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Beilstein Journal of Organic Chemistry

C–H Functionalization

Huw M. L. Davies

Editorial

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C–H Functionalization has the potential to become a paradigm-shifting strategy for organic synthesis. Over the last decade, the field has experienced explosive growth and a large variety of new C–H functionalization methodologies have been developed. In particular, regioselective functionalization of sp^2 C–H bonds has become a broadly flexible approach for the synthesis of complex aromatic carbocycles and heterocycles. In several instances the substrates have a natural preference for functionalization at specific C–H bonds. Alternatively, selective functionalization is achieved by using a directing group to orient the catalyst in a defined position. These types of synthetic strategies are already having a significant impact on the streamlined synthesis of important compounds for the pharmaceutical industry and materials science.

The selective functionalization of sp^3 C–H bonds is a more challenging proposition, but in recent years significant advances have been made to suggest that even these types of transformations can become broadly applicable. Metal-bound carbenes, nitrenes and oxo species have been particularly effective at stereoselective sp^3 C–H functionalization. However, considerable advances still need to be made to enhance the selectivity and to increase the range of functionality that can be introduced in these types of reactions.

The fundamental principles of a number of C–H functionalization transformations have been established but, in many regards, the field is still in its infancy. The ultimate goal would be to have generally programmable and controllable methods for the highly selective C–H functionalization of complex systems at will. To achieve this, it will be necessary to have an extensive toolbox of catalysts and reagents to override the natural site selectivity of any given substrate. Therefore, a greater range of reaction types need to be developed and a better mechanistic understanding of the controlling elements of the various methods has to be obtained.

This Thematic Series highlights some of the novel approaches that are applied to the field of C–H functionalization and I thank all the authors for their exciting contributions. The series covers topics that range from novel catalyst design, new synthetic methods, and cascade sequences that incorporate C–H functionalization. The articles illustrate the exciting opportunities for innovation that exist in C–H functionalization research, and hopefully, will inspire others to explore new research directions in this area.

Huw M. L. Davies

Atlanta, September 2012

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C2-Alkylation of *N*-pyrimidylindole with vinylsilane via cobalt-catalyzed C–H bond activation

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Letter

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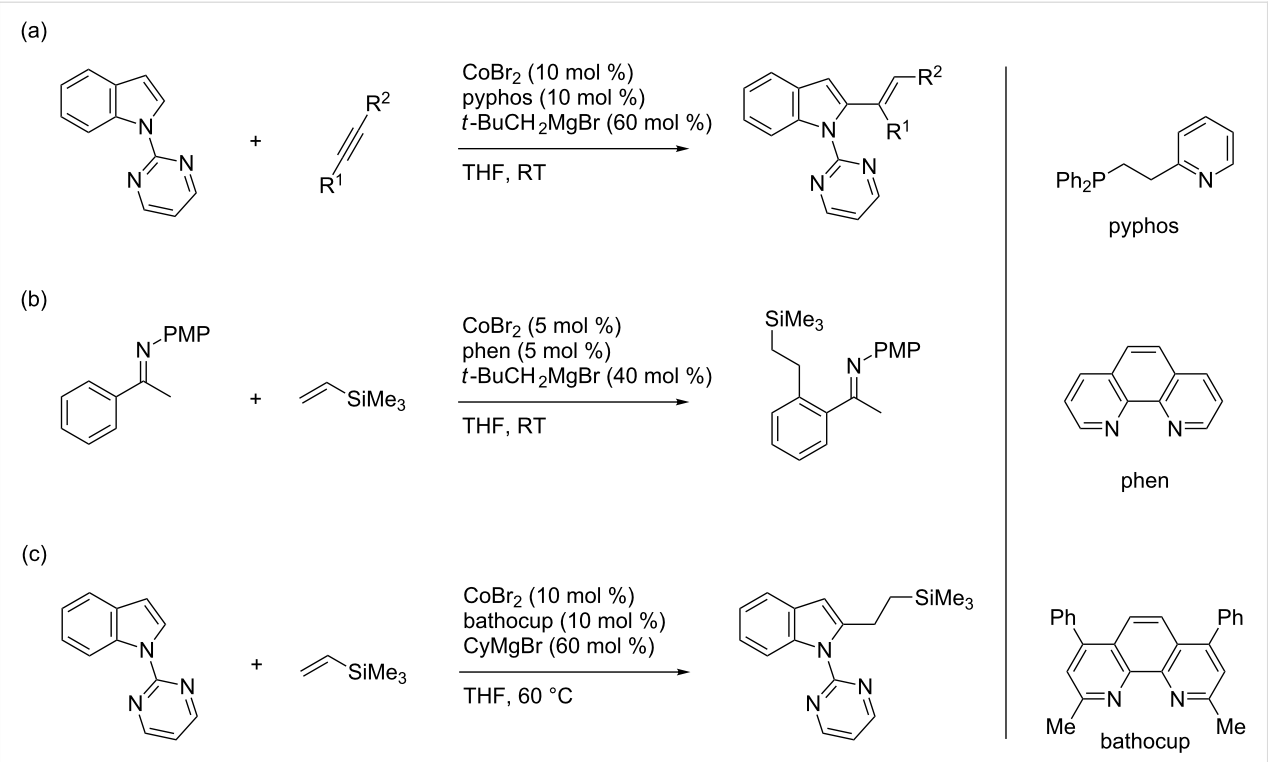
Abstract

Direct C2-alkylation of an indole bearing a readily removable *N*-pyrimidyl group with a vinylsilane was achieved by using a cobalt catalyst generated in situ from $CoBr_2$, bathocuproine, and cyclohexylmagnesium bromide. The reaction allows coupling between a series of *N*-pyrimidylindoles and vinylsilanes at a mild reaction temperature of 60 °C, affording the corresponding alkylated indoles in moderate to good yields.

Introduction

The indole ring ubiquitously occurs in biologically active natural and unnatural compounds [1-3]. Consequently, there has been a strong demand for catalytic methods allowing efficient and regioselective functionalization of indole derivatives [4-6]. Over the past decade, transition-metal-catalyzed direct functionalization has emerged as a powerful strategy for the direct introduction of aryl and alkenyl groups to the C2 and C3 positions of indole [7-9]. The situation is different when it comes to direct C–H alkylation [10,11]. The intrinsically nucleophilic C3 position of indole is amenable to a variety of catalytic alkylation reactions such as Friedel–Crafts reaction [5]. On the other hand, C2-alkylation of indoles has traditionally required 2-lithioindoles generated by C2-lithiation with a stoichiometric lithium base or indol-2-yl radicals generated from 2-halogenated indoles [12-17]. Examples of direct C2-alkylation via transition-metal-catalyzed C–H activation are still limited [18-20], while Jiao and Bach recently reported an elegant palladium-catalyzed, norbornene-mediated C2-alkylation reaction with a broad spectrum of alkyl bromides [21].

Over the past few years, our group and others have explored C–H bond functionalization reactions using cobalt complexes as inexpensive transition-metal catalysts [22], which often feature mild reaction conditions and unique regioselectivities [23-32]. As a part of this research program, we have recently reported a C2-alkenylation reaction of *N*-pyrimidylindoles with internal



Scheme 1: (a) Cobalt-catalyzed C2-alkenylation of *N*-pyrimidylindole, (b) ortho-alkylation of aryl imine, and (c) C2-alkylation of *N*-pyrimidylindole.

alkynes catalyzed by a cobalt–pyridylphosphine complex (Scheme 1a) [33], in which the pyrimidyl group functions as a readily removable directing group [34]. We also reported an ortho-alkylation reaction of aromatic imines with vinylsilanes and simple olefins using a cobalt–phenanthroline catalyst (Scheme 1b) [35]. Building on these studies, we have developed a cobalt–bathocuproine catalyst for the direct C2-alkylation reaction of *N*-pyrimidylindoles with vinylsilanes, which is reported herein (Scheme 1c).

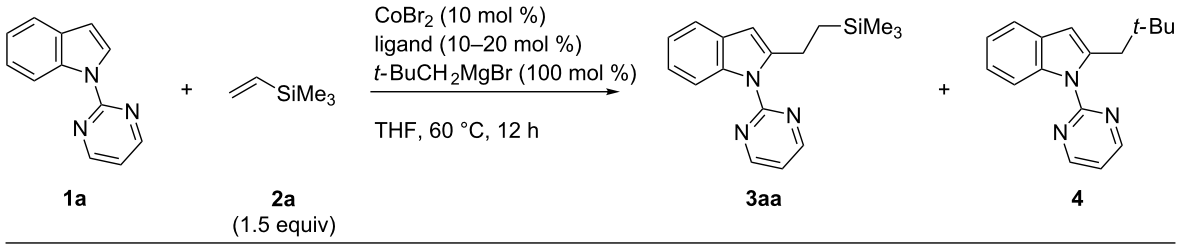
Results and Discussion

Our study commenced with the optimization of the reaction of *N*-pyrimidylindole **1a** with vinyltrimethylsilane (**2a**). The combination of $CoBr_2$ (10 mol %), 1,10-phenanthroline (phen, 10 mol %) and neopentylmagnesium bromide (100 mol %), which was effective for ortho-alkylation of aromatic imines [35], afforded the desired adduct **3aa** in only 17% yield accompanied by a small amount of a C2-neopentylated product **4** (Table 1, entry 1). Subsequent examination of phenanthroline and bipyridine-type ligands (Table 1, entries 2–5) revealed that 2,9-dimethyl-1,10-phenanthroline (neocuproine) and 2,9-dimethyl-4,7-diphenylphenanthroline (bathocuproine) improved the yield of **3aa**, while the byproduct **4** could not be suppressed (Table 1, entries 3 and 4). The *P*,*N*-bidentate ligand pyphos, which was the optimum ligand for the alkenylation reaction [33], was poorly effective (Table 1, entry 6). Additional screening of *N*-heterocyclic carbene (NHC) and phosphine ligands did not lead to an improvement of the catalytic efficiency (Table 1, entries 7–9). The reaction turned out to be sensitive to the amount of the Grignard reagent, as reduction of its loading from 100 to 60 mol % improved the yield of **3aa** while suppressing the formation of byproduct **4** (Table 1, entry 10).

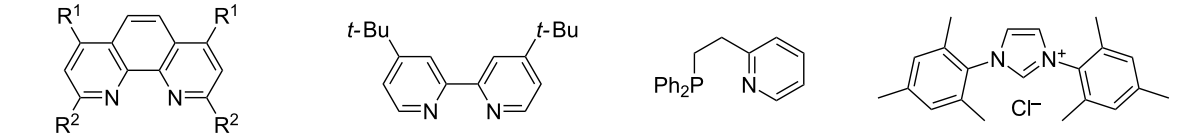
Next, we performed screening of Grignard reagents using bathocuproine as the ligand (Table 2). Among Grignard reagents without β-hydrogen atoms, neopentyl- and phenylmagnesium bromides afforded **3aa** in comparable yields (Table 2, entries 1 and 4), while trimethylsilylmethyl- and methylmagnesium chlorides gave much poorer results (Table 2, entries 2 and 3). Primary and secondary alkyl Grignard reagents also promoted the reaction, in which the reaction efficiency was strongly dependent on the alkyl group (Table 2, entries 5–10). We identified cyclohexylmagnesium bromide as the optimum Grignard reagent, which afforded **3aa** in 69% isolated yield without formation of the cross-coupling product **4** between **1a** and the Grignard reagent.

With the optimized catalytic system in hand, we explored the scope of the reaction (Scheme 2). A variety of *N*-pyrimidylindoles participated in the reaction with vinyltrimethylsilane to afford the alkylation products **3ba**–**3ia** in moderate yields, with

Table 1: Screening of ligands.[a]



1a + **2a** (1.5 equiv) → **3aa** + **4**



phen (R^1, R^2 = H)
bathophen (R^1 = Ph, R^2 = H)
neocup (R^1 = H, R^2 = Me)
bathocup (R^1 = Ph, R^2 = Me)

dtbpy

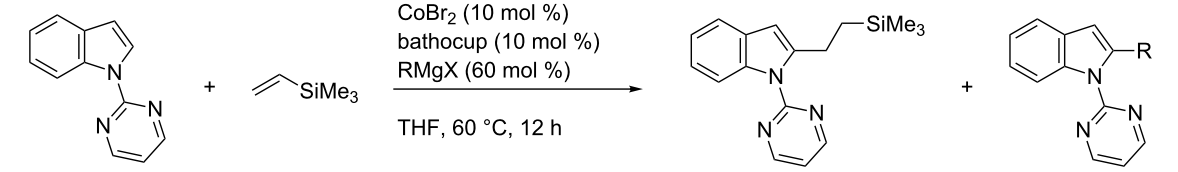
pyphos

IMes·HCl

entry	ligand (mol %)	yield (%)[b]	
		3aa	**4**
1	phen (10)	17	7
2	bathophen (10)	11	7
3	neocup (10)	32	12
4	bathocup (10)	34	20
5	dtbpy (10)	1	3
6	pyphos (10)	2	3
7	IMes·HCl (10)	4	2
8	PPh_3 (20)	9	5
9	$P(3\text{-}ClC_6H_4)_3$ (20)	23	11
10[c]	bathocup	50	10

[a]Reaction was performed on a 0.3 mmol scale. [b]Determined by GC using *n*-tridecane as an internal standard. [c]60 mol % of *t*-$BuCH_2MgBr$ was used.

Table 2: Screening of Grignard reagents.[a]



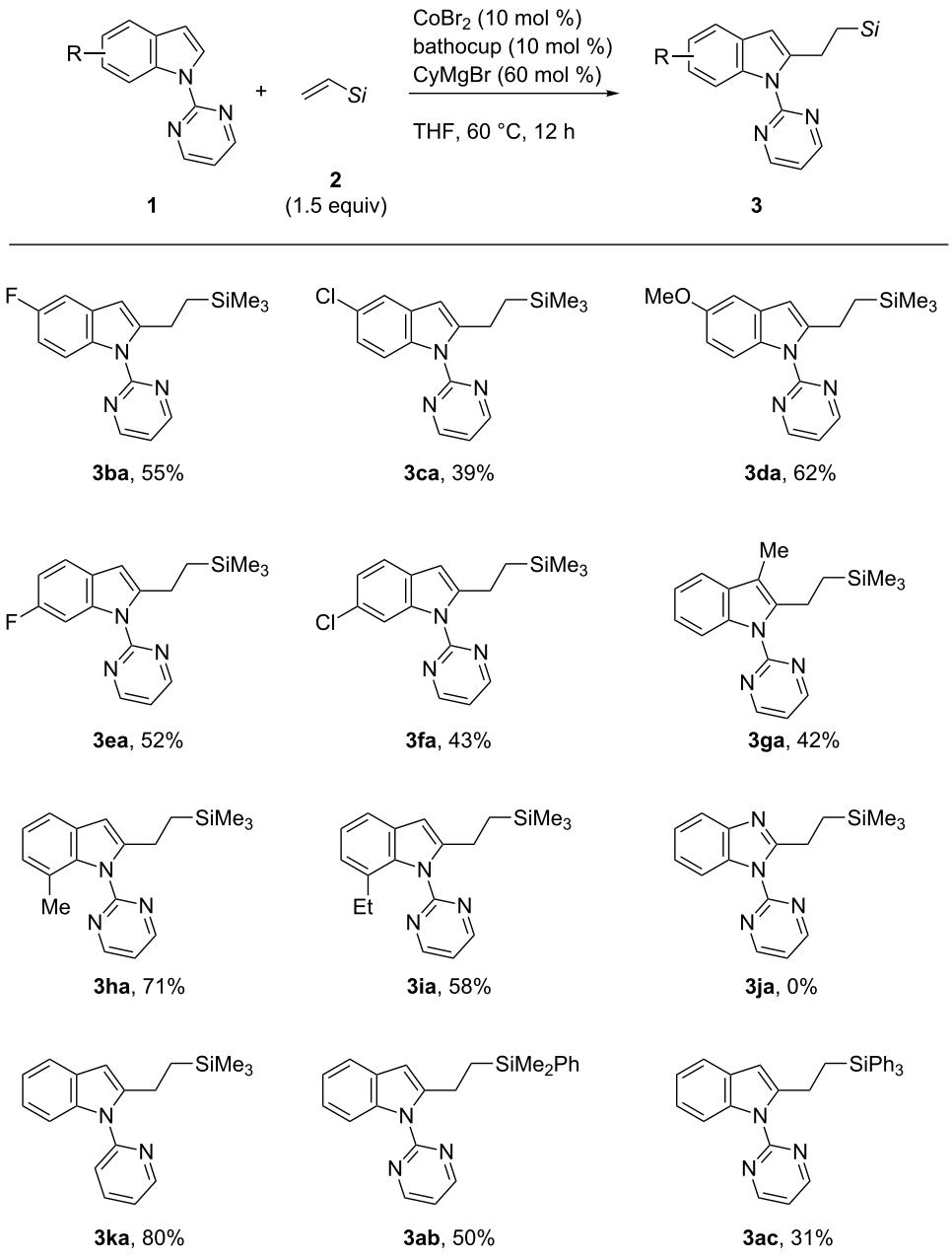
1a + **2a** (1.5 equiv) → **3aa** + **4**

entry	RMgX	yield (%)[b]	
		3aa	**4**
1	*t*-$BuCH_2MgBr$	50	10
2	Me_3SiCH_2MgCl	26	5
3	MeMgCl	14	4
4	PhMgBr	46	5
5	EtMgBr	28	3

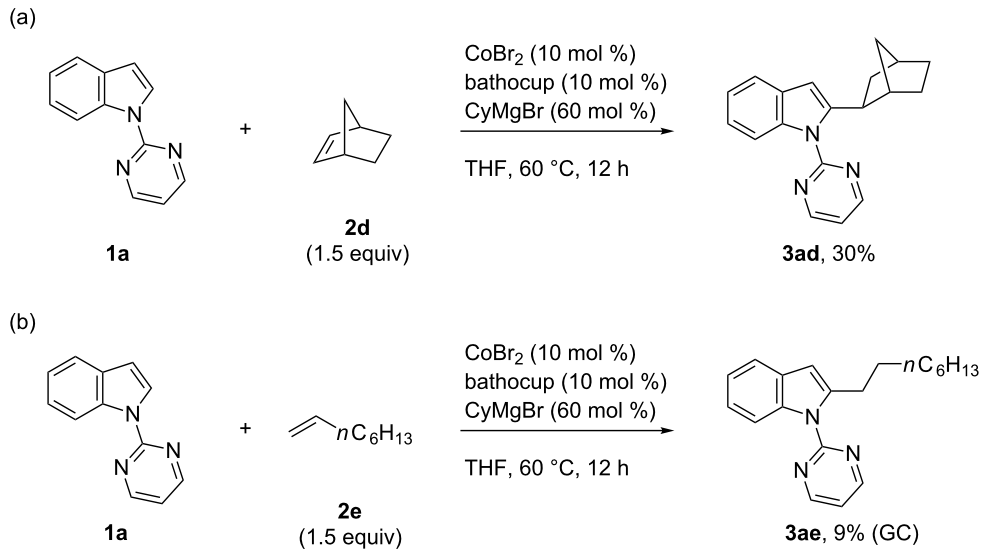
Table 2: Screening of Grignard reagents.[a] (continued)

6	BuMgBr	45	0
7	*i*-PrMgBr	49	3
8	*c*-C_3H_5MgBr	13	0
9	*c*-C_5H_9MgBr	46	0
10	*c*-$C_6H_{11}MgBr$	67 (69)[c]	0

[a]Reaction was performed on a 0.3 mmol scale. [b]Determined by GC using *n*-tridecane as an internal standard. [c]Isolated yield.



Scheme 2: Addition of *N*-pyrimidylindoles to vinylsilanes.



Scheme 3: Addition of *N*-pyrimidylindole to norbornene (a) and 1-octene (b).

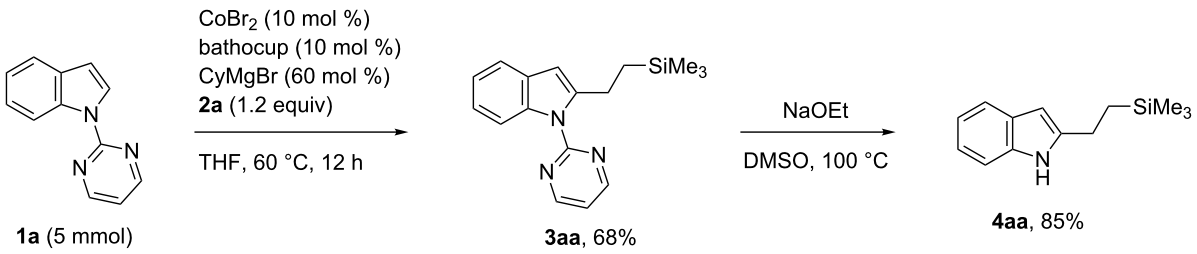
tolerance of electron-withdrawing (F and Cl) and electron-donating (OMe) substituents and steric hindrance at the C3 and C7 positions. Unlike the cobalt-catalyzed C2-alkenylation reaction (Scheme 1a) [33], the reaction did not tolerate a cyano group on the indole substrate. In addition, *N*-pyrimidyl benzimidazole did not participate in the present alkylation reaction, although it was a good substrate for the C2-alkenylation reaction. A pyridyl group served as an alternative directing group to the pyrimidyl group, affording the alkylation product **3ka** in 80% yield. On the other hand, an *N*,*N*-dimethylcarbamoyl group, which was previously used as a directing group for rhodium-catalyzed C2-alkenylation [36], was entirely ineffective. Vinylsilanes bearing dimethylphenylsilyl and triphenylsilyl groups were amenable to the addition reaction with **1a**, affording the adduct **3ab** and **3ac** in modest yields. Vinyltriethoxysilane also reacted with **1a** in 20% yield, although the product could not be separated in a pure form.

Unfortunately, the present catalytic system was not very effective for C2-alkylation with simple olefins. The reaction of **1a** with norbornene (**2d**) afforded the alkylation product **3ad** in 30% yield (Scheme 3a). The reaction of 1-octene (**2e**) was even more sluggish, affording the alkylation product **3ae** in only 9% yield (Scheme 3b). Styrene also reacted rather sluggishly to afford only a small amount of the alkylation product (3% as estimated by GC and GCMS), the regiochemistry (branched versus linear) of which has yet to be determined. An acrylate ester was not tolerable as an olefinic reaction partner because of the presence of excess Grignard reagent.

The present alkylation reaction could be performed on a preparatively useful scale. Thus, alkylation of **1a** with vinyltrimethylsilane (**2a**) on a 5 mmol scale afforded the adduct **3aa** in 68% yield (Scheme 4). Furthermore, the pyrimidyl group on **3aa** could be readily removed by heating with NaOEt in DMSO, affording the free indole **4aa** in 85% yield.

Conclusion

In summary, we have developed a cobalt–bathocuproine catalyst for C2-alkylation of *N*-pyrimidyl indoles with vinylsilanes.



Scheme 4: Gram-scale reaction and deprotection of *N*-pyrimidyl group.

The reaction could be performed at a mild temperature of 60 °C, on a preparatively useful scale. Ensuing studies will focus on the development of more broadly applicable catalytic systems for the direct alkylation of indole and other heterocycles.

Experimental

Typical procedure: Cobalt-catalyzed alkylation of *N*-pyrimidyl indole **1a** with vinylsilane **2a**

In a Schlenk tube were placed 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) (58.6 mg, 0.3 mmol), $CoBr_2$ (6.6 mg, 0.03 mmol), and bathocuproine (10.8 mg, 0.03 mmol), which were then dissolved in THF (1.3 mL). To the solution was added cyclohexylmagnesium bromide (0.60 M in THF, 0.3 mL, 0.18 mmol) at 0 °C. After stirring for 30 min at this temperature, vinyltrimethylsilane (**2a**) (66 μL, 0.45 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h, and then quenched with saturated aqueous solution of NH_4Cl (1.5 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc 100:1) afforded the title compound as a colorless oil (61.2 mg, 69%).

Supporting Information

Supporting Information File 1

Experimental details and characterization data of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-174-S1.pdf]

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Beilstein Journal of Organic Chemistry

Metal–ligand multiple bonds as frustrated Lewis pairs for C–H functionalization

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Review

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Abstract

The concept of frustrated Lewis pairs (FLPs) has received considerable attention of late, and numerous reports have demonstrated the power of non- or weakly interacting Lewis acid–base pairs for the cooperative activation of small molecules. Although most studies have focused on the use of organic or main-group FLPs that utilize steric encumbrance to prevent adduct formation, a related strategy can be envisioned for both organic and inorganic complexes, in which "electronic frustration" engenders reactivity consistent with both nucleophilic (basic) and electrophilic (acidic) character. Here we propose that such a description is consistent with the behavior of many coordinatively unsaturated transition-metal species featuring metal–ligand multiple bonds, and we further demonstrate that the resultant reactivity may be a powerful tool for the functionalization of C–H and E–H bonds.

Introduction

Orbital cooperation has long been recognized as an important contributor to the diverse reactivities exhibited by transition-metal systems with small-molecule substrates. The Dewar–Chatt–Duncanson model provides a paradigm for this sort of interaction, where molecules such as H_2 and alkenes are activated by a combination of ligand-to-metal σ donation and metal-to-ligand π backbonding [1,2]. The traditional line of thought was that main-group molecules could not mimic this sort of behavior due to their more limited redox flexibility and propensity to form inert Lewis acid–base adducts, but recent work by Power, Bertrand, and others has shown that a number of unsaturated main-group compounds can exhibit electronic properties and reactivity reminiscent of transition metals [3].

A different approach was pioneered by Stephan, who demonstrated that appropriately encumbered (i.e., "frustrated") Lewis acids and bases could achieve synergistic heterolytic cleavage of H_2 [4-6], and subsequent work in many laboratories has shown that such frustrated Lewis pairs (FLPs) may react with a variety of substrates. Most FLPs involve only main-group acids and bases (with trialkylphosphines and fluorinated triarylboranes being most common), though recent reports have

extended the approach to include transition metals as Lewis acids and bases [7,8].

In this review, we show that the FLP concept may be extended to encompass certain metal–ligand multiply bonded species, provided that the metal retains an open coordination site to facilitate cooperative reactivity. Such complexes may activate various substrates through the combined action of filled and empty orbitals on adjacent atoms: a hybrid of the classical Dewar–Chatt–Duncanson paradigm and normal FLP reactivity [9,10]. M═E FLPs include two limiting scenarios: (1) early, electropositive transition metals in high oxidation states that are attached to π-basic ligands (i.e., $M^{\delta+}$═$E^{\delta-}$), and (2) late transition metals in low oxidation states attached to π-acidic ligands (i.e., $M^{\delta-}$═$E^{\delta+}$). The reactivity engendered by such a bonding situation can in some cases be quite useful in C–H functionalization schemes that require cooperative activation of substrates. One well-defined case with iridium(I) carbenes generated by multiple C−H activations is explored as a proof of principle.

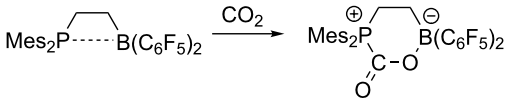
Note that the purpose of this review is not to provide an exhaustive list of examples of reactivity consistent with the description of certain metal–ligand multiple bonds as FLPs, thus there will necessarily be a number of omissions. Instead, this article is presented in order to show the similarity between many M═E species and main-group FLPs and provide some inspiration for how such multiply bonded complexes may be used in C–H functionalization schemes.

Review

Metal–ligand multiple bonds as FLPs

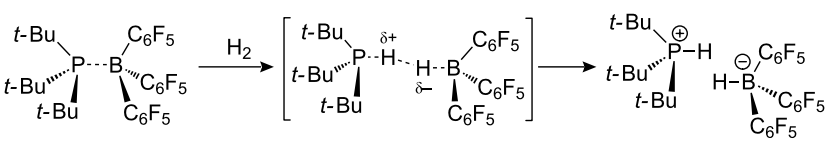
Electronic basis for FLP behavior of metal–ligand multiple bonds

As mentioned above, most FLPs rely on steric encumbrance to minimize the interaction between an electron-rich Lewis base and an electron-poor Lewis acid. The weakly interacting acid–base pair is then capable of activating various substrates by synergistically polarizing bonds, often in a concerted fashion [6,11-14]. The reaction is favorable, because the small-molecule substrates facilitate a shift in electron density away from the electron-rich Lewis base and toward the electron-deficient Lewis acid. In the case where molecular hydrogen interacts with a phosphine/borane FLP, this occurs by the formation of a phosphonium/borate ion pair (Scheme 1). For unsaturated substrates, the reaction is better described as an insertion or cycloaddition (see Scheme 2 for a representative example), but the outcome is quite similar.



