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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Strategies in asymmetric catalysis

Tehshik P. Yoon

Editorial

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Guest Editor: T. P. Yoon

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The stereochemistry of an organic compound can have a profound influence on many of its most important properties. For example, the enantiomeric forms of a drug molecule can have completely different biological effects, and polymers that differ only in the stereochemistry of their backbones can have quite dissimilar macroscopic physical characteristics. Control over the stereochemical outcome of organic reactions has thus long been recognized as a central concern across multiple sectors of modern synthetic chemistry.

In 2001, the Nobel Prize in Chemistry was awarded to Knowles, Sharpless, and Noyori for their work on the use of chiral catalysts for highly enantioselective reactions. Those of us with research interests in stereoselective synthesis lauded this award because it celebrated the creative insights of these pioneers in asymmetric catalysis and because it marked a general recognition that enantioselective catalysis has had a significant practical impact on the broader field of organic synthesis.

Despite the remarkable progress in this field over the years, however, the rational design and discovery of enantioselective reactions remains a challenging endeavor. Part of the difficulty is intrinsic: subtle energy differences of only a few kilocalories per mole can nevertheless result in very high enantioselectivities in a given reaction. These effects can be hard to predict, to rationalize, and to generalize to diverse reaction types. Moreover, even small deviations from the optimal catalyst and substrate structures can sometimes result in poor results.

Thus, the design of asymmetric catalytic systems remains an active and vital research area. Current progress in the field of asymmetric catalysis continues to be driven both by conceptual innovations as well as demonstrations of the applicability of enantioselective catalytic reactions to increasingly complex synthetic problems.

The articles collected in this Thematic Series for the *Beilstein Journal of Organic Chemistry* provide a snapshot of both types of efforts. Several of these papers report new catalyst designs or relatively new concepts in catalytic stereocontrol. Others document the application of catalytic asymmetric methods to the streamlined synthesis of complex and structurally unusual organic molecules. I would like to express my gratitude to the authors and researchers who have contributed articles to this

Thematic Series. The creativity reflected in this set of papers augurs well for the continued vitality of what I believe is an important research endeavor. I hope you will agree.

Madison, December 2016

Tehshik P. Yoon

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

NeoPHOX – a structurally tunable ligand system for asymmetric catalysis

Jaroslav Padevět, Marcus G. Schrems, Robin Scheil and Andreas Pfaltz*

Full Research Paper

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Abstract

A synthesis of new NeoPHOX ligands derived from serine or threonine has been developed. The central intermediate is a NeoPHOX derivative bearing a methoxycarbonyl group at the stereogenic center next to the oxazoline N atom. The addition of methylmagnesium chloride leads to a tertiary alcohol, which can be acylated or silylated to produce NeoPHOX ligands with different sterical demand. The new NeoPHOX ligands were tested in the iridium-catalyzed asymmetric hydrogenation and palladium-catalyzed allylic substitution. In both reactions high enantioselectivities were achieved, that were comparable to the enantioselectivities obtained with the up to now best NeoPHOX ligand derived from expensive *tert*-leucine.

Introduction

Since their introduction and first successful application in enantioselective palladium-catalyzed allylic substitution in 1993 [1-3], chiral phosphinooxazolines (PHOX ligands) have emerged as a widely used privileged ligand class [4-12]. One of the major areas of application of PHOX and related N,P ligands is the iridium-catalyzed asymmetric hydrogenation [13-16]. Compared to rhodium and ruthenium catalysts, iridium complexes derived from chiral N,P ligands show a much broader substrate scope in the hydrogenation of olefins, as they do not require any coordinating groups in the substrate.

Although high enantioselectivities were achieved with the initially developed Ir-PHOX catalysts, the range of olefins that gave satisfactory results was limited. Consequently, a variety of other ligand classes derived from oxazolines or other nitrogen heterocycles were explored and eventually, several highly effective ligand systems were found that have considerably enhanced the range of functionalized and unfunctionalized olefins that can be hydrogenated with high efficiency and excellent enantioselectivity. Among the many oxazoline-derived ligands that have been reported in the literature, SimplePHOX [17] and

ThrePHOX [18] have emerged as some of the most versatile and most easily accessible ligand classes. However, although iridium complexes derived from these ligands are air and moisture-stable, the free ligands are prone to hydrolysis and oxidation. Especially SimplePHOX ligands, although they are readily prepared from amino alcohols in just two steps, suffer from these problems resulting in low yields and difficult purification steps.

We therefore decided to explore structural analogs, in which the P–O bond had been replaced by a P–C bond [19]. We hoped that such ligands, which we named NeoPHOX because of the neopentyl backbone, would be as easily accessible as SimplePHOX but more stable against air and moisture and fulfill the criteria for a scalable high yielding synthesis (Figure 1).

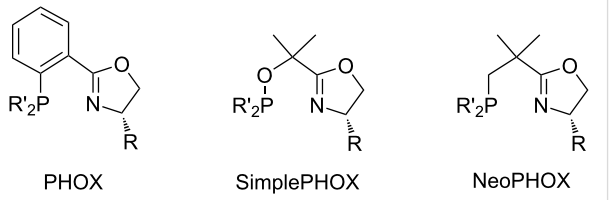
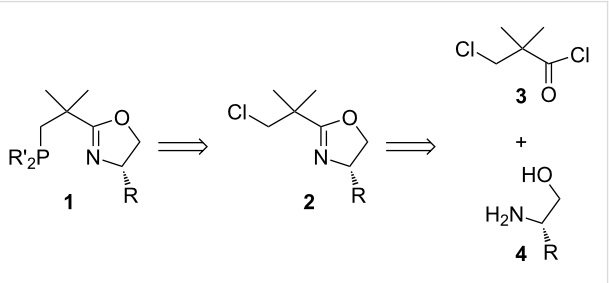


Figure 1: Structural motifs of phospinooxazoline ligands.

Results and Discussion

1st Generation NeoPHOX ligands

A potential very short route to NeoPHOX ligands starting from commercially available 3-chloropivaloyl chloride (**3**) is shown in Scheme 1. Although nucleophilic substitutions at the neopentyl carbon atoms are known to be difficult, literature precedence indicated that the introduction of the phosphine group might be possible by the reaction of a diarylphosphide anion with chloroalkyloxazoline **2**.

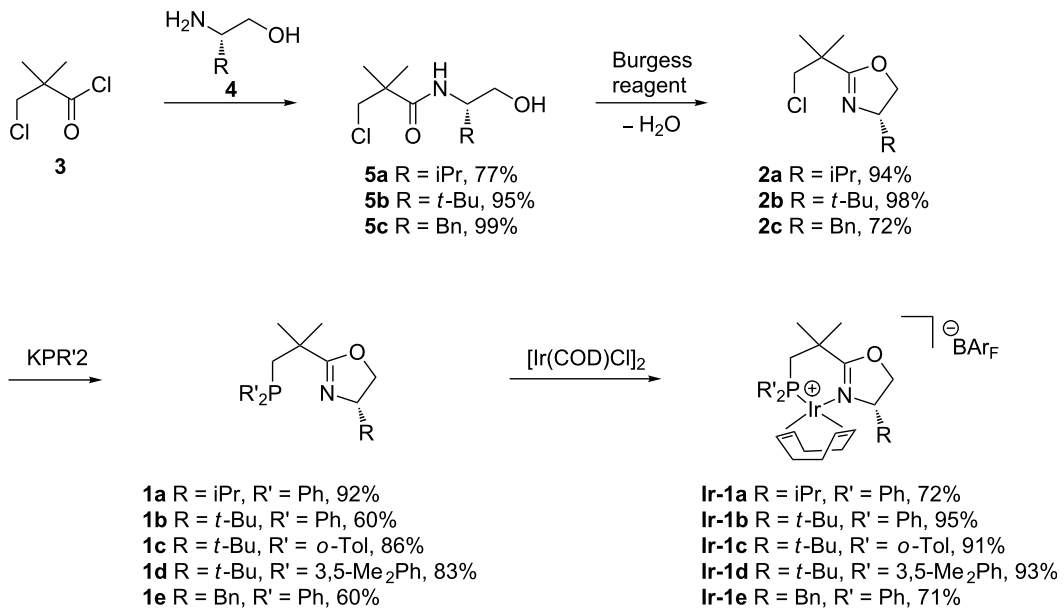


Scheme 1: Retrosynthetic analysis for NeoPHOX ligands.

Ashby et al. [20] investigated the reactivity of neopentyl halide systems with various metal diphenylphosphides and found that the reaction indeed took place. While for iodides evidence for a radical single electron transfer process as the major pathway was found, the corresponding bromides and chlorides seemed to prefer an S_N2 mechanism. Rossi et al. [21] showed that substitution products can be obtained in good yields from neopentyl chloride derivatives and sodium diphenylphosphide in liquid ammonia by an $S_{NR}2$ reaction induced by UV irradiation. Huttner and co-workers [22] on the other hand achieved high yields in nucleophilic substitutions of diarylphosphines with $MeC(CH_2Cl)_3$ in DMSO using aqueous KOH as base at elevated temperature but without irradiation.

In initial model studies using neopentyl chloride and a commercially available solution of $KPPh_2$ in THF we obtained high yields of neopentyldiphenylphosphine under reflux conditions [19]. Encouraged by these results, a series of chloroalkyl-substituted oxazolines **2** were prepared from 3-chloropivaloyl chloride (**3**) by amide formation and subsequent cyclization with the Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) using standard procedures (Scheme 2). Subsequent nucleophilic substitution with KPP_2 in refluxing THF proved to be much faster than the analogous reaction with neopentyl chloride. After 6 hours, the $KPPh_2$ was fully converted to the desired phosphinooxazoline, as evidenced by the ^{31}P NMR spectrum, which showed only the product signal. The reaction also proceeded well with other diarylphosphides such as $KP(o\text{-Tol})_2$ or $KP(3,5\text{-MePh})_2$ prepared in situ from the secondary phosphines by deprotonation with KH in refluxing THF. The NeoPHOX ligands, which were obtained by this route in high overall yield, proved to be air and moisture stable and could be obtained in analytically pure form by simple filtration through silica gel [19]. Complexation with $[Ir(COD)Cl]_2$ and subsequent anion exchange with $NaBAr_F$ (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) led to the corresponding iridium precatalysts in high yields. These complexes as well showed high stability against oxygen and moisture and could be stored in air for several months without notable decomposition.

As originally assumed, the NeoPHOX complexes **Ir-1a–e** turned out to be highly efficient catalysts. They induced similar and in some cases even higher enantioselectivities compared to the analogous SimplePHOX complexes, as shown by the results obtained in the hydrogenation of a range of test substrates (Figure 2) [19]. Considering the more practicable synthesis, which is well suited for large-scale preparation, and the higher stability of the free ligands, NeoPHOX ligands provide a superior alternative to the SimplePHOX ligands. The only drawback these compounds share with many state-of-the-art oxazoline-based ligands is the high cost of *tert*-leucinol as starting material, which reduces their potential for industrial-scale application. We therefore thought of ways to replace the *tert*-butyloxazoline ring by an equally effective oxazoline unit derived from a less expensive precursor.



Scheme 2: Synthesis of 1st generation NeoPHOX Ir-complexes [19].

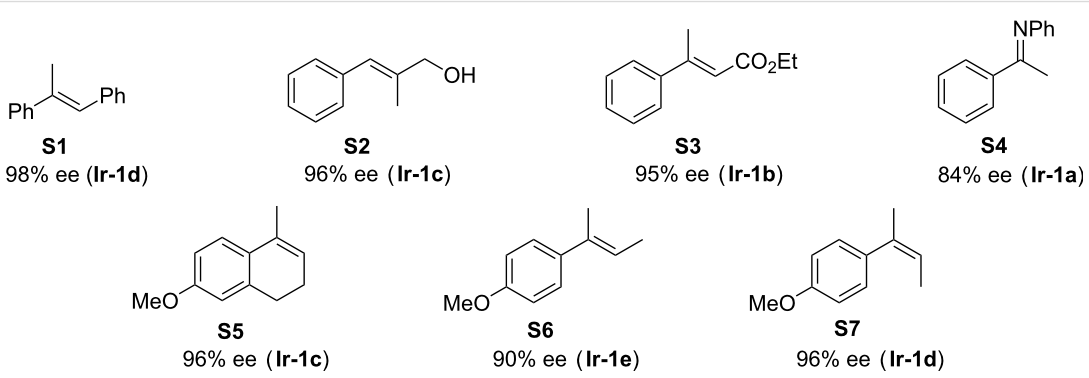


Figure 2: Asymmetric hydrogenation with iridium-NeoPHOX catalysts [19].

An option, which had been previously used in the development of PHOX ligands [23-27], is to replace the *tert*-butyl group by an isopropyl group and at the same time introducing two bulky substituents at C(5) (see Figure 3). Ligands of this type are accessible from valine, which is much less expensive than *tert*-leucine. The steric hindrance exerted by the geminal substituents at C(5) is expected to direct the isopropyl methyl groups toward the coordination sphere, creating a steric environment which resembles that of a *tert*-butyloxazoline ligand.

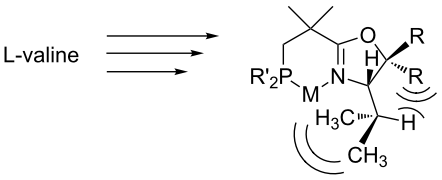
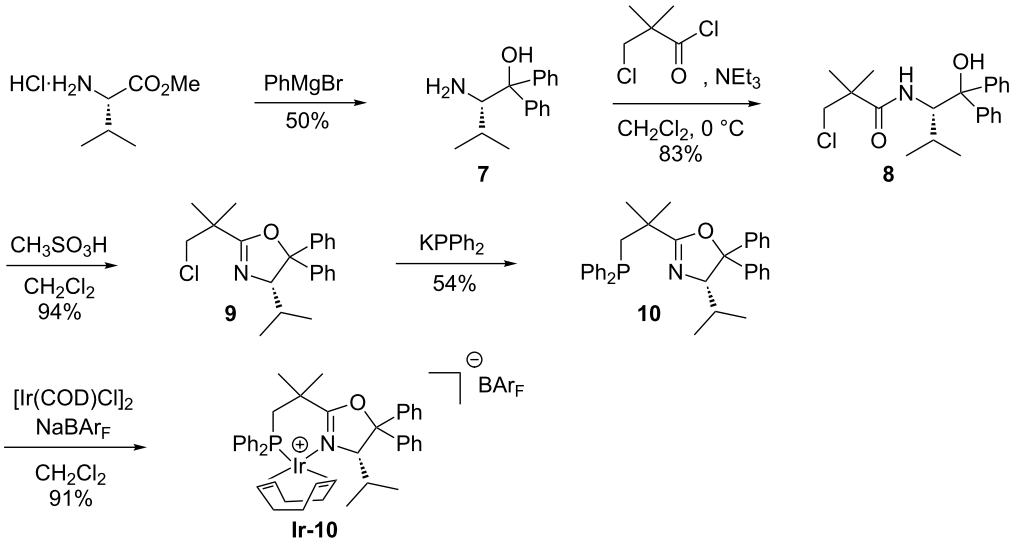


Figure 3: Employing L-valine as a starting material for C5 substituted oxazoline.

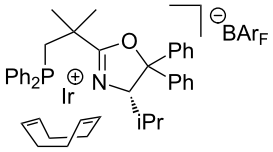
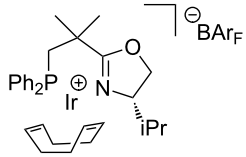
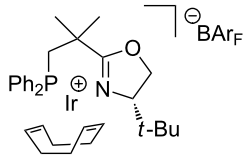
To test the viability of this approach, we synthesized the valine-derived NeoPHOX ligand **10** with two geminal phenyl substituents at C(5) according to the route shown in Scheme 3.

Unfortunately, the iridium complex **Ir-10** prepared from this ligand proved to be an inefficient catalyst. The enantioselectivities in the hydrogenation of various test substrates were much lower than those induced by the *tert*-butyloxazoline analog with the exception of the result obtained with the allylic alcohol **S2** (Table 1). Surprisingly, the presence of two geminal phenyl substituents at C(5) had a negative impact on the enantioselectivity, as shown by the substantially higher ee values induced by the analogous catalyst **Ir-1a** [28] lacking substituents at C(5).



Scheme 3: Synthesis of a C(5)-disubstituted NeoPHOX-Ir complex.

Table 1: Hydrogenation results employing 1st generation NeoPHOX catalysts.[a]

	S1 ee [%] yield [%]	**S5** ee [%] yield [%]	**S2** ee [%] yield [%]	**S3** ee [%] yield [%]
 **Ir-10**	19 (*R*) 93	35 (*S*) >99	84 (–) >99	63 (*R*) 41
 **Ir-1a**	74 (*R*) >99	53 (*S*) 89	88 (–) >99	85 (*R*) >99
 **Ir-1b**	97 (*R*) >99	92 (*S*) >99	83 (–) >99	95 (*R*) >99

[a]Reaction conditions: 50 bar, 2 h, 1 mol % catalyst, 0.1 mmol substrate, 0.5 mL CH_2Cl_2.

Based on these negative results we chose a new approach based on serine or threonine as starting materials (Figure 4). The carboxyl group of these amino acids serves as surrogate for the *tert*-butyl group of *tert*-leucine, which can be converted to a sterically demanding substituent by double addition of Grignard or alkyllithium reagents and subsequent protection of the resulting tertiary alcohol. An attractive feature of this approach is that by proper choice of the alkylmetal reagent and the protecting group, the steric properties of the ligand can be optimized for a specific application. PHOX ligands of this type have been previously prepared from serine and successfully used in iridium-catalyzed hydrogenation [29,30].

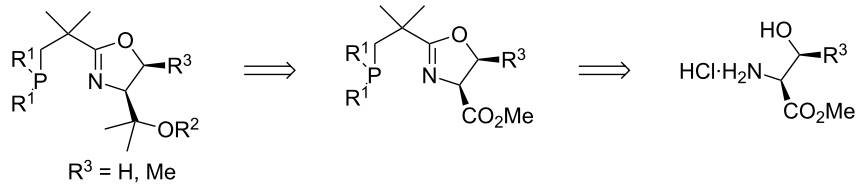


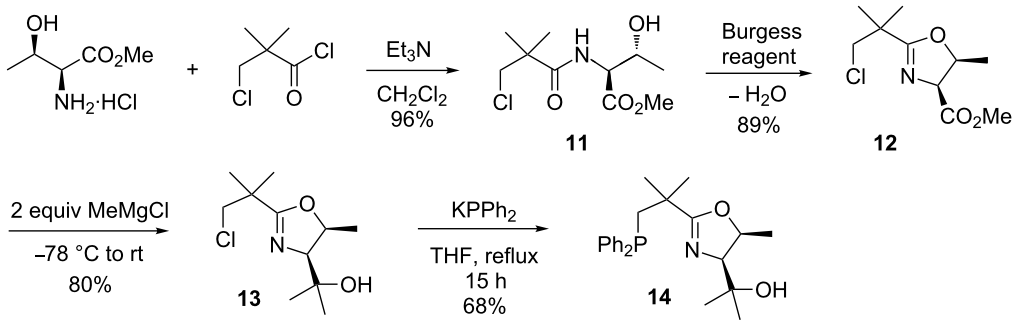
Figure 4: Retrosynthetic analysis for NeoPHOX ligands derived from serine and threonine.

Synthesis of serine- and threonine-derived NeoPHOX ligands

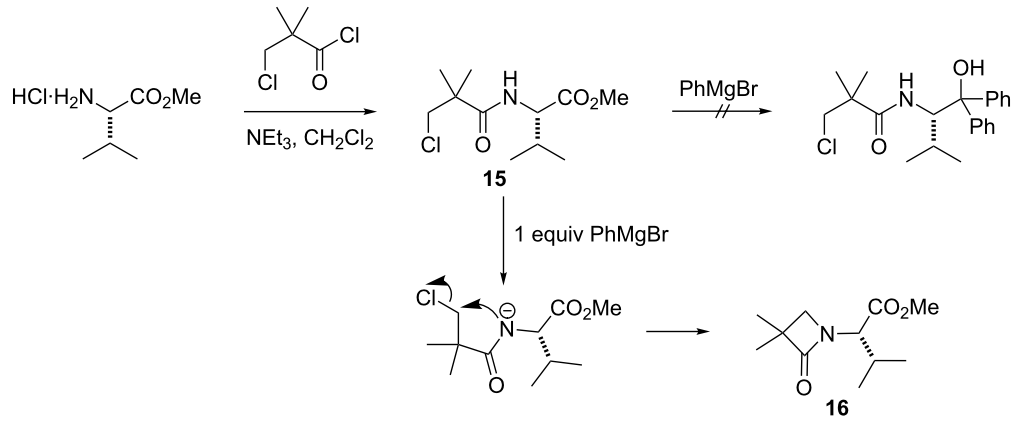
The synthesis that led to the NeoPHOX ligand **14** in 46% overall yield is shown in Scheme 4. In the first step threonine methyl ester hydrochloride was converted to the desired amide **11** in 96% yield. Subsequent cyclization with the Burgess reagent afforded the oxazoline **12** in 89% yield with clean inversion of configuration at the hydroxy-substituted carbon atom. Double addition of methylmagnesium chloride and subsequent introduction of the diphenylphosphine unit proceeded well in 68% yield following the procedures worked out for the 1st generation NeoPHOX ligands.

Alternative strategies involving Grignard addition to the threonine methyl ester or N-protected derivatives were also briefly investigated, but failed. Grignard addition to the chloro amide **11** was not attempted because earlier studies with chloro amide **15** had shown that an undesired β-lactam **16** was formed upon treatment with Grignard reagents (Scheme 5) [28].

All attempts to prepare analogous serine-derived NeoPHOX ligands by the established route for the synthesis of the threonine-derived NeoPHOX ligand **14** led to unexpected problems (Scheme 6). Oxazoline formation with the Burgess reagent did not produce the desired oxazoline (mixture of unidentified prod-



Scheme 4: Revisited synthetic strategy for the preparation of a threonine-based NeoPHOX ligand.

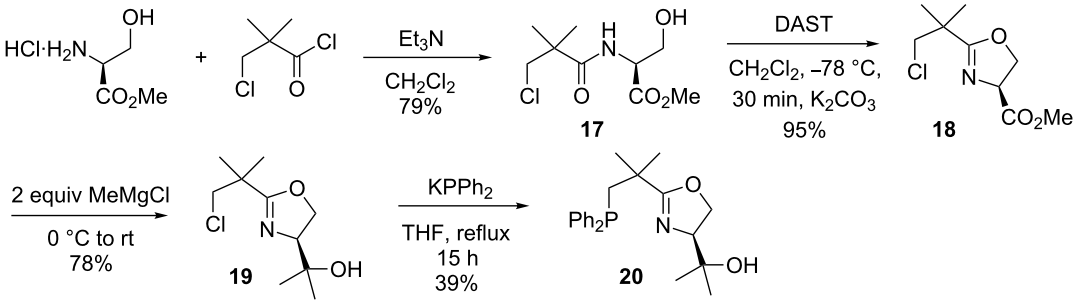


Scheme 5: Undesired β-lactam formation.

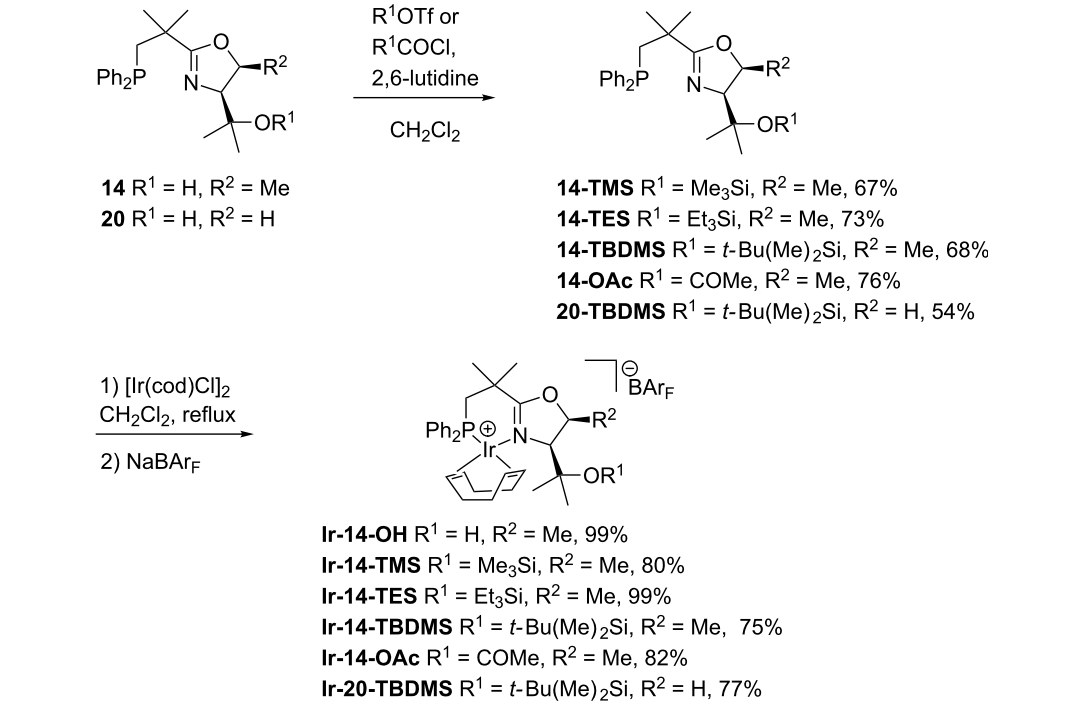
ucts). However, eventually an alternative method using diethylaminosulfurtrifluoride (DAST) [31] was found that afforded the chloroalkyloxazoline **18** in 95% yield after short reaction times at −78 °C.

Treatment of this product with methylmagnesium chloride under the same conditions used for the threonine derivative **12** (Scheme 4), led to an unidentified mixture of products. Surprisingly, when the Grignard reagent was added at 0 °C instead of −78 °C and reaction mixture subsequently warmed up to room temperature, the desired product **19** was formed in 78% yield. After having resolved these issues, the desired serine-based NeoPHOX ligand **20** was obtained in 23% overall yield from serine methylester hydrochloride.

Next we converted the tertiary alcohols **14** and **20** to a range of silylated and acetylated derivatives in order to evaluate the influence of sterically and electronically different substituents on the enantioselectivity and catalytic activity of the corresponding iridium complexes. Initial attempts to introduce a silyl or acetyl group by deprotonation with potassium hydride and subsequent reaction with silyl triflates or acetyl chloride failed. The NeoPHOX ligand **14** showed no reaction under these conditions, although this method had been successfully used for the alkylation and acylation of the tertiary alcohol function of analogous serine derived PHOX ligands [30]. Among various amines, 2,6-lutidine was finally identified as a suitable base for conversion to the desired derivatives in 67–76% yields (Scheme 7). From these ligands a library of iridium catalysts



Scheme 6: Synthetic strategy for the synthesis of the serine-derived NeoPHOX ligand.



Scheme 7: Derivatization of the 2nd generation NeoPHOX ligands and formation of their iridium complexes.

was prepared by complexation with bis(1,5-cyclooctadiene)diiridium(I) dichloride, followed by anion exchange with $NaBAr_F$.

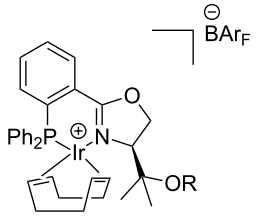
Comparative hydrogenation studies with iridium catalysts derived from 1st and 2nd generation NeoPHOX ligands and serine-based PHOX ligands

A set of seven Ir-NeoPHOX catalysts was evaluated in the asymmetric hydrogenation of three alkenes and acetophenone phenylimine (Table 2). For comparison, the results previously reported for four related serine-based Ir-PHOX complexes are included in the table. Overall, the *tert*-leucine-derived complex **Ir-1b** and complexes **Ir-14-TBDMS** and **Ir-20-TBDMS** with a bulky *tert*-butyldimethylsilyloxy group showed the highest reactivity, resulting in full conversion of all three olefins. On the other hand catalysts **Ir-14-OH** and **ser-PHOX-OMe** bearing a free hydroxy and a methoxy group, respectively, gave very low or no conversion. In the case of complex **ser-PHOX-OMe** [30] it was found that the methoxy function in the oxazoline ring induced deactivation of the catalyst due to coordination to the metal center resulting in a stable hydride-bridged dinuclear complex under hydrogenation conditions. The analogous catalysts **Ir-14-OAc** and **ser-PHOX-OAc** with an acyloxy substituent proved to be more reactive, however, conversion still remained incomplete with olefins **S1** and **S3**. Similar results were obtained with the analogous NeoPHOX complex **Ir-14-OAc** bearing an acetoxy group at the oxazoline ring. Apparently, a polar potentially coordinating substituent near the metal center reduces or can even completely inhibit catalytic activity. The deactivating effect of a coordinating oxygen function could also explain the different conversions observed with the silyl ether-bearing catalysts, decreasing in the series *t*-$BuMe_2Si$ > Et_3Si > Me_3Si. It has been shown that Ir-hydride complexes that are formed as intermediates during hydrogenation are strong Brønsted acids [32], which can cause cleavage of trimethylsilyl ethers under hydrogenation conditions [33]. So partial desilyl-

Table 2: Hydrogenation of standard substrates using serine- and threonine-derived NeoPHOX catalysts.

	S1 ee [%] yield [%]	**S2** ee [%] yield [%]	**S3** ee [%] yield [%]	**S4** ee [%] yield [%]
Ir-14-OH	n.d.	41 (+) 10	n.d.	7 (S) 4
Ir-14-OAc	87 (*S*) 59	90 (+) 92	90 (*S*) >44	16 (*S*) 73
Ir-14-TMS	92 (S) 38	88 (+) 82	82 (*S*) >40	67 (*S*) 5
Ir-14-TES	97/[b]96 (*S*) 59/[b]87	89/[b]88 (+) 60/[b]>99	90/[b]90 (*S*) 87/[b]98	68/[b]62 (*S*) 8/[b]32
Ir-14-TBDMS	96 (*S*) >99	91 (+) >99	94 (*S*) >99	49 (*S*) 79
Ir-20-TBDMS	90 (*S*) >99	84 (+) >99	92 (*S*) >99	77 (*S*) 79
Ir-1b	97 (*R*) >99	97% (-) >99	97% (*R*) >99	97 (*R*) >99
ser-PHOX-OMe [30]	n.d. 1	57 (+) 9	32 (*S*) 3	5 (R) 2
ser-PHOX-Bn [30]	92 (*S*) 27	79 (+) 43	46 (*S*) 34	21 (*S*) 1
ser-PHOX-OAc [30]	92 (*S*) 90	91 (+) >99	56 (*S*) 70	56 (*R*) 99
ser-PHOX-Bz [30]	92(*S*) 88	92 (+) >99	69 (*S*) 91	53 (*R*) >99

[a]Reaction conditions: 50 bar, 2h, 1 mol % catalyst, 0.1 mmol substrate, 0.5 mL CH_2Cl_2; [b]reaction time 16 h;



Ir-ser-PHOX-OMe: R = Me
Ir-ser-PHOX-OBn: R = Bn
Ir-ser-PHOX-OAc: R = Ac
Ir-ser-PHOX-OBz: R = Bz

ation liberating a free hydroxy group during hydrogenation may well be the reason for the low conversion obtained with catalyst **Ir-14-TMS** bearing an acid-labile trimethylsilyl ether group.

Among the NeoPHOX catalysts, the most reactive complex with a bulky TBDMS group showed also the highest enantioselectivities in the hydrogenation of alkenes **S1**–**3**. It also outperformed the most efficient serine-derived PHOX catalysts **ser-PHOX-OAc** and **ser-PHOX-OBz**. In terms of activity and enantiomeric excess the performance of this catalyst was comparable to the *tert*-leucine-derived complex **Ir-1b**. The analogous serine-based complex **Ir-20-TBDMS** gave somewhat lower enantioselectivities. In the hydrogenation of imine **S4** none of the catalysts shown in Table 2 induced high enantioselectivity.

Crystal structures of iridium NeoPHOX complexes

The three dimensional structures of several threonine and serine-derived NeoPHOX iridium complexes were determined by X-ray diffraction and compared with known phosphinooxazoline complexes. We were interested to see whether the differences in steric shielding of the coordination sphere by the protecting groups on the tertiary alcohol function correlated with the hydrogenation results. From the obtained crystal structures, it can be seen that the conformations of the threonine and serine-derived NeoPHOX iridium complexes are essentially the same as those of the *tert*-leucine-derived NeoPHOX complex with respect to the geometry of the 6-membered iridacycle, which retains a boat-shaped conformation (Figure 5). No notable divergence in the steric environment of the iridium center in the four silyloxy-bearing NeoPHOX complexes could be observed that would explain the difference in enantioselectivity induced by these catalysts.

In contrast to the methoxy-bearing serine-derived PHOX complex **ser-PHOX-OMe**, the protected tertiary alcohol group in these complexes does not point towards the iridium center. The interaction of the ether oxygen atom with the iridium center was the reason for the lack of reactivity of this serine-based PHOX complex. In case of the silyl ethers the oxygen atom is strongly shielded preventing coordination to the iridium center.

Palladium-catalyzed allylic substitution

As phosphinooxazoline ligands were originally designed for asymmetric palladium-catalyzed allylic substitutions, we tested the new NeoPHOX ligands in this reaction as well. For comparison with state-of-the-art ligands, we chose the standard test reaction of (*E*)-1,3-diphenylallylacetate with dimethyl malonate as nucleophile (Scheme 8).

The two catalysts derived from ligand **14** with a free hydroxy group and the corresponding triethylsilyl-protected derivative

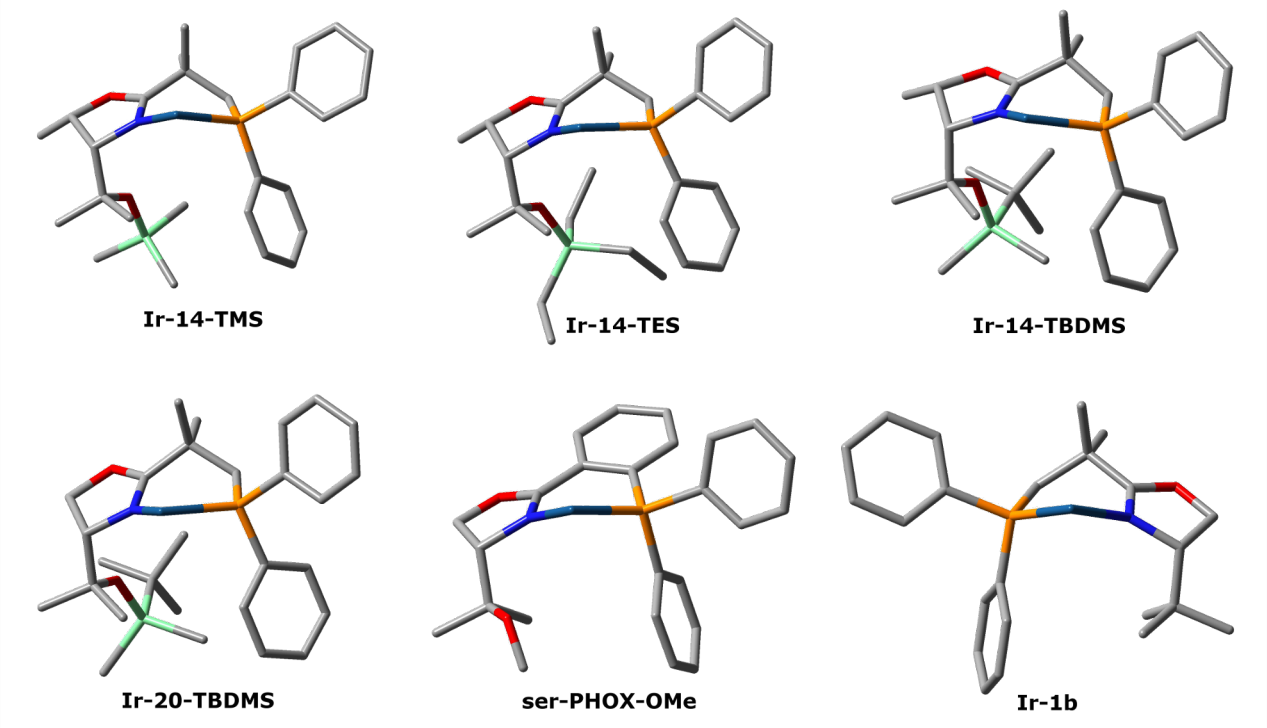
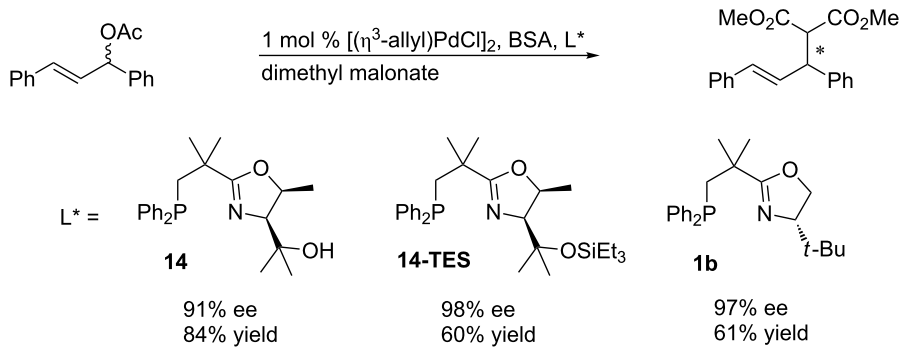


Figure 5: Crystal structures of selected Ir-complexes. Hydrogen atoms, COD and BArF anions were omitted for clarity.

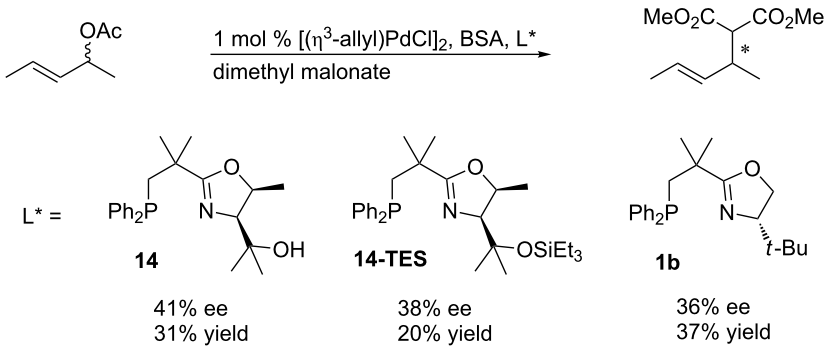


Scheme 8: Asymmetric palladium-catalyzed allylic substitution with *rac*-(*E*)-1,3-diphenylallyl acetate.

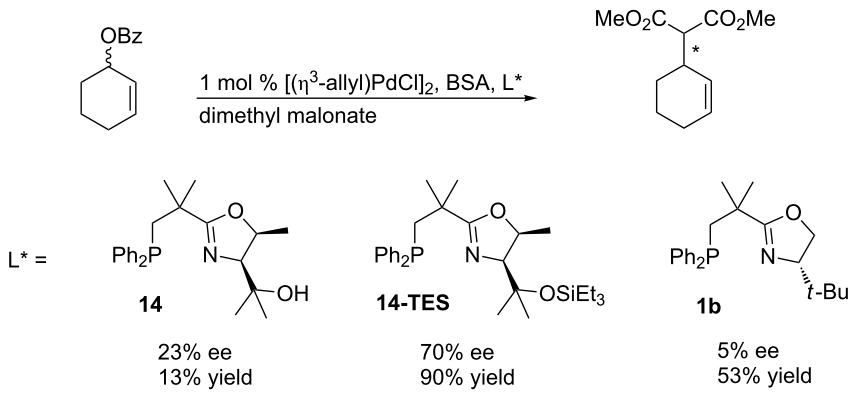
both performed well affording enantioselectivities of 90% and 98% ee, respectively. Ligand **14-TES** was even more effective than the corresponding *tert*-leucine-derived NeoPHOX ligand **1b** (97% ee).

Next, we also tested (*E*)-1,3-dimethylallyl acetate as substrate (Scheme 9). All three tested catalysts gave disappointing results. The yield was low in all cases and the enantiomeric excess reached only 41% for the best ligand **14**. Interestingly, the sterically more demanding ligand **14-TES** did not lead to higher enantioselectivity as for 1,3-diphenylallyl acetate.

Finally, the ligands were also tested on a more demanding cyclic substrate (Scheme 10). In the allylic substitution with



Scheme 9: Asymmetric palladium-catalyzed allylic substitution with *rac*-(*E*)-1,3-dimethylallyl acetate.



Scheme 10: Asymmetric palladium-catalyzed allylic substitution with a cyclic substrate.

cyclohex-2-en-1-yl benzoate a notable enantiomeric excess of 70% was achieved using ligand **14-TES**, in striking contrast to the extremely low enantioselectivities reported for analogous PHOX ligands [4]. Using ligand **14** with a free hydroxy group the result was less satisfying. Not only the yield dropped to 53% but also the ee was substantially lower than with the triethylsilyl analog **14-TES**. For NeoPHOX ligand **1b** the enantiomeric excess was even lower (5%). These results demonstrate that the 2nd generation NeoPHOX ligands possess potential for palladium-catalyzed allylic substitutions.

Conclusion

The most successful, most widely applied oxazoline-based N,P ligands are derived from the unnatural amino acid *tert*-leucine. The high price of this starting material is an impeding factor for large-scale applications. The NeoPHOX ligands derived from threonine provide an attractive alternative in this respect. Threonine as a chiral building block is available in both enantiomeric forms at a moderate price. The most effective ligand in this series, bearing a bulky CMe_2OSiMe_2t-Bu group at the stereogenic center, induced excellent enantioselectivities in the Ir-catalyzed asymmetric hydrogenation of olefins, with ee values in the same range as those reported for the best N,P ligands including the *tert*-leucine-derived NeoPHOX analog. In the asymmetric Pd-catalyzed allylic substitution as well, promising enantioselectivities were obtained, indicating a considerable potential for this ligand class in asymmetric catalysis.

A further notable feature of these ligands is their flexible synthesis, which allows easy variation of the substituent at the stereogenic center. Using different Grignard reagents in the addition to the ester group of a late stage intermediate, an array of tertiary alcohol derivatives is available. The subsequent silylation or acylation of the hydroxy group gives access to a library of diverse NeoPHOX ligands. In this way the steric size and the coordination ability of the substituent at the stereogenic center can be tuned for a specific application.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of selected molecules.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-114-S1.pdf]

Acknowledgements

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Conjugate addition–enantioselective protonation reactions

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Review

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Abstract

The addition of nucleophiles to electron-deficient alkenes represents one of the more general and commonly used strategies for the convergent assembly of more complex structures from simple precursors. In this review the addition of diverse protic and organometallic nucleophiles to electron-deficient alkenes followed by enantioselective protonation is summarized. Reactions are first categorized by the type of electron-deficient alkene and then are further classified according to whether catalysis is achieved with chiral Lewis acids, organocatalysts, or transition metals.

Introduction

Due to their ubiquity in natural products and drugs, many researchers have developed methods for the stereoselective synthesis of tertiary carbon stereocenters. One aesthetically pleasing approach is the enantioselective protonation of prochiral enolates and enolate equivalents [1-10]. While an attractive strategy, the enantioselective introduction of a proton, the smallest element in the periodic table, presents its own unique challenges. Significant racemic background reactions can compete with the desired enantioselective protonation because proton transfer is among the fastest of all processes. The α-electron withdrawing group, needed to stabilize the carbanion intermediate, also increases the stereocenter's susceptibility to racemization under the reaction conditions. Moreover, enolate intermediates can adopt *E*- or *Z*-geometries that, upon protonation, generally lead to opposite stereoisomers.

Because enantioselective protonation is a kinetic process, an overall thermodynamic driving force is required for any enantioselective protonation reaction [1]. One attractive approach is the coupling of the enantioselective protonation step with another bond forming step. Conjugation addition of an organometallic or protic nucleophile in a non-stereoselective step allows for the generation of a prochiral enolate intermediate that then undergoes enantioselective protonation (Figure 1). Two general strategies can be used when applying a conjugate addition–enantioselective protonation manifold. In the first strategy, a chiral enolate can be protonated by an achiral proton source (pathway A). In the second, an achiral enolate can be protonated by a chiral proton source (pathway B). Both strategies have been harnessed by various research groups for conjugate addition–enantioselective protonation reactions.

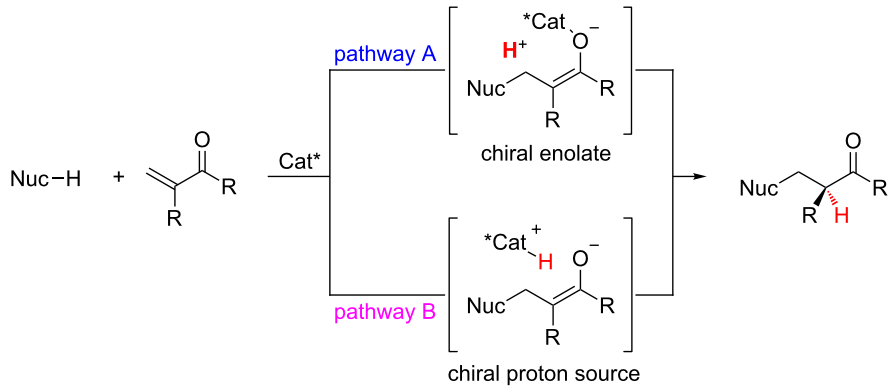


Figure 1: Two general pathways for conjugate addition followed by enantioselective protonation.

This review covers the many conjugate addition–enantioselective protonation reactions that have been reported in the literature. These reports have been grouped by class of Michael acceptor and further subdivided by the type of catalyst system used (Lewis acids, organocatalysts and transition metals). While numerous efficient methods have been developed for the enantioselective reduction of α-substituted conjugate addition acceptors, including catalytic hydrogenation, multiple reviews have already appeared on this topic, and therefore asymmetric catalytic reduction will not be covered here [11-13]. Conjugate addition followed by terminal enantioselective hydrogen atom transfer is an approach that provides products analogous to those accessed via conjugate addition–enantioselective protonation sequences. Due to the similar challenges when delivering both protons and hydrogen atoms enantioselectively, examples of conjugate addition–enantioselective hydrogen atom transfer are also included in this review.

Review

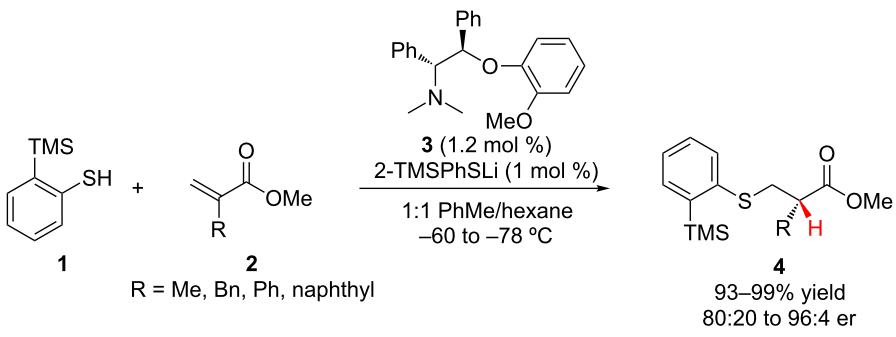
α,β-Unsaturated esters

Lewis acids

α,β-Unsaturated esters have been the most extensively studied class of electrophiles for conjugate addition–enantioselective protonation sequences. Esters are useful functional group handles for additional synthetic manipulations. Furthermore, enantioselective conjugate additions to α-amino-α,β-unsaturated esters provides rapid access to enantioenriched α-amino acid derivatives. However, α,β-unsaturated esters present some challenges; the transient enolate intermediate can adopt *E*- or *Z*-enolate geometries. Also, esters are not as electron deficient as many other electron withdrawing groups, and therefore, the presence of additional activating groups on the alkene or the use of a highly activating catalyst are often required.

In 2001, Tomioka and co-workers reported the addition of lithium arylthiolates, catalytically generated from **1,** to α-substituted acrylates **2** followed by enantioselective protonation of the resulting lithium enolate (Scheme 1) [14]. The *ortho*-trimethylsilyl substituent on the phenyl ring was necessary for achieving high levels of enantioselectivity. All of the reactions proceeded in high yield, with the best enantioselectivities being observed for α-arylacrylates (94:6 to 96:4 er).

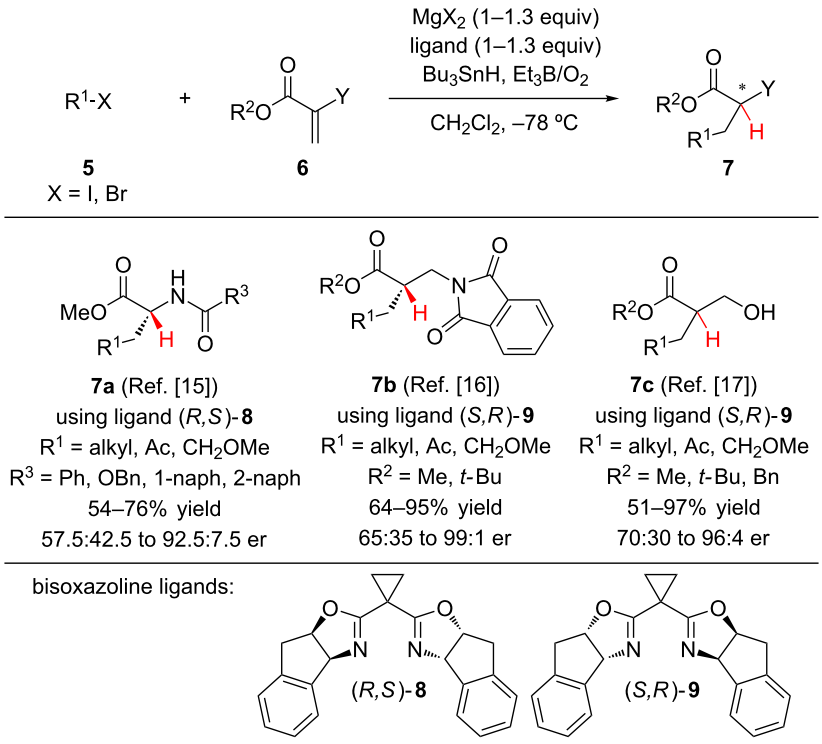
For the synthesis of enantioenriched α-amino esters **7a**, β-amino esters **7b** and 2-hydroxymethyl esters **7c**, the Sibi group has utilized a conjugate addition–enantioselective hydrogen atom



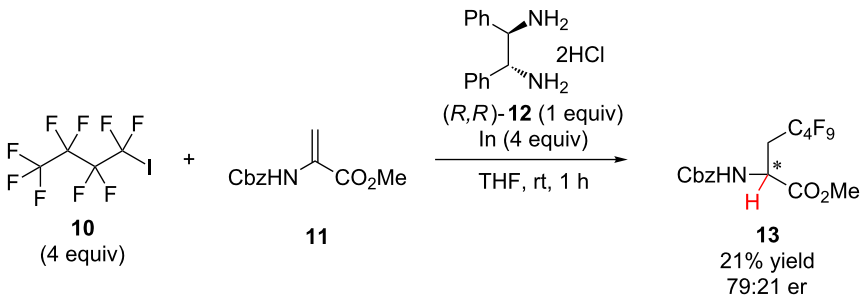
Scheme 1: Tomioka's enantioselective addition of arylthiols to α-substituted acrylates.

transfer reaction (Scheme 2) [15-17]. A Mg-(bis)oxazoline complex serves as both a Lewis acid for the activation of α-substituted acrylates **6** towards radical addition and as a chiral template for an enantioselective hydrogen atom transfer from Bu_3SnH to the α-ester radical intermediate. The authors found that the stoichiometric chiral Mg-(bis)oxazoline complex was required to achieve high enantioselectivity. Higher enantioselectivity was generally observed for reactions using secondary or tertiary alkyl halides. When performing radical conjugate additons to give 2-hydroxymethyl esters **7c**, the authors observed a complete turnover in the sense of induction based upon the ester substituent. The less bulky methyl and benzyl esters gave the (*S*)-enantiomer while the *tert*-butyl ester gave the (*R*)-enantiomer. The incorporation of aryl groups was not compatible with this reaction manifold, prompting Sibi to explore aromatic nucleophiles for the conjugate addition–enantioselective protonation of α-aminoacrylates (vide infra).

