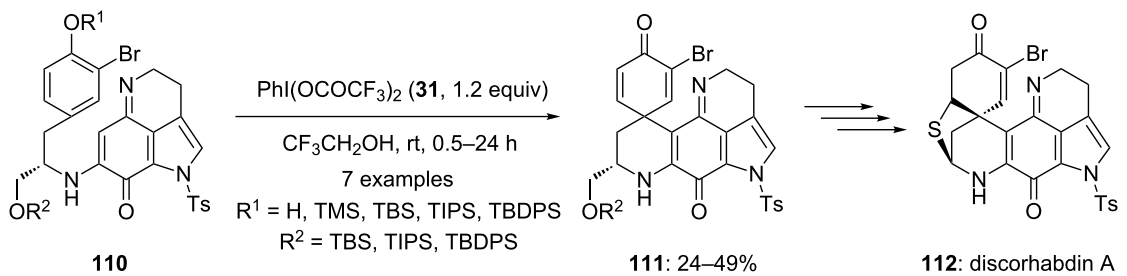
In 2003, Kita and co-workers [113,114] employed a iodine(III) reagent during the total synthesis of sulfur-containing alkaloid **112**. Initially, the substrates **110** were cyclized to spirodienone derivatives **111** in useful yields using PIFA (**31**) as source of electrophile in trifluoroethanol at room temperature (Scheme 40). Furthermore, synthesized compounds **111** were converted into the natural product discorhabdin A (**112**).

In 2006, Honda and co-workers [115] reported the total synthesis of spiro-isoquinoline alkaloid (±)-annosqualine (**1**). In this report, the substrate **113** was cyclized to form spirocyclic compound **114** via desilylation with TBAF in THF followed by reaction with *n*-BuLi in hexafluoroisopropanol using PIDA (**15**) at 4 °C (Scheme 41). This oxidative cyclization of enamide substrate **113** afforded synthetically useful spiroenamide **114**, which was used as key intermediate for total synthesis of annosqualine (**1**). The synthesis of natural product **1** was achieved in two steps starting from synthesized compound **114**.

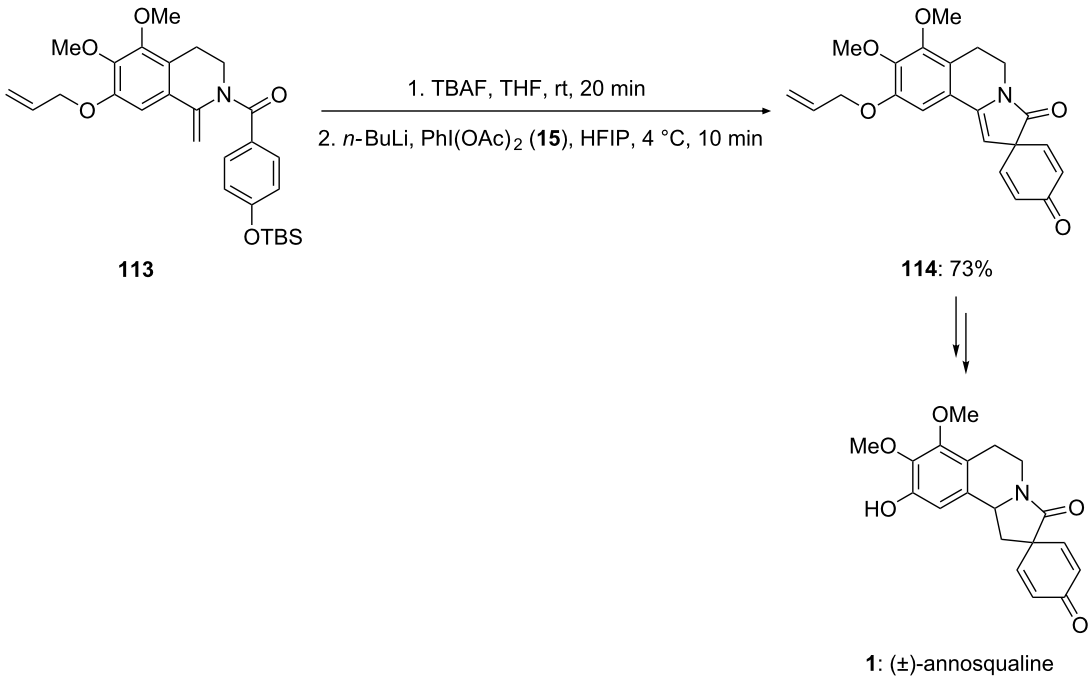
Honda and Shigehisa [116] reported the total synthesis of naturally occuring compound stepharine (**3**) starting from aro-



Scheme 39: Iodine(III)-mediated spirocarbocyclization of *ortho*-substituted phenols **107** to spirocarbocyclic compounds **109** using PIDA **15**.



Scheme 40: PIFA-mediated oxidative cyclization of substrates **110** to spirocarbocyclic compounds **111**.

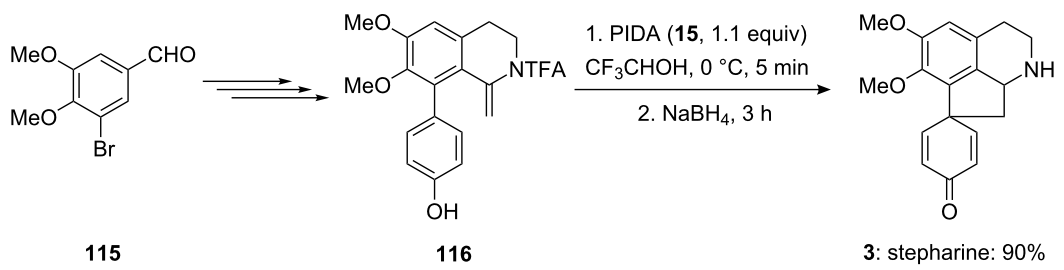


Scheme 41: Iodine(III)-mediated cyclization of substrate **113** to spirocyclic compound **114**.

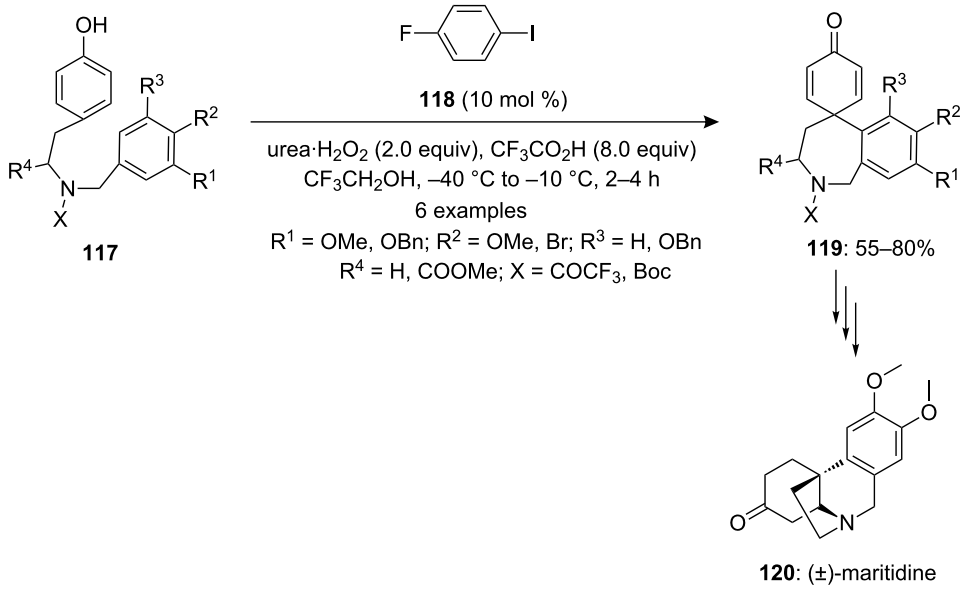
matic aldehyde **115**. Initially, substituted phenolic compound **116** was prepared in seven steps from aldehyde **115**. Furthermore, the synthesized compound **116** was converted into the natural product stepharine (**3**) by reaction with PIDA (**15**) in trifluoroethanol (TFE) followed by the reduction with $NaBH_4$. The synthesis of the natural product stepharine (**3**) was obtained in 90% yield by starting from phenolic substrate **116** (Scheme 42).

In 2008, Kita and co-workers [117] developed an iodine(III)-catalyzed approach for the spirocyclization of *p*-substituted phenols **117** to spirocarbocyclic products **119** in good yields using a catalytic amount of iodoarene **118** and urea·H_2O_2 as an oxidant. Probably, the active hypervalent iodine(III) species was generated in situ by the oxidation of iodoaerene **118** in the presence of urea·H_2O_2 oxidant (Scheme 43). Furthermore, the synthesized spirocyclic compounds were used as synthetic intermediate for the synthesis of biologically active natural product amaryllidaceae alkaloids such as (±)-maritidine (**120**) [118-120].

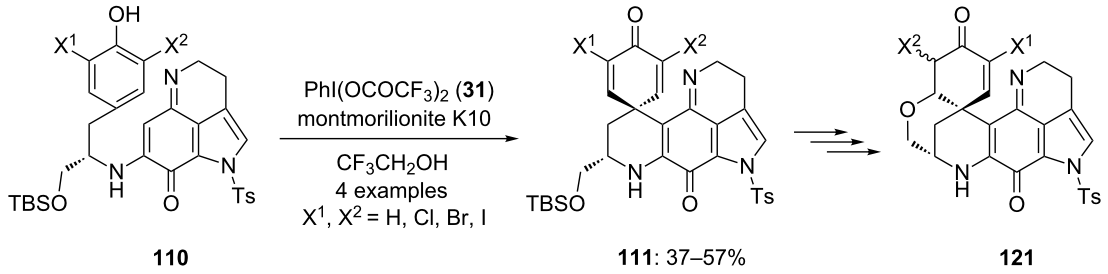
In 2009, Kita and co-workers [121] reported the synthesis of various oxygen analogues of naturally occurring compound discorhabdin A starting from substrate **110** in few chemical steps. Discorhabdin A is an alkaloid that shows various biological activities including strong cytotoxic activity [122]. During the first step, starting substrates **110** were cyclized to spirocyclic compounds **111** in useful yields using PIFA (**31**) in presence of montmorillonite K10 in trifluoroethanol (Scheme 44). Furthermore, synthesized spirocyclic compounds **111** were used as key precursors for the synthesis of oxygen analogues of discorhabdin A (**121**).



Scheme 42: Iodine(III)-mediated spirocyclization of phenolic substrate **116** to the spirocarbocyclic natural product stepharine **3** using PIDA (**15**).



Scheme 43: Iodine(III)-catalyzed spirocyclization of phenols **117** to spirocarbocyclic products **119** using iodoarene **118** in the presence of the oxidant urea·H_2O_2.



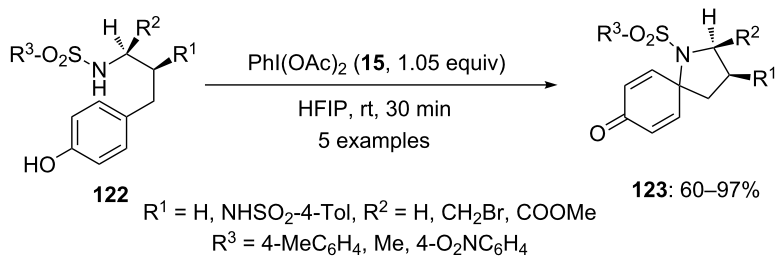
Scheme 44: PIFA-mediated spirocyclization of **110** to spirocyclic compound **111** using PIFA (**31**) as electrophile.

5. Synthesis of miscellaneous spirocyclic compounds

5.1. Using stoichiometric amounts of iodine(III) reagents

In 2002, Ciufolini and co-workers [123] reported the spirocyclization of various phenolic sulfonamides **122** to spiropyrrolidines **123** using PIDA (**15**). In this reaction, sulfonamides **122** undergo N-acylation, wherein various homotyramine sulfonamides were treated with electrophile PIDA (**15**) in hexafluoroisopropanol to give the spirocyclic products **123** in high yields (Scheme 45). However, the similar spirocyclization could not successfully applied for the construction of six-membered spiropiperidine systems.

In 2015, Jain and Ciufolini [124] developed PIDA-mediated spirocyclization of 2-naphtholic sulfonamides **124** to spiro-



Scheme 45: PIDA-mediated spirocyclization of phenolic sulfonamide **122** to spiroketones **123**.

pyrrolidine derivatives **125**. The spirocyclization reactions were carried out by treating *N*-sulfonamide substrates **124** with (diacetoxyiodo)benzene (**15**) in trifluoroacetic acid (TFA) and spiropyrrolidines **125** were isolated in good to excellent yields (Scheme 46). However, the presence of an electron-donating functionality at *para*-position to the phenolic group induced no spirocyclization product.

In 2016, Bray and Shirley [125] reported the oxidative spirocyclization of *meta*-substituted phenol **126** to tricyclic spiroketals **127a**,**b** in 56% yield using PIDA (**15**) as electrophilic species in acetonitrile at room temperature (Scheme 47). The mixture of both isomers was separated by flash column chromatography and the stereochemistry of major isomer **127a** was assigned on the basis of NOE. This spirocyclic functionality is the basic nucleus found in the *phorbaketal* family of natural products.

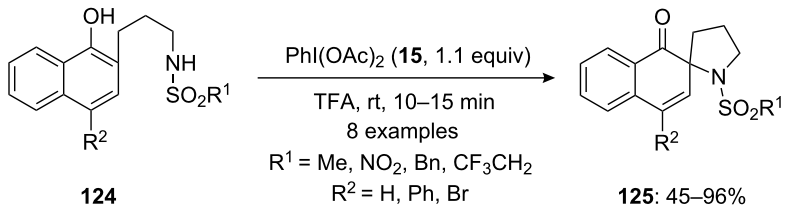
5.2. Stereoselective synthesis of chiral spirocyclic ketals

Recently, Ishihara and co-workers [126] synthesized chiral C_2-symmetric iodoarene **129a** and **129b** (Figure 3) in few steps and used as precatalyst in iodine(III)-catalyzed enantioselective synthesis of spiroketals with high selectivities.

In this report, substrates **128** were reacted with 10 mol % of chiral iodoarene **129a** and **129b** in the presence of *m*CPBA oxidant in chloroform at 0 °C. The desired *ortho*-spirocyclic ketals **130** were obtained in high yields with more than 93% enantiomeric excess (Scheme 48). Interestingly, the higher selectivities were observed with chiral hypervalent iodine(III) reagent **129b** compared to **129a**.

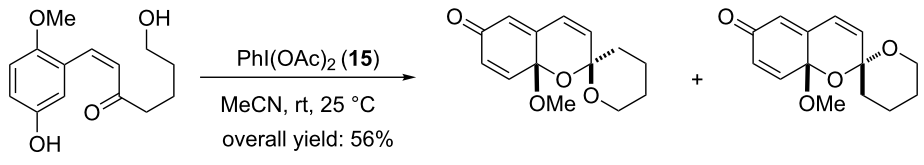
5.3. Application of miscellaneous spirocyclic compounds in natural product synthesis

Various hypervalent iodine reagents have been proved as vital reagents during the synthesis of several natural products containing spirocyclic skeleton. In 1999, Ley and co-workers [127] used polymeric PIDA reagent **132** to achieve the synthesis of spirocyclic core of natural product (+)-epidihydromaritidine (**134**). In this report, *para*-substituted phenol **131** was cyclized to spirodienone **133** using polymer supported (diacetoxy)iodobenzene reagent **132** (Scheme 49). The desired product **133** was



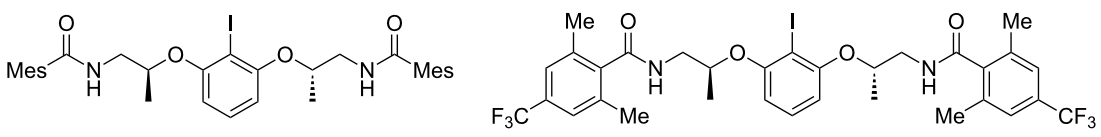
124 **125**: 45–96%

Scheme 46: Iodine(III)-mediated oxidative spirocyclization of 2-naphthol derivatives **124** to spiropyrrolidines **125**.



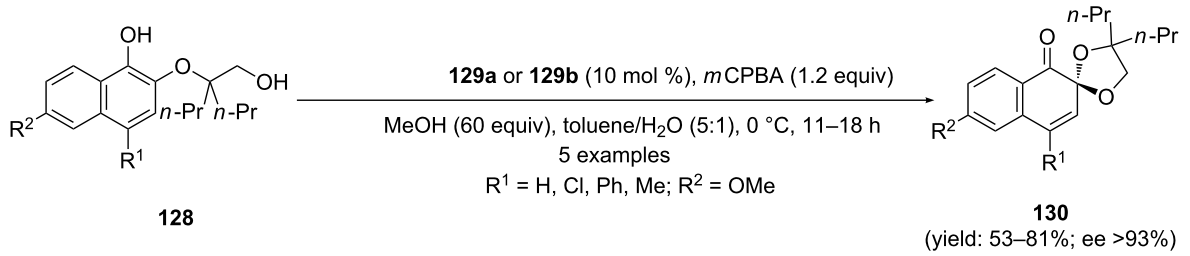
126 **127a** **127b**

Scheme 47: PIDA-mediated oxidative spirocyclization of *m*-substituted phenols **126** to tricyclic spiroketals **127**.



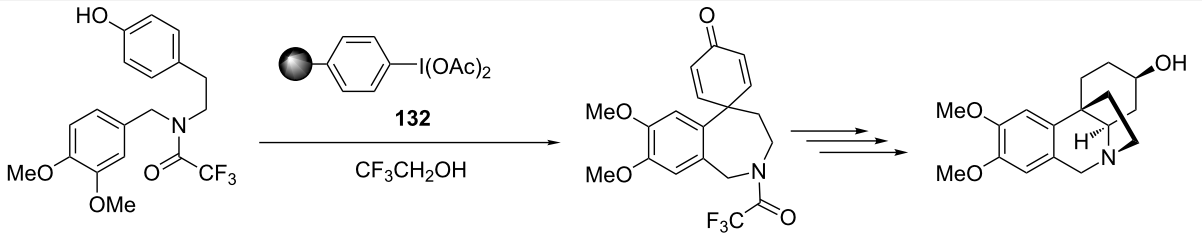
129a **129b**

Figure 3: The structures of chiral organoiodine(III) catalysts **129a** and **129b**.



128 **130** (yield: 53–81%; ee >93%)

Scheme 48: Iodine(III)-catalyzed oxidative spirocyclization of substituted phenols **128** to spirocyclic ketals **130**.

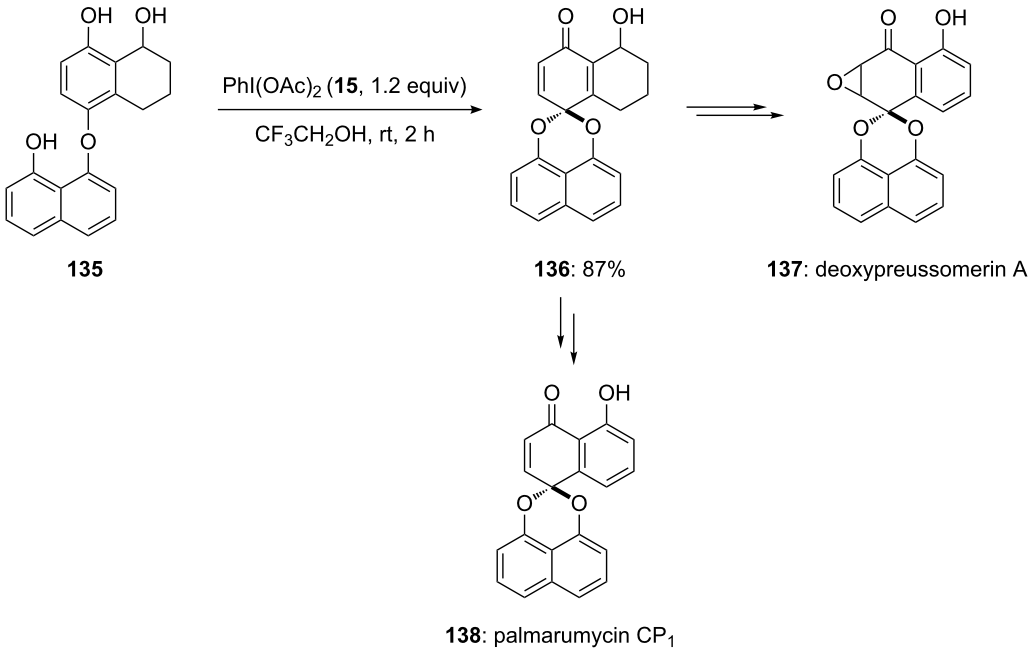


131 **133**: 70% **134**: (+)-epidihydromaritidine

Scheme 49: Oxidative spirocyclization of *para*-substituted phenol **131** to spirodienone **133** using polymer supported iodine(III) reagent **132**.

obtained in 70% yield without conventional work-up procedure and purification by chromatographic technique. Furthermore, synthesized spirocyclic compound **133** was converted into the alkaloid (+)-epidihydromaritidine (**134**) in three chemical steps.

Furthermore, Wipf and co-workers [128] reported a new synthetic route for the synthesis of deoxypreussomerin A (**137**) and palmarumycin CP_1 (**138**). During the first step, the synthesis of spirocyclic compound **136** was achieved in 87% yield by the reaction of PIDA (**15**) with the naphthol derivative **135** in trifluoroethanol at room temperature. Additionally, synthesized compound **136** was used as key intermediate in the total synthesis of natural products **137** and **138** (Scheme 50). Additionally, more analogues of palmarumycin CP_1 were synthesized later



135 **136**: 87% **137**: deoxypreussomerin A

138: palmarumycin CP_1

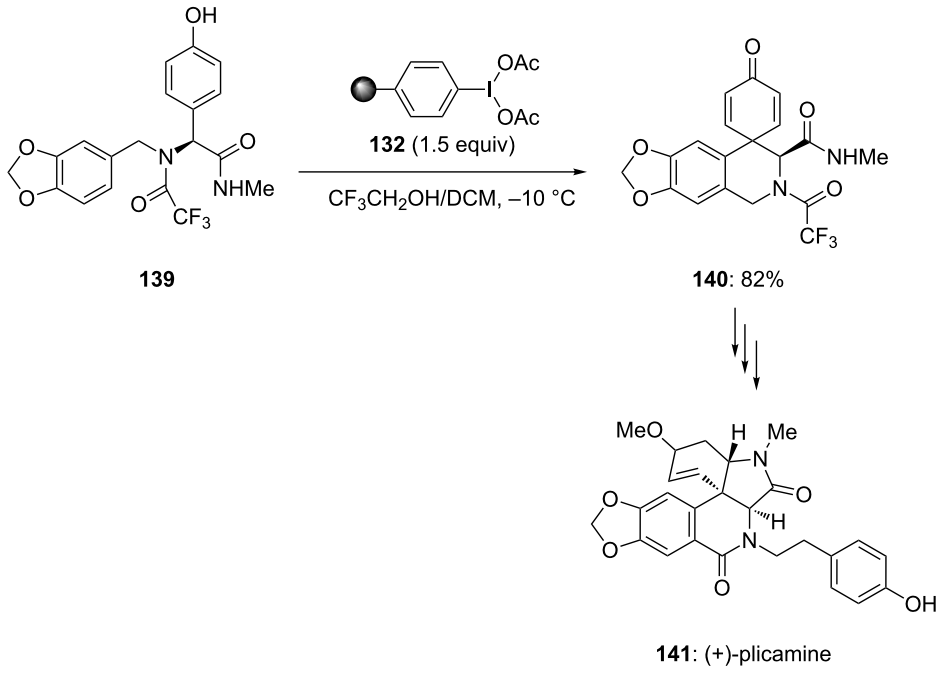
Scheme 50: Oxidative cyclization of bis-hydroxynaphthyl ether **135** to spiroketal **136** using PIDA (**15**) as an electrophile.

which were showing good thioredoxin–thioredoxin reductase (Trx-1/TrxR) inhibitory activity [129]. It was observed that the introduction of enone functionality in naphthoquinone spiroketal enhances the biological activity of palmarumycin **138**.