Scheme 2: Insertion of carbon dioxide into a phosphine/borane FLP [14].

The FLP description may easily be extended to transition-metal species containing multiple bonds to ligands, provided that two conditions are met: (1) The metal must retain a vacant coordination site or be able to dissociate a ligand to provide such a site, and (2) there must be sufficient $M^{\delta+}$═$E^{\delta-}$ or $M^{\delta-}$═$E^{\delta+}$ character (typically associated with incomplete E→M or M→E π donation) to induce reactivity with polar or polarizable substrates. The first requirement is fairly straightforward: if a transition metal is coordinatively saturated, it will be unable to react as a Lewis acid or base, irrespective or how electron poor or rich it is. The second requirement can perhaps be better conveyed by using molecular-orbital diagrams. For the $M^{\delta+}$═$E^{\delta-}$ case, which we may associate with early, electropositive transition metals in their highest oxidation states, ligand-to-metal π donation is not strong enough to fully attenuate either the π basicity of the ligand or the acidity of the metal (Figure 1a). This bonding scenario is frequently encountered, for example, with the classic Group 4 imido complexes of Bergman and Wolzcanski, or the Group 5 alkylidenes of Schrock [15,16]. The reverse $M^{\delta-}$═$E^{\delta+}$ case, in which π back-bonding from an electron-rich metal into a relatively electropositive ligand is insufficient to fully attenuate the basicity of the metal and/or the π acidity of the ligand (Figure 1b), is encountered for low-oxidation-state late-metal silylene [17], carbene [18], and borylene complexes [19], among others [20-23]. Either bonding situation can be described as electronic frustration [24], since sterics do not play a primary role in separating acidic and basic reactive sites on a molecule.



Scheme 1: Heterolytic cleavage of H_2 by a phosphine/borane FLP by H_2 polarization in the P–B cavity [5,11].

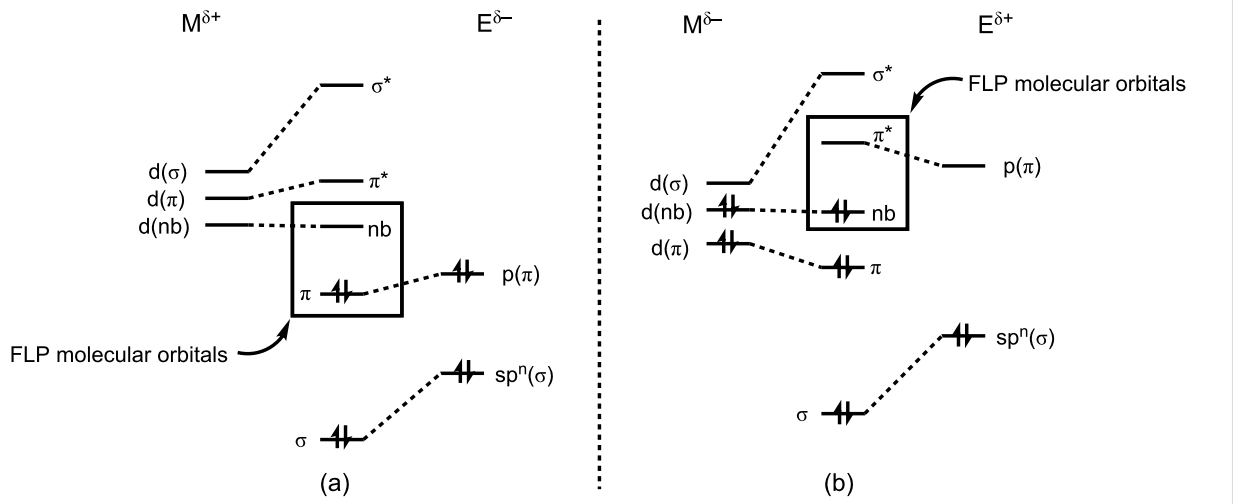


Figure 1: Simplified frontier-molecular-orbital diagrams for (a) $M^{\delta+}{=}E^{\delta-}$ and (b) $M^{\delta-}{=}E^{\delta+}$ FLPs (n = 1 for linear or terminally bound species, e.g., nitride, carbyne, linear imide, oxo, or borylene; n = 2 for bent or trigonal species, e.g., carbene, silylene, bent imide, amide, or boryl).

Steric effects nevertheless play an important role, as one can envision a bimolecular pathway to acid–base adduct formation (Figure 2a). Such dimerization does occur in cases with insufficient steric encumbrance (e.g., the bis-μ-imido zirconium complexes of Bergman, Figure 2b) [25]. Thus, as for the main-group FLPs of Stephan and others, moderately-to-severely bulky ligands must be employed to favor the most reactive monomeric M═E FLPs.

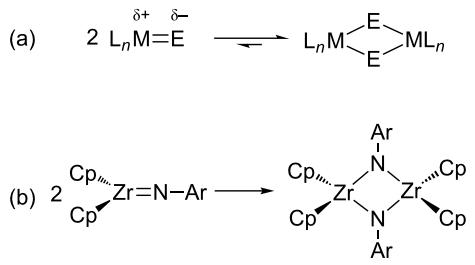
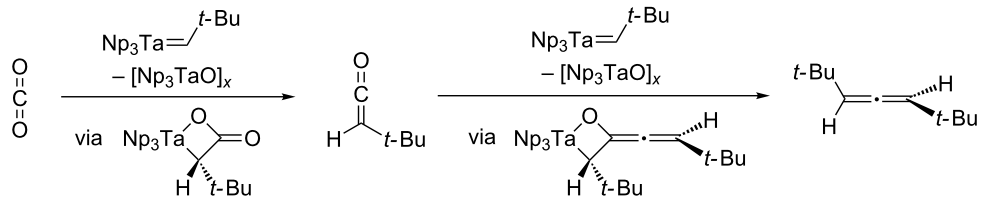


Figure 2: Quenching of M═E FLPs by dimerization: (a) generic $M^{\delta+}{=}E^{\delta-}$ case, and (b) Bergman's arylimido zirconium(IV) [25].

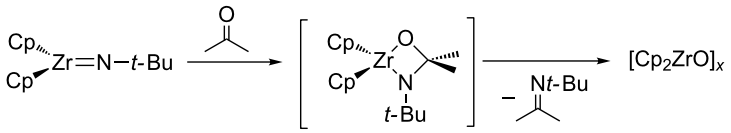
M═E FLPs with π-basic ligands: Reactions with unsaturated bonds

Species containing $M^{\delta+}{=}E^{\delta-}$ moieties have been known for some time, with the clearest examples being terminal imido and alkylidene complexes of early metals in their highest oxidation states. Such complexes may have substantial nucleophilic character at the multiply bonded group E [15,16,26], leading to well-defined reactions with various electrophiles as well as polarized and polarizable substrates. In many cases, these reactions resemble those explored more recently for main-group FLPs.

The first type of reaction exhibited by M═E FLPs containing π-basic ligands is with polar multiple bonds such as carbonyls. The nucleophilic multiply bonded group can attack the electrophilic carbon atom, ultimately leading to metallacycle formation and frequently atom or group transfer. This type of reactivity is observed upon exposure of Schrock's tris(neopentyl)neopentylidene tantalum(V) complex to CO_2, upon which *tert*-butylketene and then di-*tert*-butylallene are formed by consecutive oxygen-atom abstractions via metallacyclic intermediates (Scheme 3) [27].



Scheme 3: Oxygen-atom extrusion from CO_2 by a Ta(V) neopentylidene [27].

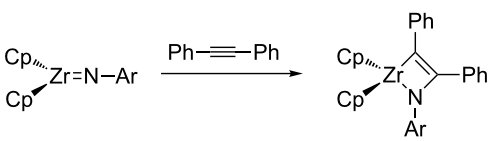


Scheme 4: Oxygen-atom transfer from acetone at a Zr(IV) imide [28].

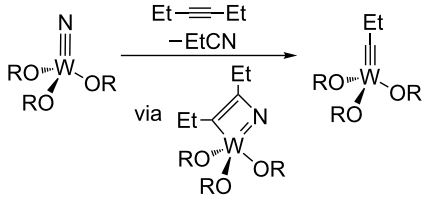
Similar reactions have been observed for nucleophilic imido complexes, in which imines can be formed by an oxo/imide metathesis at zirconium(IV). As with the Schrock neopentylidene, the reaction proceeds through a four-membered metallacycle, which eliminates the organic product through a [2 + 2] cycloreversion (Scheme 4) [28]. Other early metal imides may demonstrate similar reactivity, as seen in a reaction reported by Schrock for a tantalum(V) imide [29].

The reactions described above represent only a few of the many metal–ligand cooperative reactions of nucleophilic, multiply bonded species with polar multiple bonds. Related reactions have been observed for terminal oxo, sulfido, phosphinidene, and alkylidyne complexes of early transition metals (see references [30-33] for representative examples). Similar reactions can also occur in [3 + 2] fashion with azides [34].

As for main-group FLPs [35], $M^{\delta+}{=}E^{\delta-}$ FLPs may also react with nonpolar unsaturated substrates, such as alkenes or alkynes, by polarizing the substrate to facilitate cycloaddition. [2 + 2] cycloadditions of $M^{\delta+}{=}E^{\delta-}$ FLPs with alkenes/alkynes have been thoroughly explored in the context of olefin metathesis (where E = CR_2) and related variants such as alkyne and enyne metathesis [36,37]. Related reactivity is prevalent for other $M^{\delta+}{=}E^{\delta-}$ species such as imides and nitrides. Bergman's bis(cyclopentadienyl)zirconium(IV) imides, described above, will add alkenes and alkynes in [2 + 2] fashion across the Zr=NR bond (Scheme 5) [38]. This reaction is important for the hydroamination of alkynes by Cp_2ZrX_2 complexes, which proceeds through zirconium imido intermediates [39]. A similar [2 + 2] cycloaddition of symmetrical alkynes across a tungsten nitride is the initial step in Johnson's nitrile-alkyne cross metathesis reaction (Scheme 6) [40,41].



Scheme 5: Alkyne cycloaddition at a Zr(IV) imide [38].

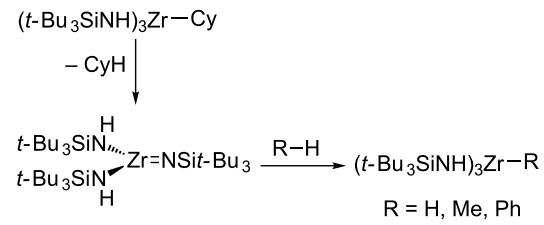


Scheme 6: Nitrile-alkyne cross metathesis at a W(VI) nitride [40,41].

M=E FLPs with π-basic ligands: Reactions with saturated bonds

$M^{\delta+}{=}E^{\delta-}$ FLPs of the type described above have also been shown to react with a number of saturated bonds. Although it should be no surprise that such basic units would deprotonate relatively acidic N–H, O–H, and related bonds, their potential utility lies in the fact that they can also react with unpolarized H–H and C–H bonds (including those of methane). The result is a 1,2-addition of X–H across the M=E bond to give a M(X)(EH) species, which may in some cases react further.

A prominent example was reported by Wolczanski, in which a Zr(IV) silylimide can react with the C–H bonds in benzene and even methane (Scheme 7) [42]. The reaction proceeds in a manner similar to the reactions of main-group FLPs with H_2,in which the substrate is polarized in the presence of the frustrated pair and ultimately added across it [43]. Intramolecular addition of a benzylic C–H bond across a Zr(IV) phosphinidene has been reported by Stephan [32]. Several C–H cleavage reactions have also been reported across alkylidenes and alkylidynes [44-46], and these may be viewed as the microscopic reverse of the α-hydrogen eliminations frequently utilized to generate such multiply bonded units.



Scheme 7: C–H and H–H addition across a zirconium(IV) imide [42].

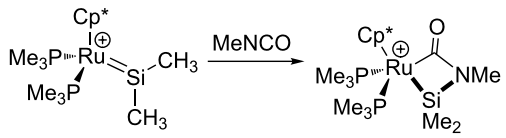
The limitations of these sorts of reactions in terms of potential catalytic applications are largely related to the reluctance of the metal center to undergo redox chemistry (e.g., N–C reductive elimination to generate an amine). The systems are constructed to favor high oxidation states, so reductive elimination is quite unfavorable relative to other non-redox processes, and insertion of unsaturated bonds is generally not observed. In a sense, this limitation is similar to what is encountered in attempts to use σ-bond metathesis processes in catalysis, in which only a few specialized systems have been reported to accomplish catalytic C–H functionalization [47-49]. In fact, the bond-breaking process across metal–ligand multiple bonds is closely related to σ-bond metathesis [43], highlighting the potential of $M^{\delta+}{=}E^{\delta-}$ FLPs to activate some of the most challenging substrates.

One phenomenally useful example of heterolytic H–H cleavage across a ruthenium–amide bond, somewhat related to those described above, is found in Noyori's ruthenium hydrogenation catalysts, which utilize metal-ligand bifunctional pathways both for breaking the H–H bond and then for transferring H_2 to polar multiple bonds [50,51]. Though the Ru–N bond polarization is not nearly as dramatic for the Noyori systems as it is for the early metal complexes described above, the nitrogen basicity and ruthenium acidity clearly play important roles in guiding the observed reactivity.

M═E FLPs with π-acidic ligands

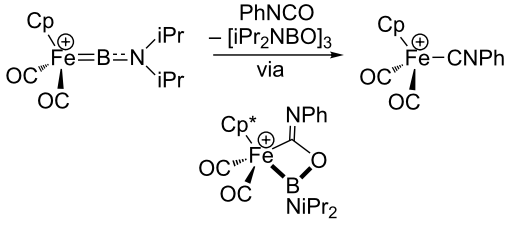
The reverse situation with respect to the metal-based FLPs described above is one in which a coordinatively unsaturated metal acts as a Lewis base and a relatively electropositive π-acidic ligand acts as a Lewis acid. We might expect this situation to be less common since metals are typically formulated as cations and are more electropositive than the majority of elements normally attached to them. However, the phenomenon of metal basicity is well known [52,53], particularly for the late transition metals in low oxidation states. There are numerous cases in which M═E π bonding is inadequate to quench the electrophilicity of the multiply bonded group (particularly for heavier main-group elements, but also for carbon- and boron-based groups), affording a bonding situation that can be described as a $M^{\delta-}{=}E^{\delta+}$ FLP.

Late metal silylenes, such as those explored by Tilley, often have substantial positive character at the silicon site (especially in cationic complexes), leading to reactivity that is dominated by the electrophilicity of silicon, with the metal playing a secondary role [17]. Prominent examples include the formation of base-stabilized silylenes [54,55], insertion of olefins into hydrosilylenes [56], and bimolecular redistribution of thiolates between ruthenium silyl and silylene complexes [57]. Reactivity that involves metal-ligand cooperation (in the sense described in this article) has been reported in the formal [2 + 2] cycloaddition of isocyanates to ruthenium(II) silylenes [58] (Scheme 8). These complexes do not react with nonpolar substrates (although a possible cycloaddition with azobenzene was reported), and the overall cycloaddition was found to proceed through initial nucleophilic attack at an electrophilic silylene, indicating that the metal center is not itself very reactive. However, the ability to stabilize the metallacycle is clearly derived from an enhanced transfer of electron density from ruthenium to silicon through an intervening heterocumulene. Unfortunately, retrocycloaddition to give silylene-group transfer and silaimine formation was not observed.



Scheme 8: Formal [2 + 2] cycloaddition of methyl isocyanate at a ruthenium silylene [58].

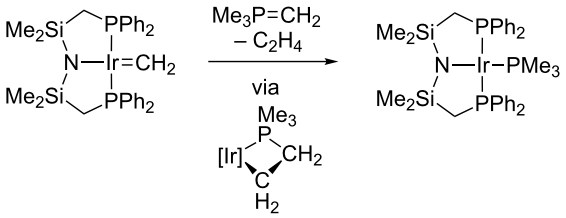
Many transition-metal borylene complexes may also be categorized as $M^{\delta-}{=}E^{\delta+}$ FLPs, undergoing reactions with heterocumulenes and other polar multiple bonds similar to those reported for silylenes [59]. The [2 + 2]-type reactions with heterocumulenes can lead to insertions or, in some cases, atom transfer [60]. One example with Aldridge's iron(II) aminoborylenes is presented in Scheme 9. In this case, Fe/B cooperation leads to scission of the C═O bond and oxygen-atom transfer to the borylene unit. As with cationic silylenes, the borylene complexes in Scheme 9 react by initial coordination of a heteroatom to the highly electrophilic boron center, followed by interaction with the metal to give a four-membered metallacycle and oxygen-atom transfer upon cycloreversion [61]. Thus, the reactions are initiated by the electrophilicity at B rather than the nucleophilic character of Fe.



Scheme 9: Oxygen-atom transfer from phenyl isocyanate to a cationic terminal borylene [60].

In contrast to the silylene and borylene examples presented above, square-planar carbene complexes of iridium(I) often

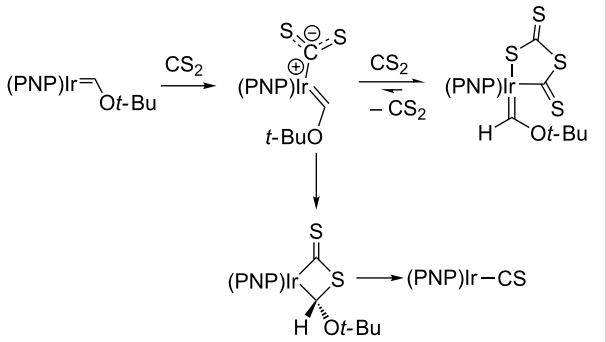
react in a fashion that is dictated by the nucleophilic metal center. An early example of this type of complex was an amidophosphine-supported iridium methylene reported by Fryzuk [62-64]. With a coordinatively unsaturated and electron-rich center, this species exhibits some reactivity that is similar to the isoelectronic Vaska's complex [65], such as oxidative addition of methyl iodide. It also reacts in dipolar fashion with an in-situ-generated phosphorus ylide to release ethylene and make an iridium(I) trimethylphosphine complex (Scheme 10). More recently, Werner reported several square-planar iridium(I) carbene complexes that react with acid to selectively protonate the iridium center (i.e., the more basic/nucleophilic site) [66,67].



Scheme 10: Coupling of a phosphorus ylide with an iridium methylene [62].

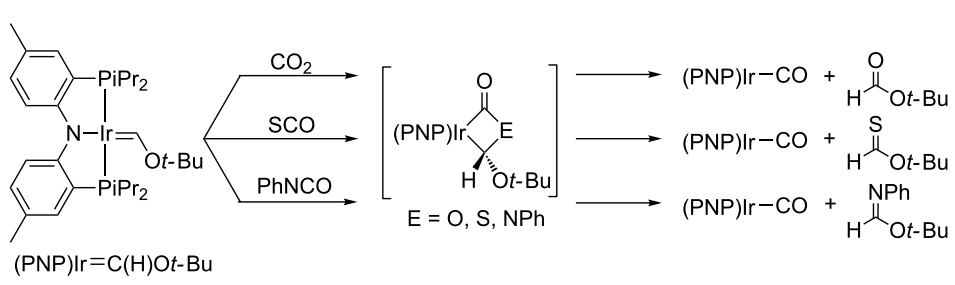
Whited and Grubbs explored the reactivity of a related iridium(I) carbene system, supported by Ozerov's amidophosphine pincer ligand and generated by multiple C–H activations [18,68-70], with a number of heterocumulenes such as those described above. Oxygen-atom, sulfur-atom, and nitrene-group transfers to the carbene were observed when carbon dioxide, carbonyl sulfide, and isocyanates were utilized, cleanly generating the Ir(I) carbonyl as a byproduct (Scheme 11) [71].

The nucleophilicity of the iridium center was demonstrated through a series of experiments. First, it was noted that the carbene complex does not react with simple nucleophiles, a departure from traditional "Fischer-type" carbene reactivity [72]. Second, the iridium center reacts with excess CS_2 to reductively couple two carbon disulfide units, generating a metallacyclic $IrC_2S_4^{2-}$ with no new bonds formed to the carbene (Scheme 12) [73]. Interestingly, this reaction is reversible and the thermodynamic product from the reaction with CS_2 is the Ir(I) thiocarbonyl, analogous to the reactions shown in Scheme 11. Finally, though the complex does not react with simple nucleophiles, a cation–π complex is formed from the interaction of silver triflate with the Ir=C bond [74], and this complex was crystallographically characterized (Figure 3). Together, these findings showed that carbenes of this type do not exhibit traditional Fischer (electrophilic at C_α) or Schrock-type (nucleophilic at C_α) reactivity, and were better classified as nucleophilic-at-metal (or "Roper-type") carbenes with significant π backbonding, consistent with Roper's predicted patterns of reactivity for metal–carbon double bonds [75].



Scheme 12: Reductive coupling of two CS_2 units at (PNP)Ir=C(H)O*t*-Bu [73].

These Roper-type carbenes also reacted with organic azides and nitrous oxide via an apparent [3 + 2] cycloaddition [76,77], leading to oxygen-atom or nitrene-group transfer and formation of (PNP)Ir–N_2 [78], and this reaction was utilized in catalytic C–H functionalization (see below). More recently, Hillhouse's nickel carbenes and imides have been shown to exhibit similar reactivity with organic azides, though reaction with CO_2 has not been observed [77].



Scheme 11: Reactions of (PNP)Ir=C(H)O*t*-Bu with oxygen-containing heterocumulenes [71].

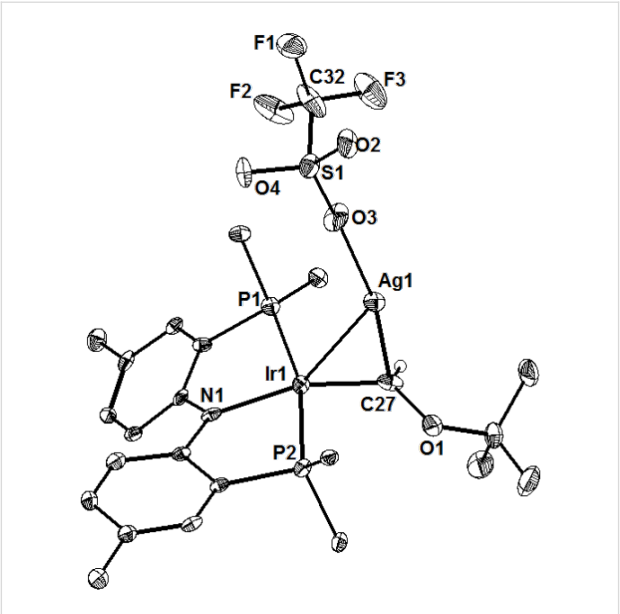
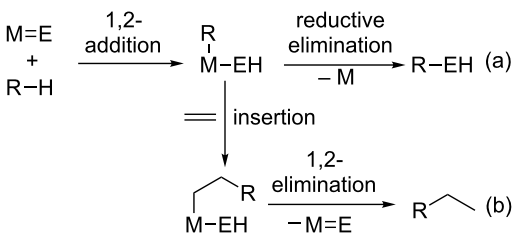


Figure 3: Single-crystal X-ray structure of a silver(I) triflate adduct of (PNP)Ir=C(H)O*t*-Bu with most H atoms and phosphine substituents (except *ipso* carbon atoms) omitted for clarity.

As described above, FLPs of the $M^{\delta-}=E^{\delta+}$ variety can be very useful for inducing atom or group transfer from heterocumulenes or other polar multiple bonds such as those in phosphine oxides. Compared with early-metal $M^{\delta-}=E^{\delta+}$ FLPs, these sorts of complexes have the advantage of greater redox activity, facilitating application in catalysis (see below). However, they also have lower reactivity due to a less polarized M=E bond, which cannot activate strong C–H or related bonds. Though H–H addition across Ir=C bonds has been reported, this almost certainly occurs by oxidative addition of H_2 at the Ir(I) center followed by hydride migration [64,79,80]. The well-developed C–H borylation chemistry of Hartwig and others provides an indication that cooperation may be operative to some extent in the activation of C–H bonds at metal boryls [81-84], though the exact mechanism of C–H cleavage seems to depend on the nature of the metal catalyst. Nevertheless, these results do provide inspiration for the development of similar C–H functionalization catalysis involving metal carbenes or silylenes (or perhaps even electrophilic nitrenes).

Utility of M=E FLPs in C–H functionalization

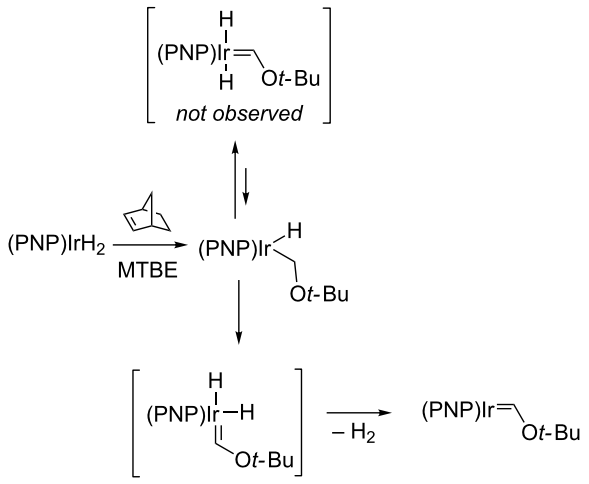
Given the types of reactivity discussed thus far, there are several distinct routes to the functionalization of C–H (or E–H) bonds using metal–ligand multiply bonded FLPs. If C–H activation is effected by 1,2-addition across a M=E bond, then reductive elimination could result in a net C–H insertion of carbene or nitrene (Scheme 13a). This would be formally related to carbene or nitrene insertions that have been shown to occur, among other cases, at dirhodium paddlewheel complexes [85], though the specific mechanism of C–H bond breaking (and hence the reaction selectivity) would be quite different. Such a transformation has not been realized with the early metal complexes that are most reactive toward C–H bonds, probably because reductive elimination is strongly disfavored relative to the 1,2-elimination of alkane. Another possibility would be an initial 1,2-addition of a C–H bond across M=E, followed by insertion of an unsaturated substrate (olefin, alkyne) and either a 1,2-elimination (to afford a hydroalkylation or hydroarylation product) or reductive elimination as described above. However, to the best of our knowledge, this type of reactivity has not been observed at early metal imido or alkylidene complexes that can cleave C–H bonds.



Scheme 13: Possible routes to C–H functionalization by 1,2-addition across a polarized metal–element multiple bond.

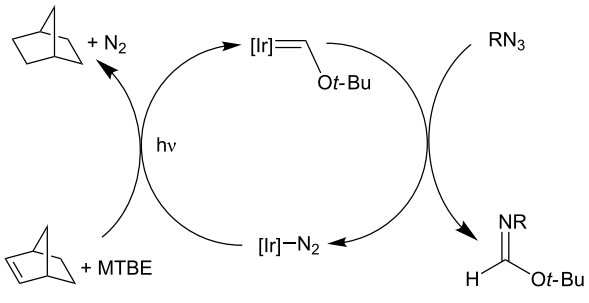
An alternative route involves the generation of a M=E FLP species by multiple C–H (or E–H) activations [18,70,86]. As mentioned above, Whited and Grubbs showed that an iridium(I) carbene system that exhibited FLP reactivity could be generated by multiple C–H cleavage events at *tert*-butyl methyl ether (MTBE) (Scheme 14) [71,87]. For the (PNP)Ir system developed by Ozerov, it was found that an initial C–H activation of the most accessible methyl C–H bond in MTBE was followed by slow α-hydrogen elimination and reductive elimination of H_2 to afford the Ir(I) alkoxycarbene. The complex could be generated stoichiometrically when norbornene was utilized as a hydrogen acceptor. The reaction was shown to be general for several methyl ethers and tetrahydrofuran, but other ethers were prone to 1,2-dehydrogenation or decarbonylation [88,89] The use of methyl amines as substrates also allowed the selective formation of dihydrido aminocarbenes, but the greater basicity of these species prevented the reductive elimination of H_2 under any of the conditions examined [90].