In 2010, Mikami and co-workers reported a hydrogen atom transfer strategy for the synthesis of β-perfluorobutyl-α-amino ester **13** in low yield and modest enantioselectivity, and the absolute configuration of the major enantiomer was not defined (Scheme 3) [18]. Indium was used to initiate the addition of a perfluorobutyl radical to α-aminoacrylate **11** followed by hydrogen atom transfer to the resulting α-amino α-ester radical from (*R,R*)-**12**.



Scheme 2: Sibi's enantioselective hydrogen atom transfer reactions.

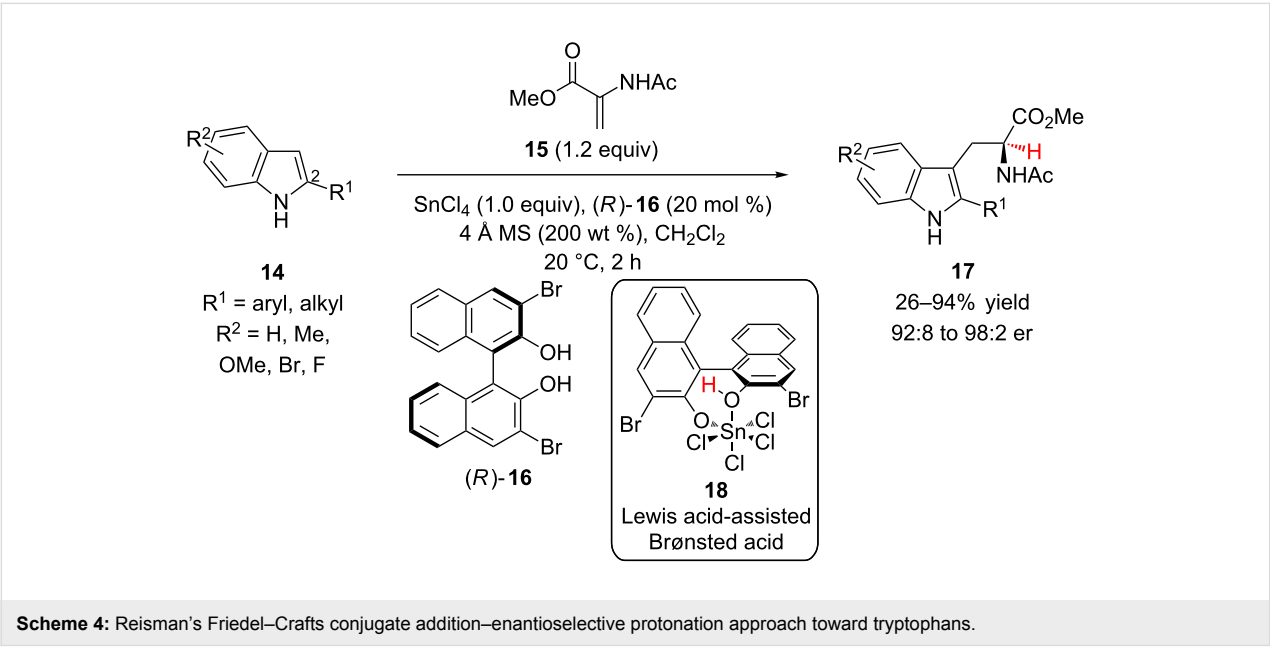


Scheme 3: Mikami's addition of perfluorobutyl radical to α-aminoacrylate **11**.

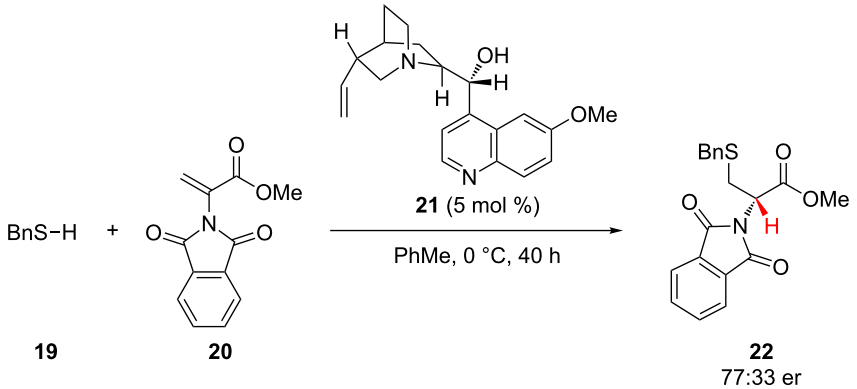
Enantioenriched tryptophan derivatives are useful building blocks for the synthesis of biologically active molecules, including natural products and drugs. The Reisman group has reported a Friedel–Crafts conjugate addition–enantioselective protonation for the synthesis of tryptophans **17** from 2-substituted indoles **14** and methyl 2-acetamidoacrylate (**15**) using catalytic (*R*)-3,3'-dibromo-BINOL (**16**) and stoichiometric $SnCl_4$ [19] (Scheme 4). The authors proposed that complex **18** acted as a chiral proton source to protonate a tin-enolate intermediate based upon related complexes that the Yamamoto group had previously used for the enantioselective protonation of silyl enol ethers [20,21]. Electron-rich and neutral indoles were efficient substrates for the reaction; however, electron-poor indoles showed attenuated reactivity even when 1.6 equivalents of $SnCl_4$ were employed (60–63% yield, 96:4 to 96.5:3.5 er). Indoles lacking substitution at the 2-position (R^1 = H) reacted in low yield and poor enantioselectivity. Sterically bulky 2-substituents (*ortho*-substituted phenyl, *tert*-butyl) showed attenuated reactivity but retained high enantioselectivity.

Organocatalysts

In a pioneering work from 1977 on conjugate addition–enantioselective protonation, Pracejus and co-workers explored the ability of chiral tertiary amines to catalyze the enantioselective addition of thiols to α-aminoacrylates (Scheme 5) [22]. The authors found that quinidine (**21**) catalyzed the enantioselective addition of benzylmercaptan (**19**) to α-aminoacrylate **20** in modest enantioselectivity. Acylation of the hydroxy group of quinidine resulted in complete loss of enantioselectivity, suggesting that hydrogen-bonding contacts between the catalyst's hydroxy group and the substrate are important for organizing the transition state.



Scheme 4: Reisman's Friedel–Crafts conjugate addition–enantioselective protonation approach toward tryptophans.

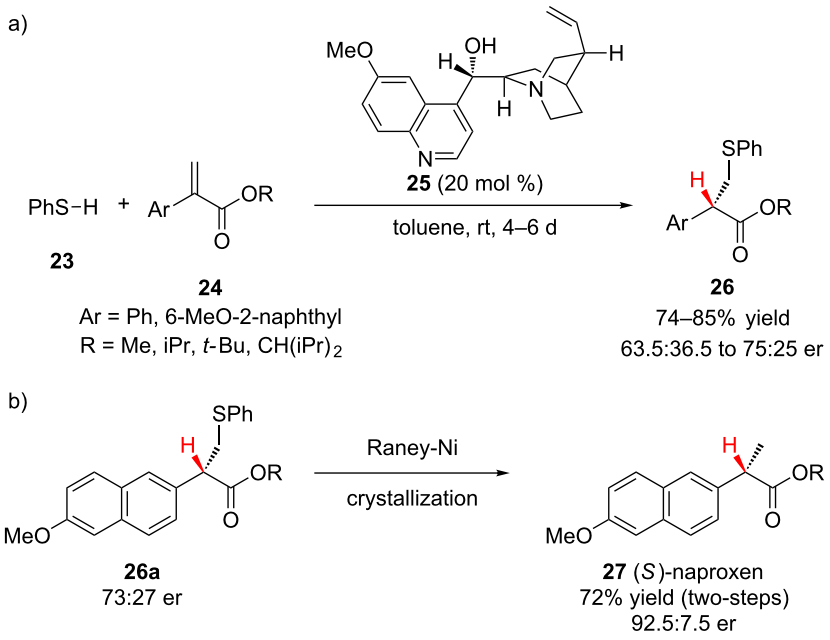


Scheme 5: Pracejus's enantioselective addition of benzylmercaptan to α-aminoacrylate **20**.

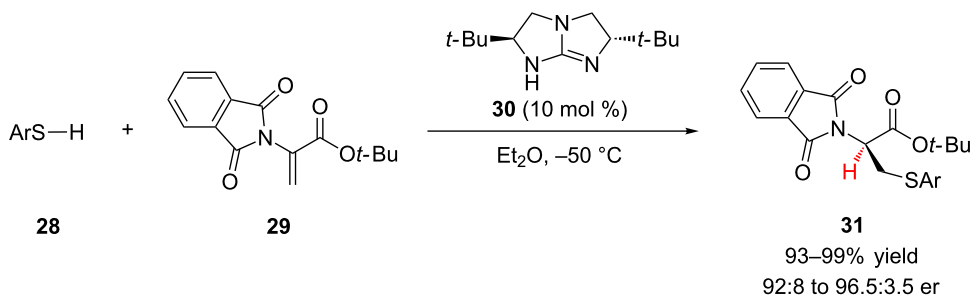
Using catalytic quinine (**25**) the pseudo-enantiomer of the quinidine catalyst employed by Pracejus, Kumar and Dike reported the enantioselective addition of thiophenol (**23**) to α-arylacrylates **24** in modest enantioselectivity (Scheme 6a) [23]. The authors found that sterically bulky esters (R = *t*-Bu, $CH(iPr)_2$) negatively impacted the enantioselectivity of the reaction (63.5:36.5 to 67.5:32.5 er). To demonstrate the utility of the transformation, the sulfur–carbon bond of **26a** was reduced using Raney nickel to access (*S*)-naproxen (**27**), an anti-inflammatory drug (Scheme 6b).

Inspired by the work of Pracejus, Tan and colleagues applied their C_2-symmetric guanidine catalyst **30** to the enantioselective addition of aromatic thiols to 2-phthalimidoacrylates **29** in high yield and good enantioselectivity (Scheme 7) [24]. A variety of electron rich, neutral, and poor thiols coupled efficiently. Impressively, the aromatic thiol **28** could be substituted with hydroxy and amino groups without significantly affecting the reaction (93–97% yield, 92:8 to 96:4 er). The authors also explored further elaboration of the products to access enantio-enriched cysteine analogues.

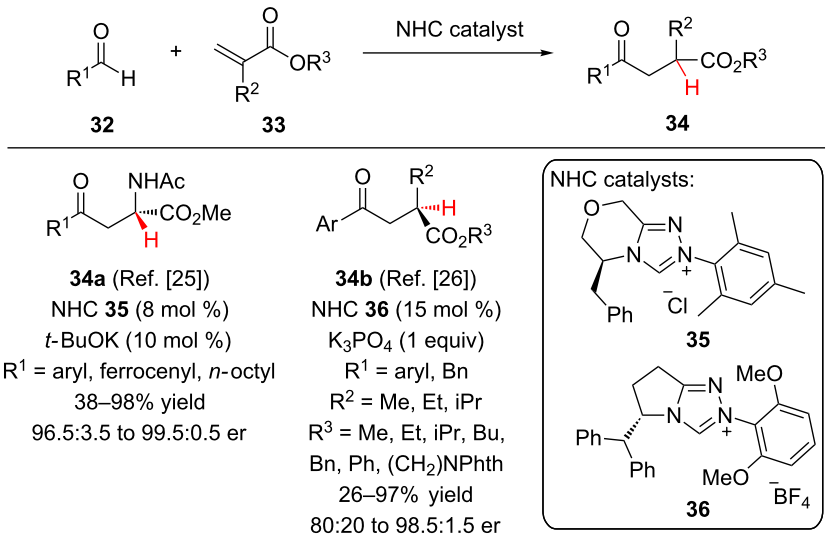
The Glorius lab has made use of N-heterocyclic carbene (NHC) catalysts for intermolecular Stetter reactions between aldehydes and α,β-unsaturated esters (Scheme 8) [25,26]. Catalyzed by triazolium NHC-catalyst **35**, electron-poor and neutral aromatic aldehydes reacted with methyl 2-acetamidoacrylate to access α-amino esters **34a** with excellent enantioselectivity [25]. As expected, less electrophilic 4-methoxybenzaldehyde led to low conversion. The use of potassium *tert*-butoxide was found to be essential to achieve good reactivity and enantioselectivity. Other amino-protecting groups (Boc, phthalimido) or tertiary *N*-methylated variants rendered the 1,4-acceptor unreactive. Glorius and co-workers proposed that an intramolecular proton



Scheme 6: Kumar and Dike's enantioselective addition of thiophenol to α-arylacrylates.



Scheme 7: Tan's enantioselective addition of aromatic thiols to 2-phthalimidoacrylates.

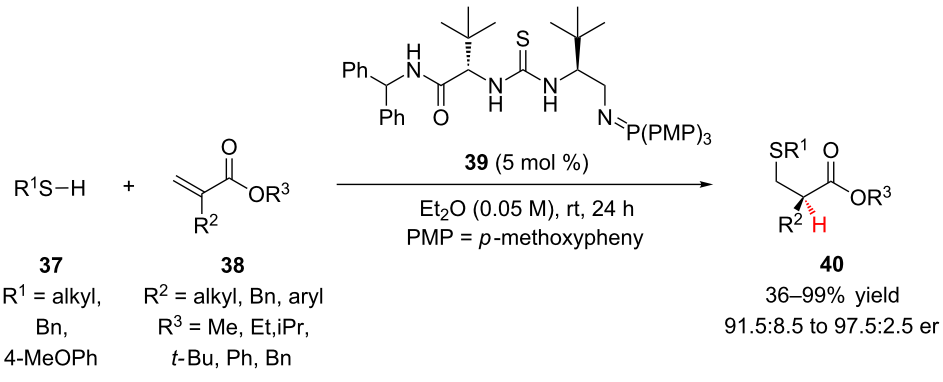


Scheme 8: Glorius' enantioselective Stetter reactions with α-substituted acrylates.

transfer was the stereodetermining step. Alternatively, Sunoj and co-workers performed DFT calculations on the mechanism of the enantioselective Stetter reaction between *p*-chlorobenzaldehyde and *N*-acetylamido acrylate and proposed that *tert*-butyl alcohol plays a key role as the proton source in the stereodetermining step [27].

In 2012, Glorius and co-workers also reported the addition of aromatic aldehydes to α-carbon substituted acrylates **33** to provide differentiated 1,4-dicarbonyls **34b** with good enantioselectivity [26]. When optimizing the catalyst's structure, the authors found that NHC's possessing a 2,6-dimethoxyphenyl moiety led to both superior reactivity and selectivity, with catalyst **36** being optimal. Catalyst **35** provided the product in less than 5% yield. It was proposed that a more electron-rich, and thereby more nucleophilic, NHC was needed because the α-carbon substituted acrylate substrates employed were less reactive than the previously utilized methyl 2-acetamidoacrylate. A variety of α-alkylacrylates were effective substrates, only when α-benzyl or α-phenylacrylates were used was there a decrease in enantioselectivity (80:20 to 90:10 er).

Recently, Dixon reported the enantioselective conjugate addition of thiols to unactivated α-substituted acrylates followed by enantioselective protonation (Scheme 9) [28]. To overcome the low inherent electrophilicity of **38**, the authors postulated that bifunctional iminophosphoran (BIMP) organocatalysts with increased Brønsted basicity were required. Employing BIMP catalyst **39**, alkylthiols, phenylmethanethiol, and 4-methoxybenzenethiol were added to α-substituted acrylates in good yield and enantioselectivity. A variety of R^2 and R^3 substituents performed well under the reaction conditions, only for the sterically bulky *tert*-butyl ester was the reactivity significantly impacted (R^2 = *n*-Pr, R^3 = *t*-Bu, 36% yield, 98:2 er).



Scheme 9: Dixon's enantioselective addition of thiols to α-substituted acrylates.

Transition metals

A handful of research groups have investigated transition metal-catalyzed conjugate addition–enantioselective protonation sequences involving α,β-unsaturated esters. A common theme has been the use of rhodium(I) transition metal catalysts and axially chiral phosphorous ligands (Figure 2). Additionally, because organometallic reagents are often utilized as nucleophiles, an exogenous proton source, which can impact the transformation's enantioselectivity, is frequently needed. In this context, Reetz and co-workers were the first to report the transition metal-catalyzed enantioselective addition of arylboronic acids to an α-substituted-α,β-unsaturated ester to provide enantio-enriched phenylalanine derivatives **48a** (Scheme 10) [29]. Notably, a BINAP-derived rhodium(I) catalyst was superbly active (100% conversion) but provided a completely racemic product. Only by utilizing a less electron-rich diphosphonite ligand **41** was enantioinduction achieved. Building on the initial report from Reetz, Frost and colleagues identified diphosphite **42** as a competent ligand for the transformation (Figure 2), accessing a handful of phenylalanine analogues **48** in moderate yield and enantioselectivity (Scheme 10) [30].

As shown in Scheme 11a, Frost and co-workers have also investigated conjugate addition–enantioselective protonation by the addition of potassium organotrifluoroborates **49** into dimethyl itaconate (**50**) in the presence of a rhodium(I) catalyst and (*R*)-BINAP ligand (**43**, Figure 2) [31]. During optimization they found that switching to potassium organotrifluoroborates from organoboronic acids was necessary to achieve high enantioinduction. Additionally, the enantioselectivity was highly de-

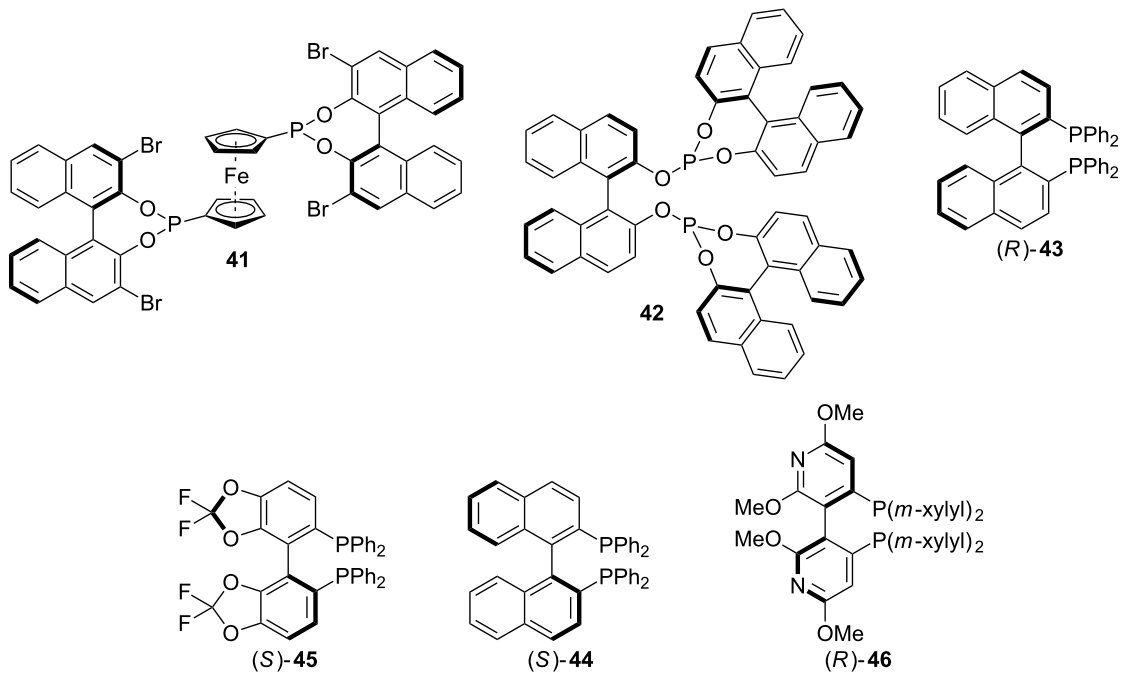
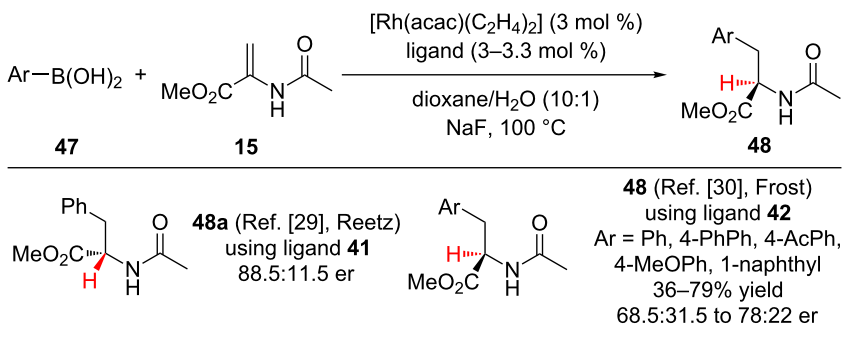
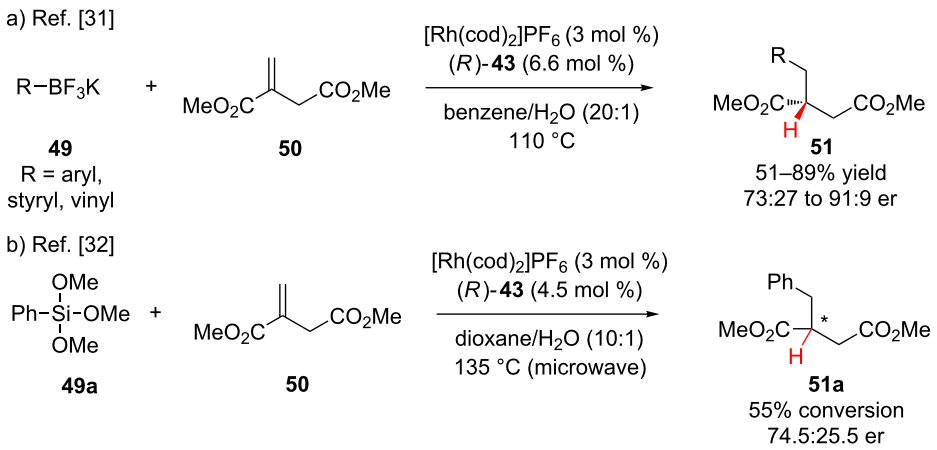


Figure 2: Chiral phosphorous ligands.



Scheme 10: Enantioselective addition of arylboronic acids to methyl α-acetamidoacrylate.

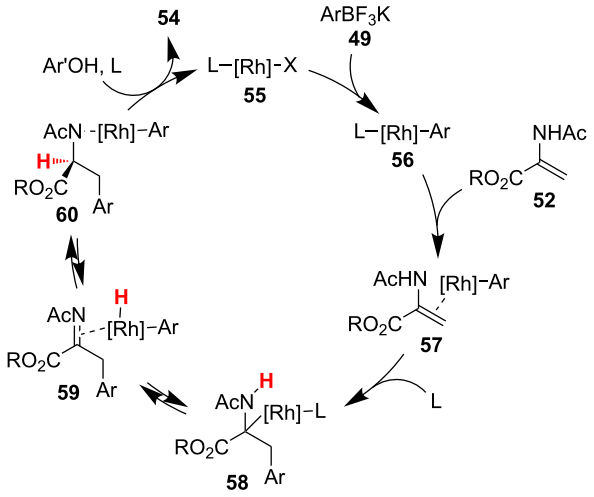


Scheme 11: Frost's enantioselective additions to dimethyl itaconate.

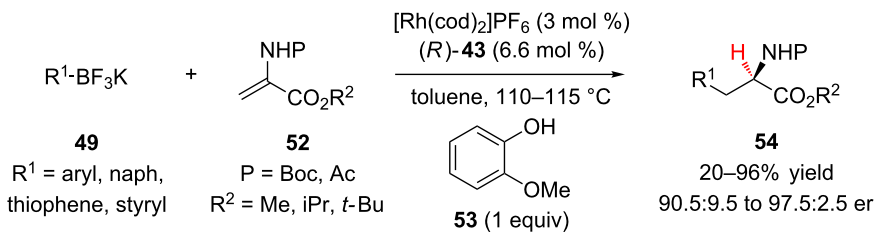
pendent on the solvent system; the enantioselectivity in benzene was significantly higher than in toluene or dioxane. Electron rich, neutral, and poor organotrifluoroborates were good substrates; however, *ortho*-substitution was not compatible and provided only trace product. In a subsequent publication, Frost reported that using the same catalyst system, phenyltrimethoxysilane (**49a**) could be added to dimethyl itaconate (**50**) with modest enantioselectivity and without defining the absolute configuration of the major stereoisomer (Scheme 11b) [32].

Darses and Genet reported the highly enantioselective Rh-catalyzed addition of potassium organotrifluoroborates **49** to α-aminoacrylates **52** to access phenylalanine derivatives **54** (Scheme 12) [33]. The authors identified guaiacol (**53**) as the optimal proton source, observing the general trend that less acidic phenols led to an increase in enantioselectivity. A wide range of aryltrifluoroborates were efficient substrates for the reaction to provide the products in good yield and enantioselectivity. Increasing the steric bulk of the ester (R^2 = iPr, *t*-Bu) decreased the yield of the reaction but did not impact its enantioselectivity.

Darses and Genet probed the mechanism of their reaction through a combination of DFT calculations, deuterium labeling studies, and control experiments (Scheme 13) [34]. The authors proposed that after migratory insertion of the rhodium–aryl bond across the acrylate, **58** undergoes β-hydride elimination of the enamide proton to generate *N*-acylimine **59**. Addition of the



Scheme 13: Proposed mechanism for enantioselective additions to α-aminoacrylates.



Scheme 12: Darses and Genet's addition of potassium organotrifluoroborates to α-aminoacrylates.

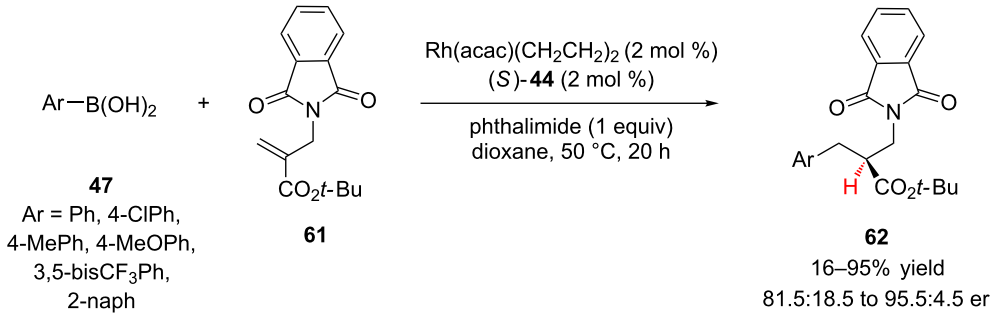
rhodium-hydride across the imine is then the enantiodetermining step, followed by protodemetalation to generate the product **54**.

Inspired by previous reports on the synthesis of α-amino esters using rhodium(I) catalysis, Sibi and co-workers investigated the enantioselective synthesis of β-amino esters **62** via the addition of arylboronic acids **47** to α-methylaminoacrylates **61** (Scheme 14) [35]. The authors identified (*S*)-difluorphos (**44**, Figure 2) and phthalimide as the optimal ligand and proton source combination, respectively. Additionally, the bulky *tert*-butyl ester was necessary for achieving both good reactivity and enantioselectivity. All of the arylboronic acids investigated, except 4-methylphenylboronic acid, added in good yield and enantioselectivity (70–95% yield, 92:8 to 95.5:4.5 er).

In 2007, Frost and co-workers reported a rhodium catalyzed conjugate addition–enantioselective protonation to prepare esters with α,α-dibenzyl substitution [36]. The addition of arylboronic acids **47** to α-benzylacrylates **63** were catalyzed by a rhodium(I) (*S*)-BINAP (**45**, Figure 2) complex with boric acid as a proton source (Scheme 15). A variety of electron-rich, neutral, and electron-poor arylboronic acids added in good yields and enantioselectivity to access esters with α,α-dibenzyl substitution and with only subtle steric and electronic differences between the two benzyl groups.

Recently, Rovis and co-workers reported a detailed study on the enantioselective hydroheteroarylation of α-substituted acrylates **66** with benzoxazoles **65** in moderate to good yields and good to excellent enantioselectivity (Scheme 16) [37]. The absolution configuration of the major enantiomer was not determined. The authors found that sterically encumbered bisphosphine ligand **46** (Figure 2) was necessary for achieving high reactivity, presumably because it minimizes undesired ligation of the benzoxazole substrates or intermediates. A variety of α-substituted acrylates as well as methacrylonitrile were good substrates. The system is sensitive to sterics, an acetate additive was needed to improve the reactivity of the more hindered acrylate substrates (e.g., R^2 = Bn) and when R^2 was phenyl or isopropyl no reactivity was observed. Substituted benzoxazoles were also effective with 4-methylbenzoxazole being a preferred substrate. The authors proposed that substitution at the 4-position disfavored rhodium catalyst binding to the benzoxazole nitrogen **68**.

Deuterium labeling studies were performed on the system and based on their results a mechanism was proposed in which the stereodetermining step is a rhodium-hydride transfer instead of protonation of an oxo-π-allylrhodium species (Scheme 17). Insertion into the C–H bond of **65** provides intermediate **70**, which then undergoes migratory insertion into acrylate **66** to give **71**. β-Hydride elimination to give the α,β-disubstituted

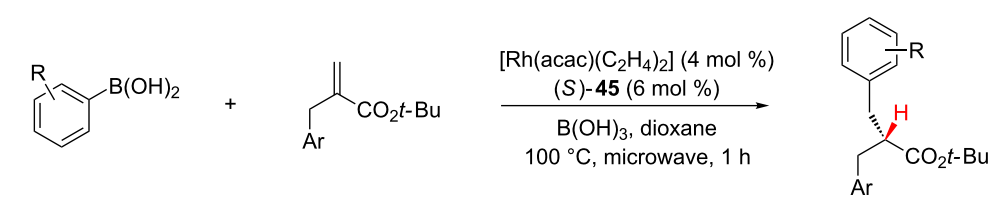


47
Ar = Ph, 4-ClPh, 4-MePh, 4-MeOPh, 3,5-bisCF_3Ph, 2-naph

61

62
16–95% yield
81.5:18.5 to 95.5:4.5 er

Scheme 14: Sibi's addition of arylboronic acids to α-methylaminoacrylates.

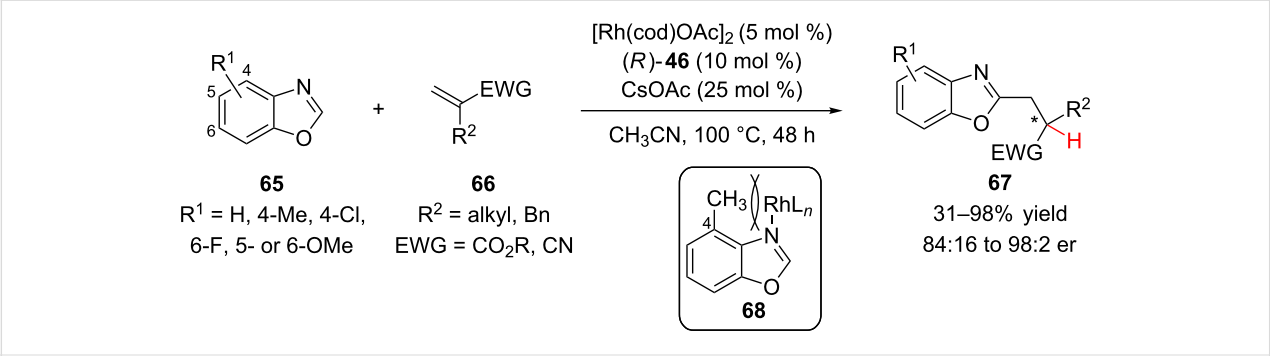


47
R = CF_3, Br, CHO, MeO, MeS, Ph, *t*-Bu

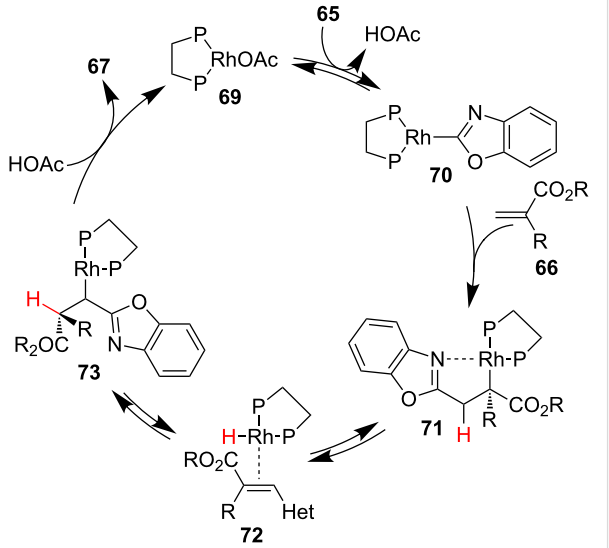
63
Ar = thiophenyl, naphthyl, MeO-Ph, F-Ph, MeS-Ph

64
67–93% yield
79:21 to 93:7 er

Scheme 15: Frost's enantioselective synthesis of α,α-dibenzylacetates **64**.



Scheme 16: Rovis's hydroheteroarylation of α-substituted acrylates with benzoxazoles.



Scheme 17: Proposed mechanism for the hydroheteroarylation of α-substituted acrylates with benzoxazoles.

acrylate **72** followed by enantioselective hydride transfer generates the chiral tertiary center in **73**. Finally, protodemetalation liberates the product and regenerates **69**. While the overall process provides the same product as a conjugate addition–enantioselective protonation sequence, mechanistically this, along with other transition metal-catalyzed reactions that invoke a conjugate addition–enantioselective protonation manifold might possibly operate via different pathways.

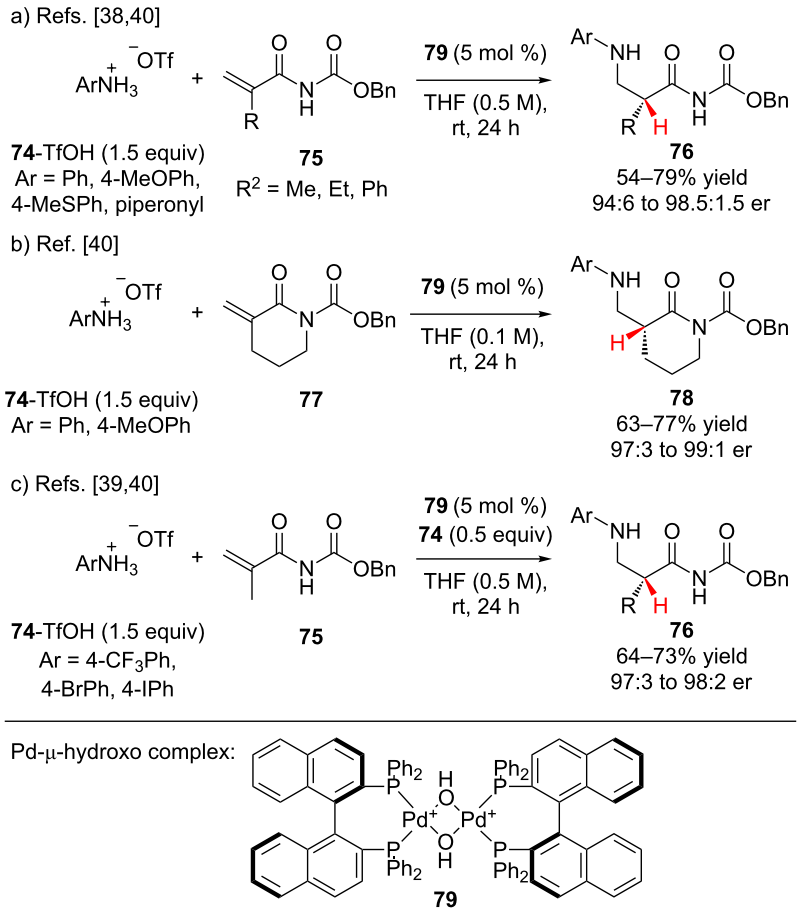
α,β-Unsaturated imides

Lewis acids

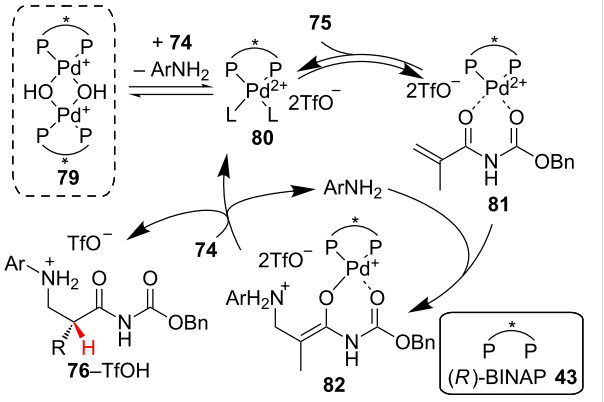
The catalytic generation of enolates in situ, while aesthetically attractive, presents its own set of challenges due to the potential for both *E*- and *Z*-enolate isomers that in some cases equilibrate under the reaction conditions. In this context, α,β-unsaturated imides are attractive substrates for conjugate addition–enantioselective protonation sequences. Imides are not only more electron withdrawing than esters, but the presence of a second carbonyl also provides an additional point of contact through which the chiral catalyst can bind and organize the transition state.

Many examples of conjugate addition–enantioselective protonation have been reported using carbon and sulfur nucleophiles, conversely relatively few examples have been reported using amines as nucleophiles. Sodeoka and co-workers have described the synthesis of β-aminocarbonyl compounds via the enantioselective addition of amine salts **74** to *N*-benzyloxycarbonyl acrylamides **75** and **77** catalyzed by a palladium-μ-hydroxo complex **79** (Scheme 18) [38-40]. Hii has used the same catalyst system and reported comparable yields and slightly lower enantioselectivities for the addition of *para*-substituted anilines to α,β-unsaturated imines [41]. Gil and Collin have also reported on the same reaction as Sodeoka, but using a samarium-BINOL catalyst system, which proceeded with lower enantioselectivity [42]. Sodeoka found that minimizing the concentration of free amine present in the reaction mixture by using the triflate salts of the amines was crucial for obtaining high enantioselectivity. Excess free amine resulted in catalyst deactivation and a racemic background reaction. Electron-rich and neutral aromatic amines added to both acyclic and cyclic *N*-benzyloxycarbonyl acrylamides **75** and **77** in moderate to good yields and high enantioselectivity (Scheme 18a,b). Due to their attenuated nucleophilicity, electron-deficient amines were unreactive under the standard reaction conditions. Addition of 0.5 equivalents of free amine was found to be optimal, providing the product with excellent enantioselectivity (Scheme 18c). Notably, the authors did not observe any side reaction between the palladium and aryl bromide or aryl iodide groups.

Using NMR analysis and ESIMS Sodeoka and co-workers probed the mechanism of the reaction, observing a complex interplay between ligand exchange and the ammonium salt (Scheme 19) [40]. Based on their findings they proposed a catalytic cycle in which the Brønsted basic dimeric palladium-μ-



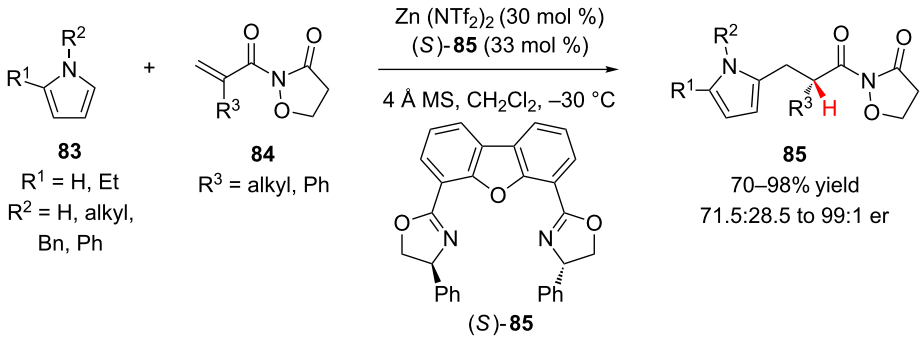
Scheme 18: Sodeoka's enantioselective addition of amines to *N*-benzyloxycarbonyl acrylamides **75** and **77**.



Scheme 19: Proposed catalytic cycle for Sodeoka's enantioselective addition of amines.

hydroxo complex **79** is broken up by the amine salt **74**, liberating Lewis acidic palladium monomer **80** and free amine. Binding of the *N*-benzyloxycarbonyl acrylamide by **80** activates it for conjugate addition of the amine to generate chiral enolate **82**. Enantioselective protonation of chiral enolate **82** by a second equivalent of amine salt liberates the product as the triflate salt and regenerates **80** and the free amine.

Building upon their previous work on enantioselective additions to α-substituted acrylates (vide ante), Sibi and colleagues reported the first example of Friedel–Crafts alkylation of an α-substituted-α,β-unsaturated imide followed by enantioselective protonation (Scheme 20) [43]. Using an in situ generated complex formed from $Zn(NTf_2)_2$ and Ph-dbfox ligand (*S*)-**85**, pyrroles **83** were added to imides **84** to produce **85** in high yield and modest to excellent enantioselectivity. Exploring a number of achiral imides, the authors found that an isoxazolidinone auxiliary enhanced the reactivity and minimized enolate $A^{1,3}$-interactions to provide the best yield and enantioselectivity. *N*-Alkylpyrroles were effective substrates, adding with high enantioselectivity (94:6 to 99:1 er). The enantioselectivity of the transformation was significantly lower only for pyrroles that lacked substitution on nitrogen and for *N*-phenylpyrroles (R^2 = H, Ph 71.5:28.5 to 90.5:9.5 er).



Scheme 20: Sibi's enantioselective Friedel–Crafts addition of pyrroles to imides **84**.

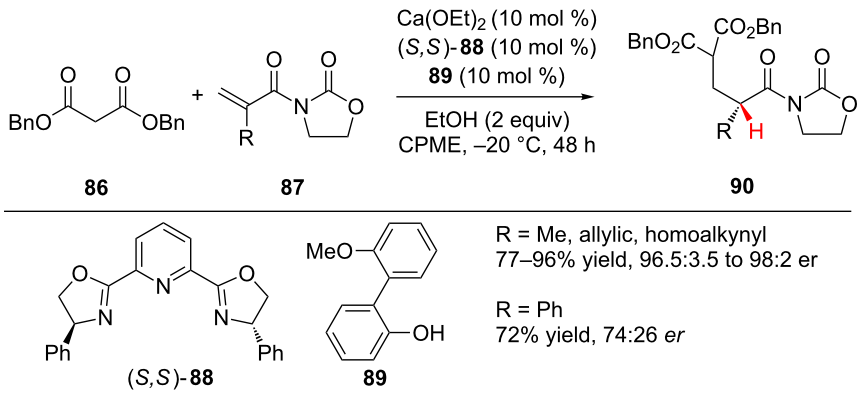
In 2010, the Kobayashi group reported the calcium-catalyzed Michael addition of dibenzylmalonate (**86**) to *N*-acryloyloxazolidinones **87** followed by enantioselective protonation of a chiral calcium enolate to access 1,5-dicarbonyl compounds **90** (Scheme 21) [44]. The chiral calcium alkoxide complex was generated in situ by mixing $Ca(OEt)_2$, PyBox ligand (*S,S*)-**88**, and phenol **89**. The authors found that the slow addition of malonate **86** and the use of phenol **89** and ethanol as additives were all crucial for achieving high yield and enantioselectivity, although the exact role of the phenol was not elucidated. 1,5-Dicarbonyl compounds **90** were accessed with excellent enantioselectivity for a variety of aliphatic α-substituents, and only when R was phenyl was there a significant loss of enantioselectivity (72% yield, 74:26 er).

Organocatalysts

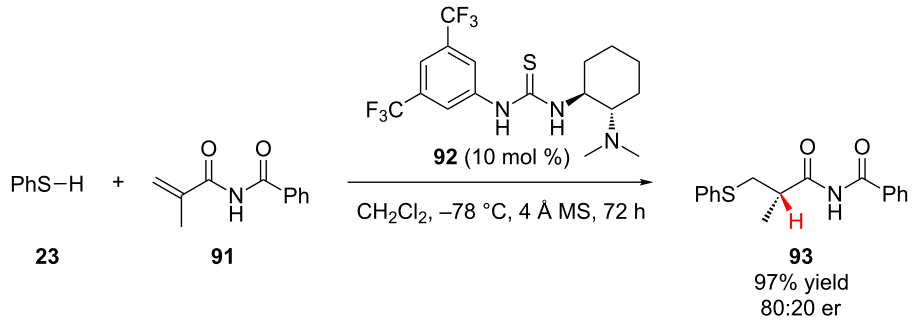
Multiple groups have developed organocatalytic conjugate addition–enantioselective protonations of α,β-unsaturated imides using thiols. Thiols are attractive nucleophiles due to their acidity, which facilitates deprotonation by amine bases and also reduces undesired competitive deprotonation and epimerization of the enolizable conjugate addition products. Additionally, the thiolate conjugate bases are highly nucleophilic, allowing ready access to sulfur functionalized products. A common theme among the organocatalytic literature examples is the use of hydrogen-bonding catalysts, which can activate the imides by hydrogen bonding to both of the carbonyl oxygens.

During the course of studying the addition of aromatic thiols to α,β-unsaturated benzamides and enones, Chen, Ding, and Wu first reported the conjugate addition of thiophenol (**23**) to *N*-methacryloyl benzamide **91** followed by enantioselective protonation using Takemoto's thiourea catalyst **92** in high yield and modest enantioselectivity (Scheme 22) [45].

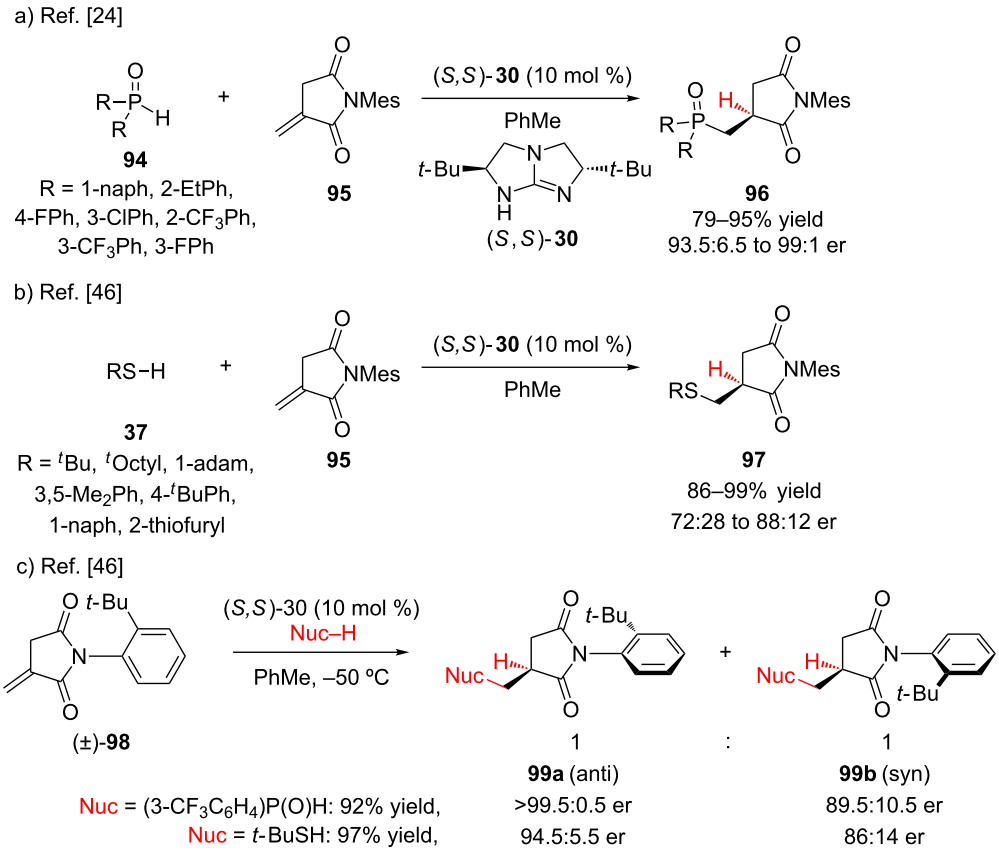
Tan and co-workers have investigated the conjugate addition–enantioselective protonation of *N*-arylitaconimides **95** using a C_2-symmetric guanidine catalyst (Scheme 23) [24,46]. Because *E*- and *Z*-enolates can exhibit different enatiofacial selectivity, the use of a cyclic imide ensured exclusive formation of the *Z*-enolate. During optimization, it was found that an *N*-aryl group containing 2,6-disubstitution was crucial for obtaining high levels of enantioselectivity. Addition of a variety of bis-aryl secondary phosphine oxides furnished **96** in high yield



Scheme 21: Kobayashi's enantioselective addition of malonates to α-substituted *N*-acryloyloxazolidinones.