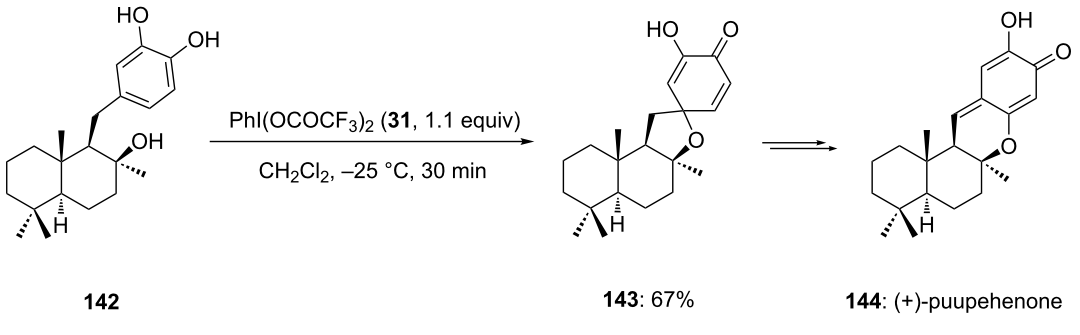
Furthermore, Ley and co-workers [130] employed polymer-supported iodine(III) reagent during the total synthesis of *Amaryllidaceae* alkaloid (+)-plicamine (**141**). In this report, spirodienone **140** was synthesized in 82% yield by the oxidative spirocyclization of *p*-substituted phenolic substrate **139** using polymer-supported iodonium diacetate **132** in 2,2,2-trifluoroethanol/DCM at −10 °C (Scheme 51). Additionally, the synthesized functionalized spirodienone **140** was used as precursor for the synthesis of (+)-plicamine (**141**).

In 2002, Quideau and co-workers [131] developed the synthesis of marine sesquiterpenoid (+)-puupehenone starting from catechol derivative **142**. Marine sesquiterpenoids are mainly known for their biological importance such as antitumor, antiviral and antibiotic properties [132]. In this report, the catechol-derived starting substrate **142** was cyclized to spirocyclic product **143** in 67% yield using PIFA (**31**) as suitable electrophile in dichloromethane at −25 °C (Scheme 52). Furthermore, the spirocyclic product **143** assists as the key synthetic intermediate in the synthesis of the marine natural product (+)-puupehenone (**144**).

In 2005, Marco and co-workers [133] reported the synthesis of naturally occurring spiroacetals aculeatin A (**146a**) and



Scheme 51: Oxidative spirocyclization of phenolic compound **139** to spirodienone **140** using polymer-supported PIDA **132**.



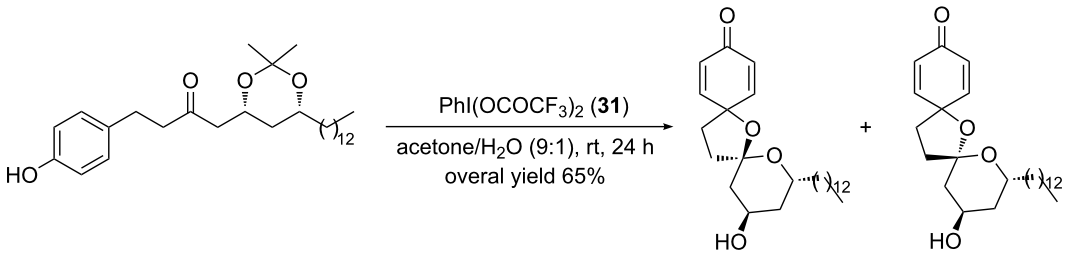
Scheme 52: PIFA-mediated oxidative cyclization of catechol derived substrate **142** to spirocyclic product **143**.

aculeatin B (**146b**) and iodine(III) reagent was used as an electrophile in one step during their synthesis. In this report, *p*-substituted phenolic substrate **145** was directly cyclized to naturally occuring spirocyclic optical isomers **146a** and **146b** using PIFA (**31**) in solvent combination of CH_3COCH_3/H_2O (9:1) at room temperature for 24 h. The spirocyclic compound **146** was obtained as two optical isomers in 5.5:1 ratio with overall 65% yield (Scheme 53).

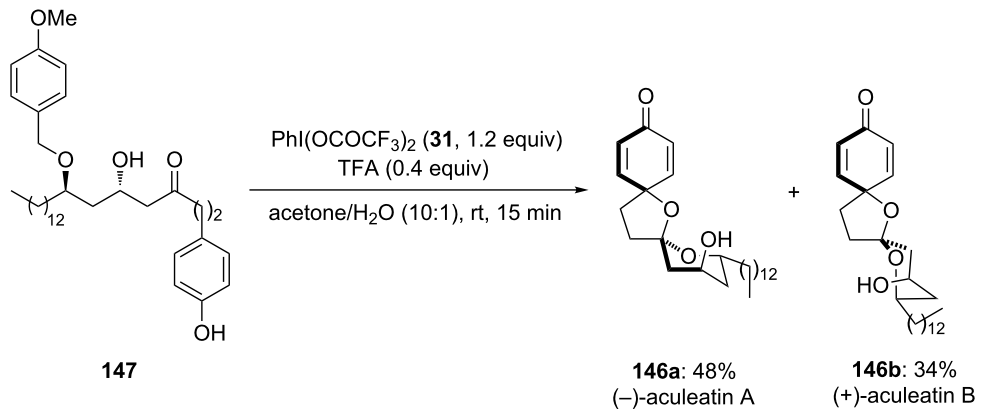
Furthermore, Peuchmaur and Wong [134] developed a new synthetic route for the total synthesis of the natural product (±)-aculeatin starting from substrate **147**. (±)-Aculeatin and its derivatives possessing spirocyclic skeleton are known for their antibacterial and antiprotozoal properties [135]. In this report, substrate **147** was cyclized to spiroketals, i.e., (−)-aculeatin (**146a**) and (+)-**146b** in 3:2 ratio. Herein, 1.0 equivalent of PIFA (**31**) was used as an electrophile, 0.4 equivalents of TFA as non-nucleophilic counter anion in solvent combination of Me_2CO/H_2O (10:1) at room temperature for 15 minutes (Scheme 54). The reaction proceeds through phenolic oxidative cyclization of phenolic substrate **147** which is the key step in the overall synthesis. The absolute configuration of the synthesised compound was determined by comparing the optical rotary values with that of natural compound (−)-aculeatin (**146a**) and (+)-aculeatin (**146b**).

In the continuation to previous work, the same research group [136] reported the synthesis of aculeatin D. In this report, the *p*-substituted phenolic compound **148** was directly cyclized to natural product aculeatin D (**149**) in 77% yield using PIFA (**31**) (Scheme 55).

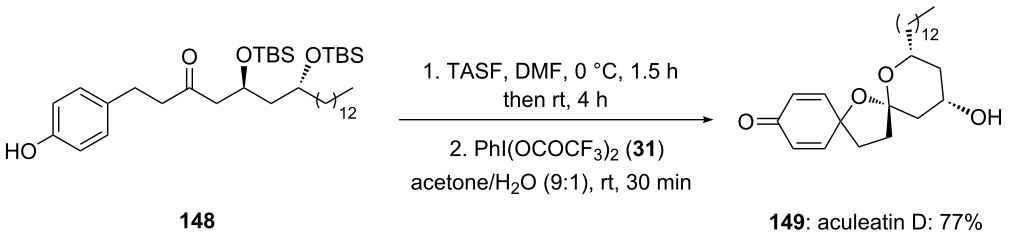
In 2006, Ley and co-workers [137] reported the total synthesis of natural product (±)-oxomaritidine (**151**) starting from phenolic substrates and polymer-supported hypervalent iodine reagent was used in one step. In this report, *p*-substituted phenolic compound **131** was cyclized to spirocyclic compound **133** in 50% yield containing a seven membered ring system. The cyclization reaction was carried out using polymer-supported PIFA reagent **150** as an electrophile and trifluoroacetic anhydride (TFAA) as an additive at 80 °C in a microreactor without using any solvent (Scheme 56). Additionally, synthesised compound **133** was used as precursor for the synthesis of (±)-oxomaritidine (**151**).



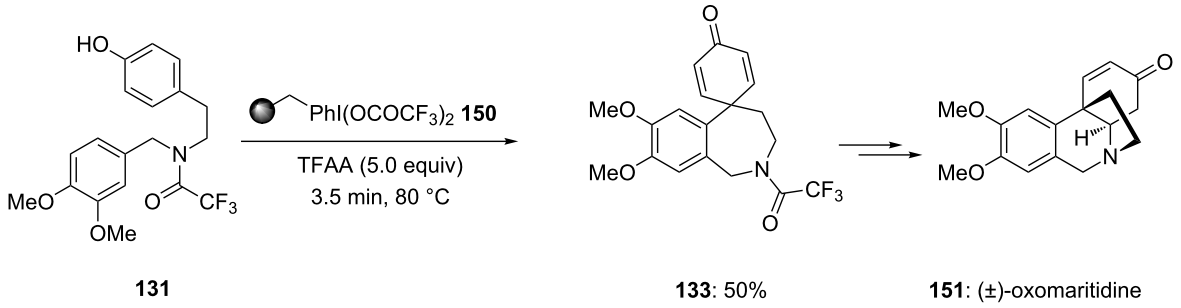
Scheme 53: Oxidative spirocyclization of *p*-substituted phenolic substrate **145** to aculeatin A (**146a**) and aculeatin B (**146b**) using PIFA (**31**).



Scheme 54: Oxidative spirocyclization of *p*-substituted phenolic substrate **147** to aculeatin A (**146a**) and aculeatin B (**146b**) using PIFA (**31**).



Scheme 55: Oxidative spirocyclization of *p*-substituted phenolic substrate **148** to aculeatin D (**149**) using electrophilic species PIFA (**31**).



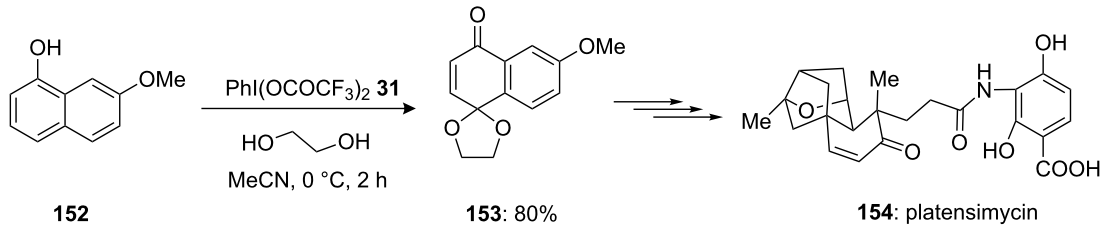
Scheme 56: Cyclization of phenolic substrate **131** to spirocyclic product **133** using polymer-supported PIFA **150**.

In 2007, Lalic and Corey [138] reported the synthetic pathway for the synthesis of the naturally occurring antibiotic platensimycin (**154**) which is isolated from *Streptomyces platensis*. In this report, 6-methoxy-1,4-naphthoquinone-4-ethylene ketal (**153**) was synthesized by intermolecular oxidative cyclization of 7-methoxy-α-naphthol (**152**) with ethylene glycol in the presence of PIFA (**31**) in acetonitrile. The reaction product **153** was isolated in 80% yield (Scheme 57). Additionally, the synthesised compound **153** was converted into the antibiotic platensimycin (**154**) after nine chemical steps.

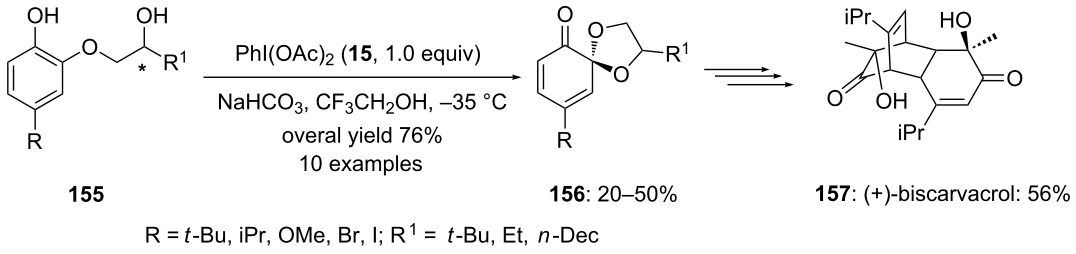
Furthermore, the same electrophilic species **15** was used to cyclize *ortho*-substituted phenolic compounds **155** to spiroketals **156** by Quideau and co-workers [139]. The cyclization reactions were performed in trifluoroethanol and spirocyclic ketals **156** were isolated in useful yields (Scheme 58). Additionally, the synthesized spiroketal **156** (R = iPr; R^1 = iPr) was used as substrate for the synthesis of natural product (+)-biscarvacrol (**157**).

Koag and Lee [140] reported the synthesis of a spiroketal by radical cyclization of a steroidal alkylamine in presence of PIDA (**15**) as oxidant and molecular iodine in dichloromethane at low temperature. It is an example of hypoiodite-mediated radical cyclization wherein the oxazaspiroketal moiety is formed which is further used as key intermediate for the synthesis of the natural product cephalostatin.

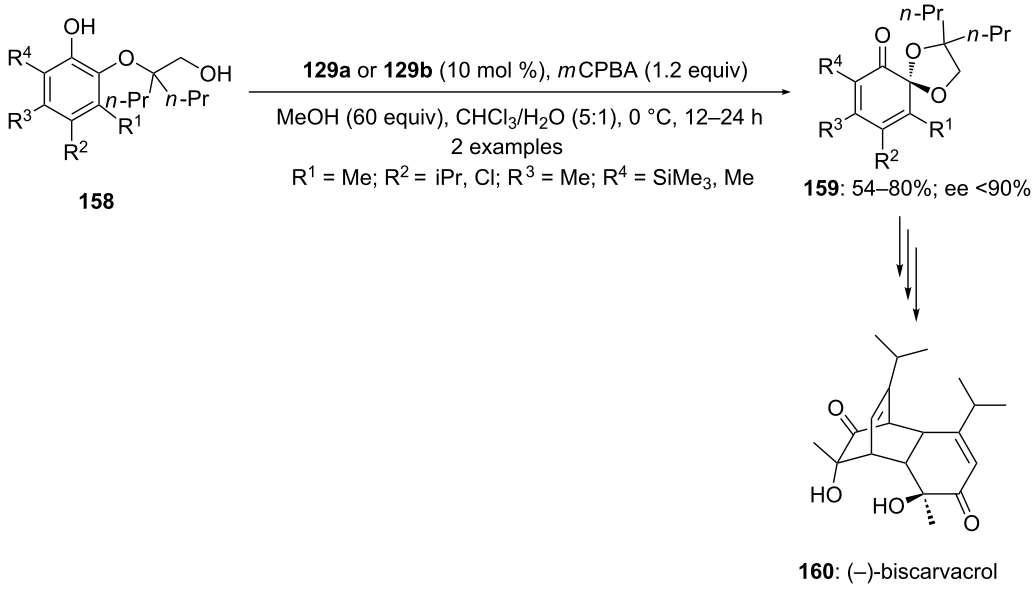
Additionally, spiroketals **159** were also synthesised by enatioselective spirocyclization of *ortho*-substituted phenols **158** using similar chiral auxiliaries **129a** or **129b** under similar reaction conditions mentioned in Scheme 48. Furthermore, the synthesized spiroketal **159** (R^2 = iPr; R^4 = $SiMe_3$) was used as synthetic intermediate for enantioselective synthesis of natural product (−)-biscarvacrol [8] (Scheme 59). Additionally, Parra and Reboredo compiled a review article where authors have covered various aspects of stereoselective spirocyclizations using chiral hypervalent iodine reagents [44]. This review article would be more interesting for readers and provides some significant



Scheme 57: Iodine(III)-mediated oxidative intermolecular spirocyclization of 7-methoxy-α-naphthol (**152**) to spirocyclic compound **153**.



Scheme 58: Oxidative cyclization of phenols **155** to spiro-ketals **156** using electrophilic species PIDA (**15**).



Scheme 59: Iodine(III)-catalyzed oxidative spirocyclization of *ortho*-substituted phenols **158** to spirocyclic ketals **159**.

information about the utility of chiral iodine(III) reagents in enantioselective spirocyclizations with suitable detail.

Conclusion

In this review article, we have summarized different approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents in stoichiometric or catalytic amounts. Various iodine(III) reagents such as (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene and Koser's reagent have been used to achieve a variety of spirocyclization reactions under mild reaction conditions. Various hypervalent iodine-catalyzed spirocyclization of functionalized phenols and aromatic amines have been successfully developed using iodoarenes as precatalyst in the presence of terminal oxidants. In addition, this review highlights various stereoselective spirocyclizations using chiral hypervalent iodine reagents. Finally, the recent applications of hypervalent iodine reagents in natural product synthesis are also covered.

Acknowledgements

Fateh V Singh is thankful to the DST New Delhi for providing Start-Up Research Grant (SB/FT/CS-068/2014) as financial support. All the authors are thankful to the chemistry division, VIT University, Chennai Campus, Chennai.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recent advances in hypervalent iodine(III)-catalyzed functionalization of alkenes

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Review

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Keywords:
asymmetric catalysis; functionalization of alkenes; hypervalent iodine(III)

Beilstein J. Org. Chem. **2018,** *14,* 1813–1825.
doi:10.3762/bjoc.14.154

Received: 07 April 2018
Accepted: 22 June 2018
Published: 18 July 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Hypervalent iodine(III) reagents have been well-developed and widely utilized in functionalization of alkenes, however, generally either stoichiometric amounts of iodine(III) reagents are required or stoichiometric oxidants such as *m*CPBA are employed to in situ generate iodine(III) species. In this review, recent developments of hypervalent iodine(III)-catalyzed functionalization of alkenes and asymmetric reactions using a chiral iodoarene are summarized.

Introduction

Hypervalent iodine(III) reagents, also named as λ^3-iodanes, have been widely used in organic synthesis since the 1990s, due to their stability, low toxicity and mild reaction conditions [1-10]. Structurally, they always adapt a distorted trigonal bipyramidal geometry in which the less electronegative aryl ring and two lone pairs of electrons are occupying the equatorial positions, and the electronegative ligands are in the apical positions (Figure 1, **1** and **2**) [8]. Hypervalent iodine(III) reagents are electrophile in nature, resulting from the node in a hypervalent nonbonding orbital, a 3-center-4-electron (3*c*-4*e*) bond (L–I–L), which is formed by the overlap of the 5p orbital of iodine atom with the orbitals of two ligands (Figure 1) [9].

The chemistry of hypervalent iodine(III) reagents is now a well-established area in organic chemistry. They are efficient oxidants in many synthetic transformations, such as oxidation of alcohols and phenols, α-functionalization of carbonyl compounds, spirocyclizations, as well as functionalization of alkenes and alkynes [10-17]. In recent years, especially the functionalization of alkenes has attracted much attention [18-20] and in some cases, hypervalent iodine(III) reagents were applied to oxidize transition metals [21-25]. In an alternative way, the electrophilic hypervalent iodine(III) reagents can activate alkenes directly in a metal-free manner. Based on this strategy, dichlorination [26], 1,2-difluorination [27], gem-diflu-

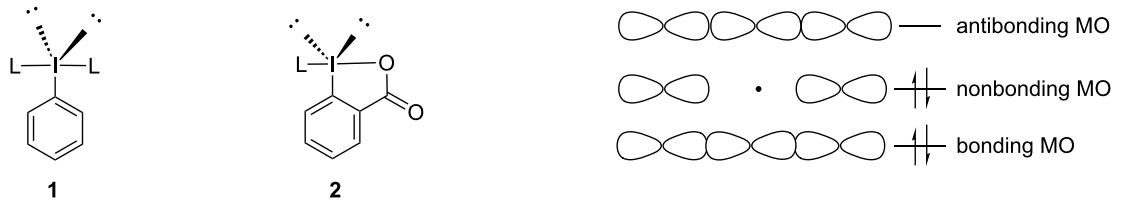
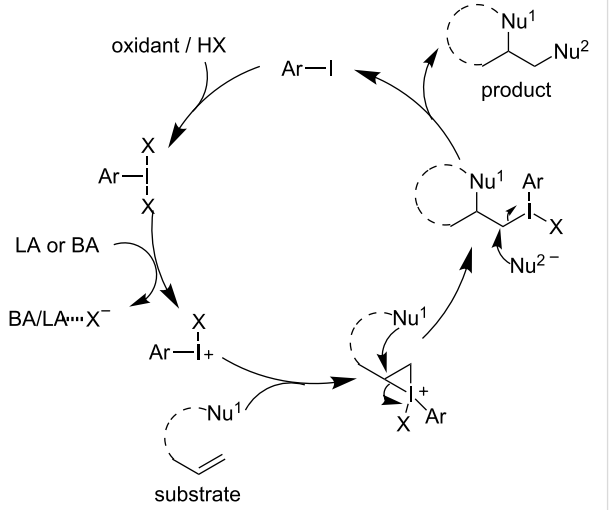


Figure 1: The structures of hypervalent iodine (III) reagents [8].

orination [28], aminofluorination [29], dioxygenation [30,31], and diamination [32,33] of alkenes could be achieved. Especially, when a nucleophile-tethered alkene is used, a cyclization product was obtained [34,35], although, stoichiometric amounts of hypervalent iodine(III) reagents were required. Due to the metal-like properties of hypervalent iodine(III), a catalytic variant would be feasible (Scheme 1) [10-17]. In the catalytic cycle, hypervalent iodine(III) can be generated by oxidation of iodoarenes in the presence of a suitable external oxidant.



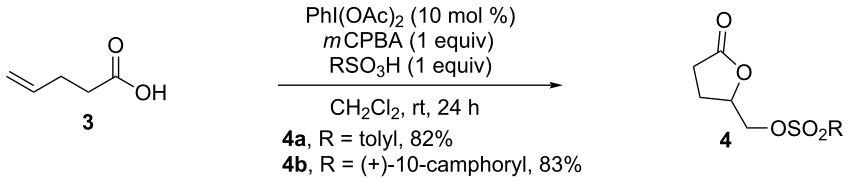
Scheme 1: Hypervalent iodine(III)-catalyzed functionalization of alkenes.

In 1994, Fuchigami and Fujita reported the first hypervalent iodine(III)-catalyzed reaction, in which the iodine(III) reagent was in situ generated by anodic oxidation under electrochemical conditions [36]. Critical to success of this process is that the oxidation potential of the catalysts should be much lower than those of the substrates and products. In addition, inorganic oxidants and peracetic acids can be used as oxidants as well. In 2005, the Ochiai and Kita groups demonstrated that *m*-chloroperbenzoic acid (*m*CPBA) was a better choice for the in situ generation of hypervalent iodine reagents through oxidation of iodoarenes [37,38]. Based on their studies, various hypervalent iodine(III)-catalyzed reactions were developed [39], including asymmetric variations [40-42]. Due to our interest in the functionalization of alkenes, this review focuses on significant progresses in hypervalent iodine(III)-catalyzed functionalization of alkenes as well as some asymmetric reactions employing a chiral iodoarene.

Review

Dioxygenation of alkenes

In 2009, Yan and co-workers reported an efficient catalytic method for the sulfonyloxylactonization of alkenoic acids (Scheme 2) [43], which employed catalytic amounts of hypervalent iodine(III) reagents and *m*CPBA as a stoichiometric terminal oxidant. The cyclization of various alkenoic acids in the presence of sulfonic acids such as *p*-toluenesulfonic acid and (+)-10-camphorsulfonic acid afforded the corresponding sulfonyloxylactones **4** in good yields. A control experiment indicated that the same result was obtained by replacing $PhI(OAc)_2$ with PhI. In addition, phosphates were suitable nucleophiles in this reaction, giving phosphoryloxylactones in good yields [44]. A similar catalytic cyclization of unsaturated amides leading to oxazolines and dihydrooxazines was developed, in which Selectfluor was used as a stoichiometric oxidant [45].