With this complex in hand, the coordinative unsaturation (and nucleophilicity) of the square-planar iridium center was utilized to explore a variety of atom- and group-transfer reactions, as described above. However, the iridium carbonyl, thiocarbonyl, or isocyanide products thus generated could not be incorporated into catalytic cycles due to the stability of the Ir–CO, –CS, and –CNR bonds [71,91]. A catalytic cycle was ultimately



Scheme 14: Alkoxycarbene formation by double C–H activation at (PNP)Ir [88].

achieved following the discovery that the reaction of (PNP)Ir═C(H)O*t*-Bu with organic azides leads to the formation of *tert*-butyl formimidates and (PNP)Ir–N_2, which is a suitable precursor for C–H activation of MTBE upon photolysis [78] (Scheme 15). Although the presence of excess azide poisoned the catalyst (presumably by irreversible formation of iridium–azide adducts), the controlled addition of azide to an MTBE solution of (PNP)Ir and norbornene, illuminated by a 23 W halogen bulb, led to efficient catalytic oxidation of MTBE. The net C–H functionalization in this case is facilitated both by the propensity of iridium to engage in multiple C–H activations to form the carbene, as well as by the $M^{\delta-}$═$E^{\delta+}$ FLP nature of the intermediate Ir(I) alkoxycarbene species.



Scheme 15: Catalytic oxidation of MTBE by multiple C–H activations and nitrene-group transfer to a $M^{\delta-}$═$E^{\delta+}$ FLP [18,78].

These results not only show that species containing metal–ligand multiple bonds with the appropriate electronic structure may exhibit reactivity consistent with a FLP description, but that this reactivity may be harnessed for catalytic C–H functionalization. Several challenges remain in the catalytic cycle presented, namely that large excesses of substrate are required, and the generality of the reaction is limited by the number of substrates than can serve as carbene precursors, but these may be overcome through the design of more-selective systems for C–H activation. The reactivity observed by Grubbs also highlights the importance of hydrogen management in processes that involve generating M═E FLPs by multiple C–H activations, since the active catalysts must either be able to eliminate H_2 without unproductive back reactions or must transfer H_2 into a sacrificial acceptor (such as norbornene in the cycle described). All in all, these findings provide a framework both for the discovery of new reactions involving M═E FLPs and for their implementation in catalytic transformations for the functionalization of C–H and E–H bonds.

Conclusion

In this article, we have proposed that many species containing polarized metal–ligand multiple bonds and coordinatively unsaturated metal centers may be described as analogues of the recently developed frustrated Lewis pairs involving main-group Lewis acids and bases. Although the manner in which "frustration" occurs is somewhat different (i.e., it is primarily electronic and not steric in origin), the types of reactivity observed are remarkably similar. One example in which this behavior has been used for the catalytic functionalization of C–H bonds has been elaborated, and several strategies for future utilization of such electronically frustrated species have been presented.

Supporting Information

Supporting Information File 1

The single-crystal X-ray structure of [(PNP)Ir═C(H)O*t*-Bu][AgOTf] is supplied in CIF format and has been deposited with the CCDC, No. 889634.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-177-S1.cif]

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Arylglycine-derivative synthesis via oxidative sp^3 C–H functionalization of α-amino esters

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Letter

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Abstract

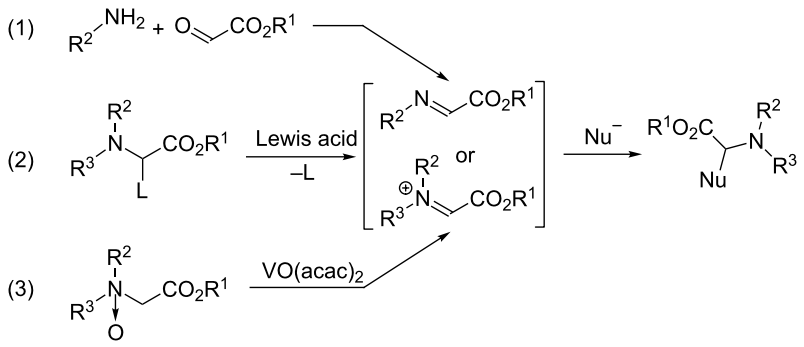
An efficient method for the synthesis of arylglycine derivatives is described. The oxidative coupling reactions of naphthols and phenols with α-amino esters proceeded smoothly in the presence of *meta*-chloroperoxybenzoic acid as an oxidant under ambient conditions, to produce arylglycine derivatives in satisfactory yields.

Findings

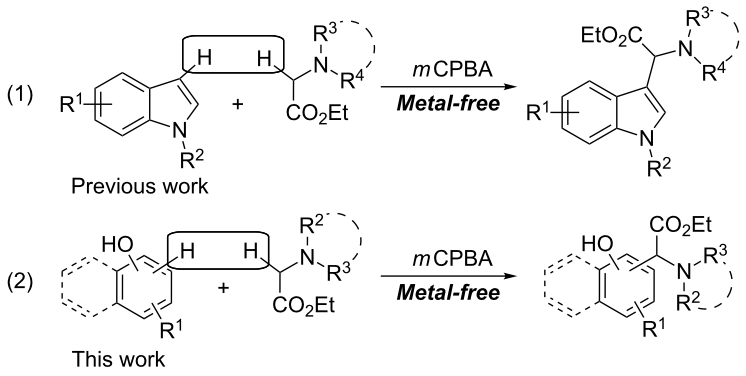
Arylglycine derivatives represent important synthetic intermediates or building blocks for drug development and natural-product synthesis [1,2]. The arylglycine moiety also occurs in several bioactive natural products [3]. Consequently, the development of convenient and efficient methods for the preparation of arylglycine derivatives has attracted considerable attention. Over the past years, many methods have been developed for the preparation of arylglycine derivatives [3]. Among these, the addition reaction of a carbon nucleophile to imines or iminium ions through Mannich-type reaction appears more useful (Scheme 1, reactions 1–3). However, these reactions need expensive arylboronic acids (Petasis reaction) [4-9] and suitable leaving groups [10-12] as well as a metal catalyst (Polonovsky reaction; this route requires the preparation of amine *N*-oxide in advance) [13,14].

We have recently reported the copper-catalyzed oxidative coupling reaction of alkynes with tertiary amine *N*-oxides [15]. This new strategy for the direct functionalization of sp^3 C–H bonds adjacent to a nitrogen atom, via tertiary amine *N*-oxide intermediates, was successfully applied to the coupling reaction of ethyl 2-(disubstituted amino)acetates with indoles to achieve indolylglycine derivatives (Scheme 2, reaction 1) [16]. In the course of our continuous research on the direct functionalization of sp^3 C–H bonds, we found that this new strategy could also be applied to the coupling reaction of naphthols and phenols with ethyl 2-(disubstituted amino)acetates. The results are reported in the current work (Scheme 2, reaction 2).

In our initial studies, the reaction of 2-naphthol (**1a**) with ethyl 2-morpholinoacetate (**2a**) was chosen as a model for opti-



Scheme 1: Synthesis of arylglycine derivatives.



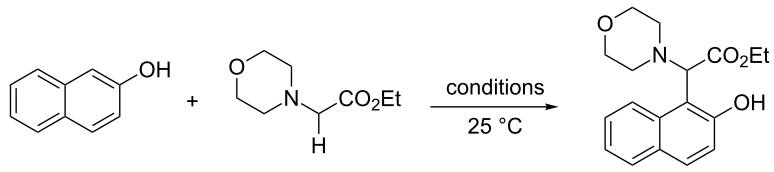
Scheme 2: Oxidative sp^3 C–H functionalization of α-amino esters.

mizing the reaction conditions. The results are shown in Table 1. The proportions of substrate **2a** and oxidant *meta*-chloroperoxybenzoic acid (*m*CPBA) were initially screened with CH_3CN as the solvent (Table 1, entries 1–3). The yield of **3a** was increased to 77% when 1.2 equiv of **2a** and *m*CPBA were used (Table 1, entry 2). Further increasing the amounts of **2a** and *m*CPBA or adding a copper catalyst could not improve the yield of **3a** (Table 1, entries 3 and 4). The solvents were then screened (Table 1, entries 5–10). The best result was observed when CH_2Cl_2 was used as the solvent (79%, Table 1, entry 5). Therefore, the subsequent reactions of naphthols and phenols with ethyl 2-(disubstituted amino)acetates were performed in the presence of *m*CPBA (1.2 equiv) in CH_2Cl_2 under ambient conditions.

The substrate scope was determined under the optimized reaction conditions, and the results are shown in Table 2. As expected, the reactions of ethyl 2-morpholinoacetate (**2a**), ethyl 2-(piperidin-1-yl)acetate (**2b**), and ethyl 2-(benzyl(methyl)-amino)acetate (**2c**) proceeded smoothly to give the corresponding products **3a**–**3c** in good yields (Table 2, entries 1–3, 64–79%). These results indicated that both α-cyclic and acyclic amino esters could be employed in this type oxidative coupling reaction. The desired products **3d**–**3f** were obtained in yields of 66–79% from the reactions of naphthols **1b**–**1d** with **2a** (Table 2, entries 4–6). However, relatively low yields were observed from the reactions of phenols **1e**–**1h** with **2a** (Table 2, entries 7–10, 30–55%). The poor reactivity of phenols **1e**–**1h** was considered to be due to their lower electron density compared to naphthols **1b**–**1d**. No reaction was observed from the mixture of phenol **1i**, bearing an electron-withdrawing Br substituent on *para*-position, and **2a** (Table 2, entry 11).

The plausible mechanism for the coupling reaction of naphthols and phenols with ethyl 2-aminoacetate derivatives is shown in Scheme 3 [16-19]. *m*CPBA oxidized **2a** to amine *N*-oxide **4** before being transformed into 3-chlorobenzoic acid. The interaction of **4** with 3-chlorobenzoic acid led to the generation of the iminium ion **5** and 3-chlorobenzoate anion. The Mannich-type reaction of **5** with 2-naphthol may have occurred to generate the coupling product **3a**. The generated 3-chlorobenzoate anion acted as a proton acceptor.

Table 1: Optimization of reaction conditions.[a]

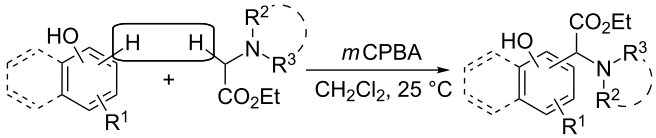


1a **2a** **3a**

Entry	**2a** (equiv)	*m*CPBA (equiv)	Time (h)	Solvent	Yield of **3a** (%)[b]
1	1.0	1.0	40	CH_3CN	63
2	1.2	1.2	40	CH_3CN	77
3	1.5	1.5	40	CH_3CN	77
4[c]	1.2	1.2	40	CH_3CN	75
5	1.2	1.2	24	CH_2Cl_2	79
6	1.2	1.2	40	THF	65
7	1.2	1.2	48	dioxane	16
8	1.2	1.2	48	CH_3CH_2OH	14
9	1.2	1.2	48	toluene	70
10	1.2	1.2	48	DMF	trace

[a]Reaction conditions: 2-naphthol (**1a**, 72.1 mg, 0.5 mmol), ethyl 2-morpholinoacetate (**2a**, 1.0 equiv to 1.5 equiv), and *m*CPBA (1.0 equiv to 1.5 equiv) in solvent (3.0 mL) under air at 25 °C. [b]Isolated yield. [c]10 mol % $Cu(OTf)_2$ was used as a catalyst.

Table 2: Oxidative coupling reaction of naphthols and phenols with α-amino esters.[a]



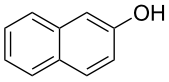
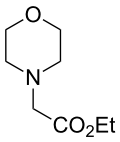
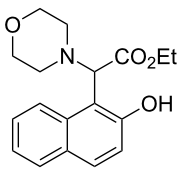
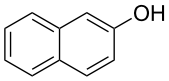
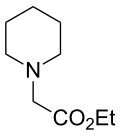
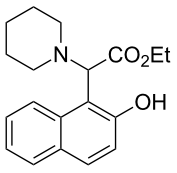
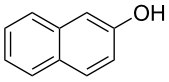
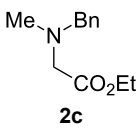
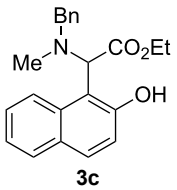
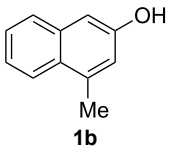
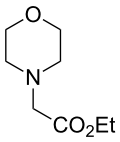
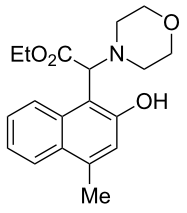
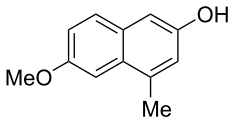
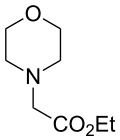
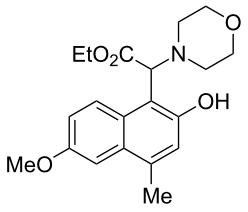
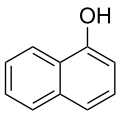
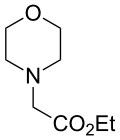
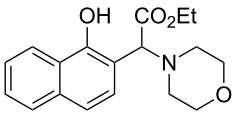
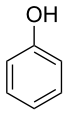
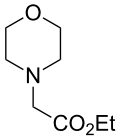
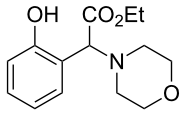
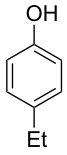
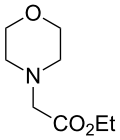
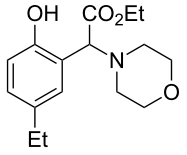
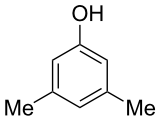
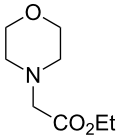
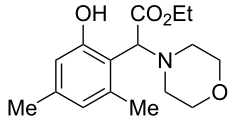
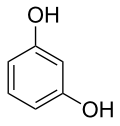
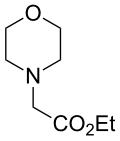
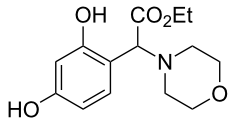
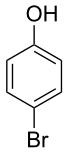
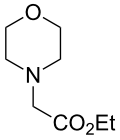
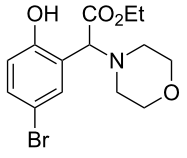
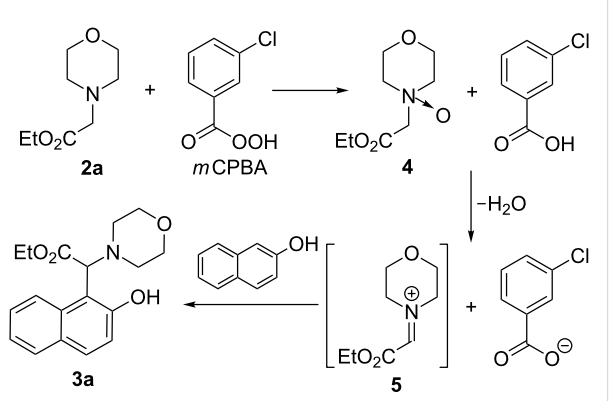
Entry	Phenol **1**	Amine **2**	Time (h)	Product **3**	Yield (%)[b]
1	 **1a**	 **2a**	24	 **3a**	79
2	 **1a**	 **2b**	24	 **3b**	64
3	 **1a**	 **2c**	36	 **3c**	64

Table 2: Oxidative coupling reaction of naphthols and phenols with α-amino esters.[a] (continued)

4	 **1b**	 **2a**	20	 **3d**	79
5	 **1c**	 **2a**	20	 **3e**	75
6	 **1d**	 **2a**	18	 **3f**	66
7	 **1e**	 **2a**	48	 **3g**	30
8	 **1f**	 **2a**	36	 **3h**	30
9	 **1g**	 **2a**	24	 **3i**	35
10	 **1h**	 **2a**	16	 **3j**	55
11	 **1i**	 **2a**	48	 **3k**	0

[a]Reaction conditions: naphthols or phenols (**1**, 0.5 mmol), α-amino esters (**2**, 0.6 mmol, 1.2 equiv), and *m*CPBA (121.8 mg, 0.6 mmol, 85% purity) in CH_2Cl_2 (3.0 mL) under air at 25 °C. [b]Isolated yield.



Scheme 3: Proposed mechanism.

In conclusion, a new strategy for the functionalization of sp^3 C–H bonds of amino esters was successfully applied to the coupling reaction of ethyl 2-(disubstituted amino)acetates with naphthols and phenols. The proposed coupling reaction proceeded smoothly in the presence of *m*CPBA as an oxidant under ambient conditions to provide arylglycine derivatives in satisfactory yields.

Supporting Information

Supporting Information File 1

General methods, characterization data and NMR spectra of all synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-178-S1.pdf]

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Synthesis of conformationally restricted glutamate and glutamine derivatives from carbonylation of orthopalladated phenylglycine derivatives

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Abstract

A new method for the regioselective synthesis of 2-alkoxycarbonyl- and 2-(aminocarbonyl)phenylglycinate methyl esters has been developed. The reaction of the orthopalladated complex [Pd(μ-Cl)(C_6H_4(CH(CO_2Me)NMe_2)-2)]$_2$ (**1**) with nucleophiles HNu under a CO atmosphere results in the selective incorporation of the C(O)Nu moiety to the phenyl ring and formation of the carbonyl species *ortho*-C_6H_4(C(O)Nu)(CH(CO_2Me)NMe_2) (**2a**–**j**) (Nu = OR, NHR, NR_2). Compounds **2a**–**j** are conformationally restricted analogues of glutamic acid and glutamine and are interesting due to their biological and pharmacological properties. The reaction of [Pd(μ-Cl)(C_6H_4(CH(CO_2Me)NHTf)-2)]$_2$ (**3**) with nucleophiles in a CO atmosphere results, however, in the formation of the cyclic isoindolinone or the open 2-carboxyphenylglycine methyl esters, with the reaction outcome being driven by the choice of the solvent.

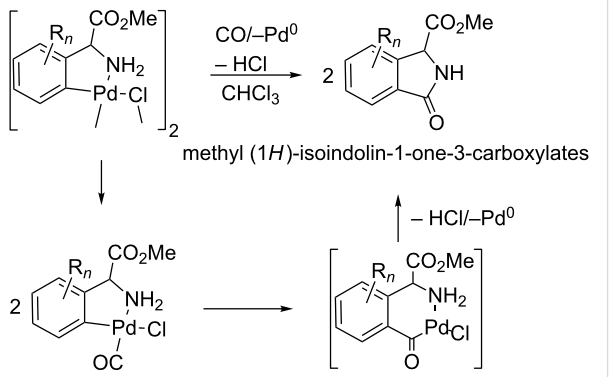
Introduction

The selective functionalization of organic molecules is, at the present time, one of the most developed areas of organic and organometallic chemistry. Several factors have contributed to this spectacular growth. The main one is the use of transition metals, such as Rh, Ru, Pd, Pt or Au, with the capability of activating and breaking C–H bonds and, thus, transforming the inert C–H unit into the reactive C–M group (M = transition metal) [1-3]. In addition, the introduction of the concept of a "directing group" enables the attack of the metal on a unique position [4], therefore affording highly selective processes and avoiding the obtainment of unwanted isomers.

Probably the aspect of this method of synthesis with the greatest impact is the oxidative coupling of two C–H bonds to give a new C–C bond, because it avoids the use of prefunctionalized substrates, minimizes the amount of waste generated during the reaction and, in general, allows for the reactions to occur under mild conditions and tolerates a variety of functional groups

[5-10]. This is advantageous when reactive or sensitive fragments are present in the molecular scaffold.

We are interested in the regioselective functionalization of α-amino acids [11-13], due to the extraordinary interest in these delicate molecules as building blocks of peptides and proteins, and because of their relevant biological activity. In this context, we have recently reported C–H bond activation processes on a variety of arylglycines substituted at the phenyl ring, and the corresponding synthesis of a new family of orthopalladated complexes [12]. The carbonylation of these compounds allows for a general synthesis of methyl (1*H*)-isoindolin-1-one-3-carboxylates under very mild reaction conditions, regardless of whether the substituents at the aryl ring R_n are electron-withdrawing or electron-releasing. This method, shown in Scheme 1, represents a real synthetic alternative to other classical preparative pathways [12].



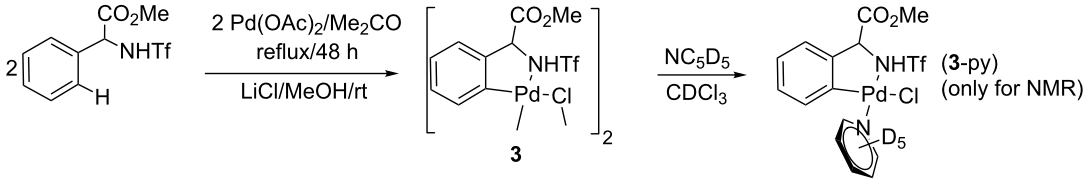
Scheme 1: Synthesis of methyl (1*H*)-isoindolin-1-one-3-carboxylates by carbonylation of phenylglycine derivatives [12].

With the aim of expanding the scope of application of this method, we report in this paper the results obtained when other functional groups on the same starting material (methyl phenylglycinate) are changed. In particular, we have detected that the presence of different types of substituents at the nitrogen atom has a critical effect on the final outcome of the reaction and that, instead of the expected (1*H*)-isoindolin-1-ones, conformationally restricted glutamines and glutamates can be obtained. The undoubted importance of conformationally constrained aminoacids is based on the fact that their incorporation into peptides constitutes a very useful strategy to reduce their flexibility and retard enzymatic degradation. Moreover, these restricted amino acids can stabilize particular conformational features, which may lead to improvements in the biological potency if the bioactive conformation is tethered [14-16].

Results and Discussion

Synthesis of new orthopalladated derivatives

Two phenylglycinate derivatives have been used as starting materials, one of them containing a sterically hindered N atom, protected by two methyl groups, namely $[C_6H_5C(H)(CO_2Me)NMe_2]$ [17,18], and the other one containing a less hindered, but strongly electron-withdrawing, triflate (Tf) group $[C_6H_5C(H)(CO_2Me)NHTf]$ [19]. The orthopalladation of $[C_6H_5C(H)(CO_2Me)NMe_2]$ has been reported previously by Ryabov and Beck [17,18], and affords complex **1** by heating of $Pd(OAc)_2$ and $[C_6H_5C(H)(CO_2Me)NMe_2]$ in acetic acid (55–60 °C over 15–20 min), followed by stirring at room temperature for 2–3 days. In this way, complex **1** is obtained in 50% yield. We did not use this method, and we present here an optimized synthesis of complex **1**, which is achieved by heating a solution of $Pd(OAc)_2$ with $[C_6H_5C(H)(CO_2Me)NMe_2]$ (1:1 molar ratio) in acetone under reflux for 24 h, followed by the typical metathesis of acetate by chloride bridging ligands in MeOH. Our improved procedure takes place in a shorter reaction time (1 versus 3 days) and affords analytically pure complex **1** in yields typically higher than 65%. The characterization of **1** was performed by comparison of its spectral data with those previously reported [18]. On the other hand, the reaction of $[C_6H_5C(H)(CO_2Me)NHTf]$ with $Pd(OAc)_2$ (1:1 molar ratio) affords the orthometallated $[Pd(\mu\text{-}Cl)(C_6H_4CH(CO_2Me)NHTf\text{-}2)]_2$ (**3**), after metathesis of acetate by chloride bridging ligands, as shown in Scheme 2. In this case the reaction also takes place in acetone under reflux, but 48 h of heating is necessary to achieve completion. Complex **3** was characterized following the usual techniques. Both microanalytical and mass spectral data are in good agreement with the proposed dinuclear stoichiometry for **3**. The ^{1}H NMR spectrum of **3** shows broad signals, probably due to different equilibrium processes. These could involve the interconversion between the two possible diastereo-



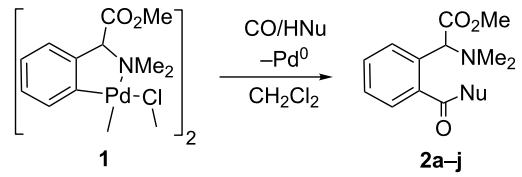
Scheme 2: Synthesis and NMR characterization of orthometallated complex **3**.

isomers (*RR*/*SS* and *RS*/*SR*) through cleavage of the chloride bridges, as well as the potential formation of *cisoid* and *transoid* geometric isomers. The breakage of the chloride bridging system by NC_5D_5 and "in situ" formation of the corresponding mononuclear derivative (**3**-py, see Scheme 2), which is static on the NMR time scale, simplifies notably the NMR spectra. The ^1H NMR spectrum shows then the presence of four well-spread signals, one of them (H6) strongly shifted upfield due to the anisotropic shielding of the *cis*-pyridine ring. This observation, together with the presence of six different peaks in the ^{13}C NMR spectrum, one of them clearly deshielded (C1, 151.41 ppm), points to the presence of the PdC_6H_4 unit. All the other features of the NMR data are in keeping with the structure depicted in Scheme 2.

Synthesis of conformationally restricted glutamates and glutamines

Complex **1** reacts with CO in the presence of alcohols or amines (even aminoesters) affording the corresponding alkoxycarbonylated (**2a**–**f**) or aminocarbonylated species (**2g**–**j**), as shown in Scheme 3 and Figure 1, under very mild reaction conditions (CH_2Cl_2, 1 atm CO, 25 °C).

The clear formation of black palladium indicates the progress of the reaction, which is completed typically in 16 h in all studied cases. After removal of the Pd^0 the workup of the reaction is very simple, since the evaporation of the solvent affords **2a**–**j** as analytically pure yellow oils. Compounds **2a**–**f** can be considered as glutamic acid derivatives, while **2g**–**j** are analogues of glutamine, in which the β- and γ-positions belong to an aryl ring and display, therefore, a severe conformational restriction.



Scheme 3: Carbonylation of **1** to afford glutamate and glutamine derivatives **2a**–**j**.

The present method appears to be quite general, since it is valid for a wide range of alcohols and amines. In the case of alcohols, primary (**2a**, **2b**, **2d**, **2e**) and secondary (**2c**) aliphatic alcohols, and even arylic substrates (**2f**) have been incorporated into the phenylglycine scaffold. Very good yields are obtained with acidic alcohols, such as methanol (**2a**), ethanol (**2b**) or even 1,2-ethanediol (**2d**). These values drop when 2-propanol (**2c**) or phenol (**2f**) are used, and moderate yields are obtained (≈40%), whereas no reaction at all is observed for bulky tertiary alcohols, for example when Me_3COH is used.

In alkoxycarbonylation reactions the nucleophile finally incorporated into the carbonyl group (an alkoxide) usually comes from the reaction solvent (an alcohol). This fact guarantees the full displacement of the reaction, but sometimes hampers the purification of the target products, mainly when alcohols of high boiling point and/or viscosity are involved. However, in our method, CH_2Cl_2 is used as the solvent and stoichiometric amounts of the nucleophiles are used instead, without any problem in the purification step.

Interestingly, there is a clear difference in the reactivity of **1** with CO, depending on the presence or lack of nucleophiles. The reaction of **1** with CO in CH_2Cl_2 has been reported previously by Beck [18], and this process affords the γ-lactam displayed in Scheme 4. Assuming the mechanism shown in Scheme 1, it seems that, in the absence of any other nucleophile, the intramolecular C–N coupling takes place with concomitant formation of a *N,N*-dimethylisoindolinonium salt, which undergoes further elimination of a methyl group by

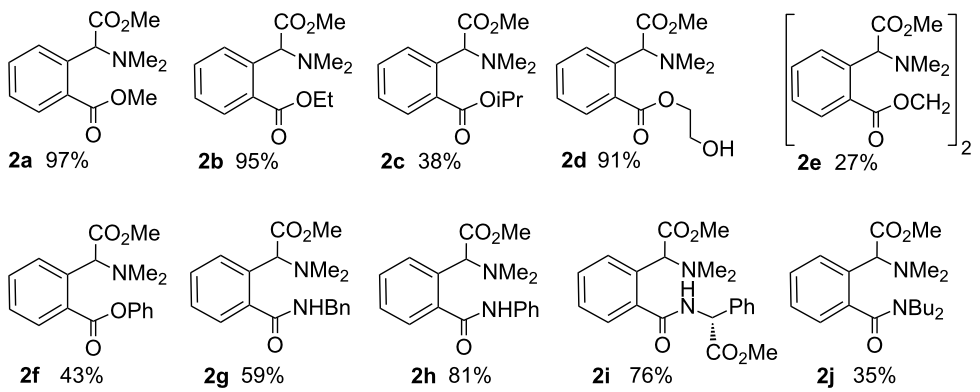
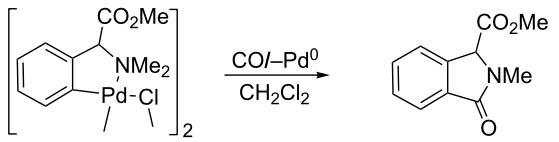


Figure 1: Scope of the carbonylation reaction.