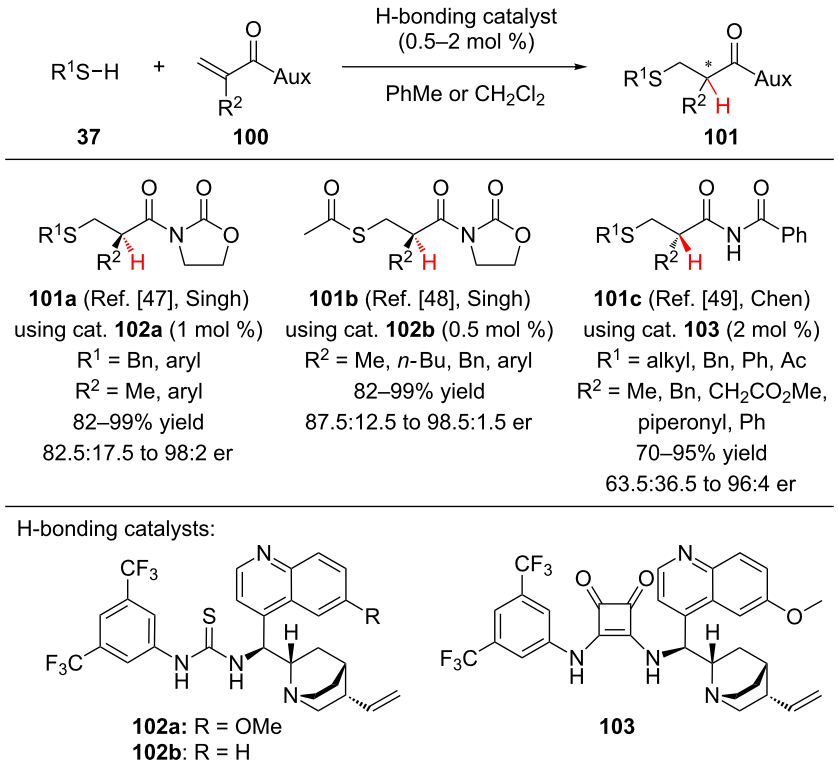
Scheme 22: Chen and Wu's enantioselective addition of thiophenol to *N*-methacryloyl benzamide.



Scheme 23: Tan's enantioselective addition of secondary phosphine oxides and thiols to *N*-arylitaconimides.

and enantioselectivity (Scheme 23a) [24]. Thiols also added efficiently to itaconimide **95** using the same guanidine catalyst system. In general, sterically hindered tertiary thiols added with higher enantioselectivity (85.5:14.5 to 88:22 er) than aromatic thiols (72:28 to 79.5:20.5 er) (Scheme 23b) [46]. This enantioselective addition process could be applied to a racemic mixture of axially chiral *N*-(2-*tert*-butylphenyl)itaconimide (**98**), furnishing atropisomers **99a** and **99b** as a stable and separable 1:1 mixture. A higher enantioselectivity was observed for the *anti*-diastereomer (Scheme 23c).

Following Tan's work on the conjugate addition–enantioselective protonation of cyclic itaconimide **95**, both the Singh and Chen groups investigated the addition of thiol nucleophiles to acyclic imides. Utilizing thiourea catalyst **102a**, Singh and co-workers reported the catalytic enantioselective addition of thiols to *N*-acryloyloxazolidinones, accessing **101a** (Scheme 24) [47]. A variety of electron-rich, neutral, and electron-poor thiols were efficiently coupled under the reaction conditions, including unprotected 2-aminobenzenethiol, although with lower enantioselectivity (82.5:17.5 er). Building on their addition of



Scheme 24: Enantioselective addition of thiols to α-substituted *N*-acryloylamides.

benzylic and aromatic thiols to *N*-acryloyloxazolidinones, Singh and colleagues demonstrated that thiourea **102b** catalyzes the addition of thioacetic acid to *N*-acryloyloxazolidinones in high yields and enantioselectivity to provide thioester **101b** [48].

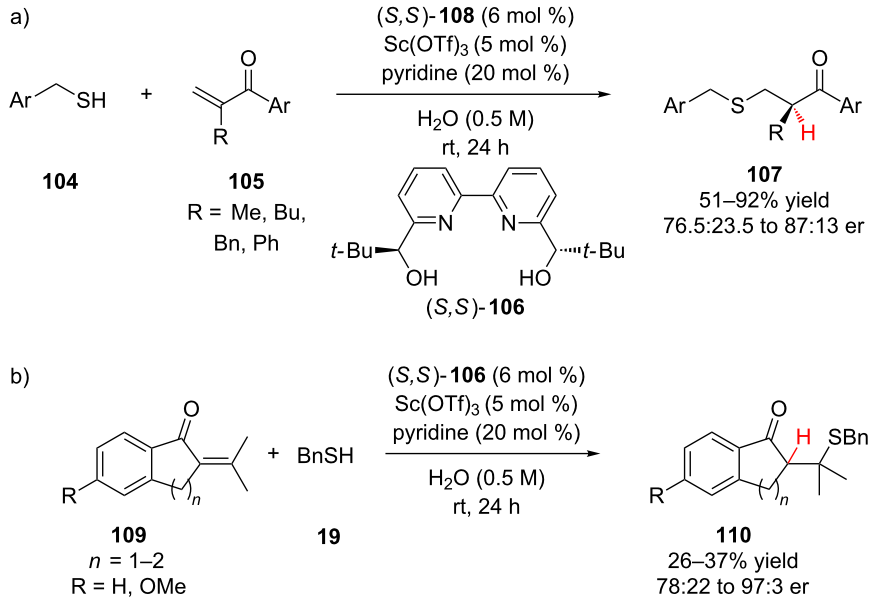
In a related transformation, Chen and co-workers showed that squaramide **103** catalyzes the addition of thiols to *N*-acryloylbenzamides to access thioether **101c** [49]. The authors found that exclusion of water by addition of 4 Å molecular sieves as a desiccant was essential for achieving good enantioselectivity. When the R^2 substituent was aliphatic, good enantioselectivity was observed (87.5:12.5 to 96:4 er); however, aromatic and piperonyl groups greatly diminished the enantioselectivity of the transformation (63.5:36.5 to 73:27 er).

α,β-Unsaturated ketones

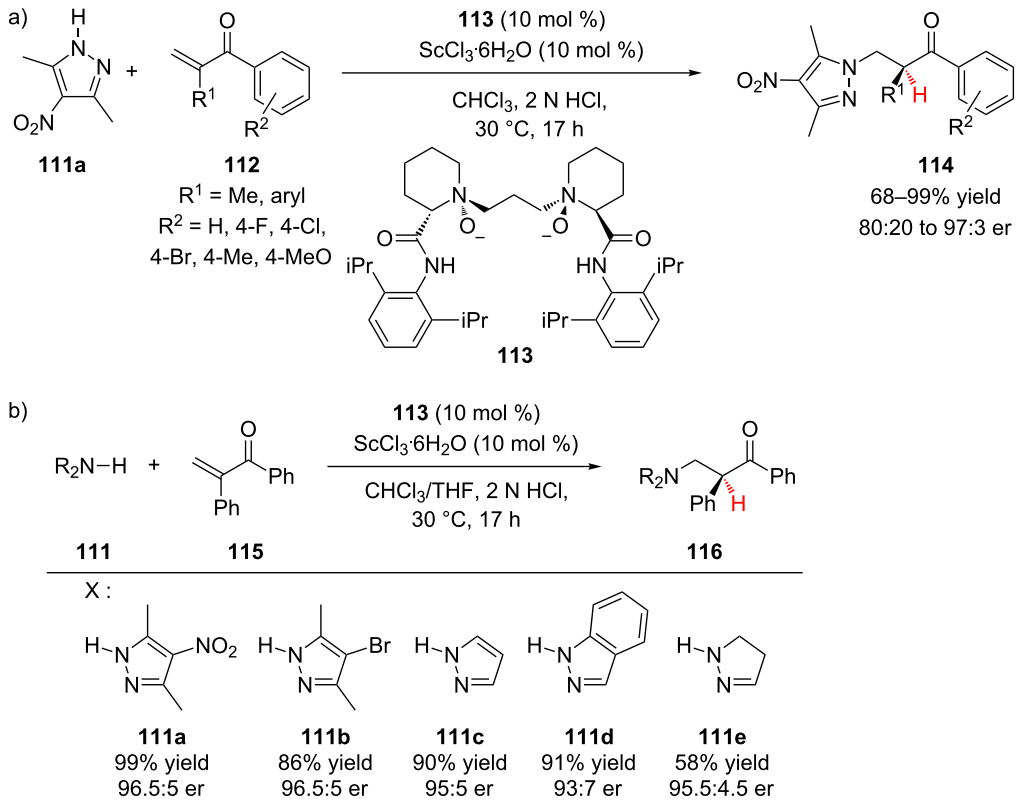
Lewis acids

In 2012, Kobayashi and co-workers reported the Sc-catalyzed enantioselective addition of benzylic thiols **104** to α,β-unsaturated ketones **105** (Scheme 25a) [50]. Interestingly, water was found to be the optimal solvent for this transformation, switching to organic solvents (CH_2Cl_2, THF, toluene) resulted in diminished reactivity and poor enantioselectivity. Solvent mixtures of water and THF or ethanol also provided poor reactivity and enantioselectivity. A variety of electron-rich and electron-poor aryl ketones and benzylic thiols were effective substrates. The authors observed that a fast racemic background reaction proceeded in the presence of pyridine. However, in the absence of pyridine the reaction proceeded significantly slower and all enantioselectivity was lost, suggesting the importance of a thiolate intermediate in the catalytic cycle. To suppress the undesired base-catalyzed racemic pathways, β,β-dimethyl substituted tetralone ($n = 2$) and indanone ($n = 1$) substrates **109** were investigated (Scheme 25b). While these substrates displayed diminished reactivity, the tetralones showed a significant boost in enantioselectivity (96:4 to 97:3 er), though only moderate enantioselectivity was observed for the indanone substrate (R = H, 78:22 er).

The Feng group has reported the conjugate addition of pyrazoles to α-substituted aromatic vinyl ketones followed by enantioselective protonation of the enolate intermediate using an *N,N'*-dioxide–Sc(III) catalyst system (Scheme 26) [51]. During optimization, the authors found that incorporation of bulky amides into ligand **113** was crucial for achieving high enantioselectivity. A wide variety of α-aryl vinyl ketones **112** were effective substrates, and only when R^1 was methyl did the enantioselectivity drop below 92:8 er to 80:20 er (Scheme 26a). The



Scheme 25: Kobayashi's enantioselective addition of thiols to α,β-unsaturated ketones.



Scheme 26: Feng's enantioselective addition of pyrazoles to α-substituted vinyl ketones.

authors also investigated a number of pyrazole nucleophiles **111**, which all reacted with high enantioselectivity, including pyrazoline **111e** (Scheme 26b).

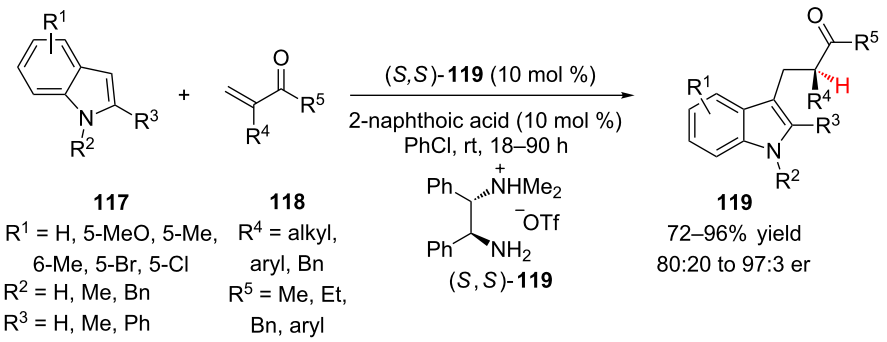
Organocatalysts

Building on their earlier work with α,β-unsaturated aldehydes (vide infra), Luo and Cheng have extensively explored the use

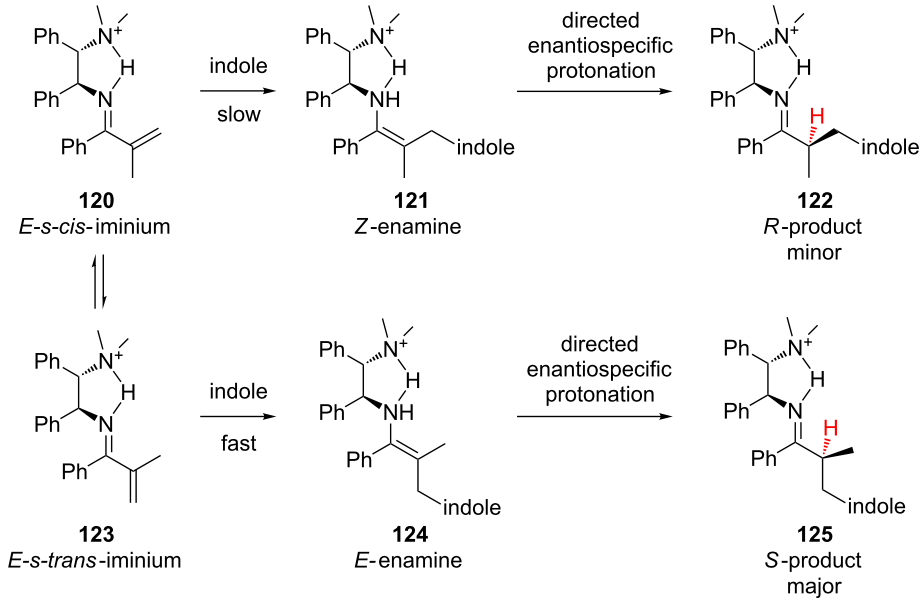
of enamine catalysis for conjugate addition–enantioselective protonation of vinyl ketones. Using primary amine catalyst (*S,S*)-**119**, the authors were able to catalyze the Friedel–Crafts addition of indoles **117** to vinyl ketones **118** followed by enantioselective protonation (Scheme 27) [52]. During optimization it was found that addition of a weak acid, 2-naphthoic acid, improved both the yield and enantioselectivity of the transformation by facilitating the formation of the iminium ion intermediates. A variety of vinyl ketones **118** were explored for the reaction, and when R^4 was benzylic, shorter reaction times could be employed (41–48 h) and higher yields and enantioselectivities were observed (78–86% yield, 93:7 to 97:3 er). Aromatic vinyl ketones were also reactive, but required higher temperatures (40–60 ºC). Various indoles **117** were investigated, and although substitution on both the aromatic ring and nitrogen were accommodated, when R^3 was H, lower enantioselectivity was observed (86.5:13.5 to 89:11 er).

Luo and Cheng also explored the mechanism of the Friedel–Crafts addition of indole to α-substituted vinyl ketones [52,53]. Based on DFT studies, the authors proposed that the stereoselectivity of the reaction was under Curtin–Hammett control (Scheme 28). During the reaction, the iminium ions rapidly interconvert via single-bond rotation. After irreversible C–C bond formation the *E-s-cis*- and *E-s-trans*-iminiums give rise to the *Z*- and *E*-enamines, respectively, which undergo a directed enantiospecific protonation to give either the *R*- or *S*-product. Thus, the enantioselectivity is determined by the ratio of *Z*- to *E*-enamine, which in turn depends on the activation energy difference in the irreversible C–C bond forming steps.

Having developed an enamine catalysis system where the iminium's conformation in the conjugate addition step determines the enantioselectivity of the reaction, Lou and Cheng



Scheme 27: Luo and Cheng's addition of indoles to vinyl ketones by enamine catalysis.

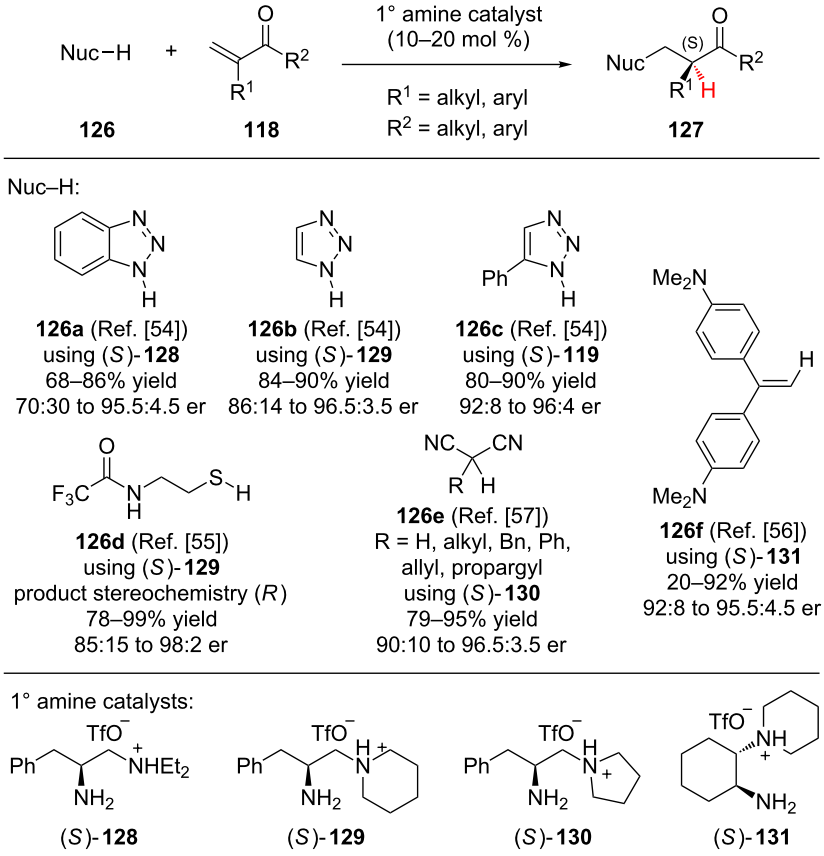


Scheme 28: Curtin–Hammett controlled enantioselective addition of indole.

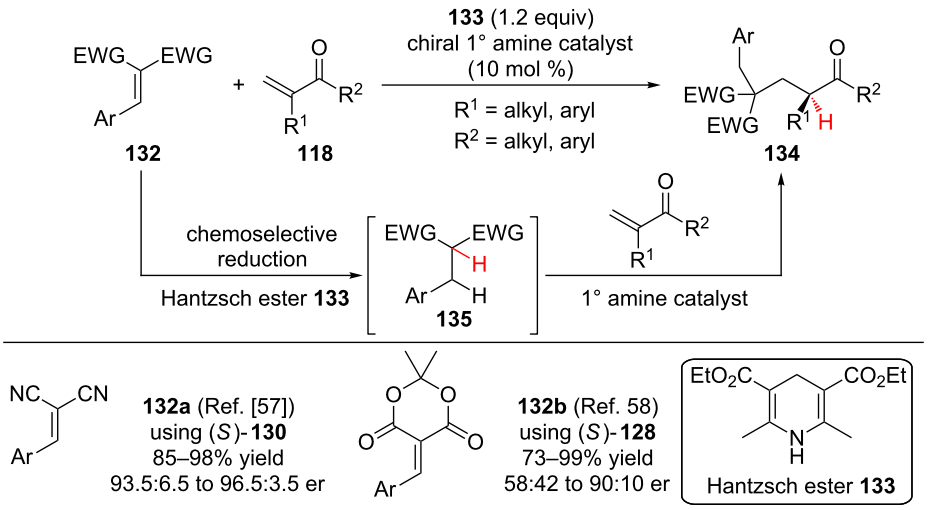
explored the addition of various nitrogen [54], sulfur [55], and carbon nucleophiles [56,57] to α-branched vinyl ketones (Scheme 29). The nitrogen heterocycles benzotriazole (**126a**), triazole (**126b**), and 5-phenyltriazole (**126c**), all reacted smoothly with vinyl ketone **118**. To achieve optimal reactivity and selectivity, each nucleophile required a slightly different chiral amine catalyst. Interestingly, vinylaniline **126f** could also be added to enone **118** in moderate to good yield and with good enantioselectivity. *N*-Trifluoroacetyl-1,2-aminothiol (**126d**) reacted to give thioether products in high yield and enantioselectivity. Only when R^1 was phenyl did the enantioselectivity of the thiol addition drop below 91.5:8.5 er to 85:15 er. The addition of a variety of α-substituted malononitriles **126e** also proceeded in high yield and enantioselectivity. During the exploration of different nucleophiles some common selectivity trends were observed. Aromatic enones (R^2 = aryl) generally provided higher levels of enantioselectivity than aliphatic enones (R^2 = alkyl). Additionally, for all of the nucleophiles, except thiols, increasing the steric bulk at R^1 resulted in diminished enantioselectivity.

Building on his asymmetric conjugate additions to α-substituted enones, Luo demonstrated that Hantzsch ester **133** chemoselectively reduces activated alkenes **132** in the presence of α-substituted vinyl ketones **118**, generating carbon nucleophiles **135** in situ. These nucleophiles then reacted with the α-substituted vinyl ketones **118** via an enamine catalysis conjugate addition–enantioselective protonation pathway (Scheme 30). Lou first applied this strategy of reduction–conjugate addition–enantioselective protonation to α,β-unsaturated malononitriles **132a**, to provide the product in comparable yield and enantioselectivity as when the enantioselective conjugate addition was performed using α-substituted malononitriles (**126e**, Scheme 29) [57]. In a subsequent report, Lou and co-workers demonstrated that Meldrum's acid derivatives **132b** were also operative in the reduction–conjugate addition–enantioselective protonation pathway [58]. Aromatic α-methyl enones (R^1 = Me, R^2 = aryl) reacted in good yield and enantioselectivity. However, when larger R^1 substituents or an α-methyl enone were used in the reaction, the product was obtained with diminished enantioselectivity (58:42 to 69.5:30.5 er).

After the submission of this review, Lou and co-workers reported an additional example of conjugate addition–enantioselective protonation involving an α,β-unsaturated ketone. In the



Scheme 29: Luo and Cheng's enantioselective additions to α-branched vinyl ketones.



Scheme 30: Lou's reduction–conjugate addition–enantioselective protonation.

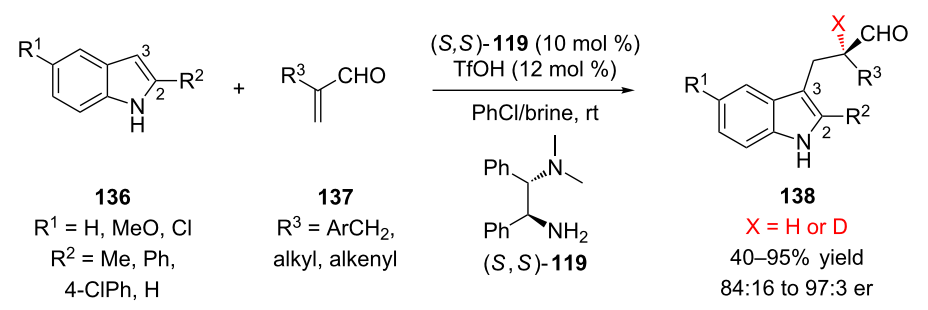
new report, a chiral primary amine catalyzed conjugate addition of a 1,3-diketone nucleophile into an in situ generated *ortho*-quinone methide was followed by an enamine based retro-Claisen reaction. The resulting enamine was stereoselectively protonated to access α-tertiary alkylated ketones [59].

α,β-Unsaturated aldehydes

Organocatalysts

In 2011, Luo and Cheng reported the first example of conjugate addition followed by enantioselective protonation using enamine catalysis [60]. Two challenges to using enamine catalysis for enantioselective protonation are the many conformations the reactive iminium intermediates can adopt and the potential for racemization of the enantioenriched product by the basic catalyst. Using the triflate salt of diamine **119**, Luo and Cheng were able to catalyze an enantioselective Friedel–Crafts reaction between indole **136** and α-substituted acrolein **137** (Scheme 31). Acroleins containing a benzyl α-substituent performed best in the reaction with 2-methylindole (72–95% yield, 93.5:6.5 to 97:3 er). Alkyl and alkenyl substituted acroleins also reacted with 2-methylindole, but resulted in lower yields and diminished enantioselectivity (52–80% yield, 87.5:12.5 to 94.5:95.5 er). Electron-rich, neutral, and electron-poor indoles were effective substrates, provided that they contained an R^2 substituent. The use of indoles unsubstituted at the 2-position (R^2 = H) led to lower enanantioselectivity (84:16 to 87:13 er). Products were not observed when either α-heteroatom-substituted acroleins or 3-substituted indoles were used as starting materials. When either the enantioenriched or racemic products **138** were resubmitted to the reaction conditions their enantiomeric ratios did not change, indicating that the reaction is not reversible.

During reaction optimization the authors found that the addition of a large excess of brine improved the enantioselectivity of the transformation. Additionally, they found that by using saturated NaCl/D_2O, α-deuterated products could be obtained in similar enantiomeric ratios as the α-protonated products. Luo and Cheng went on to further investigate this reaction using kinetic studies and DFT calculations [53,60]. Based on their studies, they proposed TS-**141** involving a water molecule stabilized by an O–H/π interaction with the indole ring to



Scheme 31: Luo and Cheng's primary amine-catalyzed addition of indoles to α-substituted acroleins.

explain the improvement in enantioselectivity of the protonation step when brine is used as an additive (Scheme 32).

α,β-Unsaturated thioesters

Lewis acids

In one of the early examples of conjugate addition–enantioselective protonation, Shibasaki and co-workers demonstrated that chiral lanthanum and samarium tris(BINOL) complexes (Figure 3), developed by the Shibasaki group for asymmetric Michael additions using malonates and organometallic reagents, are effective catalysts for the sequential conjugate addition of 4-*tert*-butyl(thiophenol) to α,β-unsaturated thioesters followed by enantioselective protonation (Scheme 33) [61].

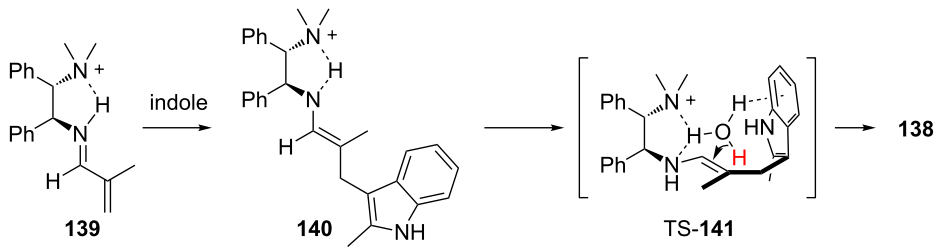
During their initial investigations Shibasaki and co-workers examined the (*R*)-La-**142** catalyzed enantioselective addition of 4-*tert*-butyl(thiophenol) to ethyl methacrylate **145** (X = O) (Scheme 33a), while good enantioselectivity could be achieved, the saturated ester product **146** could not be obtained in greater than 50% yield. In contrast, the unsaturated thioester **145** (X = S) provided the product in high yield and enantioselectivity. By switching to samarium catalyst (*R*)-Sm-**143**, the catalyst loading could be halved and a further improvement in enantioselectivity was observed (Scheme 33b). For example, for R = Me an 86% yield and 96.5:3.5 er was obtained [61].

The Shibasaki group went on to apply their conjugate addition–enantioselective protonation of α,β-unsaturated thioesters to the total synthesis of epothilones A and B, natural products that inhibit microtubule function [62]. The enantioselective addition of 4-*tert*-butyl(thiophenol) to **149** using 5 mol % of (*S*)-Sm-**144** was used to set the C8 stereocenter in the final product (Scheme 34).

α,β-Unsaturated amides

Lewis acids

In 2009, the Shibasaki group reported the catalytic cyanation–enantioselective protonation of α-substituted α,β-unsaturated *N*-acylpyrroles **151** using a chiral polynuclear Gd complex (Scheme 35) [63]. Using a gadolinium catalyst derived from tridentate ligand **152**, conjugate addition of cyanide followed by enantioselective protonation occurred with high yield and enantioselectivity for both α-alkyl and α-aryl conjugate addition acceptors. Alkyl substrates reacted smoothly at 25 °C (90–98% yield, 90:10 to 95.5-4.5 er) even when R was a more sterically demanding isopropyl or cyclohexyl group. Aryl substrates required lower reaction temperatures and longer reaction times (−30 or −78 °C). The average yield and enantioselectivity for the aryl substrates was lower than for the alkyl substrates; however, many of the aryl substituted products were crystalline and could be recrystallized up to greater than 98.5:1.5 er. Inter-



Scheme 32: Luo and Cheng's proposed mechanism and transition state.

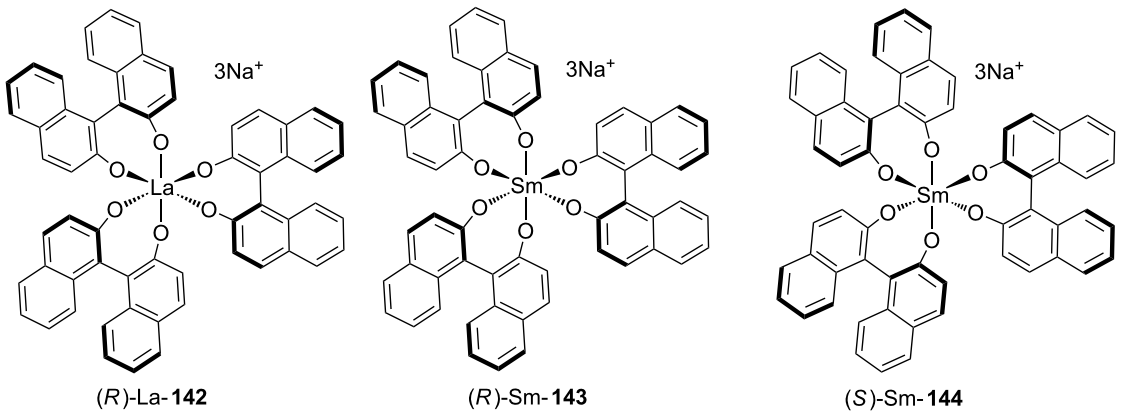
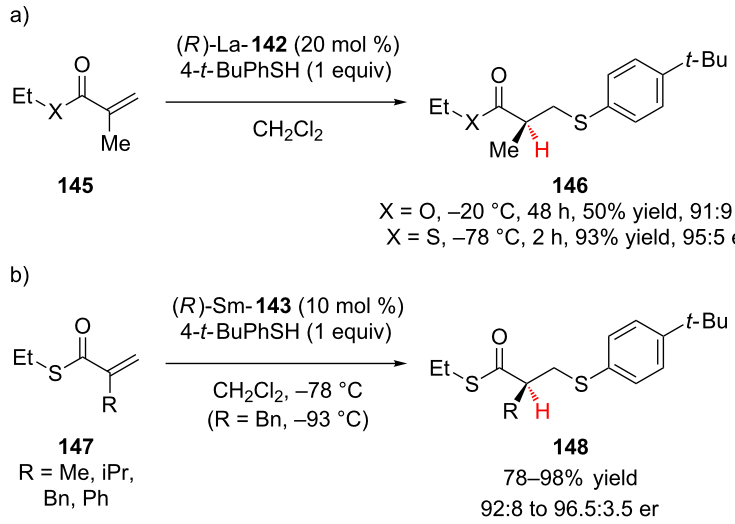
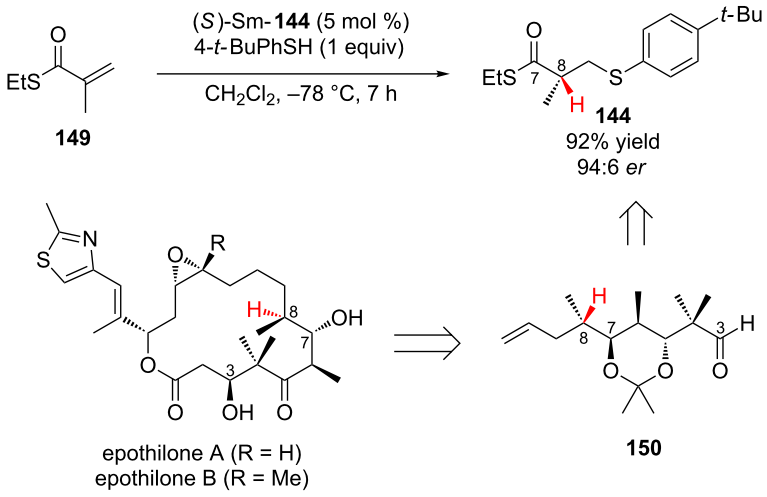


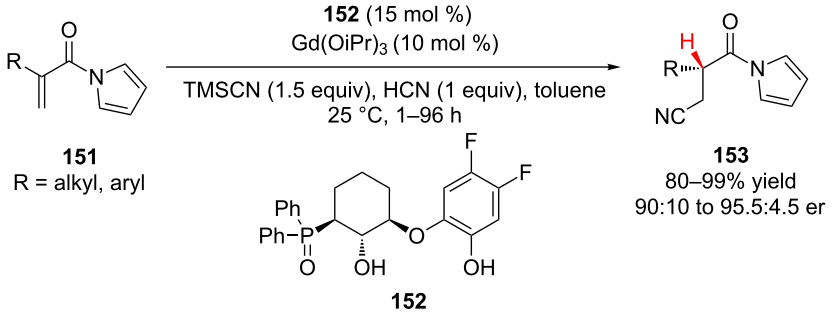
Figure 3: Shibasaki's chiral lanthanum and samarium tris(BINOL) catalysts.



Scheme 33: Shibasaki's enantioselective addition of 4-*tert*-butyl(thiophenol) to α,β-unsaturated thioesters.



Scheme 34: Shibasaki's application of chiral (*S*)-SmNa$_3$tris(binaphthoxide) catalyst **144** to the total synthesis of epothilones A and B.



Scheme 35: Shibasaki's cyanation–enantioselective protonation of *N*-acylpyrroles.

estingly, when attempting to use catalytic amounts of trimethylsilyl cyanide (10 mol %) a significant decrease in reaction rate and enantioselectivity was observed.

Transition metal catalysts

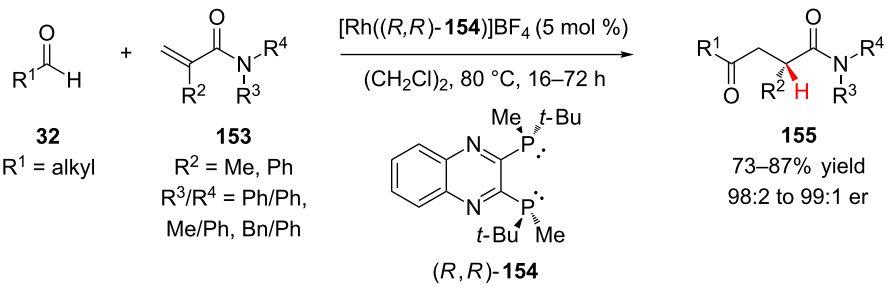
Conjugate addition–enantioselective protonation of α,β-unsaturated tertiary amides can also be performed with transition metal catalysts. Using a cationic rhodium(I)/QuinoxP* **154** complex, Tanaka and co-workers achieved the enantioselective hydroacylation of α-substituted acrylamides **153** using aliphatic aldehydes **32** to provide 1,4-ketoamides **155** in high yields and excellent enantioselectivity (Scheme 36) [64]. A variety of aliphatic aldehydes were effective substrates, including the α-branched cyclohexyl and cyclopentyl carboxaldehydes. However, pivaldehyde was completely unreactive, and when benzaldehyde was examined as a substrate, the reaction was slow and the enantioselectivity was poor (12% yield and 79:21 er).

α,β-Unsaturated nitroalkenes

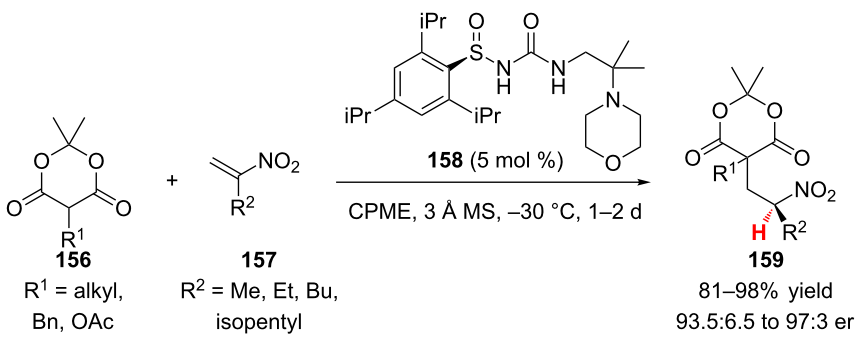
Organocatalysts

In the first reported example of the enantioselective protonation of a nitronate, Ellman and co-workers demonstrated that an *N*-sulfinylurea organocatalyst could be used to catalyze the addition of α-substituted Meldrum's acids to terminally unsubstituted nitroalkenes (Scheme 37) [65]. Interestingly, the optimal organocatalyst for the transformation was chiral only at sulfur, when chiral amine motifs were explored, e.g., 1,2-cyclohexanediamine, poor enantioselectivity was observed (≤75:25 er). A variety of R^1 substituents on Meldrum's acid **156** were compatible with the reaction, including alkyl, phenethyl, pendant esters and thioethers, and an α-acetyloxy group (81–98% yield, 95.5:4.5 to 97:3 er). Slightly lower enantioselectivity was observed only when R^1 was benzyl (93.5:6.5 er). Methyl, ethyl, *n*-butyl, and isopentyl R^2 substituted nitroalkenes were efficient substrates (84–98% yield, 95.5:4.5 to 97:3 er). The resulting nitroalkane adduct **159** could be reduced and cyclized to access α,γ-disubstituted γ-lactams.

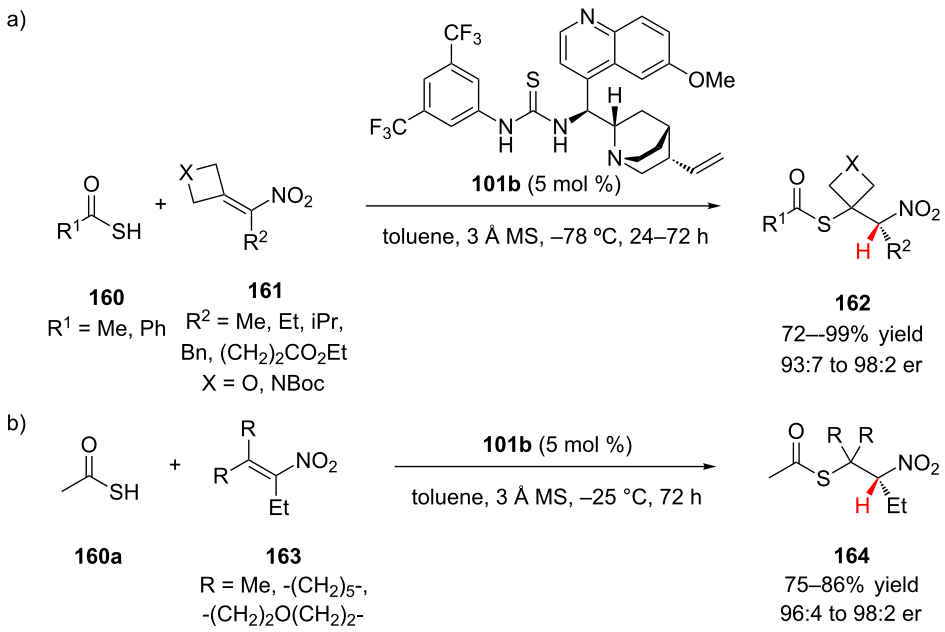
Ellman and co-workers, in the second example of conjugate addition–enantioselective protonation with nitroalkenes, showed that thioacids **160** could be added in high yields and with high enantioselectivity to α,β,β-trisubstituted nitroalkenes **161** using a thiourea organocatalyst **101b** (Scheme 38) [66]. This report was the first example of enantioselective addition to a trisubstituted nitroalkene and was the first example of conjugate addition–enantioselective protonation using a fully substituted alkene. Nitroalkenes that were activated by the incorporation of an oxetane or *N*-Boc-azetidine ring at the β-position reacted well with both thioacetic acid and thiobenzoic acid (Scheme 38a). Various R^2 substituents were compatible with the reaction, including an isopropyl group and a pendent methyl



Scheme 36: Tanaka's hydroacylation of acrylamides with aliphatic aldehydes.



Scheme 37: Ellman's enantioselective addition of α-substituted Meldrum's acids to terminally unsubstituted nitroalkenes.



Scheme 38: Ellman's enantioselective addition of thioacids to α,β,β-trisubstituted nitroalkenes.

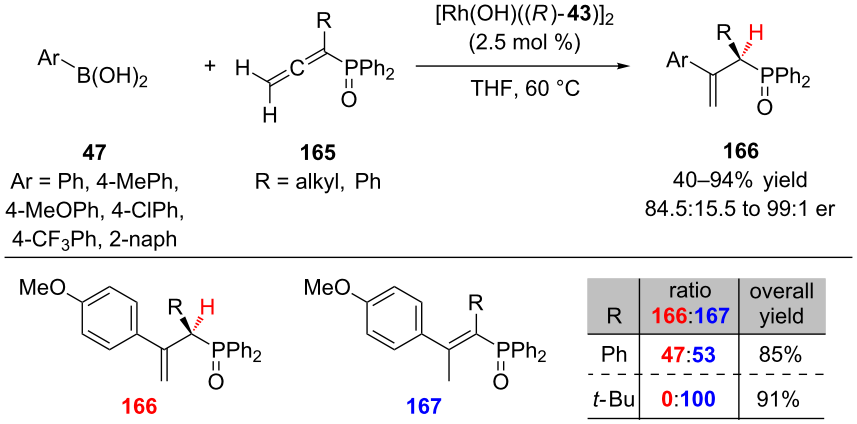
ester. Generally, the azetidine nitroalkenes provided the 1,2-nitrothioacetates in higher yields and enantioselectivity (81–99% yield, 95:5 to 98:2 er). The oxetane and *N*-Boc azetidine nitroalkenes were activated toward conjugate addition by the release of ring-strain. However, thioacetic acid (**160a**) also adds in good yield and high enantioselectivity to unstrained nitroalkenes **163** (Scheme 38b). Additions to β-cyclohexyl and β-4-tetrahydropyran nitroalkenes as well as an acyclic β,β-dimethyl nitroalkene all proceeded with good conversion when the reaction temperature was raised to −25 °C.

After the submission of this review, Ellman and co-workers published an additional example of enantioselective nitronate protonation, which was accomplished using an *N*-sulfinylurea organocatalyst to catalyze the addition of a pyrazol-5-one nucleophile to a trisubstituted nitroalkene [67].

α,β-Unsaturated phosphonates and phosphine oxides

Transition metal catalysts

In 2006, Hayashi and co-workers reported the first conjugate addition–enantioselective protonation of allenes **165** bearing a phosphine oxide (Scheme 39) [68]. Incorporation of the phosphine oxide allowed for selective protonation forming the less stabilized terminal chiral alkene **166** over the internal achiral isomer **167**, an inherent challenge in the hydroarylation of ter-



Scheme 39: Hayashi's enantioselective hydroarylation of diphenylphosphinylallenes.

minal allenes. Electron-rich, neutral, and electron-poor arylboronic acids **47** added to alkyl (R = Me, Et, *n*-Bu) diphenylphosphinylallenes **165** in high yield and excellent enantioselectivity (85–94% yield, 98:2 to 99:1 er). With sterically bulky α-substituents (R = Ph, *t*-Bu), competitive formation of the achiral internal alkene was preferred.

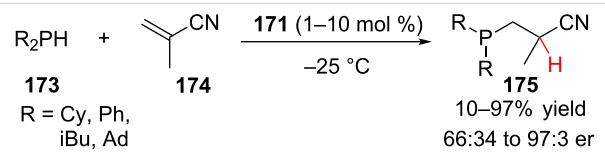
Enantioenriched α-amino phosphonic acids and their derivatives are important motifs that have been utilized by the pharmaceutical and agrochemical industries as α-amino acid analogues. Darses and co-workers reported a novel approach to the synthesis of enantioenriched α-amino phosphonates **170** via a rhodium(I) catalyzed enantioselective 1,4-addition of potassium aryltrifluoroborates **168** to dehydroaminophosphonates **169** (Scheme 40) [69]. α-Amino phosphonates **170** were obtained with high levels of enantioselectivity for electron-rich, neutral, and electron-poor aryltrifluoroborates **168**. Electron-rich organoboron reagents (4-*t*-Bu, 4-MeO, and 3-MeO) gave slightly lower yields (51–77%) than the electron-poor reagents (65–86%), with potassium phenyltrifluoroborate giving the highest yield (91%). Phenylboronic acid was also shown to be a competent coupling partner, providing the corresponding product in 92% yield and 96.5:3.5 er.

Methacrylonitrile

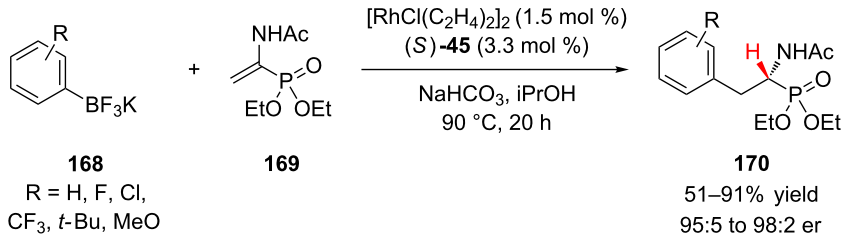
Lewis acids

In the literature, conjugate addition–enantioselective protonation using α,β-unsaturated nitriles has remained unexplored for substrates other than methacrylonitrile. The Togni lab has explored using ferrocenyl tridentate nickel(II) and palladium(II) complexes as chiral Lewis acid catalysts for the hydrophosphination and hydroamination of methacrylonitrile (Figure 4) [70-74]. Other researchers have reported platinum [75], nickel [76], and zirconium [77] catalysts for the hydrophosphination and hydroamination of methacrylonitrile; however, these examples provided product with significantly lower enantioselectivity.

In 2004, the Togni lab reported the hydrophosphination of methacrylonitirle **174** catalyzed by nickel(II)/(*R,R*)-Pigiphos complex **171** (Scheme 41) [71]. The reaction proceeded in good



Scheme 41: Togni's enantioselective hydrophosphination of methacrylonitrile.



Scheme 40: Hayashi's enantioselective hydroarylation of diphenylphosphinylallenes.

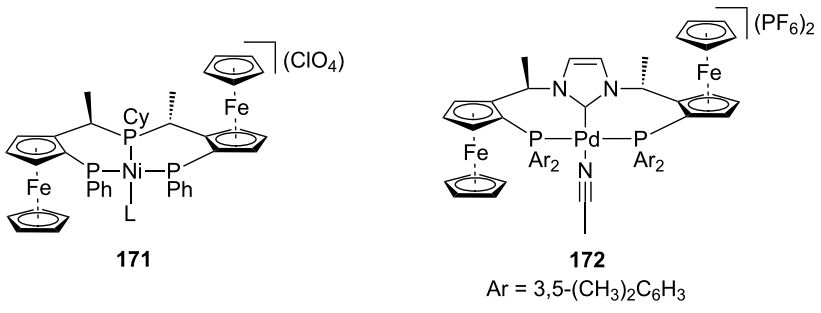
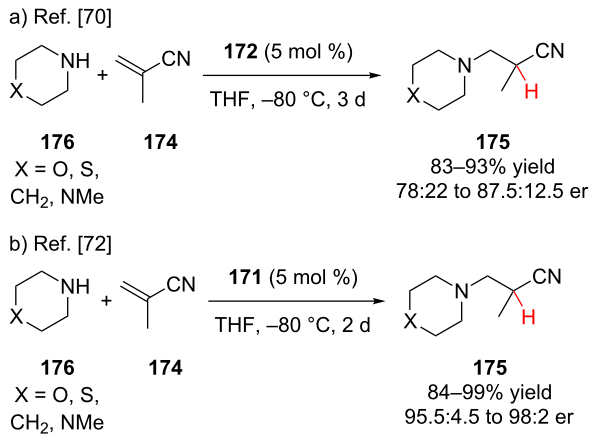


Figure 4: Togni's chiral ferrocenyl tridentate nickel(II) and palladium(II) complexes.

yield for alkyl phosphines (71–97% yield) and with higher enantioselectivity for the more sterically encumbered alkyl groups (R = Ad, 97:3 er).

Togni and co-workers subsequently reported the hydroamination of methacrylonitrile **174** using palladium(II) catalyst **172** (Scheme 42a) [72]. Low temperature and bulky aryl groups on the catalyst were necessary to achieve good levels of enantioselectivity. In a later study, their nickel(II) catalyst **171** proved to be much more selective under the same reaction conditions (Scheme 42b) [74]. Togni and co-workers also investigated the hydroamination of methacrylonitrile using benzylamine and aniline; however, these substrates gave products with low enantioselectivity (55:45 to 61:29 er).



Scheme 42: Togni's enantioselective hydroamination of methacrylonitrile.

Conclusion

As described above, many conjugate addition–enantioselective protonation reactions have been employed for the synthesis of enantioenriched amino esters and other carboxylic acid derivatives. Additions to α,β-unsaturated esters and imides have historically been the most extensively investigated substrates with additions to other classes of Michael acceptors only being reported more recently. While many examples using sulfur and carbon nucleophiles have been reported, the addition of other heteroatom nucleophiles remains relatively unexplored. This approach for the synthesis of tertiary carbon stereocenters continues to generate interest, both for the challenges the transformation presents and the ability to efficiently access useful motifs.

Acknowledgements

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Synergistic chiral iminium and palladium catalysis: Highly regio- and enantioselective [3 + 2] annulation reaction of 2-vinylcyclopropanes with enals

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Abstract

A cooperative catalytic strategy of chiral iminium catalysis by regioselective activation of the C=C bond in enals and a transition metal promoting to open the 2-vinylcyclopropanes for highly regio- and enantioselective [3 + 2] cycloaddition reaction of 2-vinylcyclopropanes with α,β-unsaturated aldehydes has been developed.