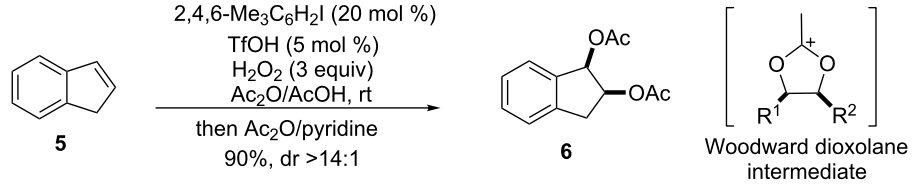
Scheme 2: Catalytic sulfonyloxylactonization of alkenoic acids [43].

In contrast to the intramolecular cyclization, the intermolecular reaction is much more attractive. Li and co-workers reported a *syn*-diacetoxylation of alkenes, using iodoarenes as catalyst which was oxidized to hypervalent iodine(III) by hydrogen peroxide in the presence of acetic anhydride [46]. As the peroxy compounds can react with alkenes, leading to the *anti*-products via epoxy intermediates, substrates must be added slowly by a syringe pump to provide reasonable yields and diastereoselectivity. The diastereoselectivity of the reaction can be rationalized by Woodward dioxolane intermediates (Scheme 3).

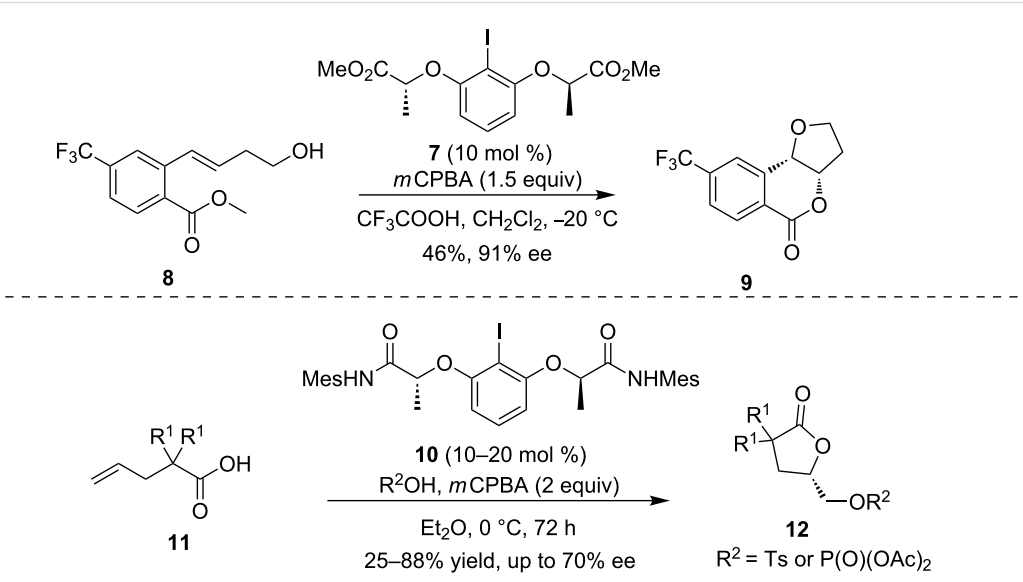
Stereoselective dioxygenation using catalytic amounts of chiral hypervalent iodine reagents is a comparatively new area in hypervalent iodine chemistry. Fujita and co-workers described a stereoselective oxylactonization reaction in the presence of a chiral hypervalent iodine catalyst [47,48]. Additionally, *m*CPBA and trifluoroacetic acid were utilized as terminal oxidants and activators, respectively. This reaction provided a series of 4-oxyisochroman-1-ones, which are found in natural products and bioactive polyketide metabolites. For example, the reaction of hydroxylated substrate **8** afforded the dihydrofuran-fused isochromanone **9** with up to 91% ee (Scheme 4, top) [48].

The enantioselective control mode is the same as that described in stoichiometric reactions [49]. Recently, Masson and co-workers described an enantioselective iodoarene-catalyzed sulfonyl- and phoshoryloxylactonization of alkenoic acids **11** with additional nucleophiles (Scheme 4, bottom) [50], in which a bisamide chiral precatalyst was applied [51]. This reaction provides an efficient access to various interesting enantioenriched γ-lactones through a tandem sequence in acceptable yields and moderate to excellent enantioselectivities.

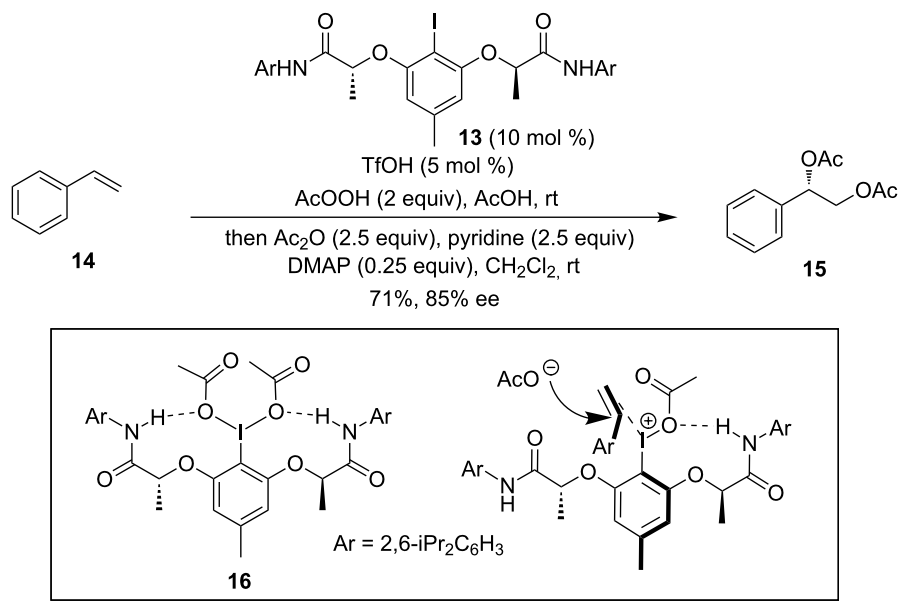
Recently, an intermolecular asymmetric dioxygenation reaction has been disclosed by Muñiz and co-workers (Scheme 5) [52]. They found that the chiral iodoarene catalyst **13**, bearing sterically hindered *N*-arylamido substituents, was essential for the asymmetric induction. The NH group engages hydrogen bonding with the acetoxy groups located at an iodine(III) center to form two nine-membered rings, which were confirmed by the crystal structure of the iodine(III) reagent **16** [53]. The hydrogen bonding effect is crucial to a supramolecular helical chiral environment at the iodine center. Mechanistically, the iodine(III) **16** is activated by triflic acid generating a free coordination site at the iodine(III) center [54]. The coordination of



Scheme 3: Catalytic diacetoxylation of alkenes [46].



Scheme 4: Intramolecular asymmetric dioxygenation of alkenes [48,50].



Scheme 5: Intermolecular asymmetric diacetoxylation of styrenes [52].

the alkene to the activated iodine(III) center generates the required prochiral face differentiation and the nucleophilic attack of acetates to the exposed *re*-face establishes the *S*-configured benzylic C–O bond.

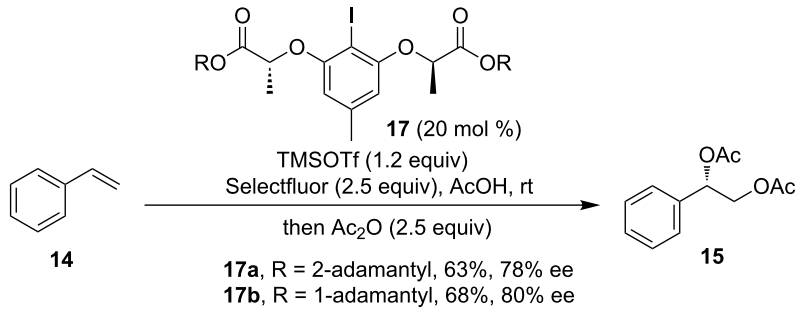
Without the hydrogen bonding effect, the same reaction with a diester-containing iodoarene catalyst was explored [55]. The sterically hindered adamantyl-substituted catalysts **17** were demonstrated to be efficient to afford the diacetoxylation products in moderate yields and enantioselectivity when using Selectfluor as a terminal oxidant (Scheme 6).

Diamination of alkenes

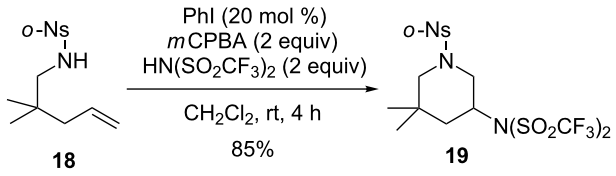
The diamination of alkenes is attractive due to the significance of diamino moieties in diverse fields of the biomedicinal and pharmaceutical sciences. During the study of the hypervalent iodine-mediated intramolecular diamination of alkenes, Blakey and co-workers found that a catalytic version could be achieved in the presence of *m*CPBA to give the same product in 85% yield, which is slightly lower than the yield of the stoichiometric reaction (96%, Scheme 7) [56].

Later, Wirth and co-workers developed the first highly stereoselective intramolecular diamination of alkenes using a novel, simple hypervalent iodine(III) catalyst **20** (Scheme 8) [57]. In this reaction sodium perborate was the best terminal oxidant rather than *m*CPBA. Furthermore, the selected protecting group can be removed easily under reducing conditions, providing the free diamine derivatives. However, the substrate scope was limited to alkenes bearing phenyl substituents on the backbone.

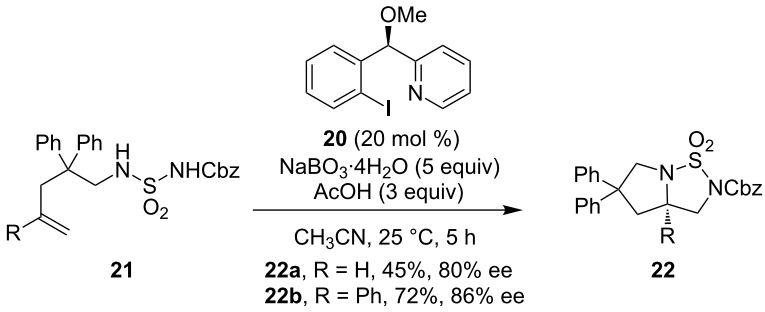
On the contrary, the intermolecular diamination of alkenes presented a big challenge under metal-catalyzed conditions, due to the high affinity of the diamine products to metal catalysts.



Scheme 6: Diacetoxylation of alkenes with ester groups containing catalysts **17** [55].

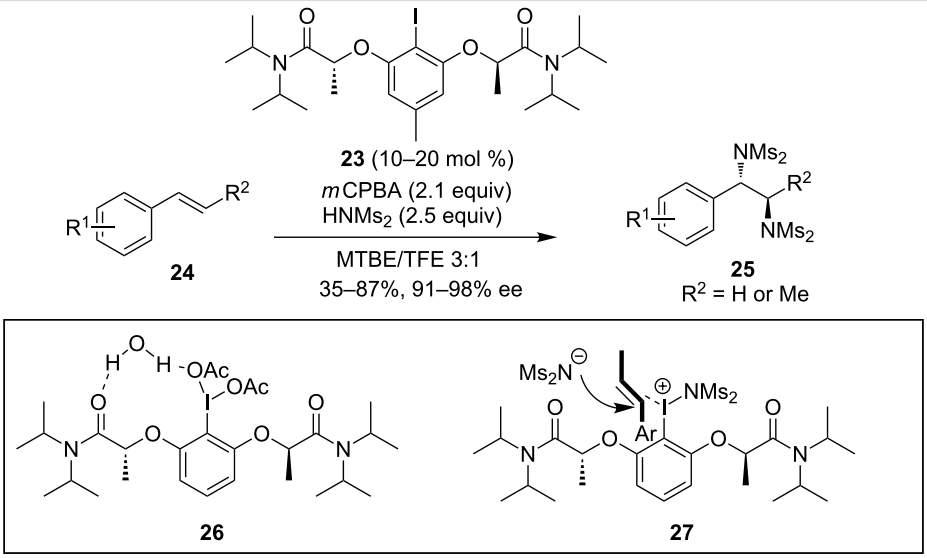


Scheme 7: Intramolecular diamination of alkenes [56].



Scheme 8: Intramolecular asymmetric diamination of alkenes [57].

Thus an iodoarene-catalyzed strategy provides a valuable alternative way to the diamination of alkenes. Recently, Muñiz and co-workers reported a chiral iodoarene-catalyzed intermolecular diamination of styrene derivatives (Scheme 9) [58]. An iodoarene precatalyst **23** bearing the tertiary amide on the lactic side chains was the most effective. *m*CPBA was used as a stoichiometric oxidant and bismesylimide as an amine source. It is noteworthy that solvent was a key factor to suppress the undesired epoxidation products. Not only terminal styrenes but also internal alkenes were suitable to this reaction, affording the *anti*-diamination products. The exact mode of stereoinduction with the new catalyst **23** was examined, and the single crystal X-ray structural analysis of **26** revealed that a water molecule engages in double hydrogen bonding to form an 11-membered ring, resulting in the chiral helicity. The helical chirality induced in iodine(III) derivatives of **23** bearing the bislactamide motif was described for **27** with an efficient differentiation of the enantiotopic faces of the styrene substrate. This protocol acted as an asymmetric gateway to the useful vicinal diamines.



Scheme 9: Intermolecular asymmetric diamination of alkenes [58].

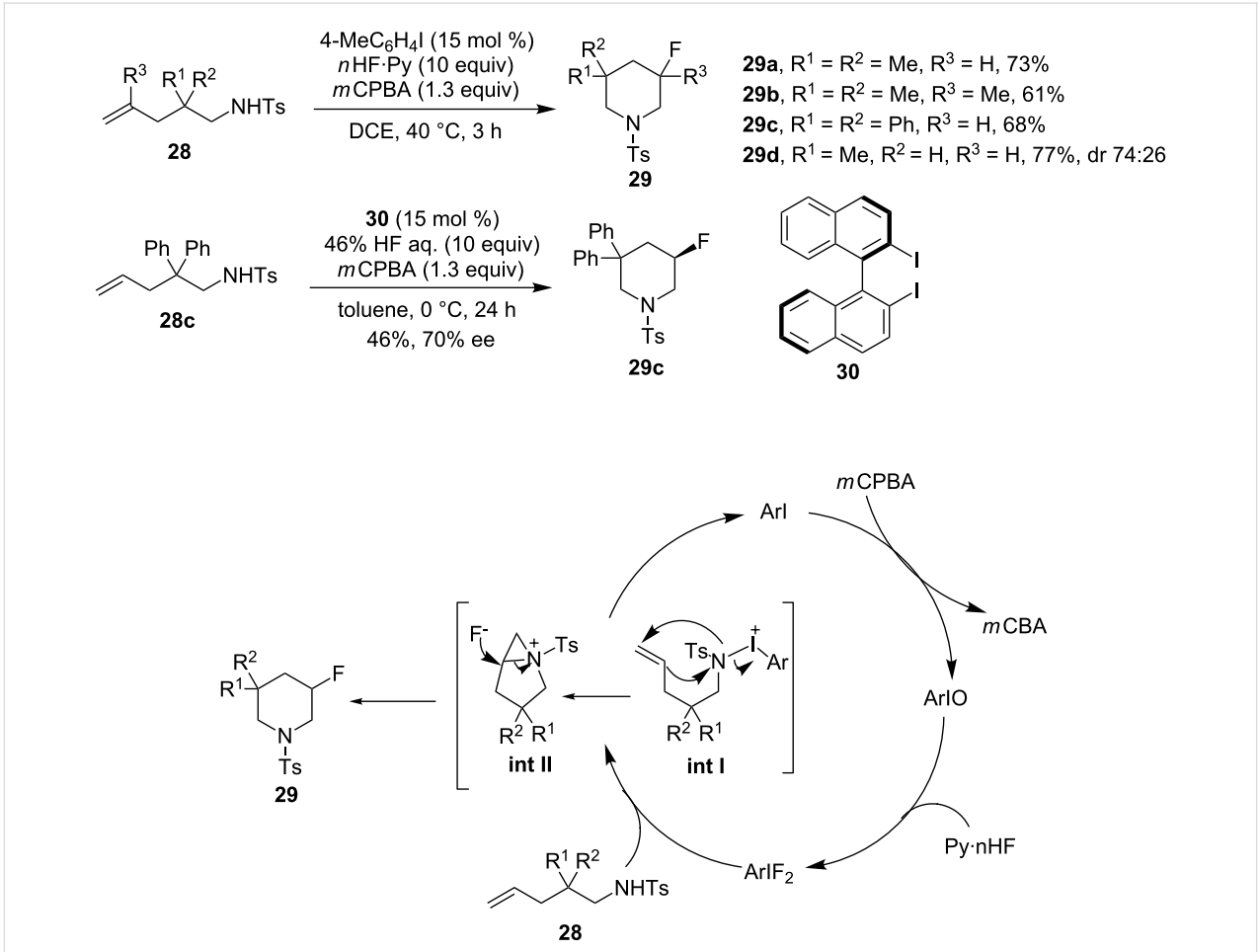
Aminofluorination of alkenes

(Difluoroiodo)arenes (Ar-IF_2), which can be prepared from HF with iodosoarenes, are hypervalent iodine compounds suitable for the fluorination of alkenes [59]. Based on Nevado's stoichiometric aminofluorination [29], Shibata, Kita and co-workers reported the iodoarene-catalyzed aminofluorination of amino-tethered alkenes to yield fluorinated cyclic amines [60]. The mechanism for the catalytic aminofluorination of alkenes is shown in Scheme 10. The iodosyl species, ArI=O, produced by the oxidation of ArI with *m*CPBA, reacted with HF to provide the corresponding in situ-generated difluoroiodoarenes. An aziridinium intermediate **II**, which underwent nucleophilic attack by fluoride on the multisubstituted carbon to afford the *endo*-cyclized products **29**, was proposed in Nevado's reaction [29]. Employing the binaphthyldiiodide **30** as a catalyst was found to be effective for the asymmetric induction. However, the substrate scope of the reaction was still limited to diphenyl-substituted alkenes. This catalytic system could be applied to the aminofluorination of homoallylamines giving *N*-tosyl-3-fluoropyrrolidines in good to high yields [61].

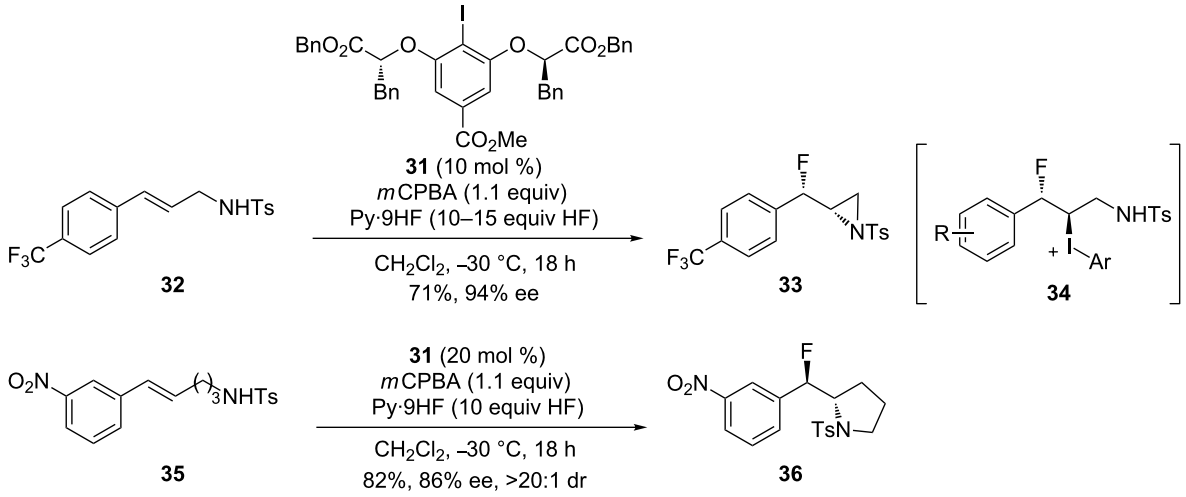
Recently, Jacobsen and co-workers reported the stereoselective synthesis of *syn*-β-fluoroaziridine building blocks via a chiral aryl iodide-catalyzed fluorination of allylic amines (Scheme 11) [62]. On the basis of their previous work, the C_2-symmetric aryl iodide **31** as a catalyst was applied in this reaction. A $C(sp^3)$–I(III) intermediate **34**, which was trapped by vicinal nitrogen nucleophiles to form the chiral *syn*-β-fluoroaziridine **33**, was proposed. Both fluoroaziridines **33** and β-fluoropyrrolidines **36** were obtained in good yields and high *anti*-stereoselectivity. However, the reaction of substrates bearing either two or four methylene groups between the alkene and sulfonamide failed to provide the fluoroheterocycles.

Difluorination of alkenes

Hara and co-workers reported a vicinal difluorination of unactivated alkenes in the presence of stoichiometric amounts of difluoro iodotoluene [27]. Based on this seminal work, Gilmour and co-workers reported a catalytic difluorination of alkenes using an inexpensive *p*-iodotoluene as the catalyst and Selectfluor as the terminal oxidant [63]. Terminal olefins proved to be



Scheme 10: Iodoarene-catalyzed aminofluorination of alkenes [60,61].

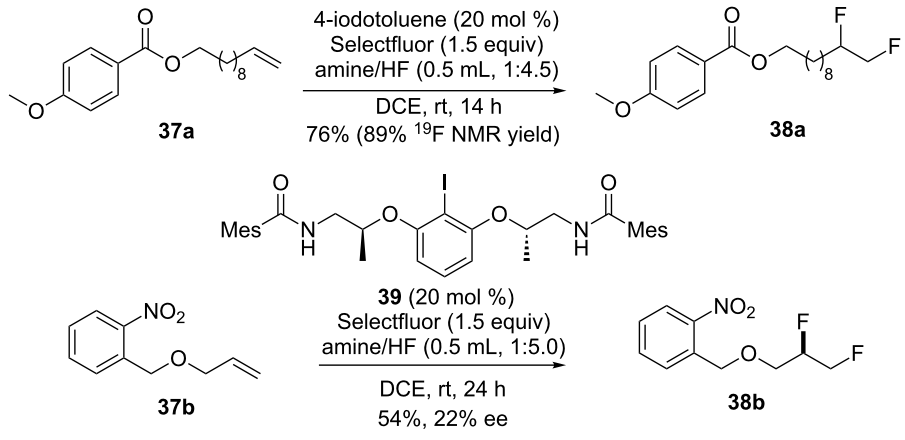


Scheme 11: Iodoarene-catalyzed aminofluorination of alkenes [62].

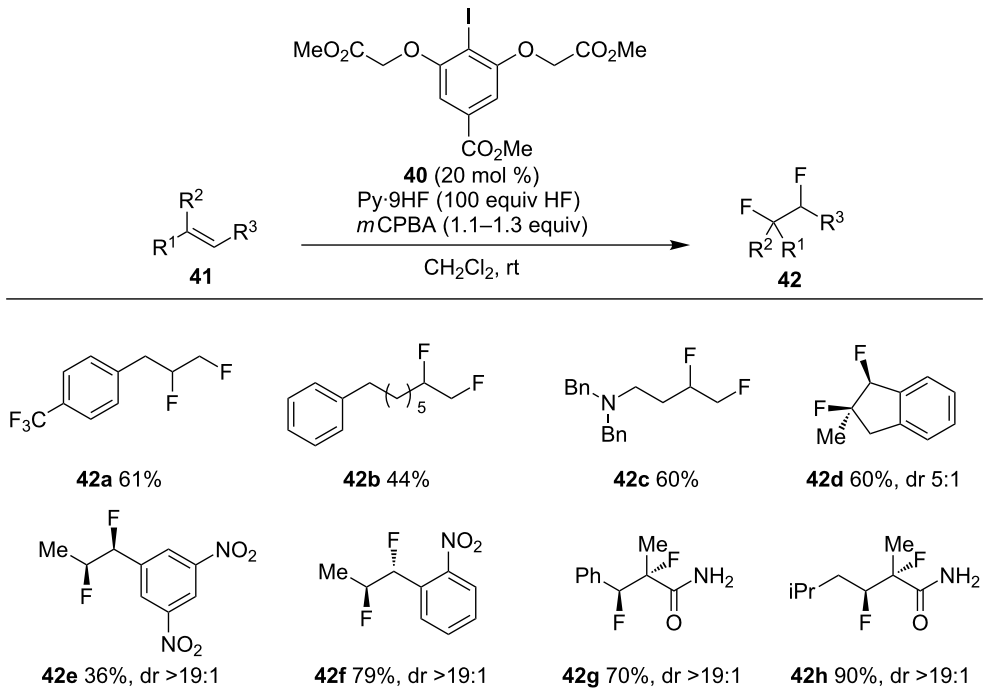
viable substrates for this reaction. It is worth noting that the ratio of amines and HF was important for obtaining reasonable yields. Indeed, excellent ^{19}F NMR yields albeit lower isolated yields were obtained in this reaction (Scheme 12). In an attempt to induce enantioselectivity, the chiral aryl iodide derivative **39** only gave a moderate enantioselectivity (22% ee).