Scheme 4: Reaction of **1** and CO in CH_2Cl_2 [18].

1,2-shift of the Me unit from the N atom to the Pd centre, as previously reported by Heck et al. [20].

As we have shown previously in Scheme 3, in the presence of nucleophiles the process results in the formation of conformationally restricted glutamate derivatives. This is mainly due to the fact that the demethylation of the NMe_2 unit shown in Scheme 4 is not a very favourable process, and the reaction can take a different outcome, especially if alternative pathways are accessible. Taking into account these facts, we can propose a sensible explanation for the different reactivity. Therefore, the attack of the oxygen of an O-bonded alcohol on the electrophilic acyl carbon in our complexes seems to be favoured, since no demethylation is involved, and the C–O coupling occurs selectively instead of the intramolecular C–N bond formation. It seems that the reaction is driven by the pathway that tends to avoid the demethylation, while the comparison of the different nucleophilic abilities of the species coordinated to the metal (O-bonded alcohols versus N-bonded amines) plays in this case only a minor role.

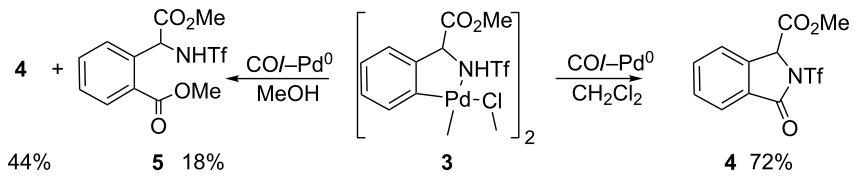
Using the same arguments we can explain the different reactivity found for **1**, and shown in Scheme 3, when compared to related Pd complexes previously reported by us [12], resumed in Scheme 1. Therefore, the synthesis of the methyl (1*H*)-isoindolin-1-one-3-carboxylates by carbonylation of $[Pd(\mu\text{-}Cl)(C_6H_4CH(CO_2Me)NH_2\text{-}2)]_2$ occurs by C–N coupling, irrespective of the presence of additional nucleophiles, since the cyclization generates an isoindolinonium salt, from which it is relatively easy to promote a simple deprotonation.

Very interestingly, the reactivity of **1** is not limited to the addition of alcohols, and primary amines, secondary amines, and even α-aminoesters can also be coupled to the *N,N*-dimethyl-arylglycine fragment, as stated above. Then, the reaction of **1** with CO, in CH_2Cl_2, and in the presence of stoichiometric amounts of benzylamine, aniline, methyl (*R*)-phenylglycinate or di-*n*-butylamine, occurs with smooth insertion of CO into the Pd-C_{aryl} bond and further incorporation of the $C(O)NHCH_2Ph$ (**2g**), C(O)NHPh (**2h**), $C(O)NHCH(CO_2Me)Ph$ (**2i**) or $C(O)NBu_2$ (**2j**) moieties into the *ortho*-position of the $C_6H_4C(H)(CO_2Me)NMe_2$ ligand. This results in the synthesis of the corresponding conformationally restricted glutamines **2g–j** in moderate to good yields, as shown in Figure 1. This means that the process can be efficiently performed not only with a variety of O-nucleophiles, but also with different types of N-nucleophiles.

In comparison with other aminocarbonylations found in the recent literature [21-24], our method is remarkable since it occurs under very mild reaction conditions (1 atm CO, 25 °C) and, mainly, because it occurs through C–H bond activation processes without the need to use prefunctionalized substrates. Typical aminocarbonylations catalysed by Pd usually start from the corresponding iodides or bromides, and require high CO pressures and high reaction temperatures. Obviously, further efforts in our systems have to be directed to the transformation of the stoichiometric process into a catalytic one, a challenge that is still not accomplished in the case of the aminocarbonylation, even though several catalytic examples are known of the related alkoxycarbonylation reaction [25-30].

Once we had determined the reactivity of complex **1**, having a *N,N*-dimethyl-phenylglycine ligand, we focused our attention on complex **3**, possessing a triflate as a *N*-protecting group, in order to study the influence of the substituents at the N atom in the carbonylation further. The reaction of **3** with CO (1 atm) in CH_2Cl_2 at room temperature, that is, in the absence of nucleophiles, occurs with C–N coupling and formation of the methyl 3-oxo-2-((trifluoromethyl)sulfonyl)isoindoline-1-carboxylate (**4**) in good yields, as shown in Scheme 5 (right).

This means that the N atom is still nucleophilic enough to promote the cyclization, in spite of the presence of the highly electron-withdrawing triflate group. It is also clear that, after C–N coupling, the resulting ammonium salt eliminates easily



Scheme 5: Reactivity of **3** with CO in the presence (left) and absence (right) of nucleophiles.

HCl (formally) affording the neutral amine, in close similarity to the process shown in Scheme 1. However, when the reaction of **3** with CO (1 atm) is performed in MeOH, a mixture of the compounds derived from intramolecular cyclization (**4**) and alkoxycarbonylation (**5**) is obtained (molar ratio **4**/**5** 2.4:1). This mixture can be separated by column chromatography, and pure isolated compound **5** has been characterized as containing the NHTf group and two different CO_2Me moieties, as represented in Scheme 5 (left). This result can be interpreted as a competing reaction between the nucleophilic abilities of the N atom of the glycine moiety and the oxygen atom of the methanol, which in this case is the reaction solvent. It is clear that the introduction of the triflate group decreases the electron density of the N atom, which is now less nucleophilic in comparison, for example, with the complex containing the NH_2 unit, shown in Scheme 1. In that case the N was quite nucleophilic, and cyclization occurred regardless of the solvent used for the reaction [12]. In the present case the N is less nucleophilic and competes with other nucleophiles, giving mixtures **4** and **5** in the presence of methanol. Obviously, in absence of additional nucleophiles, **4** is obtained selectively. We attempted several reaction conditions in order to prepare selectively compound **5**, but it seems to be difficult to quench the intramolecular cyclization, and in all studied cases the **4**/**5** mixture is obtained. Due to this fact, we have not studied other alcohols.

Conclusion

The reactivity of the orthopalladated dimers [Pd(μ-Cl){C_6H_4(CH(CO_2Me)NR_2)-2}]$_2$ (NR_2 = NMe_2, NHTf) towards CO in the presence of alcohols or amines as nucleophiles allows for the synthesis of conformationally restricted glutamates or glutamines, respectively, through alkoxycarbonylation or aminocarbonylation intermolecular processes. In spite of the presence of an intramolecular nucleophile (the N atom of the NR_2 group), the formation of the cyclic isoindolinone derivatives has been observed only in one case. This means that the nitrogen atoms of the NMe_2 or the NHTf groups behave as weaker nucleophiles than the oxygen or nitrogen atoms of the external nucleophiles involved (alcohols, amines). In addition, the results also show that the nucleophilic abilities of the N atom in the starting materials [Pd(μ-Cl)(C_6H_4CH(CO_2Me)NR_2)]$_2$ (NR_2 = NMe_2, NHTf) are weaker than those observed in [Pd(μ-Cl)(C_6H_4CH(CO_2Me)NH_2)]$_2$, for which a systematic intramolecular aminocarbonylation was observed.

Experimental

General Methods. The general methods are reported in the Supporting Information File 1. The complex [Pd(μ-Cl)(C_6H_4CH(CO_2Me)NMe_2-2)]$_2$ (**1**) has been prepared following previously reported procedures [17,18].

Synthesis of methyl *N,N*-dimethyl-α-(2-methoxycarbonylphenyl)glycinate (**2a**)

Methanol (13 μL, 0.300 mmol) was added to a solution of **1** (100.0 mg, 0.150 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred under a CO atmosphere for 16 h. Decomposition to black metallic palladium was observed. The mixture was filtered through a plug of Celite. The light yellow solution was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated to give compound **2a** as a yellow oil. Yield: 72.9 mg, 0.290 mmol, 97%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.7 Hz, 1H, C_6H_4), 7.68 (d, J = 7.7 Hz, 1H, C_6H_4), 7.50 (t, J = 7.7 Hz, 1H, C_6H_4), 7.35 (t, J = 7.7 Hz, 1H, C_6H_4), 5.12 (s, 1H, CH), 3.89 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.31 (s, 6H, NMe_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.08 (s, CO), 168.36 (s, CO), 137.60 (s, C), 131.96 (s, CH), 130.99 (s, C), 130.32 (s, CH), 129.03 (s, CH), 127.88 (s, CH), 68.42 (s, CH), 52.34 (s, OCH_3), 51.88 (s, OCH_3), 42.97 (s, NMe_2); IR (ν, cm^{-1}) 1724 (C=O), 1257 (C-O); ESIMS (positive mode) (*m*/*z*): 251.9 $[M + H]^+$; anal. calcd for $C_{13}H_{17}NO_4$ (251.12): C, 62.14; H, 6.82; N, 5.57; found: C, 62.35; H, 6.91; N, 5.36.

Synthesis of [Pd(μ-Cl)(C_6H_4CH(CO_2Me)NHTf-2)]$_2$ (**3**)

To a solution of $Pd(OAc)_2$ (421.1 mg, 1.836 mmol) in acetone (30 mL), PhCH(CO_2Me)NHTf [19] (545.8 mg, 1.836 mmol) was added, and the resulting mixture was heated under reflux for 48 h. After the reaction time, the solution was evaporated to dryness, the residue was treated with CH_2Cl_2 (40 mL), and the resulting suspension was filtered over a Celite pad. The resulting clear solution was again evaporated to dryness, and the residue was dissolved in MeOH and allowed to react with NaCl (243.6 mg, 4.167 mmol) at room temperature for 4 h. The pale yellow solution was evaporated to dryness, the dry residue extracted with CH_2Cl_2 (30 mL), and the resulting suspension filtered to eliminate the excess of NaCl. Evaporation of this clear solution and treatment of the residue with pentane afforded **3** as a yellow–brownish solid. Yield: 452.6 mg, 0.516 mmol, 56.2% yield.

^{1}H NMR (300 MHz, $CDCl_3$ + py-d_5) δ 7.21 (dd, J = 7.6, 1.5 Hz, 1H, C_6H_4), 6.94 (td, J = 7.4, 1.2 Hz, 1H, C_6H_4), 6.71 (td, J = 7.5, 1.5 Hz, 1H, C_6H_4), 5.91 (dd, J = 7.7, 1.2 Hz, 1H, C_6H_4), 5.38 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 2.24 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$+py-d_5) δ 173.94 (s, CO), 151.41 (s, C, C_6H_4), 149.54 (m, CD, py), 146.10 (s, C, C_6H_4), 135.55 (m, CD, py), 132.49 (s, CH, C_6H_4), 125.57 (s, CH, C_6H_4), 124.46 (s, CH, C_6H_4), 123.29 (m, CD, py), 122.69 (s, CH, C_6H_4), 120.82 (q, J = 324.6 Hz, CF_3), 72.37 (s, CH), 52.30 (s, OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$ + py-d_5) δ −76.71 (s, CF_3); IR (ν,

cm^{-1}): 3375 (br, N-H), 1742 (νCOO); ESIMS (positive mode) (*m*/*z*): 439 [M/2 + H]$^+$; anal. calcd for $C_{20}H_{18}Cl_2F_6N_2O_8Pd_2S_2$ (876.23): C, 27.41; H, 2.07; N, 3.20; S, 7.32; found: C, 26.93; H, 2.02; N, 3.45; S, 6.98.

Synthesis of methyl 3-oxo-2-((trifluoromethyl)sulfonyl)isoindoline-1-carboxylate (**4**)

A solution of **3** (50.0 mg, 0.057 mmol) in dichloromethane was stirred under a CO atmosphere for 16 h. Decomposition to black palladium was observed. The mixture was filtered through a plug of Celite, and the yellow solution was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated to give **4** as a yellow oil. Yield: 26.7 mg, 0.083 mmol, 72%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 7.7, 1.0 Hz, 1H, C_6H_4), 7.79 (td, *J* = 7.6, 1.2 Hz, 1H, C_6H_4), 7.68 (dd, *J* = 7.8, 0.9 Hz, 1H, C_6H_4), 7.65 (td, *J* = 7.5, 0.7 Hz, 1H, C_6H_4), 5.72 (s, 1H, CH), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.65 (s, CO), 164.37 (s, CO), 139.43 (s, C), 135.84 (s, CH), 130.87 (s, CH), 127.63 (s, C), 126.49 (s, CH), 123.54 (s, CH), 119.59 (q, *J* = 323.5 Hz, CF_3), 63.20 (s, CH), 53.94 (s, OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.04 (s, CF_3); IR (ν, cm^{-1}): 1758 (COO). ESIMS (positive mode) (*m*/*z*): 324.0 [M + H]$^+$; anal. calcd for $C_{11}H_8F_3NO_5S$ (323.01): C, 40.87; H, 2.49; N, 4.33; S, 9.92; found: C, 40.94; H, 2.53; N, 4.41; S, 10.05.

Synthesis of methyl *N*-trifluoromethylsulfonamido-α-(2-methoxycarbonylphenyl)glycinate (**5**)

A solution of **3** (100.0 mg, 0.114 mmol) in methanol was stirred under a CO atmosphere for 16 h. During the reaction, the formation of Pd^0 was evident. The black material was eliminated by filtration through a plug of Celite, and the resulting light yellow solution was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated to give an oily residue characterized as the mixture of compounds **4** and **5**. This mixture was separated by column chromatography (silica, hexane/CH_2Cl_2: 3/7), yielding pure **5** as a colourless oil. Yield: 14.2 mg, 0.040 mmol, 18%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.5 Hz, 1H, C_6H_4), 7.61 (td, *J* = 7.5, 1.5 Hz, 1H, C_6H_4), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H, C_6H_4), 7.41 (dd, *J* = 7.6, 1.5 Hz, 1H, C_6H_4), 7.00 (d, *J* = 9.4 Hz, 1H, NH), 5.42 (d, *J* = 9.3 Hz, 1H, CH), 3.92 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.89 (s, CO), 168.43 (s, CO), 137.53 (s, C), 133.86 (s, C), 132.59 (s, CH), 132.01 (s, CH), 129.68 (s, CH), 127.30 (s, CH), 119.53 (q, *J* = 320.7 Hz, CF_3), 61.35 (s, CH), 53.42 (s, OCH_3), 53.03 (s, OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.53 (s, CF_3); IR (ν, cm^{-1}): 3282 (br, N-H), 1747 (COO), 1711 (COO); ESIMS (positive mode) (*m*/*z*): 324.2 [M − OMe]$^+$, 356.0 [M + H]$^+$; anal. calcd for $C_{12}H_{12}F_3NO_6S$ (355.03): C, 40.57; H, 3.40; N, 3.94; S, 9.03; found: C, 40.42; H, 3.24; N, 3.82; S, 8.93.

Supporting Information

Supporting Information File 1

General methods and experimental and analytical data of compounds **2b**–**j**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-179-S1.pdf]

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Extending the utility of [Pd(NHC)(cinnamyl)Cl] precatalysts: Direct arylation of heterocycles

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Full Research Paper

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Abstract

The use of [Pd(NHC)(cinnamyl)Cl] precatalysts in the direct arylation of heterocycles has been investigated. Among four different precatalysts, [Pd(SIPr)(cinnamyl)Cl] proved to be the most efficient promoter of the reaction. The C–H functionalization of sulfur- or nitrogen-containing heterocycles has been achieved at low catalyst loadings. These catalyst charges range from 0.1 to 0.01 mol % palladium.

Introduction

As a powerful addition to the classic palladium cross-coupling reactions, C–H bond functionalization has become a growing field of research over the last few years. The ubiquity of C–H bonds makes them a convenient and cost-effective anchoring position within viable substrates, as no derivatisation to form an organometallic reagent is required. Moreover, among the plethora of C–H bonds present on a molecule, it is often possible to target one C–H linkage specifically, taking advantage of directing groups or particular catalyst selectivity [1-5]. Thus, heteroaromatic scaffolds, which are a common feature in biologically relevant compounds and in materials science [6,7] can be selectively arylated as the heteroatom can act as an intrinsic orientating group [8].

Despite the efficiency of well-defined palladium catalysts bearing NHC (N-heterocyclic carbene) ancillary ligands in classical cross-coupling reactions, they have rarely been applied to direct arylation procedures [9-16]. Among the family of [Pd(NHC)] complexes, the [Pd(NHC)(cin)Cl] (cin = cinnamyl) species are known for their ease of activation through the reduction of the metal centre from Pd(II) to Pd(0) [17]. Therefore, we have investigated the use of such precatalysts in the direct arylation of heteroaromatic compounds in order to compare them to ligand-free or phosphine-bearing catalytic systems, and in the end to see whether the reactivity and application scope of these commercially available complexes could be broadened to include C–H bond functionalization transformations.

We now report the activity of the [Pd(NHC)(cin)Cl] complexes **1**–**4** in the direct arylation of heterocycles with NHC ligands being SIPr (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene), IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), IPr* (1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) and IPr*^{Tol} (1,3-bis(2,6-bis(di-*p*-tolylmethyl)-4-methylphenyl)imidazol-2-ylidene) (Figure 1). Complexes **1** and **2** are commercially available and have proven to be highly efficient in Suzuki–Miyaura coupling and Buchwald–Hartwig amination reactions [17-20]. We have also evaluated the recently reported [Pd(IPr*)(cin)Cl] (**3**), which has shown potency in Suzuki–Miyaura couplings [21] and Buchwald–Hartwig N-arylations [22] even with challenging substrates. To complete this study and to examine the effect of bulky ligands about the metal centre, we have synthesised a new complex [Pd(IPr*^{Tol})(cin)Cl] (**4**), which is a IPr* congener.

Results and Discussion

The study begins with the preparation of the palladium complex **4**. Following the strategy recently reported by Markó [23], we were successful in the synthesis of the IPr*^{Tol}·HCl imidazolium salt **5** in a 53% overall yield (see Supporting Information File 1). Subsequently, **5** was treated with KO*t*-Bu in dry THF to generate the corresponding free carbene in situ. The expected [Pd(IPr*^{Tol})(cin)Cl] was then obtained in an excellent yield (97%) by a simple fragmentation of the palladium dimer [{Pd(cin)(μ-Cl)}$_2$] using the free carbene solution (Scheme 1).

The newly synthesized complex **4** was unequivocally characterised by X-ray diffraction [24] (Figure 2, Supporting Information File 2 and Supporting Information File 3) after suitable crystals were grown from slow diffusion of hexane in dichloromethane. Based on this crystal structure, the percentage buried volume (%V_{Bur}) of the IPr*^{Tol} ancillary ligand was determined by using the "Samb*V*ca" web application [25] and compared to complexes **1**–**3** (Table 1) [21]. IPr*^{Tol} featured a %V_{Bur} in the same range as IPr* (+0.4% difference). SIPr and IPr have been reported as less hindered ligands with %V_{Bur} of 37.0 and 36.7, respectively. The length of the Pd–C1 bond in **4** was also examined and is close to the one observed in **3**.

With complexes **1**–**4** in hand, their catalytic activity towards the direct arylation of heteroaromatic compounds was evaluated. For this purpose, the arylation of benzothiophene (**6**) with

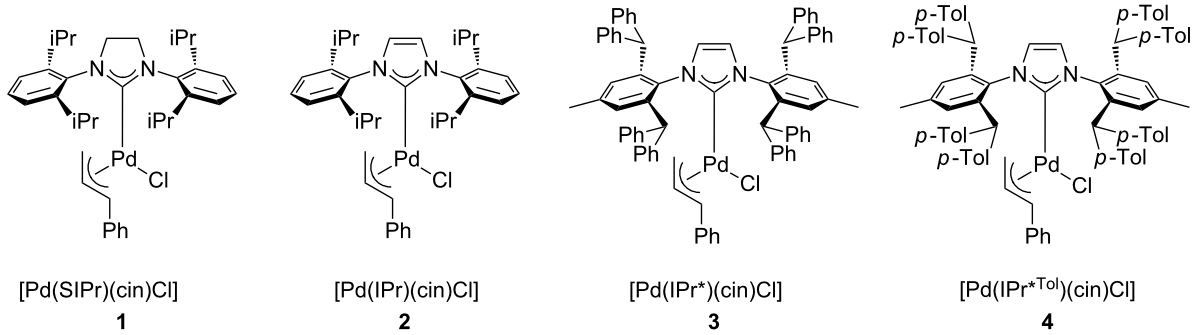
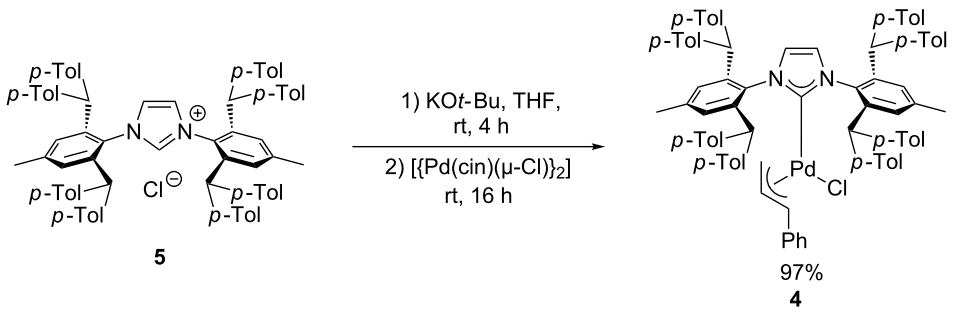


Figure 1: [Pd(NHC)(cin)Cl] catalysts examined in direct arylation.



Scheme 1: Synthesis of [Pd(IPr*^{Tol})(cin)Cl] (**4**).

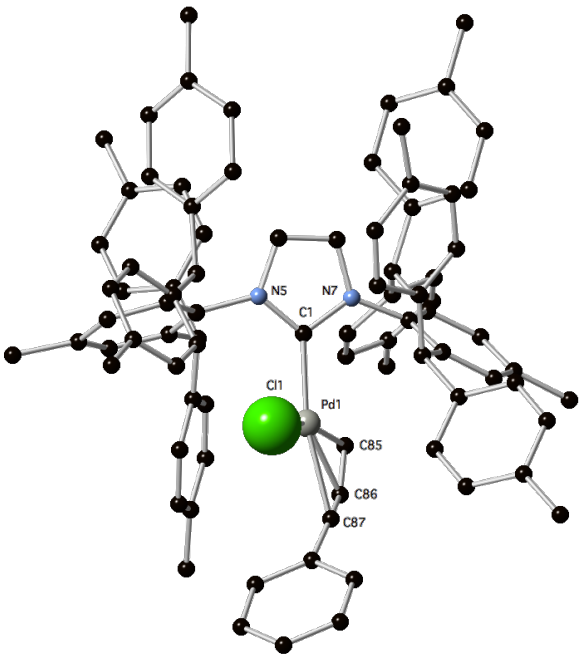


Figure 2: Molecular structure of **4**. H atoms were omitted for clarity. Selected bond lengths (Å) and angles (°): Pd1–C1 2.034(0), Pd1–Cl1 2.352(5), Pd1–C85 2.132(8), Pd1–C86 2.119(7), Pd1–C87 2.226(6); C1–Pd1-C85 102.9(5), C85–Pd1–C87 71.2(6), C87–Pd1–Cl1 93.3(8), Cl1–Pd1–C1 91.8(6).

Table 1: Comparison of the %V_{Bur} and d(Pd–C1) in the [Pd(NHC)(cin)Cl] family.

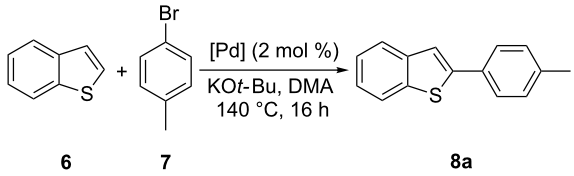
NHC	%V_{Bur}[a]	Pd–C1 (Å)
SIPr	37.0	2.025(7)
IPr	36.7	2.041(9)
IPr*	44.6	2.038(6)
IPr*^{Tol}	45.0	2.034(0)

[a]%V_{Bur} calculated for a 2.00 Å Pd–C1 length.

4-bromotoluene (**7**) was selected as a benchmark reaction (Table 2). This C–H functionalization, initially described by Ohta [26], was then reported by Bhanage and Mori using 2–10 mol % of well-defined palladium catalysts [27,28] (Figure 3). Alternatively, Fagnou and Kappe proposed a Pd/phosphine system involving 1–2 mol % of palladium and 2–4 mol % of phosphine [29,30], but no example of this reaction involving a well-defined [Pd(NHC)] complex has been described. However, it is noteworthy that variously substituted benzothiophene cores have been extensively studied in the direct arylation process [4,31-37].

Initial screening of precatalysts **1**–**4** was performed with a 2 mol % loading, by using KO*t*-Bu as the base, which is known

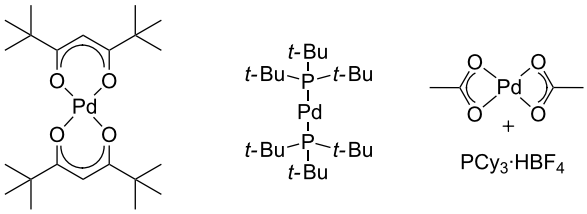
Table 2: Catalyst screening for the direct arylation of benzothiophene (**6**).



6 **7** **8a**

Catalyst	Conversion (%)[a]
[Pd(SIPr)(cin)Cl] (**1**)	76
[Pd(IPr)(cin)Cl] (**2**)	50
[Pd(IPr*)(cin)Cl] (**3**)	8
[Pd(IPr*^{Tol})(cin)Cl] (**4**)	49

[a]Conversion of the starting material into C–H arylated product determined by GC, [**6**] = 0.3 M.



Bhanage [27] Mori [28] Fagnou [29] Kappe [30]

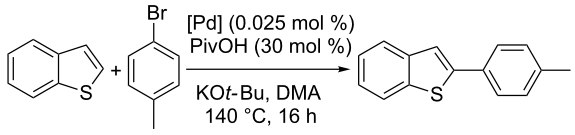
Figure 3: Previously reported catalytic systems in the direct arylation of benzothiophene (**6**).

to efficiently activate the [Pd(NHC)(cin)Cl] precatalysts [17]. DMA was selected as the solvent and the reaction was conducted at 140 °C.

This survey showed that **1** is the most efficient precatalyst under these reaction conditions with 76% conversion of the starting material. Precatalysts **2** and **4** exhibited closely related activity, with 50 and 49% conversion, respectively. However, complex **3** gave relatively poor conversion of the benzothiophene (**6**).

Thus, selecting **1** as the best precatalyst, the use of other solvents, bases and additives was evaluated to optimize the reaction (see the Supporting Information File 1). From this optimization study, it was found that 0.1 mol % of **1** with K_2CO_3 in DMA as solvent at 140 °C in the presence of a catalytic amount of pivalic acid (30 mol %) generated the best reaction conditions. Under these optimized parameters, a second precatalyst screening was performed. As shown in Table 3, better activity was observed for precatalysts **1** and **2**, which have smaller ligands when compared to the NHCs in **3** and **4**. This result

Table 3: Catalyst screening under optimised conditions.



6 **7** **8a**

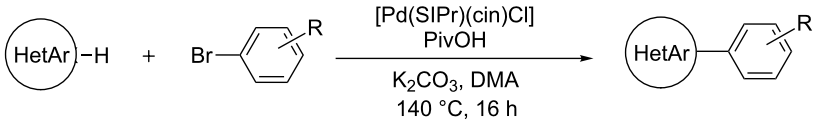
Catalyst	Conversion (%)[a]
[Pd(SIPr)(cin)Cl] (**1**)	80
[Pd(IPr)(cin)Cl] (**2**)	75
[Pd(IPr*)(cin)Cl] (**3**)	57
[Pd(IPr*^{Tol})(cin)Cl] (**4**)	58

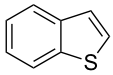
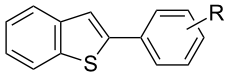
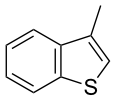
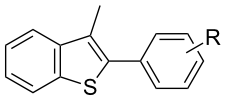
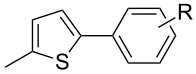
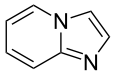
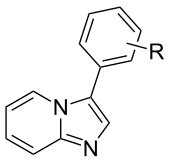
[a]Conversion of the starting material into C–H arylated product determined by GC, [**6**] = 0.3 M.

suggests a strong dependence of the activity on the steric properties of the NHC ligand. Moreover, the small difference between **1** and **2** underlines the fact that the difference in the σ-donation properties of the NHC ligands [38-41] is not likely to play a crucial role in the catalytic activity.