Introduction

The power of "donor–acceptor" (D–A) cyclopropanes as versatile 1,3-dipolar components is fuelled by its capacity of serving a complementary approach to a wide array of 5-membered ring structures, which are difficult or impossible to access by classic [3 + 2] cycloaddition reactions [1-34]. In recent years, significant efforts have been devoted to developing a catalytic enantioselective version of the processes. In this context, the D–A cyclopropanes have been applied for the reaction with highly active dipolarophiles, such as electrophilic C=O [35], e.g., aldehydes [36-38], ketones [38,39], and imines [40], and nucleophilic enol ethers [38,41], enamides [42], and indoles [43]. Nonetheless, the reactions with the α,β-unsaturated aldehydes and ketones face important challenges. To the best of our knowledge, so far merely two catalyst manifolds have been realized to effect the transformations with C=C double bonds instead of C=O in the α,β-unsaturated systems. Tsuji described the first organometallic promoted non-asymmetric reaction between D–A cyclopropanes and methyl vinyl ketone and α,β-unsatu-

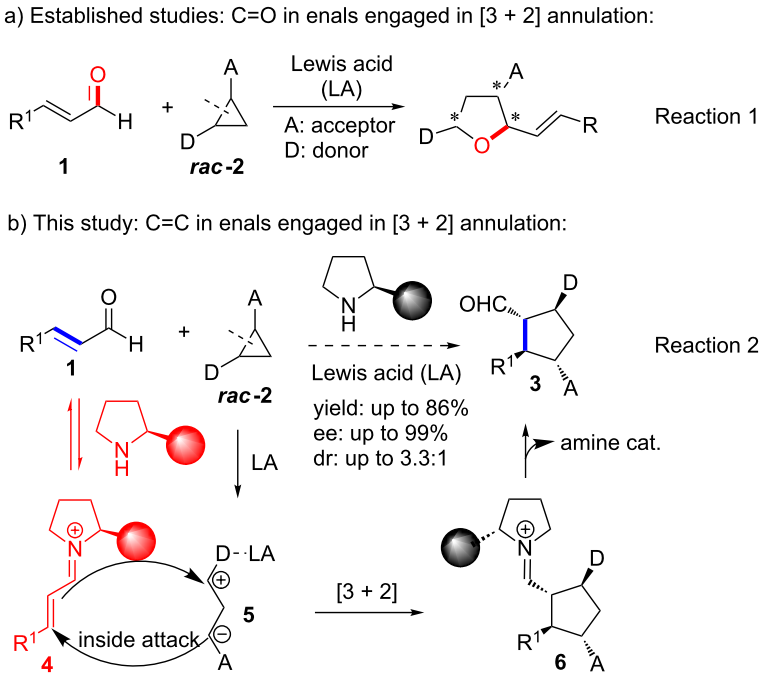
rated esters [44]. Trost and co-workers orchestrated the only example of the enantioselective reaction of D–A cyclopropanes with C=C double bonds with Meldrum's acid and alkylidenes or azlactone alkylidenes, catalyzed by the chiral Trost Pd(0)-complexes [45]. However, it is difficult to apply the catalytic system for the regio-controlled reaction with C=C bonds in α,β-unsaturated carbonyl compounds, particularly enals. The highly active aldehyde functionality reacts more favorably with the D–A cyclopropane resulting 1,3-dipoles, as elegantly demonstrated by Johnson and Waser for the formation of chiral tetrahydrofurans (Scheme 1, reaction 1) [36,38]. Achieving a regioselective control at the C=C bond rather than at C=O in enals represents a challenge and has not been reported.

Synergistic catalysis is a very important and useful strategy in organic synthesis by offering power for improving reaction efficiency and/or realizing impossible processes [46-55]. Recently, we developed an enantioselective addition of aldehydes to vinylpyridines and vinylarenes catalyzed by synergistic catalysis of iminium catalyst and Brønsted acid [56]. Herein we wish to disclose the first synergistic catalytic enantioselective [3 + 2] annulation reaction between 2-vinylcyclopropanes and enals via 1,4-addition (Scheme 1, reaction 2). The process proceeds highly regio- and enantioselectively with C=C bonds in enals. Notably, a synergistic catalytic system is implemented and makes this previously inaccessible [3 + 2] annulation transformation possible.

Results and Discussion

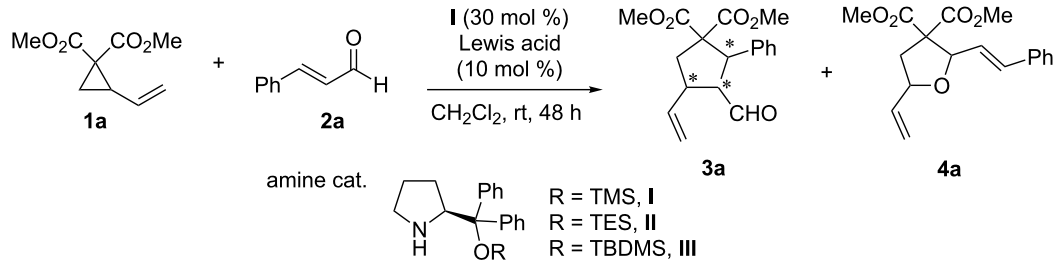
To render the [3 + 2] annulation reaction to selectively act on the C=C double bond rather than on the aldehyde in enals **1**, we proposed a new cooperative iminium and Lewis acid (LA) catalysis strategy (Scheme 1, reaction 2) [49,50,57-76]. The iminium catalysis plays an important dual role in the process. The formed iminium ion **4** derived from aldehyde **1** and an amine catalyst activates the C=C bond and sterically blocks the attack of the C=N iminium ion functionality posed by the bulky amine catalyst. In parallel, a LA promotes to open the D–A cyclopropanes **2**. The cooperative activation of two independent substrates by respective iminium and Lewis acid catalysis may enable an unprecedented catalytic regio- and enantioselective [3 + 2] annulation process, which offers a new approach to synthetically important heavily functionalized chiral cyclopentane structures **3**, bearing at least 3 stereogenic centers in this one-pot operation [77,78].

To test the feasibility of the designed [3 + 2] annulation process [79-94], we started our investigation by carrying out the reaction between the commonly used D–A system dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**1a**) and *trans*-cinnamaldehyde (**2a**) catalyzed in the presence of a LA and chiral amine **I** in CH_2Cl_2 at rt for 48 h (Table 1). A series of Lewis acids were initially screened. $FeCl_3$ and $Cu(OTf)_2$ gave the 1,2-cycloaddition product tetrahydrofuran **4a** (Table 1, entries 1 and 2). It is also disappointing that others Lewis acids, such as $CuCl_2$,



Scheme 1: Catalytic regio- and enantioselective [3 + 2] annulation reactions of 2-vinylcyclopropanes with enals.

Table 1: Screening of lewis acids.[a]



Entry	LA	Yield (%)[b], **3a**	Yield (%)[b], **4a**
1	$FeCl_3$	0	53
2	$Cu(OTf)_2$	0	47
3	$CuCl_2$	0	0
4	MgI_2	0	0
5	$ZnBr_2$	0	0
6	$ZnCl_2$	0	0
7	$FeCl_2$	0	0
8[c]	$Pd_2(dba)_3$	48	0

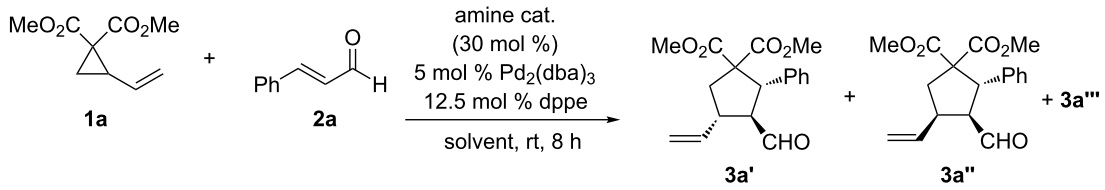
[a]The reaction was carried out with **1a** (36.8 mg, 0.2 mmol) and **2a** (26.4 mg, 0.2 mmol) in the presence of 10 mol % LA and 30 mol % amine **I** in 0.8 mL of CH_2Cl_2 at rt for 48 h. [b]Isolated yields; [c]5 mol % $Pd_2(dba)_3$ and 12.5 mol % dppe was used.

MgI_2, $ZnBr_2$, $ZnCl_2$ and $FeCl_2$ failed to promote these processes (Table 1, entries 3–7). Inspired by Trost's work of Pd(0)-catalyzed annulations of D–A cyclopropanes with C=C double bonds with Meldrum's acid and alkylidenes or azlactone alkylidenes [45], we probed the $Pd_2(dba)_3$-dppe complex for the 1,4-addition cycloaddition reaction (Table 1, entry 8). It was found that the reaction took place to afford the desired cyclopentane **3a**.

Encouraged by this result, we carried out further investigations of the co-catalysts promoted process (Table 2). First, we determined the diastereo- and enantioselectivity of the reaction. The ^{1}H NMR of the reaction crude mixture showed three diastereoisomers. The two major diastereoisomers were determined to be (2*S*,3*S*,4*S*)-**3a'** and (2*S*,3*S*,4*R*)-**3a''** in 2:1 ratio (Table 2, entry 1) based on single X-ray crystallographic analysis (see Scheme 2). Unfortunately, the third diastereoisomer **3a'''** was too hard to be separated to determine its stereochemistry. The enantioselectivities of two major diastereoisomers are even more encouraging (80 and 76% ee). Further investigations of solvents revealed the medium-dependent effect (Table 2, entries 1–8). No reaction happened in toluene (Table 2, entry 2). Disappointing outcomes were also received in DCE, ether, CH_3CN and EtOAc (Table 2, entries 3–6). Gratifyingly, in $CHCl_3$ this reaction proceeded smoothly to furnish the desired cyclopentanes in 63% yield with 99% ee for major **3a'** and 83% ee for minor **3a''** with a dr ratio of 1.7:1 (Table 2, entry 7). The reaction performed in THF was interesting: No reaction occurred at rt (Table 2, entry 8), but at 50 °C, 54% yield with high enantioselectivity for both isomers while **3a''** as the major product (dr: **3a''**:**3a'** = 5:1, Table 2, entry 9) was obtained. We decided to further optimize the reaction in $CHCl_3$ accordingly (Table 2, entries 10–13). A longer reaction time helped to increase the reaction yield (60 h, 76% yield entry 10). More steric hindered amine catalysts with bigger TES and TBDMS groups, **II** and **III**, were then probed and gave rise to the slight drop of enantioseletivity (Table 2, entries 11 and 12). A further optimization of reaction conditions found that the addition of additional 0.5 equiv **1a** into the reaction mixture in 4 portions significantly improved the reaction yield (83%, Table 2, entry 13). In order to improve the diastereoselectivity of this reaction, other cyclopentanes used in Trost's system were also tested in this reaction [45]. Unfortunately, the reactions proceeded slowly to afford the cycloaddition products in less than 10% yield.

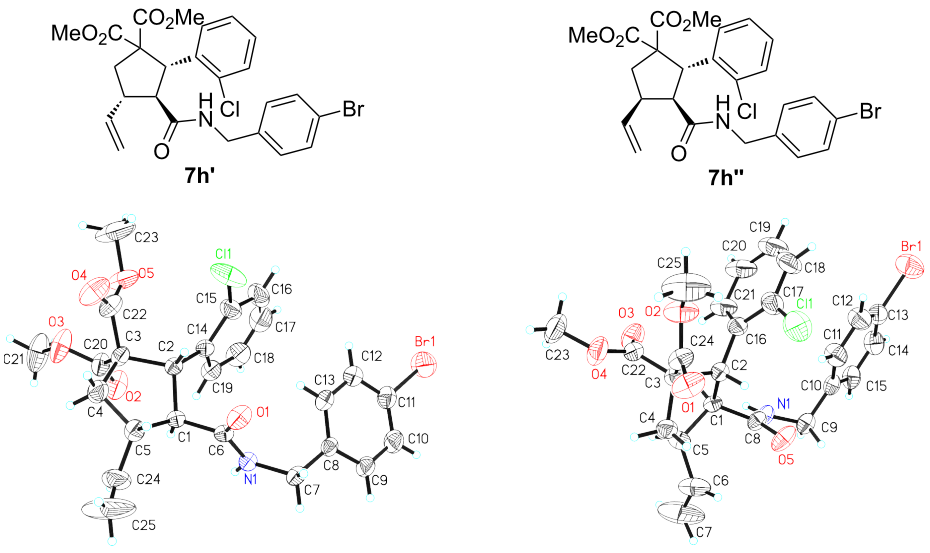
We then selected the use of co-catalysts of $Pd_2(dba)_3$ and organocatalyst **I** in $CHCl_3$ at room temperature to evaluate the generality of this [3 + 2] annulation process by the variation of vinylcyclopropanes and enals (Table 3). The results exhibit that the synergistic catalyzed enantioselective [3 + 2] annulation process serves as a general approach to structurally chiral cyclopentanes bearing 3-consecutive stereogenic centers with high regio- and enantioselectivities. It was found that a wide range of aromatic α,β-unsaturated aldehydes can effectively participate in the process (Table 3, entries 1–12). The aromatic α,β-unsaturated aldehydes tethering electron-neutral, -with-

Table 2: The optimization of reaction conditions.[a]



Entry	Amine cat.	Solvent	Yield (%)[b]	ee (**3a'**, **3a''**)[c]	dr (**3a'**:**3a''**)[d]
1	I	CH_2Cl_2	48	80, 76	2:1
2	I	toluene	–	–	–
3	I	DCE	< 20	–	–
4	I	ether	< 20	–	–
5	I	CH_3CN	< 20	–	–
6	I	EtOAc	< 20	–	–
7	I	$CHCl_3$	63	99, 83	1.7:1
8	I	THF	–	–	–
9[e]	I	THF	54	90, 90	1:5
10[f]	I	$CHCl_3$	76	99, 83	1.7:1
11[f]	II	$CHCl_3$	76	96, 80	1.7:1
12[f]	III	$CHCl_3$	61	97, 82	1.7:1
13[f,g]	I	$CHCl_3$	83	99, 83	1.7:1

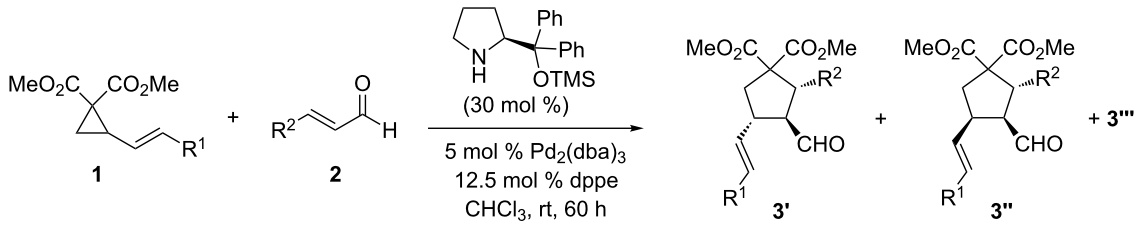
[a]The reaction was carried out with **1a** (36.8 mg, 0.2 mmol) and **2a** (26.4 mg, 0.2 mmol) in the presence of 5 mol % $Pd_2(dba)_3$, 12.5 mol % dppe and 30 mol % organic catalyst in 0.8 mL of solvent at rt for 48 h. [b]Isolated yields. [c]Determined by HPLC analysis. [d]Determined by ^{1}H NMR spectroscopy of the crude mixture. [e]The reaction was run at 50 °C. [f]The reaction was stirred for 60 h. [g]Additional 0.5 equiv **1a** in 0.4 mL of $CHCl_3$ was added into the reaction mixture in 4 portions every 12 h.



Scheme 2: Single X-ray crystal structures of **7h'** and **7h''**.

drawing, and -donating substituents at the *para*-position of the phenyl ring gave good to high yields and excellent enantioselectivities for major isomer **3'** and minor **3'''** products, while the electronic effect on enantioselectivity is more pronounced for minor **3''** (Table 3, entries 1–5). A similar trend is observed with the aromatic α,β-unsaturated aldehydes with electron-withdrawing at *meta*-position (Table 3, entries 6 and 7). Those with electron-withdrawing, and -donating groups at *ortho*-position

Table 3: Scope of the [3 + 2] annulation reaction of D–A cyclopropanes with enals.[a]



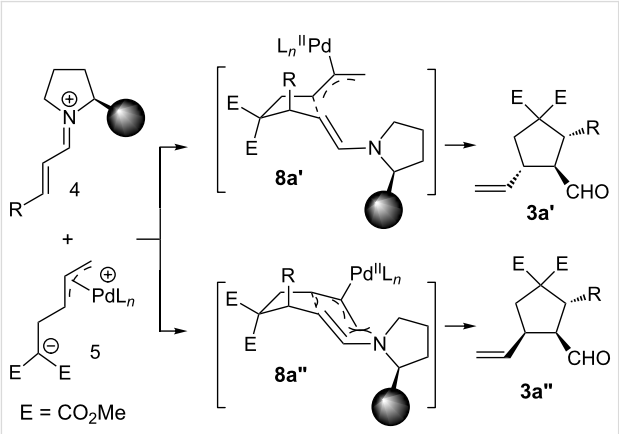
Entry	R^1, R^2, **3**	Yield (%)[b]	ee (**3a'**, **3a''**,**3a'''**)[c]	dr (**3a'**:**3a''**,**3a'''**)[d]
1	H, Ph, **3a**	83	99, 83, 99	1.7:1:0.7
2	H, 4-ClC_6H_4, 3**b**	86	97, 77, 99	2:1:0.4
3	H, 4-BrC_6H_4, **3c**	84	94, 70, 99	2.5:1:0.5
4	H, 4-MeC_6H_4, **3d**	70	99, 85, 99	2:1:0.7
5	H, 4-$MeOC_6H_4$, **3e**	71	99, 99, 86	2:1:0.5
6	H, 3-FC_6H_4, 3**f**	85	97, 99, 76	2.5:1:0.6
7	H, 3-$CF_3C_6H_4$, **3g**	61	90, 66, 99	3.3:1:0.5
8	H, 2-ClC_6H_4, 3**h**	65	98, 88, –	1.7:1:0.6
9	H, 2-BrC_6H_4 **3i**	77	99, 90, –	2.5:1:0.8
10	H, 2-MeC_6H_4, **3j**	72	99, 91, 99	3.3:1:0.4
11	H, 2-$MeOC_6H_4$, **3k**	81	99, 99, 92	2:1:0.8
12	H, 2-furanyl, **3l**	70	99, 97, 72	1.3:1:0.7
13[e]	Ph, 4-ClC_6H_4, **3m**	46	92, 86, 99	1.7:1:0.2

[a]Unless specified, see experimental section for details. [b]Isolated yields. [c]Determined by HPLC analysis. [d]Determined by ^{1}H NMR spectroscopy of crude product. [e]The reaction was run at 50 °C for 120 h.

furnished excellent enantioselectivities for both **3'** and **3''** products in cases studied (Table 3, entries 8–11). Moreover, the heteroaromatic furanyl α,β-unsaturated aldehyde **2l** can also be tolerated with good yield and 97% ee for the major product (Table 3, entry 12). More significantly, the more steric demanding D–A cyclopropane bearing a phenyl ring instead of H can effectively participate in the process to deliver the desired product with achieving an excellent level of enantioselectivity albeit a relatively low yield (Table 3, 46%, entry 13). It is noteworthy that although aliphatic enals also can engage in this [3 + 2] annulation reaction. Unfortunately, we could not separate them on chiral HPLC column for the determination of the enantioselectivity by all means we have attempted (data not shown).

The absolute configuration of cyclopentanes **3'** and **3''** were determined based on the derivatives **7h'** and **7h''** of **3h** (Scheme 2) [95].

We proposed two possible transition states (TS) **8a'** and **8a"** to rationalize the observed configurations (Scheme 3). The *trans*-C=C double bond in iminium ion **4** dictates the R group at pseudo axial position in the cyclic 5-membered ring TS **8a'** and **8a"**. This orientation avoids the A[1,3] strain induced by the catalyst-derived enamine. The Pd(II)-π3 complex moiety at



Scheme 3: The proposed transition states.

pseudo axial and equatorial positions leads to respective TS **8a'** and **8a"**, while **8a'** is more stable due to the minimization of the A[1,3] interaction. Therefore, it is observed **3a'** produced from corresponding **8a'** as the major diastereomer whereas **3a"** as minor one.

Conclusion

We have developed a cooperative catalytic strategy for highly regio- and enantioselective [3 + 2] cycloaddition reactions of

vinylcyclopropanes with α,β-unsaturated aldehydes for the first time. The combination of a chiral iminium catalyst, which activates the C=C bond and blocks the C=O bond in enals, and a Lewis acid promoting to open the vinylcyclopropanes enables the annulation process to proceed with the challenging C=C bond. A high level of enantioselectivity could be achieved here. This previously unattainable [3 + 2] annulation transformation serves as a general approach to the preparation of new densely functionalized chiral cyclopentanes. This synergistic catalysis strategy holds great potentials for further exploration of new cycloaddition reactions involving enals and other D–A systems. The endeavor is being pursued in our laboratories.

Experimental

General procedure for the [3 + 2] annulation

A mixture of **1a** (0.2 mmol, 36.8 mg), **2a** (0.2 mmol, 26.4 mg), $Pd_2(dba)_3$ (0.01 mmol, 9.2 mg), dppe (0.025 mmol, 10 mg) and **I** (0.06 mmol, 18.5 mg) in 0.8 mL $CHCl_3$ was stirred for 60 h at rt. During this period, **1a** (0.1 mmol, 18.4 mg) in 0.4 mL $CHCl_3$ was added into the solution for total 4 times every 12 h, the mixture was purified by column chromatography on silica gel, eluted by petroleum ether/EtOAc = 20:1 to 10:1 to give the desired product **3a** in 83% yield as a colorless oil.

Supporting Information

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-127-S1.pdf]

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95. CCDC-1032267 and -1032268 for compounds **7h**' and **7h**", respectively contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk.

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Selective bromochlorination of a homoallylic alcohol for the total synthesis of (−)-anverene

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Full Research Paper

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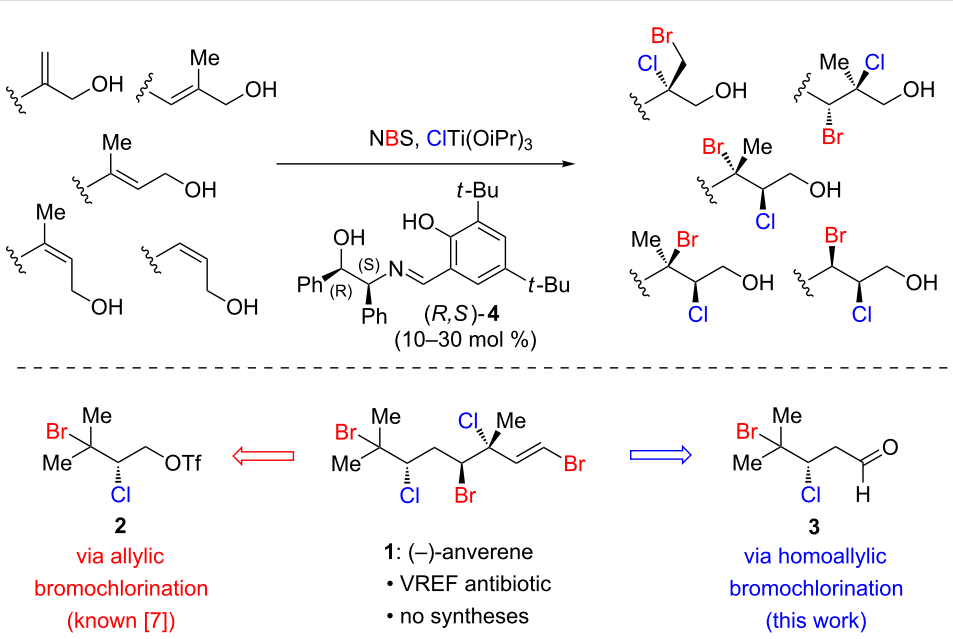
Abstract

The scope of a recently reported method for the catalytic enantioselective bromochlorination of allylic alcohols is expanded to include a specific homoallylic alcohol. Critical factors for optimization of this reaction are highlighted. The utility of the product bromochloride is demonstrated by the first total synthesis of an antibacterial polyhalogenated monoterpene, (−)-anverene.

Introduction

The directed enantioselective functionalization of olefins is an extremely powerful tool in synthesis. A preeminent example is the Sharpless asymmetric epoxidation (SAE), which has been featured in countless syntheses of enantioenriched small molecules [1,2]. While the generality and scope of such catalytic enantioselective methods may be large, limitations often exist. In the case of the SAE, allylic alcohols are viable substrates, but homoallylic alcohols undergo epoxidation at slower rates and with diminished yields and enantioselectivities [3]. This particular limitation has inspired the development of several remote epoxidation methods for homoallylic and bishomoallylic alcohols [4,5], now allowing chemists to directly access a greater variety of enantioenriched epoxides.

Several years ago our laboratory developed the first catalytic enantioselective dibromination of cinnamyl alcohols [6]. Unfortunately, this method suffered from the requirement for electronically biased substrates, and the catalyst system was not applicable to other dihalogenation reactions. In 2015, we disclosed a much-improved catalytic enantioselective bromochlorination protocol that is able to override inherent substrate regioselectivity [7]. This development vastly expanded the substrate scope to include a larger subset of alkyl-substituted allylic alcohols (Scheme 1, top); the relative and absolute stereochemical configurations of all resulting bromochlorides have been assigned and are shown for the (*R*,*S*) Schiff base ligand [7-9]. Furthermore, the reaction conditions could now be modulated to



Scheme 1: Selective bromochlorination and possible disconnections for anverene (**1**).

affect both catalytic enantioselective dichlorination and dibromination of allylic alcohols [9]. The utility of this method has been demonstrated by highly selective total syntheses of several important polyhalogenated natural product targets including (+)-halomon [8] and (−)-danicalipin A [9].

While exploring the scope of this bromochlorination reaction, we discovered that slight modifications allow for the bromochlorination of a homoallylic alcohol with synthetically useful levels of regio- and enantioselectivity. Disclosed herein, this discovery has enabled the first total synthesis of (−)-anverene (**1**) (Scheme 1, bottom), a secondary metabolite from the algae *Plocamium cartilagineum* with selective antibiotic activity against vancomycin-resistant *Enterococcus faecium* (VREF) [10]. (−)-Anverene (**1**) is a member of a large and synthetically challenging family of polyhalogenated acyclic monoterpenes, for which few stereoselective synthetic approaches exist [11].

Results and Discussion

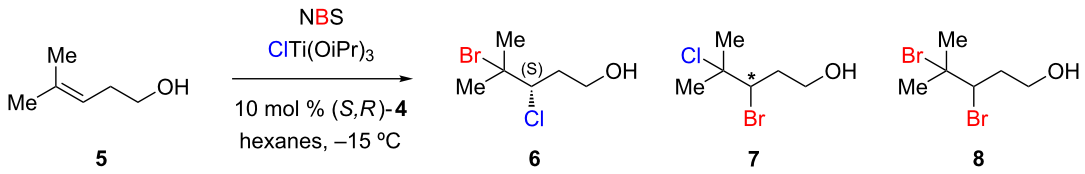
In considering a retrosynthesis of anverene (**1**) we initially identified prenol bromochlorotriflate **2** (Scheme 1, bottom) as a useful synthon, as it is readily accessible from prenol using our original bromochlorination protocol [7]. In a forward sense, this intermediate could be coupled with a vinyl organometallic to introduce the remainder of the carbon skeleton of **1**. While we have achieved moderate success in the copper-catalyzed cross coupling of an analogous dichlorotriflate [9], in our hands **2** failed to engage in productive carbon–carbon bond formation. An alternative retrosynthesis traced **1** back to bromochloroaldehyde **3**, which should readily engage in standard olefination reactions. As **3** could arise from a bromochlorinated homoallylic alcohol, we viewed this as an impetus for developing conditions for the bromochlorination of 4-methyl-3-pentenol (homoprenol, **5**).

Optimization

Under our published conditions for allylic alcohols, homoprenol (**5**) underwent bromochlorination to deliver the target isomer **6** in 46% yield and 84% ee (Table 1, entry 1). Constitutional isomer **7** was also observed (4:1 ratio of **6**:**7**), as well as dibromide **8** and other racemic brominated byproducts (see Supporting Information File 1). The absolute configuration of **6** was assigned through its subsequent conversion into (−)-anverene (**1**, see below), the absolute configuration of which was determined by the isolation chemists on natural material by X-ray crystallography [10]. Interestingly, using the same enantiomer of ligand, the bromochlorides derived from prenol and homoprenol (**5**) have the same absolute configuration. This is in stark contrast to the SAE, for which the facial selectivity of epoxidation for homoallylic alcohols is the opposite of that seen for allylic alcohols [3]. Additional information on the scope of the bromochlorination for other homoallylic alcohols is presented in Supporting Information File 1. In the subsequent optimization, three critical factors came to the fore: concentration, the inclusion of additional $Ti(OiPr)_4$, and stirring rate.

When unoptimized bromochlorination reactions of homoprenol were quenched at low and high conversion, different distribu-

Table 1: Optimization of a selective homoallylic bromochlorination reaction.[a]



entry	additive	concentration	yield **6**/ee **6** (%)	yield **7**/ee **7** (%)	cr (**6**:**7**)	yield **8**, others (%)
1	–	0.1 M	46/84	13/23	4:1	6, 34
2	–	0.025 M	45/82	10/19	5:1	3, 27
3	$Ti(OiPr)_4$[b]	0.1 M	50/89	10/18	5:1	7, 28
4	$Ti(OiPr)_4$[b]	0.025 M	57/89	6/38	10:1	6, 16

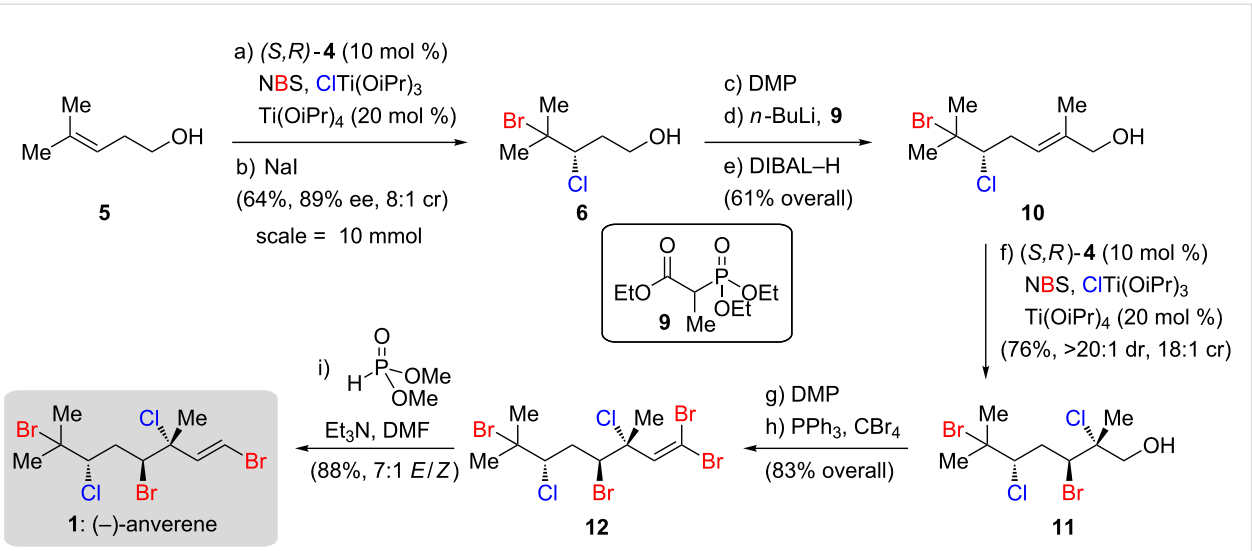
[a]Reactions were conducted on 0.1 mmol scale with 1.2 equiv NBS, 1.1 equiv $ClTi(OiPr)_3$; [b]20 mol %.

tions of side products were obtained. Unlike Table 1, entry 1, which was taken to completion, bromochlorinations quenched at low conversion exhibited high enantioselectivity for **6**, but also constitutional isomer ratios (cr) as low as 2:1 for **6**:**7** (not shown). These observations are consistent with a highly selective catalytic reaction competing with several nonselective background processes. By both lowering the concentration and adding 20 mol % of $Ti(OiPr)_4$ (Table 1, entries 2–4), much of the background reactivity was minimized; adding more than 20 mol % of $Ti(OiPr)_4$ did not result in further improvement. While the structure of the active bromochlorination catalyst is not yet known, we speculate that the procedural changes in entries 2–4 do not alter its structure, but rather change the distribution of titanium species responsible for off-cycle reactivity. Titanium alkoxides are known to undergo facile ligand exchange at −20 °C, and can adopt both monomeric and oligomeric structures, several of which can be catalytically active [12]. When $Cl_2Ti(OiPr)_2$ is used in place of $ClTi(OiPr)_3$, bromochloride **7** forms very quickly with no enantioselectivity and with inherent substrate regioselectivity. The additional $Ti(OiPr)_4$ may limit the trace formation of these highly reactive dichlorotitanium species early in the reaction, thereby preventing background bromochlorination. Lowering the concentration of the reaction may favour lower-order titanium aggregates over oligomeric species [12].

It has been our observation that high stirring rates are critical for obtaining optimal results in these heterogeneous bromochlorination reactions of both allylic and homoallylic alcohols. The origin of this stirring dependence is not definitively known, but we suspect that it facilitates the dissolution of *N*-bromosuccinimide (NBS) into hexanes and/or its incorporation into the active catalyst. The bromochlorination of homoprenol (**5**) proved to be especially sensitive to stirring. This may be due to the slower rate of selective bromochlorination of homoallylic alcohols, leading to closer competition with nonselective background halogenation than the same reaction with allylic alcohols. Consistent results were obtained when bromochlorination reactions were run in round-bottomed flasks, using rod-shaped magnetic stir bars roughly the length of the flask radius, and with stirring at no less than 1500 rpm (see Supporting Information File 1 for images). Under optimized conditions, bromochloroalcohol **6** was produced in 57% yield and 89% enantiomeric excess (ee) with small amounts of undesired bromochloride **7** (6%) and other brominated byproducts (**8** + others, 22% combined) (Table 1, entry 4). The trace dibromide **8** was quantitatively and chemoselectively decomposed, via a reductive de-dihalogenation pathway to the corresponding olefin, by heating the crude material to reflux in acetone with sodium iodide.

Total synthesis of anverene

With scalable access to **6**, a total synthesis of (−)-anverene (**1**) was explored (Scheme 2). Homoprenol (**5**) was subjected to the two-step bromochlorination/de-dibromination protocol on 10 mmol scale, furnishing bromochloride **6** in 64% overall yield and 89% ee as an 8:1 ratio of constitutionally isomeric bromochlorides. Early incorporation of the sensitive vicinal bromochloride moiety in **6** necessitated a strategy that avoided exposure to strong bases or reducing agents, a limitation that significantly guided the choice of reagents and conditions for the subsequent steps. Dess–Martin periodinane oxidation of alcohol **6** followed by Horner–Wadsworth–Emmons olefination with triethyl 2-phosphonopropionate (**9**) furnished the targeted unsaturated ester (not shown). In initial investigations into the formation of this unsaturated ester, Masamune–Roush conditions [13] were attempted but led to sluggish reactivity and concomitant base-mediated elimination of the bromo-



Scheme 2: Selective total synthesis of (−)-anverene. Reagents and conditions: a) NBS (1.2 equiv), $ClTi(OiPr)_3$ (1.1 equiv), 20 mol % $Ti(OiPr)_4$, 10 mol % (*S,R*)-**4**, 0.025 M hexanes, −15 °C, 17 h; b) NaI (2 equiv), acetone, 65 °C, 3 h; c) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, 0 °C to rt; d) triethyl 2-phosphonopropionate **9** (1.5 equiv), *n*-BuLi (1.2 equiv), 1:1 THF/acetonitrile, 0 °C, 5 min; e) DIBAL−H (3 equiv), CH_2Cl_2, −78 °C, 20 min; *f)* NBS (1.2 equiv), $ClTi(OiPr)_3$ (1.1 equiv), 20 mol % $Ti(OiPr)_4$, 10 mol % (*S,R*)-**4**, 0.025 M hexanes, −15 °C, 42 h; g) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, 0 °C to rt; h) CBr_4 (2 equiv), PPh_3 (4 equiv), CH_2Cl_2, 0 °C, 10 min; i) Et_3N (5 equiv), dimethyl phosphonate (4 equiv), DMF, rt, 5 min.

chloride. This decomposition pathway was minimized by the stoichiometric generation of the lithium carbanion of **9** with *n*-BuLi prior to addition of the corresponding aldehyde, and by maintaining very short (<10 minutes) reaction times at 0 °C. This protocol led to complete conversion exclusively to the *E*-unsaturated ester without any observed elimination.

The unsaturated ester was then reduced with DiBAl–H to allylic alcohol **10**, which was isolated as an unchanged 8:1 mixture of regioisomeric bromochlorides, strongly suggesting that no stereochemical or regiochemical isomerization had taken place over the previous three steps from **6**. When **10** was subjected to ligandless bromochlorination with $ClTi(OiPr)_3$ and NBS in hexanes, a surprisingly high dr of 7:1 favouring tetrahalide **11** was observed, indicating significant inherent substrate diastereocontrol for the *anti*-1,3-dihalide over the *syn* alternative. Alternatively, when **10** was subjected to the bromochlorination protocol with 10 mol % (*S,R*)-**4**, the product tetrahalide **11** was isolated in >20:1 dr favouring the same *anti*-1,3-dihalide. Interestingly, we observed considerable enrichment in the regioisomeric bromochloride ratio for the left hand side, which had roughly doubled from 8:1 to 18:1, and the recovered starting material was found to have a regioisomeric bromochloride ratio that was lowered to 1.6:1. Taking into account that the minor bromochloride constitutional isomer (**7**, Table 1) is formed in 20–40% ee, these results are consistent with the catalyst system being capable of selective resolution between two enantiomers (or pseudoenantiomers) of a substrate allylic alcohol.

Tetrahalide **11** was then oxidized to the corresponding aldehyde. Installation of the vinyl bromide was found to be difficult using traditional methods. Takai olefination [14] with $CHBr_3$ and $CrBr_2$ resulted in significant de-dihalogenation, likely due to the presence of reducing agents such as Cr(II) or residual $LiAlH_4$ from the preparation of $CrBr_2$. Fortuitously, an efficient and high-yielding alternative to these routes was found. Following Ramirez dibromomethylenation [15], 1,1-dibromoolefin **12** was isolated and subsequently reduced with dimethyl phosphonate [16,17]. While the mechanism of this Hirao reduction is not fully understood, the reaction was exquisitely mild and proceeded with high chemoselectivity for the geminal dihalide, delivering (−)-anverene (**1**) in high yield as a 7:1 mixture of *E*/*Z* isomers. Following recrystallization, over 100 mg of **1** was isolated as a single diastereomer and constitutional isomer, culminating a 9-step route with an overall yield of 21.8%.

Conclusion

In conclusion, a new protocol for the catalytic enantioselective bromochlorination reaction has been developed which has enabled the highly efficient and selective synthesis of **1** via homoprenol bromochloride **6**. The factors addressed in the optimization of the bromochlorination for homoprenol, namely concentration, the inclusion of additional $Ti(OiPr)_4$, and vigorous stirring, are expected to be generally important to other challenging substrates. Work is ongoing in our laboratory to better understand and predict the matched/mismatched effect seen for

chiral substrates, in particular by studying the kinetic resolution of racemic allylic alcohols. Detailed mechanistic and computational studies are underway to better understand the active catalyst structure and the origins of selectivity.

Supporting Information

Supporting Information File 1

Experimental procedures, full characterization of new compounds, and spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-129-S1.pdf]

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Development of chiral metal amides as highly reactive catalysts for asymmetric [3 + 2] cycloadditions

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Letter

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Abstract

Highly efficient catalytic asymmetric [3 + 2] cycloadditions using a chiral copper amide are reported. Compared with the chiral CuOTf/Et_3N system, the CuHMDS system showed higher reactivity, and the desired reactions proceeded in high yields and high selectivities with catalyst loadings as low as 0.01 mol %.

Findings

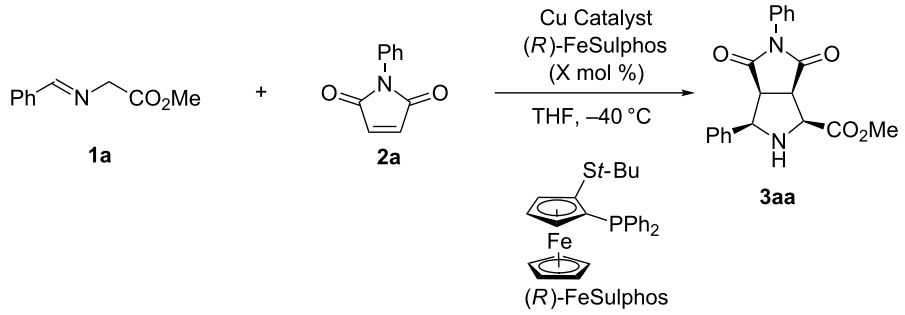
Catalytic asymmetric synthesis is an ideal method to prepare optically active compounds [1]. In this context, catalytic asymmetric carbon–carbon bond-forming reactions that can be used for the efficient construction of fundamental frameworks of complex chiral molecules such as biologically active compounds are particularly important. Chiral Lewis acid/Brønsted base-catalyzed carbon–carbon bond-forming reactions are one of the most efficient methods from the viewpoint of atom economy because only proton transfer occurs between starting materials and target products [2]. Several kinds of chiral Lewis acid/Brønsted base-catalyst systems have been developed; however, decreasing the catalyst loading is sometimes problematic either because of the low reactivity of catalysts or because the catalyst activity can be reduced through Lewis acid–Lewis base interaction between catalysts and the formed products (product inhibition). To overcome such issues, the design and development of more reactive catalysts is required.

Our group has focused on the development of metal amides as highly reactive Lewis acid/base catalysts in carbon–carbon bond-forming reactions [3]. Recently, we have developed asymmetric [3 + 2] cycloadditions [4-8] and asymmetric Mannich-type reactions [9] by using chiral silver or copper amides as catalysts. In these reactions, it has been revealed that the metal amides have higher activity than typical silver or copper acid/base catalysts, and that less reactive substrates react smoothly to

afford the desired products in high yields with high stereoselectivities. Based on these results, it was considered that metal amide catalysts might also achieve high catalyst turnover. Here, we report chiral copper amide-catalyzed asymmetric [3 + 2] cycloadditions of Schiff bases of glycine ester that proceed with low catalyst loadings (ca. 0.01 mol %).

Catalytic asymmetric [3 + 2] cycloadditions of Schiff bases of α-amino esters to olefins are useful for synthesizing optically active pyrrolidine derivatives [10-12], and many highly stereoselective reactions have been reported; for example, Co [13], Cu [14-23], Ag [24-32], Zn [33,34], Ni [35,36], and Ca [37-39] catalyst systems, and organocatalysts [40-45] have been successfully employed. In most cases, however, relatively high catalyst loadings (0.5–25 mol %) are required to achieve high yield and selectivities [15,45]. First, we investigated the catalytic asymmetric [3 + 2] cycloaddition of Schiff base **1a**, prepared from glycine methyl ester and benzaldehyde, with *N*-phenylmaleimide (**2a**) in the presence of $CuN(SiMe_3)_2$ (CuHMDS) and the FeSulphos ligand, with the latter being related to the system reported by Carretero et al. [15]. The reaction produced **3aa** smoothly with 3 mol % catalyst loading at −40 °C, and high *endo* selectivity and high enantioselectivity were obtained (Table 1, entry 1). On the other hand, application of CuOTf, FeSulphos, and Et_3N gave only 47% yield of the product (Table 1, entry 2). This result indicated that the CuHMDS catalyst had higher catalyst activity than CuOTf with the additional amine base. The copper amide catalyst also showed high reactivity and selectivity with 1 mol % catalyst loading (Table 1, entry 3), and similar results were obtained in other solvents such as Et_2O and toluene, although the reactivity and enantioselectivity both decreased slightly in dichloromethane (DCM, Table 1, entries 4–6). It was found that the use of the chiral CuHMDS catalyst also afforded the product with high enantioselectivity at lower catalyst loadings of 0.1 mol % (Table 1, entry 7). The effect of the amide part of the structure was then examined. Copper dialkylamides were not as reactive as CuHMDS, and lower yields were obtained (Table 1, entries 8 and 9). Interestingly, mesitylcopper also worked in a similar fashion, and good yields and high selectivities were obtained (Table 1, entry 10). This result indicated that the reaction proceeded through a product base mechanism [46-48]; however, the reactivity was lower than that of the CuHMDS system. Decreasing the catalyst loading further revealed that the reaction

Table 1: Chiral copper amide-catalyzed asymmetric [3 + 2] cycloadditions[a].



Entry	Cu catalyst	Solvent	X	Time (h)	Yield (%)	*endo*/*exo*	ee (%, *endo*)
1	CuHMDS	THF	3	6	99	>99:1	99
2[b]	CuOTf + Et_3N	THF	3	6	47	98:2	99
3[c]	CuHMDS	THF	1	6	98	>99:1	>99
4[c]	CuHMDS	Et_2O	1	6	91	99:1	98
5[c]	CuHMDS	toluene	1	6	95	99:1	99
6[c]	CuHMDS	DCM	1	6	67	99:1	93
7[d]	CuHMDS	THF	0.1	18	94	>99:1	96
8[d]	$CuNMe_2$[e]	THF	0.1	18	53	>99:1	94
9[d]	CuTMP[e]	THF	0.1	18	46	>99:1	98
10[d]	Cu(mesityl)	THF	0.1	18	86	>99:1	97
11[f]	CuHMDS	THF	0.01	48	94	>99:1	95

[a]The [3 + 2] cycloaddition reaction of 0.5 M **1a** (0.30 mmol) with **2a** (1.1 equivalents, 0.33 mmol) were conducted at −40 °C in the presence of the copper amide prepared from CuOTf·0.5toluene complex/KHMDS/FeSulphos (1.1:1.0:1.1) in situ unless otherwise noted. [b]CuOTf·0.5toluene complex (0.0090 mmol) and Et_3N (0.0090 mmol) were used. [c]The reaction was conducted with **1a** (1.0 mmol). [d]The reaction was conducted with **1a** (10 mmol). [e]The copper amides were prepared in situ by mixing CuOTf·0.5toluene complex, FeSulphos and $LiNMe_2$ or lithium 2,2,6,6,-tetramethylpiperidide (LiTMP). [f]The reaction was conducted with 1.25 M **1a** (50 mmol).

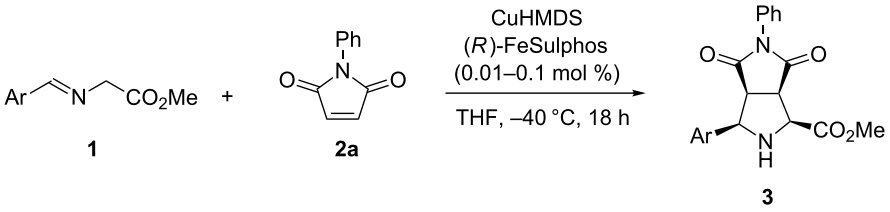
proceeded with 0.01 mol % loading of chiral CuHMDS catalyst without significant loss of selectivity (Table 1, entry 11).

We then examined the substrate scope of the [3 + 2] cycloaddition with respect to the Schiff base (Table 2). The Schiff bases prepared from tolualdehydes were successfully employed in the reaction with **2a**, and high reactivities and enantioselectivities were observed by using 0.1 mol % catalyst loading (Table 2, entries 1–4). The Schiff base from *p*-methoxybenzaldehyde was a good substrate (Table 2, entry 5) and reacted even in the presence of 0.01 mol % catalyst loading, albeit with a slight decrease in the enantioselectivity (Table 2, entry 6). The use of Schiff bases bearing either electron-donating or electron-withdrawing substituents were also suitable, and high yields and enantioselectivities were obtained with both 0.1 and 0.01 mol % catalyst loading (Table 2, entries 5–9). Sterically hindered substrates were also viable, and high enantioselectivities were obtained with 0.01 mol % catalyst loading (Table 2, entries 10–13).

Other electrophiles were also successfully employed with 0.1 mol % catalyst loading (Scheme 1). *N*-Methylmaleimide reacted with **1a** in high yield with high diastereo- and enantioselectivities. The reaction with methyl acrylate also proceeded in high yield with high enantioselectivity; however, in this case the *exo*/*endo* selectivity was moderate. Methyl vinyl ketone and methyl methacrylate reacted with **1a** to afford the desired [3 + 2] adducts in high yields with high selectivities. Notably, the chiral CuHMDS catalyst worked well with catalyst loadings of both 0.1 and 0.01 mol %.

A proposed catalytic cycle is shown in Figure 1. Thus, the chiral CuHMDS deprotonates Schiff base **1a** to generate the corresponding chiral Cu enolate **B** through the efficient formation of pseudo-intramolecular transition state **A**. Intermediate **B** reacted with maleimide **2a** to form Cu-pyrrolidine intermediate **C**. H-HMDS then reacted with the latter to regenerate the chiral CuHMDS and release the product to complete the catalytic cycle. The result obtained by using a mesitylcopper catalyst suggests that the reaction could also proceed through a product base mechanism in which the Cu-pyrrolidine intermediate **C** deprotonates the Schiff base **1a** directly; however, the higher reactivity observed upon catalysis by CuHMDS and the basicity of the intermediate indicates that the proposed cycle is reasonable when CuHMDS is used as catalyst. The high catalyst turnover may be due to the stronger Brønsted basicity of

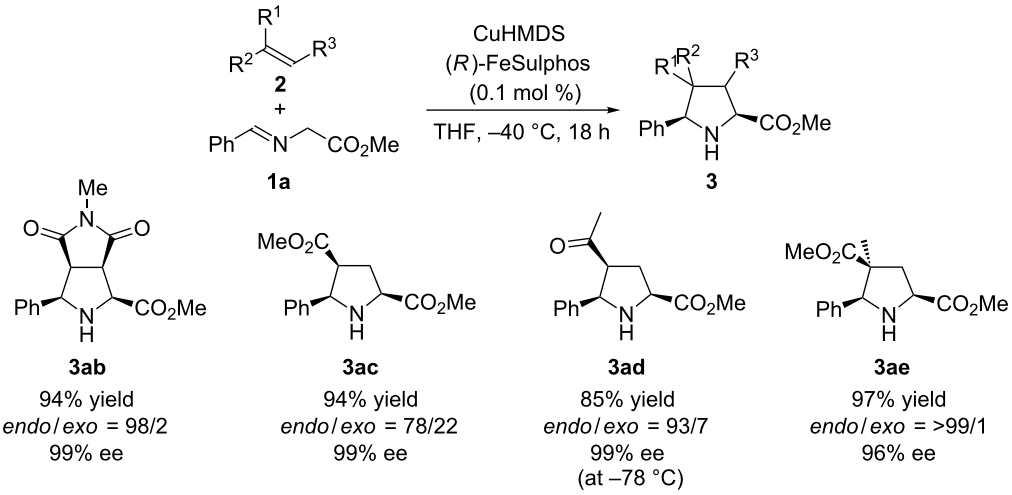
Table 2: Scope of the reaction with respect to Schiff bases[a].



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

Entry	Ar	1	FeSulphos (mol %)	3	Yield (%)	*Endo*/*exo*	ee (%, *endo*)
1	*p*-MeC_6H_4	**1b**	0.1	**3ba**	92	>99:1	>99
2	*p*-MeC_6H_4	**1b**	0.01	**3ba**	91	>99:1	85
3	*m*-MeC_6H_4	**1c**	0.1	**3ca**	93	>99:1	>99
4	*o*-MeC_6H_4	**1d**	0.1	**3da**	92	97:3	>99
5	*p*-$MeOC_6H_4$	**1e**	0.1	**3ea**	91	97:3	99
6	*p*-$MeOC_6H_4$	**1e**	0.01	**3ea**	91	>99:1	93
7	*p*-ClC_6H_4	**1f**	0.1	**3fa**	96	98:2	92
8	*p*-FC_6H_4	**1g**	0.1	**3ga**	96	>99:1	99
9	*p*-FC_6H_4	**1g**	0.01	**3ga**	96	>99:1	98
10	2-naphthyl	**1h**	0.1	**3ha**	94	>99:1	99
11	2-naphthyl	**1h**	0.01	**3ha**	87	>99:1	97
12	1-naphthyl	**1i**	0.1	**3ia**	76	>99:1	99
13	1-naphthyl	**1i**	0.01	**3ia**	91	>99:1	98

[a]Reaction conditions: For 0.1 mol % catalyst loading: the [3 + 2] cycloaddition reactions of 0.5 M **1** (10 mmol) with **2a** (11 mmol) were conducted at −40 °C for 18 h by using the chiral copper amide prepared from CuOTf·0.5toluene complex (0.011 mmol), KHMDS (0.010 mmol), and FeSulphos (0.011 mmol) in situ. For 0.01 mol % catalyst loading: the [3 + 2] cycloaddition reactions of 1.25 M **1** (50 mmol) with **2a** (55 mmol) were conducted at −40 °C for 48 h by using the chiral copper amide prepared from CuOTf·0.5toluene complex (0.0055 mmol), KHMDS (0.0050 mmol), and FeSulphos (0.0055 mmol) in situ.