Meantime, a similar work was independently reported by Jacobsen and co-workers, in which the reactive iodoarene difluoride could be in situ generated by oxidation of aryl iodide **40** with *m*CPBA [64]. The reaction showed a wide substrate scope, with toleration of terminal, internal alkenes as well as electron-deficient unsaturated carbonyl compounds (Scheme 13). In general, terminal alkenes were found to undergo 1,2-difluorination **42a**–**c**. The reaction of internal alkenes usually afforded the *syn*-difluorination products **42d** and **42e**. However, the opposite result was observed in the reaction of the *o*-nitrostyrene derivative **42f**, due to the Lewis basicity of the nitro group. These stereochemical outcomes were also observed in the reaction of acrylamides by means of anchimeric assistance.

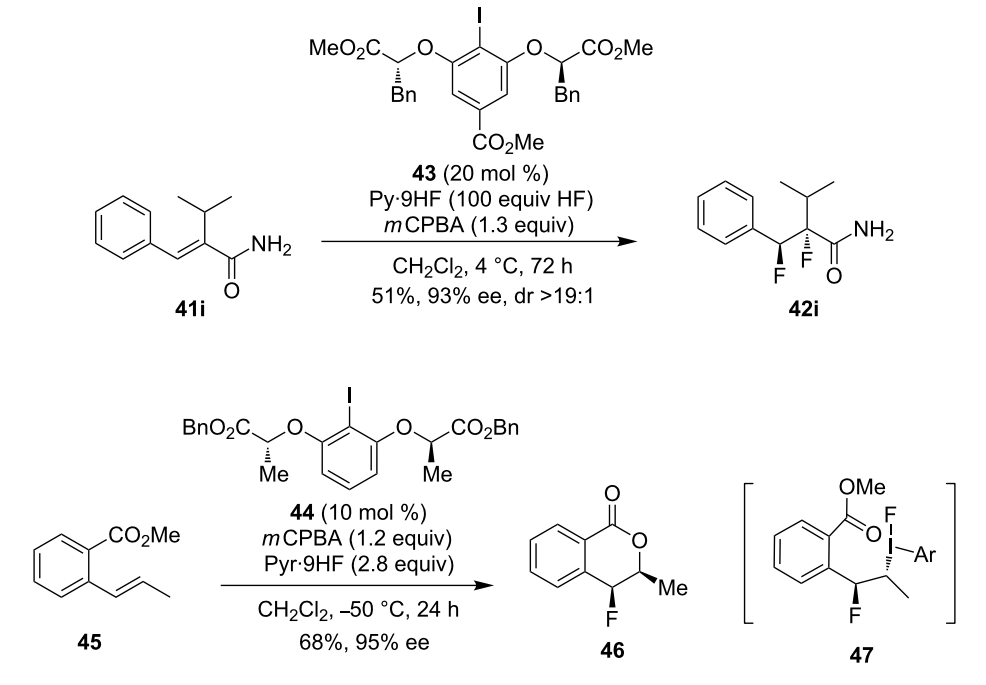
Preliminary studies to identify asymmetric variants indicated that, in the presence of lactate-based chiral iodoarene catalyst **43**, the cinnamamide **41i** could be transformed to the corresponding difluorination product **42i** with excellent enantioselectivity and high stereoselectivity, albeit in moderate yields (Scheme 14, top) [64]. Inspired by the propensity for such anchimeric assistance in these reactions, an enantio- and diastereoselective catalytic fluorination was developed by the same group (Scheme 14, bottom) [65] using the lactate-based resorcinol derivative **44** as the catalyst. By this route chiral 4-fluoroisochromanones **46** could be accomplished in high enantio-



Scheme 12: Catalytic difluorination of alkenes with Selectfluor [63].



Scheme 13: Iodoarene-catalyzed 1,2-difluorination of alkenes [64].



Scheme 14: Iodoarene-catalyzed asymmetric fluorination of styrenes [64,65].

and diastereoselectivity. The same I(III) intermediate **47** was trapped by an *o*-carboxylic ester group leading to the *syn*-diastereoisomeric outcome.

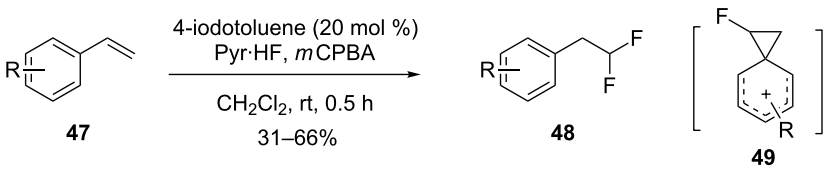
An aryl rearrangement might be realized via benzenium ions in the iodine(III)-mediated reactions of styrenes [66]. Oyamada and co-workers reported the synthesis of 2,2-difluoroethyl-

arenes mediated by iodine(III) reagents. Moreover, they found that this fluorination also proceeds with catalytic amounts of the iodoarenes in the presence of *m*CPBA as a terminal oxidant, albeit in lower yields (Scheme 15) [67]. Mechanistically, the 1,2-aryl shift could arise via phenonium intermediates **49** to deliver the geminal difluorination products.

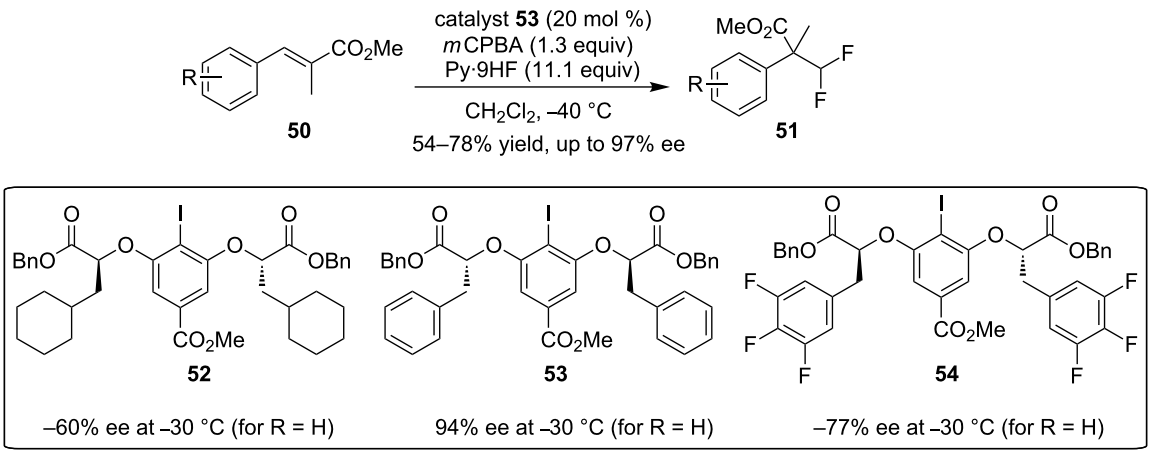
Recently, Jacobsen and co-workers reported a highly enantioselective gem-difluorination of various cinnamic acid derivatives through the same oxidative rearrangement (Scheme 16) [68]. During the catalysts screening, they found that the benzylic unit in the catalysts was essential for a high enantioselectivity (**52** vs **53**). Moreover, the more electron-deficient 3,4,5-trifluorophenyl analog **54** was found to be less enantioselective. The authors proposed that the benzylic groups can stabilize the cationic intermediates and/or transition states through cation–π interactions, which play an important role in the stereodifferentiation step.

Other functionalizations of alkenes

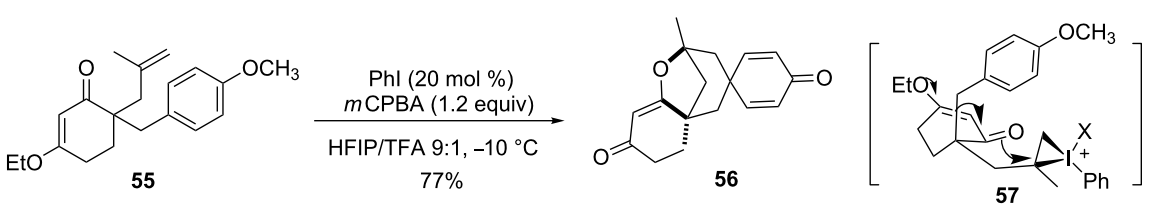
In addition to heteroatom-containing nucleophiles, electron-rich aromatic groups were also reported as nucleophiles to form the C–C bonds [69,70]. In this context, Lupton, Hutt and co-workers reported an iodobenzene-catalyzed 1,2-olefin functionalization via C–C and C–O bond formation, in which electron-rich aromatic groups and vinylogous esters acting as independent nucleophiles to provide oxabicyclo[3.2.1]octanes (Scheme 17) [71]. Mechanistically, the olefin is activated by



Scheme 15: Gem-difluorination of styrenes [67].



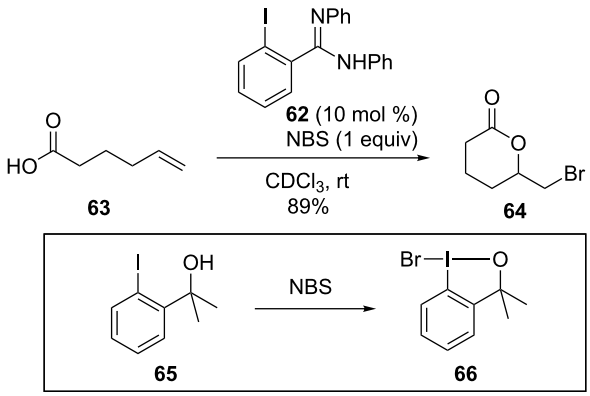
Scheme 16: Asymmetric gem-difluorination of cinnamic acid derivatives [68].



Scheme 17: Oxyarylation of alkenes [71].

iodine(III) to form species **57** which is followed by first a nucleophilic attack from the vinylogous ester, then by the aromatic group, providing the final outcomes.

Wirth and co-workers developed an oxidative rearrangement of alkenes to chiral α-aryl ketones, in which electron-deficient chiral lactic acid-based hypervalent iodine reagents were synthesized and applied [72]. The regioselective methoxylation of diphenyl alkene with chiral hypervalent iodine **58** afforded a mixture of **60** and **61** in moderated yield and good enantioselectivity. However, the catalytic reaction afforded the opposite regioselectivity to give rearrangement product **60** in dramatically decreased yield and enantioselectivity (Scheme 18). Similar oxidative rearrangement reactions with haloalkenes generated α-halo ketones [73].



Scheme 19: Bromolactonization of alkenes [75].

NBS also oxidizes iodoarene **65** to form the brominating agent **66** [74]. Braddock and co-workers reported an organocatalyzed transformation of electrophilic bromines to alkenes, using *ortho*-substituted iodobenzene **62** as an organocatalyst (Scheme 19) [75]. A control experiment indicated that only trace amounts of products were observed in the absence of iodoarene catalyst (2%). A similar work involving a rearrangement of imides, which delivered α,α-disubstituted-α-hydroxycarboxylamides, was disclosed by Gulder and co-workers [76].

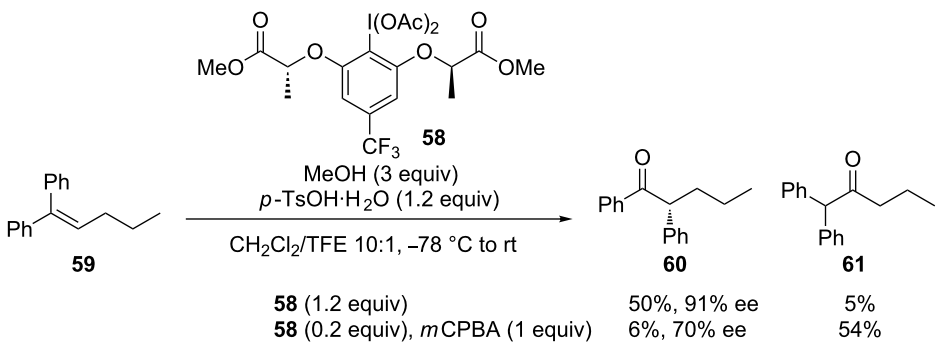
This catalytic system was applied to the bromination of alkenes by Gulder and co-workers. For example, the iodine(III)-catalyzed halocyclization of methacrylamide **68** generated the brominated oxindole **69** (Scheme 20) [77]. In addition, electron-rich aromatics present in the substrates were also brominated. During the screening of the iodoarene pre-catalysts, a dihalogenation product was detected in the presence of iodoarenes bearing electron-donating side chains **70**. A diastereoselective dihalogenation method was established under mild conditions [78]. The authors proposed a radical pathway involving the in situ generation of Br_2, which opens the avenue for a reliable, ecologically benign, and safe dibromination method.

Conclusion

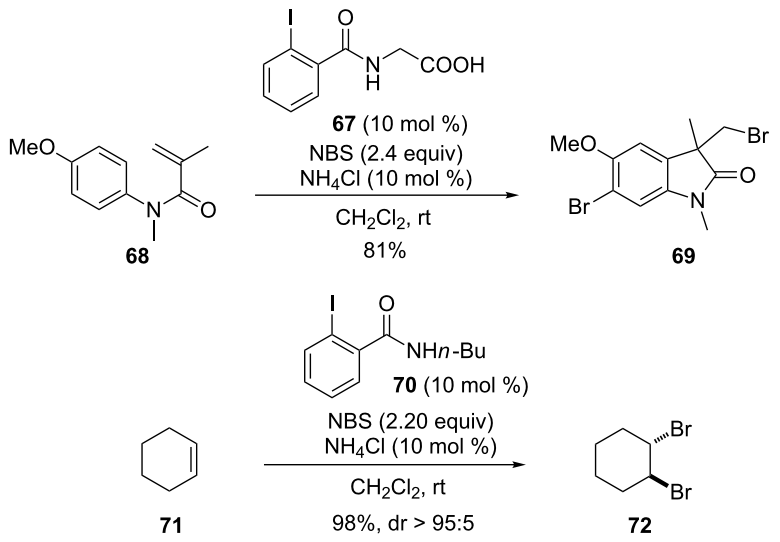
In the last two decades, great progress was made in hypervalent iodine(III) catalytic systems. On the basis of these improvements, it is no longer necessary to prepare hypervalent iodine compounds, as the iodide precursors can be used catalytically. The recently developed enantioselective hypervalent iodine(III)-mediated transformations could be a breakthrough for the application of these reagents in chiral synthesis.

As outlined, there have been achieved great advances in the hypervalent iodine-mediated functionalization of alkenes. However, the types of chiral iodoarene catalysts are limited and new chiral iodoarene scaffolds should be developed for highly stereoselective reactions.

Compared to the diverse reactivity profiles of transition metal-catalyzed functionalization of alkenes, hypervalent iodine (III)-



Scheme 18: Asymmetric oxidative rearrangements of alkenes [72].



Scheme 20: Bromination of alkenes [77,78].

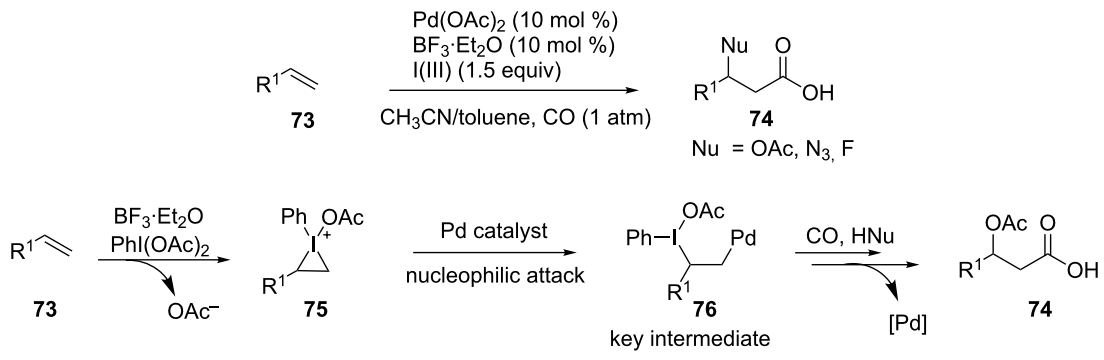
mediated reactions are limited to nucleophilic substitution processes. Recently, Liu and co-workers reported a novel cooperative strategy by combining palladium catalysis and hypervalent iodine-mediated reactions to achieve the intermolecular oxycarbonylation [79], azidocarbonylation [80] and fluorocarbonylation [81] of alkenes. Mechanistic studies showed that $PhI(OAc)_2$ is activated by the aid of $BF_3{\cdot}OEt_2$ and then reacts with an alkene to form a three-membered iodonium ion intermediate **75**. Subsequently, this intermediate is attacked by the palladium catalyst under a CO atmosphere to form the alkyl palladium species **76**. Finally, the reductive elimination at the iodine(III) center and CO insertion into the newly formed C–Pd bond, affords the oxycarbonylation products **74** (Scheme 21). This strategy provides an attractive development tendency in hypervalent iodine(III) chemistry. It is fascinating to realize such transformations with catalytic amounts of iodoarenes as well as chiral iodoarene reagents to induce enantioselectivity.

Acknowledgements

We are grateful for financial support from the National Nature Science Foundation of China (Nos. 21532009, 21672236, 21790330 and 21761142010), the National Basic Research Program of China (Grant 973-2015CB856600), the Shanghai Rising-Star Program (17QA1405200), the Strategic Priority Research Program (No. XDB20000000), and the Key Research Program of Frontier Science (No. QYZDJSSW-SLH055) of the Chinese Academy of Sciences.

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Scheme 21: Cooperative strategy for the carbonylation of alkenes [79].

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Preparation and X-ray structure of 2-iodoxybenzenesulfonic acid (IBS) – a powerful hypervalent iodine(V) oxidant

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Keywords:
hypervalent iodine; iodine; 2-iodoxybenzenesulfonic acid; oxidation; X-ray

Beilstein J. Org. Chem. **2018,** *14,* 1854–1858.
doi:10.3762/bjoc.14.159

Received: 14 May 2018
Accepted: 11 July 2018
Published: 20 July 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Associate Editor: J. A. Murphy

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Abstract

The selective preparation of 2-iodoxybenzenesulfonic acid (IBS, as potassium or sodium salts) by oxidation of sodium 2-iodobenzenesulfonate with Oxone or sodium periodate in water is reported. The single crystal X-ray diffraction analysis reveals a complex polymeric structure consisting of three units of IBS as potassium salt and one unit of 2-iodoxybenzenesulfonic acid linked together by relatively strong I=O···I intermolecular interactions. Furthermore, a new method for the preparation of the reduced form of IBS, 2-iodosylbenzenesulfonic acid, by using periodic acid as an oxidant, has been developed. It has been demonstrated that the oxidation of free 2-iodobenzenesulfonic acid under acidic conditions affords an iodine(III) heterocycle (2-iodosylbenzenesulfonic acid), while the oxidation of sodium 2-iodobenzenesulfonate in neutral aqueous solution gives the iodine(V) products.

Introduction

Recently, the interest in synthetic applications of hypervalent iodine compounds as stoichiometric reagents or catalysts has experienced an explosive growth [1-8]. Hypervalent iodine(V) compounds represent an important class of oxidative reagents extensively employed in organic synthesis [9-11]. 2-Iodoxybenzoic acid (IBX) and the product of its acetylation Dess–Martin periodinane (DMP) are the most common oxidants used for selective oxidation of alcohols to carbonyl compounds as well as for a variety of other synthetically useful oxidative transformations [10,11]. IBX and DMP are mild oxidants with a relatively low reactivity towards some substrates. Moreover, these reagents are generally not suitable as active species in catalytic reactions due to the low reactivity and harsh conditions required for their in situ generation. In 2009, Ishihara and co-workers have reported an extremely active catalytic system for oxidation of alcohols based on 2-iodoxybenzenesulfonic

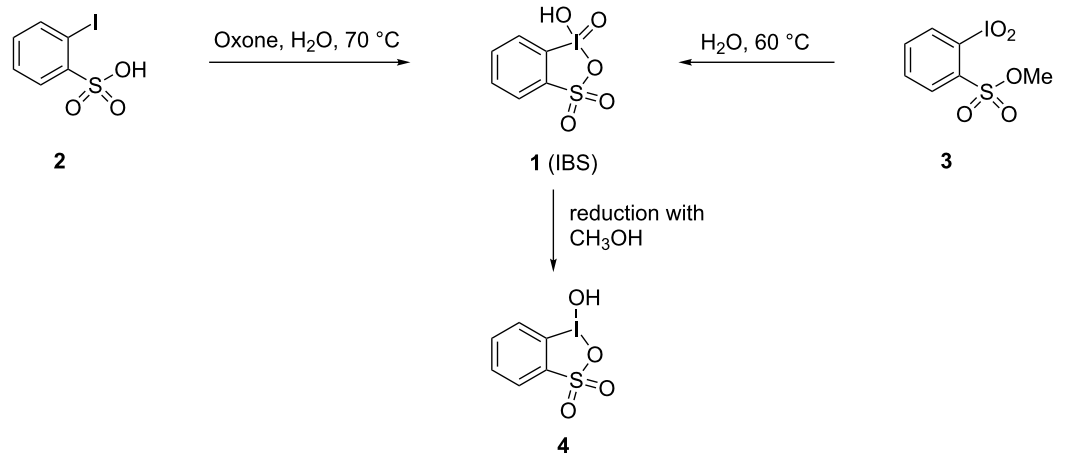
acid (IBS) as the active species [12,13]. IBS (or its sodium salt) is much more active as catalyst than IBX derivatives. In particular, it can be used as a highly efficient and selective catalyst (0.05–5 mol %) for the oxidation of primary and secondary alcohols to the respective carbonyl compounds with Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in nitromethane, acetonitrile, or ethyl acetate [13]. Recent research has revealed the extreme activity of IBS as a catalyst in numerous other oxidations, such as: the oxidation of benzylic and alkane C–H bonds [14], the oxidation of phenols to 1,2-quinones [15], the cyclization and cross-coupling reactions [16], and the site-selective hydroxylative dearomatization of 2-substituted phenols to either 1,2-benzoquinols or their cyclodimers [17].

The first preparation and isolation of IBS (**1**) was attempted in 2006 using two different approaches: direct oxidation of 2-iodobenzenesulfonic acid (**2**) by Oxone or hydrolysis of methyl 2-iodoxybenzenesulfate (**3**, Scheme 1) [18].

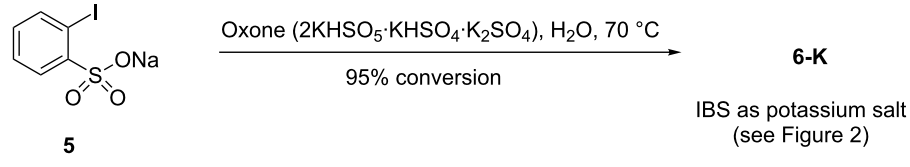
The hydrolysis of sulfonic ester **3** forms IBS as a mixture with methanol which is quickly oxidized by IBS in situ producing the corresponding iodine(III) heterocycle, 2-iodosylbenzenesulfonic acid (**4**) as main product. The direct oxidation of 2-iodobenzenesulfonic acid (**2**) with Oxone leads to the formation of the desired IBS (**1**, Scheme 1), however, contaminated with inorganic impurities. Because of the high solubility of IBS in water, this mixture is difficult to separate. The resulting IBS is insoluble in nonpolar solvents (dichloromethane, chloroform, etc.). Moreover, IBS has high reactivity towards polar organic solvents (acetonitrile, DMSO, methanol) being readily reduced to 2-iodosylbenzenesulfonic acid upon contact with these solvents. Despite these problems, IBS was previously characterized by ^1H and ^{13}C NMR, IR spectroscopy, high-resolution mass spectrometry, and elemental analysis. However, all previously reported attempts to grow single crystals of IBS from methanol or acetonitrile resulted in reduction with the formation of 2-iodosylbenzenesulfonic acid as confirmed by X-ray diffraction analysis [17]. In the present work, we report the preparation and isolation of IBS (as potassium or sodium salts) and its structural study by X-ray analysis. Furthermore, we have developed a new method for the preparation of the IBS reduced form, 2-iodosylbenzenesulfonic acid (**4**), with the use of periodic acid as an oxidant.