In comparison with the previously mentioned methodologies to perform this C–H functionalization [27-30], the catalyst loading can be decreased by at least 10-fold without drastically affecting the yield (Table 4, entry 1). Using the optimized reaction conditions, we examined the scope and the limitations of this catalytic system using various aryl bromides and heterocycles (Table 4). It appeared that the sterics of the aryl bromide had almost no impact on the reaction. Indeed, *para*-, *meta*- and *ortho*- substituted aryl bromides could be employed to arylate **6** in good yields. (Table 4, entries 1–3, 77–89%). However, *ortho*-disubstituted aryl bromide, such as bromomesitylene appeared

Table 4: Palladium-NHC catalysed direct arylation of heterocycles with arylbromides.



Entry[a]	Heterocycles	Products	R	Yield[b]
1[c]	 **6**	 **8**	4-Me, **8a**	89%
2[c]			3-Me, **8b**	80%
3[c]			2-Me, **8c**	77%
4[c]			4-OMe, **8d**	70%
5[c]			4-Cl, **8e**	49%
6[c]			4-F, **8f**	53%
7[c]			4-CHO, **8g**	37%
8	 **9**	 **10**	4-Me, **10a**	85%
9			2-Me, **10b**	83%
10			4-F, **10c**	52%
11	 **11**	 **12**	4-Me, **12a**	90%
12			4-OMe, **12b**	75%
13			4-F, **12c**	57%
14	 **13**	 **14**	4-Me, **14a**	74%
15[d]				69%
16[d]			4-OMe, **14b**	53%
17[d]			4-F, **14c**	76%

[a]Unless noted, reactions were performed on 0.6 mmol scale with: Heterocycle (1 equiv), aryl bromide (1 equiv), [Pd(SIPr)(cin)Cl] (0.1 mol %), PivOH (30 mol %), K_2CO_3 (1.5 equiv), DMA (2 mL), 140 °C. [b]Isolated yields, average of two independent runs. [c]**6** (1.2 equiv). [d][Pd(SIPr)(cin)Cl] (0.01 mol %).

to be too sterically demanding and led to no conversion (data not shown). Concerning the electronic properties of the aryl bromide, electron-withdrawing (EWG) and electron-donating groups (EDG) were tolerated, although the presence of EWGs resulted in decreased yields (Table 4, entries 4–6, 49–70%). The substrate 4-bromobenzaldehyde was also successfully involved in the direct arylation of **6**. Despite its electron-withdrawing nature as well as its high reactivity, the expected biaryl was obtained in moderate yield (Table 4, entry 7). The limits of the scope were determined by switching from benzothiophene (**6**) to the more sterically demanding 3-methylbenzothiophene (**9**) (Table 4, entries 8–10). Closely related reactivity was observed for **6** and **9**, as these were arylated in comparable yields (Table 4, entry 1 vs 8, 3 vs 9 and 6 vs 10).

A more challenging heterocycle, 2-methylthiophene (**11**), was investigated. Simple thiophene rings are known to be less reactive in C–H functionalization reactions [42]; nevertheless, **11** was successfully arylated in moderate to good yields, depending on the electronic properties of the bromobenzene substituents (Table 4, entries 11–13, 57–90%). Electron rich 4-methoxybromobenzene reacted more efficiently than the electron poor 4-fluorobromobenzene. An opposite effect of the electronics was observed by Doucet et al. in their ligandless procedure at low catalyst loadings [43,44]. This is surely due to the nature of the catalyst and thus offers complementary direct arylation methods for thiophene derivatives.

To complete the study, experiments were performed at lower catalyst loading using imidazopyridine (**13**). This class of substrate has recently been involved, by Doucet et al. [45], in direct arylation with a catalytic charge of $Pd(OAc)_2$ ranging from 0.1 to 0.01 mol %. In our case, comparable yields were obtained when the catalyst loading was decreased from 0.1 to 0.01 mol %, highlighting the high efficiency of the catalytic system (Table 4, entries 14 and 15). Following the same trend as reported by Doucet [45], a better reactivity was observed with bromobenzenes substituted with EWGs compared to with EDGs (Table 4, entries 16 and 17).

Conclusion

In summary, we report here the synthesis and characterization of a new member of the [Pd(NHC)(cin)Cl] family, [Pd(IPr*^{Tol})(cin)Cl]. The catalytic activity of this family of complexes was surveyed in the direct arylation of heterocycles. The bulkiness of the NHC ligand appears to play a major role in the catalytic efficiency, whereas the σ-donation properties (within the small electronic space examined) have little influence. Among the four complexes, [Pd(SIPr)(cin)Cl] exhibited the highest catalytic efficiency and was investigated for the arylation of various benzothiophenes, thiophene and imidazopyridine. C–H functionalization of such heterocycles was performed in moderate to good yields by using only 0.1–0.01 mol % of precatalyst. This study highlights the fact that [Pd(NHC)(cin)Cl] complexes are multipurpose precatalysts as they may be utilised in various cross-coupling and, now, C–H-bond-functionalization reactions.

Experimental

General procedure for the direct arylation of heterocycles

In a glovebox, a vial containing a stirring bar was charged with K_2CO_3 (124 mg, 0.9 mmol, 1.5 equiv) and pivalic acid (0.18 mmol, 18 mg, 30 mol %), and sealed with a screw cap fitted with a septum. The heterocycle (0.6 mmol, 1.0 equiv) and/or the arylbromide (0.6 mmol, 1.0 equiv) were added at this point if in solid form, and DMA (1.9 mL) was poured into the vial. Outside of the glovebox, the heterocycle and/or the aryl bromide were added at this point if in liquid form. Finally, [Pd(SIPr)(cin)Cl] (**1**) was added as a 0.06 M solution in DMA (0.6–6 μmol, 10–100 μL, 0.01–0.1 mol %), and the vial was heated to 140 °C for 16 h. The solution was then cooled down to room temperature, diluted with 40 mL of ethyl acetate, and washed with water (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was finally purified by either trituration in pentane (if not soluble) or silica-gel column chromatography using pentane as the eluent.

Supporting Information

Supporting Information File 1

Synthesis and characterization of complex **4**; compound characterization data for all the direct arylated products and copies of their ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-187-S1.pdf]

Supporting Information File 2

CIF-Check for compound **4**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-187-S2.pdf]

Supporting Information File 3

Crystal structure data for compound **4**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-187-S3.cif]

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Palladium-catalyzed dual C–H or N–H functionalization of unfunctionalized indole derivatives with alkenes and arenes

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Review

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Abstract

This review highlights the development of palladium-catalyzed C–H and N–H functionalization reactions involving indole derivatives. These procedures require unactivated starting materials and are respectful of the basic principle of sustainable chemistry tied to atom economy.

Introduction

The development of mild and selective reactions for the direct conversion of carbon–hydrogen bonds into carbon–carbon and carbon–heteroatom bonds is a challenging goal in organic chemistry [1-3]. The coupling of C–H/C–H or C–H/N–H bonds in an oxidative system is an attractive target since hydrogen or water would be the only formal byproduct. In this field, (hetero)aryl–(hetero)aryl, (hetero)aryl–alkenyl, and (hetero)aryl–alkyl reactions represent some of the most important tools for planning the synthesis of a wide range of different kinds of molecules. Synthetic approaches using unfunctionalized reagents rather than halogenated compounds have attracted strong attention, above all due to their atom- and step-economical characteristics.

Thus, the applicability of these transformations on the multiscale level paves the way to cheaper processes, resulting in minimal waste production and raising the possibility of application in multistep synthetic sequences. Many transition metals, including Pd, Au, Ru, Rh, Cu, and Pt, have been proven to be highly efficient for the formation of new bonds without prefunctionalized starting materials [4-10]. Among the transition metals suitable for this purpose, palladium plays a pivotal role due to its versatility in different synthetic protocols and tolerance towards many functional groups, often avoiding the need for protecting-group chemistry [11-16]. Moreover, palladium-catalyzed reactions involving ethylenic double bonds can also lead to domino processes such as carboaminations [17-19],

diaminations [20,21], aminooxygenations [22,23], and aminohalogenations [24,25]. The most common reactions of C–H functionalization on unactivated substrates typically occur with electrophilic Pd(II) catalysts and require an oxidizing agent in order to make possible the reoxidation of the Pd(0) species, generated in the final elimination step, for a new catalytic cycle [12-15].

The well-established features of natural or man-made compounds containing an indole backbone are of wide interest in pharmacological and agrochemical fields [26-28]. Thus, indole and carbazole nuclei are used in medicine for their antibacterial, antimicrobial, and anti-inflammatory effects and occupy a relevant role in the discovery of active antitumor drugs [29-31]. Carbazole derivatives also find applications in organic materials as chromophores and photoconductors [32]. For several years, the development of methodologies concerning indole synthesis and functionalization has been one of the most attractive goals in organic chemistry [33-39]. In the search for clean and sustainable synthetic protocols suitable to construct and convert the indole core motif into more complex structures, palladium-based catalytic systems were proven to be fruitful tools for organic chemists [40-42].

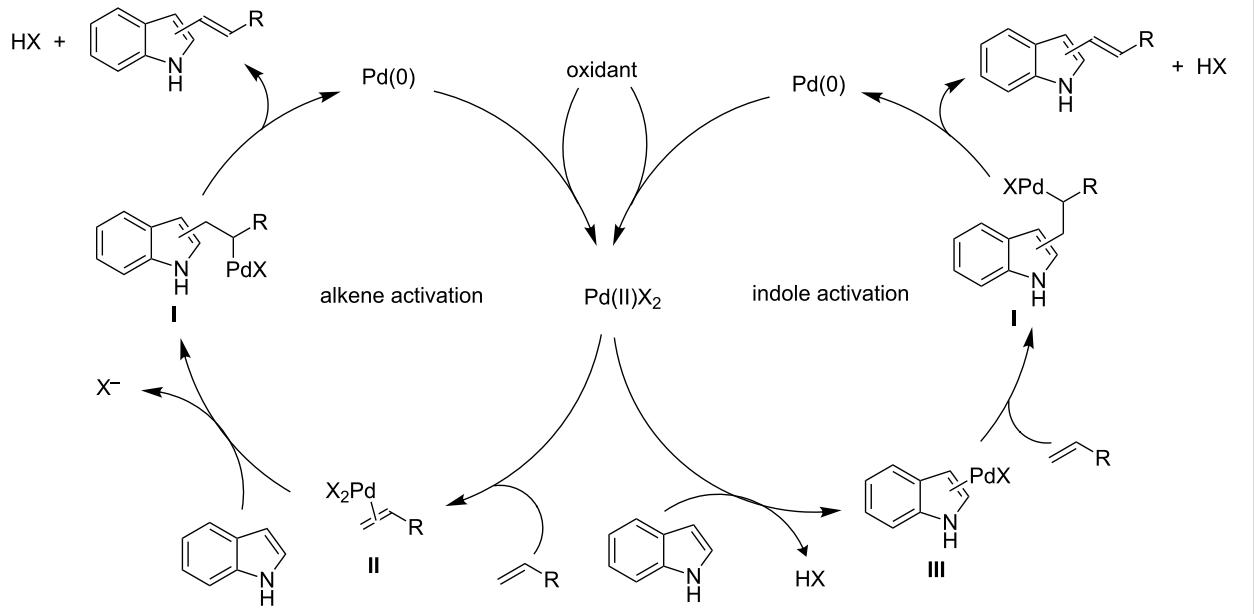
This review highlights methodologies based on the use of palladium catalysts, devoted to the functionalization of indole derivatives involving carbon–hydrogen and nitrogen–hydrogen bonds. The synthetic procedures are classified as intermolecular and intramolecular alkenylations, arylations, and domino processes.

Review

Intermolecular reactions involving alkenes

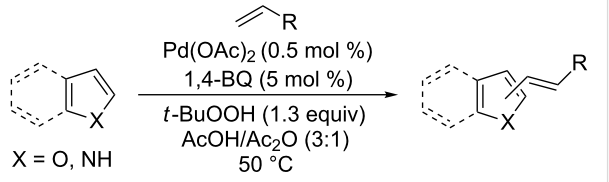
Alkenylation reactions of indoles run through a key C–H activation step involving an electrophilic palladation and an electron-deficient Pd(II) catalyst. The mechanism of these reactions involves the generation of a σ-alkyl complex **I**, which is the rate-determining step of the reaction, and conversion into the alkenylindole by a *syn*-β-hydride elimination process (Scheme 1) [43-45]. Beside the formation of the final product, the last step results in the elimination of HX and Pd(0) species, justifying the need for an oxidant agent to regenerate a Pd(II) species as active catalyst. Although seldom unambiguously determined, two alternative pathways, based either on "alkene activation" or "indole activation", have been proposed to explain the formation of the σ-alkyl complex **I**. The former involves the coordination of the Pd(II) catalyst to the olefin, giving the π-olefin complex **II**, which is converted by nucleophilic attack of the indole into the intermediate **I**. On the other hand, an electrophilic attack of the Pd(II) catalyst on the indole to generate the indolyl-palladium(II) complex **III**, in turn susceptible to attack by the olefin, may be hypothesized as a plausible way to form the σ-alkyl complex **I**. In both pathways, indole may be involved directly at the C-2 or C-3 positions as well as preferentially at the C-3 position, in the latter case affording the final 2-substituted product by the intrinsic tendency toward C-3/C-2 rearrangement that is operative during the alkylation of indoles [46].

In 1969, Fujiwara and Moritani reported the alkenylation of arenes catalyzed by $Pd(OAc)_2$, using $Cu(OAc)_2$ or AgOAc as



Scheme 1: Typical catalytic cycle for Pd(II)-catalyzed alkenylation of indoles.

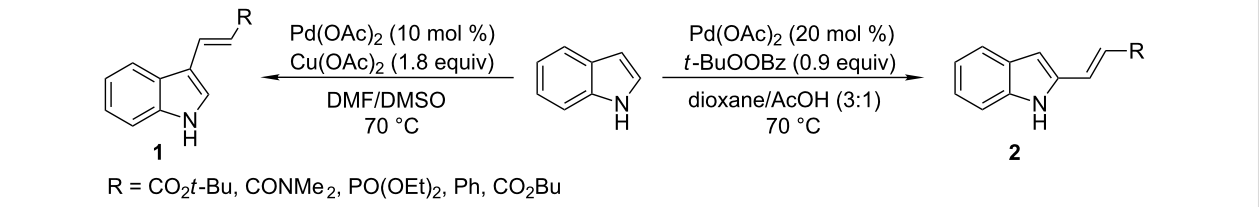
oxidants [47]. This strategy provides a convenient method for the synthesis of olefins linked to heteroarenes, including indole, furan, and benzofuran rings (Scheme 2) [48]. Working with indole and methyl acrylates in the presence of $Pd(OAc)_2$ and 1,4-benzoquinone in catalytic quantity with *tert*-butyl hydroperoxide as oxidant, 3-alkenyl-substituted products were obtained.



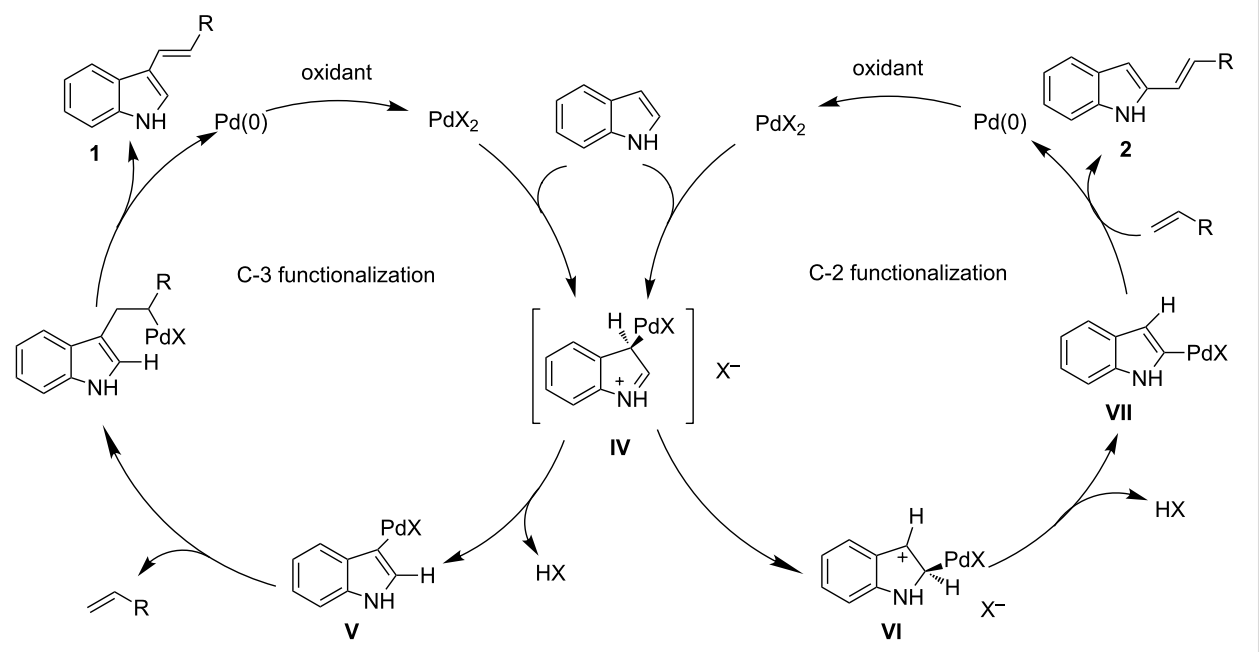
Scheme 2: Application of Fujiwara's reaction to electron-rich heterocycles.

The synthetic value of the direct catalytic C–H alkenylation of the C-2 and C-3 positions of the unprotected indole nucleus was recognized under different conditions published several years ago. In 2005, Gaunt and co-workers disclosed a general method for the selective intermolecular alkenylation of the unprotected indoles through an oxidative palladium-catalyzed reaction (Scheme 3) [49]. The reaction can involve the formation of carbon–carbon or carbon–nitrogen bonds, which is strongly dependent on the solvent used. When the reaction is carried out in aprotic polar solvents, such as DMSO and DMF, with $Cu(OAc)_2$ as reoxidizing agent, the alkenylation occurs at the 3-indolyl position, yielding products **1**. Conversely, the use of dioxane with the addition of acetic acid as a polar coordinating co-solvent in the presence of *tert*-butyl benzoyl peroxide, directs the selectivity in favor of the C-2 substituted indoles **2**. It should be noted that the same chemistry has been successfully extended to the pyrrole ring [50].

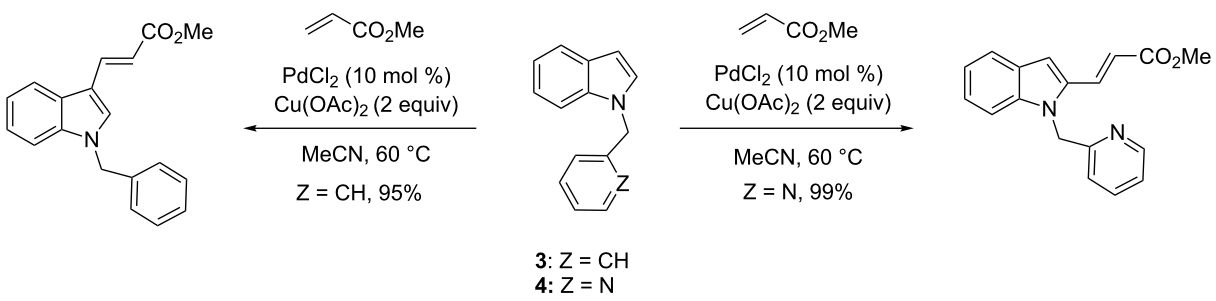
A rational explanation for the outcome of these reactions is described in Scheme 4. In both cases, intermediate **IV** is involved as the result of a direct palladation at the C-3 position. Working under neutral conditions, a proton can be easily removed from **IV** by the anion formed from the initial palladium salt with generation of the 3-indolyl-palladium complex



Scheme 3: Regioselective alkenylation of the unprotected indole.



Scheme 4: Plausible mechanism of the selective indole alkenylation, adapted from [49].



Scheme 5: Directing-group control in intermolecular indole alkenylation.

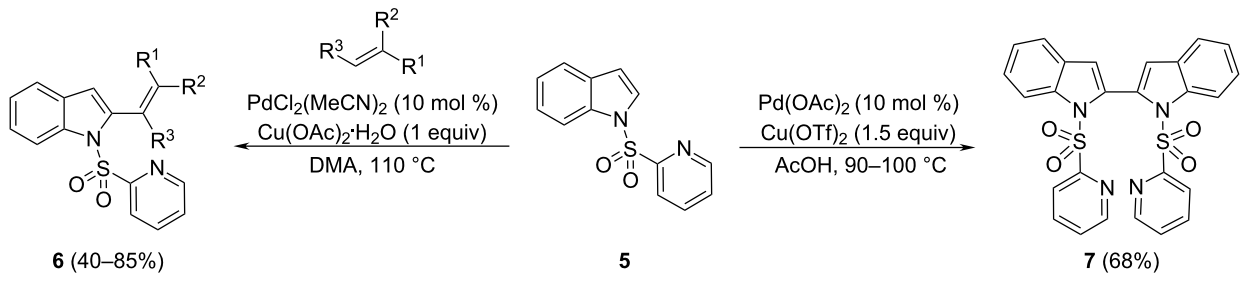
V, which evolves a Heck-type reaction to give the 3-alkenylindoles **1**. Conversely, the deprotonation of the C-3 position is difficult in acidic medium, favoring the transfer of metal species to the 2-indolyl carbon of **IV**, activated as an iminium carbon. The so-formed intermediate **VI** undergoes loss of HX with generation of the complex **VII**, which finally reacts with alkenes giving the 2-alkenylindoles **2** and a Pd(0) species.

An alternative approach to address the regioselective alkenylation of the C-2 position is based on the directing control of a group attached to the indole nitrogen. Under the same conditions, i.e., $PdCl_2$ as catalyst and $Cu(OAc)_2$ as oxidant in acetonitrile at 60 °C, alkenylation of *N*-benzyl-protected indole **3** took place selectively at the C-3 position, while the reaction of the *N*-(2-pyridylmethyl)-substituted indole **4** resulted in the functionalization of the C-2 position by directing coordination to the pyridyl nitrogen (Scheme 5) [51].

The control of the regioselectivity in the Pd(II)-catalyzed C–H alkenylations towards the indole C-2 position can be exerted by the *N*-(2-pyridyl)sulfonyl group, which can be easily installed and removed [52,53]. The reaction of **5** with a wide range of mono-, 1,1- and 1,2-disubstituted alkenes in the presence of a catalytic system based on $PdCl_2(MeCN)_2$ (10 mol %) and $Cu(OAc)_2$ (1 equiv) in DMA, furnishes the product **6** in moderate to good yield (Scheme 6). A mechanism including an electrophilic palladation involving the pyridinyl chelation was thought to be plausible taking into account the outcome of the reaction performed on isotopically labeled substrates as well as by kinetic studies of variously substituted indoles. This *N*-(2-pyridyl)sulfonyl-directing strategy has also been extended to the development of a protocol for the intermolecular, dehydrogenative homocoupling of indole, providing 2,2'-bisindoles **7**.

Intermolecular Pd(II)-catalyzed N–H functionalization has also been successfully used to achieve *N*-substituted indoles. Coupling of indole and 2-methyl-2-butene in the presence of $Pd(OAc)_2$ (40 mol %), $Cu(OAc)_2$ and AgOTf as the co-oxidants in MeCN constitutes a simple route to *N*-prenylated indoles **8** (Scheme 7) [54]. This mild reaction, which exhibits broad functional-group tolerance, can be successfully performed for the prenylation of tryptophan and tryptamine derivatives, as well as peptides containing tryptophan.

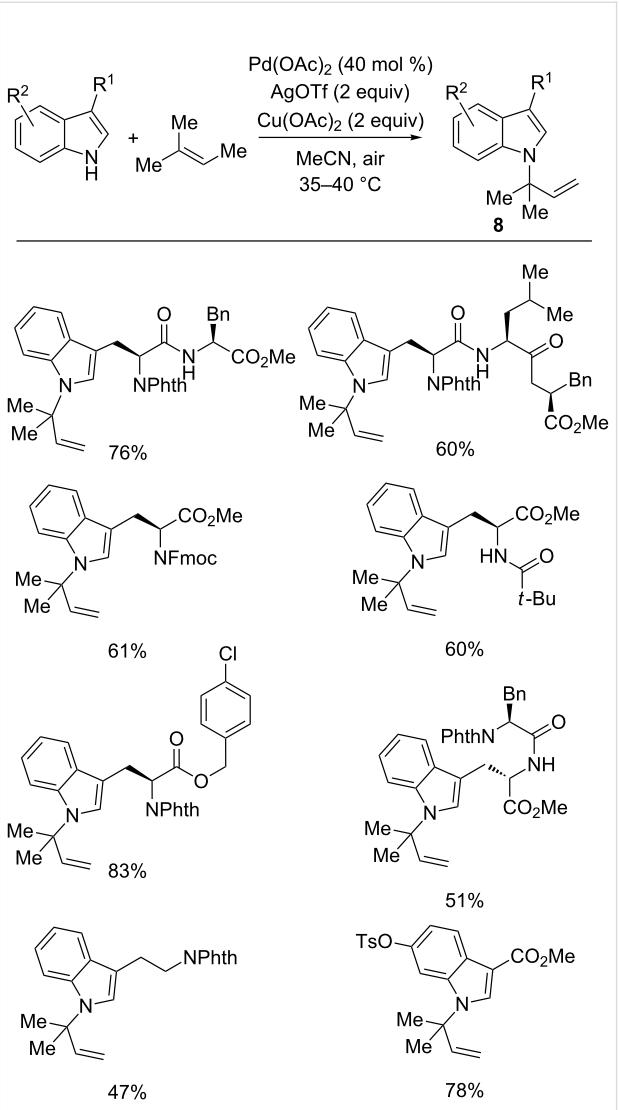
Taking into account some experimental evidence obtained from the use of 2-methyl or 2-deuterium-substituted indoles and from [1,1,1-D_3]3-methyl-2-butene, the mechanism shown in Scheme 8 was thought to explain the outcome of the reaction.



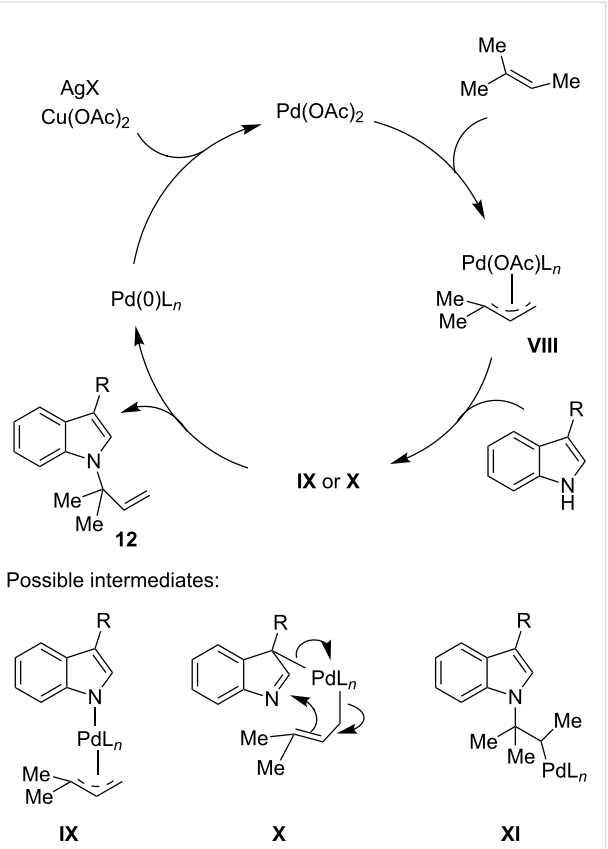
6 (40–85%) **5** **7** (68%)

R^1 = COOMe, $CONMe_2$, $COP(O)(OMe)_2$, alkyl, aryl, CH=CH-Ph, CH=CH-COOMe
R^2 = H, COOMe, CHO, Ph
R^3 = H, Me

Scheme 6: Direct C–H alkenylation of *N*-(2-pyridyl)sulfonylindole.