Scheme 1: Scope of the reaction with other electrophiles. The [3 + 2] cycloaddition reaction of 0.5 M **1a** (10 mmol) with **2** (11 mmol) was conducted at −40 °C for 18 h by using the chiral copper amide prepared from CuOTf·0.5toluene complex (0.011 mmol), KHMDS (0.010 mmol), and FeSulphos (0.011 mmol) in situ.

CuHMDS, which enables rapid deprotonation of the Schiff base.

Conclusion

In conclusion, highly efficient asymmetric [3 + 2] cycloadditions catalyzed by chiral CuHMDS have been described. Compared with catalysis by using the CuOTf/Et_3N system, the Cu amide system showed higher reactivity, and the reactions proceeded with high enantioselectivities even with 0.01 mol % catalyst loading. Further investigations that are focused on the application of metal amide catalysts in other reactions are ongoing.

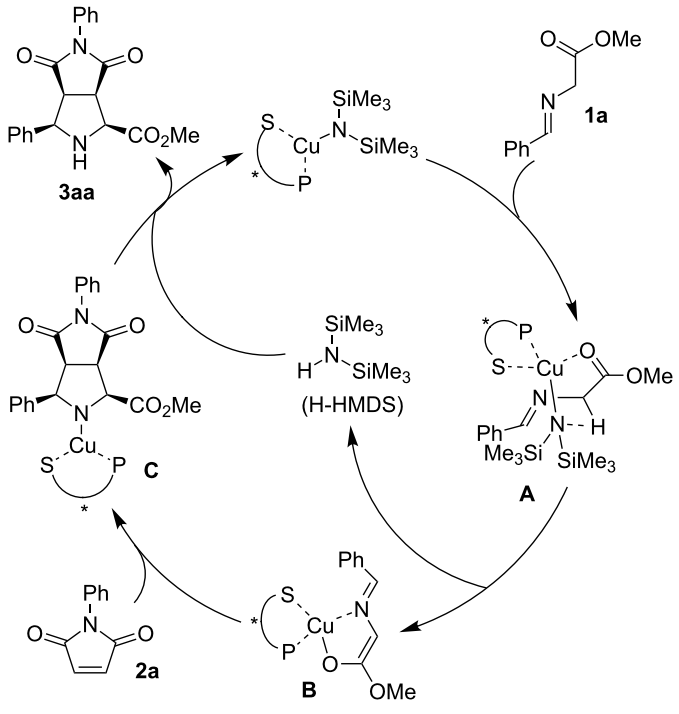


Figure 1: Proposed catalytic cycle.

Experimental

A general experimental procedure for conducting catalytic asymmetric [3 + 2] cycloaddition reactions with 0.01 mol % catalyst loading is described. Under an Ar atmosphere, a solution of the preformed chiral CuHMDS catalyst [prepared from KHMDS (1.0 mg, 0.0050 mmol), CuOTf·0.5toluene (1.3 mg, 0.0055 mmol) and FeSulphos (2.3 mg, 0.0050 mmol) in anhydrous THF (5 mL) with heating at 40 °C for 1 h] was transferred into a well-dried 50 mL single-necked flask attached to a three-way cock (sealed with grease). The solution was cooled at −40 °C, and a mixture of **1** (50 mmol) and **2a** (55 mmol) in anhydrous THF (35 mL) was added by using a cannula. The whole was stirred for 48 h at −40 °C, then the reaction was quenched by the addition of H_2O, and the mixture was extracted with dichloromethane. The organic layers were combined and dried over anhydrous Na_2SO_4. The selectivities were determined by ^{1}H NMR analysis and HPLC analysis after purification of a small amount of the separated crude solution. After filtration and concentration under reduced pressure, the crude product obtained was purified by recrystallization and column chromatography to determine the isolated yield of the desired product. Obtained compounds were characterized by ^{1}H and ^{13}C NMR and by HPLC analyses using HPLC with chiral columns. The physical data for the products were consistent with reported values [49-54].

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See for product **3ca**.

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Enantioconvergent catalysis

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Review

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Abstract

An enantioconvergent catalytic process has the potential to convert a racemic starting material to a single highly enantioenriched product with a maximum yield of 100%. Three mechanistically distinct approaches to effecting enantioconvergent catalysis are identified, and recent examples of each are highlighted. These processes are compared to related, non-enantioconvergent methods.

Review

Enantioconvergent synthetic sequences are powerful methods which convert a racemic starting material to a highly enantioenriched product in up to 100% yield (Figure 1a) [1]. These routes circumvent the inefficiency inherent to many traditional enantioselective reactions with racemic materials (e.g., kinetic and classical resolution), which generally have a maximum chemical yield of 50%. Enantioconvergent synthesis requires partitioning the synthetic pathway into two distinct sequences, and then merging the materials to the same product and is therefore a compromise in terms of step economy [2]. Despite the additional synthetic operations required, enantioconvergent synthesis has seen broad applications in the construction of complex molecules [3-5].

A more efficient strategy is to employ a single catalytic asymmetric transformation capable of converting a racemate directly

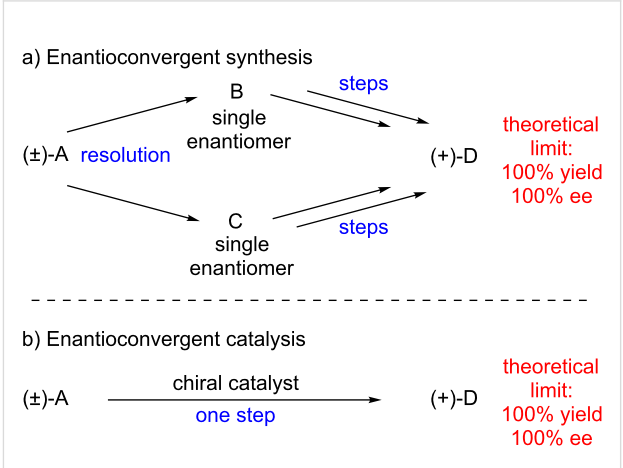


Figure 1: Enantioconvergent methods.

to a highly enantioenriched product in high chemical yield (Figure 1b). Noyori has stated that this complex transformation is an "ideal asymmetric catalysis" [6]. There are several potential challenges in designing such a reaction, including kinetic resolution of the starting material and double stereodifferentiation [7] of intermediates. Despite these potential pitfalls, significant advances toward this goal have been realized. Examples of several of these successes are identified in this review.

Enantioconvergent catalytic processes can be classified according to differences in their mechanistic pathways and the hypothesized reactive intermediates. Three important types of enantioconvergent catalysis are specifically discussed herein: type I – stereomutative, type II – stereoablative [8], and type III – parallel kinetic resolution [9]. The primary criteria for all enantioconvergent catalytic reactions are:

1. The starting material must be racemic.
2. A catalyst must be involved in the reaction process and induce the asymmetry in the product.
3. The product must be isolated in enantioenriched form.
4. Each antipode of the racemic starting material must lead to the same major enantiomer of product.

Type I: Stereomutative enantioconvergent catalysis

Type I (stereomutative) enantioconvergent catalysis typically involves two distinct catalytic cycles: the first performs a rapid equilibration between the two enantiomers of the racemic starting material – a process known as stereomutation – while the second cycle selectively converts one enantiomer to product (Figure 2). Additionally, the rate of starting material racemization must be significantly faster than the rate of kinetic resolution in order to achieve maximum yield and selectivity.

Perhaps the most well-developed class of type I enantioconvergent catalysis is dynamic kinetic resolution (DKR) [10-16]. Processes of this type were first described by Noyori in the enantioselective hydrogenation of β-ketoesters ((±)-**1** → **2**, Scheme 1) [6]. In the event, the resident stereocenter of the substrate **1** can

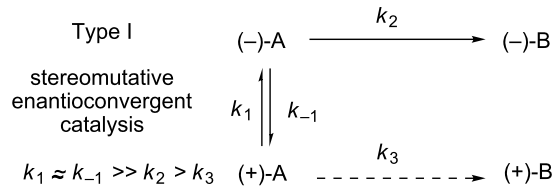
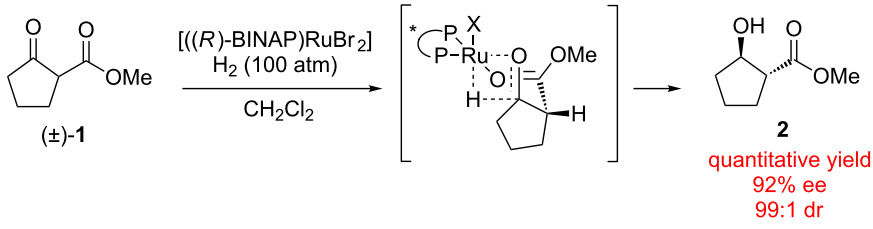


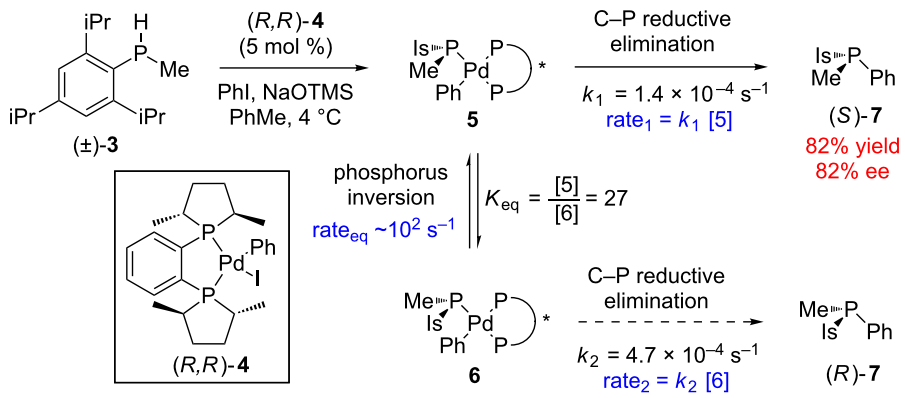
Figure 2: Stereomutative enantioconvergent catalysis.

epimerize via tautomerization to the enol form. Deuterium labeling experiments have shown that the hydrogenation reaction occurs only on the chiral keto tautomer, and therefore the catalyst selects one enantiomer of the substrate when the reduction takes place.

Enantioconvergent methods are not limited to carbon stereocenters. An exceptional example of type I enantioconvergent catalysis was reported by Glueck for the preparation of enantioenriched *P*-chiral phosphines (Scheme 2) [17]. In this process, enantiopure Pd complex (*R*,*R*)-**4** reacts with racemic phosphine **3** to form phosphido complexes **5** and **6**. Although the rate of configurational inversion of these two complexes was not observed directly for this system, extrapolation from related systems gives a rate more than 10^5 times greater than the observable rates of C–P reductive elimination. Since the rate of inversion is much greater than the rate of bond formation, Curtin–Hammett/Winstein–Holness kinetics [18] were employed to elucidate to the overall process. Interestingly, although the observed rate constants (k_1 and k_2) indicate that bond formation occurs more rapidly from complex **6** (leading to (*R*)-**7**), the equilibrium strongly favors the diastereomeric intermediate **5**, and the corresponding difference in concentration leads to a greater observed rate for the formation of (*S*)-**7** (i.e., $rate_1 > rate_2$). Notably, if this stereomutation pathway were absent (the case of simple kinetic resolution) then the relative rate difference between the two complexes would fall outside the typical range considered synthetically useful for synthesis. This example specifically highlights the importance of relative reaction rates in stereomutative enantioconvergent catalysis.



Scheme 1: Dynamic kinetic resolution by hydrogenation.



Scheme 2: Enantioconvergent synthesis of phosphines governed by Curtin–Hammett/Winstein–Holness kinetics (TMS = trimethylsilyl, Is = 2,4,6-triisopropylphenyl).

Type II: Stereoablative enantioconvergent catalysis

Type II (stereoablative [8]) enantioconvergent catalysis (Figure 3) is composed of processes in which a racemic starting material is irreversibly transformed into an achiral intermediate that subsequently undergoes an enantioselective conversion to the product. Reports of this type are predominantly in the areas of prochiral enolates and prochiral metal π-allyl complexes [19-21]. Critical to the success of such a method is a comparable rate of reaction for the two components of the racemate with respect to the stereoablative mechanistic step (i.e., $k_1 \approx k_2$, Figure 3). If this condition is not met, significant kinetic resolution will occur, causing product yield to suffer. Additionally, there must be a significant difference in the rates of product formation (i.e. $k_3 > k_4$). If this condition is not met, enantioselectivity will suffer.

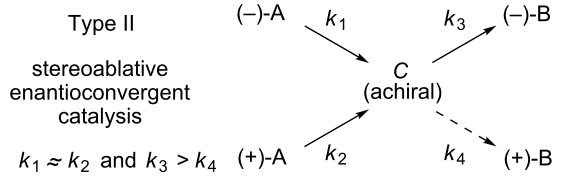
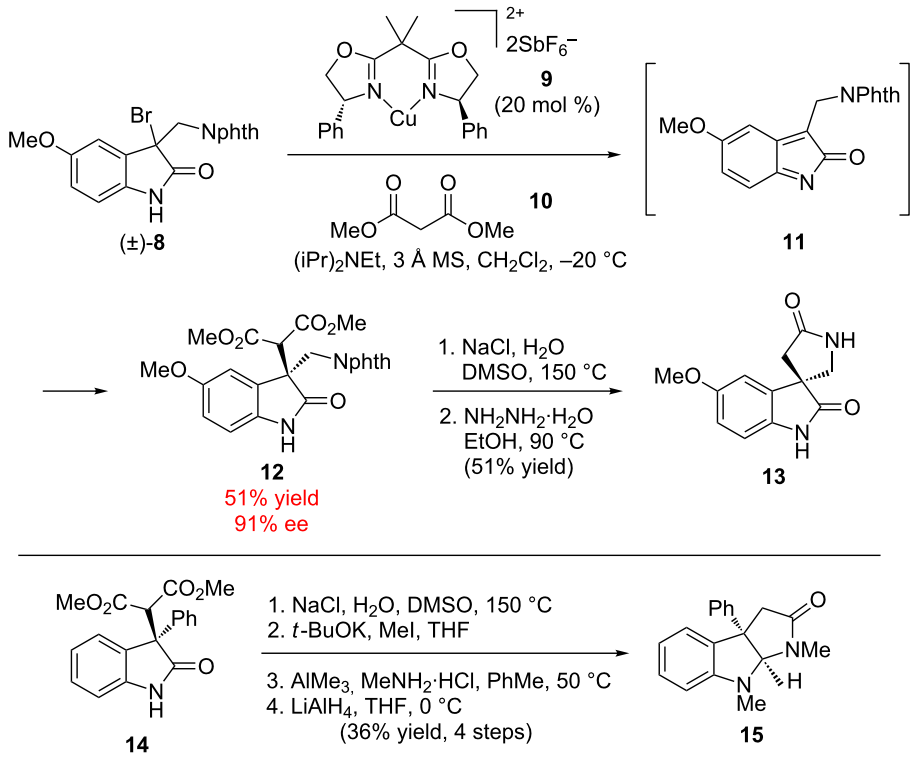


Figure 3: Stereoablative enantioconvergent catalysis.

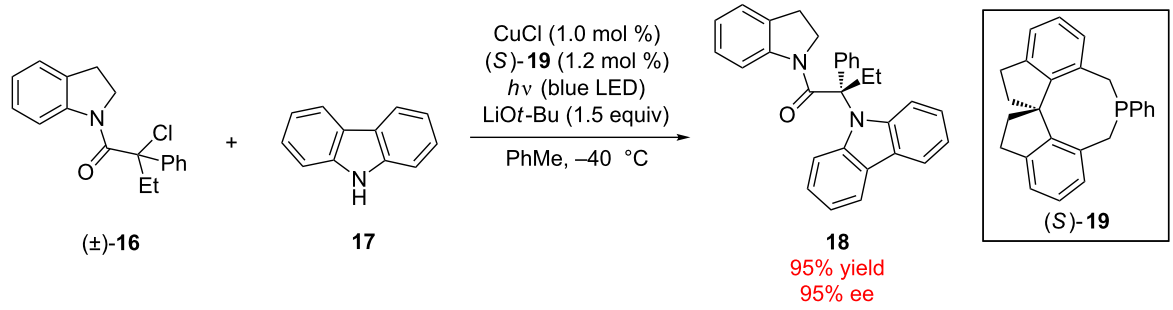
Stoltz and co-workers have reported an approach for the preparation of enantioenriched oxindole derivatives from racemic oxindole halides using a stereoablative approach (Scheme 3) [22,23]. Deprotonation and elimination of the halide in oxindole (±)-**8** leads to achiral azaxylylene intermediate **11**, which is trapped with malonate nucleophiles to form all-carbon quaternary centers. The overall transformation is unusual since oxindoles are typically nucleophilic, but in this case the stereoablative step in the mechanism leads to an electrophilic intermediate. The use of Cu(box) complex **9** rendered the reaction enantioselective, forming C-3 quaternary oxindole **12** in 91% ee (up to 94% ee for related substrates). This strategy is useful for constructing spiro- and fused-pyrrolidinoxindole architectures, such as lactam **13** and aminal **15**, found in several natural product families. Related approaches with organic catalysts were explored in 2012 by Yuan and co-workers [24,25] and in 2014 with tertiary amine squaramide catalysis by Lou and co-workers [26].

The generation of radical intermediates from chiral sp^3-hybridized halides presents another opportunity for type II enantioconvergent catalysis. Peters and Fu have reported a system for the Cu-catalyzed C–N cross-coupling of racemic tertiary alkyl halide electrophiles with carbazole nucleophiles induced by visible light (Scheme 4) [27]. Although the mechanism continues to be studied, it is hypothesized that irradiation of the copper–carbazole complex leads to an excited-state adduct that is capable of generating achiral tertiary alkyl radical intermediates through electron transfer with a racemic alkyl halide (e.g., (±)-**16**). Subsequently, the achiral radical combines with the chiral Cu catalyst and undergoes an enantioselective bond-formation step in conjunction with the carbazole nucleophile to form α-aminoamide **18**. This report fuses both enantioconvergent and photoredox catalysis, two powerful and modern methods. A similar strategy was employed by Fu and MacMillan in 2016 [28].

Type II enantioconvergent catalysis is especially powerful when a single reagent effects both the stereoablative (typically bond-breaking) and stereoselective (bond-forming) steps of the process. An example of such a reaction was reported by Stoltz for the generation of enantioenriched all-carbon quaternary stereocenters from racemic allyl β-ketoesters (e.g., (±)-**20** → (+)-**23**, Scheme 5) [29]. This particular reaction is especially



Scheme 3: Stoltz' stereoablative oxindole functionalization.

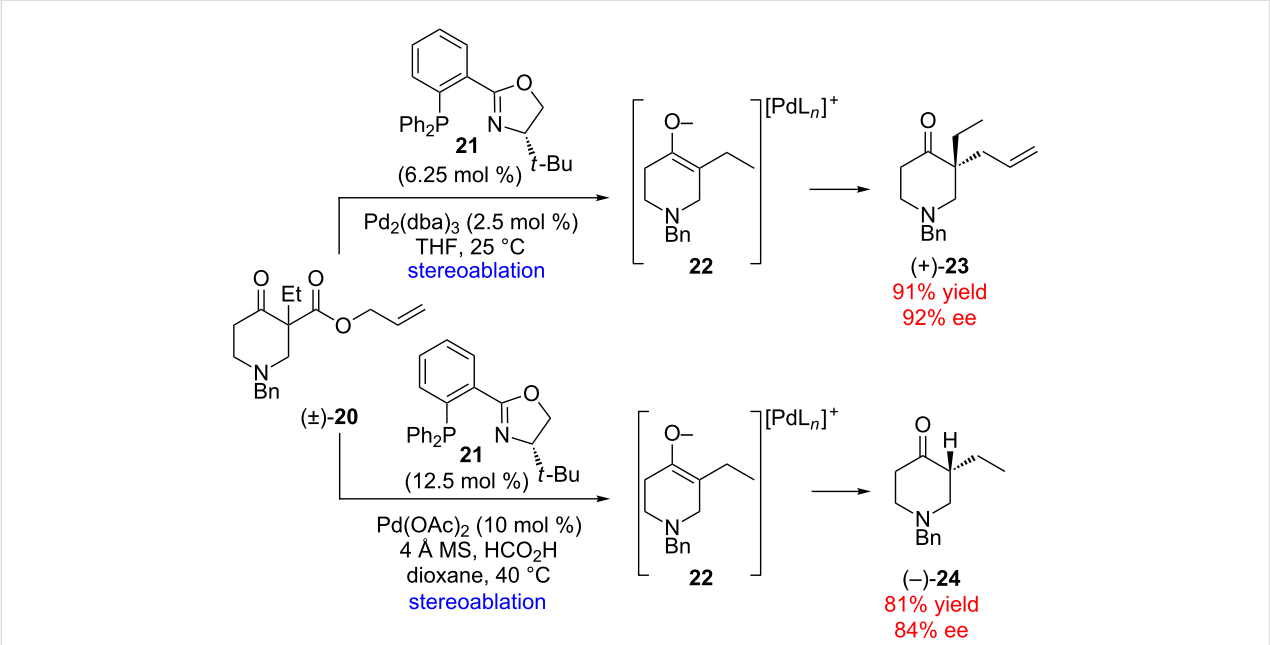


Scheme 4: Fu's type II enantioconvergent Cu-catalyzed photoredox reaction.

unusual since the stereoablative step requires scission of a C–C bond at a quaternary carbon stereocenter to form achiral enolate intermediate **22**. Since no kinetic resolution of the racemic starting material was observed, yields in excess of 90% with up to 92% ee could be obtained.

In further studies, it was found that the putative enolate intermediate could also be trapped by a proton source to yield α-tertiary cycloalkanones in high ee (e.g., (±)-**20** → (–)-**24**) [30]. Interestingly, in the reactions of certain substrates the enolate face functionalized by the electrophilic allyl group is opposite to the face functionalized by the proton (Scheme 5). This observation indicates that the two enantioconvergent reactions, though related, must proceed through substantially different mechanisms of enantioinduction. The differential reactivity demonstrated by the enolate intermediate **22** highlights the power of accessing different mechanistic pathways via stereoablative initiation.

Examples with multiple racemic starting materials are rare since each additional racemic substrate exponentially increases the number of stereochemical combinations. However, Kalek and Fu have demonstrated that racemic allenoates (±)-**26** and racemic azalactones (±)-**25** may be combined in the presence of

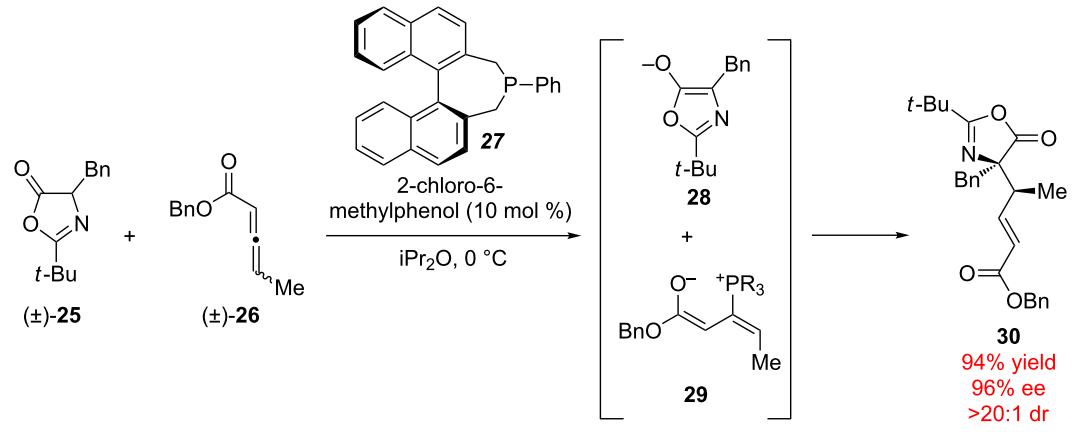


Scheme 5: Stereoablative enantioconvergent allylation and protonation (dba = dibenzylideneacetone).

an enantiopure phosphine catalyst **27** in order to generate the coupled product **30** with both high ee and dr (Scheme 6) [31]. Presumably, the allenyl stereochemistry is destroyed upon 1,4-addition of the phosphine catalyst, resulting in chiral phosphonium adduct **29** that further reacts with deprotonated oxazole **28**. The resulting intermediate undergoes proton transfer and elimination of the phosphonium moiety, resulting in product **30** and regeneration of the catalyst. This exceptional demonstration of stereocontrol requires that the catalysts precisely organize both the electrophilic and nucleophilic reactants to control the formation of asymmetric carbons on each fragment. The doubly stereoconvergent nature of this reaction represents one of the most complex examples of stereoablative enantioconvergent catalysis to date.

Type III: Enantioconvergent parallel kinetic resolution

A third approach to enantioconvergent catalysis is depicted in Figure 4. Similar to type I, reactions of this type involve a kinetic resolution of the racemic starting material. However, in this case the two enantiomers undergo separate modes of reactivity, each leading to an identical product. Reactions of this type are variants of the powerful parallel kinetic resolution (PKR) strategy [32,33], owing to the two parallel processes



Scheme 6: Enantioconvergent allylic alkylation with two racemic starting materials.

occurring simultaneously. Although PKR reactions significantly increase the observed product ee relative to a simple kinetic resolution system, the theoretical maximum yield for a traditional PKR is still limited to 50%. In contrast, an enantioconvergent PKR process allows formation of enantiopure materials in up to 100% yield.

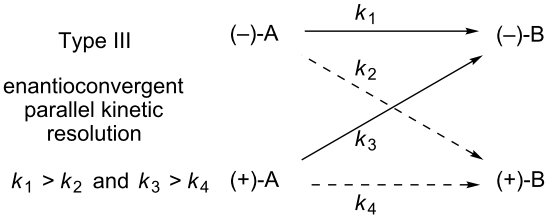
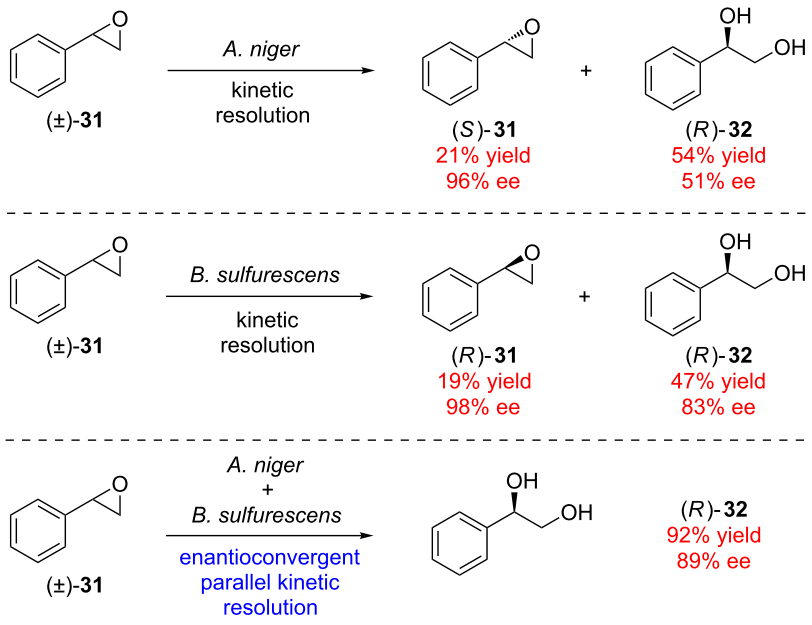


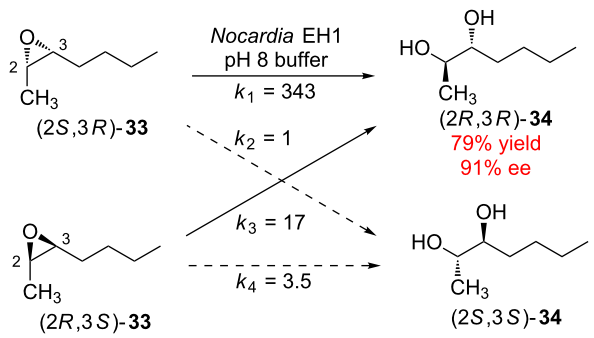
Figure 4: Enantioconvergent parallel kinetic resolution.

Although examples of enantioconvergent PKR are rare, some biocatalysts have succeeded in effecting this unusual transformation [34]. Furstoss found that two microorganisms (*Aspergillus niger* and *Beauveria sulfurescens*) were capable of resolving racemic styrene oxide (**31**, Scheme 7) by hydrolytic kinetic resolution [35]. It was recognized that these two biocatalysts exhibited opposite enantiomer preference in the kinetic resolution event. Moreover, the major hydrolysis byproduct **32** of each of these kinetic resolutions had the same absolute configuration. Combining these two complementary catalysts leads to a highly efficient parallel process wherein each catalyst enantioselectively hydrolyzes one enantiomer of the epoxide, ultimately forming diol (*R*)-**32** in 92% yield with 89% ee [36].

An especially remarkable example of type III enantioconvergent catalysis utilizes a single enzymatic catalyst. Faber observed that *Nocardia* EH1 is capable of catalyzing the hydrolysis of racemic epoxide **33** to the corresponding diol (2*R*,3*R*)-**34** in 79% chemical yield with 91% ee (Scheme 8) [37]. The observed product arises from hydrolysis of each enantiomer of epoxide at the *S*-configured carbon atom. Isotopic labeling studies with $^{18}OH_2$ not only confirmed this mechanistic hypothesis, but also facilitated kinetic studies to determine relative rate constants for each of the four reaction pathways (k_1–k_4, Scheme 8). It was found that (2*S*,3*R*)-**33** hydrolyzes rapidly (k_1 = 343) with preference for addition at C(2), forming (2*R*,3*R*)-**34**. Hydrolysis of the enantiomeric epoxide occurs selectively at C(3) (k_3 = 17), which also leads to (2*R*,3*R*)-**34**. Interestingly, kinetic resolution of the starting material occurs with modest selectivity relative to many enzymatic processes ($k_{rel} = (k_1 + k_2)/(k_3 + k_4) = 17$). In fact, for optimal performance in PKR, it is desirable to obtain a similar rate of reaction for the two enantiomers of the starting material in order to maintain the ideal 1:1 substrate ratio and maximize the selectivity [29]. While the typical kinetic resolution suffers from a decline in product ee at >50% conversion, the enantioconvergent nature of this process maintains high enantiopurity even at very high conversion. To date, purely chemical methods of catalysis that rival these interesting type III transformations are limited and represent a challenge to the field.



Scheme 7: Enantioconvergent parallel kinetic resolution by two complementary biocatalysts.



Scheme 8: Enantioconvergent PKR by *Nocardia* EH1.

Conclusion

Enantioconvergent catalysis is a powerful method for the efficient construction of enantiopure materials for a variety of synthetic uses. Although these transformations are often complicated by unfavorable double stereodifferentiation, the recent appearance of several mechanistically unique methods to address this problem is indicative of a bright future for this chemistry. As demonstrated by the examples in this review, precise understanding of the kinetic factors at play in a reaction is critical to its success. Continuing development in this field may lead to the "ideal asymmetric catalysis" [3].

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Chiral ammonium betaine-catalyzed asymmetric Mannich-type reaction of oxindoles

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Letter

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Abstract

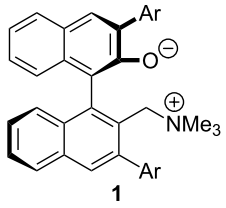
A highly diastereo- and enantioselective Mannich-type reaction of 3-aryloxindoles with *N*-Boc aldimines was achieved under the catalysis of axially chiral ammonium betaines. This catalytic method provides a new tool for the construction of consecutive quaternary and tertiary stereogenic carbon centers on biologically intriguing molecular frameworks with high fidelity.

Introduction

Chiral indole alkaloids possessing C-3 quaternary indoline frameworks are an important class of biologically relevant molecules, and numerous efforts have been made for the development of reliable synthetic methodologies to enable the installation of the C-3 stereogenic center [1-4]. Among them, the direct stereoselective functionalization of 3-monosubstituted oxindoles is a straightforward method for accessing a wide array of chiral indoline skeletons [5-8]. The most common strategy in this approach is to utilize an oxindole enolate as a nucleophile, because facile deprotonation from the C-3 carbon is ensured by the inductive effect of the α-carbonyl group and by the enolate stability arising from the aromatic character. Accordingly, a number of catalytic methods are available for the asymmetric functionalization of oxindole enolates with various different electrophiles. However, successful examples of Mannich-type reactions with imines are surprisingly limited despite allowing efficient construction of vicinal quaternary and tertiary stereocenters [9-22]. In particular, the application of 3-aryl substituted oxindoles seems problematic; hence, the full potential of this useful carbon–carbon bond formation is yet to be realized [12,14].

Ammonium betaines are defined as intramolecular ion-pairing quaternary ammonium salts. In 2008, we employed this struc-

turally distinct molecular scaffold for designing a novel bifunctional organic base catalyst [23], namely axially chiral ammonium betaines of type **1** (Figure 1) [24,25], and uncovered their extraordinary catalytic performance [26-35]. The salient feature of **1** is that, upon abstracting a proton from a pro-nucleophile, the resulting conjugate acid, **1**·H, has the ability to recognize the nucleophilic anion through cooperative electrostatic (ionic) and hydrogen-bonding interactions, thereby precisely controlling the stereochemical outcome of the subsequent bond-forming event. Taking advantage of this unique property, we have developed a series of highly stereoselective transformations, and disclose herein the effectiveness of **1** in solving a challenging problem regarding the rigorous control of the relative and absolute stereochemistry in the asymmetric Mannich-type reaction of 3-aryloxindoles.



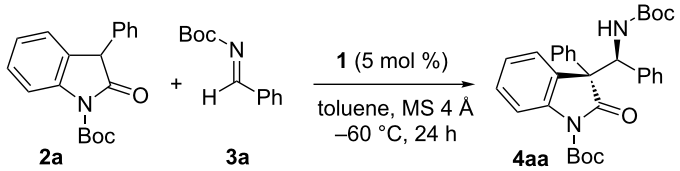
1a: Ar = Ph
1b: Ar = 4-$CF_3C_6H_4$
1c: Ar = 4-*t*-BuC_6H_4
1d: Ar = 3,5-$(CF_3)_2C_6H_3$
1e: Ar = 3,5-*t*-$Bu_2C_6H_3$
1f: Ar = 2,4,6-$Me_3C_6H_2$

Figure 1: Chiral ammonium betaines.

Results and Discussion

As an initial attempt, the reaction of *N*-Boc 3-phenyloxindole (**2a**) with benzaldehyde-derived *N*-Boc imine **3a** [36] was conducted in the presence of a catalytic amount of chiral ammonium betaine **1a** (5 mol %) in toluene with 4 Å molecular sieves (MS 4 Å) at −60 °C. Bond formation occurred smoothly and, after 24 h of stirring, the desired Mannich adduct **4aa** was isolated as a mixture of diastereomers in 90% yield. Although the diastereomeric ratio was moderate (dr = 7.3:1), the enantiomeric excess (ee) of the major isomer was determined to be 98% (Table 1, entry 1). The investigation then focused on the effects of the catalyst structure, primarily on diastereocontrol, which revealed the importance of steric bulk at the periphery of aromatic substituents at the 3,3'-positions of both naphthyl units (Ar), rather than their electronic attributes (Table 1, entries 2–6). For instance, while 4-trifluoromethylphenyl-substituted betaine **1b** had no positive impact on the reaction profile (Table 1, entry 2), the use of **1c**, bearing a 4-*tert*-butylphenyl group, delivered a critical improvement in diastereoselectivity, affording **4aa** quantitatively and establishing consecutive quaternary and tertiary stereocenters with almost complete fidelity (Table 1, entry 3). Further examination of the reactions under the influence of **1d**, having 3,5-bis(trifluoromethyl)phenyl groups, and **1e**, bearing 3,5-bis(*tert*-butyl)phenyl groups, showed similar tendencies, but a considerable decrease in reactivity and selectivity was observed when using **1d** (Table 1, entries 4 and 5). On the other hand, however, the introduction of 2,4,6-trimethylphenyl appendages (**1f**), which extended steric hindrance over the catalytically active sites, eroded the catalytic activity and diastereocontrol (Table 1, entry 6). These observations demonstrated the superior capability of **1c** in facilitating this stereoselective Mannich-type transformation, for

Table 1: Optimization of catalyst structure.[a]



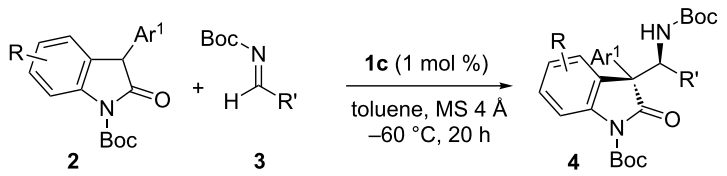
entry	Ar (**1**)	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph (**1a**)	90	7.3:1	98/28
2	4-$CF_3C_6H_4$ (**1b**)	>99	7.3:1	98/6
3	4-*t*-BuC_6H_4 (**1c**)	>99	>20:1	99/–
4	3,5-$(CF_3)_2C_6H_3$ (**1d**)	54	1:1.3	98/−35
5	3,5-*t*-$Bu_2C_6H_3$ (**1e**)	>99	10:1	98/–
6	2,4,6-$Me_3C_6H_2$ (**1f**)	73	1.8:1	98/63
7	**1c**[e]	92	>20:1	97/–
8	**1c**[e,f]	>99	>20:1	98/–

[a]Unless otherwise noted, reactions were conducted with 0.1 mmol of **2a**, 0.12 mmol of **3a**, and 5 mol % of **1** in toluene (1.0 mL) containing 100.0 mg of MS 4 Å at −60 °C for 24 h. [b]Isolated yield was indicated. [c]The diastereomeric ratio was determined by ^{1}H NMR (400 MHz) analysis of crude aliquot. [d]Enantiomeric excess was analyzed by chiral stationary phase HPLC (DAICEL CHIRALPAK AD-3). Absolute configuration of **4aa** was assigned by analogy to **4ca** (see Figure 2). [e]1 mol % of **1c** was used. [f]The reaction was performed on a 1.0 gram scale regarding **2a**.

which the loading was reduced to 1 mol % without sacrificing reaction efficiency (Table 1, entry 7). It is noteworthy that the present system is scalable; the reaction with 1.0 g of **2a** reached completion within 20 h to afford **4aa** with a similar degree of stereoselectivity (Table 1, entry 8), and subsequent recrystallization furnished 0.83 g of essentially stereochemically pure **4aa**.

Having identified **1c** as an optimal catalyst, the substrate scope of this asymmetric Mannich protocol was explored. As seen in representative results summarized in Table 2, excellent enantioselectivities were generally attained irrespective of the steric and electronic properties of both oxindoles **2** and *N*-Boc aldimines **3**, but reactivity and diastereoselectivity sometimes fluctuated depending on the structure of these substrates. While significant variation in the imine substituents was feasible, the introduction of electron-withdrawing groups at the *meta*-position slightly reduced diastereoselectivity (Table 2, entries 1–4). Sterically demanding 2-tolualdehyde-derived imine **3f** served as a good electrophile and the corresponding Mannich adduct **4af** was isolated as virtually a single stereoisomer (Table 2, entry 5). 3-Thiophenyl aldimine **3g** was also well tolerated, but a substantial decrease in diastereoselectivity was observed in the reaction with 2-furyl aldimine **3h**, owing to the requisite higher reaction temperature (Table 2, entries 6 and 7). Catalysis with **1c** was also applicable to aliphatic imines, which required prolonged reactions and slightly higher catalyst loadings to achieve adequate conversions; the desired adducts, **4ai** and **4aj**, were obtained with high enantioselectivities and moderate diastereoselectivities (Table 2, entries 8 and 9). With respect to oxindoles **2**, the electronic nature of the 3-aryl moiety affected the diastereoselection; the incorporation of electron-deficient aromatics proved beneficial and the presence of electron-rich aryl components seemed detrimental (Table 2, entries 10–14). However, the diastereoselectivity was robust with regard to electronic differences in the oxindole core, and both 5-fluoro- and methoxy-substituted **2g** and **2h** were efficiently converted into **4ga** and **4ha** with rigorous relative and absolute stereocontrol (Table 2, entries 15 and 16). The absolute configuration of **4ca** was unequivocally determined by X-ray crystallographic analysis (Figure 2), and the stereochemistry of the remaining examples was assumed to be analogous.

Table 2: Substrate scope.[a]



entry	Ar[1], R (**2**)	R' (**3**)	yield (%)[b]	dr[c]	ee (%)[d]	**prod.**
1	Ph, H (**2a**)	4-$MeOC_6H_4$ (**3b**)	96	>20:1	99	**4ab**
2	Ph, H (**2a**)	4-ClC_6H_4 (**3c**)	96	>20:1	99	**4ac**
3	Ph, H (**2a**)	3-$MeOC_6H_4$ (**3d**)	92	>20:1	97	**4ad**
4	Ph, H (**2a**)	3-BrC_6H_4 (**3e**)	>99	14:1	99	**4ae**
5	Ph, H (**2a**)	2-MeC_6H_4 (**3f**)	95	>20:1	99	**4af**
6	Ph, H (**2a**)	3-thiophenyl (**3g**)	90	>20:1	99	**4ag**
7[e]	Ph, H (**2a**)	2-furyl (**3h**)	86	9:1	97	**4ah**
8[f]	Ph, H (**2a**)	$Ph(CH_2)_2$ (**3i**)	55	5:1	98/75	**4ai**
9[g]	Ph, H (**2a**)	$Me(CH_2)_7$ (**3j**)	44	3.5:1	93/60	**4aj**
10	4-$MeOC_6H_4$, H (**2b**)	Ph (**3a**)	96	12:1	99	**4ba**
11	4-ClC_6H_4, H (**2c**)	Ph (**3a**)	92	>20:1	97	**4ca**
12	3-$MeOC_6H_4$, H (**2d**)	Ph (**3a**)	89	4:1	98/81	**4da**
13	3-MeC_6H_4 (**2e**)	Ph (**3a**)	87	13:1	99	**4ea**
14	3-$CF_3C_6H_4$, H (**2f**)	Ph (**3a**)	80	>20:1	99	**4fa**
15	Ph, 5-F (**2g**)	Ph (**3a**)	85	>20:1	97	**4ga**
16	Ph, 5-MeO (**2h**)	Ph (**3a**)	89	>20:1	96	**4ha**

[a]Unless otherwise noted, reactions were performed on 0.2 mmol scale with 1.2 equiv of **3a** in the presence of **1c** (1 mol %) and MS 4 Å (100.0 mg) in toluene (1.0 mL) at −60 °C for 24 h. [b]Isolated yield was reported. [c]The diastereomeric ratio was determined by ^{1}H NMR (400 MHz) analysis of crude aliquot. [d]Enantiomeric excess of the major isomer was indicated except for entries 8, 9, and 12, which was analyzed by chiral stationary phase HPLC. Absolute configuration of **4ca** was determined by single crystal X-ray diffraction analysis (Figure 2) and that of other **4** was assumed to be analogous. [e]The reaction was conducted at –40 °C for 110 h. [f]The reaction was stirred for 117 h. [g]The reaction time was 72 h.

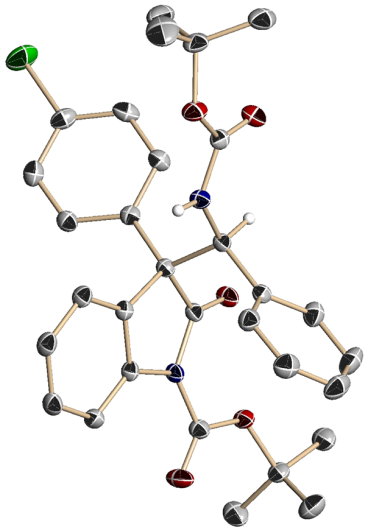


Figure 2: ORTEP diagram of **4ca** (Ellipsoids displayed at 50% probability. Calculated hydrogen atoms except it attaches to stereogenic carbon are omitted for clarity. Black: carbon, Red: oxygen, Blue: nitrogen, Green: chlorine).

Conclusion

In summary, we have clearly demonstrated that chiral ammonium betaine **1c** acts as a uniquely effective catalyst in promoting a Mannich-type reaction between 3-aryloxindoles and *N*-Boc aldimines with high levels of diastereo- and enantioselectivity under mild conditions. This study greatly expands the scope of this mode of stereoselective Mannich-type reaction, which involve the generation of vicinal quaternary and tertiary stereocenters. Further investigations into the potential utility of ammonium betaine catalysis are underway in our laboratory.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, copies of NMR charts and HPLC traces, and X-ray data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-199-S1.pdf]

Supporting Information File 2

Crystallographic information file of compound **4ca**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-199-S2.cif]

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Determination of the absolute stereostructure of a cyclic azobenzene from the crystal structure of the precursor containing a heavy element

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Full Research Paper

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Abstract

Single crystal X-ray diffraction has been used as one of the common methods for the unambiguous determination of the absolute stereostructure of chiral molecules. However, this method is limited to molecules containing heavy atoms or to molecules with the possibility of functionalization with heavy elements or chiral internal references. Herein, we report the determination of the absolute stereostructure of the enantiomers of molecule (*E*)-**2**, which lacks the possibility of functionalization, using a reverse method, i.e., defunctionalization of its precursor of known stereostructure with bromine substitution (*S*-(−)-(*E*)-**1**). A reductive debromination of *S*-(−)-(*E*)-**1** results in formation of one of the enantiomers of (*E*)-**2**. Using a combination of HPLC and CD spectroscopy we could safely assign the stereostructure of one of the enantiomers of (*E*)-**2**, the reduced product *R*-(−)-(*E*)-**1**.

Introduction

Chirality is a topic of fundamental importance in several branches of science [1-5]. Homochirality in nature was one of the most important challenges for researchers and the origin is still unsolved [6-8]. It is well known that biological functions of most living systems are determined by the stereostructure of biologically active molecules [9]. Beyond the academic interest, the synthesis and separation of chiral molecules plays a key role in chemical industry, particularly as catalysts [10] and pharmaceutical ingredients [11]. In addition to the special interest in molecular chirality in diverse fields of biology and pharmaceutical chemistry, several chiral molecules have been synthesised and studied for their stereostructure-dependent physical properties such as optical activity [12-22] and magnetic properties [23-25]. Hence, the chiral separation and the determination of absolute stereostructure are important aspects of stereochemistry for the complete understanding of the role of chiral structures in various physical and biological functions.

Until date there have been several spectroscopic, diffraction methods developed to determine the absolute stereostructure of

chiral molecules [26-35]. The non-empirical methods employed to determine the absolute configuration of a molecule include circular dichroism, exciton chirality methods [28,29], NMR spectroscopy [30-32], X-ray diffraction [33-35], etc. In addition to these methods, many researchers explored a combination of vibrational circular dichroism and quantum mechanical calculations to determine the absolute stereostructures [36-38]. Among various methods used for determining the absolute stereostructure of the molecules, the X-ray diffraction methods obtained more credibility, especially the method using a single parameter viz. 'Flack Parameter' [33-35] which clearly identifies the absolute structure rather than measuring the intensity of the Bijvoet pairs [39]. However, the requirement of heavy atoms for the better anomalous dispersion, limits the usage of X-ray diffraction in determining the absolute stereostructure. In many of the molecules, the requirement of a heavy atom leads either to functionalization of the molecules with groups containing an heavy atom [40-44] or the relative position of the chiral centre is estimated in relation to an internal reference of known chirality [26]. Nevertheless, this approach can be applicable only to the molecules with easily functionalizable groups. Hence, it is important to provide an alternative method for the determination of the absolute stereostructure of a molecule without the possibility of functionalization.

Recently our group reported the synthesis of several cyclic azobenzene molecules and their properties [45-50]. All these molecules share a comparable cyclic structure, with a photoisomerizable azobenzene unit linked to a substituted or unsubstituted aromatic unit such as naphthalene or benzene. Generally the molecules are of three categories (i) achiral (irrespective of the isomerized state of the azobenzene, i.e., *E* or *Z*), (ii) chiral in *E*-state and achiral in *Z*-state of azobenzene, (iii) chiral in both states of the azobenzene unit. We have explored the property of planar chirality of these molecules and carried out the optical resolution to demonstrate various properties such as molecular brakes, chiroptical switches and chirality sensors for light and solvent etc. [45-50]. Although we could separate the enantiomers of all these chiral cyclic azobenzenes, the experimental determination of the absolute stereostructure by X-ray diffraction was difficult due to the lack of heavy elements.

In the present study, we demonstrate the determination of the absolute stereostructure of a molecule without any functional groups for the introduction of heavy atoms. We used a reverse reaction, i.e., not a reaction to add a heavy atom auxiliary to the chiral cyclic azobenzene but a reaction to remove the heavy atom from the precursor molecule with known chirality to obtain the target molecule. We could determine the stereostructure of the cyclic azobenzene by comparing the HPLC data obtained with a chiral column and the circular dichroism (CD) spectra of the product obtained by reduction of the enantiopure precursor and the target molecule.