Results and Discussion

We have investigated the oxidation of 2-iodobenzenesulfonic acid as sodium salt and as a free acid using Oxone, sodium periodate or periodic acid. The oxidation of sodium 2-iodobenzenesulfonate (**5**) by Oxone was performed under Ishihara's conditions [13] in water at 70 °C (Scheme 2). NMR



Scheme 1: Previously reported preparation of IBS (**1**) [17].



Scheme 2: Oxidation of 2-iodobenzenesulfonate **5** by Oxone in water.

monitoring indicated 95% conversion of the starting sodium salt **5** to the iodine(V) product **6** after about 3 h stirring at 70 °C (Figure S1 in Supporting Information File 1). After cooling the aqueous solution to room temperature, the formation of a precipitate consisting of needle-shaped organic crystals and microcrystalline powder of inorganic salts was observed. The needle-shaped organic crystals were manually separated from the inorganic salts and analysed by NMR spectroscopy and X-ray crystallography. ^{1}H and ^{13}C NMR spectra of these crystals were in full agreement with the NMR spectra of IBS provided in the Supporting Information of Ishihara's paper [13] and, in particular, displayed the characteristic signals of the *ortho*-protons (relative to iodine(V)) at 8.28 ppm.

The structure of IBS-K crystals obtained by this reaction (Scheme 2) was established by single-crystal X-ray crystallography (for crystallographic details, see Table S1 in Supporting Information File 1). The X-ray structure of an independent unit of IBS-K is shown in Figure 1, and the corresponding structural drawing with interatomic bond distances is presented in Figure 2.

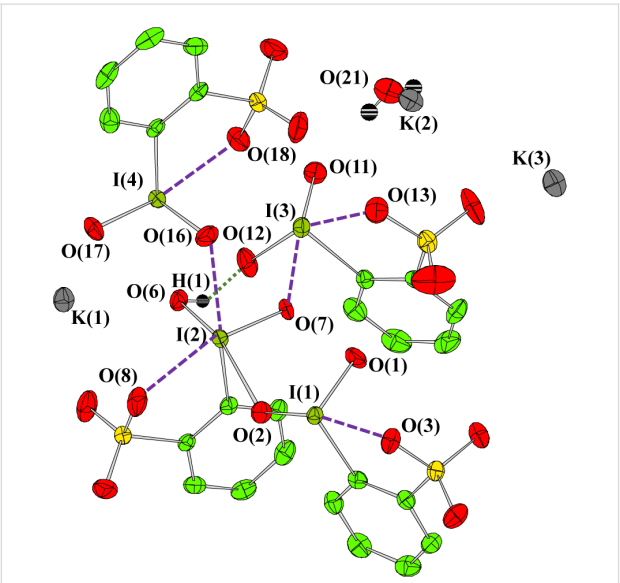


Figure 1: X-ray structure of an independent crystal unit of IBS **6-K**.

The X-ray crystal structure **6-K** is quite interesting. Each independent unit consists of a tetrameric aggregate, which holds together by relatively strong I=O···I intermolecular interactions formed between molecules of **6** (Figure 2). Two out of three molecules of **6** (those that include I(1) and I(4) centers) have very similar structures that consist of tetracoordinated iodine centers with two short (≈1.8 Å) I=O bonds, one regular I–C bond and one relatively long (≈2.54–2.60 Å) I···OSO_2 interaction. In each fragment, one of the I=O oxygen atoms (O(2) and

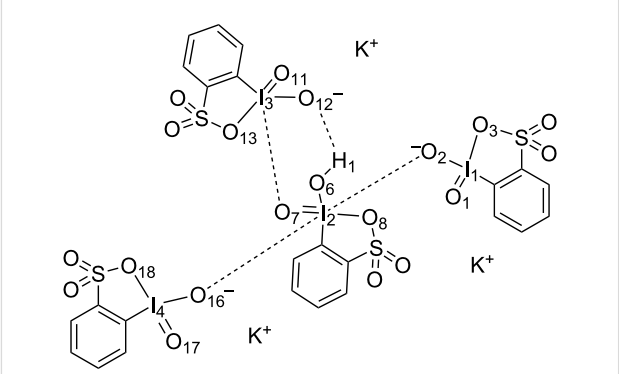


Figure 2: Simplified representation of structure **6-K**. Selected interatomic distances (Å): I(1)=O(1) 1.79; I(1)=O(2) 1.81; I(1)–O(3) 2.54; O(2)–I(2) 2.46; I(2)=O(7) 1.81; I(2)–O(6) 1.88; I(2)–O(8) 2.60; I(2)–O(16) 2.71; I(3)=O(11) 1.80; I(3)=O(12) 1.87; I(3)–O(13) 2.49; I(3)–O(7) 2.63; I(4)=O(17) 1.8; I(4)=O(16) 1.81; I(4)–O(18) 2.60.

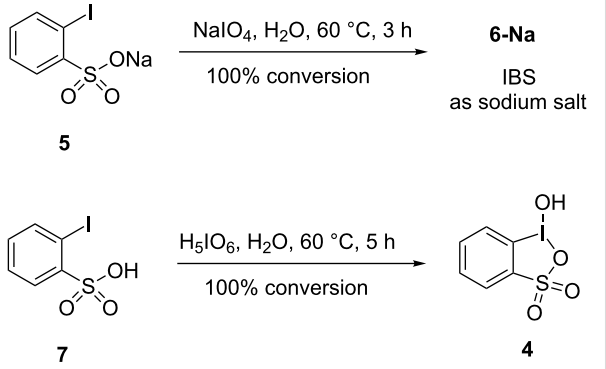
O(16)) forms a long (≈2.46 Å for I(1)=O(2)···I(2) and ≈2.71 Å for I(4)=O(16)···I(2)) secondary contact with the I(2) center. In contrast, the third molecule of **6** has pentacoordinated iodine(V) center formed by two short I(3)=O bonds, one I–C bond, a relatively long (≈2.49 Å) I···OSO_2 intramolecular interaction and a relatively long (≈2.63 Å) I(2)=O(7)···I(3) intermolecular interactions. Unlike I(1)=O and I(4)=O centers, the I(3)–O(12) bond distance is significantly longer (≈1.87 Å) compared to the other I=O bond distances (≈1.80 Å), which is explained below. Finally, the "inner" I(2) center is hexacoordinated with two short (≈1.81 Å for I(2)=O(7) and ≈1.88 Å for I(2)–O(6)) bonds, one regular I(2)–C bond, one usual (2.60 Å) I(2)···OSO_2 intramolecular contact and two (≈2.71 Å for I(4)=O(16)···I(2) and ≈2.46 Å for I(1)=O(2)···I(2)) intermolecular contacts. Three potassium ions were also identified in the crystal structure of **6**. In addition, a water molecule was observed in the crystal structure of **6**, which forms two strong hydrogen bonds (≈2.05 Å for O(21)–H(2)···O(11) and ≈2.07 Å for O(21)–H(3)···O(5)) with neighbouring oxygen atoms and two short donor–acceptor interactions with K(1) and K(2) potassium ions. Overall, the structure of the aggregate is indicative of only three potassium counterions and a neutral water molecule thus leaving the anionic iodine-containing tetramer. Careful examination of the electron density map and the geometry of this tetramer indicates on the two rather long I(2)–O(6) and I(3)–O(12) bonds (≈1.87–1.88 Å), their short (≈2.59 Å) O(6)···O(12) distance, and a small electron density close to O(6) and O(12). Thus, a proton was added at the small electron density region to the O(6) atom. Such proton positioning results in the formation of an expected strong hydrogen bond (≈1.87 Å) in the O(6)–H(1)···O(12) fragment.

Manual separation of organic crystals of **6-K** from inorganic salts resulting from reduction of Oxone is a time-consuming,

impractical procedure. Therefore, we investigated the use of oxidants different from Oxone for the oxidation of sodium 2-iodobenzenesulfonate (**5**). It is known from the literature that sodium periodate can oxidize various ArI to $ArIO_2$ in boiling water or aqueous acetic acid [19,20]. We have found that according to NMR monitoring (Figure S2 in Supporting Information File 1), the reaction of sodium 2-iodobenzenesulfonate (**5**) with sodium periodate in water selectively affords the respective iodine(V) product after heating at 60 °C for 16 h with almost quantitative conversion. The aqueous solution containing IBS-Na (as sodium salt) and inorganic products resulting from the reduction of $NaIO_4$ was treated with silver nitrate to precipitate I^- and IO_3^- anions. The precipitate of silver salts was filtered off, and the mother liquor was concentrated using blowing air to about half of the initial volume. The concentrated aqueous solution was left for several days resulting in the formation of a microcrystalline precipitate of IBS-Na isolated in 61% yield. ^1H and ^{13}C NMR spectra of this product in D_2O were identical to the spectra of IBS-K (**6-K**). Oxidation of sodium 2-iodobenzenesulfonate **5** with periodic acid under similar conditions afforded **6-Na** in a mixture with 2-iodosylbenzenesulfonic acid (**4**, see Figure S3 in Supporting Information File 1).

In order to avoid the formation of salts, we have investigated the oxidation of free 2-iodobenzenesulfonic acid with periodic acid (H_5IO_6). 2-Iodobenzenesulfonic acid (**7**) was prepared from sodium 2-iodobenzenesulfonate (**5**) by ion exchange using Amberlyst 15 (H^+). The oxidation reaction was carried out at 60 °C and monitored by NMR (Figure S5 in Supporting Information File 1). To our surprise, only the organoiodine(III) product 2-iodosylbenzenesulfonic acid (**4**) was formed under these conditions. Product **4** precipitated from the reaction mixture upon cooling to room temperature and was isolated in 87% yield by simple filtration. ^1H and ^{13}C NMR spectra of product **4** are identical to the previously reported spectroscopic data for 2-iodosylbenzenesulfonic acid [18,21,22]. In particular, the ^1H NMR displayed the characteristic signal of the *ortho*-proton (relative to iodine(III)) at about 8.0 ppm and ^{13}C NMR exhibited the *ipso* C–I(III) carbon at 112.1 ppm.

These results clearly indicate that the oxidation of free 2-iodobenzenesulfonic acid affords iodine(III), while the oxidation of its salt gives the iodine(V) products (Scheme 3). It is a potentially important observation allowing to selectively synthesize IBS (as a salt) in neutral aqueous solution or 2-iodosylbenzenesulfonic acid under acidic conditions. This result can be explained by a greater stability of the heterocyclic molecule of 2-iodosylbenzenesulfonic acid towards disproportionation in comparison to the unknown salt of 2-iodosylbenzenesulfonic acid, which probably has a noncyclic (or pseudocyclic) structure of $2\text{-}OIC_6H_4SO_2ONa$. Indeed, X-ray analysis of 2-iodosylbenzenesulfonic acid (**4**) indicated a cyclic structure with a I–O bond length of 2.38 Å in the benziodoxathiole ring [18], while in the anionic iodine(V) benziodoxathiole ring in aggregate **6** (Figure 2) the I–O bonds are much longer (≈2.5–2.6 Å). It is known from the literature that the preparation of iodine(V) species from ArI and an oxidant involves initial formation of ArIO followed by disproportionation to ArI and $ArIO_2$ [23]. Such disproportionation is significantly impeded or even impossible in the cyclic structure of 2-iodosylbenzenesulfonic acid.



Scheme 3: Comparison of the oxidation of sodium 2-iodobenzenesulfonate (**5**) with $NaIO_4$ and 2-iodobenzenesulfonic acid (**7**) with H_5IO_6 in water.

Conclusion

In conclusion, we have reported a selective preparation of IBS (as potassium or sodium salts) and investigated its structure by X-ray analysis. Furthermore, we have developed a new method for the preparation of the reduced form of IBS, 2-iodosylbenzenesulfonic acid, by using periodic acid as an oxidant. We have demonstrated that the oxidation of free 2-iodobenzenesulfonic acid under acidic conditions affords an iodine(III) heterocycle, while the oxidation of sodium 2-iodobenzenesulfonate in neutral aqueous solution gives the iodine(V) products.

Supporting Information

Supporting Information File 1

Experimental details and NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-159-S1.pdf]

Supporting Information File 2

Crystallographic information file of compound **6**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-159-S2.cif]

Acknowledgements

This work was supported by the grant of the Russian Science Foundation (№ 16-13-10081), the grant of the Tomsk Polytechnic University Competitiveness Enhancement Program (VIU-195/2018), the National Science Foundation (CHE-1759798) and the Royal Society (IE160304).

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Hypervalent iodine compounds for anti-Markovnikov-type iodo-oxyimidation of vinylarenes

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Keywords:
free radicals; hypervalent iodine; imide-*N*-oxyl radicals; iodination; *N*-hydroxyimides; oxidative functionalization

Beilstein J. Org. Chem. **2018,** *14,* 2146–2155.
doi:10.3762/bjoc.14.188

Received: 27 May 2018
Accepted: 31 July 2018
Published: 16 August 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

The iodo-oxyimidation of styrenes with the *N*-hydroxyimide/I_2/hypervalent iodine oxidant system was proposed. Among the examined hypervalent iodine oxidants (PIDA, PIFA, IBX, DMP) $PhI(OAc)_2$ proved to be the most effective; yields of iodo-oxyimides are 34–91%. A plausible reaction pathway includes the addition of an imide-*N*-oxyl radical to the double C=C bond and trapping of the resultant benzylic radical by iodine. It was shown that the iodine atom in the prepared iodo-oxyimides can be substituted by various nucleophiles.

Introduction

The presented work opens a new chapter in the chemistry of *N*-hydroxyimides in combination with hypervalent iodine compounds with formation of imide-*N*-oxyl radicals. These radicals were used as reagents for the addition to a terminal position of the double bond of styrenes with subsequent iodination of the resulting benzylic radical.

It is important to note, that nitroxyl radicals are widely used in organic and biological chemistry, and in material design [1-3]. These radicals are applied in the development of monomolecular magnets [4,5], spintronics [2,6], magneto-LC effect studies [7,8], organic voltaic cells [9], electrodes for electrochemical synthesis [2], and as mediators of living polymeriza-

tion [10,11]. In organic synthesis more stable types of *N*-oxyl radicals can be used as carbon-centered radical scavengers [12], oxidation catalysts, mainly for conversion of alcohols to carbonyl compounds [11,13-17]. Less stable imide-*N*-oxyl radicals are used as effective mediators for CH-functionalization with formation of C–C, C–O, C–S, and C–N bonds [11,16,18-42].

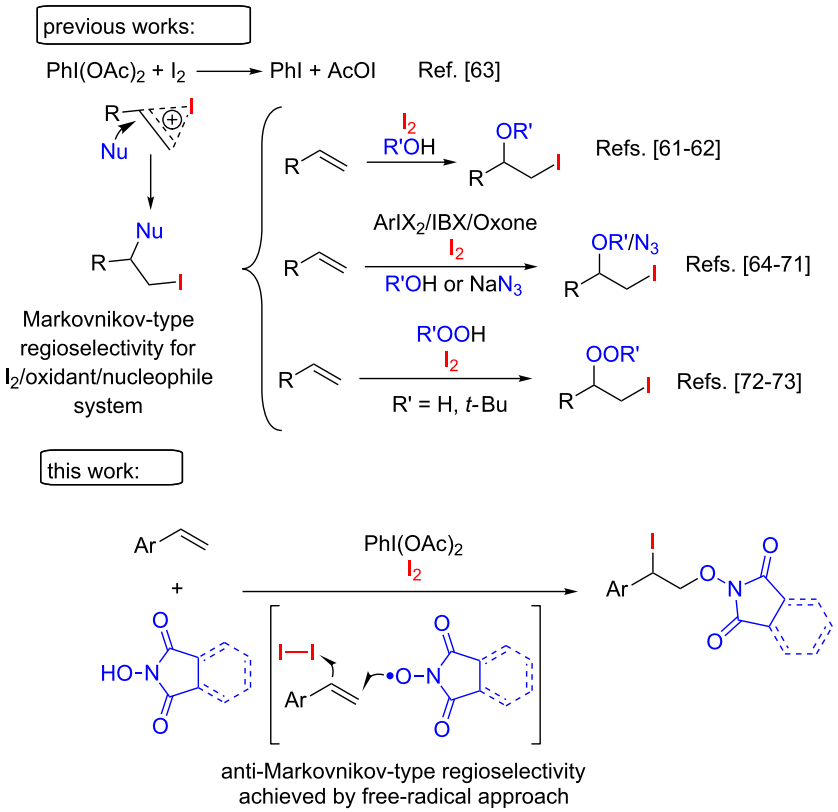
Phthalimide-*N*-oxyl (PINO) is one of the most known imide-*N*-oxyl radicals that is generated from an inexpensive *N*-hydroxyphthalimide (NHPI). This radical was used in various aerobic oxidations of bulk chemicals [18,19,43,44].

In the present work imide-*N*-oxyl radicals were used for the addition to the C=C bonds of styrenes with subsequent functionalization of the resulting benzylic radicals.

Recently, the precursors of *N*-oxyl radicals, such as *N*-hydroxyphthalimide (NHPI), *N*-hydroxysuccinimide (NHSI), *N*-hydroxybenzotriazole (HOBt) and hydroxamic acids, have been used in the reactions of radical oxygenation of styrenes [45]. Growth of interest is observed concerning the reactions of styrenes with imide-*N*-oxyl radicals, in which the latter add to the terminal position of the double C=C bond with the formation of stabilized benzyl radicals, which undergo the subsequent functionalization. In the presence of oxygen or *tert*-butyl hydroperoxide, oxidation proceeds to form the C–O [46-51] or the C=O [52-55] moiety. More complex reagents and reaction systems allows to form C–C [56,57] and C–N [58,59] bonds.

Among the above-mentioned methods, there are no examples of C–Hal bond formation despite the wide usage of organohalides in chemical syntheses. In the row of organohalides, iodides are the most reactive and versatile reagents for the following transformations [60].

One of the purposes of our work was to introduce iodine in the process of difunctionalization of styrenes with imide-*N*-oxyl radicals. Iodine atom in the product can act as a versatile leaving group for further transformations. The involvement of the iodine in the radical reactions of styrenes is complicated by the fact that unsaturated compounds readily undergo electrophilic iodination with the addition of an external nucleophile [61,62]. The oxidants used for the preparation of imide-*N*-oxyl radicals, in particular the hypervalent iodine compounds and peroxides [63-73], also generate electrophilic iodinating intermediates (Scheme 1).



Scheme 1: Difunctionalization of double C=C bond with the formation of C–O and C–I bonds.

For several decades, a number of papers on the electrophilic iodination of C=C bonds by iodine-containing oxidative systems with the addition of various nucleophiles have been published, all of these processes have common mechanism and the same regioselectivity. The free-radical approach developed in the present work affords the opposite (anti-Markovnikov) regioselectivity of the addition to the double bond.

Results and Discussion

In the present work, the reaction of styrenes **1a**–**k** and *N*-hydroxyimides **2a**,**b** with the formation of iodo-oxyimidated products **3aa**–**ka**, **3ab**–**db**, **3fb**, **3hb** and **3kb** was carried out (Scheme 2).

The key feature of the developed process is the non-standard regioselectivity of the formation of C–I and C–O bonds, which implies the radical pathway of the reaction.

The iodo-oxyimidation of styrenes was studied in the model reaction of styrene (**1a**) with *N*-hydroxyphthalimide (**2a**). During the optimization, the oxidant and the iodine source, as well as the nature of the solvent and the reaction time were varied (Table 1).

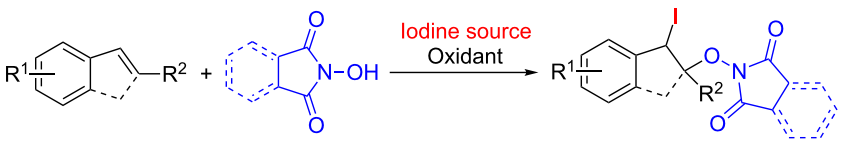
In general, the iodo-oxyimidation reaction is characterized by the following: The product **3aa** is formed regardless what kind of hypervalent iodine compound is used (Table 1, entries 1-14) and Oxone (Table 1, entries 15 and 16) as the oxidant. The best yield of **3aa** (90%) was obtained using $PhI(OAc)_2$ (Table 1, entry 2). Other iodine-based oxidants, such as $PhI(OCOCF_3)_2$ (Table 1, entry 10, yield 31%), IBX (Table 1, entries 11 and 12, yield 32–54%), DMP (Table 1, entries 13–14, yield 52%), showed less efficacy in this process. Peroxide oxidants, such as TBHP, TBAI/TBHP system [74], $(NH_4)_2S_2O_8$, and DDQ were ineffective in the studied process (Table 1, entries 17–22). A satisfactory yield of **3aa** (44%) was achieved using Oxone as the oxidant (Table 1, entry 15). The addition of a catalytic amount of 2-iodobenzoic acid, which forms hypervalent iodine compounds in the presence of Oxone [75], did not lead to an increased yield of **3aa** (Table 1, entry 16).

Dichloromethane proved to be the best solvent for the reaction, as carrying out the reaction in other solvents led to a decrease in the yield of **3aa** (Table 1, entries 5–7). Increasing the amount of $PhI(OAc)_2$ from 0.6 mmol to 1.5 mmol (Table 1, entry 4) leads to a decrease in the yield of **3aa** presumably due to the enhancing the role of side oxidation processes. The optimal reaction time was 10 min, a reaction of 5 min resulted in a significant decrease in the yield of the desired product (Table 1, entry 1). Prolongation of the reaction time to 24 h led to a slight decrease in the yield of **3aa** (Table 1, entry 3) due to its instability under the reaction conditions.

The possibility of using iodide salts (NaI and TBAI) was shown in Entries 8 and 9, however, the yield of **3aa** in that cases is lower than in the case of molecular iodine.

In the optimized reaction conditions (Table 1, entry 2) iodo-oxyimidation of various vinylarenes were performed in order to study the scope of the developed method (Figure 1).

The iodo-oxyimidation successfully proceeded using styrenes having both electron-withdrawing (Cl, F, Br) substituents in the aromatic ring (products **3ca**, **3da**, **3fa**, **3ha**, **3cb**–**hb**,



1a–k

1a: R^1 = H, R^2 = H;
1b: R^1 = *p*-Me, R^2 = H;
1c: R^1 = *p*-Cl, R^2 = H;
1d: R^1 = *p*-F, R^2 = H ;
1e: R^1 = *m*-Me, R^2 = H;
1f: R^1 = *m*-Br, R^2 = H;
1g: R^1 = *o*-Me, R^2 = H;
1h: R^1 = perfluoro, R^2 = H;
1i: R^1 = H, R^2 = Me;
1j: R^1 = H, R^2 = Ph;
1k: indene

2a,**b**

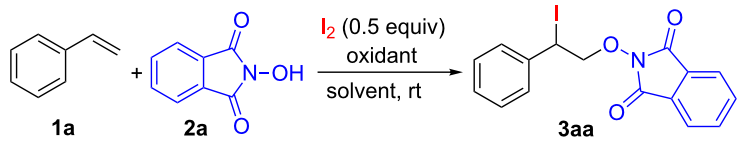
2a: *N*-hydroxyphthalimide;
2b: *N*-hydroxysuccinimide

3xy:
3aa–ka, **3ab–db**, **3fb**, **3hb**, **3kb**

the first letter (x) stands for the employed vinyl arene **1a–k**, the second letter (y) - imide **2a**,**b**

Scheme 2: Iodo-oxyimidation of styrenes **1a–k** with preparation of products **3aa–ka**, **3ab–db**, **3fb**, **3hb**, and **3kb**.