Scheme 7: *N*-Prenylation of indoles with 2-methyl-2-butene.



Scheme 8: Proposed mechanism of the *N*-indolyl prenylation.

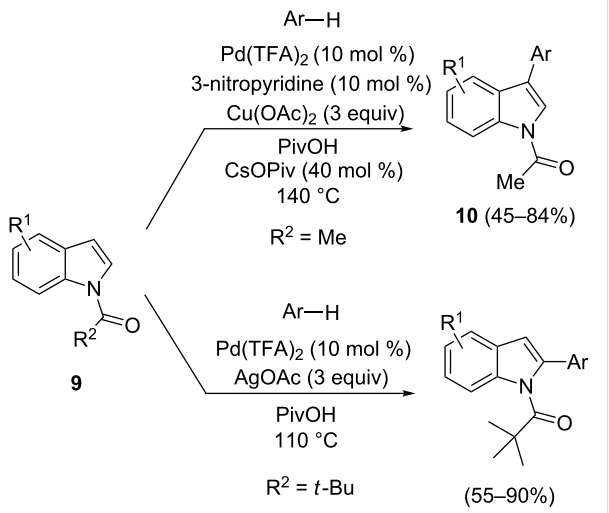
Firstly, Pd(II) catalyst promotes the formation of the π-allyl-palladium complex **VIII**, which can evolve by coordination of the N-1 or C-3 positions of the indole nucleus giving the palladium complexes **IX** and **X**, respectively. The latter quickly converts into the σ-alkyl-palladium intermediate **XI** by a Claisen-type rearrangement that involves the metal species. A mechanism through the typical π-olefin-palladium complex as the precursor of the σ-alkyl-palladium complex **XI** cannot, however, be ruled out. In every case, a Pd(0) species was released from **XI** and reoxidized with the Ag(I) and Cu(II) salts.

Intermolecular reactions involving arenes

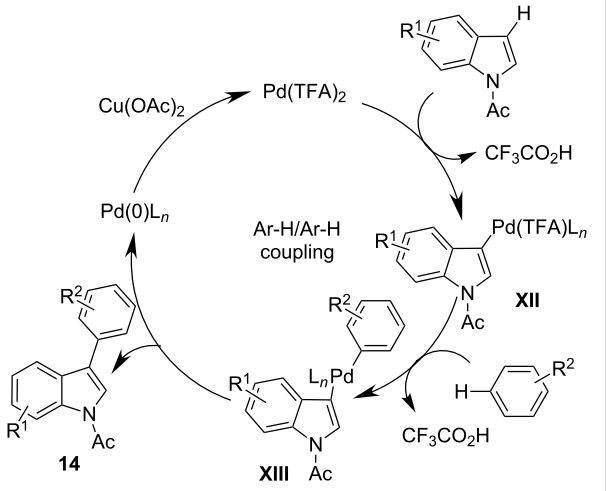
The formation of homo-coupling products is one of the most common drawbacks in intermolecular reactions between arenes without preactivation of the substrates. In 2006, Lu and co-workers reported one of the first articles providing conditions to access asymmetric biaryl compounds by dual C–H functionalization [55].

In 2007, Fagnou and co-workers combined, in a single catalytic cycle, the reactivity of electron-deficient palladium(II) complexes with electron-rich arenes (through an electrophilic C–H activation mechanism) and the reactivity of some Ar-Pd(II) complexes with arenes (through a proton-transfer palladation mechanism), depending on the C–H acidity rather than the arene nucleophilicity. Synthetic procedures based on this strategy allowed the direct arylation at C-2 and C-3 positions of indoles **9** with a high degree of regioselectivity (Scheme 9) [56,57]. 3-Arylindoles **10** were selectively achieved on *N*-acylindoles by using catalytic $Pd(TFA)_2$ and a stoichiometric amount of $Cu(OAc)_2$. The use of additives, such as 3-nitropyridine and caesium pivalate, was proven essential to achieve optimized conditions.

It is plausible that the presence of pyridine can stabilize the final Pd(0) species favoring its reoxidation and avoiding the precipitation of palladium black. The use of AgOAc as oxidant induces an inversion of selectivity, improving the C-2 arylation



Scheme 9: Regioselective arylation of indoles by dual C–H functionalization.



Scheme 10: Plausible mechanism of the selective indole arylation.

process. A high level of C-2 selectivity was achieved by using the *N*-pivalyl-substituted indole in the absence of additives. From the mechanistic point of view, as depicted in Scheme 10, the C–H activation on the electron-rich indole, selectively directed by the strongly electrophilic behavior of the $Pd(TFA)_2$ catalyst, is plausible giving the Pd(II) intermediate **XII**. The subsequent selective coordination of the arene generates the complex **XIII**, which in turn undergoes reductive elimination providing the final product and a Pd(0) species. The reoxidation of the latter giving the active Pd(II) catalyst completes the catalytic cycle.

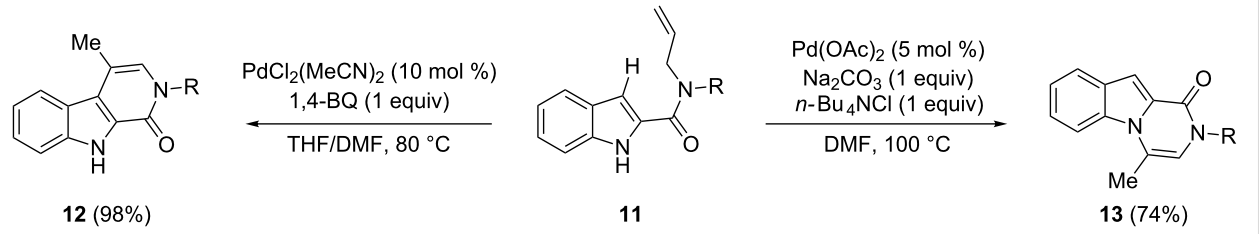
In addition to the effect of $Cu(OAc)_2$ and AgOAc as oxidant, a determinant role on the selectivity of direct C–H to C–H cross-coupling reactions was played by the acidity of the medium, as shown by reactions carried out in the presence of AcOH [58,59]. Based on experimental and computational data, a concerted metalation–deprotonation of the arene was hypothesized to explain the mechanism for C–H palladation.

Intramolecular reactions involving alkenes

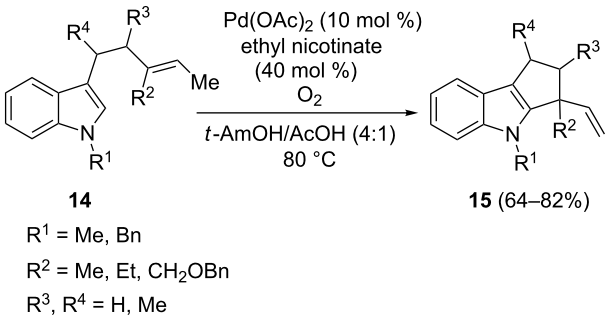
The first example of intramolecular indole alkenylation was reported in 1978 by Trost, who applied reaction conditions based on stoichiometric amounts of $PdCl_2(MeCN)_2$ and silver ions in the key step of the total synthesis of ibogamine alkaloids [60].

Palladium-catalyzed cyclization of *N*-allyl-1*H*-indole-2-carboxamides **11** is a fruitful procedure to access β-carbolinones **12** or pyrazino[1,2-*a*]indoles **13** (Scheme 11) [61,62]. The use of $PdCl_2(MeCN)_2$ as the catalyst with 1,4-benzoquinone as the oxidant in a mixture of DMF/THF resulted in the C-3 functionalization of the indole nucleus. Conversely, switching to $Pd(OAc)_2$ with Na_2CO_3 as a base and Bu_4NCl as an additive in DMF provided the indole N–H functionalization. This strategy has also been proven to be operative in effecting intramolecular alkenylation on a range of other electron-rich heterocycles, including pyrroles, furans and thiophenes [63,64].

The intramolecular Pd(II)-catalyzed reaction of the 3-alkenylindoles **14** gave rise to the carbocyclic 5-membered ring-fused



Scheme 11: Chemoselective cyclization of *N*-allyl-1*H*-indole-2-carboxamide derivatives.

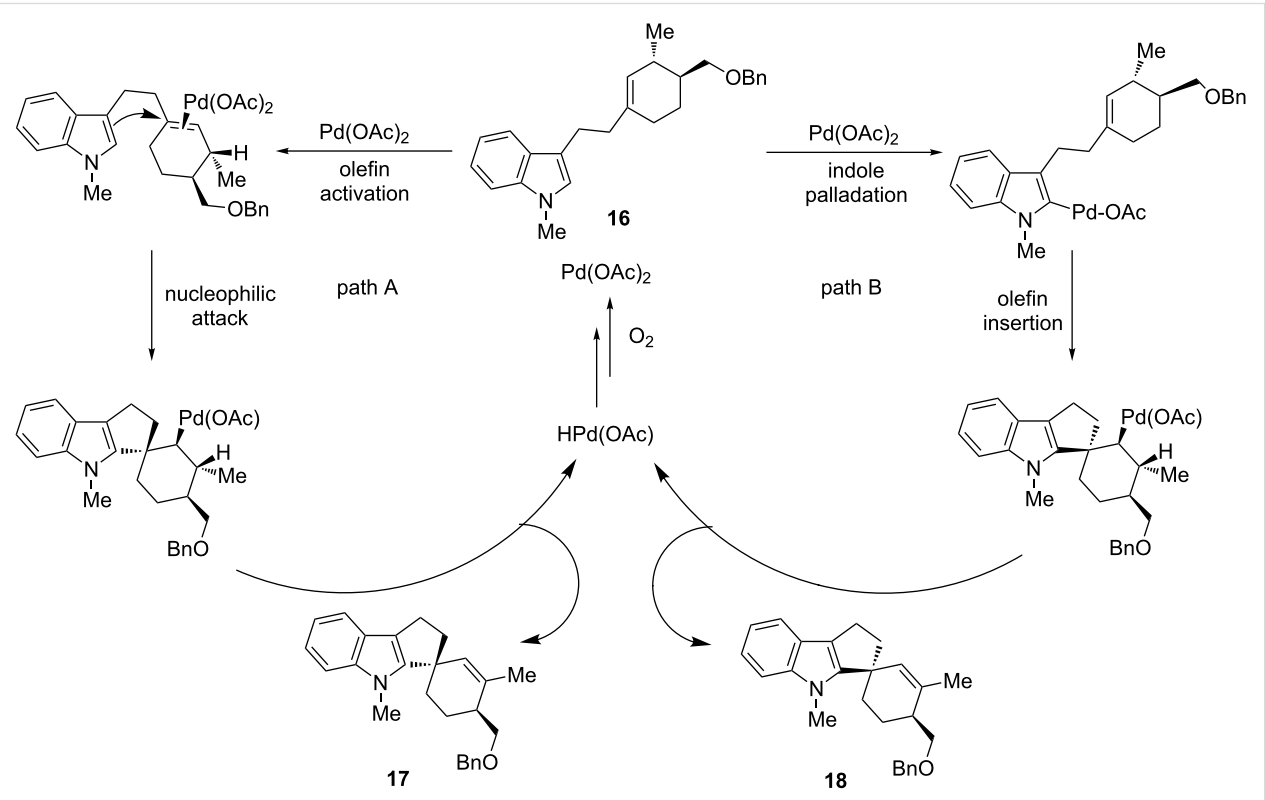


Scheme 12: Intramolecular annulations of alkenylindoles.

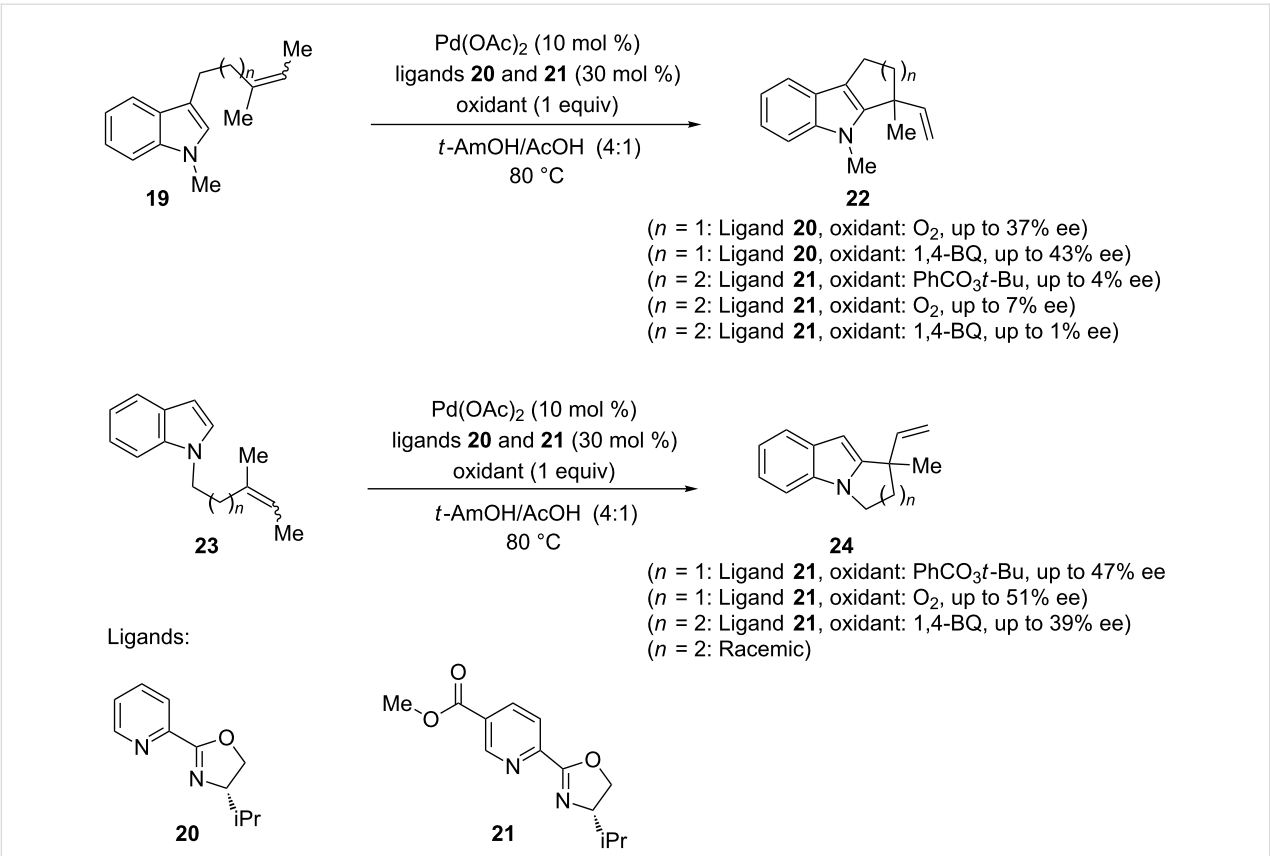
products **15** (Scheme 12) [65,66]. This procedure involves O_2 as the sole oxidant. Among the various pyridine ligands and solvents tested to optimize the conditions, 3-carbethoxypyridine in a polar solvent (i.e., *tert*-amyl alcohol/AcOH in 4:1 ratio) was proven to be the most effective in providing satisfactory yields. The oxidative cyclization led also to a new 6-membered ring, once again producing vinyl-substituted products. An analogous process for the direct intramolecular C–H functionalization of inactive alkenyl aryl ethers, giving benzofuran and dihydrobenzofuran derivatives, was successfully developed [67].

Both possible mechanistic pathways based on the initial coordination of the Pd(II) catalyst to the 2-indolyl position or to the carbon–carbon double bond, can be hypothesized for this reaction. Elucidation of the outcome of the reaction was achieved by cyclization of the diastereoisomerically pure cyclohexenylindole **16**, which could give the spiro-products **17** and **18** (Scheme 13). The sole formation of the annulated indole **18** as a single diastereoisomer suggests a mechanism that is strictly closer to the classical oxidative Heck reaction (pathway B) rather than to a Wacker-type reaction (pathway A). In fact, the formation of the product **18** is explainable by an indolyl palladation and a β-hydride elimination, which typically occurs in *syn* manner. The formation of the diastereoisomeric product **17** would have been justified by a nucleophilic attack of the indole on the π-olefin complex, which is known to occur in *anti* fashion, before the β-hydride elimination.

Palladium–pyridine systems were subsequently investigated with chiral ligands to catalyze enantioselective processes involving alkenylindoles. Several enantioselective indole annulations with formation of a stereogenic quaternary carbon atom were performed by using chiral oxazoline ligands with pyridine or nicotine platforms (PyOx and NicOx, respectively) [68,69]. A moderate level of enantiocontrol (up to 51 % ee) was seen in 5-*exo*-trig cyclization of the 3-alkenylindole **19** (n = 1) in the



Scheme 13: A mechanistic probe for intramolecular annulations of alkenylindoles, adapted from Ferreira et al. [66].

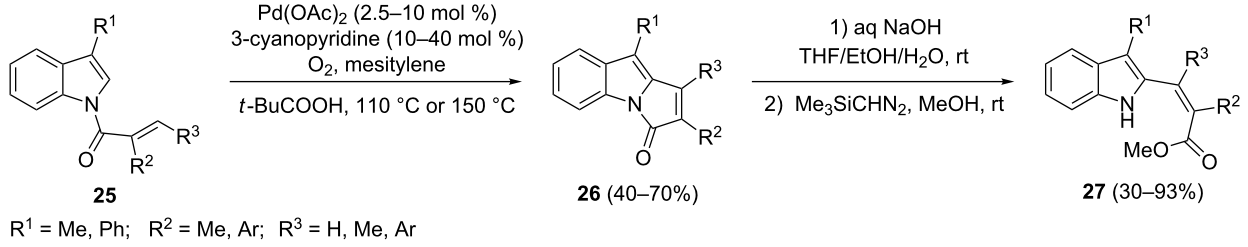


Scheme 14: Asymmetric indole annulations catalyzed by chiral Pd(II) complexes.

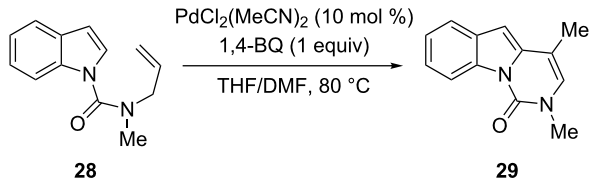
presence of ligands **20** and **21**, to yield **22**, whilst the outcome of the 6-*exo*-trig cyclization of indole **19** ($n = 2$) resulted essentially in racemic products (Scheme 14). The same behavior, in terms of the degree of enantioselectivity depending on the ring size of the newly formed ring, was observed in the cyclization of the *N*-alkenylindole **23** to give the pyrrolo[1,2-*a*]indole **24** (up to 51% for 5-*exo*-trig cyclization).

A strategy involving an intramolecular C–H bond alkenylation of trisubstituted alkenes, followed by ring opening of the so-formed ring, was planned to achieve the diastereocontrolled formation of tetrasubstituted double bonds tethered to C-2 indole. The Pd(II)-catalyzed 5-*endo*-trig cyclization of *N*-alkenoylindoles **25** in the presence of 3-cyanopyridine as the ligand and under aerobic conditions afforded the tricyclic products **26** (Scheme 15) [70]. The subsequent amide cleavage carried out in aqueous NaOH and following ester formation by treatment with Me_3SiCHN_2 in methanol led to the 2-alkenylated indoles **27**.

The pyrimido[3,4-*a*]indole skeleton **29** was proven to be accessible by intramolecular 6-*exo*-trig cyclization of the *N*-alkenylindole **28** with $PdCl_2(MeCN)_2$ as catalyst and 1,4-benzoquinone as oxidant in THF/DMF at 80 °C (Scheme 16) [51].



Scheme 15: Aerobic Pd(II)-catalyzed *endo* cyclization and subsequent amide cleavage/ester formation.

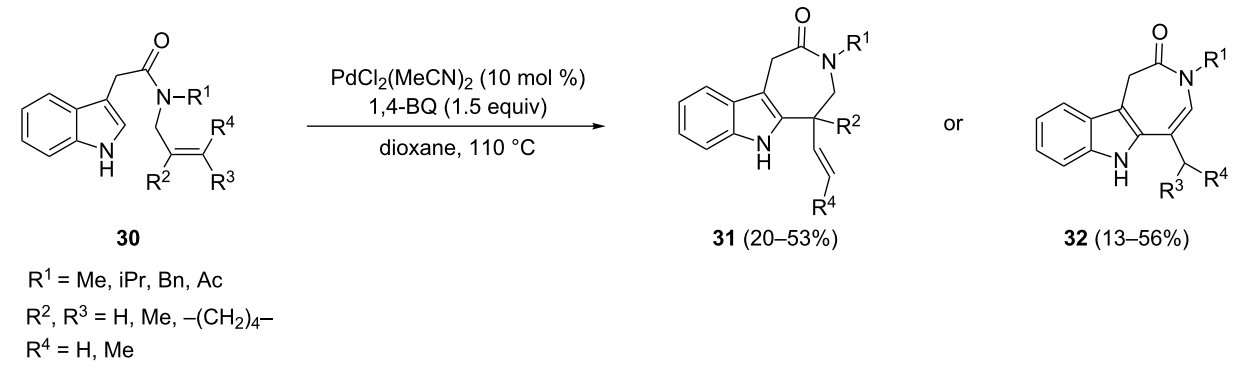


Scheme 16: Synthesis of the pyrimido[3,4-*a*]indole skeleton by intramolecular C-2 alkenylation.

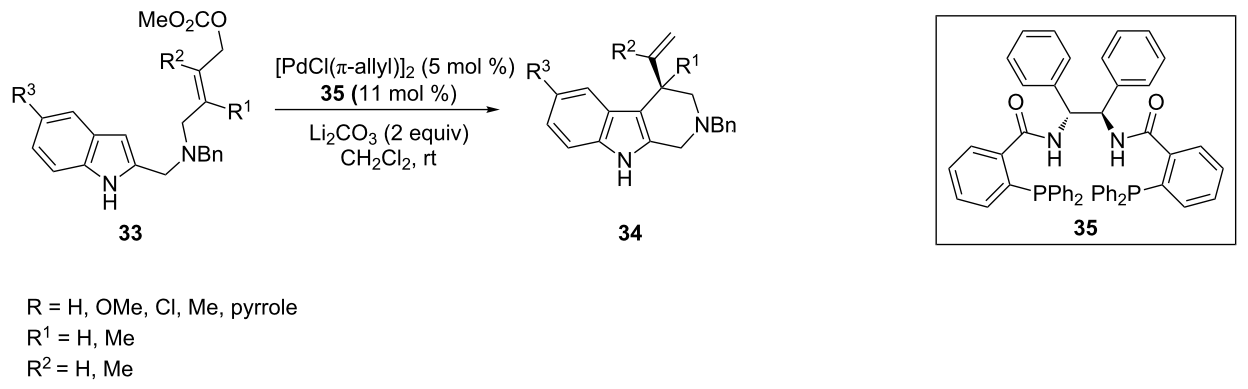
Catalytic oxidative Heck reactions allowed also the construction of seven-membered ring-fused indoles. Readily available *N*-alkenyl-3(1*H*)-indoleacetic amides **30** were converted into the azepinoindole derivatives **31** or **32** by using the combination of $PdCl_2(MeCN)_2$, 1,4-benzoquinone and dioxane at 110 °C (Scheme 17) [71]. Although these reactions achieve only moderate yields, this strategy constitutes an alternative choice to the palladium-catalyzed cyclization of indole amides bearing a carbon–halogen bond to give medium and large ring-fused indoles [72].

Although a stoichiometric amount of $Pd(OAc)_2$ is needed, intramolecular alkenylations of suitable 3-alkenylindoles in an atmosphere of molecular oxygen provided dihydroindoloazocine compounds that are key intermediates in the total synthesis of the austamide derivatives and the okaramine family of polycyclic bisindole alkaloids [73,74].

Enantioselective synthesis of vinyl-substituted tetrahydro-β-carbolines and tetrahydro-γ-carbolines was performed starting from 2- and 3-alkenylindoles by Pd-catalyzed asymmetric allylic alkylation. A series of (*E*)-5-substituted indolylcarbonates **33**, easily available from the 2-indolylcarbaldehyde, undergo cyclization through a π-allyl-palladium complex by treatment with $[PdCl(\pi\text{-allyl})]_2$ as the catalyst and Li_2CO_3 in CH_2Cl_2 in the presence of C1- and C2-symmetrical P/P and P/N ligands to yield 4-vinyl-tetrahydro-β-carbolines **34** (Scheme 18) [75,76]. The best results in terms of enantioselectivity were achieved by using **35** as a ligand, which provided products with (*R*)-configuration of the newly formed stereocenter in enantiomeric excesses up to 97%. Remarkably, the same catalytic



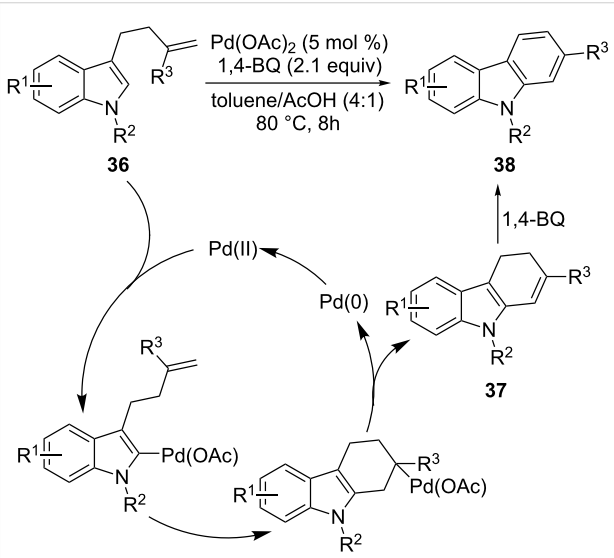
Scheme 17: Synthesis of azepinoindoles by oxidative Heck cyclization.



Scheme 18: Enantioselective synthesis of 4-vinyl-substituted tetrahydro-β-carbolines.

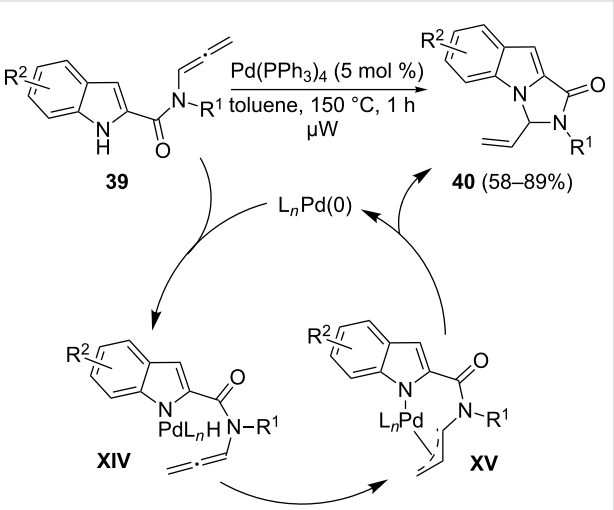
system was successfully applied to 3-indolylcarbonates, giving 1-vinyl-tetrahydro-γ-carbolines with high enantiomeric excesses.

The intramolecular reaction of 3-(alken-4-yl)indoles **36** was achieved with $Pd(OAc)_2$ as the catalyst and 1,4-benzoquinone as the oxidant, providing carbazole derivatives **38** (Scheme 19) [77]. The products arise from an *endo*-cyclization which gives the initially formed dihydrocarbazoles **37**, which are easily oxidized to the products **38** by the excess of 1,4-benzoquinone. Although better yields were obtained with electron-donating groups, this synthetic approach tolerates a range of substituents on the indole ring.