Results and Discussion

Figure 1 shows the schematic representation of experiments involved in the separation and reductive debromination of the enantiomer (*E*)-**1**$_{\mathbf{B}}$. The enantiomers of molecules (*E*)-**1** and (*E*)-**2** are previously reported as photocontrolled chiroptical switches for various nematic liquid crystalline hosts for tuning

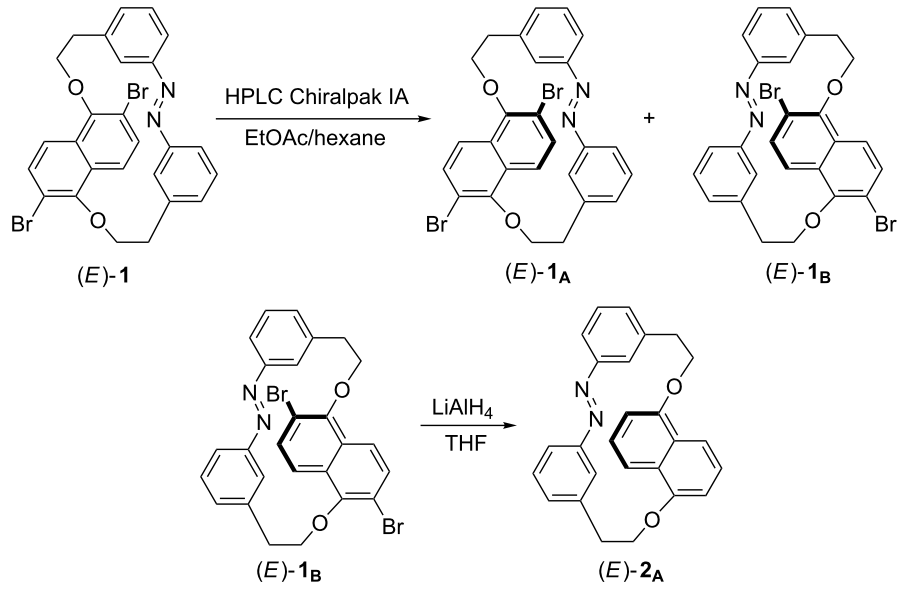


Figure 1: Schematic representation of the steps to enantiomer (*E*)-**2**$_{\mathbf{A}}$.

the reflection colors through the entire visible region [45,46]. The molecule (*E*)-**1** has been also used to demonstrate the completely photocontrolled rotation of the micro glass rods on the chiral nematic liquid crystalline films induced by the rotational reorganization of the polygonal finger print texture [45]. Molecule (*E*)-**1** contains a 2,6-dibromo-1,5-dihydroxynaphthalene part linked to an azobenzene unit through bismethylene spacers. The constricted rotation of the naphthalene unit in the cyclic structure gives planar chirality to this molecule with separable enantiomers. The presence of the bromine substitution in the naphthalene unit gives an added advantage in determining the absolute stereostructure of the separated enantiomers. The determination of the absolute stereostructure of one of the enantiomers of (*E*)-**1** by X-ray diffraction has been presented in our previous report [45]. In this study, we employ this enantiomer as a precursor for the determination of the absolute configuration of its reduced product, which is expected as one of the enantiomers of (*E*)-**2**.

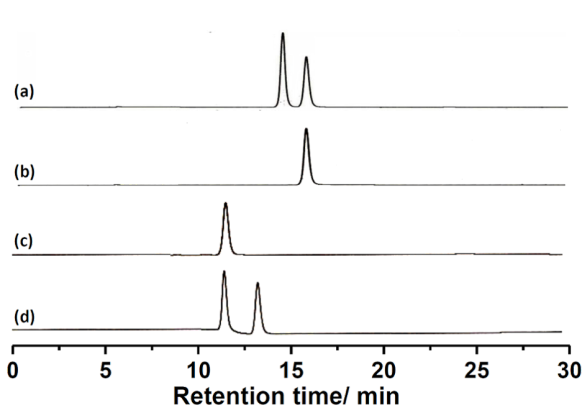


Figure 2: Chromatogram (Chiral HPLC) obtained for (a) racemic mixture of (*E*)-**1** (b) sample used for reductive debromination (second eluted enantiomer S-(−)-(*E*)-**1)** (c) recorded after the $LiAlH_4$ reduction of S-(−)-(*E*)-**1** and (d) the chromatogram of racemic (*E*)-**2**. (Column: Chiralpak IA, eluent: ethyl acetate/hexane (10:90), Flow rate: 3 mL/min)

In order to characterize the reduced product we have carried out the ^{1}H NMR spectroscopy of the compound and found that the spectrum completely matches with the previously reported compound (*E*)-**2** [46]. To confirm the formation of compound (*E*)-**2** we have carried out chiral HPLC studies on a Chiralpak IA column using a mixture of ethyl acetate and hexane (10:90) as the eluent to characterize the nature of the enantiomer formed by the reductive debromination. In the previous study with the combination of density functional theoretical calculations (DFT) and electronic circular dichroism (ECD), we have assigned the first and second eluted enantiomers of (*E*)-**2** as *R*-(−)-(*E*)-**2** and *S*-(+)-(*E*)-**2**, respectively, on a chiralpak IA column using hexane and ethyl acetate as eluent [46]. Figure 2a shows the chromatogram obtained for the racemic (*E*)-**1** with two peaks corresponding to the first (14.6 min) and second (15.9 min) eluted *trans* enantiomers, *R*-(+)-(*E*)-**1** and *S*-(−)-(*E*)-**1**, respectively. Whereas, Figure 2b shows the chromatogram recorded for the crystalline sample of *S*-(−)-(*E*)-**1** which is used for the reductive debromination. The chromatogram shows a single peak at 15.9 min ascertaining the enantiomeric purity of the sample. After reduction of *S*-(−)-(*E*)-**1** we have carried out the HPLC of the reduced sample where the chromatogram shows a single peak with a retention time of 11.9 min (Figure 2c). In order to obtain an idea about the enantiomeric nature of the reduced product we have recorded the chromatogram for the pure racemic sample of (*E*)-**2.** The chromatogram shows two peaks corresponding to first and second eluted enantiomers, respectively with the retention time of 11.9 and 13.5 min (Figure 2d). Comparing the chromatograms of the reduced product and the racemic mixture, it is clear that the reduced product is the first eluted enantiomer of (*E*)-**2**.

To further confirm the formation of (*E*)-$\mathbf{2_A}$ we studied the chiroptical properties of the product obtained by reductive debromination. Figure 3 shows the circular dichroism spectra of the reduced product along with that of *S*-(−)-(*E*)-**1**. From the spectral features and band intensity ratios, it is clear that the reduced product shows completely different cotton bands with that of *S*-(−)-(*E*)-**1**. We compared the spectra of the reduced product with that of the previously reported spectra of the enantiomers of (*E*)-**2** and found that the spectra matches the CD spectra of (*E*)-$\mathbf{2_A}$ [46]. Thus from the HPLC and CD data it is clear that the reduced product of *S*-(−)-(*E*)-**1** gives the first eluted enantiomer of (*E*)-**2**.

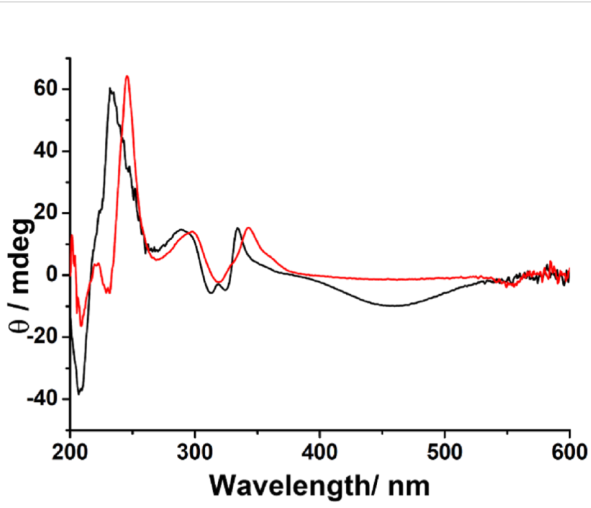


Figure 3: CD spectra recorded for solutions in THF for *S*-(−)-(*E*)-**1** (red curve) and for the reduced product of *S*-(−)-*E*-**1**, i.e., *R*-(−)-(*E*)-**2** (black curve).

According to the Cahn–Ingold–Prelog (CIP) priority rules [51], the absolute configuration of the reduced product should be '*R*'. The priorities of the functional groups on the reduced product reverse on removal of the bromine atom from the parent structure. Comparing the HPLC and CD data with structural data of *S*-(−)-(*E*)-**1** the absolute stereostructure of its reduced product is determined as *R*-(−)-(*E*)-**2**. The experimentally derived stereostructure completely matches with the absolute structure previously predicted from theoretical calculations.

In summary, we demonstrated the determination of the absolute configuration of the enantiomers of a molecule from its precursor with known stereostructure. More importantly, this method can be used for the determination of stereostructures of molecules without functional groups for the functionalization with heavy elements or chiral internal references.

Experimental

All solvents and chemicals were obtained from commercial sources and used without further purification, unless otherwise stated. NMR (^{1}H and ^{13}C) spectra were recorded with a JEOL ECX 400 spectrometer using tetramethylsilane as an internal standard. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI–TOFMS) was performed with an Applied Biosystems Voyager-DE pro instrument. Absorption spectra were recorded with an Agilent 8453 spectrophotometer and the CD spectra were recorded with a JASCO J-S720 CD spectrophotometer. High-performance liquid chromatography (HPLC) was conducted with a Hitachi Elite La Chrome HPLC system using CHIRALPAK IA (DAICEL Chemical Industries Ltd.) column with solvent mixtures of ethyl acetate in hexane, 10:90 as eluent for the HPLC experiments at a flow rate of 3 mL/min.

Reductive debromination of compound (*E*)-$\mathbf{1_B}$

To a solution of freshly separated enantiomer (*E*)-$\mathbf{1_B}$ (30 mg, 0.054 mmol) in THF, $LiAlH_4$ (20.49 mg, 0.54 mmol) in THF was added in drops at room temperature and stirred overnight. The reaction mixture was carefully quenched by adding water dropwise and the reaction mixture was filtered to remove the precipitate. The filtrate was separated with ethyl acetate, evaporated and column chromatographed over silica gel using a mixture of ethyl acetate in hexane (10:90) as eluent to obtain the debrominated product (yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 6.8 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.79 (s, 2H), 6.60 (d, *J* = 7.6 Hz, 2H), 4.76 (m, *J* = 14.6 Hz, 2H), 4.60 (m, 2H), 3.21 (dd, *J* = 3.2, 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 152.3, 140.4, 130.6, 128.9, 127.9, 125.6, 125.0, 120.0, 114.6, 107.7, 68.4, 35.9.

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Highly chemo-, enantio-, and diastereoselective [4 + 2] cycloaddition of 5*H*-thiazol-4-ones with *N*-itaconimides

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Full Research Paper

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Keywords:
[4 + 2] annulation; asymmetric organocatalysis; dipeptide-based Brønsted bases; 5*H*-thiazol-4-ones; *N*-itaconimides

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Abstract

A dipeptide-based urea-amide tertiary amine (DP-UAA) was shown to be an effective Brønsted base catalyst for the first asymmetric annulation reaction between 5*H*-thiazol-4-ones and *N*-itaconimides. High levels of enantioselectivity (up to 99% ee) and diastereoselectivity (>19:1 dr) were obtained for a series of spirocyclic 1,4-sulfur-bridged piperidinone-based succinimides.

Introduction

Sulfur-containing tetrasubstituted carbon stereocenters are widely present in a number of natural and non-natural products with significant biological activities [1]. In the past few decades, diverse competent asymmetric strategies have been established to access these chiral entities [1-4]. Among them, catalytic asymmetric functionalization of *S*-containing prochiral carbon centers can be considered to be one of the most efficient and expedient approach [1-4]. The development of novel *S*-containing substrates has therefore attracted the attention of chemists [1-4]. For example in 2013, Palomo and co-workers introduced 5*H*-thiazol-4-ones as a new class of sulfur-containing pro-nucleophiles in a highly enantio- and diastereoselective conjugate addition to nitroalkenes, providing α,α-disubstituted α-mercapto carboxylic acids [5]. Since then, several asymmetric variants using 5*H*-thiazol-4-ones as nucleophiles have been disclosed; such as amination [6], allylation [7], conjugate addition to enones [8], and γ-addition with allenoates [9]. All these examples focused on nucleophilic addition reactions of the C5 atom of 5*H*-thiazol-4-ones.

Recently, we described an organocatalytic asymmetric [4 + 2] cyclization of 5*H*-thiazol-4-ones with a series of activated alkenes, including nitroalkenes, 4-oxo-4-arylbutenones, 4-oxo-4-arylbutenoates and methyleneindolinones [10]. This work elucidated the feasibility of the electrophilic addition to the C2 position of 5*H*-thiazol-4-ones. More importantly, it provided a direct and convenient approach to synthesize three kinds of biologically important chiral 1,4-sulfur-bridged piperidinones and

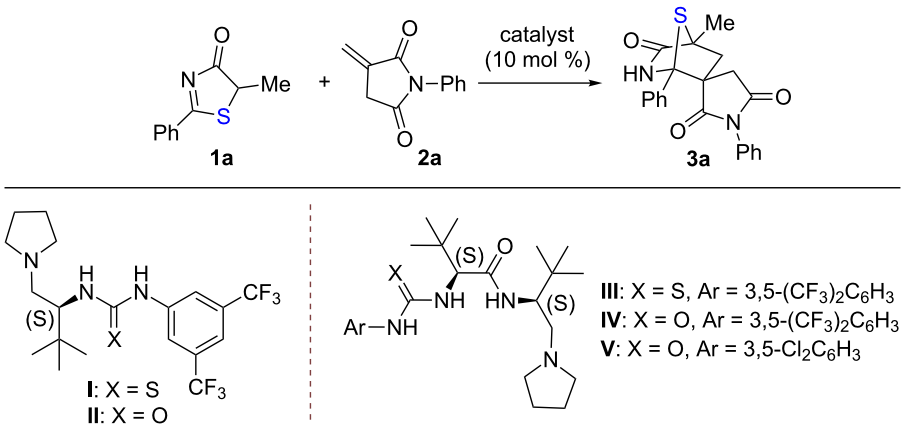
their related derivatives [10]. In order to develop novel chiral *S*-containing polycyclic scaffolds, the development of [4 + 2] annulations of 5*H*-thiazol-4-ones with unusual activated alkenes still remains highly desirable.

Succinimides are present in many biologically significant molecules and are investigated as potential pharmacophores in the research of drug discovery [11,12]. Our group has recently devised *N*-itaconimides for the assembly of succinimide frameworks [13-18]. As an extension of these works, herein, we report an asymmetric [4 + 2] annulation reaction of 5*H*-thiazol-4-ones with *N*-itaconimides. The method features excellent chemo-, enantio, and diastereoselectivities, thus leading to a series of chiral spirocyclic 1,4-sulfur-bridged piperidinone-based succinimides with excellent results.

Results and Discussion

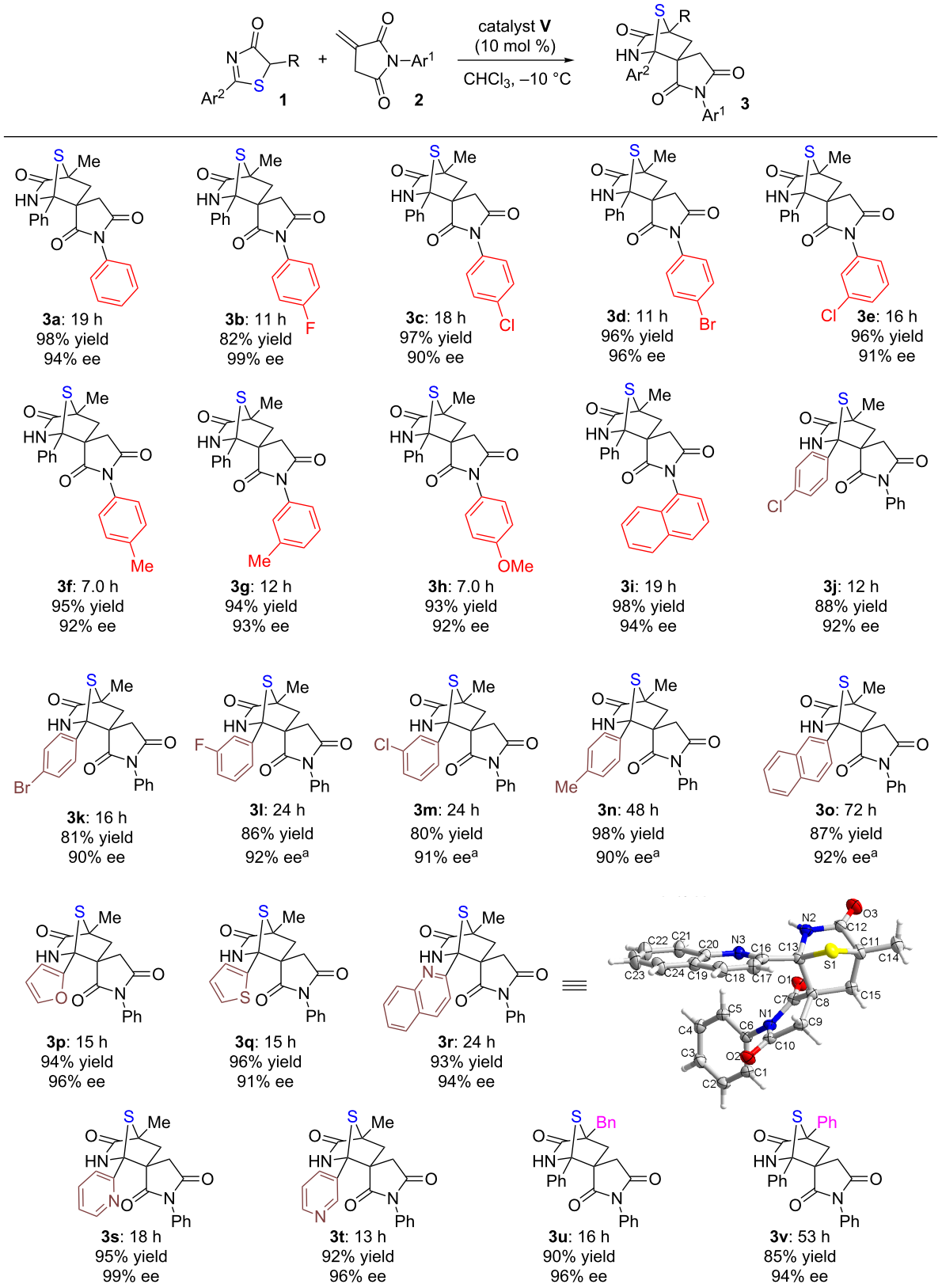
Our studies were initiated by examining a model reaction between 5*H*-thiazol-4-one **1a** and *N*-phenyl itaconimide **2a** (Table 1). The reaction was first evaluated in toluene at 25 °C and using *L*-*tert*-leucine-based thiourea−tertiary amine **I** as the catalyst (Table 1, entry 1), with excellent catalytic efficacy as demonstrated in a series of asymmetric reactions [18]. It was found that the reaction was completed after 48 hours, affording the desired [4 + 2] annulation adduct **3a** in 55% yield with 64% ee. A significant amount of conjugate addition adduct led to the unsatisfactory chemoselectivity and thus the moderate yield. When the H-bond donor was changed from thiourea to urea (catalyst **II**), it did not provide better results (Table 1, entry 2) [17,19]. In the [4 + 2] annulation of 5*H*-thiazol-4-ones with nitroalkenes, dipeptide-based thiourea−amide−tertiary amine **III** (DP-TAA) was devised and demonstrated as a competent catalyst to furnish excellent chemo- and stereoselectivity [10]. Therefore, we examined catalyst **III** for this reaction (Table 1, entry 3); annulation adduct **3a** was obtained in 60% yield with 70% ee. The increased in enantioselectivity indicates the potential of dipeptide-based tertiary amine for this type of reaction. By modifying the thiourea moiety of **III** to urea lead us to catalyst DP-UAA **IV**, which could further increase the enantioselectivity (Table 1, entry 4). Subsequently, we screened the solvent effect with **IV** as the catalyst (Table 1, entries 5–7), and the results revealed that chloroform was the best reaction medium regarding the enantioselectivity (Table 1, entry 7). By changing the reaction temperature (Table 1, entries 8 and 9), we found

Table 1: Optimization of reaction conditions[a].



Entry	Catalyst	Solvent	*T* (°C)	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**I**	toluene	25	48	55	64
2	**II**	toluene	25	48	50	62
3	**III**	toluene	25	48	60	70
4	**IV**	toluene	25	48	62	74
5	**IV**	CH_2Cl_2	25	48	68	77
6	**IV**	Et_2O	25	48	50	76
7	**IV**	$CHCl_3$	25	48	72	86
8	**IV**	$CHCl_3$	0	48	70	89
9	**IV**	$CHCl_3$	−10	60	60	92
10	**V**	$CHCl_3$	−10	18	98	93

[a]The reaction was performed in a 0.05 mmol scale; [b]yield was isolated by flash column; [c]ee was determined by HPLC.



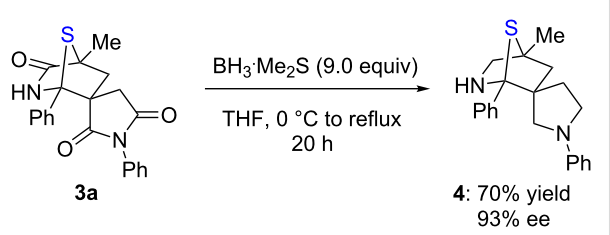
Scheme 1: Substrate scope of the [4 + 2] annulation. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **V** (0.01 mmol), $CHCl_3$ (1.0 mL) at −10 °C. All drs are >20:1; ees were determined via chiral HPLC analysis. [a]20 mol % of **V** was used, T = 0 °C.

that the yield of **3a** was decreased to 60% but the ee value was increased to 92% at −10 °C (Table 1, entry 9). To improve the chemoselectivity, we synthesized a series of DP-UAAs through tuning of the substituent groups of the urea. We were pleased to find that the reaction rate could be tremendously increased by utilizing DP-UAA **V** as the catalyst, and **3a** was obtainable with high enantioselectivity, high chemoselectivity and excellent yield of 98% (Table 1, entry 10).

With the optimal reaction conditions in hand, we examined the substrate scope of the enantioselective [4 + 2] cycloaddition between 5*H*-thiazol-4-ones **1** and *N*-itaconimides **2**, catalyzed by DP-UAA **V** (Scheme 1). Firstly, with **1a** as the model 5*H*-thiazol-4-one substrate, a series of *N*-itaconimides containing various *N*-aryl groups were transformed to the corresponding [4 + 2] annulation adducts **3a–i** in 82−98% yield with 90−96% ee. We then investigated substrates with diverse aromatic (**3j–o**) and heteroaromatic (**3p–t**) groups on the 2-position of 5*H*-thiazol-4-ones, and found the reactions completed within 12−72 hours, affording the corresponding annulation adducts **3j–t** in 80−98% yield with 90−99% ee. Altering the R group on 5*H*-thiazol-4-ones for a benzyl (**3u**) or phenyl (**3v**) substituent also presented **3u** and **3v** in high yields and excellent enantioselectivities. The absolute configurations of annulation adducts **3** were assigned based on X-ray crystallographic analysis of a single crystal of **3r** [20].

Through an analysis of the absolute configuration of adduct **3**, it is proposed that a plausible reaction mechanism should be similar to the DP-TAA-catalyzed [4 + 2] annulation between 5*H*-thiazol-4-ones and nitroalkenes [10]. In this stepwise process, the use of 3,5-dichlorophenyl as the substituent group of the urea in catalyst **V** would remarkably increase the free energy difference between *R*- and *S*-selection in the first Michael addition step, and also decreases the free energy of the second formal Mannich reaction, thus improving the reaction rate and chemoselectivity of the [4 + 2] cycloaddition.

To extend the usefulness of this reaction, we demonstrate that the adduct can be efficiently reduced with borane. As shown in Scheme 2, **3a** was readily reduced to afford a spirocyclic sulfur-bridged *N*-heterocycle **4** in 70% yield and without compromising its ee value.



Scheme 2: Transformation of adduct.

Conclusion

In conclusion, we have developed the first asymmetric reaction of 5*H*-thiazol-4-ones with *N*-itaconimides. By employing a DP-UAA catalyst, the reaction undergoes a [4 + 2] annulation process with excellent chemoselectivity and with a broad substrate scope, affording a series of valuable chiral spirocyclic 1,4-sulfur-bridged piperidinone-based succinimides in high yields (up to 98%) and excellent enantio- and diastereoselectivities (up to 99% ee and >19:1 dr). Further investigations involving new [4 + 2] annulation of 5*H*-thiazol-4-ones using DP-TAAs and DP UAAs are currently ongoing and will be reported in due course.

Experimental

Representative procedure for the synthesis of 3a: *N*-Phenyl itaconimide **2a** (0.15 mmol, 1.5 equiv) and catalyst **V** (0.01 mmol, 0.1 equiv) were dissolved in chloroform (1.0 mL) and stirred at −10 °C for 10 min. This is followed by the addition of 5*H*-thiazol-4-one **1a** (0.1 mmol, 1.0 equiv). The reaction mixture was stirred at −10 °C and monitored by TLC. Upon complete consumption of **1a**, the reaction mixture was directly loaded onto a short silica gel column, followed by gradient elution with DCM/MeOH mixture (500:1−200:1 ratio). Removing the solvent in vacuo, afforded product **3a**.

Supporting Information

Supporting Information File 1

Experimental information and spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-222-S1.pdf]

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20. CCDC 1495751 (**3r**) contains the supplementary crystallographic data for this paper.

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Copper-catalyzed asymmetric sp^3 C–H arylation of tetrahydroisoquinoline mediated by a visible light photoredox catalyst

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Full Research Paper

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Abstract

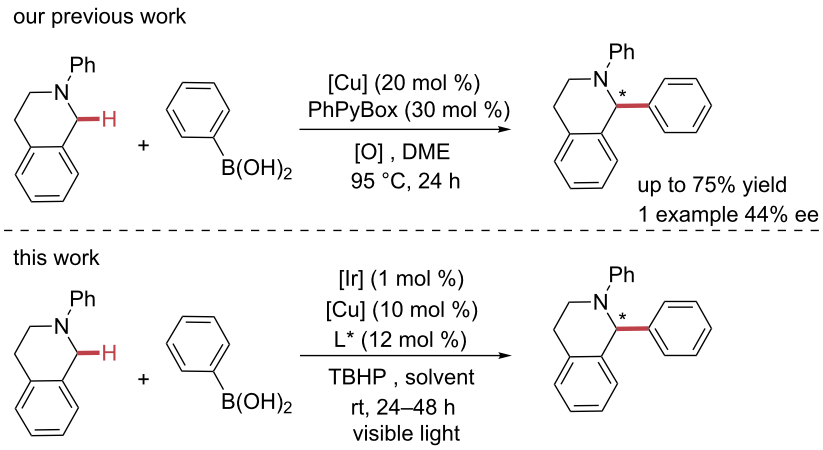
This report describes a highly enantioselective oxidative sp^3 C–H arylation of *N*-aryltetrahydroisoquinolines (THIQs) through a dual catalysis platform. The combination of the photoredox catalyst, $[Ir(ppy)_2(dtbbpy)]PF_6$, and chiral copper catalysts provide a mild and highly effective sp^3 C–H asymmetric arylation of THIQs.

Introduction

Functionalization of sp^3 C–H bonds is a unique and powerful transformation in modern organic synthesis, which remains a challenging process despite the advances that have been made in this field [1]. The directing group strategies are widely used and developed to achieve enantioselective metal-catalyzed C–H bond functionalizations in recent years. Unactivated alkyl C–H bond activation (i.e., without any directing group) is of great interest in terms of atom economy, nevertheless enantioselectivity is difficult to control due to often-required harsh reaction conditions. Therefore, the development of simple and facile processes to functionalize sp^3 C–H bonds under mild conditions in the absence of directing groups is of great interest [2].

The emerging and expanding field of visible-light-mediated photoredox catalysis presents unique opportunities for the conception of new synthetic routes [3-12]. Upon exposure to visible light, photoredox catalysts can function as both reductant and oxidant, thereby providing extremely important tools for potential transition-metal-catalyzed enantioselective reactions of sp^3 C–H bonds, which could be carried out at low temperature and under mild reaction conditions [13,14]. We envisioned that combining photoredox catalysis with typical cross-coupling methods will allow us to design a visible-light-mediated photoredox asymmetric arylation of tetrahydroisoquinolines (THIQs) [15-20].

During the last decade, numerous examples of sp^3 C–H bond arylation procedures have been developed [1,21-29]. In 2008, our group developed the first direct sp^3 C–H arylation of THIQ with arylboronic acids using a copper catalyst (Scheme 1) [30].



Scheme 1: Design light-mediated arylation of THIQs.

Oxygen gas and *tert*-butyl hydroperoxide (TBHP) were used as external oxidants, which gave moderate to good isolated yields (up to 75%). In addition, we demonstrated the first enantioselective arylation of THIQ using phenylboronic acid with 44% enantiomeric excess (ee), but very poor yield of the optically active products. Lowering the reaction temperature, in order to increase the corresponding ee, resulted in inhibition of the reaction.

More recently, Liu et al. have demonstrated the arylation of THIQs with arylboronic esters via asymmetric organocatalysis methodology [25,28]. The use of chiral tartaric acid derivatives, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and high temperature (70 °C) were found to be the optimal conditions to obtain the desired arylated product with acceptable yield and good enantioselectivity. However, this methodology has shown limitations in terms of substrate scope: only phenylboronic esters with electron-donating substituents yielded the corresponding products.

We herein report the first visible light-mediated asymmetric cross-coupling arylation of sp^3 C–H bonds adjacent to nitrogen, combining photoredox catalysis with metal-catalyzed transformations.

Results and Discussion

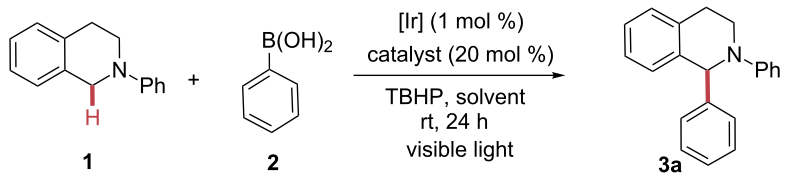
Optimisation of reaction conditions

In our previous work on arylation of *N*-aryltetrahydroisoquinoline [30], we demonstrated that lowering the temperature from 90 °C to room temperature in the reaction with copper(I) bromide caused a significant drop in yield. During optimisation of the reaction system, TBHP was found to be the best external oxidant for this reaction over many others [31]. To accelerate the reaction at lower temperature, we reasoned that a light-mediated photoredox system might help, which indeed has improved the reaction yield and enantioselectivity. Different iridium and ruthenium photoredox catalysts were evaluated and $[Ir(ppy)_2(d\mathit{t}bbpy)]PF_6$ was found to be the most efficient [32]. With this iridium photoredox catalyst, TBHP, and copper(I) bromide co-catalyst in DME as solvent, we observed a trace amount of the desired product at room temperature. When different copper salts were evaluated, it was found that CuBr was less active (Table 1, entry 1) and copper(II) bromide provided the highest yield for the arylation of THIQ with phenylboronic acid (**2**, Table 1, entry 2). Other copper salts such as $Cu(OTf)_2$ and $Cu(OAc)_2$ were much less effective (Table 1, entries 3 and 4). A significant increase of yield was observed when the stoichiometry of the system was changed to a slight excess of arylboronic acid. When more than 1.6 equivalents of **2** were involved in the reaction, a drastic acceleration of the reaction was observed, leading to up to 85% yield (Table 1, entries 5 and 6). During the investigation of solvent influence on the formation of **3a**, it was found that polar solvents such as DCE gave the best yields, compared to less polar solvents such as toluene and THF (Table 1, entries 7 and 8). On the other hand, highly polar solvents such as MeCN and MeOH were not beneficial for the formation of the desired product **3a** (Table 1, entries 9 and 10). Control experiments performed in the absence of photoredox catalyst and/or transition metal copper(II) salt (Table 1, entries 11–13) showed very poor reactivity. Moreover, in the absence of light, an extremely poor yield was obtained (Table 1, entry 14).

General scope of reaction

With the optimized reaction conditions in hand, the substrate scope was investigated (Figure 1). *N*-Phenyltetrahydroisoquinoline (**1**) combined with phenylboronic acid (**2**) gave rise to 85% yield of the corresponding arylated product **3a**. *N*-Phenyl-

Table 1: Optimization of reaction conditions[a].



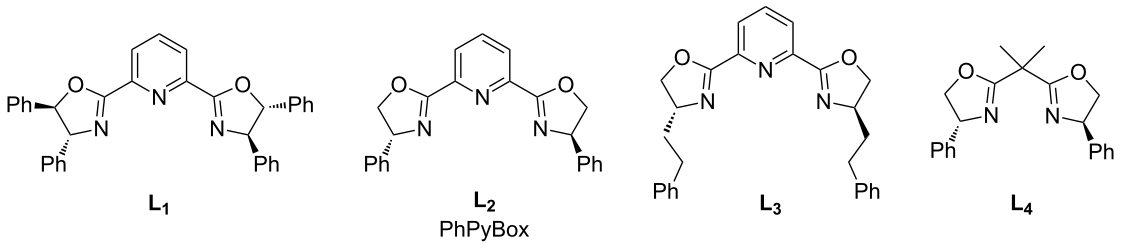
Entry	Catalyst	Solvent	**2** (equiv)	Yield of **3a** (%)
1	CuBr	DCE	1.6	19
2	$CuBr_2$	DCE	1.6	29
3	$Cu(OTf)_2$	DCE	1.6	2
4	$Cu(OAc)_2$	DCE	1.6	14
5	$CuBr_2$	DCE	2	72
6	$CuBr_2$	DCE	3	**85**
7	$CuBr_2$	THF	3	15
8	$CuBr_2$	toluene	3	23
9	$CuBr_2$	MeCN	3	11
10	$CuBr_2$	MeOH	3	13
11[b]	$CuBr_2$	DCE	3	12
12[b]	–	DCE	3	0
13[b,c]	$CuBr_2$	DCE	3	0
14[d]	$CuBr_2$	DCE	3	12

[a]Reaction conditions: THIQs (0.10 mmol), arylboronic acid (0.30 mmol), TBHP (0.16 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.001 mmol), $CuBr_2$ (0.02 mmol), DCE (0.5 mL), under argon atmosphere. NMR yields are reported. [b]Reaction carried out without Ir(III) photoredox catalyst. [c]Reaction carried out without TBHP. [d]Reaction performed in absence of light. All reported yields were determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard.

substituted THIQs bearing electron-donating groups (EDG), such a OMe and Me, were tolerated in our reaction system. We were surprised to see that strong electron-donating substituents such as OMe gave lower yields (**3b**, **3c** and **3d**), which we attribute to the lowered oxidation potentials of the tertiary amine, favouring side reactions. It is notable that weaker EDG substituents on the aryl moiety (e.g., Me) resulted in higher yields (**3e**). Electron-withdrawing groups (EWG) such as Br were tolerated and yielded the desired product in 80% yield (**3f**). Aromatic boronic acids possessing both electron-withdrawing and electron-donating substituents were evaluated under our reaction conditions and all resulted in good yields. While aromatic boronic acids substituted with electron-withdrawing groups (e.g., acyl, F or CF_3) were likewise tolerated well (**3g–j**). Aromatic boronic acids substituted with electron-donating groups resulted in the formation of the corresponding arylated products with higher yields (**3k–n**).

Enantioselective arylation reaction

Subsequently, we explored the asymmetric version of this arylation reaction with various chiral ligands (see Scheme 2 and Supporting Information File 1, Table S3, for a detailed



Scheme 2: Evaluation of chiral ligands.

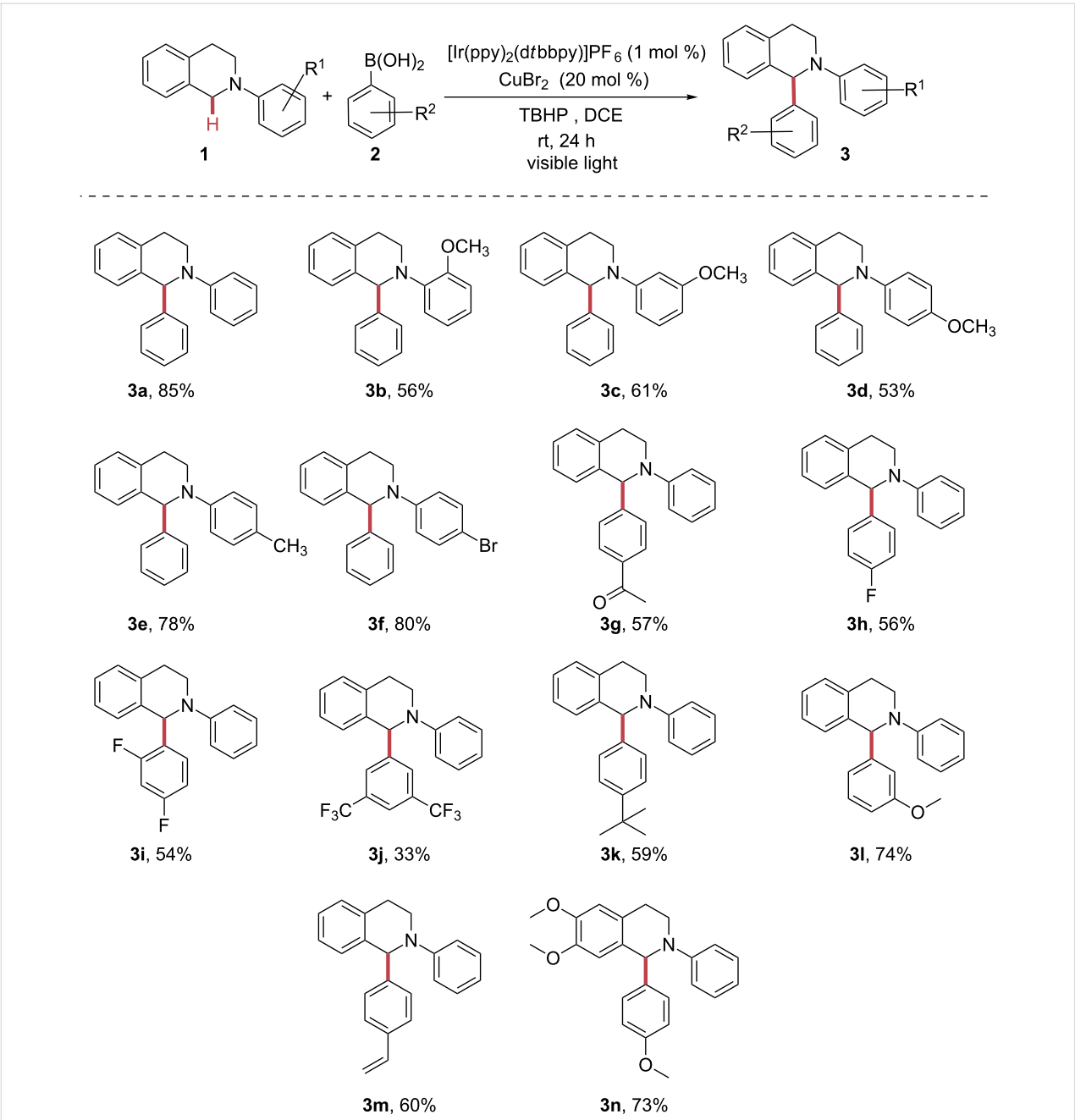
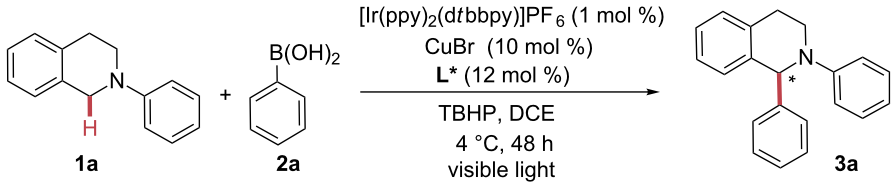


Figure 1: Reaction scope. Reaction conditions: THIQs (0.10 mmol), arylboronic acid (0.30 mmol), TBHP (0.2 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.001 mmol), $CuBr_2$ (0.02 mmol), DCE (0.5 mL), under argon atmosphere.

screening table). Among them, Box-type ligands have demonstrated a good performance in this reaction, affording low to good enantioselectivities.

We began our study by evaluating the efficiency of the ligands using the standard arylation of THIQ with phenylboronic acid. A modest enantiomeric ratio (er) of the C−H coupling reaction was obtained using $\mathbf{L_1}$ ligand (Table 2, entry 1) at low temperature (4 °C). On the other hand, the commercially available mono-arylated PyBox $\mathbf{L_2}$ gave very good er under our reaction conditions (Table 2, entry 2). It is noteworthy that the er observed was higher when copper(I) bromide was used as a co–catalyst, compared to copper(II) bromide (Table 2, entry 3), possibly due to the Lewis acidity difference of Cu(I) and Cu(II). However, the yield of the desired optically active product **3a** dropped by about half, when CuBr was used as catalyst. Alkyl-substituted PyBox such as $\mathbf{L_3}$ was not beneficial to the enantioselectivity (Table 2, entry 4). The efficacy of N,N-Box ligand

Table 2: Effect of chiral ligand on the enantioselectivity of coupling of *N*-phenyltetrahydroisoquinoline with phenylboronic acid[a].



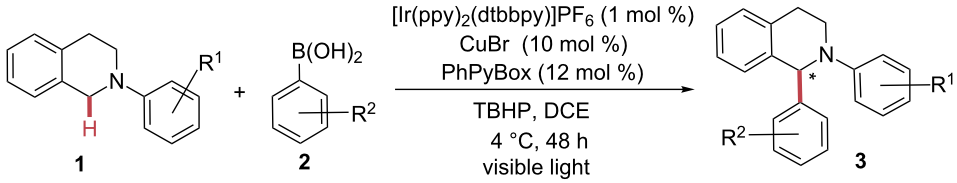
Entry	L*	er
1	L_1	69:31
2	L_2	82:18
3[b]	L_2	68:32
4	L_3	54:46
5	L_4	54:46

[a]Reaction conditions: THIQs (0.10 mmol), arylboronic acid (0.30 mmol), TBHP (0.2 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.001 mmol), CuBr (0.01 mmol), **L*** (0.012 mmol), DCE (0.5 mL), under argon atmosphere. [b]$CuBr_2$ was used. All reported enantiomeric ratios were determined using a Chiralcel OD-H column and 96:4 hexane/isopropanol as an eluent (Supporting Information File 1).

(L_4) was investigated and it appeared that the pyridine motif was extremely important to achieve high enantioselectivity (Table 2, entry 5).

To evaluate the scope of the enantiomeric selectivity of the arylation reaction, copper(I) bromide together with (*R*,*R*)-PhPyBox L_2 at 4 °C was used as the standard conditions. We were pleased to see that our model reaction yielded **3a** with good enantiomeric ratio (Table 3, entry 1). In the presence of the other enantiomer of L_2, (*S*,*S*)-PhPyBox, the reaction afforded good er. When *N*-(2-methhoxyphenyl)tetrahydroisoquinoline was used, the corresponding enantiomer was obtained with similar enantioselectivity (Table 3, entry 2). *N*-Aryl-substituted THIQs gave high er, when either EDG or EWG were present (Table 3, entries 3–6). High and moderate enantiomeric ratios were obtained, respectively, when vinyl-substituted arylboronic acids and fluoro-substituted arylboronic acids were subjected to the reaction system (Table 3, entries 7 and 8).

Table 3: Enantioselective arylation reaction[a].



Entry	Product	R^1	R^2	er
1	**3a**	H	H	19:81
2[b]	**3b**	2-OMe	H	84:16
3	**3c**	3-OMe	H	10:90
4	**3d**	4-OMe	H	15:85
5	**3e**	4-Me	H	24:76
6	**3f**	4-Br	H	19:81
7	**3m**	H	4-vinyl	19:81
8	**3j**	H	2,4-difluoro	37:63

[a]Reaction conditions: THIQs (0.10 mmol), arylboronic acid (0.30 mmol), TBHP (0.2 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.001 mmol), CuBr (0.01 mmol), (*R*,*R*)-2,6-Bis(4-phenyl-2-oxazolinyl)pyridine (0.012 mmol), DCE (0.5 mL), under argon atmosphere. [b](*S*,*S*)-2,6-bis(4-phenyl-2-oxazolinyl)pyridine was used instead. All reported yields enantiomeric ratios were determined using a Chiralcel OD-H column and 96:4 hexane/isopropanol as an eluent (Supporting Information File 1).

A tentative reaction mechanism has been proposed in Scheme 3, in order to rationalize this arylation reaction. Upon visible light irradiation, $[Ir(ppy)_2(dtbbpy)]PF_6$ **I** was converted into an excited state **II**, Ir(III)* [11,33-37]. The THIQ undergoes a single electron transfer (SET), reducing the iridium complex to Ir(II) **III** and oxidizing the the nitrogen of THIQ **IV** to its radical cation **V**, which then undergoes a hydride abstraction to form the iminium salt form **VI**, of the THIQ. The pre-formed chiral PhCu–PyBox complex [38], coordinates to the iminium cation **VI**, followed by stereofacial nucleophilic addition of the arylboronic acid to produce the desired enantioenriched arylated product **VII**. The Ir(III) is regenerated in the presence of the sacrificial external oxidant TBHP.

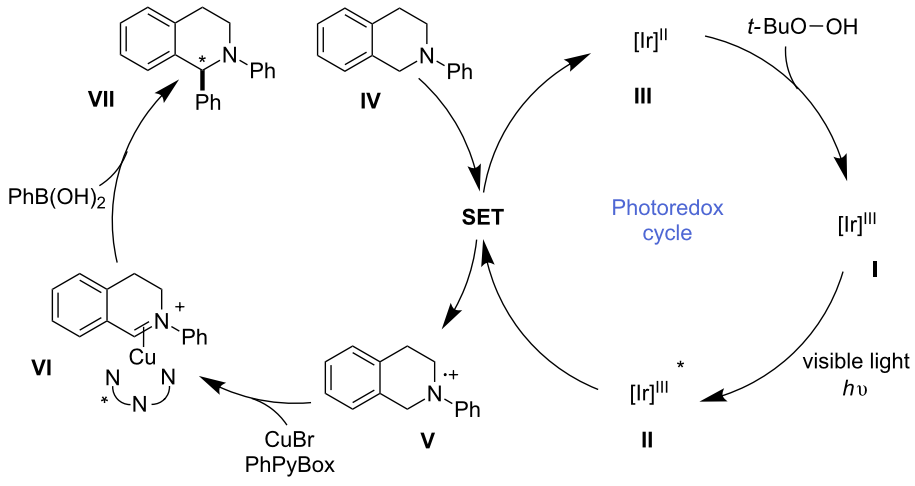
Conclusion

In conclusion, we have successfully developed a highly efficient light-mediated coupling method for the direct asymmetric arylation of *N*-arylated tetrahydroisoquinolines (THIQs) with arylboronic acids. Using $[Ir(ppy)_2(dtbbpy)]PF_6$ as photoredox catalyst provided a novel facile method to build important arylated compounds in very high yields under very mild conditions. The combination of copper salts and PhPyBox as chiral ligand have demonstrated its efficiency producing good enantioselectivity and tolerated a fairly diverse substrate scope. We envisioned that this visible light-mediated asymmetric arylation reaction could be extended to other sp^3 C–H bonds. The development of new light-mediated processes for stereoselective functionalization of unactivated C−H bonds is currently undergoing in our laboratory.

Experimental

General procedure for the sp^3 C–H arylation of THIQs with boronic acid derivatives (Figure 1). A V-shaped 10 mL Biotage reaction vial was charged with $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %, 1.0 mg), $CuBr_2$ (10 mol %, 2.23 mg), *N*-phenyl-tetrahydroisoquinoline (0.1 mmol), and the corresponding phenylboronic acid (0.3 mmol), evacuated and refilled with argon three times. DCE (0.5 mL) was added, followed by subsequent slow addition of TBHP (0.16 mmol). The reaction vessel was sealed, placed under white light bulbs irradiation with vigorous stirring (approx. 1000 rpm) and hold for 24 h. The mixture was diluted with ethyl acetate (2 mL), washed with water (2 mL), filtered through a pad of silica, and rinsed with additional ethyl acetate. The combined organic phase was concentrated and purified by column chromatography or preparative thin-layer chromatography on silica gel to yield the corresponding arylated compound **3**. Dibromomethane was used as internal standard for ^1H NMR analysis.

Variation for enantioselective sp^3 C–H arylation of THIQs with boronic acid derivatives (Table 3). A V-shaped 10 mL Biotage reaction vial was charged with CuBr (10 mol %, 1.43 mg) and PhPybox (12 mol %, 4.43 mg), evacuated and refilled with argon three times, and then 0.1 mL of DCE was added. The reaction was stirred for 30 min. *N*-Phenyltetrahydroisoquinoline (0.1 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %, 1.0 mg) and the corresponding phenylboronic acid (0.3 mmol) were added, and then the atmosphere was evacuated and refilled with argon three times. DCE (0.4 mL) was added followed by subsequent slow addition of TBHP (0.16 mmol). The reaction vessel was sealed, placed under white light bulbs irradiation with vigorous stirring (approx. 1000 rpm) and held for 48 h in a cold room (4 °C). The mixture was diluted with ethyl acetate (2 mL), washed with water (2 mL), filtered through a pad of silica, and rinsed with additional ethyl acetate. The combined organic phase was concentrated and purified by column chro-



Scheme 3: Proposed reaction mechanism.

matography or preparative thin-layer chromatography on silica gel to yield the corresponding arylated compound **3**. Dibromomethane was used as internal standard for ^{1}H NMR analysis.

Supporting Information

Supporting Information File 1

Experimental and copies of spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-260-S1.pdf]

Acknowledgements

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Chromium(II)-catalyzed enantioselective arylation of ketones

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Full Research Paper

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Abstract

The chromium-catalyzed enantioselective addition of carbo halides to carbonyl compounds is an important transformation in organic synthesis. However, the corresponding catalytic enantioselective arylation of ketones has not been reported to date. Herein, we report the first Cr-catalyzed enantioselective addition of aryl halides to both arylaliphatic and aliphatic ketones with high enantioselectivity in an intramolecular version, providing facile access to enantiopure tetrahydronaphthalen-1-ols and 2,3-dihydro-1*H*-inden-1-ols containing a tertiary alcohol.