Table 1: Optimization of the synthesis of iodo-oxyimidation product **3a** from styrene **1a** and *N*-hydroxyimide **2a** [a].



entry	oxidant (molar ratio: mol/mol of **1a**)	solvent	time	yield of **3aa**[b] (%)
1	$PhI(OAc)_2$ (0.6)	DCM	5 min	63
2	$PhI(OAc)_2$ (0.6)	DCM	10 min	90
3	$PhI(OAc)_2$ (0.6)	DCM	24 h	84
4	$PhI(OAc)_2$ (1.5)	DCM	10 min	73
5	$PhI(OAc)_2$ (0.6)	MeCN	10 min	73
6	$PhI(OAc)_2$ (0.6)	AcOH	10 min	65
7	$PhI(OAc)_2$ (0.6)	PhMe	10 min	84
8[c]	$PhI(OAc)_2$ (2)	DCM	10 min	7
9[d]	$PhI(OAc)_2$ (2)	DCM	10 min	52
10	$PhI(OCOCF_3)_2$ (0.6)	DCM	10 min	31
11	IBX (1.0)	DCM	24 h	54
12	IBX (0.3)	DCM	24 h	32
13	DMP (0.6)	DCM	30 min	52
14	DMP (0.3)	DCM	30 min	52
15	Oxone (2)	DCM/H_2O (2:1)	4 h	44
16	2-iodobenzoic acid (0.1), Oxone (2)	DCM/H_2O (2:1)	4 h	44
17	TBHP (70% aq) (2)	DCM	12 h	ND
18	TBHP (70% aq) (2)	MeCN	12 h	ND
19	TBHP (70% aq) (2)	AcOH	12 h	ND
20	TBAI (0.1), TBHP (70% aq) (2)	MeCN	12 h	ND
21	$(NH_4)_2S_2O_8$ (1.5)	DCM/H_2O (2:1)	12 h	5
22	DDQ (2)	MeCN	30 min	5

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), I_2 (0.5 mmol), oxidant (0.3–2 mmol), solvent (6.0 mL), 20–25 °C, 5 min–24 h, under air. For entries where a mixture of solvents was used, the v/v ratio is given in parentheses. [b]Isolated yield. ND = not detected. [c]NaI·$2H_2O$ (1 mmol) was employed instead of I_2. [d]TBAI (1 mmol) was employed instead of I_2.

yield 34–91%), and an electron-donating methyl group (products **3ba**, **3ea**, **3ga**, **3bb**, yield 39–85%). Good yields (60–79%) were achieved with a cyclic analogue of styrene – indene (**1k**, compounds **3ka**, **3kb**). β-Substituted styrenes (β-methyl styrene (**1i**) and (*E*)-stilbene (**1j**) also underwent the studied transformation giving iodo-oxyimides **3ia** (yield 51%) and **3ja** (yield 83%). The reaction of NHPI (**2a**) with *p*-methoxystyrene under standard conditions led to a complex mixture of products, possibly due to an increased tendency of the substrate to electrophilic addition of iodine. The use of allylbenzene in the reaction did not result in the formation of the desired iodo-oxyimide, presumably due to a side process of oxidation of the allylic methylene fragment. The use of *N*-hydroxyphthalimide (**2a**) gives iodo-oxymidation products with yields generally higher (25% on average) than that of *N*-hydroxysuccinimide (**2b**).

Structures of the iodo-oxyimides **3aa**–**ka**, **3ab**–**db**, **3fb**, **3hb** and **3kb** were confirmed by 1D and 2D NMR spectroscopy, IR spectroscopy, high-resolution mass spectrometry and elemental analysis. An additional confirmation of the structure of **3ca** was made using X-ray crystallographic analysis (Figure 2). Details of the data collection and refinement are provided in Supporting Information File 1 and can be obtained free of charge via the web at https://www.ccdc.cam.ac.uk/structures/ (CCDC-1845323).

Proposed mechanism of the iodo-oxyimidation

Based on the literature data describing the formation of the phthalimide-*N*-oxyl radical (PINO) from NHPI under the action of $PhI(OAc)_2$ [34,55,59,76,77], and based on information about the reaction of the PINO radical with styrenes [45] and interac-

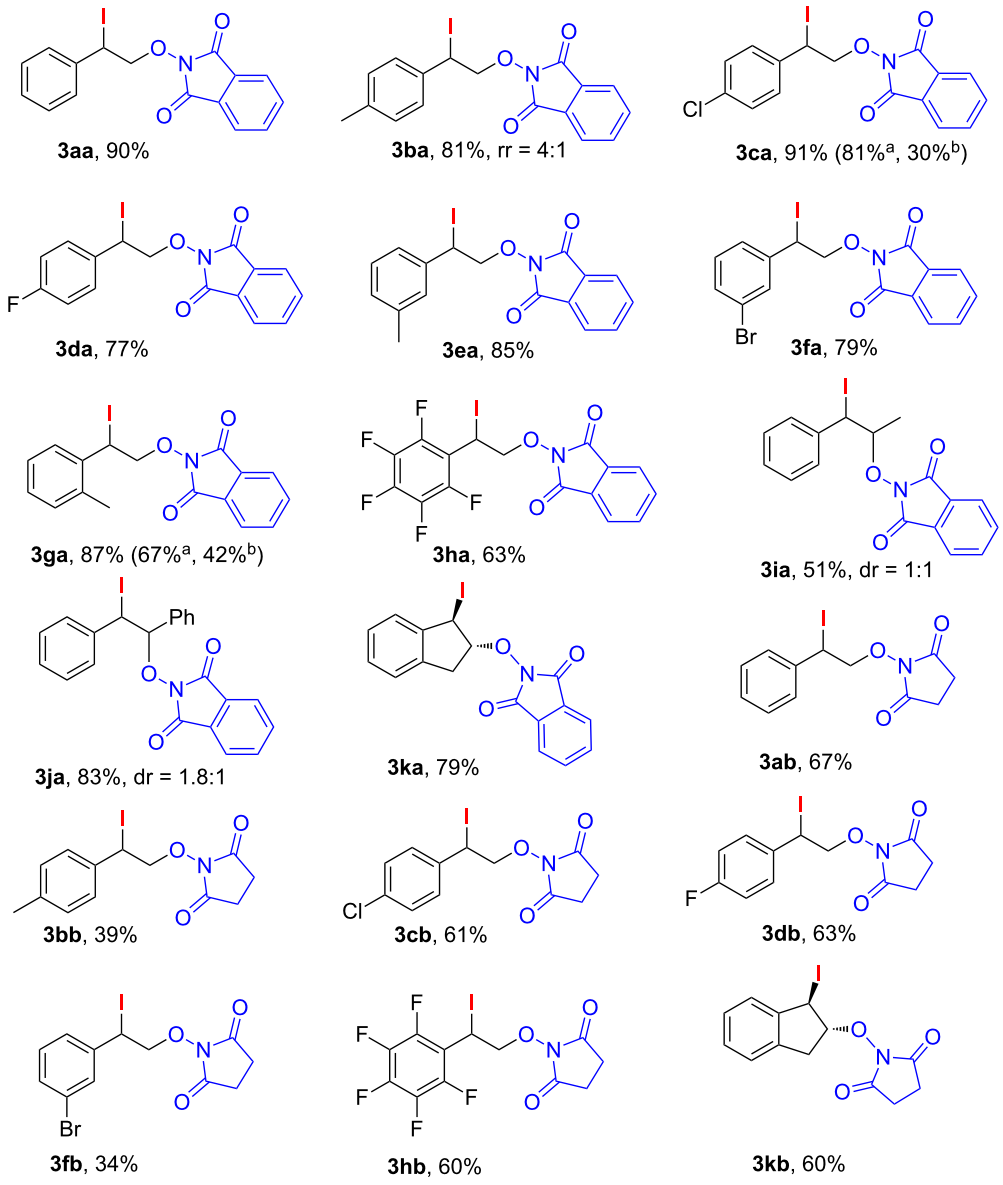


Figure 1: Scope of the iodo-oxyimidation of vinylarenes with I_2/PhI(OAc)$_2$ system. Reaction conditions: vinylarene **1a**–**k** (0.5 mmol), *N*-hydroxyimide **2a**,**b** (0.5 mmol), I_2 (0.25 mmol), PhI(OAc)$_2$ (0.3 mmol), DCM (3.0 mL), 20–25 °C, 10 min, under air. rr = regioisomers ratio. [a]IBX (0.5 mmol) was used instead of PhI(OAc)$_2$, reaction time: 24 h. [b]DMP (0.15 mmol) was used instead of PhI(OAc)$_2$, reaction time 30 min.

tion of benzyl radicals with iodine [78,79], a mechanism for the reaction of iodo-oxyimidation of styrenes under the action of the NHPI/I_2/PhI(OAc)$_2$ system was proposed (Scheme 3).

On the first step, NHPI (**2a**) is oxidized by PhI(OAc)$_2$ to form PINO radical. The addition of PINO to the double C=C bond of styrene (**1a**) leads to the formation of intermediate **A**. At the final step the iodine traps benzyl radical **A** to form the final product **3aa**.

Electrochemical studies

Cyclic voltammetry (CV) experiments on a working glassy-carbon electrode were carried out for deeper understanding of the plausible reaction mechanism. As CH_2Cl_2 is not suitable as a solvent due to the poor solubility of NHPI, thus MeCN was used. Tetrabutylammonium tetrafluoroborate, which cannot be oxidized in such experimental conditions [80], was chosen as a supporting electrolyte. Cyclic voltammograms of styrene (**1a**), NHPI (**2a**), I_2 and PhI(OAc)$_2$ in MeCN solution were registered (Figure 3).

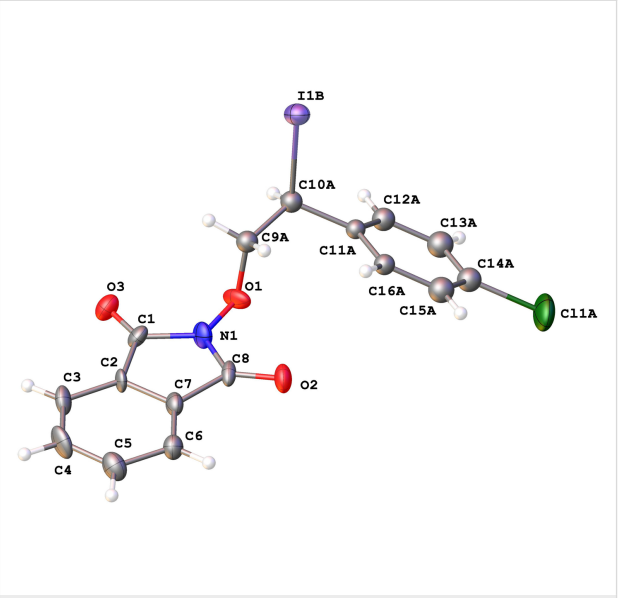


Figure 2: Molecular structure of **3ca**. Atoms are presented as anisotropic displacement parameters (ADP) ellipsoids (50% probability). For clarity, only one set of positions of the disordered ethylene bridge and Ph groups is shown.

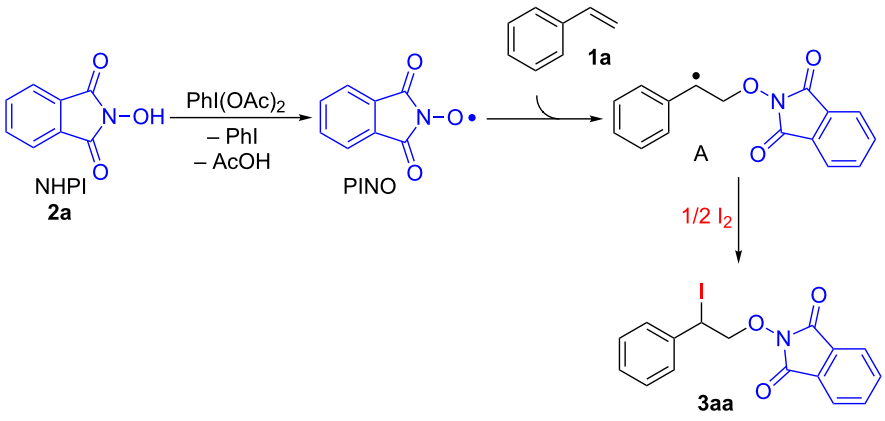
The NHPI oxidation peak is observed at +2.18 V, whereas iodine is oxidized at slightly higher potential (+2.27 V), and styrene oxidation peak is not so pronounced. Therefore, we can conclude that under experimental conditions NHPI is oxidized preferentially over iodine providing PINO radicals that leads to the observed regioselectivity. The contribution of the oxidation of styrene to the overall process is unlikely.

Practical application of the iodo-oxyimidation

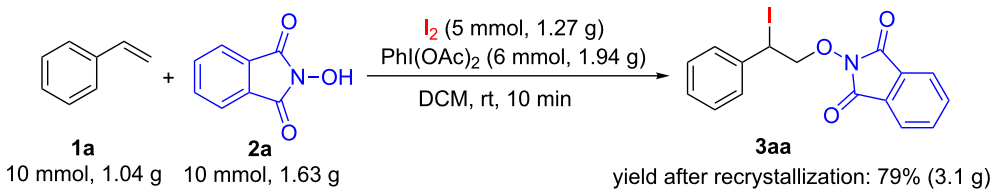
The applicability of the developed method for the gram-scale preparation was demonstrated by the synthesis of **3aa** (3.1 g, 79%) without column chromatography (Scheme 4).

The synthetic utility of the obtained products **3aa** and **3ab** was demonstrated by the substitution of the iodine atom with O- (methanol), S- (benzenesulfinate) and N- (azide) nucleophiles (Scheme 5).

It is noteworthy that the reaction of compound **3aa** with sodium benzenesulfinate results in the nucleophilic substitution of



Scheme 3: The proposed mechanism of iodo-oxyimidation of styrene (**1a**) using the NHPI/I_2/PhI(OAc)$_2$ system with the formation of product **3aa**.



Scheme 4: Gram-scale synthesis of compound **3aa**.

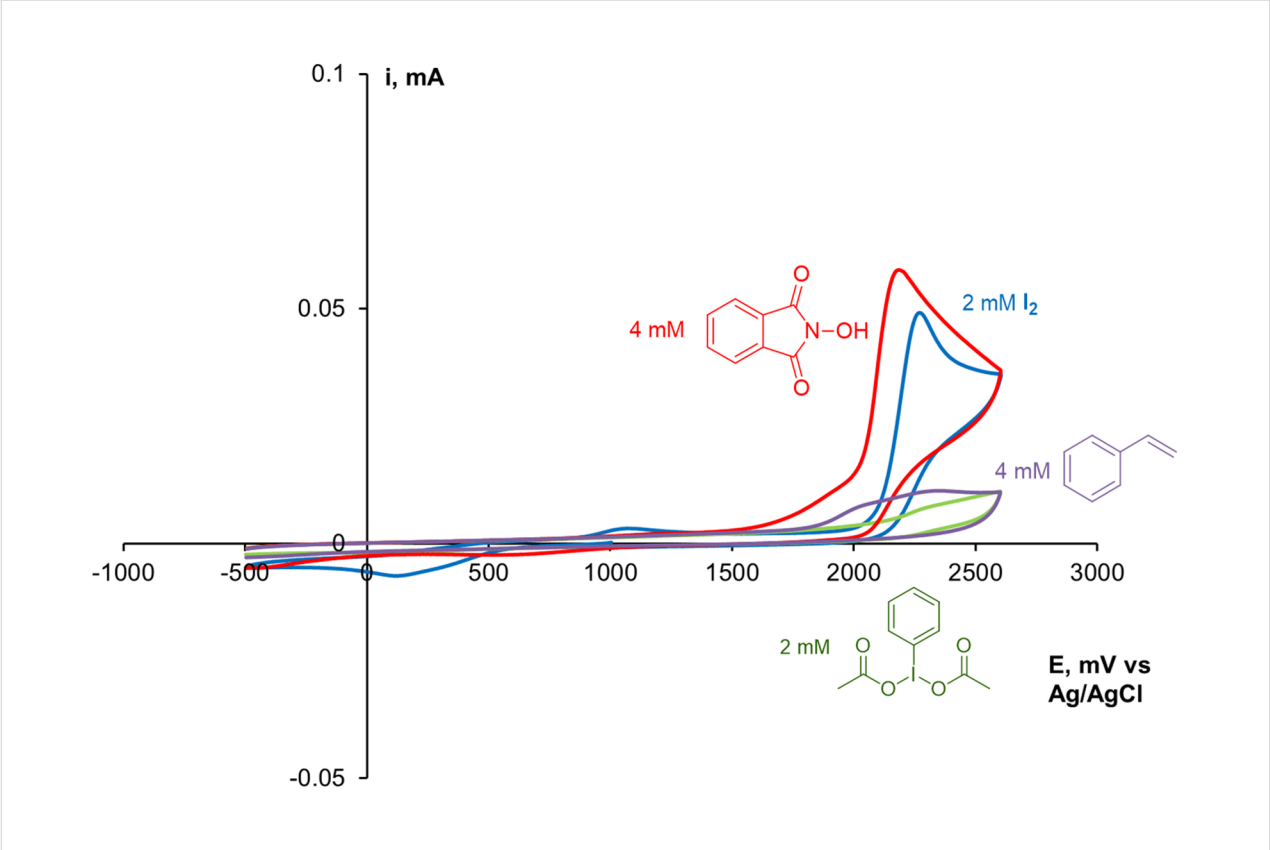
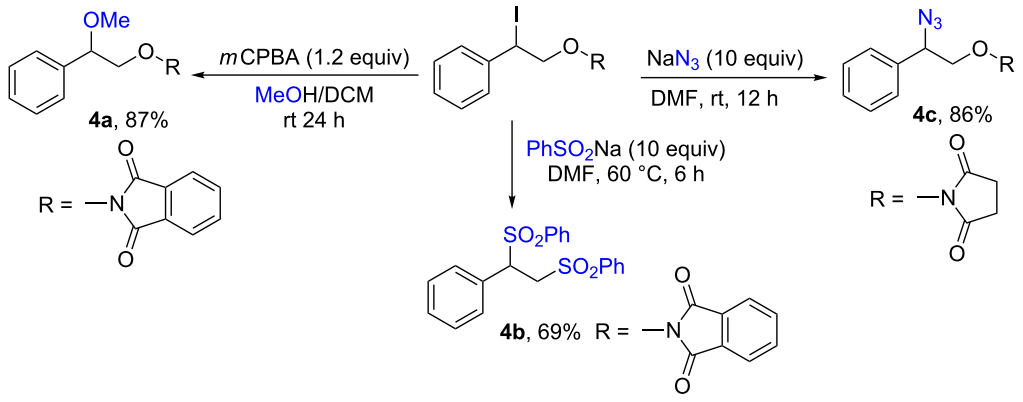


Figure 3: CV curves of styrene (**1a**, purple), NHPI (**2a**, red), I_2 (blue) and $PhI(OAc)_2$ (green) in 0.1 M *n*-Bu_4NBF_4/MeCN at a scan rate of 100 mV/s on a working glassy-carbon electrode.



Scheme 5: Synthetic utility of the iodo-oxyimides **3aa** and **3ab**.

both the iodine atom and the oxyphthalimide moiety to form a vicinal disulfone **4b**.

Conclusion

Iodo-oxyimidation of vinylarenes using *N*-hydroxyphthalimide and *N*-hydroxysuccinimide was developed. $PhI(OAc)_2$ was the best oxidant for the synthesis of the target products (yields up to 91%). In contrast to previous studies in which oxidants promote the electrophilic addition of iodine to the C=C bond, radical addition predominates in the discovered process. Radical pathway starts from the attack of imide-*N*-oxyl radicals on the double C=C bond, which allows for anti-Markovnikov type regioselectivity of C–O and C–I bond formation. Electrochemical mechanistic studies based

on cyclic voltammetry (CV) data confirm proposed reaction mechanism. Possible ways of using the obtained iodo-oxyimidated products via substitution of iodine atom were demonstrated.

Experimental

General procedure for the synthesis of compounds **3aa–ka**, **3ab–db**, **3fb**, **3hb** and **3kb** (Figure 1)

Iodine (64 mg, 0.25 mmol) was added to a stirred mixture of vinylarene **1a–k** (52–97 mg, 0.50 mmol) and *N*-hydroxyimide **2a**,**b** (58–82 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) at 20–25 °C. Then, $PhI(OAc)_2$ (97 mg, 0.30 mmol) was added. In the additional experiments compounds **3ca** and **3ga** were prepared using IBX (140 mg, 0.50 mmol) or DMP (64 mg, 0.15 mmol) instead of $PhI(OAc)_2$. After stirring for 10 min under air atmosphere at 20–25 °C, CH_2Cl_2 (30 mL) was added. The resulting mixture was washed with an aqueous solution of $Na_2S_2O_3{\cdot}5H_2O$ (200 mg in 20 mL of water), saturated aqueous $NaHCO_3$ solution (20 mL), and with water (20 mL), dried over anhydrous $MgSO_4$ and filtered. CH_2Cl_2 was evaporated at 20–25 °C under water-jet vacuum (20–30 mm Hg). Products **3aa–ka**, **3ab–db**, **3fb**, **3hb** and **3kb** were isolated by column chromatography on silica gel using with EtOAc/DCM eluent (with the volume part of EtOAc gradually increased from 0% to 2.5%).

Iodo-oxyimides **3aa–ka**, **3ab–db**, **3fb**, **3hb** and **3kb** should be stored in a freezer and handled with minimal heat due to their instability at elevated temperatures.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, copies of ^1H, ^{13}C and ^{19}F NMR spectra, copies of HRMS and FT-IR spectra and the ORTEP diagram and X-ray data for compound **3ca**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-188-S1.pdf]

Supporting Information File 2

X-ray structure analysis data for **3ca** (CCDC-1845323).
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-188-S2.cif]

Acknowledgements

This work was supported by the Russian Science Foundation (18-13-00027).

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.14.188

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Determining the predominant tautomeric structure of iodine-based group-transfer reagents by ^{17}O NMR spectroscopy

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Full Research Paper

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Keywords:
electrophilic; hypervalent iodine; ^{17}O NMR spectroscopy; trifluoromethylation; trifluoromethylthiolation

Beilstein J. Org. Chem. **2018,** *14,* 2289–2294.
doi:10.3762/bjoc.14.203

Received: 14 February 2018
Accepted: 23 July 2018
Published: 30 August 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Cyclic benziodoxole systems have become a premier scaffold for the design of electrophilic transfer reagents. A particularly intriguing aspect is the fundamental I^{I}–I^{III} tautomerism about the hypervalent bond, which has led in certain cases to a surprising re-evaluation of the classic hypervalent structure. Thus, through a combination of ^{17}O NMR spectroscopy at natural abundance with DFT calculations, we establish a convenient method to provide solution-phase structural insights for this class of ubiquitous reagents. In particular, we confirm that Shen's revised, electrophilic SCF_3-transfer reagent also adopts an "acyclic" thioperoxide tautomeric form in solution. After calibration, the approach described herein likely provides a more general and direct method to distinguish between cyclic and acyclic structural features based on a single experimental ^{17}O NMR spectrum and a computationally-derived isotropic shift value. Furthermore, we apply this structural elucidation technique to predict the constitution of an electrophilic iodine-based cyano-transfer reagent as an NC–I–O motif and study the acid-mediated activation of Togni's trifluoromethylation reagent.

Introduction

The remarkable stability and reactivity of Togni's hypervalent iodine-based trifluoromethylation reagents (e.g., **4a**) [1] have inspired the development of analogous compounds, including a well-known SCF_3-transfer reagent **5** in 2013 by Shen and co-workers [2,3]. In the presence of $AgSCF_3$, chloroiodane **2a** afforded an isolable and powerful electrophilic SCF_3 source, which was used, for example, in α-ketone functionalizations among other reactions [2,3]. While at the time the proposed cyclic hypervalent iodine structure **5a** appeared reasonable in analogy to other well-established transfer reagents, it was

unequivocally demonstrated to exist as the acyclic thioperoxide tautomer **5b** by Buchwald and co-workers in 2014 [4]. The structural reassignment was prompted by a series of remarkable, detailed inspections of ^{1}H NMR spectra of precursors and congeners. A final structural corroboration came about by successfully encapsulating **5b**, an oil under ambient conditions, in a metal-organic framework (**5b**@MOF). This non-trivial protocol rendered it amenable to X-ray diffraction studies confirming the aforementioned structural reassignment. From a theoretical standpoint, acyclic isomer **5b** is predicted to be thermodynamically favored over the cyclic form **5a** by more than 10 kcal/mol by DFT calculations [5]. However, this type of computational analysis is in general still not decisive. For example, while Togni reagent **4a** is thermodynamically less favorable than its acyclic isomer **4b** by over 50 kcal/mol, a high kinetic barrier suppresses the [**a** → **b**] isomerization (Figure 1) [5,6].