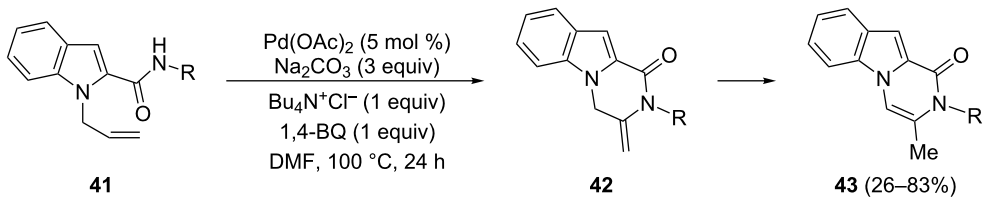
Scheme 19: Pd-catalyzed *endo*-cyclization of 3-alkenylindoles for the construction of carbazoles.

In 2010, our group disclosed a general route towards 3-vinylimidazo[1,5-*a*]indole derivatives **40** by the unusual and atom-economical intramolecular Pd-catalyzed hydroamination of the allenes **39**, easily accessible by prototropic isomerization of the corresponding propargylamides (Scheme 20) [78]. The selective 5-*exo*-allylic hydroamination occurs in mild conditions in the presence solely of $Pd(PPh_3)_4$ under microwave irradiation by an initial coordination of the Pd(0) catalyst to the indole nitrogen giving the Pd(II)-hydride complex **XIV**. Such an intermediate would be susceptible to insertion of the allene group into the Pd–H bond to generate the π-allyl-Pd(II) complex **XV**, which in turn would undergo the intramolecular formation of the new carbon–nitrogen bond, which regenerates the Pd(0) species.



Scheme 20: Pd-catalyzed hydroamination of 2-indolyl allenamides.

The intramolecular Pd(II)-catalyzed reaction of the 1-allyl-2-indolecarboxamides **41** leads to the pyrazino[1,2-*a*]indoles **43** through the conversion of the olefinic C–H bond into a C–N bond (Scheme 21) [79]. The cyclization process resulted in the initially formed exomethylenic tricyclic derivatives **42**, which undergo an inside double-bond migration to give the final products **43**. This synthetic protocol is founded on two established features: the presence of a base and tetrabutylammonium chloride, essential for the cyclization step, and the stoichiometric amount of an oxidant in order to achieve reoxidation of the Pd(0) species to Pd(II).

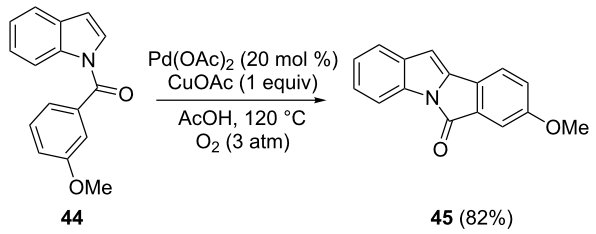


R = phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-nitrophenyl, cyclohexyl, (ethoxycarbonyl)methyl, benzyl, (2-furyl)methyl

Scheme 21: Amidation reaction of 1-allyl-2-indolecarboxamides.

Intramolecular reactions involving arenes

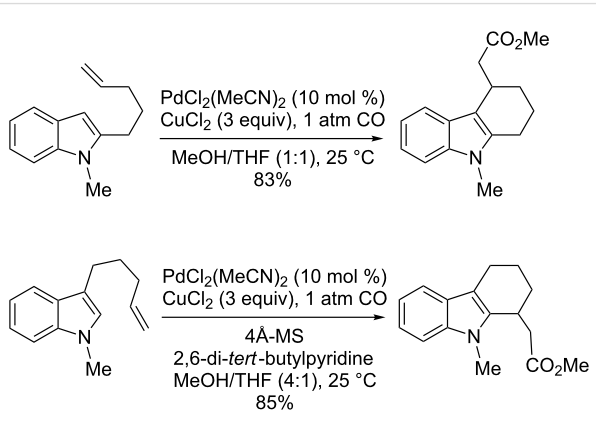
Intramolecular arylations by oxidative coupling were investigated by DeBoef and co-workers as a tool for synthesizing heteropolycyclic compounds [80]. The aerobic Pd(II)-catalyzed reaction of the *N*-benzoylindole **44** occurred in the cyclization providing the tetracyclic compound **45** (Scheme 22). The presence of an electron-donating group on the linked arene was proven to be essential for obtaining the product in high yield.



Scheme 22: Intramolecular cyclization of *N*-benzoylindole.

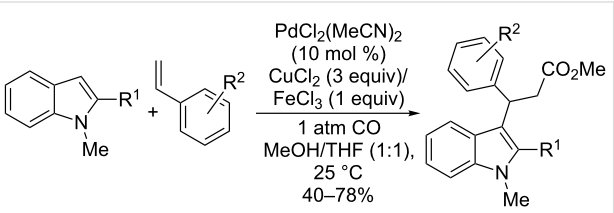
Alkenylation reactions involving domino processes

In 2004, Widenhoefer described the cyclization of alkenylindoles by Pd(II) catalysis under carbonylative conditions [81,82]. This approach, based on the use of copper(II) chloride as oxidant, has been applied to 2- and 3-alkenylindoles, resulting in a domino process that involves an alkenylation/carboxylation sequence (Scheme 23). Thus, exploiting the nucleophilicity of the C-2 and C-3 indolyl positions and the subsequent addition of carbon monoxide and the proper alcohol, a broad range of alkoxycarbonyl-substituted indoles fused to various sizes of rings has been achieved under mild conditions.



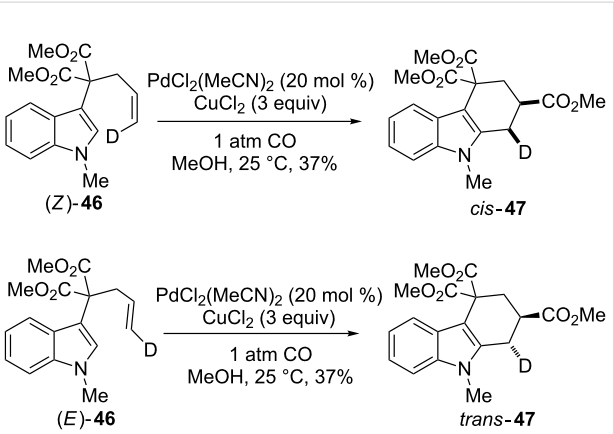
Scheme 23: Intramolecular alkenylation/carboxylation of alkenylindoles.

A similar intermolecular version of the alkenylation/carboxylation sequence was successfully performed by reaction of styrene compounds with 2-substituted indoles to give 3-benzylindoles bearing an ester group (Scheme 24). It should be pointed out that the presence of a functional group at the C-2 indolyl position is essential to obtain a satisfactory outcome of the reaction. Conversely, different substituents on the styrene substrates affected only the yield of the reaction.



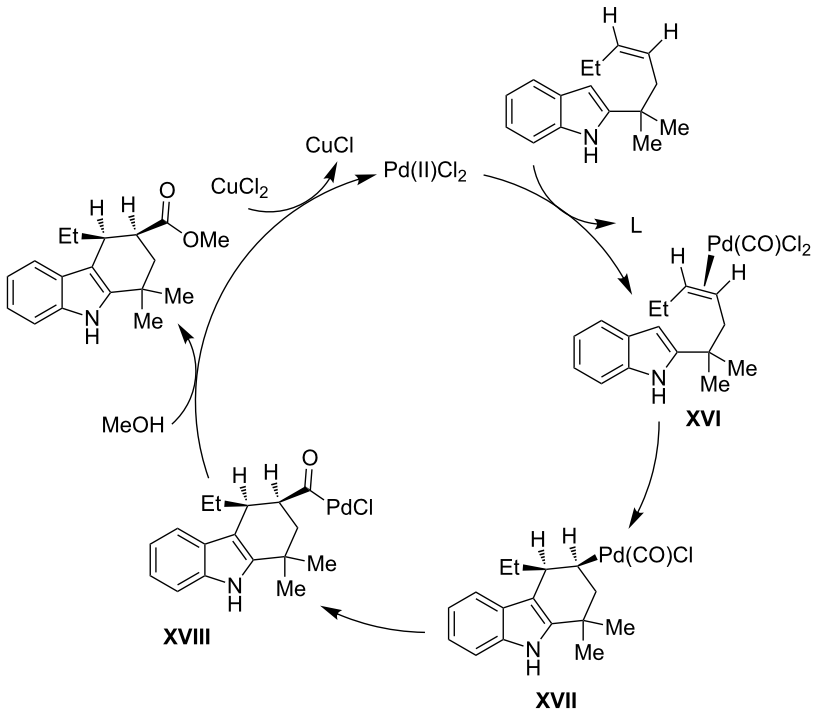
Scheme 24: Intermolecular alkenylation/carboxylation of 2-substituted indoles.

The intramolecular reaction has a stereospecific outcome, as demonstrated by the cyclization of the (*Z*) and (*E*)-deuteroindoles **46** (Scheme 25). In fact, (*Z*) and (*E*)-substrates furnished the *cis* and *trans*-products **47**, respectively, as single diastereoisomers. This behavior is the result of an *anti*-addition of the indolyl nucleus and the alkoxycarbonyl group to the ethylenic bond.



Scheme 25: Mechanistic investigation of the cyclization/carboxylation reaction.

The stereochemical findings obtained with the cyclization of the (*Z*)-alkenylindoles (as depicted in Scheme 26) give evidence for a mechanism based on the initial coordination of the metal to the olefin with generation of the π-olefin-intermediate **XVI**. The latter is able to undergo an outer-sphere attack by the indole, occurring in the cyclization step with the σ-alkyl-palladium complex **XVII**. The subsequent transfer of carbon monoxide with stereochemical retention determines the generation of the σ-acyl-palladium complex **XVIII**, which in turn is converted in

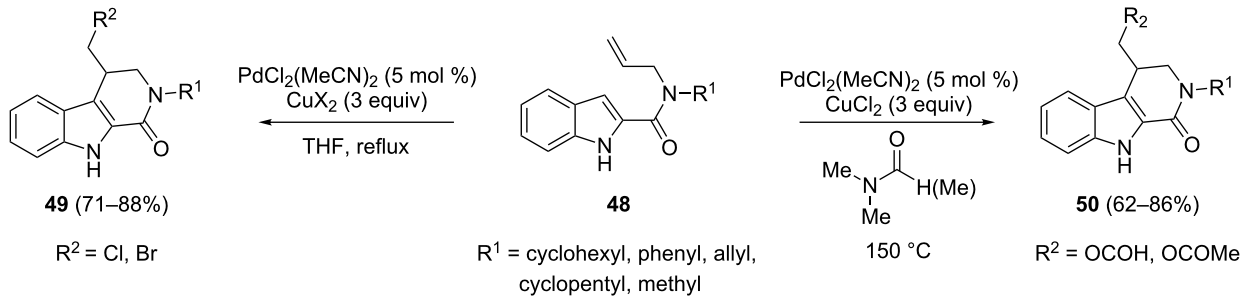


Scheme 26: Plausible catalytic cycle for the cyclization/carboxylation of alkenylindoles, adapted from Liu et al. [81].

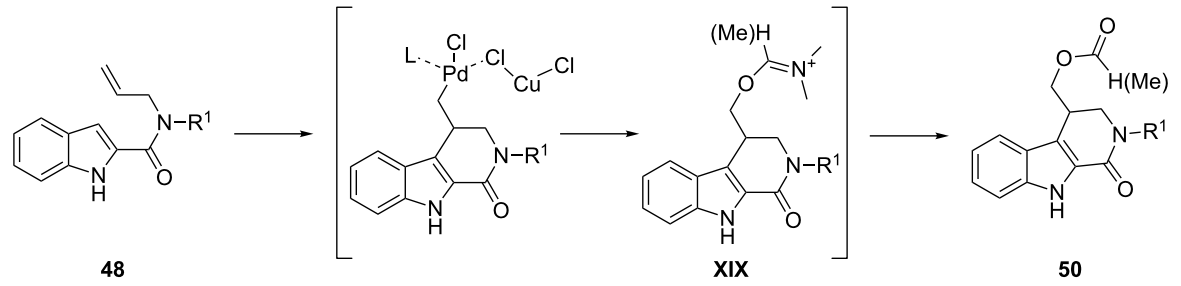
the final *cis*-substituted tetrahydrocarbazole by methanolysis giving the carboxylation step. Again, the released Pd(0) species requires an oxidation by the copper(II) salt to the Pd(II) species, which is then suitable to restart a new catalytic cycle.

Recently, the oxidative Pd(II)-catalyzed strategy for the cyclization of alkenylindoles has been extended to the intramolecular domino reactions of indolylallylamides by using the same couple $PdCl_2(MeCN)_2/CuX_2$ as catalyst and oxidant, respectively. 2-Indolylallylcarboxamides **48** have been found to be suitable substrates to access variously substituted β-carbolinones **49** and **50** through alkenylation/halogenation or alkenylation/esterification processes selectively obtained by switching reaction solvent and temperature (Scheme 27) [83].

The unforeseen formation of alkenylation/esterification products plausibly arises from a direct intervention of dimethylformamide or dimethylacetamide used as the solvent. The presence of $CuCl_2$ slows the β-hydride-elimination process from the σ-alkyl-palladium complexes, favoring a transient palladium



Scheme 27: Intramolecular domino reactions of indolylallylamides through alkenylation/halogenation or alkenylation/esterification processes.

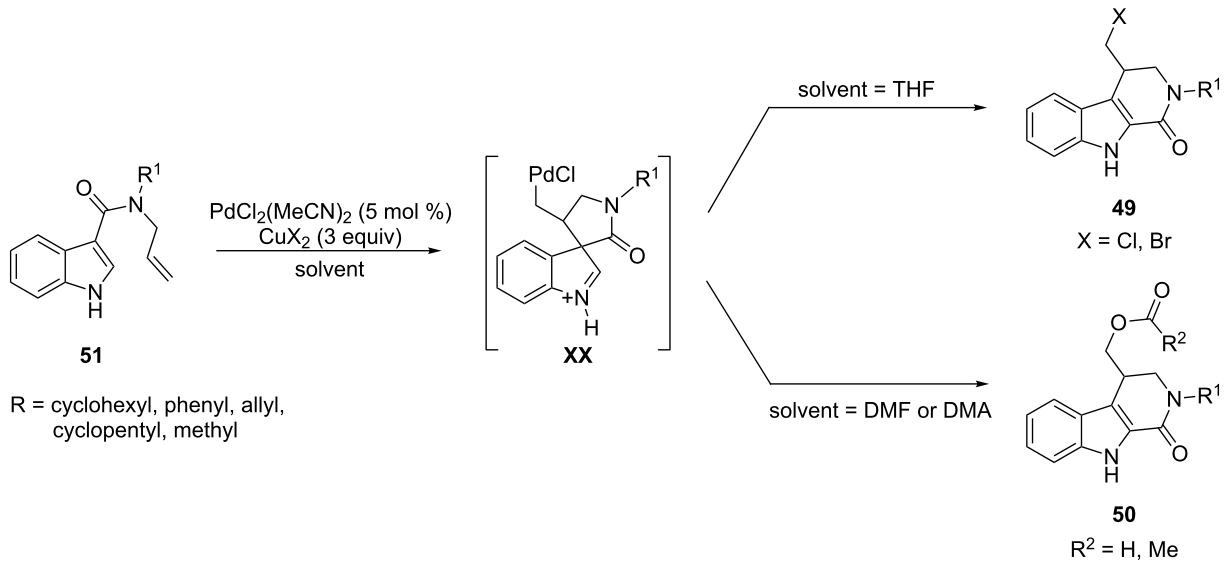


Scheme 28: Proposed mechanism for the alkenylation/esterification process through iminium intermediates.

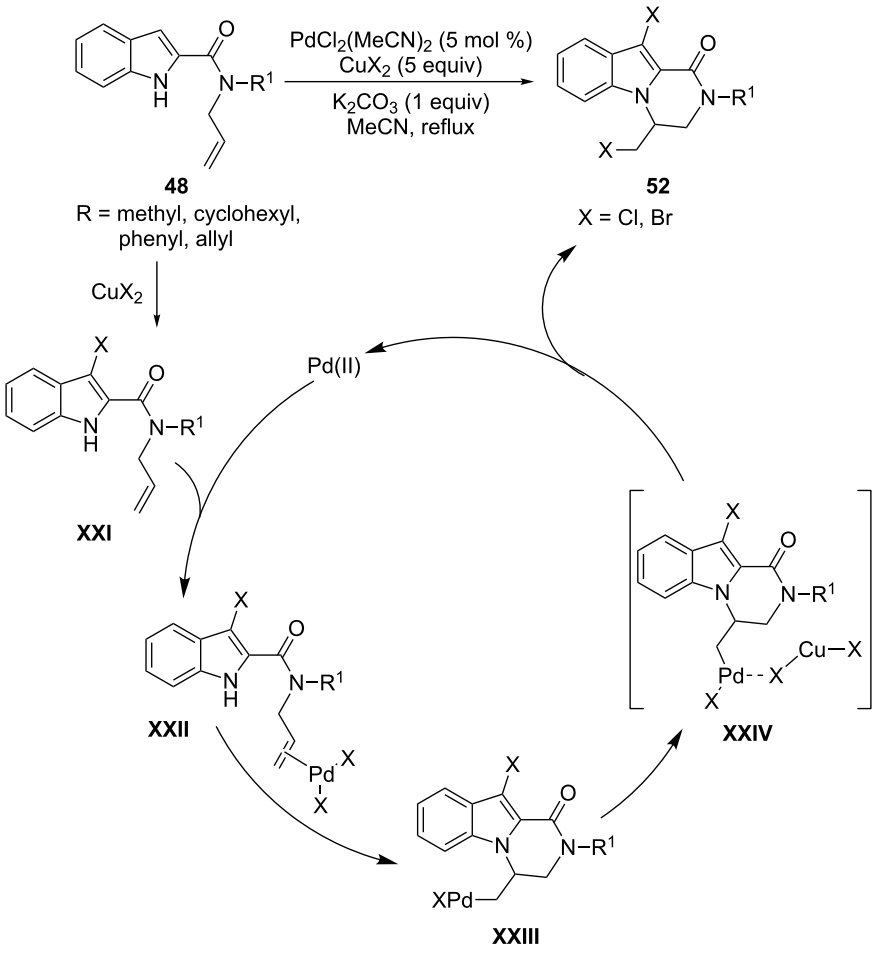
oxidation or the generation of hetero-bimetallic palladium/copper intermediates, which may undergo nucleophilic attack by the solvent on the exocyclic carbon to give the iminium intermediates **XIX** (Scheme 28). Finally, the latter may be converted into the esters **50** by hydrolysis.

The same reactivity was satisfactorily tested also on the 3-indolylallylcarboxamides **51**, giving, however, compounds **49** and **50** already obtained from the substrates **48** (Scheme 29). The formation of **49** and **50** may be reasonably justified by the intervention of the spiro-intermediates **XX**, arising from a cyclization involving the C-3 indolyl position, and which evolve by selective transfer of the acyl group from the quaternary center.

The cyclization of 2-indolylallylamides **48**, performed with $PdCl_2(MeCN)_2$ as the catalyst in the presence of CuX_2 in a large excess and K_2CO_3 with acetonitrile as the solvent, allowed the formation of the dihalogenated pyrazino[1,2-*a*]indole derivatives **52** by an unusual aminohalogenation/halogenation sequence (Scheme 30). The formation of the 3-haloderivatives **XXI**, ascribable solely to the action of the Cu(II) salt [84], and the cyclization of the π-olefin complexes **XXII** by aminopalladation leading to the intermediates **XXIII**, are involved as independent steps in the mechanism of the reaction. The final compounds **52** arise from the halide migration on the σ-alkyl-palladium complexes **XXIV**, stabilized by the presence of CuX_2 in the medium of the reaction [85].



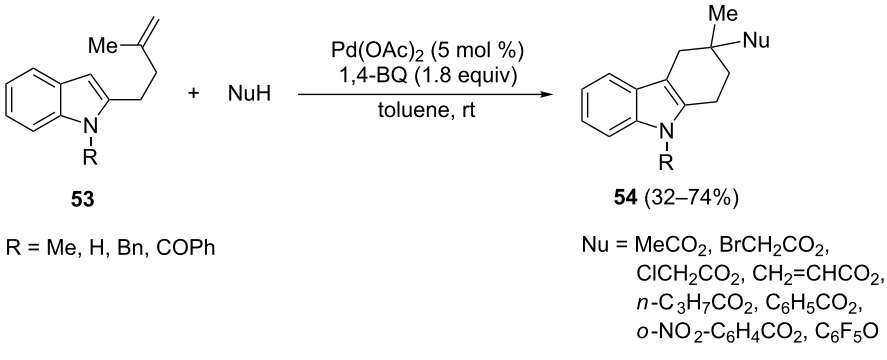
Scheme 29: Cyclization of 3-indolylallylcarboxamides involving 1,2-migration of the acyl group from spiro-intermediates.



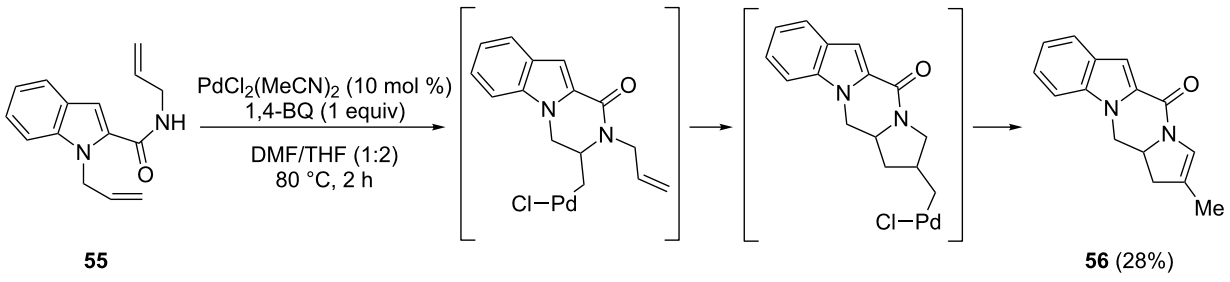
Scheme 30: Domino reactions of 2-indolylallylcarboxamides involving N–H functionalization.

A mild cyclization of 2-alkenylindoles **53** involving an alkenylation/acyloxylation process resulted in the formation of the 1,2,3,4-tetrahydrocarbazoles **54** bearing oxygen-containing functionalized groups (Scheme 31) [86]. Reactions were carried out by using 1,4-benzoquinone as the oxidizing agent in the presence of different nucleophiles suitable to generate the σ-alkyl-palladium complexes, which give the final products **54** by reductive elimination.

The amide of 2-indolecarboxylic acid bearing two allylic groups (**55**) undergoes a domino process with generation of the tetracyclic product **56** (Scheme 32) [79]. Indeed, the reaction carried



Scheme 31: Cyclization/acyloxylation reaction of 3-alkenylindoles.



Scheme 32: Doubly intramolecular C–H functionalization of a 2-indolylcarboxamide bearing two allylic groups.

out with 10 mol % of $PdCl_2(MeCN)_2$ as catalyst and a stoichiometric amount of 1,4-benzoquinone in DMF/THF as solvent underwent an oxidative cascade process involving the sequential intramolecular formation of C–N and C–C bonds, with an oxidative coupling triggered after the initial amidation step.

Conclusion

Palladium-catalyzed reactions to construct bonds by coupling of C–H/C–H or C–H/N–H bonds have been widely investigated in recent years. This interest arises from the need for unfunctionalized starting materials and from the presence of waste products that are easy to handle, such as hydrogen or water. This strategy, usually tolerant of a wide range of functionalities, has become a very powerful tool in the relevant field of indole chemistry, opening new perspectives for the functionalization of complex molecules avoiding protecting-group chemistry. Despite the results already obtained, many challenges remain, above all related to the improvement in scope and mildness of the reaction conditions for many synthetic protocols described.

Acknowledgements

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Copper-catalyzed CuAAC/intramolecular C–H arylation sequence: Synthesis of annulated 1,2,3-triazoles

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Full Research Paper

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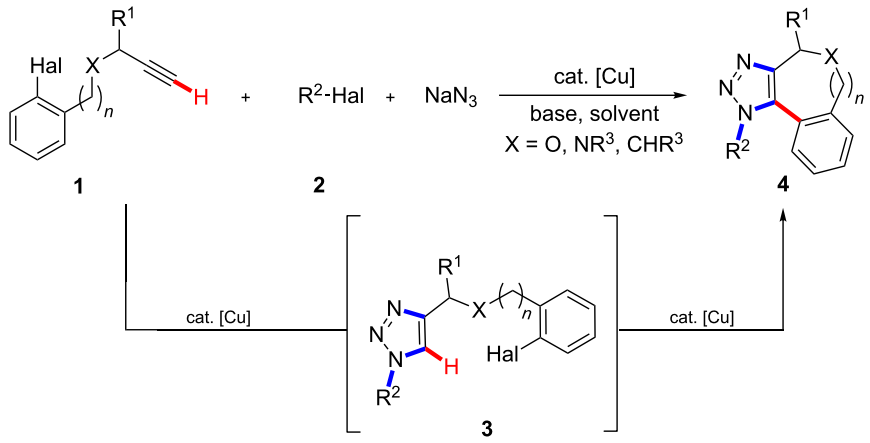
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Abstract

Step-economical syntheses of annulated 1,2,3-triazoles were accomplished through copper-catalyzed intramolecular direct arylations in sustainable one-pot reactions. Thus, catalyzed cascade reactions involving [3 + 2]-azide–alkyne cycloadditions (CuAAC) and C–H bond functionalizations provided direct access to fully substituted 1,2,3-triazoles with excellent chemo- and regioselectivities. Likewise, the optimized catalytic system proved applicable to the direct preparation of 1,2-diarylated azoles through a one-pot C–H/N–H arylation reaction.

Introduction

Transition-metal-catalyzed C–H bond functionalizations are increasingly viable tools for step-economical syntheses of various valuable bioactive compounds [1-3], which avoid the preparation and use of preactivated substrates [4-16]. This streamlining of organic synthesis has predominantly been accomplished with palladium [4-16], rhodium [17-19] or ruthenium [20-22] complexes [4-16]. However, less expensive nickel, cobalt, iron or copper catalysts bear great potential for the development of economically attractive transformations [23-50]. In this context, we previously reported on the use of cost-effective copper(I) catalysts for direct arylations of 1,2,3-triazoles. Thus, we showed that intermolecular copper-catalyzed C–H bond functionalizations could be combined with the Huisgen [51] copper(I)-catalyzed [52,53] [3 + 2]-azide–alkyne cycloaddition (CuAAC)[54], while C–H bond arylations of 1,2,3-triazoles were previously only accomplished with more expensive palladium [55-62] or ruthenium [63-66] catalysts. Notably, this strategy allowed for the atom-economical synthesis of fully substituted 1,2,3-triazoles in a highly regioselective fashion [54,67]. While the research groups of Rutjes [68] as well as Sharpless [69] elegantly devised alternative approaches exploiting 1-haloalkynes [70], we became interested in exploring a single [71-73] inexpensive copper catalyst for one-pot reaction sequences comprising a 1,3-dipolar cycloaddition



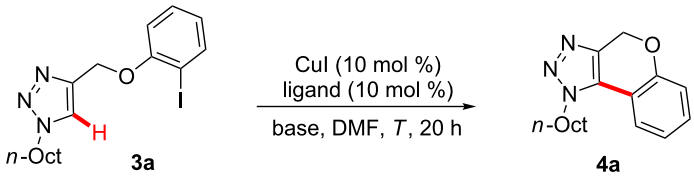
Scheme 1: Copper-catalyzed step-economical C–H arylation-based cascade reaction.

along with an intramolecular C–H bond arylation; in particular, because of the notable biological activities exerted by fully substituted 1,2,3-triazoles [74-88]. As a consequence, we wish to present herein novel cascade reactions, in which cost-effective copper(I) compounds serve as the catalyst for two mechanistically distinct transformations for the synthesis of fully substituted annulated 1,2,3-triazoles as well as for twofold N–H/C–H bond arylations. Notable features of our strategy include (i) the development of a chemoselective C–H arylation-based three-component reaction, as well as (ii) the use of inexpensive CuI for the formation of up to one C–C and three C–N bonds in a site-selective fashion (Scheme 1).