Introduction

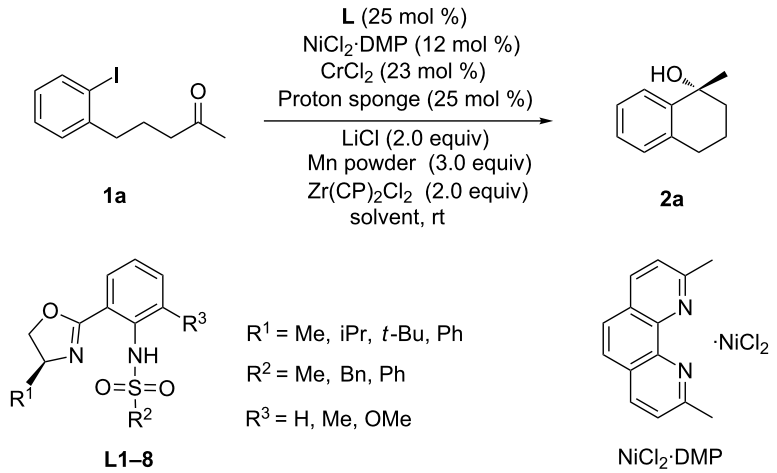
Catalytic enantioselective carbon–carbon bond formation reactions have achieved enormous development during the last few decades as a consequence of the growing demand for enantiopure compounds in modern industry, especially the pharmaceutical industry. The chromium (Cr)-catalyzed enantioselective addition of carbo halides to carbonyl compounds is one of the most reliable methods in organic chemistry for chemoselective and structurally diverse synthesis [1-9]. To date, the Cr-catalyzed enantioselective carbonyl addition reactions mainly focused on allylation, propargylation, alkenylation and alkylation of aldehydes [10,11]. Since the first example of enantioselective allylation of aldehydes catalyzed by a Cr(II)–salen complex in 1999 by Cozzi and co-workers [12], several elegant catalytic enantioselective allylation and propargylation reactions have been developed by the groups of Nakada [13,14], Berkessel [15], Kishi [16], Sigman [17], Yamamoto [18], Guiry [19], Chen [20], Gade [21], White [22], and Zhang [23-25], respectively. The alkenylation and alkylation reactions were mainly explored by the Kishi group [26-30], and they established a toolbox approach to search for the specific ligand with a given substrate in the Cr-catalyzed process [28]. They successfully applied the method to the natural product total synthesis like halichondrin B and norhalichondrin B, and in the subsequent pharmaceutical study, finally leading to the discovery of the anticancer drug Eribulin [31-35]. However, to our knowledge, the Cr-catalyzed enantioselective arylation of carbonyl

compounds has rarely been explored. On the other hand, most of the reactions focused on aldehyde components, while asymmetric addition to ketones remains a big challenge probably due to the decreased reactivity and selectivity [36,37]. A breakthrough was made by the Sigman group who reported the catalytic enantioselective addition of allylic bromides and propargyl halides to arylaliphatic ketones using oxazoline ligands with high enantioselectivity (up to 95% ee) [38-41]. After that, the Chen group also disclosed enantioselective allylation of ketones using spirocyclic chiral borate and chiral bipyridyl alcohol ligands with the ee value ranging from 27% to 97% [42,43]. However, as far as we know, a Cr-catalyzed enantioselective arylation of ketones has never been reported to date [44]. Tetrahydronaphthalen-1-ol bears a chiral tertiary alcohol center and is a common structural motif in numerous biologically active natural products and clinical drugs [45]. The method to prepare these compounds through intramolecular arylation of ketones would be highly desired. Herein, we report the first Cr-catalyzed enantioselective arylation of ketones in an intramolecular version.

Results and Discussion

Initially, the Cr-catalyzed asymmetric intramolecular arylation of arylaliphatic ketone 5-(2-iodophenyl)pentan-2-one (**1a**) was selected as the model reaction for optimization employing Kishi's oxazoline/sulfonamides as the chiral ligands. A series of oxazoline/sulfonamide ligands (**L1**–**L8**) were tested and the results were summarized in Table 1. Four subgroups of R^1 were studied (entries 1–4, Table 1) and isopropyl substituted oxazoline proved to be the best ligand with a 42% ee. Afterwards, R^2 (Table 1, entries 2, 5 and 6) and R^3 (Table 1, entries 6–8) substituents were also examined, and **L8** bearing a methyl

Table 1: Screening conditions of the catalytic enantioselective Cr-mediated arylation of ketone.[a]

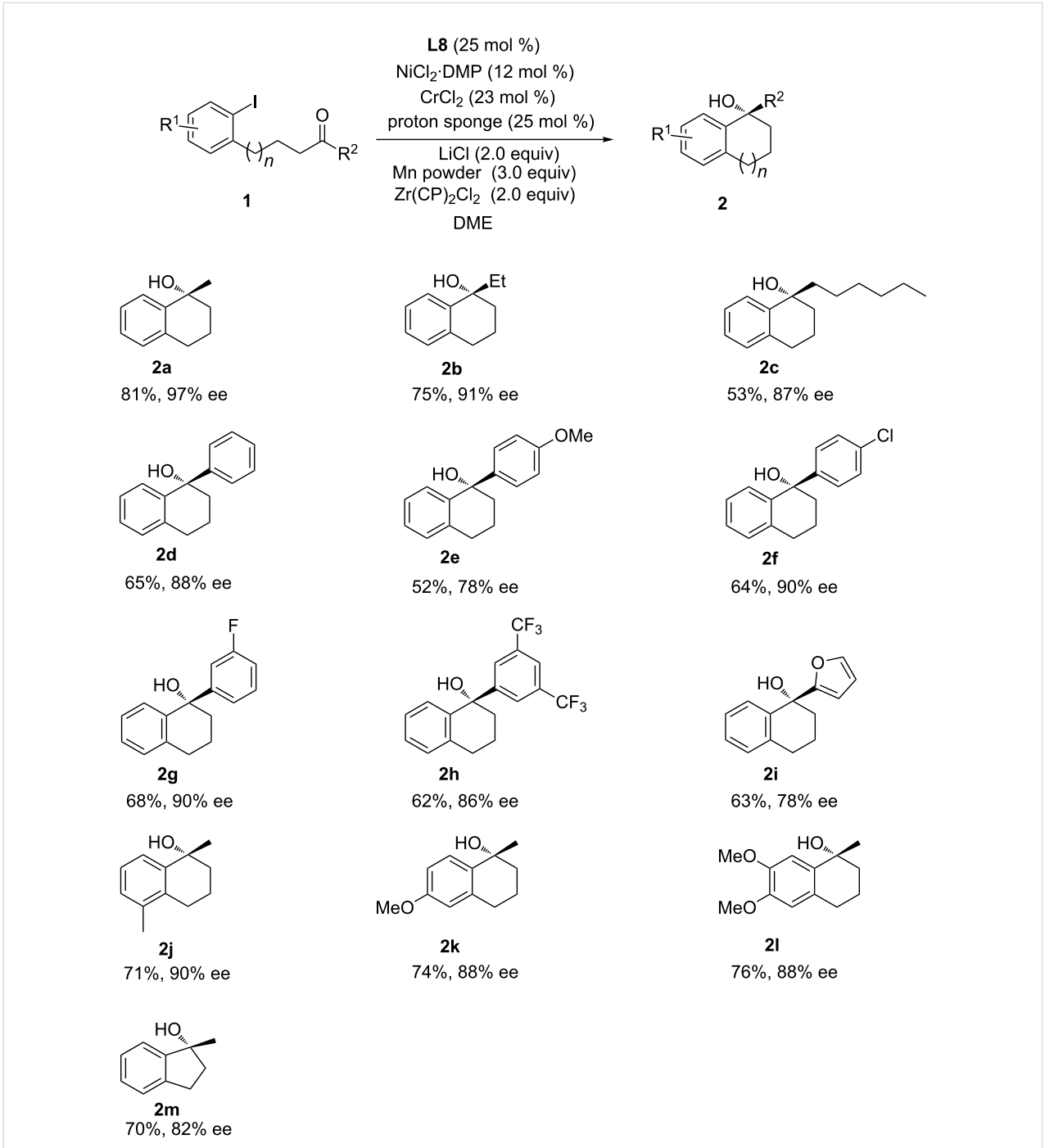


entry	L	R^1	R^2	R^3	Solvent	Yield (%)[a]	ee[b]
1	**L1**	Me	Ph	H	MeCN	43	28
2	**L2**	iPr	Ph	H	MeCN	50	42
3	**L3**	*t*-Bu	Ph	H	MeCN	47	25
4	**L4**	Ph	Ph	H	MeCN	51	21
5	**L5**	iPr	Bn	H	MeCN	12	37
6	**L6**	iPr	Me	H	MeCN	49	56
7	**L7**	iPr	Me	OMe	MeCN	75	75
8	**L8**	iPr	Me	Me	MeCN	85	82
9	**L8**	iPr	Me	Me	THF	93	81
10	**L8**	iPr	Me	Me	DME	90	86
11[c]	**L8**	iPr	Me	Me	DME	86	92
12[d]	**L8**	iPr	Me	Me	DME	81	97
13[e]	**L8**	iPr	Me	Me	DME	51	83
14[d,f]	**L8**	iPr	Me	Me	DME	35	70

[a]Yield of isolated product. [b]Determined by HPLC analysis on a chiral column. [c]Reaction at 0 °C for 24 h. [d]Reaction at −20 °C for 24 h. [e]Reaction at −40 °C for 24 h. [f]Aryl bromide used instead of aryl iodide.

group in both R^2 and R^3 gave the best enantiocontrol. The solvent effect was then investigated, and 1,2-dimethoxyethane (DME) was identified to be the best choice (Table 1, entries 8–10). Lowering the reaction temperature was found to be beneficial for improving the enantioselectivity, and when the reaction was performed at −20 °C, expected **2a** was isolated in 81% yield with 97% ee (Table 1, entries 10–13). Aryl bromide proved to be an inferior coupling component, providing **2a** in 35% yield and 70% ee (Table 1, entry 14).

With the optimized conditions in hand, the scope of the ketone component was first explored (Scheme 1). Aliphatic ketones with (longer) alkyl chain such as ethyl (**1b**) and *n*-hexyl ketones (**1c**), were also tolerated albeit with slightly decreased



Scheme 1: Scope of the catalytic enantioselective Cr-mediated arylation of ketones.

yield and selectivity. The asymmetric arylation of various arylaliphatic ketones also went smoothly (**1d**–**h**). Phenyl ketone **1d** and ketones with electron-withdrawing groups in different substituent patterns gave the expected products with good enantiocontrol, while the enantioselectivity for ketone **1e** bearing an electron-donating group decreased. The mild process exhibited excellent functional group tolerance, with chloride (**2f**), fluoride (**2g**), and CF_3 moieties (**2h**) well tolerated for further manipulation [46,47]. Heteroaryl ketones such as furan-substituted ketone (**1i**) were also suitable substrate, giving product **2i** in 78% ee. The scope of the aryl halide component was next explored (**1j**–**l**). Aryl halides bearing different substituent patterns were tolerated giving the tetrahydronaphthalen-1-ols with good ee values. When 4-(2-iodophenyl)butan-2-one (**1m**) was used, enantiopure indan-1-ol was obtained in 70% yield and 82% ee.

Conclusion

In summary, we have developed the first Cr-catalyzed enantioselective arylation of ketones in an intramolecular version using oxazoline/sulfonamide **L8** as the catalyst. Both aliphatic and arylaliphatic ketones proceeded smoothly, providing corresponding tetrahydronaphthalen-1-ols bearing a tertiary alcohol center with good enantioselectivities (up to 97% ee).

Experimental

General procedure for the chromium(II) catalyzed enantioselective arylation of ketones: The solution of **L8** (0.25 equiv, 0.025 mmol), proton sponge (0.25 equiv, 0.025 mmol) and $CrCl_2$ (0.23 equiv, 0.023 mmol) in DME (1.0 mL) was stirred at room temperature in a glove-box for 1 h. Then the substrate **1** (1.0 equiv, 0.1 mmol), LiCl (2.0 equiv, 0.2 mmol), Mn powder (3.0 equiv, 0.3 mmol), $NiCl_2$·DMP (0.12 equiv, 0.012 mmol) and $Zr(CP)_2Cl_2$ (2.0 equiv, 0.2 mmol) were added successively and the mixture was stirred at indicated temperature for 24 h. After that, the mixture was filtered through a short pad of celite and purified by flash chromatography using silica gel or alumina (200–300 mesh) to give the product **2**.

Supporting Information

Supporting Information File 1

Experimental procedures, analytical data for products, copies of NMR spectra and HPLC chromatograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-275-S1.pdf]

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New approaches to organocatalysis based on C–H and C–X bonding for electrophilic substrate activation

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Review

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Abstract

Hydrogen bond donor catalysis represents a rapidly growing subfield of organocatalysis. While traditional hydrogen bond donors containing N–H and O–H moieties have been effectively used for electrophile activation, activation based on other types of non-covalent interactions is less common. This mini review highlights recent progress in developing and exploring new organic catalysts for electrophile activation through the formation of C–H hydrogen bonds and C–X halogen bonds.

Review

Introduction

Over the past century chemists have gathered great amounts of information about the factors governing enzymatic reactions. These studies have helped to realize the importance of non-covalent interactions within the receptor, and many subsequent efforts have been focused on adopting the knowledge learned from nature to the rational design of small molecule-based catalysts mimicking enzymatic function. A significant number of such efforts has been dedicated to designing new catalysts to enhance the electrophilicity of organic molecules through non-covalent interactions, and many important areas of organocatalysis have emerged from these efforts. The use of synthetic hydrogen bond donors for the activation of neutral or ionic electrophiles has been one of the major focuses of these research efforts in the past two decades (Figure 1) [1]. Many privileged hydrogen bond donor scaffolds capable of forming single or double hydrogen bonds with the substrate have been developed and explored as catalysts of numerous organic transformations [2-15]. Such catalysts (i.e., **I–IX**) [16] may contain one or several highly polarized A–H···A bonds, where A is oxygen or nitrogen and are often designed to mimic enzymatic reactions through the electrostatic substrate activation or stabilization of charged transition states or reaction intermediates. At the same time, recent studies highlight the importance of other types of non-covalent interactions such as the activation through the for-

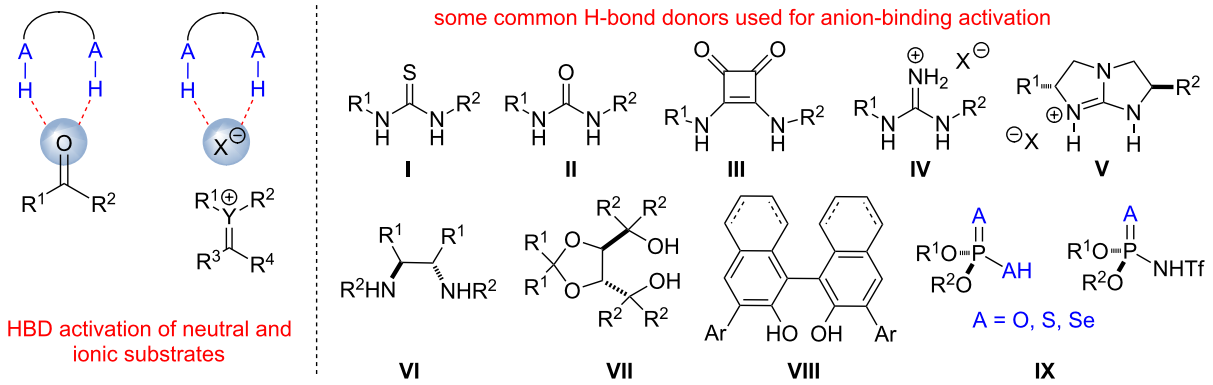


Figure 1: Electrophile Activation by Hydrogen Bond Donors [1-16].

mation of C–H···A hydrogen bonds or halogen bonding (C–X···X or C–X···A interactions) in organocatalyst design. Such non-covalent interactions have been traditionally viewed as "weak" when compared to classical A–H···A hydrogen bonds. However, in some cases the term "weak" may be misleading as an increasing number of examples demonstrate the effectiveness of such interactions for organocatalyst design. While C–H···A hydrogen bonds have been invoked in biological processes, halogen bonding is not commonly observed in natural enzyme-catalyzed reactions. Therefore, application of these new interactions for small molecule activation allows expanding the repertoire of existing organic catalysts beyond what is found in biological systems.

This mini review highlights recent progress on organocatalysis that is based on C–H···A or halogen (C–X···X or C–X···A) bonds for substrate activation.

C–H hydrogen bonds

It is well established that the C–H moiety can serve as a hydrogen bond donor and form hydrogen bonds with oxygen, nitrogen or halogens of neutral molecules or anions [17]. However, such interactions have been considered negligible in comparison to much stronger A–H···A hydrogen bonds (A = N, O, F). While Glasstone proposed the formation of a C–H hydrogen bond between chloroform and ethereal solvents in 1935 [18], and Lipscomb discovered hydrogen bonding in solid hydrogen cyanide in 1951 [19], until recently C–H hydrogen bonds have been mostly observed in the solid state (Figure 2). Recent studies in supramolecular chemistry have demonstrated that hydrogen bonds formed by C–H bonds are not necessarily "weak", and in certain cases are almost as strong as more traditional A–H···A bonds [20]. The C–H hydrogen bonding between the substrate and the catalyst could be of great significance for transition state organization and energy, and is often invoked to rationalize the outcome of various transformations [21-27]. However, until recently C–H hydrogen bond-based interactions have not been employed in rational organic catalyst design, and more traditional A–H hydrogen bond donors such as **I–IX** (Figure 1) have been utilized to enhance the electrophilicity of organic molecules.

Recent spectroscopic and computational studies provided evidence that arenes might form strong hydrogen bonds between aryl C–H groups and anions (Cl^-, NO_3^-, ClO_4^-, etc.) in the gas phase [28]. In addition, the introduction of an electron-with-

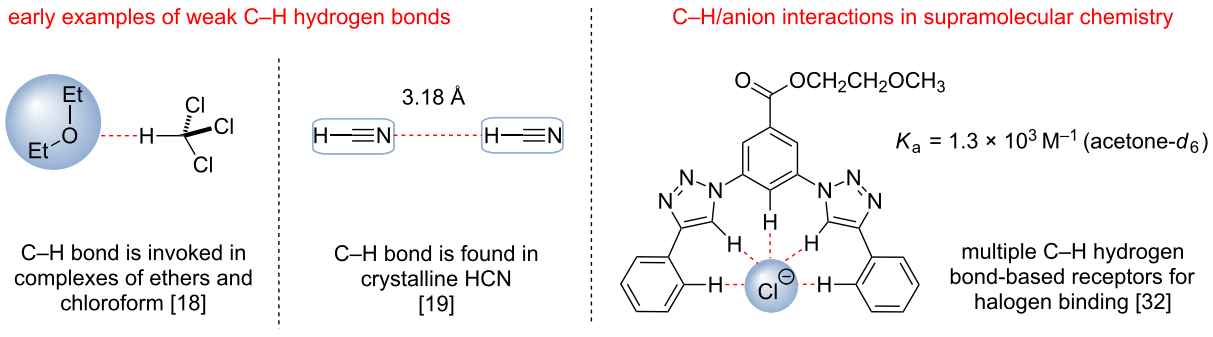


Figure 2: Early examples of C–H hydrogen bonds and their recent use in supramolecular chemistry [18,19,32-34].

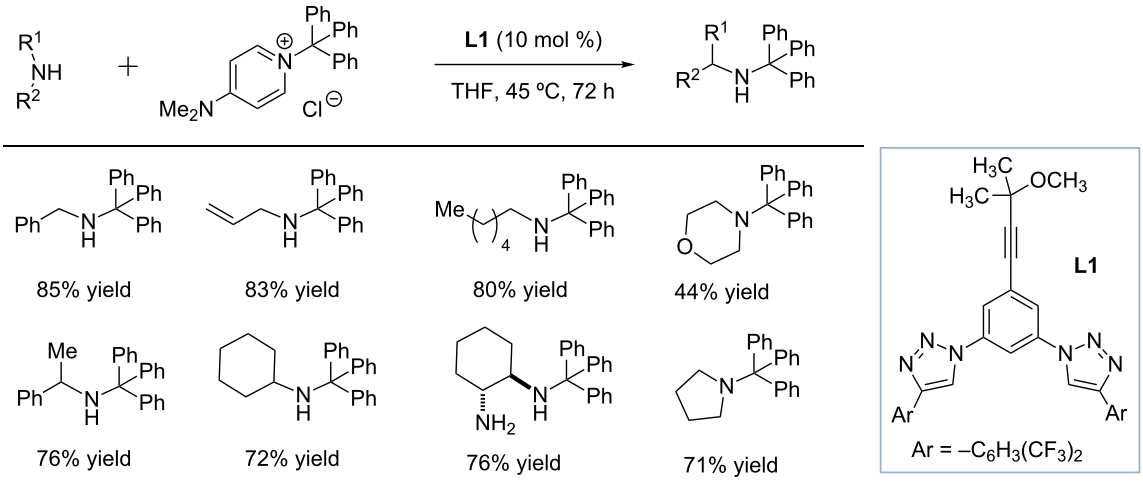
drawing group into the aryl ring (i.e., NO_2, CN, CF_3, etc.) could significantly enhance this binding and result in stronger hydrogen bonds between the arene and the anion. Thus, the gas-phase binding energy of the nitrobenzene and chloride anion complex containing two C–H hydrogen bonds was estimated to be −16.8 kcal/mol whereas the corresponding binding energy for the H_2O/Cl^- complex was determined to be −15.4 kcal/mol. Electron-deficient heterocyclic compounds such as 1,2,3-triazoles may also serve as strong C–H hydrogen bond donors. Substituted 1,2,3-triazoles possess a substantial dipole moment (≈4.5 D) almost aligned with the C5–H bond and the relatively high acidity of this position ($pK_{a(DMSO)}$ = 27–28, for the 1*H*-tautomer). These heterocycles, which are easily available from 1,3-cycloaddition of alkynes and azides, can both form strong C–H bonds with hydrogen bond acceptors and also act as electron-withdrawing substituents when attached to other aromatic rings thus enhancing benzene's ring C–H hydrogen bonding [29-31]. Recent studies by the Flood group and the Craig group suggested that receptors containing arylated 1,2,3-triazoles could form stable supramolecular complexes with anions [32-34]. The stability of such complexes correlated with the number of C–H bonds that could be formed by the receptor, and strong binding comparable to the more traditional X–H bonding based hydrogen bond donors was observed for the receptors forming 5–9 hydrogen bonds with halides ($K_a \approx 10^3$–10^4 M^{-1} in acetone-d_6). Not surprisingly, a higher number of hydrogen bonds with an anion correlated with the higher stability of the receptor/anion complex.

1,2,3-Triazole-based catalysts for the dearomatization of *N*-heteroarenes

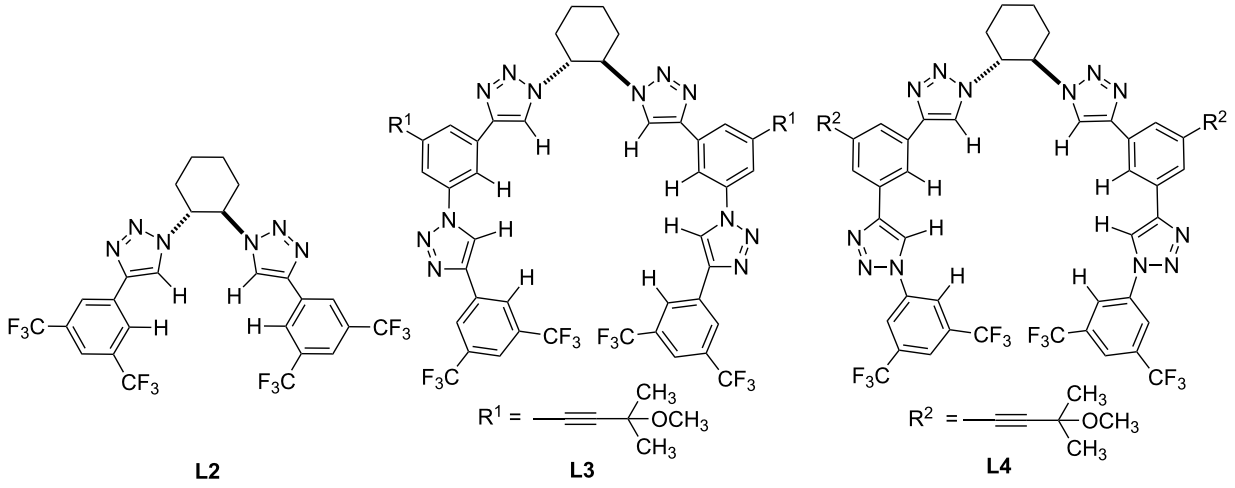
The Mancheno group recently explored triazole-based receptor **L1** as the organic catalysts for counterion activation (Scheme 1) [35]. Receptor **L1** capable of forming 5 hydrogen bonds was found to form a stable supramolecular complex with chloride in acetone (K_a = 458 M^{-1} in acetone-d_6), and promoted efficient trityl group transfer from tritylated DMAP chloride to various primary and secondary amines. The authors propose that **L1** binding with chloride results in a more electrophilic tritylated DMAP cation, and the binding affinity of the catalyst was found to correlate with the *N*-alkylation rate.

Following the aforementioned studies, the Mancheno group designed and synthesized various chiral triazole-based complexes such as **L2–L4** (Scheme 2) [36-39]. It was proposed that while these triazole derivatives are conformationally flexible, upon their binding to halogen anions these complexes adopt a reinforced chiral helical conformation. The resultant close chiral anion-pair complexes would then undergo a chiral counterion-controlled asymmetric reaction with a nucleophile. This proposal was validated experimentally, and a chloride-induced conformational switch to form a helical backbone was experimentally observed by circular dichroism (CD) during the titration of **L4** with TBAC [37].

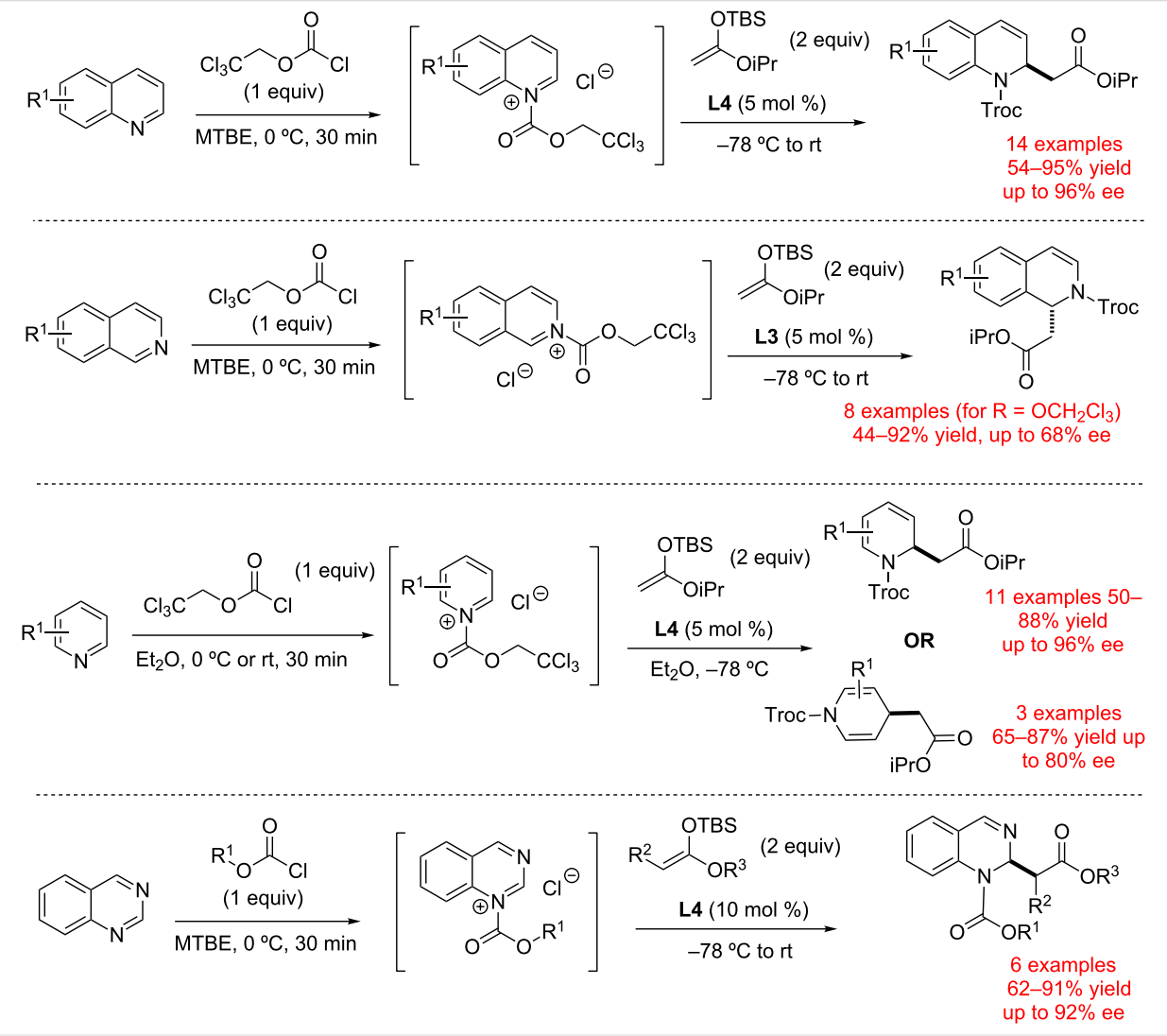
Catalysts **L3** and **L4** were successfully applied to the asymmetric dearomatization of electron-deficient *N*-heteroarenes (Scheme 3). Various nitrogen-containing heterocycles such as pyridines [36], quinolines [38], isoquinolines [38], etc. were reacted with TrocCl to form the corresponding salts, and these generated in situ ion pairs were treated with silyl enol ethers in the presence of chiral catalysts **L2–L4** to form chiral addition products. High levels of chirality transfer were generally observed for various 6-membered nitrogen-containing heterocyclic substrates, and chiral products were obtained in good yields and selectivities. Remarkably, the performance of tetra-



Scheme 1: Design of 1,2,3-triazole-based catalysts for trityl group transfer through chloride anion binding by Mancheno and co-workers [35].



Scheme 2: Examples of chiral triazole-based catalysts for anion activation designed by Mancheno and co-workers [36-39].

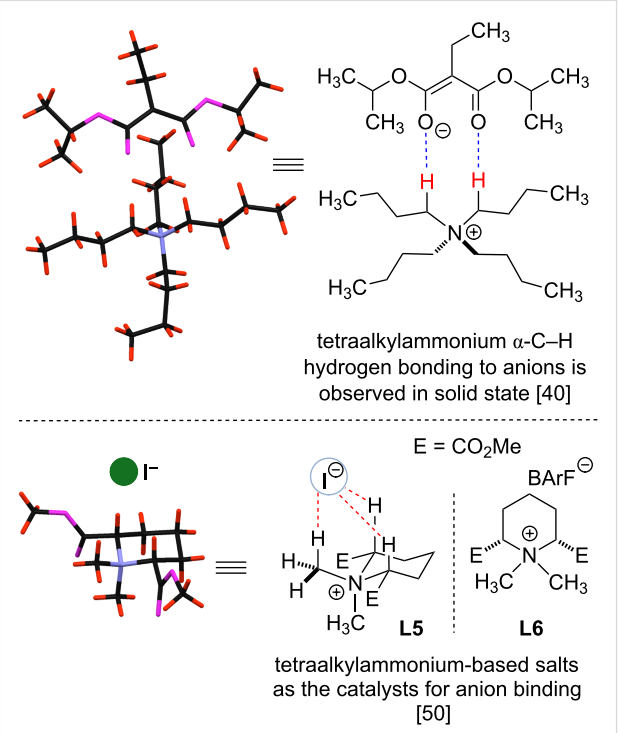


Scheme 3: Application of chiral triazole-based catalysts **L3** and **L4** for counterion activation of pyridinium, quinolinium and isoquinolinium salts by Mancheno and co-workers [36-39].

kistriazoles was found to be comparable (or in some cases superior) to the well-established thiourea- and squaramide-based catalysts developed for similar transformations.

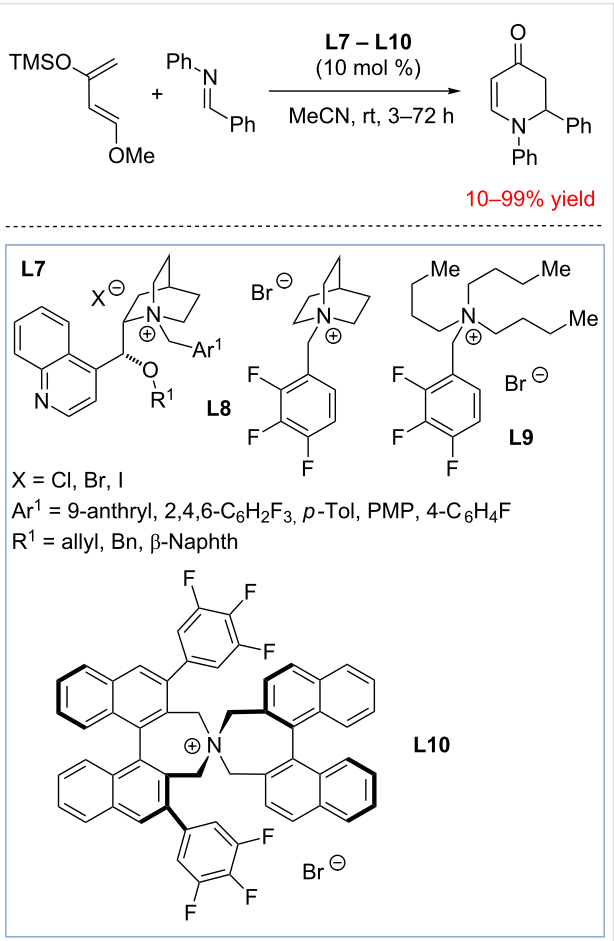
Quaternary tetraalkylammonium and alkylpyridinium salts as C–H hydrogen bond donors

While quaternary ammonium salts have extensively been used as phase transfer catalysts to activate ionic nucleophiles, recent studies suggest that these compounds can also serve as effective hydrogen bond donors. In 1993 Reetz and co-workers provided crystallographic evidence that the alpha C–H bonds of tetraalkylammonium salts are highly polarized, and can form multiple hydrogen bonds with enolates in the solid state (Scheme 4) [40-45]. The existence of alpha C–H hydrogen bonds has also been invoked in the computational studies rationalizing the outcome of various asymmetric phase-transfer reactions [46-49]. However, despite these developments until recently [50,51] the use of tetraalkylammonium salts as hydrogen bond donor catalysts has not been explored.



Scheme 4: Ammonium salt anion binding via C–H hydrogen bonds in solid state [40-45,50,51].

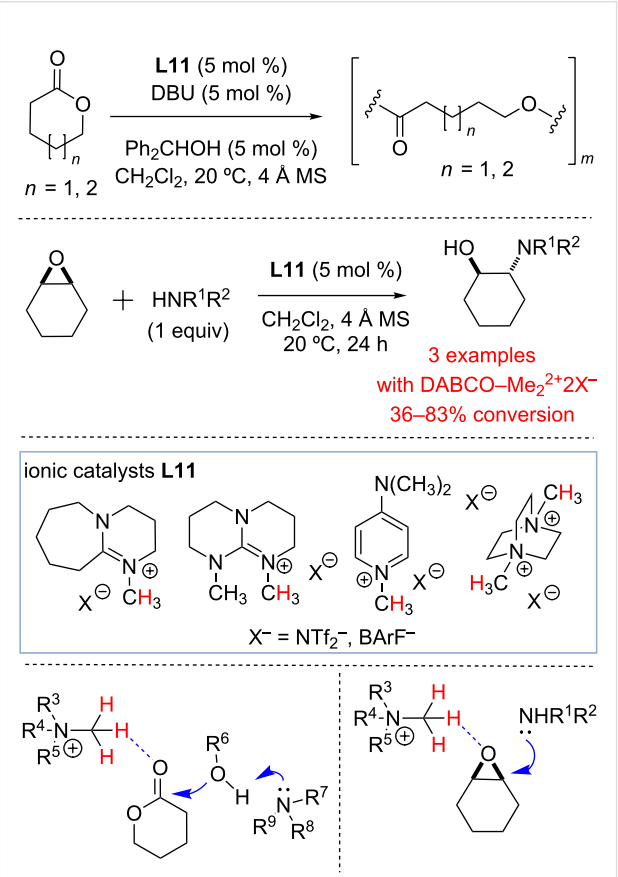
In 2011 the Park group investigated ammonium salts as catalysts for aza-Diels–Alder reactions of Danishefsky's diene with imines (Scheme 5) [52]. A variety of ammonium salts (**L7–L10**) including chiral cinchonidine derivatives **L7** and catalyst **L10** were found to promote the reaction in low-to-good yields albeit with no enantioselectivity. Although it is perhaps one of the first examples of utilizing tetralkylammonium salts as hydrogen bond donor catalysts, the authors provided no mechanistic proposal for the catalytic activity of **L7–L10**, and the activation of the imine by the formation of a C–H···N hydrogen bond was proposed later by Maruoka and Shirakawa [50,51].



Scheme 5: Early examples of ammonium salts being used for electrophilic activation of imines in aza-Diels–Alder reactions [52].

In 2013 Bibal and co-workers investigated the use of methylated amines, pyridines and guanidines (**L11**) as hydrogen bond-donor catalysts for the activation of cyclic esters toward ring-opening polymerization (ROP) [53]. Ionic catalysts **L11** (5 mol %) were successfully employed in combination with DBU and initiator (Ph_2CHOH) to accomplish C=O activation and to promote the polymerization reactions (Scheme 6). Highly charged tetraalkylbisammonium salts (i.e., DABCO-Me_2·2X) were found to be particularly active catalysts. Based on computational studies, the authors proposed that substrate activation is accomplished through a C–H hydrogen bond with cyclic ester carbonyls. The following study by the Bibal group

described the use of catalysts **L11** as hydrogen bond donors for the activation of epoxides toward ring-opening aminolysis with amines (Scheme 6) [54]. Significant rate enhancement was observed under mild conditions with **L11**. The activity of catalysts **L11** was found to be comparable to the activity of common thiourea-based hydrogen bond donors, and double-charged catalyst DABCO-Me_2·2X was found to be one of the most active catalysts. As before [53], the activity of ammonium salts **L11** was attributed to their ability to form a hydrogen bond with the oxygen of epoxide.



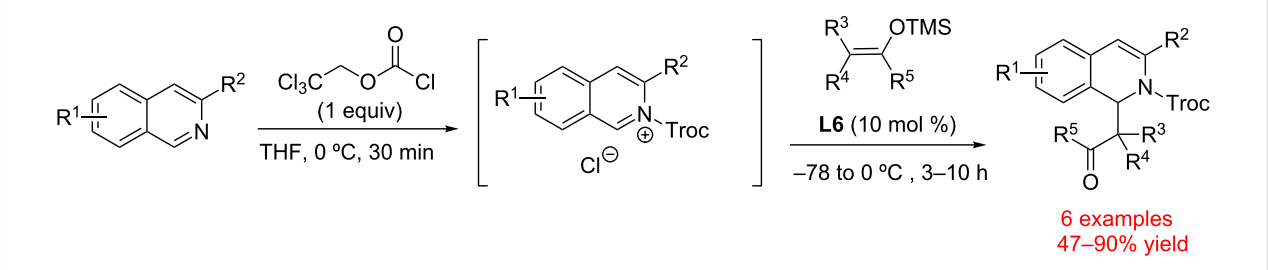
Scheme 6: Ammonium salts as hydrogen bond-donor catalysts by Bibal and co-workers [53,54].

In 2015 Shirakawa and Maruoka demonstrated that ammonium salts **L5** and **L6** could serve as effective catalysts for isoquinolinium and pyridinium salt Mannich reactions (Scheme 7) [50]. Catalysts **L5** and **L6** were selected due to their conformational rigidity that results in a better alignment of alpha C–H groups, relatively high polarization of the alpha C–H bonds due to the presence of electron-withdrawing ester functionalities, and ease of preparation (1–2 steps from commercially available piperidine). Interestingly, the authors assessed the strength of C–H hydrogen bonds to the iodide anion in **L5** relative to the *N*-methylpiperidinium iodide salt by measuring the distances between the alpha-hydrogen atom and iodide in the solid state. Thus, the C–H···I hydrogen bonds for **L5** were found to be 0.2–0.4 Å shorter than for *N*-methylpiperidinium iodide.

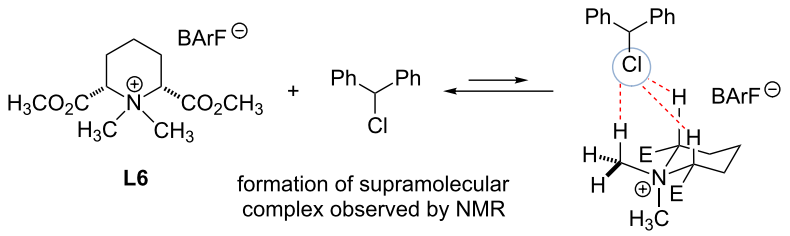
Both **L5** and **L6** were found to promote the Mannich reaction between *N*-Troc-isoquinolinium chlorides and silyl enol ethers. Catalyst **L6** with non-coordinating $BArF^-$ counterion was found to have a significantly higher activity than **L5** with iodide counterion, probably, due to the competitive binding with iodide. Both **L5** and **L6** were inhibited by the addition of tetrabutylammonium chloride, which reinforces the proposal that these salts act as HBDs. Interestingly, NMR titration studies revealed that **L6** could form a supramolecular complex not only with a chloride anion, but also with chlorine atoms covalently bonded to a benzylic carbon (Scheme 8).

In 2016 Maruoka and Shirakawa followed up the aforementioned studies by demonstrating that tetraalkylammonium salts **L5**, **L6**, **L11** and **L12** as well as TBAI could activate imines toward aza-Diels–Alder reaction with Danishefsky's diene (Scheme 9) [51]. Catalyst **L11** was selected as the catalyst of choice due to its simplicity and activity. Based on the ^{1}H NMR studies and X-ray crystallographic analysis the authors concluded that tetralkylammonium salts act as hydrogen bond donors through the formation of a C–H···N hydrogen bond.

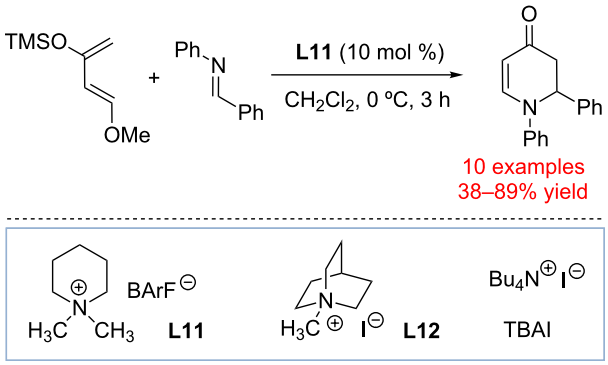
In 2014, Berkessel and co-workers reported the use of *N*-alkylated 3,5-di(carbomethoxy)pyridinium ions **L13** to catalyze the reaction between 1-chloroisochroman and silyl ketene acetals



Scheme 7: Tetraalkylammonium catalyst (**L6**)-catalyzed dearomatization of isoquinolinium salts [50].



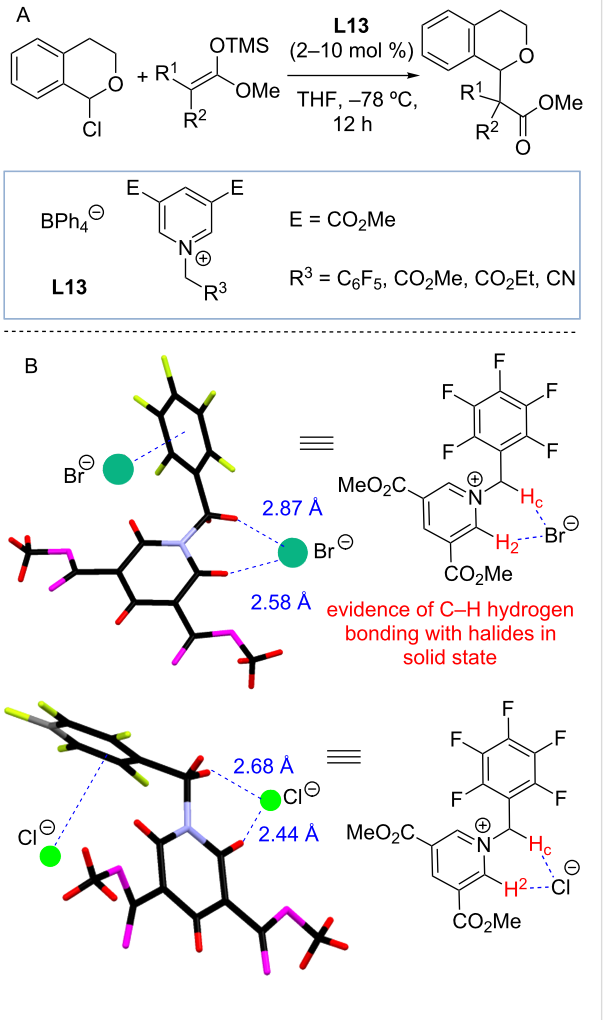
Scheme 8: Tetraalkylammonium catalyst **L6** complexation to halogen-containing substrates [51].



Scheme 9: Tetraalkylammonium-catalyzed aza-Diels–Alder reaction by Maruoka and co-workers [52].

(Scheme 10A). Catalyst **L13** with $R^3 = C_6F_5$ was found to be particularly active, and was found to efficiently form the product at 2 mol % loading without significant erosion in yield or reaction time [55]. Interestingly, the ability of catalysts **L13** to catalyze the reaction was attributed to 1-chloroisochroman activation through Coulombic interactions coupled with anion–π bonding. Thus, **L13** was proposed to promote ionization of 1-chloroisochroman followed by anion exchange. The resultant oxocarbenium/tetraphenylborate ion pair undergoes a nucleophilic attack by silyl ketene acetal, which is followed by scavenging the trimethylsilyl cation with a chloride anion to result in chlorotrimethylsilane and the product. Mechanistic studies were conducted to establish that **L13** forms weak 1:1 complexes with chloride and bromide anions. Thus, ^{1}H NMR titration studies of **L13** with $R^2 = C_6F_5$ demonstrated the formation of the corresponding chloride complex with 1:1 stoichiometry and $K_a \approx 200\ M^{-1}$.

In light of the recent studies by Shirakawa and Maruoka [50,51], we propose that catalysts **L13** could act not only through Coulombic interactions, but also as hydrogen bond donors. While various factors including Coulombic interactions between the pyridinium (or ammonium) salt and the chloride undoubtedly play an important role in promoting substrate ionization and chloride complexation, the provided X-ray data



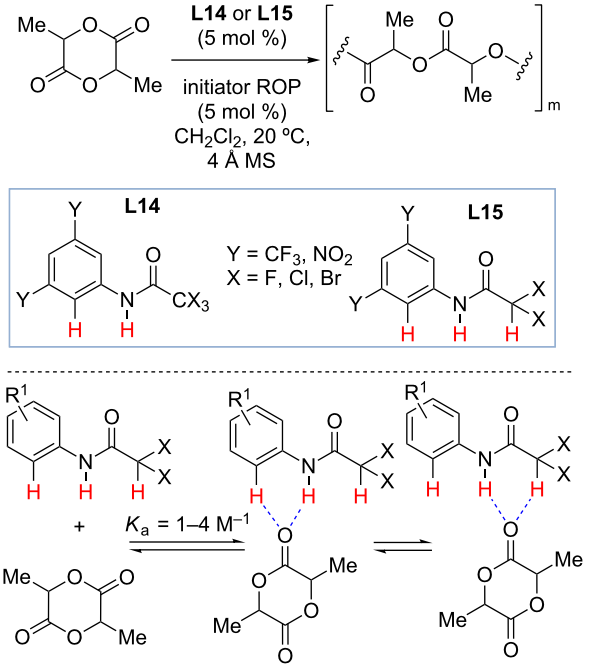
Scheme 10: (A) Alkylpyridinium catalysts **L13**-catalyzed reaction of 1-isochroman and silyl ketene acetals by Berkessel and co-workers. (B) Evidence of **L13** C–H···X^- hydrogen bonding in solid state [55].

are consistent with **L13** acting as hydrogen bond donors (Scheme 10B). The published X-ray data for the chloride and bromide salts of **L13** with $R^2 = C_6F_5$ indeed provide evidence of anion–π bonding with the C_6F_5 group. In addition, we also noted that there is evidence for two hydrogen bonds formed be-

tween the halide or bromide anion and C–H_2/C–H_c bonds of another cation **L13**.

Mixed N–H/C–H hydrogen bond donors as organocatalysts

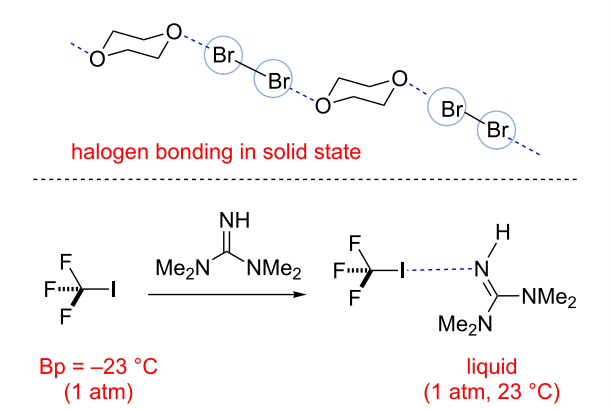
The involvement of the ortho C–H bond in the binding event with Lewis-basic sites was proposed by Etter in the late 1980s and later demonstrated by Schreiner in a detailed study of hydrogen-bonding thiourea organocatalysts containing a 3,5-bis(trifluoromethyl)phenyl group as the privileged motif [56-58]. A recent example of utilizing such interactions in catalysis was demonstrated by Bibal and co-workers [58]. In this study, Bibal and co-workers explored the use of α-halogenated acetanilides **L14** and **L15** as hydrogen-bonding organocatalysts that activate the carbonyl functionality of lactide and thus enhance their reactivity toward ROP (Scheme 11). In addition to their ability to form more conventional N–H hydrogen bonds, **L14** and **L15** were proposed to form additional C–H hydrogen bonds between arene or α-halogenated acetyl groups and the carbonyl of lactide. X-ray crystallographic analysis and molecular modeling provided the evidence of such interactions in solid state, and the titration studies established weak binding ($K_a \approx 1–4\ M^{-1}$) between **L14** or **L15** and lactide in solution. The α-dichloro and α-dibromoacetanilides **L14** containing electron-deficient aromatic groups (i.e., *m,m*'-NO_2 substitution on phenyl ring) afforded the most active catalysts with the strongest N–H···O···H–CX_2 interactions.



Scheme 11: Mixed N–H/C–H two hydrogen bond donors **L14** and **L15** as organocatalysts for ROP of lactide by Bibal and co-workers [58].

Halogen bonds as alternatives to hydrogen bonds

The ability of halogens and halogenated organic compounds to form stable complexes with nucleophiles has been known for more than two centuries [59-61]. One of the earliest examples of such complexes were the adducts formed by the reaction of iodine and amylose or ammonia described by Colin in 1814 [62]. While the stoichiometry of such complexes was not established at the time, Guthrie in 1863 [63] and Norris in 1896 [64] were able to generate complexes formed between molecular halogens (I_2, Br_2, and Cl_2) and ammonia or methylamines and characterized them. Numerous studies attempting to elucidate the nature of halogen complexes have emerged since then; however, the structural features of these interactions were unclear until the work of Mulliken who proposed the formation of donor–acceptor complexes [65,66] and Odd Hassel who conducted crystallographic studies of bromine complexed with 1,4-dioxane in 1970 [67]. The evidence of the actual bonding were found in these complexes as the O−Br distance in the crystal was about 2.71 Å (Scheme 12), which is 20% smaller than the sum of the van der Waals radii of oxygen and bromine (3.35 Å) while the angle between the O−Br and Br−Br bond was found to be ≈180°.