With SCF_3 reagent **5a**/**5b**, structure determination was notably challenging and solely provides a solid-state structural perspective. Thus, we wondered whether a correct structural assignment of reagent **5a**/**b** would have been feasible without having to resort to the preparation of crystalline congeners and/or the preparation of **5b**@MOF. Importantly, establishing a reliable way to differentiate cyclic (**a**) from acyclic (**b**) isomers in solution would facilitate future structure determination of similar iodine-based group-transfer reagents and provide greater mechanistic insight into reactivity of these reagents (Figure 1). Accordingly, we describe herein how ^{17}O NMR spectroscopy in tandem with gauge-independent atomic orbital (GIAO) calculations may be a viable approach to establishing the predominant tautomer in solution.

Results and Discussion

Arguably, the most common methods for structural elucidation of small organic molecules are one-dimensional ^{1}H and ^{13}C NMR spectroscopic techniques in combination with suitable two-dimensional experiments (COSY, HMBC, NOESY, etc.) [7]. However, in many cases (e.g., **5a** versus **5b**) these may only provide limited information, as neither nucleus is a primary constituent of the central iodine(III) (**a**, X–I–O) or iodine(I) (**b**, O–X) motif of interest. In stark contrast, changes in the oxygen ligand's environment should be readily traceable upon oxidation from alcohol **1** to chloroiodane **2a** (Figure 1, maroon), as well as during ensuing ligand substitutions, for example to fluoroiodane **3a**. In particular, whether oxygen is covalently bound to iodine or another element may heavily influence its shielding and thereby provide structural information by means of ^{17}O NMR spectroscopy.

While natural abundance ^{17}O NMR has been employed previously, including the analysis of hypervalent iodine compounds [8-10], this spectroscopic method has not yet found its entry into the organic chemist's standard NMR toolbox. This, in large part, may be attributed to the extremely low natural abundance of the ^{17}O isotope (<0.04%) [11,12]. Consequently, the experiment requires high sample concentrations and relatively long

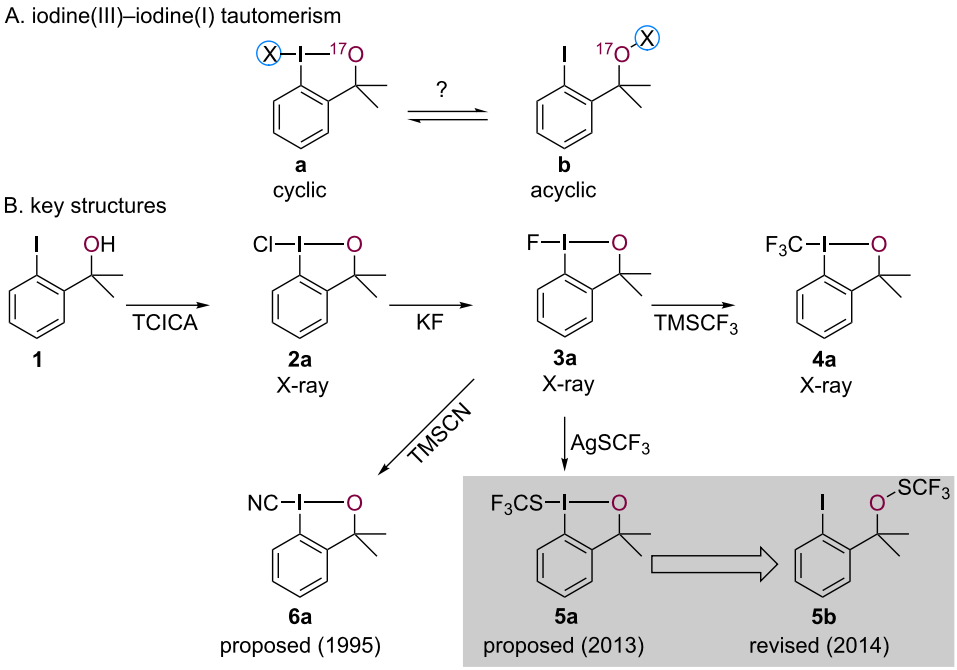


Figure 1: Tautomerism in iodine-based group-transfer reagents probed by ^{17}O NMR spectroscopy (A) and key structures investigated herein (B).

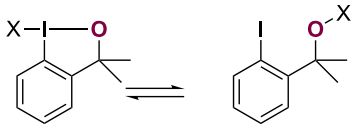
experimental times, and ultimately fairly broad signals are observed. Yet, due to the large chemical shift range available (>1000 ppm), the technique may still prove diagnostic, especially when paired with calculated oxygen isotropic shift values. In order to substantiate this working hypothesis, five pairs of cyclic (**a**) vs acyclic (**b**) structural isomers **2**–**6** were investigated initially by DFT at the ωB97XD/aug-cc-pVDZ (aug-cc-pVDZ-PP basis set for iodine [6,13]) level of theory using Gaussian 09 [14,15]. The ωB97XD functional was chosen as a reasonably cost-effective way to include long-range dispersion [14].

Geometry optimizations of both cyclic and acyclic isomers were followed by calculation of oxygen isotropic shift values (δ_{iso}) using the GIAO method (Table 1) [8-10]. Furthermore, these computed isotropic shift values (δ_{iso}) were not referenced, for example to water, since they were directly correlated to experimentally determined ^{17}O NMR shifts (vide infra). In addition, note that the calculations did not include treatment of spin-orbit-induced heavy-atom effects [16]. While undoubtedly important in the framework of classical bonding paradigms, they will only have a negligible effect on oxygen shifts derived for hypervalent iodine species. Specifically, spin-orbit effects heavily depend on and propagate through s-character rich bonds. However, within classical bonding theory the hypervalent bond about iodine comprises purely of p-orbitals (Rundle-Pimentel model) and most recently, this notion was corroborated for structure **4a** in a computational study [17]. Hence, effects on oxygen isotropic shifts will be minor at best and systematic and therefore, be accounted for by the abovementioned referencing to experimentally determined values.

We found that the calculated δ_{iso}-values for the two isomers **2a**/**b** and **4a**/**b** differ by $\Delta\delta_{iso} \approx 20$; these differences are significantly larger for **3a**/**b** ($\Delta\delta_{iso} = -399.1$), **5a**/**b** ($\Delta\delta_{iso} = 81.2$) and **6a**/**b** ($\Delta\delta_{iso} = 52.7$). Given that the larger the difference $\Delta\delta_{iso}$, the more likely a successful structural assignment based on ^{17}O NMR spectroscopy becomes, this technique may indeed prove useful for the identification of the isomeric pairs **2**–**6**. Accordingly, spectral data on **1**, **2a**, **3a**, **4a**, **5** (assuming no assignment), and **6** (unassigned) were acquired and further supplemented with values from some additional, structurally well-characterized hypervalent iodine compounds available in the literature (see Table 1 and Supporting Information File 1). Thus, a data set with a total of 11 entries was obtained.

To obtain experimental ^{17}O NMR shifts, we used samples prepared in chloroform-*d* at a concentration of approximately 1.3 M. The obtained resonances typically featured a full-width at half maximum of around 1000–1500 Hz (Figure 2A). Therefore, the uncertainties of the determined ^{17}O chemical shift values δ_{obs} are rated at a minimum of ±10 ppm, and thus, a reliable structural assignment should become feasible if predicted shift differences between the constitutional isomers **a** and **b** are greater. The observed ^{17}O NMR chemical shifts ranged from 32 ppm (**5**) to 137 ppm (a C_2F_5-transfer reagent). Compounds **2a** and **4a** resonate at similar frequencies, with respective chemical shifts of 116 ppm and 130 ppm. For compound **5**, an

Table 1: Compilation of δ_{iso}, δ_{obs} and δ_{calc} values.



a **b**

entry	tautomer	δ_{iso}[a]	δ_{obs}[b] [ppm]	δ_{calc}[c] [ppm]	$\lvert\delta_{calc} - \delta_{obs}\rvert$
1	–	249.7	67	42	25
2 (X = Cl)	**a**	192.7	116	116	0
	b	203.6	–	102	–
3 (X = F)	**a**	236.2	59	60	1
	b	−162.9	–	575	–
4 (X = CF_3)	**a**	180.1	130	132	2
	b	203.8	–	101	–
5 (X = SCF_3)	**a**	173.6	–	140	–
	b	254.8	32	36	4
6 (X = CN)	**a**	186.3	115	124	9
	b	239.0	–	56	–

[a]δ_{iso}: computed isotropic shift value; [b]δ_{obs}: observed (experimental) chemical shift; [c]δ_{calc}: calculated (predicted) chemical shift.

approximately 100 ppm smaller chemical shift value was observed with δ_{obs} = 32 ppm, and for unassigned structure **6** we measured 115 ppm. It is noteworthy to indicate that under certain circumstances the absolute ^{17}O NMR shift alone may be misleading in structure determination. For instance, the experimental value of 59 ppm for the known cyclic fluoroiodinane **3a** is closer to the observed values of acyclic **1** (67 ppm) and **5b** (32 ppm) than it is to cyclic **2a** and **4a**. However, assessment of the DFT-calculated isotropic shift values (δ_{iso}) in tandem with experimental ^{17}O NMR data (δ_{obs}) lends credence to the aforementioned structural assignment. Specifically, for the "unassigned" compounds mentioned above, the best R^2-value for a linear relationship $\delta_{obs} \sim \delta_{iso}$ is obtained when **5** and **6** are assigned as **5b** and **6a**, where the additional known compounds serve as calibration (Figure 2B) [18]. Based on the thus derived equation, ^{17}O NMR chemical shifts δ_{calc} can be predicted for both isomers. A notable exception is the free alcohol **1**, which is not part of the linear relationship and consequently displays a large residual value (Table 1). Conceivably, this may be due to intermolecular hydrogen bonding with the solvent or other alcohol molecules in the concentrated solution. In fact, including a methanol solvent molecule as a hydrogen-bond donor in the DFT calculation will shift the δ_{calc} in the right direction for **1** (i.e., to δ_{calc} = 47 ppm based on δ_{iso} = 245.8, although $|\delta_{calc} - \delta_{obs}|$ is still 20 ppm).

For the pair **5a**/**b** a difference $\Delta\delta_{calc}$ of 104 ppm is obtained and a value of 68 ppm results for **6a**/**b** (Figure 2). Both figures are significantly larger than the ^{17}O chemical shift's lower-bound uncertainty estimate of ±10 ppm. While **5a**/**b** indeed has been shown to exist as the thioperoxide **5b** (vide infra), a crystallographic study on **6a**/**b** is required to corroborate our prediction as **6a**.

To further gauge the utility of this approach, the activation of Togni reagent **4a** was studied, in particular its protonation with a strong acid [1]. This brings about a significant elongation of the I–O bond from 2.203(5) Å in **4a** to 2.4991(13) Å in the fully protonated form **4c** [1,19]. Most recently, Toste and co-workers studied this activation strategy too and demonstrated that in the presence of an equivalent of gaseous HCl compound **4a** afforded an isolable iodonium-type structure [20]. Although this activation can be conveniently followed by ^{19}F NMR spectroscopy with **4a** resonating at −40.1 ppm and the fully protonated "iodonium" congener **4c** at −20 ppm [1], this technique provides no indication on how to best represent **4c** in solution. Does the compound resemble the molecular structure obtained in the solid state with oxygen still coordinated to iodine or would a free alcohol be a more accurate representation? In order to generate **4c**, reagent **4a** was treated with five equivalents of trifluoroacetic acid (TFA) and then subjected to spectroscopic

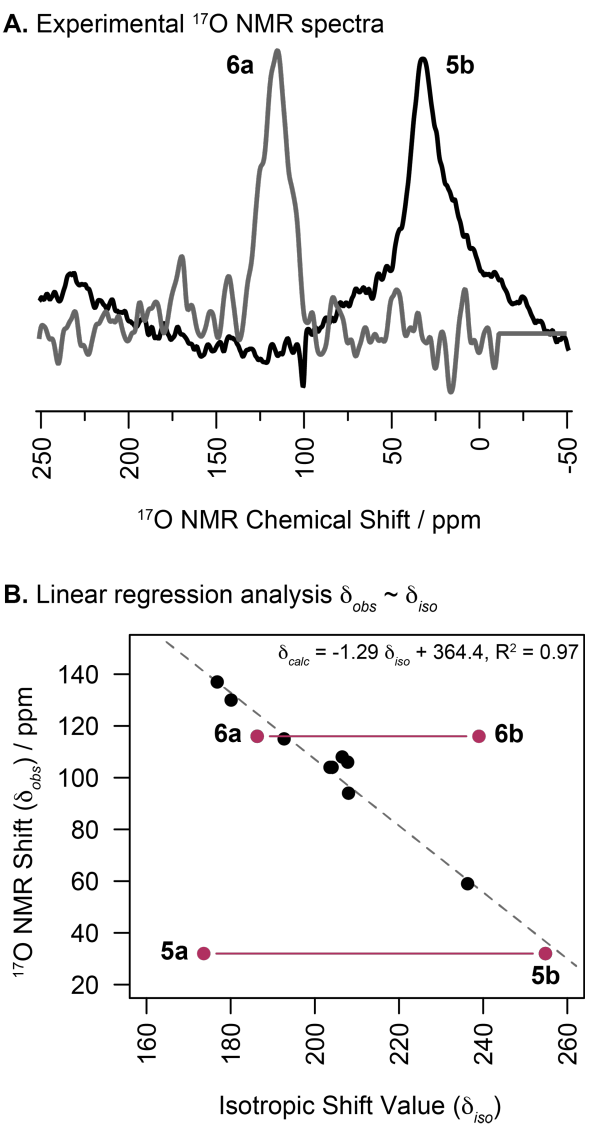


Figure 2: Assignment of acyclic (**b**) and cyclic (**a**) structures to **5** and **6**, respectively, based on computed isotropic shift values (δ_{iso}) and experimental ^{17}O NMR chemical shifts (δ_{obs}).

analysis. A ^{19}F NMR chemical shift of −23.2 ppm was obtained, thereby confirming the presence of **4c**. However, under these strongly acidic and activating conditions, the compound is unstable over a prolonged period of time (12 h). During the acquisition of the ^{17}O NMR data, approximately 36% of **4c** had decomposed to the corresponding α-methylstyrene derivative as indicated by ^{1}H NMR spectroscopy (see Supporting Information File 1). As this byproduct is ^{17}O NMR silent, the spectral data acquisition was unhampered and a chemical shift δ_{obs} = 77 ppm was measured. This value is larger than the chemical shift obtained for the free alcohol **1** (67 ppm) and at the same time, also significantly smaller than the value obtained for the native reagent **4a** (130 ppm). Structure **4c** was computed in the gas phase in absence of a counter anion and ge-

ometry optimization furnished a minimum reminiscent of the pictographic representation of **4c** with an intact but significantly elongated I–O bond of 2.55 Å (Figure 3) and qualitatively, the NMR data are in support of this notion. From a quantitative point of view, the data points (δ_{iso}, δ_{obs}) for **1**, **4b**, and **4c** afforded a perfect linear correlation with $R^2 = 1$, thus lending further credence to the representation of the protonated form **4a** in solution as **4c** (see Supporting Information File 1).

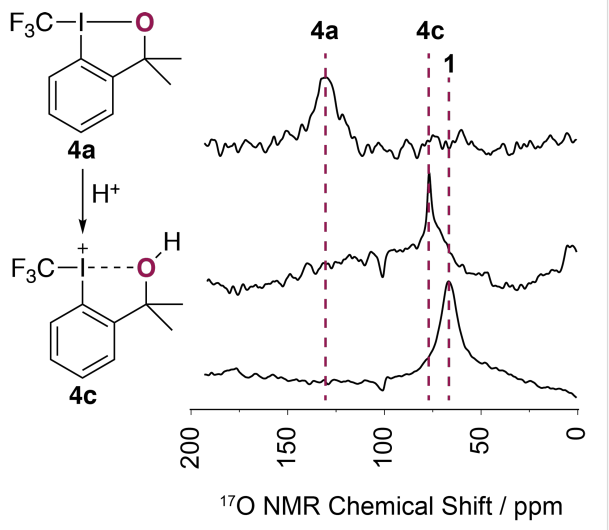


Figure 3: Protonation of **4a** with trifluoroacetic acid (5 equiv) affords **4c**, followed by ^{17}O NMR spectroscopy.

Conclusion

In summary, the present study demonstrates that ^{17}O NMR spectroscopy at natural abundance coupled with DFT-calculated isotropic shift values can be used to gain insight into the solution-phase tautomerism observed in iodine-based group-transfer reagents. In particular, we confirm that Shen's revised, electrophilic SCF_3-transfer reagent adopts an "acyclic" thioperoxide tautomeric form in solution whereas an electrophilic cyanide source prefers the "cyclic" iodane. Since ^{17}O NMR experiments are easily implemented on contemporary spectrometers, this method may provide the most convenient spectroscopic handle to re-evaluate known structures, facilitate further mechanistic studies, and provide a complimentary approach to solid-state structural analysis.

Supporting Information

Supporting Information File 1

^{17}O NMR spectra and calculated molecular geometries.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-203-S1.pdf]

Acknowledgements

This work was generously supported by the Swiss National Science Foundation (N. S., P3P3P2_167744), ETH Zürich Postdoctoral Fellowship Program (C. R. P.) and the National Science and Engineering Research Council of Canada (B. J. J.). The authors gratefully acknowledge the support of Prof. Dr. D. Günther and Prof. Dr. A. Togni (ETH Zürich).

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18. Note that calibrations using other functionals may provide inferior coefficients of determination. For instance, using the same basis set at B3LYP, R2 ≈ 0.49.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.14.203

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

The mechanochemical synthesis of quinazolin-4(3*H*)-ones by controlling the reactivity of IBX

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Full Research Paper

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Keywords:
ball-mill; contact explosive; IBX; mechanochemical synthesis; quinazolin-4(3*H*)-one

Beilstein J. Org. Chem. **2018,** *14,* 2396–2403.
doi:10.3762/bjoc.14.216

Received: 11 June 2018
Accepted: 24 August 2018
Published: 12 September 2018

This article is part of the Thematic Series "Hypervalent iodine chemistry in organic synthesis".

Guest Editor: T. Wirth

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Abstract

Performing any synthesis using several arylamines and hypervalent iodine(V) reagents by direct mixing is unrealistic because of the high exothermic reaction or explosion. Herein we demonstrate, when anilines were substituted with an amide group at the *ortho*-position, successful chemical reactions could be performed due to intramolecular control. At maximum contact of the reacting substances, i.e., under solvent-free mechanochemical conditions, 2-aminobenzamides, aryl-, alkylaldehydes and the iodine(V) reagent *o*-iodoxybenzoic acid (IBX) led to substituted quinazolin-4(3*H*)-one derivatives in fair yields.

Introduction

An iodine and ammonia mixture is a well-known contact explosive due to formation of NI_3 [1]. Similarly, hypervalent iodines as oxidizing compounds [2] react violently with amines under solvent-free conditions [3]. Aryliodonium imides or iminoiodanes can be prepared by the treatment of electron-deficient amines with iodine(III). However, these compounds explode at higher temperatures [4] and hence are stored under inert atmosphere and low temperature [5]. Polyvalent iodine derivatives are versatile reagents for C–N bond constructions [4,6]. Mechanochemical conditions such as ball milling are considered to be one of the premium techniques in solvent-free synthesis [7]. Under these conditions, maximum concentration is expected to put those systems under high stress and therefore violent exothermic reactions or even explosions may take place between hypervalent iodine reagents and electron-rich amines. For this reason, synthetic methods based on hypervalent iodine reagents and primary amines under solvent-free conditions or constrained media are limited [8]. Recently, we have described a method for the successful reaction of primary amines and hypervalent iodine(III) reagents by controlling the reactivity using an acid salt, $NaHSO_4$, as additive [9].

Results and Discussion

The last few decades have witnessed a significant growth in organic synthesis using hypervalent iodines [10-12]. Their easy availability, high stability, controlled oxidizing ability, and en-

vironmentally benign nature make them highly suitable for the development of new synthetic transformations [13-17]. The chemistry of iodine(V) reagents has been well documented in a number of reviews [18-20]. In continuation of our research focus on the development of synthetic methods using iodine-based reagents [21-26], we here report a method for the synthesis of quinazolin-4(3*H*)-ones [27,28] (Figure 1) from 2-aminobenzamide and aldehydes in the presence of *o*-iodoxybenzoic acid (IBX) [29]. However, when mixing benzaldehydes, aniline and IBX under ball-milling conditions an explosion was observed (Figure 1a; Caution! see experimental section) [30,31] and similar observations were made with Dess–Martin periodinane (DMP). On the other hand, benzamide was found to be unreactive with IBX and no reaction was observed under similar conditions (Figure 1b). Also no explosion was observed when 2-aminobenzamide was treated with IBX in absence of any aldehyde (Figure 1c). However, reacting 2-aminobenzamide with aldehydes in the presence of IBX under similar conditions was found to be successful affording the corresponding quinazolin-4(3*H*)-ones (Figure 1d).

In a recent report we have shown a successful dehydrogenative cross-coupling or CDC reaction using a combination of primary amines and phenyleneiodine diacetate (PIDA) under solvent-free ball-milling conditions, i.e., at the highest possible contact of the reactants [9]. During the reaction with the stronger oxidant PIDA, the basicity of the amine was regulated using an externally added acid salt, $NaHSO_4$ (Figure 2a). In Figure 2b, a comparison in the reactivities of arylamines in the presence of non-iodine-based oxidant oxone [32] and IBX (iodine-based oxidant) is shown. Anilines readily reacted with oxone leading to the formation of the azo derivatives [32], while their treatment with IBX led to explosive decomposition. The reactions of 2-aminobenzamide with arylaldehydes in the presence of IBX afforded quinazolin-4(3*H*)-ones at maximum contact of the reactants, i.e., under ball-milling conditions (Figure 2c).

Towards optimization of the reaction conditions, 2-aminobenzamide (**1**) and 4-ethylbenzaldehyde (**2a**) were chosen as model substrates (Table 1). Initially, 70% of 2-(4-ethylphenyl)quinazolin-4(3*H*)-one (**3a**) were obtained, when **1**, **2a** and 1.1 equiv of IBX were milled together for 1.5 h in a 10 mL ball-milling jar (Table 1, entry 1). However, the yield increased to 91% when IBX was added after 30 min of milling of the reactants **1** and **2a** (Table 1, entry 2). Conversely, changing the amount of IBX to other than 1.1 equiv, a decrease in the prod-

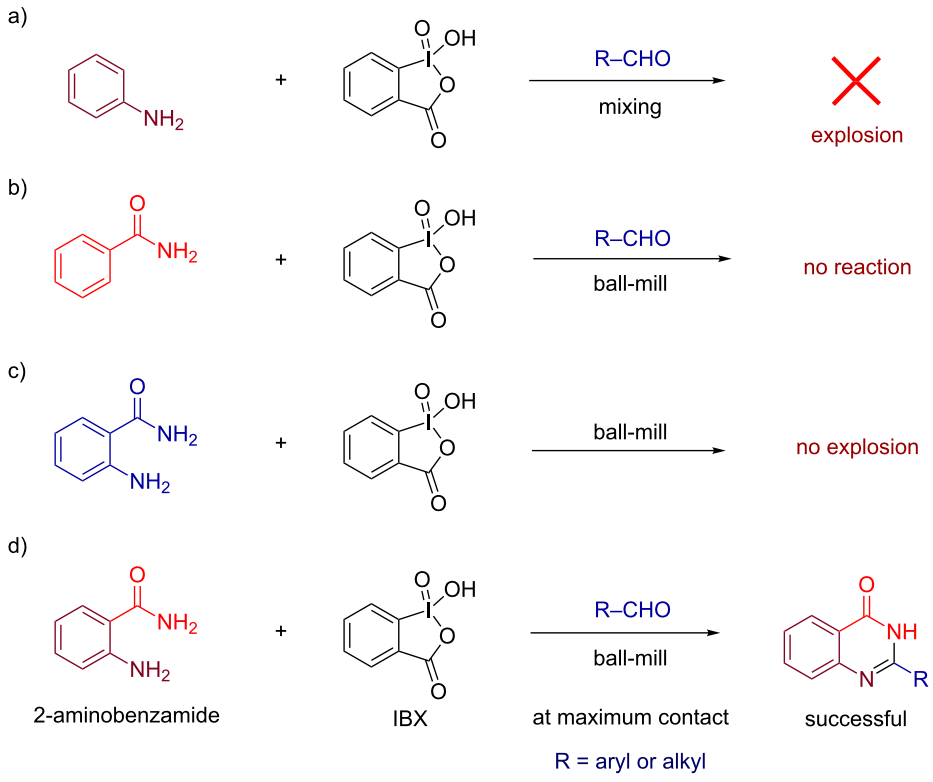


Figure 1: a) Explosion was observed when an arylamine was mixed with aldehydes in the presence of IBX. b) Benzamide was found to be unreactive with IBX. c) Treatment of 2-aminobenzamide with IBX did not lead to any explosion. d) Reaction of 2-aminobenzamide and aldehydes in the presence of IBX as oxidant afforded quinazolin-4(3*H*)-ones at maximum interaction of the reactants, i.e., under ball-milling conditions.

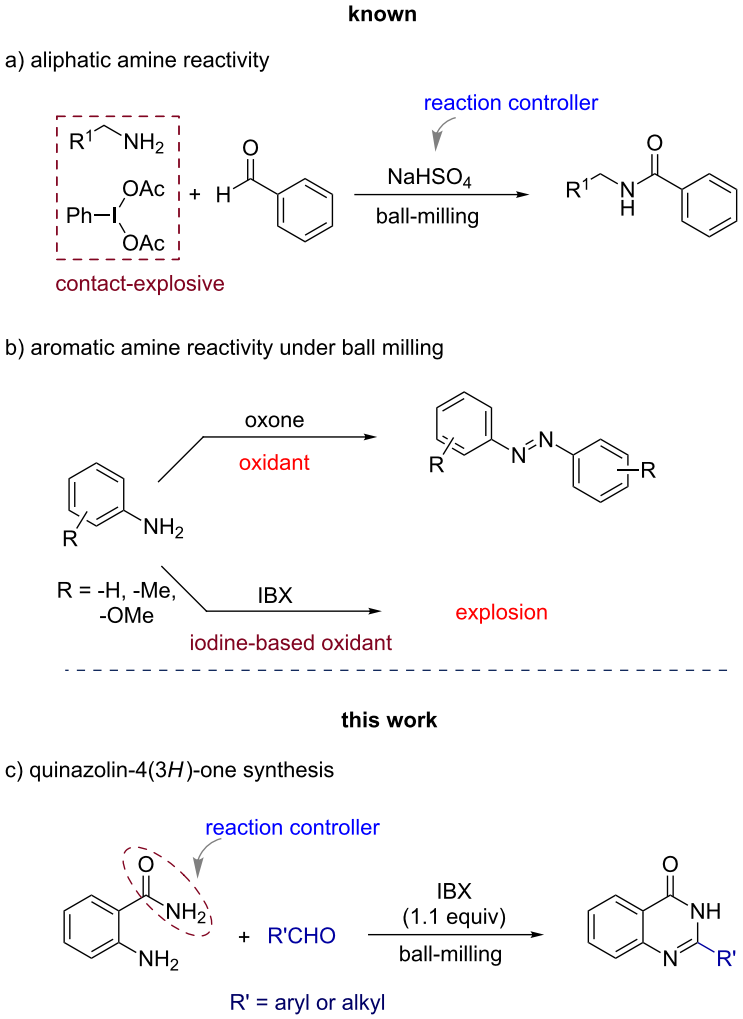
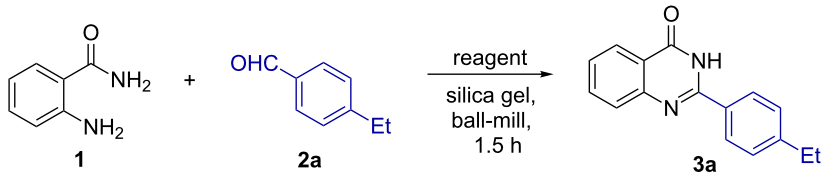


Figure 2: Comparison of the current work with the existing literature reports.

Table 1: Optimization of the reaction conditions.[a]



Entry	Reagent (equiv)[b]	Yield (%)[c]
1[d]	IBX (1.1)	70
2	IBX (1.1)	91
3	IBX (1)	78
4	IBX (1.2)	85
5[e]	IBA (1.1)–oxone (1.5)	59
6[f]	IBX (1.1)	90

[a]Reaction conditions: **1a** (1 equiv) and **2a** (1 equiv) and 60 mg silica gel for approximately 60 μL of **2a**; [b]reagent was added after 30 min; [c]isolated yields. [d]**1**, **2a** and IBX were added together; [e]2-iodobenzoic acid (IBA). [f]IBX added after 1 h.

uct yield was observed (Table 1, entries 3 and 4). The reaction also took place, albeit affording the product in lower yield, with in situ-generated IBX [33], i.e., by using an IBA (2-iodobenzoic acid)–oxone combination (Table 1, entry 5). Interestingly, when silica gel [34] was used as additive during the handling of liquid aldehydes, the yields of the products were found to be constant and reproducible. Interestingly no violent decomposition was observed, when IBX was added at the beginning of the reaction (Table 1, entry 1), after 30 min (Table 1, entry 2) or 1 h (Table 1, entry 6) of milling **1** and **2**. Thus we conclude that the current method is explosion free.

After optimization of the reaction conditions, the scope of the synthesis of quinazolin-4(3*H*)-one derivatives was explored (Figure 3 and Figure 4) and the desired products were isolated in fair yields. The yields of quinazolin-4(3*H*)-one derivatives

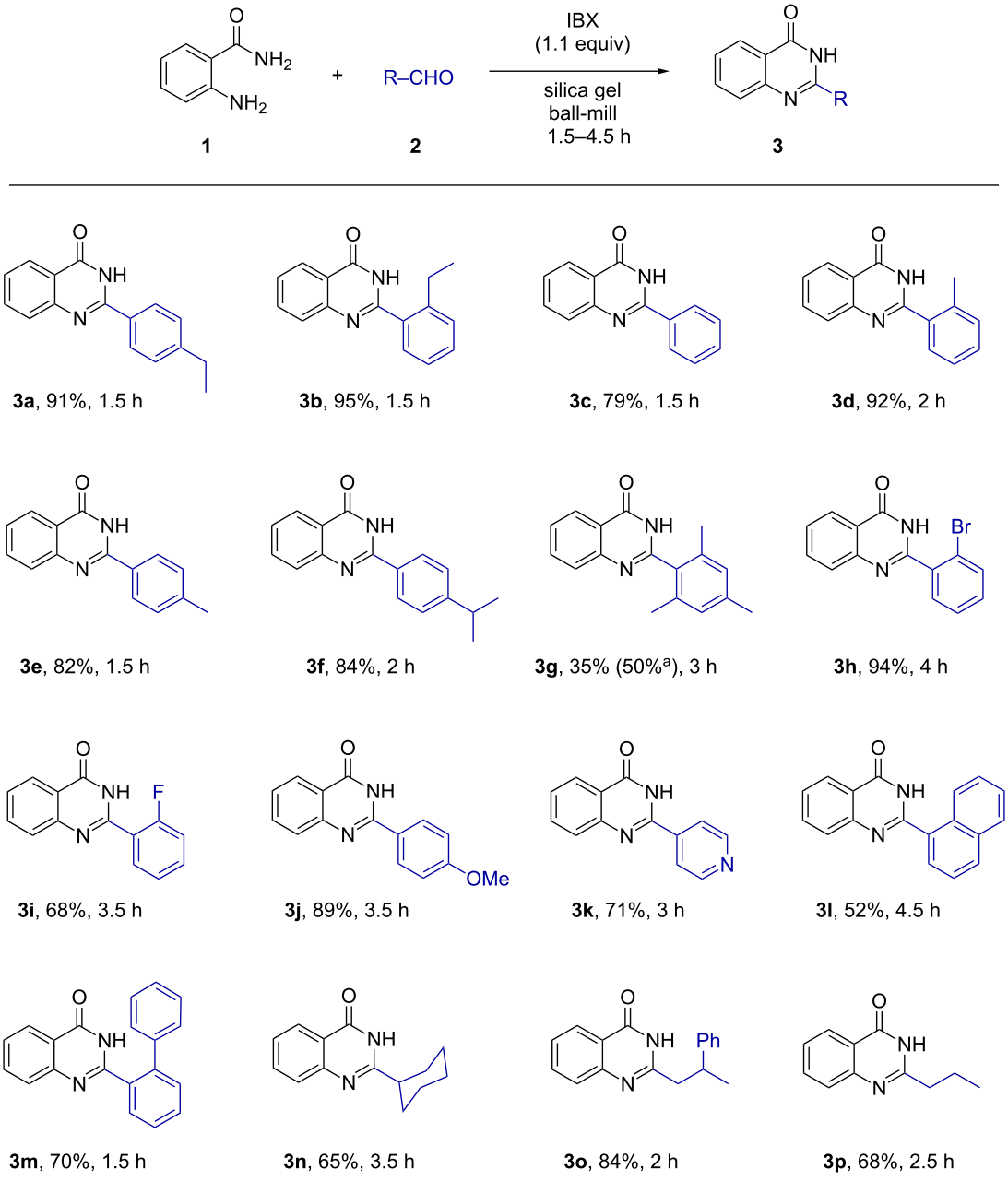


Figure 3: Synthesis of quinazolin-4(3*H*)-one derivatives from the reaction of **1** with liquid aldehydes. [a]Yields with respect to recovered aldehydes, for compound **3k** IBX was added after 1 h.

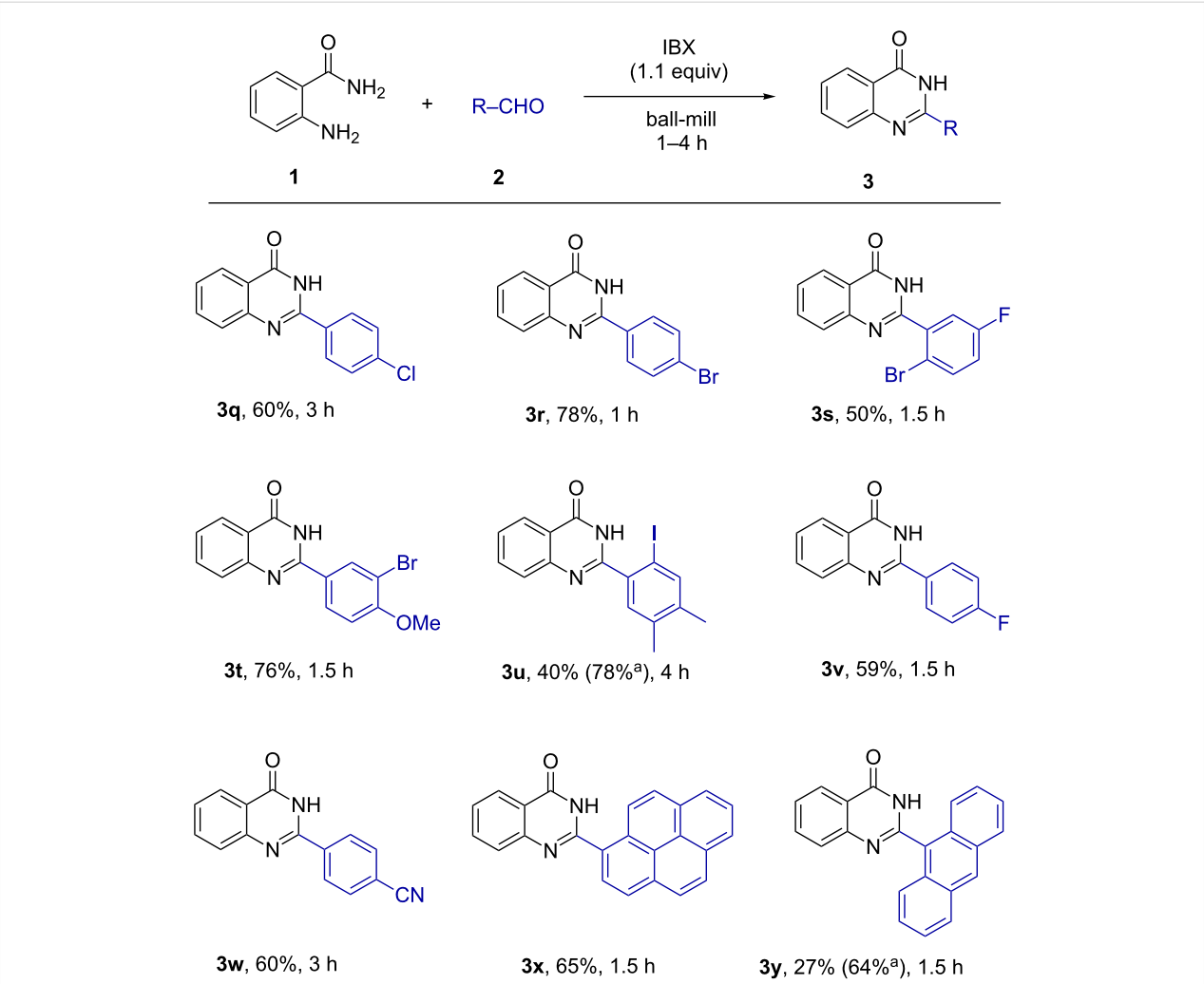


Figure 4: Synthesis of quinazolin-4(3*H*)-one derivatives from reaction of **1** and solid aldehydes. [a]Yields with respect to recovered aldehydes, for compound **3y**, IBX was added after 1 h.

were higher when monoalkyl-substituted benzaldehydes (**3a**,**b** and **3d**–**f**) were used compared to the reaction with unsubstituted benzaldehyde (**3c**). However, sterically congested aromatic aldehydes afforded the desired quinazolin-4(3*H*)-ones **3g** and **3u** in relatively poor yields. The reactions were found to proceed smoothly and moderately yielding with halogenated aldehydes (**3h**, **3i**, **3q**–**s**, **3v**) and the *p*-cyano-substituted aldehyde (**3w**). Methoxy-substituted aldehydes were giving quinazolin-4(3*H*)-ones in high yields (**3j**, **3t**). Likewise, the reaction was found to be successful with aldehydes containing fused aromatic ring systems like naphthyl (**3l**), pyrenyl (**3x**), anthryl (**3y**), etc. Several aliphatic aldehydes like cyclohexyl (**3n**), 3-phenylbutraldehyde (**3o**) and butyraldehyde (**3p**) furnished the corresponding heterocycles with higher efficiency. The synthesized products were characterized by standard analytical methods and the structure of **3a** was confirmed by X-ray crystallographic analysis (Figure 5).

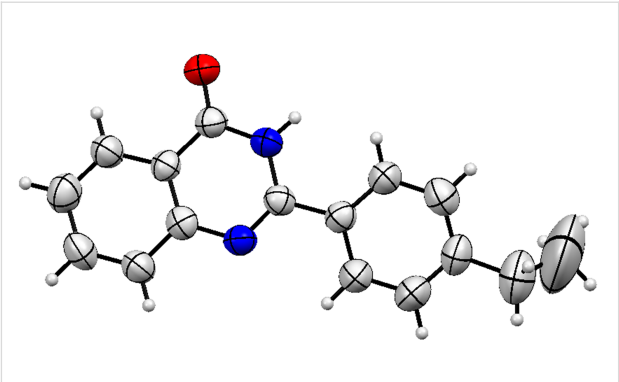


Figure 5: Crystal structure of **3a** (CCDC No. 1823611).

Based on the results collected in Table 1 and literature precedence [35,36], a mechanism of the quinazolin-4(3*H*)-ones synthesis is proposed and depicted in Figure 6. As it has been ob-

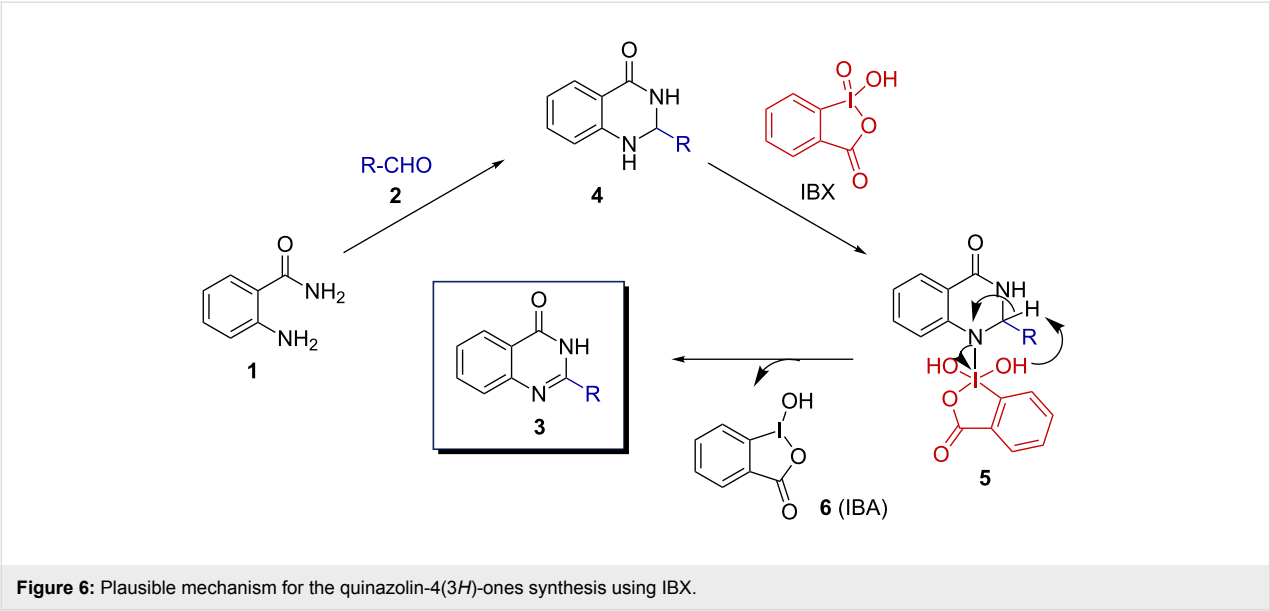


Figure 6: Plausible mechanism for the quinazolin-4(3*H*)-ones synthesis using IBX.

served that the yield of the reaction significantly increased when IBX was added after 30 min of initial milling of the reactants **1** and **2** it is anticipated that 2-aminobenzamide and the arylaldehyde formed the adduct **4**. This intermediate then further reacted with IBX to generate **5**. Finally, **5** led to the quinazolin-4(3*H*)-one **3** with the generation of IBA (**6**).

Arylamines caused explosion and benzamide was found to be unreactive with IBX. However, the reaction was found to be successful with 2-aminobenzamide under similar conditions (Figure 1). 2-Aminobenzamide having one highly reactive amine part and another unreactive part, can be considered an aniline derivative with moderate reactivity. Therefore, we anticipate that the controlled reactivity of IBX under mechano-milling conditions led to successful reaction with 2-aminobenzamide.

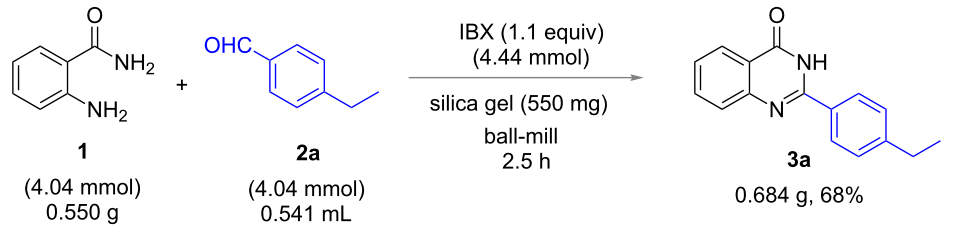
Finally, a large scale synthesis was performed to prove the synthetic utility of this methodology. By taking anthranilamide (**1**, 0.550 g) and 4-ethylbenzaldehyde (**2a**, 0.541 mL), the reaction was carried out under optimized conditions. The 2-(4-ethylphenyl)quinazolin-4(3*H*)-one (**3a**) was isolated in 68% yield (Scheme 1).

Conclusion

In conclusion, we have successfully demonstrated the synthesis of quinazolin-4(3*H*)-ones by the controlled use of IBX in the presence of 2-aminobenzamides. We foresee that controlled reactions of IBX in the presence of amines have certain advantages, e.g., many difficult reactions can be performed easily by choosing the appropriate reaction environment. The described methodology also highlights the advancement of quinazolin-4(3*H*)-ones synthesis chemistry and may find application in the context of mechanochemical reactions towards natural product synthesis and pharmaceutical chemistry.

Experimental

General methods. Ball-milling experiments were carried out open to atmosphere and at room temperature in a Retsch MM 200 high speed vibration mixture milling instrument (21 Hz). All yields mentioned are isolated yields after column chromatographic purifications of the compounds using silica gel



Scheme 1: Large scale synthesis of **3a**.

(230–400 mesh) and hexane/ethyl acetate mixtures as eluent, unless otherwise specified. NMR spectra were recorded on either a 400 MHz or a 700 MHz instrument at 25 °C. The chemical shift values are reported in ppm (parts per million) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) or DMSO (2.5 ppm for ^{1}H and 39.5 for ^{13}C). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet), coupling constant (Hz) and integration. High-resolution mass spectra (HRMS) were recorded on an ESI–TOF (time of flight) mass spectrometer. IR (infrared) spectral data are reported in wave numbers (cm^{-1}). Melting points (mp) of the compounds were determined using a digital melting point apparatus and are uncorrected.

Caution. When aniline and IBX are mixed under solvent-free conditions or at maximum contact, immediate explosion was observed. However, no explosion could be observed under similar conditions when 2-aminobenzamide and arylaldehydes were reacted in the presence of IBX. However, it is highly recommended to consult the general safety protocols at the laboratory and all reactions should be carried out in a fume hood behind a blast shield.

2-Iodoxybenzoic acid (IBX) was prepared by following reported literature procedure [37].

General procedure for preparation of quinazolin-4(3*H*)-ones. 2-Aminobenzamide (**1**, 0.44 mmol, 1.0 equiv), aldehyde (**2**, 0.44 mmol, 1.0 equiv), 60 mg silica gel (only for liquid aldehydes) and a stainless-steel milling ball were added into a 10 mL stainless-steel jar. Milling was carried out for 30 min and then IBX (0.484 mmol, 1.1 equiv) was added to the mixture and milling was continued for 1 h. The progress of the reaction was monitored by TLC after taking a small portion of the reaction mixture and dissolving it in DCM (with the appropriate solvent as eluent). After completion of the reaction, dichloromethane was used for extracting the compound from the solid reaction mixture. The solvent was evaporated to dryness and the crude reaction mixture was purified by silica gel column chromatography using an appropriate hexane/ethyl acetate mixture.

Large scale preparation of 3a: One third of the 25 mL stainless steel milling jar was filled with 2-aminobenzamide (550 mg, 4.04 mmol), 4-ethylbenzaldehyde (541.5 µL, 4.04 mmol), 550 mg silica gel and one ball (15 mm diameter). After 1 h of milling, IBX (1.24 g, 4.44 mmol) was added and milling continued for 1.5 h. Then, after extraction of the reaction mixture with DCM, followed by silica gel column chromatography with ethyl acetate/hexane 1:5 as eluent provided product **3a** (684 mg, 68%).

Supporting Information

Supporting Information File 1

Characterization data, NMR spectra and crystallographic information.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-216-S1.pdf]

Acknowledgements

The activity was supported by DST (New Delhi, India). We are thankful to Dr. Milan Kr. Barman (NISER, Bhubaneswar) for X-ray crystallographic analysis. MTA and SM are thankful to UGC (India) and CSIR (India) for fellowship, respectively.

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