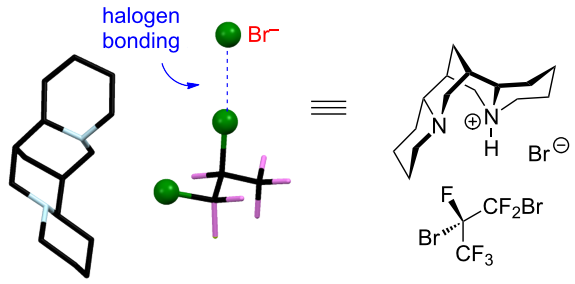


Scheme 12: Examples of stable complexes based on halogen bonding [68,69].

Since these reports, numerous other examples of halogen bonding have been uncovered, and halogen bonding has become of great importance to the fields of chemistry and materials science. Not only halogens, but also neutral halogen-containing organic molecules were found to form stable adducts with neutral and charged Lewis bases, and to account for this IUPAC provided the following recommendation "A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity" [68]. Such complexes may have

substantially different properties from the uncomplexed organohalides, which is well exemplified by the at room temperature liquid complex of gaseous iodotrifluoromethane (BP = −23 ºC) and tetramethylguanidine containing a halogen (I···N) bond [70].

When chiral organohalides form halogen bonds with chiral acceptors, diastereomeric complexes may be formed. Thus, in 1999, Resnati reported the resolution of racemic 1,2-dibromohexafluoropropane through halogen-bonded supramolecular helices (Scheme 13) [69]. When (−)-sparteine hydrobromide in chloroform was treated with racemic 1,2-dibromohexafluoropropane, a yellow co-crystal was isolated. The structure of the co-crystal was confirmed by single-crystal X-ray diffraction, and it showed that the co-crystal was made up from one molecule of (−)-sparteine hydrobromide and one molecule of (*S*)-1,2-dibromohexafluoropropane. The $Br^-\cdots Br$ distance (Scheme 13) is about 3.3 Å, which is approximately 20% shorter than the sum of the van der Waals radii. The angle between $Br^-\cdots Br–C$ is about 175º. The strong $Br^-\cdots Br–C$ halogen bonds are robust enough to drive the self-assembly and are critical for the resolution. This example clearly demonstrate the great potential of halogen bonds as tools for asymmetric catalysis.

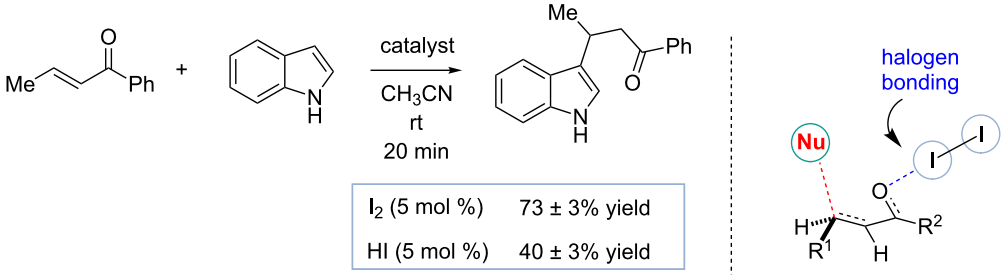


Scheme 13: Interaction between (−)-sparteine hydrobromide and (*S*)-1,2-dibromohexafluoropropane in the cocrystal through halogen bonds [69].

Early uses of halogen bond donors in catalysis and organocatalysis

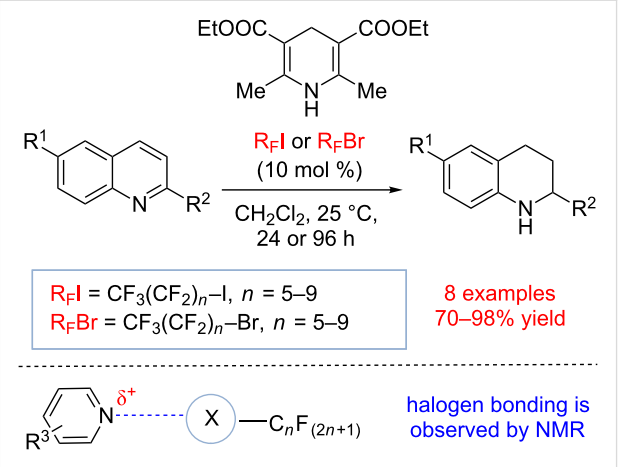
Like hydrogen bonds, halogen bonds possess important features such as strength and directionality that might make these interactions of a great value to the field of organocatalysis [71-73]. Molecular iodine has been used for many decades as a mild catalyst or promoter of various organic transformations such as conjugate addition, imine formation or aldolate dehydration reactions [74-79]. Interestingly, such reaction mechanisms are not well understood, and the formation of trace quantities of hydroiodic acid rather than the direct substrate activation by molecular iodine has been frequently invoked to rationalize the outcome of these studies. Recently, Breugst and co-workers have re-evaluated the molecular iodine-catalyzed conjugate addition to α,β-unsaturated carbonyls or nitrostyrenes (Scheme 14) [80]. Based on their computational studies, they proposed that iodine activates the enone moiety by forming a halogen bond with the carbonyl and thus forming a more reactive complex with the LUMO. These results are further backed up by control experiments demonstrating that catalytic quantities of hydroiodic acid were less effective in promoting this reaction than molecular iodine, and hidden Brønsted acid catalysis is unlikely to be operational in these studies.

In 2008 the Bolm group explored the use of halogen bond donors in organocatalysis. They discovered that perfluorinated alkyl halides could activate 2-substituted quinolines toward reduction by Hantzsch ester (Scheme 15) [81]. These studies explored various C_6 to C_{10} perfluorinated bromides and iodides. It was discovered that organic iodides were more reactive than the corresponding bromides and that the product yield increased with increasing lengths of the perfluorinated carbon chain. Thus, $CF_3(CF_2)_9I$ was found to be the most effective at 10 mol % loading and the product could be isolated in 98% yield after 24 h. Remarkably, when the catalyst loading was reduced to 1 mol %, the product could still be obtained in 69% yield after 96 h. Although the hidden acid catalysis due to the trace amounts of HI was not ruled out, the proposed *N*-halogen bond formation between quinolone and perfluo-



Scheme 14: Iodine-catalyzed reactions that are computationally proposed to proceed through halogen bond to carbonyl [80].

roiododecane during the catalytic process was supported by ^{13}C and ^{19}F NMR studies.

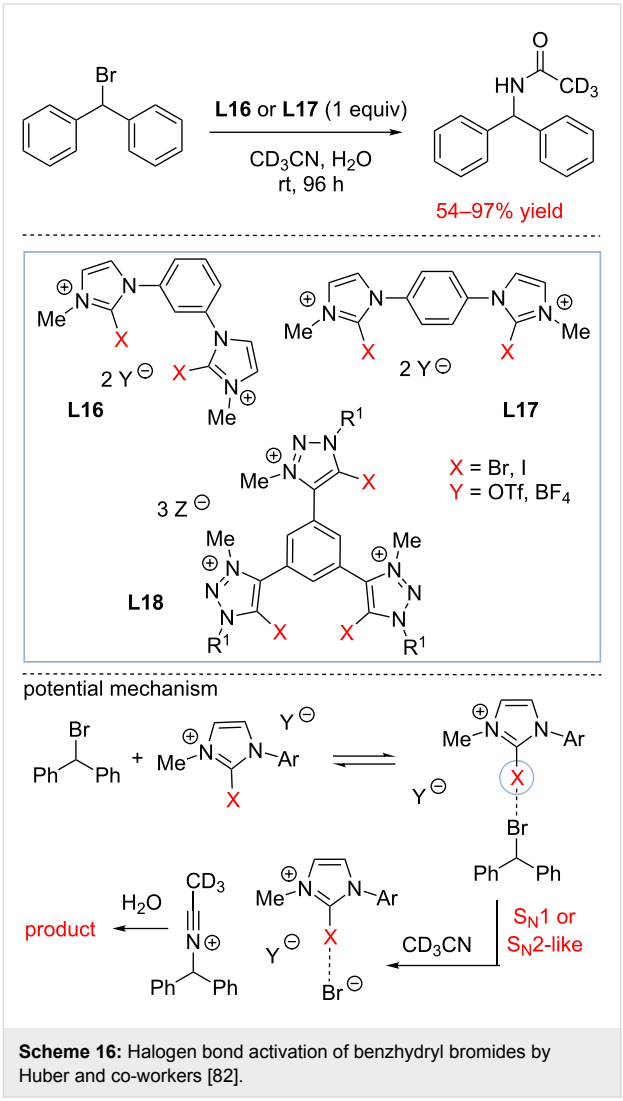


Scheme 15: Transfer hydrogenation of phenylquinolines catalyzed by haloperfluoroalkanes by Bolm and co-workers [81].

Halogen bond donor organocatalysis based on aryl halides

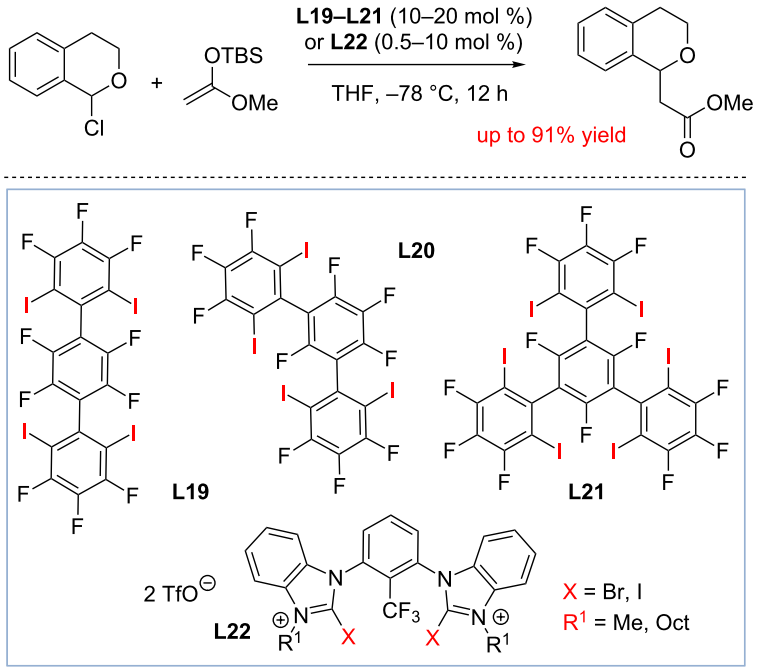
The pioneering study of Bolm has attracted significant attention and a number of important studies have emerged since then. In particular, the Huber group has contributed to the development of a new design of organocatalysts based on aryl iodides as halogen bond donors [73,82-88]. These catalysts were found to act as organic Ag^+ surrogates and activate an ionizable substrate by halide anion scavenging. Thus, in 2011, Stefan M. Huber and his colleagues investigated the activation of a C–Br bond by novel halogen-bond donors **L16** and **L17** [82]. The authors synthesized compounds **L16** and **L17** as well as some other halogen bond donors and tested their ability to promote the Ritter reaction of (bromomethylene)dibenzene (Scheme 16). The stoichiometric amounts of **L16** and **L17** were found to promote the formation of a benzhydryl acetamide product in good-to-excellent yields. The control experiments with deiodinated **L16** and **L17** confirmed the importance of halogen bonding for this transformation. A strong counterion effect was observed in these studies, and the BF_4^- salt of **L16** were found to be significantly more reactive than the corresponding TfO^- salts. Interestingly, **L16** that can potentially form two halogen bonds with the same bromine atom were found to be marginally less active promoters in comparison to compounds **L17**. Finally, the control experiments ruled out hidden acid catalysis due to the formation of trace quantities of HBr through hydrolysis of the substrate.

To further enhance the reactivity of the halogen bond donors, Huber and colleagues later designed 5-iodo-1,2,3-triazolium-based multidentate salts **L18** [83,84]. Triazolium salts **L18** were



Scheme 16: Halogen bond activation of benzhydryl bromides by Huber and co-workers [82].

found to be particularly good in promoting the formation of benzhydryl acetamide (95% after 96 h). Due to the formation of the strong inhibitor, hydrobromic acid that acts as the source of bromide anion as the reaction progresses, the aforementioned studies required a stoichiometric amount of halogen bond donors. However, catalytic halogen scavenging with halogen bond donors is also possible if the products are not inhibiting the catalyst. One of such transformations explored by the Huber group is the addition of ketene silyl acetals to 1-chloroisochroman (Scheme 17) [85,87]. The chloride anion produced in this reaction will eventually form chlorotrialkylsilane, which does not inhibit the catalyst. As a result, catalytic amounts of neutral HBDs **L19–L21** were found to promote this transformation at 10–20 mol % catalyst loading. Unlike the Ritter reaction study summarized in Scheme 16, the activity of the catalyst was found to directly correlate with the stability of supramolecular complex, and **L21** capable of forming multiple halogen bonds at the same time was found to be the most active



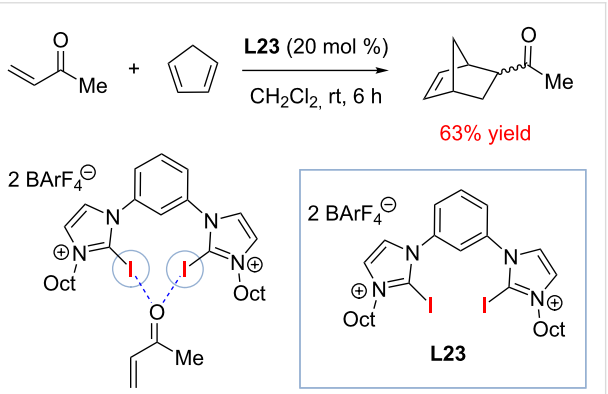
Scheme 17: Halogen bond-donor-catalyzed addition to oxocarbenium ions by Huber and co-workers [89].

catalyst. The binding properties of **L19–L21** toward halides in the solid state, in solution, and in the (calculated) gas phase were further investigated by Huber [89].

Following the aforementioned studies, the Huber group has designed structurally rigid electron-deficient cationic catalysts **L22** based on the bis(halobenzimidazolium) scaffold [87]. These catalysts were found to be particularly active, and the catalyst with X = I, and R = Oct promoted the reaction between 1-chloroisochroman and silyl enol ether at 0.5 mol % catalyst loadings (70% yield, 6 h). A good correlation was observed between the catalytic activity and halogen affinity, and the K_a of **L22** with X = I, R = Oct with bromide anion was determined to be 3.5×10^6 M^{-1} (CH_3CN). In addition to the aforementioned studies, recent results by Huber and Codée indicate that not only 1-chloroisochroman, but also more complex substrates such as 2,3,4,6-tetra-*O*-benzylglucosyl chloride could undergo halogen bond-donor-catalyzed solvolysis [86].

Further studies by the Huber group and others suggest that halogen bond donors based on the bis(halobenzimidazolium) scaffold could promote other types of reactions that are typically observed with hydrogen bond donors such as thioureas [88]. Thus catalyst **L23** was found to catalyze the reaction of methyl vinyl ketone (MVK) and 1,3-cyclopentadiene (Scheme 18).

Catalyst **L23** was proposed to form two halogen bonds with the carbonyl group of MVK and thus activate it by lowering the

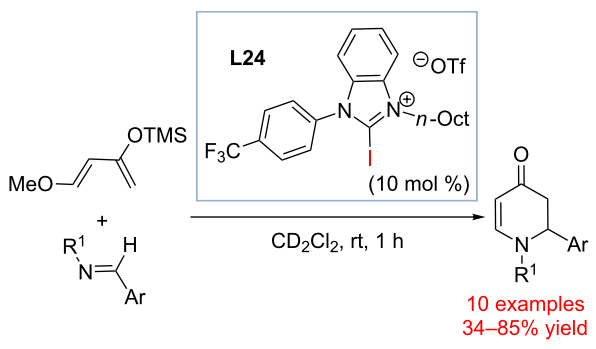


Scheme 18: Halogen bond-donor activation of α,β-unsaturated carbonyl compounds in the [2 + 4] cycloaddition reaction of MVK and cyclopentadiene [88].

energy of its LUMO. Remarkably, the non-coordinating counterion $BArF_4^-$ was required for **L23** to act as the catalyst with the less coordinating TfO^- anion did not accelerate the cycloaddition.

In 2015, Takeda, Minakata and co-workers demonstrated that 2-iodoimidazolium salt **L24** could serve as an efficient catalyst of the aza-Diels–Alder reaction of aldimines and Danishefsky diene (Scheme 19) [90].

Other organohalides such as perfluoroiodooctaine or perfluoroiodobenzene were initially explored as the catalysts; however,



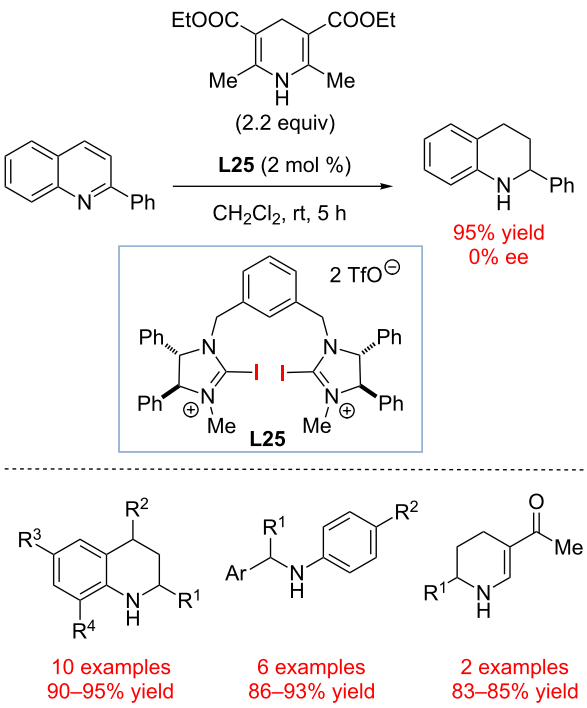
Scheme 19: Halogen bond donor activation of imines in the [2 + 4] cycloaddition reaction of imine and Danishefsky's diene [90].

no product formation was observed. The following evaluation of iodoimidazoles and iodoiimidazolium salts helped identifying **L24** as the catalyst of choice (yield 85%). When **L24** lacking the iodide activating site was used, no product was formed. The halogen bond nature of the reaction was further confirmed by adding an acid scavanger (K_2CO_3) that does not inhibit the reaction and by including *n*-Bu_4NCl, which inhibited the reaction. The authors also did titration experiments and ^{1}H NMR studies. These results strongly supported that halogen bonding was the key interaction for catalyst action.

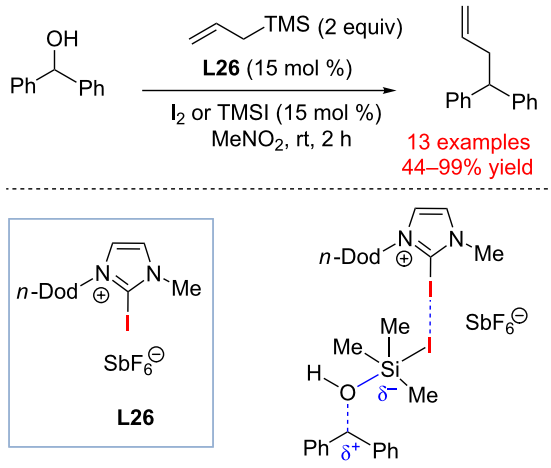
In 2014, the Tan group revisited the original study by Bolm and co-workers and re-investigated halogen bond induced hydrogen transfer to C=N bonds (Scheme 20) [91]. Various charged and uncharged electron-deficient iodoarenes were tested as potential catalysts, and chiral catalyst **L25** was identified as the catalyst of choice. Although no chirality transfer was observed during the reduction of 2-phenylquinoline, **L25** was found to be a very active catalyst promoting transfer hydrogenation of a C=N group containing heterocycles and imines with significantly greater reaction times than $CF_3(CF_2)_9I$ originally published by the Bolm group. As before, ^{1}H NMR studies and calorimetric titration were used to validate the proposed halogen bond-based activation of substrates.

Halogen bond-donor catalysis can be relevant to the processes in which a halogen-containing acceptor is formed in transient quantities. Thus, in 2015, Takemoto and co-workers described a halogen bond donor-catalyzed dehydroxylative coupling reaction of benzyl alcohols and allyltrimethylsilane (Scheme 21) [92].

This transformation requires catalytic quantities of the halogenating agent (I_2 or TMSI, 15 mol %). These additives may undergo activation by **L26** to result in more Lewis acidic species that ionize benzylic alcohols. Alternatively, addition of I_2 or TMSI may accomplish in situ transformation of benzylic



Scheme 20: Transfer hydrogenation catalyzed by a chiral halogen bond donor by Tan and co-workers [91].



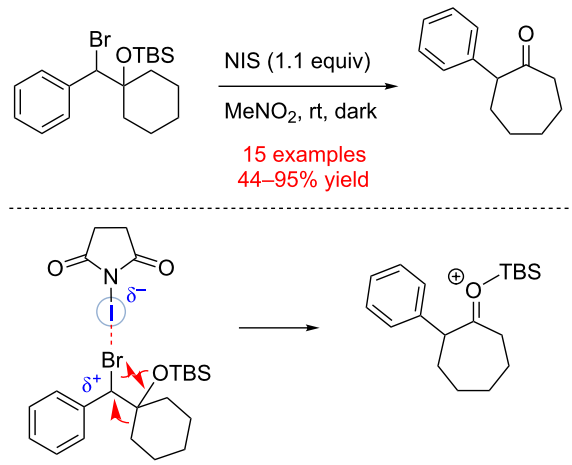
Scheme 21: Allylation of benzylic alcohols by Takemoto and co-workers [92].

alcohols to benzyl iodides. These intermediates underwent coordination to halogen bond donor catalyst **L26** to provide an electrophilic complex equivalent to a benzyl cation. This substrate was trapped with allyltrimethylsilane to provide the corresponding product. It was found that catalyst **L26** required a hexafluoroantimonate (SbF_6^-) counterion and polar $MeNO_2$ as the solvent of choice. Other nucleophiles such as

trimethyl(phenylethynyl)silane, trimethylsilanecarbonitrile and (cyclohex-1-en-1-yloxy)trimethylsilane could be used as substrates albeit with somewhat lower yield. Importantly, catalyst **L26** was found not to bind iodotrimethylsilane, which is the condition essential for achieving turnover in this reaction.

Organocatalysis based on halogen bond donors with *N*-halogenated moiety

A variety of *N*-halogenated organic molecules has been developed and utilized for halo-functionalization of olefins. Considering the electrophilic nature of a halogen in such molecules, these compounds could serve as effective halogen bond donors. In 2014, Takemoto and co-workers reported that electrophilic *N*-iodinated compounds could induce a semipinacol rearrangement (Scheme 22) [93]. Thus, the benzyl bromide moiety of substrates was activated upon treatment with *N*-iodosuccinimide (NIS) in nitromethane. The resultant carbocation-like species presumably underwent a 1,2-alkyl shift to provide a silylated oxocarbenium ion. The following silyl cation trapping with a bromide anion resulted in 2-phenylcycloheptanone. When a chiral substrate (59% ee) was treated with NIS, a product with significantly lower ee (11%) was observed. These results suggest that the reaction might proceed mainly in a stepwise S_N1-like manner, via a benzylic carbocation intermediate.



Scheme 22: NIS induced semipinacol rearrangement via C–X bond cleavage [93].

Despite the fact that several variants of chiral halogen bond-donor catalysts have been synthesized, to the best of our knowledge no successful asymmetric catalytic transformation based on the direct substrate activation with a chiral halogen bond donor has been reported. Therefore, this represents a fruitful area for further developments.

Conclusion

While the N–H or O–H-based hydrogen bond donors have traditionally dominated the field of organocatalysis, numerous recent examples highlight the importance of other types of non-covalent interactions for electrophilic substrate activation. The use of C–H and C–X bonds with halogens or electron-rich heteroatoms has been particularly useful in new organocatalyst design. These interactions (and C–H hydrogen bonds in particular) have been traditionally ascribed as "weak"; however, this term could be rather misleading as both C–H hydrogen bonds as well as halogen bonds could be similar in strength to hydrogen bonds. Not surprisingly, some of the examples highlighted in this review demonstrate that the catalysts based on such interactions could match or even outperform the existing O–H/N–H hydrogen bond donors such as thioureas. Several different variants of C–H hydrogen bond donors have been developed; however, the most successful designs have involved the use of 1,2,3-triazole, ammonium and pyridinium based catalysts. While the asymmetric transformations catalyzed by chiral 1,2,3-triazoles are now well precedented, the feasibility of asymmetric transformations promoted by other types of chiral C–H hydrogen bond donors is yet to be demonstrated. Similarly, compared with the N–H and O–H hydrogen bond catalysis, asymmetric halogen bond-donor catalysis is still underdeveloped and the possibility of utilizing chiral halogen bond donors for the asymmetric transformations is yet to be demonstrated. This is somewhat surprising, given the fact that a number of different scaffolds for halogen bond donors containing C–X bonds (including the chiral variants) have been developed. Considering that the use of organic halogen bond donors could offer some significant advantages, it is reasonable to anticipate the emergence of asymmetric halogen bond-donor catalysis in the near future.

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Synthesis of new pyrrolidine-based organocatalysts and study of their use in the asymmetric Michael addition of aldehydes to nitroolefins

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Full Research Paper

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Abstract

New pyrrolidine-based organocatalysts with a bulky substituent at C2 were synthesized from chiral imines derived from (*R*)-glyceraldehyde acetonide by diastereoselective allylation followed by a sequential hydrozirconation/iodination reaction. The new compounds were found to be effective organocatalysts for the Michael addition of aldehydes to nitroolefins and enantioselectivities up to 85% ee were achieved.

Introduction

In the first decades of the 21st century, the enantioselective organocatalysis has witnessed a tremendous development [1-4] and it is now considered to be the third pillar of enantioselective catalyses together with metal complex-mediated catalysis and biocatalysis. Among the different structures usually found in organocatalysis, the five-membered secondary amine structure of pyrrolidine has proven to be a privileged motif [5] with a powerful capacity in aminocatalysis [6-10]. In this context diarylprolinol silyl ethers have proven to be extremely efficient organocatalysts for a wide variety of chemical transformations [11].

In the course of our research we have been involved in the synthesis of new tuneable catalytic motifs to be used in organocatalysis starting from the chiral pool. Highly modular chiral aminodiol derivatives were obtained by the addition of organometallic reagents to chiral imines derived from (*R*)-glyceraldehyde – which is easily accessible from D-mannitol – and

these were evaluated as chiral organocatalysts in the enantioselective α-chlorination of β-ketoesters, with excellent results obtained after optimisation of the organocatalyst structure [12].

In an effort to identify new, easily accessible and tuneable organocatalysts with the privileged pyrrolidine motif from the chiral pool, we have now focused on the synthesis of new chiral pyrrolidines capable of creating a sterically demanding environment due to the presence of a bulky 2,2-disubstituted-1,3-dioxolan-4-yl moiety at C2 from chiral imines derived from (*R*)-glyceraldehyde. The Michael addition of aldehydes to nitroolefins was selected as a model reaction to evaluate the effectiveness of the new pyrrolidine-based organocatalysts in aminocatalysis.

Results and Discussion

We reasoned that pyrrolidines of type **C** with a bulky 2,2-disubstituted-1,3-dioxolan-4-yl moiety at C2 could provide the appropriate environment to lead to high levels of enantioselectivity in asymmetric transformations in which enamine intermediates are formed. The substituent R^1 in the 1,3-dioxolane moiety in pyrrolidines **C** could be varied to modulate the reactivity and selectivity of the new organocatalysts.

The sequential hydrozirconation/iodination of chiral homoallylic amines has been described as a straightforward approach to enantiomerically pure 2-substituted pyrrolidines [13,14]. Therefore we decided to test this methodology to gain access to the pyrrolidine ring in compound **C**. The required chiral homoallylic amines **B** can be easily obtained by the addition of allylmagnesium bromide to imines derived from (*R*)-glyceraldehyde acetonides **A** (Figure 1) according to our previously described methodology [15]. The configuration at C2 of the pyrrolidine ring would be determined in the diastereoselective allylation of the starting chiral imines.

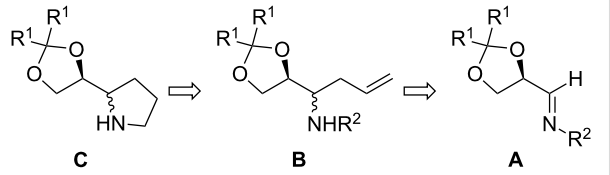
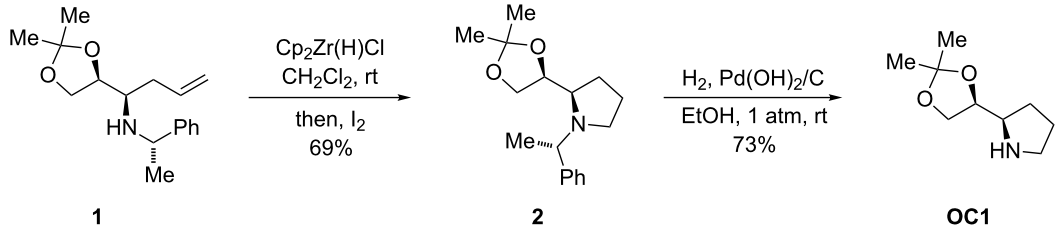


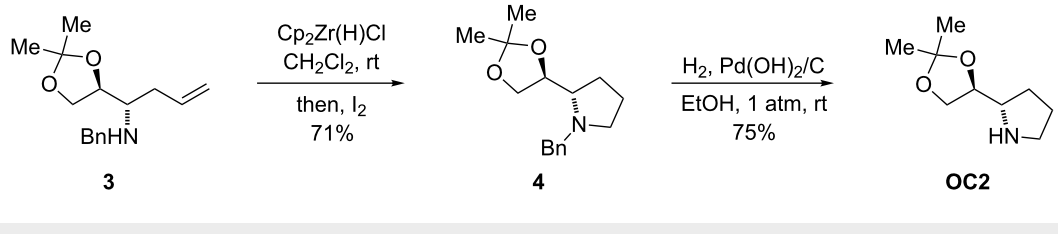
Figure 1: Strategy for the preparation of 2-substituted pyrrolidines **C**.

The homoallylic amine **1** with *syn*-configuration was obtained by the reaction of the corresponding imine with allylmagnesium bromide as previously described [15]. The amine **1** was reacted with the Schwartz reagent in CH_2Cl_2 at room temperature to afford the hydrozirconated intermediate, which was immediately treated with iodine to yield *N*-benzylpyrrolidine **2** in 69% isolated yield. The subsequent exposure of compound **2** to molecular hydrogen in the presence of $Pd(OH)_2/C$ as a catalyst afforded the desired organocatalyst **OC1** in 73% yield (Scheme 1).

The same reaction sequence led to organocatalyst **OC2** in 52% overall yield starting from homoallylic amine **3** having *anti*-configuration, which was obtained by reaction of the corresponding $BF_3{\cdot}OEt_2$ pre-complexed imine with allylmagnesium bromide as previously described [15] (Scheme 2). It is worth mentioning that the starting homoallylic amines **1** and **3** can be obtained on a multigram scale from the chiral pool.



Scheme 1: Synthesis of the new organocatalyst **OC1**.

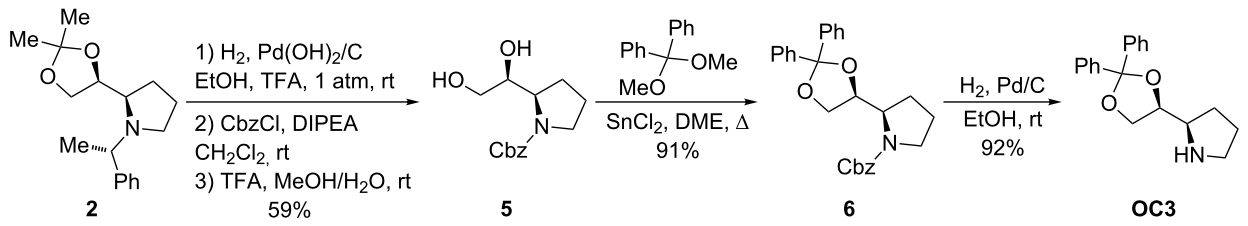


Scheme 2: Synthesis of new organocatalyst **OC2**.

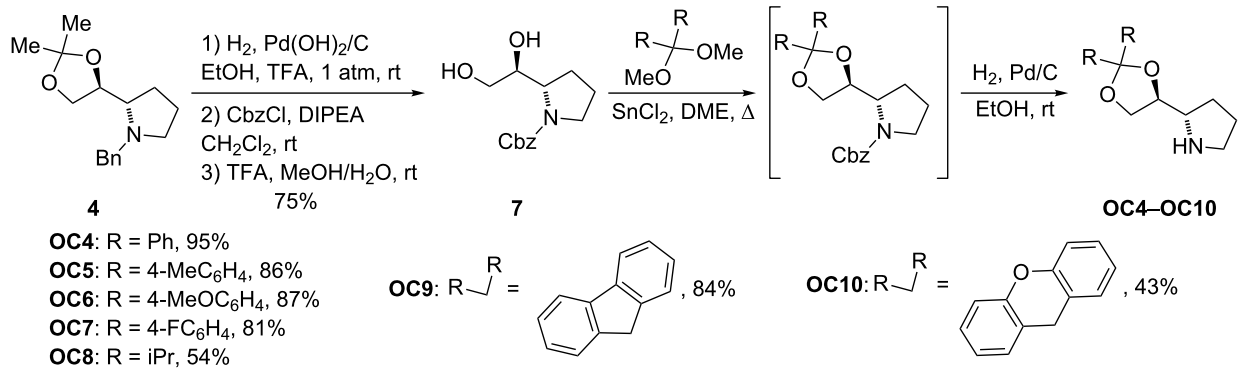
In order to obtain a series of new organocatalysts with substituents of different sizes and stereoelectronic properties in the dioxolane moiety, the following reaction sequence was applied to compounds **2** and **4**: a) N-deprotection by hydrogenolysis of the benzylic group with molecular hydrogen using $Pd(OH)_2/C$ as a catalyst in the presence of trifluoroacetic acid, b) reprotection of the amino group as benzylcarbamate by treatment of the crude reaction mixture with benzyl chloroformate in the presence of diisopropylethylamine, c) hydrolysis of the dioxolane moiety with trifluoroacetic acid, d) reconstruction of the dioxolane moiety by reaction of the diol with the corresponding dimethoxyacetal in the presence of $SnCl_2$ and e) N-deprotection of the pyrrolidine by exposure of the benzylcarbamate to molecular hydrogen in the presence of catalytic Pd/C. In this way organocatalysts **OC3**–**OC10** were obtained (Scheme 3 and Scheme 4).

In addition another new organocatalyst, **OC11**, with a different bulky substituent at C2 in the pyrrolidine moiety was prepared. Reacting diol **7** with 1,3-dichlorotetraisopropyldisiloxane in the presence of imidazole and subsequent hydrogenolysis of the benzylcarbamate with molecular hydrogen in the presence of catalytic Pd/C (Scheme 5) afforded **OC11** in 43% overall yield for the two steps.

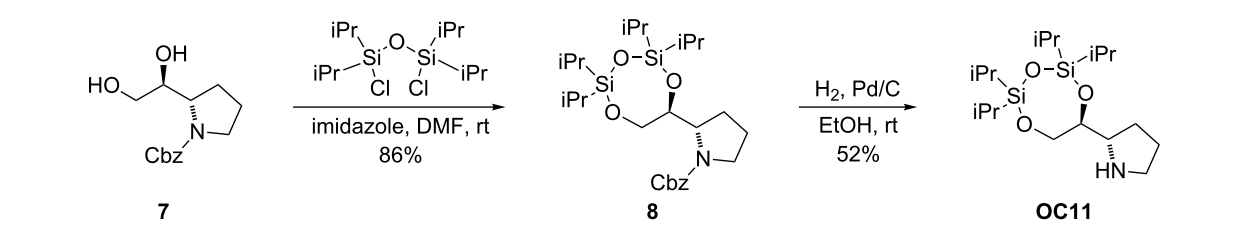
With this series of pyrrolidines at hand, the well-established Michael addition of aldehydes to nitroolefins [16-18] was selected as a benchmark reaction to study their behaviour as organocatalysts. Compounds with a related structure prepared from proline by Diez et al. have proven to work well as organocatalysts in the Michael addition of cyclohexanones to nitrostyrenes [19,20].



Scheme 3: Synthesis of new organocatalyst **OC3**.



Scheme 4: Synthesis of new organocatalysts **OC4**–**OC10**.

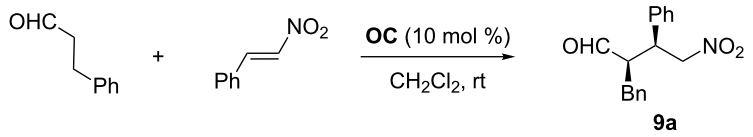


Scheme 5: Synthesis of new organocatalyst **OC11**.

We first tested organocatalysts **OC1**–**OC4** in the reaction of *trans*-β-nitrostyrene with 3-phenylpropionaldehyde in order to determine the influence that the relative configuration of the pyrrolidine had on the results (Table 1). The reaction was initially carried out at room temperature in the presence of 10 mol % of the catalyst and using CH_2Cl_2 as solvent. Under these conditions the yield of the Michael adducts was 95–99% within 7 hours. The diastereoselectivity was moderate (dr = 70:30–78:22) in favour of the *syn*-diastereoisomer and enantioselectivites were ee ≈ 68% for the *syn*-adducts and ee = 44–63% for the *anti*-adducts. The stereochemistry of the major compound depended on the stereochemistry of the organocatalyst and Michael adducts of opposite configuration were obtained on using *syn* or *anti*-pyrrolidines with similar levels of enantioselectivity for the major *syn*-diastereoisomer.

Next, the effect of the solvent and temperature was studied using **OC4** as the organocatalyst (Table 2). The best results

Table 1: Initial screening of catalysts for the Michael addition of 3-phenylpropionaldehyde to *trans*-β-nitrostyrene.[a]

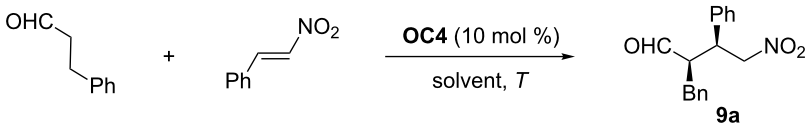


9a

Catalyst	*t* (h)	Yield[b] (%)	*syn*:*anti*[b]	ee *syn*[c] (%)	ee *anti*[c] (%)
OC1	7	95	70:30	−68	−63
OC2	7	97	78:22	68	46
OC3	7	99	74:26	−68	−44
OC4	7	96	77:23	66	44

[a]Reaction performed in CH_2Cl_2 (2 mL) at room temperature using 0.2 mmol of β-nitrostyrene, 0.4 mmol of 3-phenylpropionaldehyde and 10 mol % of catalyst. [b]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC.

Table 2: Optimization of the reaction conditions for the Michael addition of 3-phenylpropionaldehyde to *trans*-β-nitrostyrene using catalyst **OC4**.[a]



9a

Solvent	*T* (°C)	*t* (h)	Yield[b] (%)	*syn*:*anti*[b]	ee *syn*[c] (%)	ee *anti*[c] (%)
CH_2Cl_2	rt	7	96	77:23	66	44
THF	rt	7	86	80:20	71	51
toluene	rt	7	82	84:16	74	44
$CHCl_3$	rt	7	89	78:22	57	43
EtOH	rt	7	85	76:24	62	21
cyclohexane	rt	7	87	86:14	81	67
MTBE	rt	7	96	87:13	63	35
MeCN	rt	7	87	77:23	57	23
$CF_3C_6H_4$	rt	7	93	89:11	78	75
C_6F_6	rt	7	90	92:8	80	62
$C_6F_{11}CF_3$	rt	7	85	68:32	76	74
$C_{10}F_8$	rt	7	82	73:27	76	73
methylcyclohexane	0	24	87	92:8	85	58
toluene	0	24	84	86:14	80	39
methylcyclohexane	−20	24	77	94:6	85	40

[a]Reaction performed using 0.2 mmol of β-nitrostyrene, 0.4 mmol of 3-phenylpropionaldehyde and 10 mol % of **OC4** in the given solvent (2 mL). [b]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC.

were obtained with methylcyclohexane as the solvent at 0 °C reaction temperature. Under these conditions after 24 h the reaction yield was high (87%), the observed diastereoselectivity was 92:8 in favour of the *syn*-adduct and the enantioselectivity reached 85% ee for the major *syn*-adduct. A further decrease in temperature did not improve these results substantially but did diminish the reaction yield (Table 2).

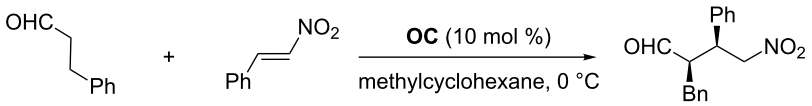
The organocatalysts **OC1**–**OC11** were then screened to reveal the influence of the substituent R attached to the dioxolane moiety on the reaction outcome and the results are collected in Table 3. However, the variation of this substituent did not result in any significant improvement of the diastereo- or enantioselectivity and based on these results organocatalyst **OC4** was found to be the most efficient and stereoselective organocatalyst. It is worth mentioning that on reducing the catalyst loading to 5 mol % the reactivity remained good and the diastereoselectivity and enantioselectivity were only slightly affected.

It has been reported that additives present in the reaction medium can lead to improved results without changing other reaction conditions [21]. For example, in secondary amine-catalysed asymmetric reactions a Brønsted acid additive was found to accelerate the formation of the enamine intermediate and thus to improve not only the reactivity but also the diastereoselectivity and enantioselectivity [22,23]. On the other hand, the presence of thiourea additives could activate nitroalkenes when used as substrates by double hydrogen bonding, which lead to improved reactivities [24]. Based on these findings, we decided to explore the effect of a Brønsted acid or an achiral thiourea as additive on the reaction between *trans*-β-nitrostyrene and 3-phenylpropionaldehyde promoted by **OC4** (Table 4). When thioureas were used as additives the reaction was performed in toluene in order to improve the solubility.

The addition of benzoic or acetic acid increased the reactivity and *anti*-enantioselectivity but it was detrimental for the diastereoselectivity and *syn*-enantioselectivity. On the other hand, in the presence of trifluoroacetic acid the reaction proceeded slowly and the diastereoselectivity decreased to some extent. The presence of an achiral thiourea did not improve the results.

Finally, we considered the possibility of accelerating the formation of the enamine intermediate and simultaneously activating the nitroalkene by using a combination of organocatalyst **OC4**, a Brønsted acid and an achiral thiourea. Thus the reaction was repeated in the presence of a combination of benzoic acid and *N*,*N*'-diphenylthiourea (**TU1**) as additives. The enantioselectivity of both *syn* and *anti*-adducts reached quite good values (87% ee and 91% ee, respectively) but the diastereoselectivity dropped to 67:33.

Table 3: Screening of organocatalysts **OC1**–**OC11** for the Michael addition of 3-phenylpropionaldehyde to *trans*-β-nitrostyrene.[a]

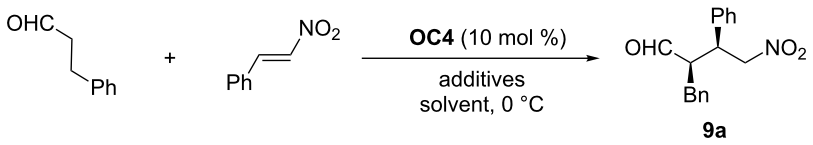


9a

Catalyst	Yield[b] (%)	*syn*:*anti*[b]	ee *syn*[c] (%)	ee *anti*[c] (%)
OC1	84	84:18	77	72
OC2	77	94:6	81	50
OC3	91	78:22	77	65
OC4	87	93:7	85	58
OC5	99	92:8	84	63
OC6	86	88:12	80	61
OC7	90	92:8	83	57
OC8	91	93:7	73	70
OC9	93	93:7	76	n.d.
OC10	83	93:7	85	n.d.
OC11	72	87:13	63	n.d.
OC4[d]	81	89:11	82	59
OC4[e]	23	78:22	82	45

[a]Reaction performed using 0.2 mmol of β-nitrostyrene, 0.4 mmol of 3-phenylpropionaldehyde and 10 mol % of catalyst in methylcyclohexane (2 mL) at 0 °C for 24 h. [b]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC. [d]Catalyst loading 5 mol %. [e]Catalyst loading 2 mol %.

Table 4: Screening of additives for the Michael addition of 3-phenylpropionaldehyde to *trans*-β-nitrostyrene using catalysts **OC4**.[a]



9a

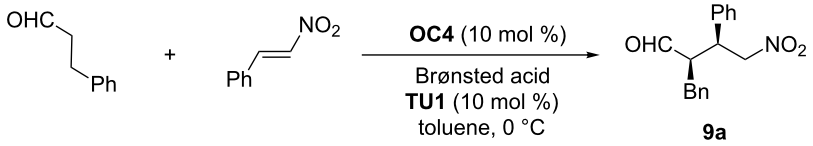
Acid[b]	TU[c]	Solvent	Yield[d] (%)	*syn*:*anti*[d]	ee *syn*[e] (%)	ee *anti*[e] (%)
none	none	methylcyclohexane	87	93:7	85	58
$PhCO_2H$	none	methylcyclohexane	93	75:25	77	83
AcOH	none	methylcyclohexane	98	60:40	75	83
TFA	none	methylcyclohexane	32	76:24	83	82
none	none	toluene	84	86:4	80	39
none	**TU1**	toluene	92	76:24	72	63
none	**TU2**	toluene	87	87:13	61	24
$PhCO_2H$	**TU1**	toluene	94	67:33	87	91
AcOH	**TU1**	toluene	90	80:20	80	58
$PhCO_2H$	**TU2**	toluene	94	74:26	83	80
AcOH	**TU2**	toluene	85	90:10	77	36

[a]Reaction performed using 0.2 mmol of β-nitrostyrene, 0.4 mmol of 3-phenylpropionaldehyde, 10 mol % of **OC4** and 10 mol % of additive in the given solvent (2 mL) at 0 °C for 24 h. [b]AcOH = acetic acid, TFA = trifluoroacetic acid. [c]TU1 = *N*,*N*'-diphenylthiourea, TU2 = *N*,*N*'-bis[3,5-di(trifluoromethyl)phenyl]thiourea. [d]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [e]Determined by chiral HPLC.

The aryl group of benzoic acid was varied (Table 5) in an effort to improve the diastereoselectivity. The best results in terms of diastereoselectivity were obtained with the combination *p*-methoxybenzoic acid/*N*,*N*'-diphenylthiourea.

Finally, with the most efficient organocatalyst **OC4** at hand we surveyed the scope of this transformation with respect to the aldehyde and the nitroolefin (Table 6). Other aliphatic aldehydes were less reactive and the reaction temperature had to be increased. Linear aliphatic aldehydes reacted with β-nitrostyrene to provide the Michael adducts in good yields when the reaction was conducted at room temperature. The diastereoselectivity was moderate to good (dr = 79:21–95:5) in favour of the *syn*-diastereoisomer and enantioselectivites ranged from 75–84% ee. The reaction of butyraldehyde with other *trans*-β-nitroolefins at room temperature also provided the Michael adducts with moderate to good distereoselectivity (dr = 74:26–92:8) in favour of the *syn*-diastereoisomer and enantioselectivites from 72–84% ee.

Table 5: Screening of benzoic acids as additives for Michael addition of 3-phenylpropionaldehyde to *trans*-β-nitrostyrene using catalysts **OC4**.[a]

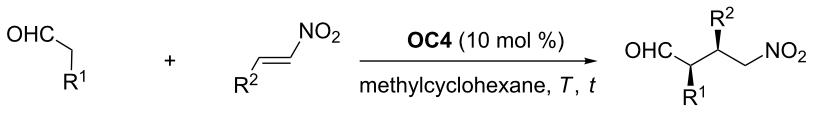


9a

Acid	Yield[b] (%)	*syn*:*anti*[b]	ee *syn*[c] (%)
$PhCO_2H$	94	67:33	87
4-$MeC_6H_4CO_2H$	89	63:37	86
4-$NO_2C_6H_4CO_2H$	91	61:39	90
4-$FC_6H_4CO_2H$	90	63:37	87
4-$ClC_6H_4CO_2H$	96	72:28	85
4-$MeOC_6H_4CO_2H$	92	80:20	85

[a]Reaction performed using 0.2 mmol of β-nitrostyrene, 0.4 mmol of 3-phenylpropionaldehyde, 10 mol % of **OC4**, 10 mol % of *N*,*N*'-diphenylthiourea, and 10 mol % of the given benzoic acid in toluene (2 mL) at 0 °C for 24 h. [b]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC.

Table 6: Scope of Michael addition of aldehydes to *trans*-β-nitroolefins using catalyst **OC4**.[a]



9a–m

Product	R^1	R^2	*T* (ºC)	*t* (h)	Yield[b] (%)	*syn*:*anti*[b]	ee *syn*[c] (%)
9a	Bn	Ph	0	24	87	93:7	85
9b	*n*-Pr	Ph	0	48	18	66:34	72
9b	*n*-Pr	Ph	rt	48	100	85:15	75
9c	Et	Ph	rt	22	100	77:23	82
9d	Me	Ph	rt	20	100	79:21	83
9e	*n*-Hex	Ph	rt	24	94	86:14	83
9f	CH_2=$CH(CH_2)_7$	Ph	rt	70	100	95:5	84
9g	*n*-Pr	2-furyl	rt	24	88	74:26	72
9h	*n*-Pr	4-$MeOC_6H_4$	rt	44	100	87:14	80
9i	*n*-Pr	4-MeC_6H_4	rt	46	100	89:11	84
9j	*n*-Pr	4-ClC_6H_4	rt	24	100	88:12	85
9k	*n*-Pr	4-BrC_6H_4	rt	22	92	89:11	82
9l	*n*-Pr	3-BrC_6H_4	rt	31	100	93:7	84
9m	*n*-Pr	2-BrC_6H_4	rt	33	100	92:8	82

[a]Reaction performed using 0.2 mmol of nitroolefin, 0.4 mmol of aldehyde, 10 mol % of **OC4**, in methylcyclohexane (2 mL). [b]Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC.

Conclusion

In conclusion, we have prepared 2-substituted pyrrolidines using a hydrozirconation/iodination reaction of chiral homoallylic amines. The latter were obtained on a multigram scale from imines derived from glyceraldehyde. These easily available compounds are new tuneable organocatalysts with the privileged pyrrolidine motif. When used in the asymmetric Michael addition of aldehydes to nitroolefins, diastereoselectivities of up to 93:7 and enantioselectivities of up to 85% enantiomeric excess for the *syn*-adduct were obtained in the presence of the most effective organocatalyst **OC4**.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-59-S1.pdf]

Supporting Information File 2

NMR spectra and HPLC chromatograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-59-S2.pdf]

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