Results and Discussion

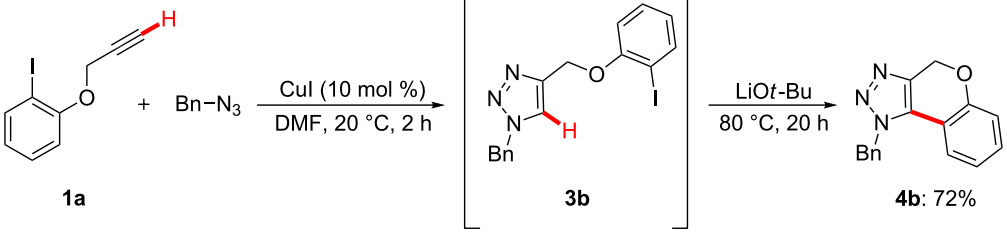
We initiated our studies by exploring reaction conditions for the key copper-catalyzed intramolecular direct C–H bond arylation, employing substrate **3a** (Table 1). Notably, the envisioned C–H bond functionalization occurred readily with the aryl iodide **3a** when catalytic amounts of CuI were used, even at a reaction temperature as low as 60 °C, with optimal yields being obtained

Table 1: Optimization studies for the intramolecular direct arylation of triazole **3a**.[a]



entry	base	ligand	*T* [°C]	isolated yield [%]
1	LiO*t*-Bu	–	140	82
2	LiO*t*-Bu	–	120	97
3	LiO*t*-Bu	–	100	91
4	**LiO*t*-Bu**	–	**80**	**93**
5	LiO*t*-Bu	–	60	72
6	LiO*t*-Bu	–	20	<2[b]
7	K_3PO_4	DMEDA	140	5[b]
8	K_3PO_4	*N*,*N*-dimethylglycine	140	5[b]
9	K_3PO_4	2,2-bipyridyl	140	4[b]
10	K_3PO_4	1,10-phenanthroline	140	11

[a]General reaction conditions: **3a** (1.00 mmol), CuI (10 mol %), ligand (10 mol %), DMF (3.0 mL).
[b]By ^{1}H NMR spectroscopy.



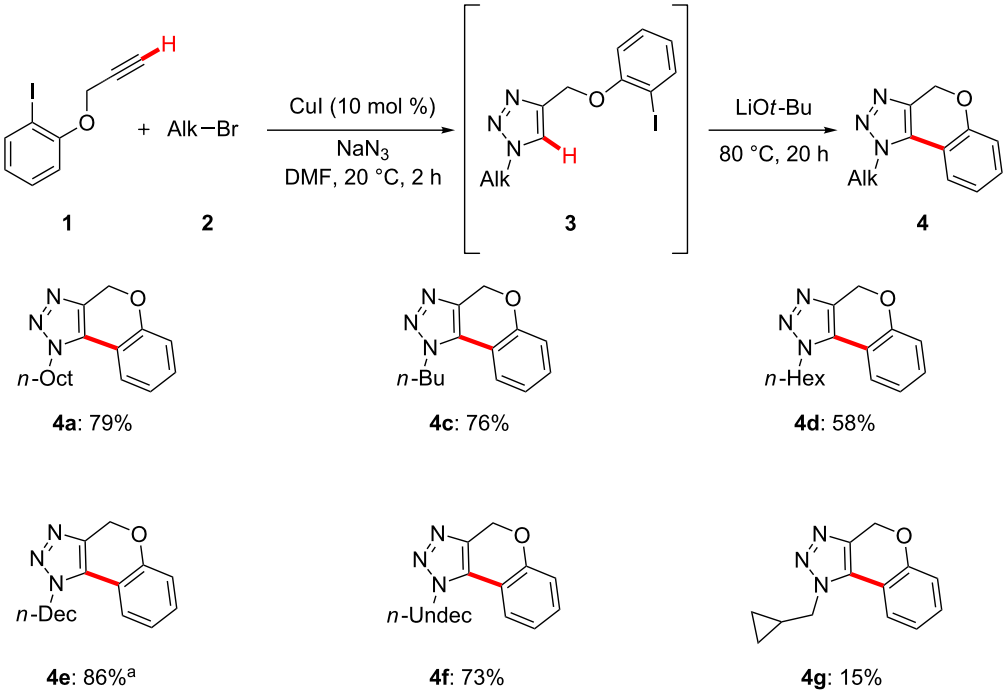
Scheme 2: Copper-catalyzed sequential catalysis with alkyne **1a**.

at 80 °C (Table 1, entries 1–6). While the transformation proceeded efficiently with LiO*t*-Bu as the stoichiometric base, K_3PO_4 only led to unsatisfactory results, even when additional stabilizing ligands were used (Table 1, entries 7–10).

With optimized reaction conditions for the intramolecular direct arylation in hand, we tested the possibility of its implementation in a sequential synthesis of 1,4-dihydrochromeno[3,4-*d*][1,2,3]triazole (**4b**, Scheme 2). We were delighted to observe that the desired reaction sequence consisting of a copper-catalyzed 1,3-dipolar cycloaddition and an intramolecular C–H bond arylation converted alkyne **1a** to the desired product **4b** with high catalytic efficacy.

Subsequently, we explored the extension of this approach to the development of a chemoselective three-component one-pot reaction. Thus, we found that alkyl bromides **2** could be directly employed as user-friendly substrates for the in situ formation of the corresponding organic azides (Scheme 3). Notably, the catalytic system proved broadly applicable, and a variety of organic electrophiles **2**, thereby, delivered differently decorated *N*-substituted 1,4-dihydrochromeno[3,4-*d*][1,2,3]triazoles **4**.

Importantly, performing the one-pot reaction in a sequential fashion was not found to be mandatory. Indeed, our strategy turned out to be viable in a nonsequential manner by directly employing equimolar amounts of the three substrates. Hence,



Scheme 3: Copper-catalyzed reaction sequence using alkyl bromides **2**. General reaction conditions: **1** (1.00 mmol), **2** (1.00 mmol), NaN_3 (1.05 mmol), CuI (10 mol %), DMF (3.0 mL), LiO*t*-Bu (2.00 mmol); yields of isolated product. [a]60 °C in the first step.

inexpensive CuI allowed the direct assembly of aryl iodides **1**, alkyl bromides **2** and NaN_3 with excellent chemo- and regioselectivities (Scheme 4). Thereby, a variety of annulated 1,2,3-triazoles **4** were obtained, featuring six- or seven-membered rings as key structural motifs. It is particularly noteworthy that the copper-catalyzed transformation enabled the formation of one C–C and three C–N bonds in a chemoselective manner, and thereby provided atom- and step-economical access to annulated carbo- as well as O- and N-heterocycles.

Finally, we found that the catalytic system also proved to be applicable to the one-pot copper-catalyzed direct arylation of various azoles **5** through N–H/C–H bond cleavages with aryl iodides **6** as the organic electrophiles (Scheme 5).

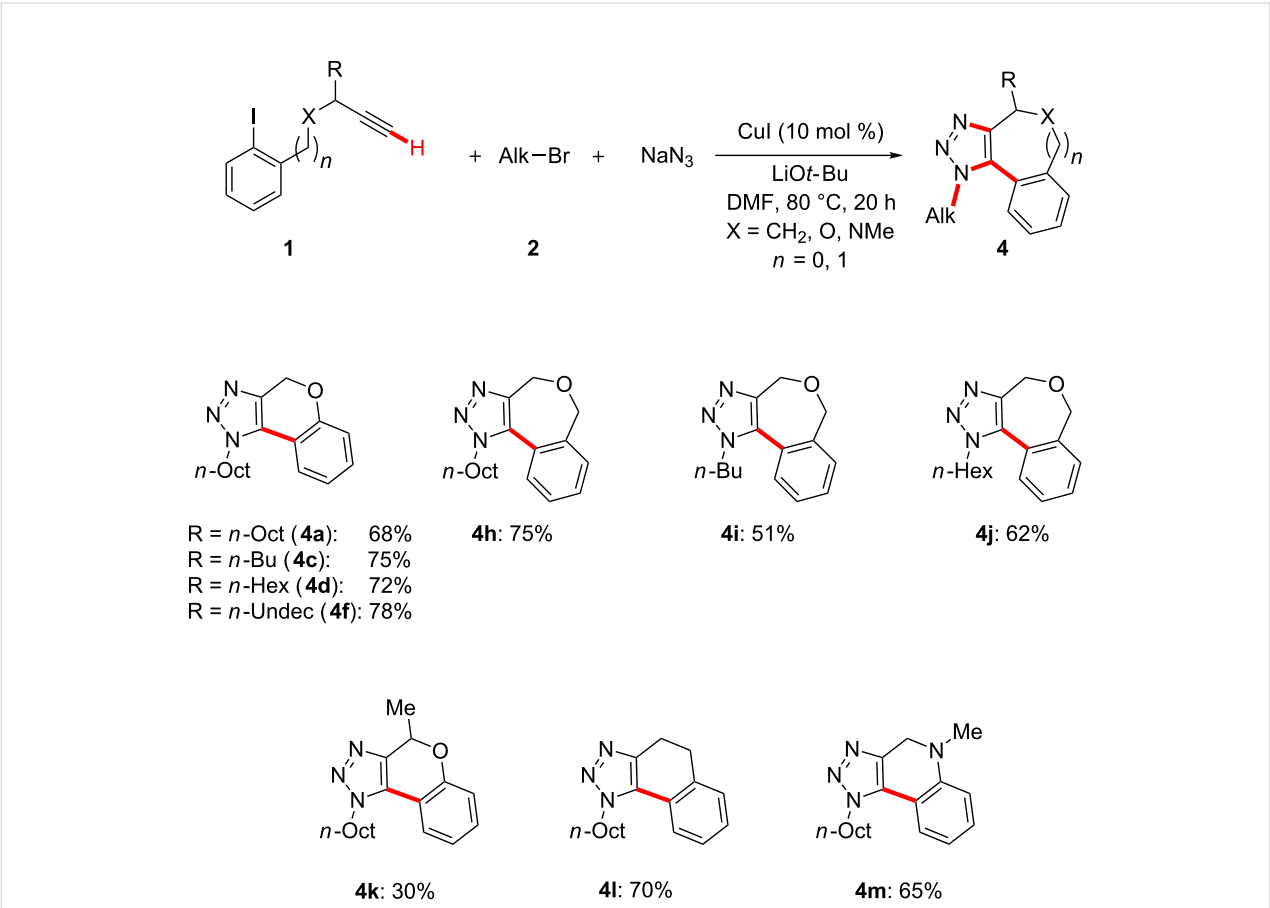
Conclusion

In summary, we have reported on the use of inexpensive copper(I) complexes for step- and atom-economical sequential catalytic transformations involving direct C–H bond arylations. Thus, CuI enabled the synthesis of fully substituted 1,2,3-triazoles through cascade reactions consisting of copper(I)-catalyzed [3 + 2]-azide–alkyne cycloadditions (CuAAC) and intramolecular C–H bond arylations. Notably, the optimized copper catalyst accelerated two mechanistically distinct transformations, which set the stage for the formation of up to one C–C and three C–N bonds in a chemo- and regioselective fashion, and also allowed for twofold C–H/N–H bond arylations on various azoles.

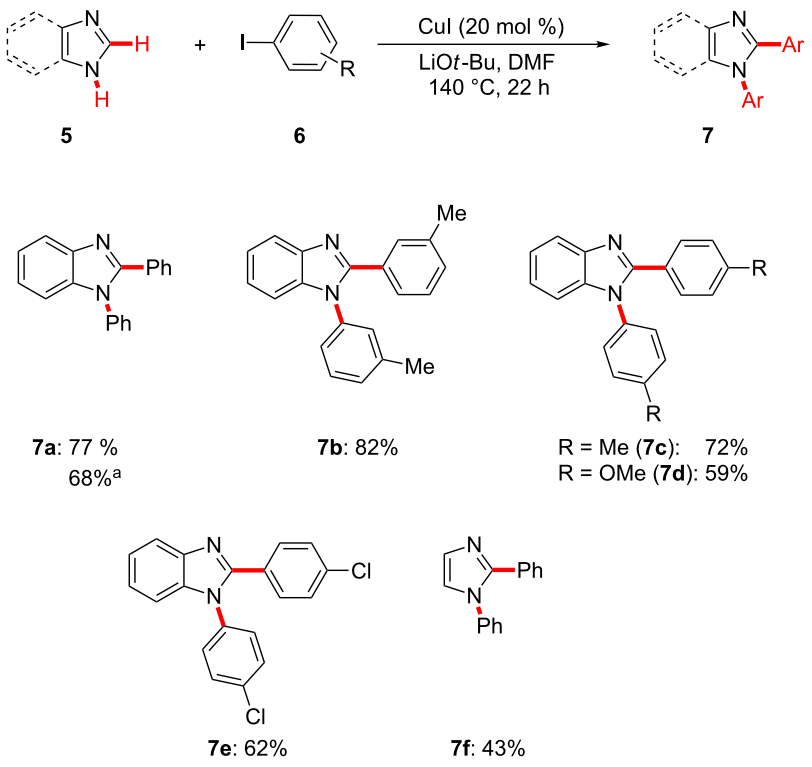
Experimental

General information

Catalytic reactions were carried out under an inert atmosphere of nitrogen using predried glassware. All chemicals were used as received without further purification unless otherwise specified. DMF was dried over CaH_2. Alkynes **1** [89-92] and triazoles **3** [93] were synthesized according to previously described methods. CuI (99.999%) was purchased from ABCR with the following specifications: Ag <3 ppm, Ca = 2 ppm, Fe = 1 ppm, Mg <1 ppm, Zn <1 ppm. Yields refer to isolated compounds, estimated to be >95 % pure, as determined by ^1H NMR. Thin-



Scheme 4: Nonsequential cascade synthesis of fully substituted triazoles **4**. General reaction conditions: **1** (1.00 mmol), **2** (1.00 mmol), NaN_3 (1.05 mmol), CuI (10 mol %) DMF (3.0 mL), LiO*t*-Bu (2.00 mmol); yields of isolated product.



Scheme 5: Copper-catalyzed one-pot twofold C–H/N–H arylation with azoles **5**. [a]Reaction performed at 120 °C.

layer chromatography (TLC) was carried out on silica gel 60 F254 aluminum plates (Merck). Chromatography: Merck silica gel 60 (40–63 µm). NMR: Spectra were recorded on Varian Unity 300, Mercury 300 or Inova 500 in the solvent indicated; chemical shifts (δ) are given in parts per million (ppm). All IR spectra were taken on a Bruker FTIR Alpha device. MS: EIMS-spectra were recorded with Finnigan MAT 95, 70 eV; high-resolution mass spectrometry (HRMS) with APEX IV 7T FTICR, Bruker Daltonic. Melting points were determined with a Stuart melting-point apparatus SMP3, Barlworld Scientific; values are uncorrected.

General procedure for the synthesis of triazoles 4

NaN_3 (1.05 equiv), CuI (10 mol %), LiO*t*-Bu (2.00 equiv), alkyne **1** (1.00 equiv) and alkyl bromide **2** (1.00 equiv) were dissolved in DMF (3.0 mL) and stirred at 80 °C for 20 h. Then, H_2O (50 mL) was added at ambient temperature, and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aq NH_4Cl (50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Supporting Information

Supporting Information containing all experimental details and analytical data of new compounds as well as their ^1H and ^{13}C spectra are provided.

Supporting Information File 1

Experimental procedures, characterization data, and NMR spectra for new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-202-S1.pdf]

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Rh(III)-catalyzed directed C–H bond amidation of ferrocenes with isocyanates

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Letter

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Abstract

[RhCp*$(OAc)_2(H_2O)$] [Cp* = pentamethylcyclopentadienyl] catalyzed the C–H bond amidation of ferrocenes possessing directing groups with isocyanates in the presence of 2 equiv/Rh of HBF_4·OEt_2. A variety of disubstituted ferrocenes were prepared in high yields, or excellent diastereoselectivities.

Introduction

Ferrocene and its derivatives are among the most useful organometallic compounds because of their chemical and thermal stabilities, structures, and redox activity [1,2]. One of the most remarkable applications of ferrocene derivatives is as chiral ligands [3,4]. A variety of chiral ferrocenyl ligands with several substitution patterns have been successfully utilized for enantioselective catalysis in both academia and industry. In particular, planar chiral 1,2-disubstituted ferrocenyl scaffolds have been extensively studied, and are among a few premier chiral ligand structures. For instance, a 1,2-disubstituted ferrocenyl ligand, Xyliphos ((*R*)-1-[(*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyl bis(3,5-dimethylphenyl)phosphane) is used for iridium-catalyzed enantioselective hydrogenation to produce the herbicide (*S*)-metolachlor on a scale of more than 10000 tons/year [5].

Planar chiral 1,2-disubstituted ferrocene derivatives are usually synthesized by using diastereoselective *ortho*-lithiation of monosubstituted ferrocenes with an appropriate chiral *ortho*-directing substituent such as chiral amines, sulfoxides, and oxazolines [3]. However, this method suffers from low atom economy, and requires stoichiometric amounts of metal reagents. Functionalization of ferrocene derivatives by transition-metal-catalyzed enantioselective C–H activation is a potentially more atom-economical alternative. However, only a few catalytic C–H activation reactions of ferrocenes have been

reported to date, and there is only one report of enantioselective C–H activation of ferrocenes [6-9]. Schmalz et al. reported the first catalytic C–H activation of ferrocenes using a Cu-catalyzed intramolecular carbene insertion into a Cp–H bond [6]. Further, they showed that the reaction could be enantioselective if chiral bisoxazoline ligands were used. However, the substrate scope of this reaction is narrow because of intramolecular reaction. More recently, chiral oxazoline-directed diastereoselective arylation of ferrocenes was reported based on a Pd(II)-catalyzed oxidative coupling reaction [8]. Most of the reactions in this report are, however, stoichiometric, and the yields of the catalytic reactions were low. Although there are a number of reports on stoichiometric directed C–H activation of ferrocenes by using electrophilic metal centers such as Pd(II), Pt(II), and Ru(II) [10-12], this communication describes a metal-catalyzed directed electrophilic C–H activation of an electron-rich Cp ring of ferrocene.

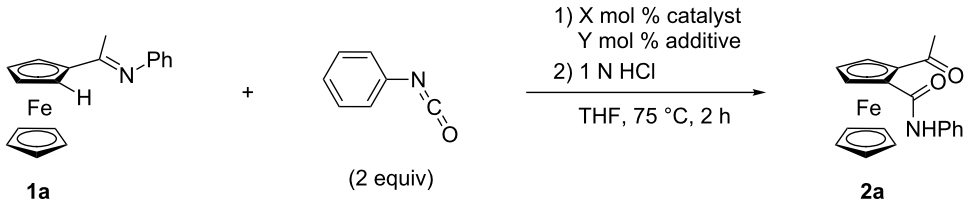
Pentamethylcyclopentadienyl (Cp*)Rh(III) is known to catalyze electrophilic activation of aryl C–H bonds, typically in the presence of an acetate ligand, and is used for oxidative C–C-bond-formation reactions [13]. Recently, several reports of cationic Cp*Rh(III)-catalyzed nonoxidative C–C-bond-formation reactions have been disclosed [14-22]. For example, Ellman et al. and Shi et al. reported that Cp*Rh(III) complexes catalyzed the reaction of aryl C–H bonds to imines, isocyanates, and aldehydes by directed electrophilic activation of aryl C–H bonds at relatively low temperature and under oxidant-free conditions [15-21]. We also reported that cationic Cp*Ir(III) complexes, combined with 1 equiv/Ir of $Cu(OAc)_2$, catalyzed the directed C–H activation of aryl C–H bonds at room temperature [23]. In this manuscript, we report application of this nonoxidative Rh(III) catalysis to synthesize planar chiral 1,2-disubstituted ferrocene derivatives.

Results and Discussion

We chose the reaction of ferrocenyl imine **1a** and phenyl isocyanate as a model reaction and screened several catalysts (Table 1). The cationic Cp*Ir(III) catalyst, which was used in our previous report [23], did not catalyze the reaction at all (Table 1, entry 1). Under copper-salt-free conditions, cationic Cp*Ir(III) catalyst did not give the product, but cationic Cp*Rh(III) selectively afforded monoamidated 1,2-disubstituted ferrocene derivative **2a**, albeit in low yield (Table 1, entries 2 and 3). The catalyst with BF_4^- anion showed the highest activity (Table 1, entries 3–5). The reaction also proceeded in the presence of an isolated cationic Cp*Rh catalyst, which simplifies the reaction setup and is required to prevent the redox reaction between $AgBF_4$ and **1a** [24]. However, the use of $[RhCp^*(MeCN)_3](BF_4)_2$ [17] resulted in lower yield likely due to the coordination of MeCN (Table 1, entry 6). The yield significantly increased when the combination of $[RhCp^*(OAc)_2(H_2O)]$ [25] and 2 equiv/Rh of $HBF_4{\cdot}OEt_2$ was used to form dicationic Cp*Rh species in situ (Table 1, entry 7) [26].

We examined a variety of isocyanates under the same reaction conditions given in entry 7 in Table 1 except with a lower catalyst loading of $[RhCp^*(OAc)_2(H_2O)]$. The reaction proceeded smoothly with 5 mol % of $[RhCp^*(OAc)_2(H_2O)]$ along with a slight decrease of yield (Table 2, entry 1). Both electron-rich and -poor aryl isocyantes showed similar reactivity in the

Table 1: Screening of catalysts.

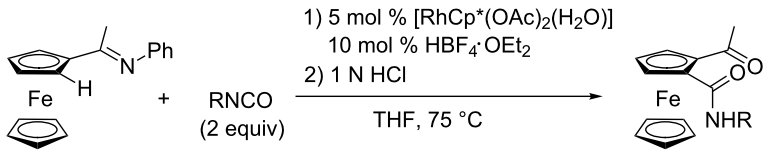


1a (2 equiv) **2a**

entry	catalyst (mol %)	additive (mol %)	yield (%)
1[a]	$[IrCp^*Cl_2]_2$ (5)	$AgSbF_6$ (20), $Cu(OAc){\cdot}H_2O$ (20)	0
2	$[IrCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	0
3[b]	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	30
4[b]	$[RhCp^*Cl_2]_2$ (2.5)	AgOTf (10)	20
5[b]	$[RhCp^*Cl_2]_2$ (2.5)	$AgBF_4$ (10)	42
6	$[RhCp^*(MeCN)_3](BF_4)_2$ (10)	none	29
7	$[RhCp^*(OAc)_2(H_2O)]$ (10)	$HBF_4{\cdot}OEt_2$ (20)	86

[a]The reaction was examined at 100 °C for 1 h in 1,2-dichloroethane using 4-methoxyphenyl isocyanate. [b]The reaction time was 24 h.

Table 2: Scope of isocyanates.



1a **2a–f**

entry	R	time (h)	product	yield (%)
1	Ph	3	**2a**	74
2	4-$MeOC_6H_4$	3	**2b**	85
3	4-ClC_6H_4	3	**2c**	87
4	benzyl	3	**2d**	84
5	*n*-butyl	24	**2e**	41
6	cyclohexyl	24	**2f**	19

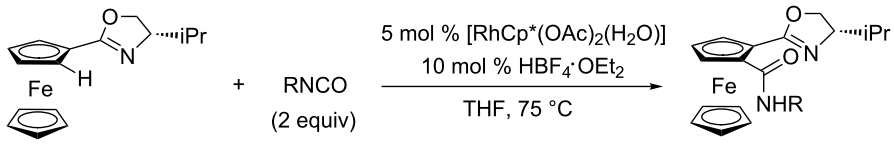
present reaction (Table 2, entries 2 and 3). The use of benzyl isocyanate also formed the monoamidated product **2d** (Table 2, entry 4). It required a longer reaction time, but alkyl isocyanates were also available.

We next examined a diastereoselective reaction using a commercially available chiral oxazolyl ferrocene **1b**, and the reaction was conducted under the same reaction conditions used in Table 2. Several isocyanates were submitted to the reaction with **1b**, and planar chiral 1,2-disubstituted ferrocenes **3a**–**f** were obtained with high diastereoselectivity, but the yields in all cases were moderate because of a low conversion ratio (Table 3). Lower coordination ability of the oxazolyl group compared to the imino one probably decreased the reactivity. The absolute configuration of planar chirality in **3c** was determined to be *S* by X-ray crystallography (Figure 1). The absolute configuration is consistent with the previous report of diastereoselective *ortho*-lithiation of **1b** [27].

Conclusion

In conclusion, a Cp*Rh(III)-catalyzed reaction between ferrocenyl C–H bonds and isocyanates was developed to synthesize a variety of 1,2-disubstituted ferrocenes. The use of the commercially available chiral oxazolyl ferrocene enabled us to synthesize planar chiral 1,2-disubstituted ferrocenes with excellent diastereoselectivity. The present reaction is a rare example of catalytic methods to construct planar chiral ferrocenes. We are currently investigating an enantioselective reaction.

Table 3: Diastereoselective reaction by using chiral oxazolyl ferrocene **1b**.



1b single diastereomer **3a–f**

entry	R	time (h)	product	yield (%)
1	Ph	2	**3a**	43
2	4-$MeOC_6H_4$	2	**3b**	24
3	4-ClC_6H_4	2	**3c**	38
4	benzyl	2	**3d**	32
5	*n*-butyl	24	**3e**	69
6	cyclohexyl	24	**3f**	38

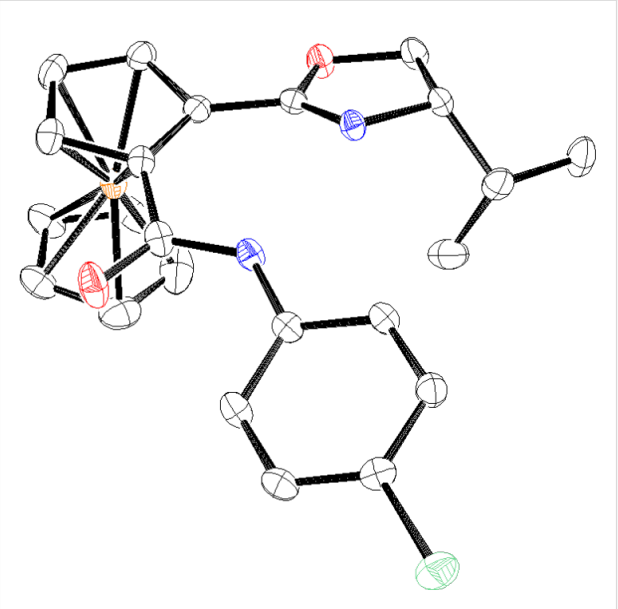


Figure 1: The ORTEP drawing of **3c** with 30% probability ellipsoids, and Flack absolute structure parameter of 0.003(12).

Supporting Information

Supporting Information File 1

Experimental procedures and physical properties of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-212-S1.pdf]

Supporting Information File 2

CIF of complex **3c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-212-S2.cif]

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Alkyne hydroarylation with Au N-heterocyclic carbene catalysts

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Full Research Paper

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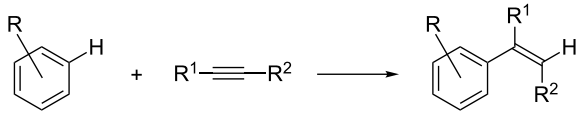
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Abstract

Mono- and dinuclear gold complexes with N-heterocyclic carbene (NHC) ligands have been employed as catalysts in the intermolecular hydroarylation of alkynes with simple unfunctionalised arenes. Both mono- and dinuclear gold(III) complexes were able to catalyze the reaction; however, the best results were obtained with the mononuclear gold(I) complex IPrAuCl. This complex, activated with one equivalent of silver tetrafluoroborate, exhibited under acidic conditions at room temperature much higher catalytic activity and selectivity compared to more commonly employed palladium(II) catalysts. Moreover, the complex was active, albeit to a minor extent, even under neutral conditions, and exhibited lower activity but higher selectivity compared to the previously published complex $AuCl(PPh_3)$. Preliminary results on intramolecular hydroarylations using this catalytic system indicate, however, that alkyne hydration by traces of water may become a serious competing reaction.

Introduction

The hydroarylation of alkynes (Scheme 1) is arguably one of the most intensively studied reactions leading to aromatic C–H bond functionalization [1-7]. In this reaction, the C–H bond of an arene adds formally *trans* to the triple bond of an alkyne, generally forming the thermodynamically less favoured *cis*-arylalkene as the major product.



Scheme 1: Hydroarylation of alkynes.

The study of this reaction was pioneered by the group of Fujiwara (hence the alternative name "Fujiwara reaction" for the intermolecular hydroarylation of alkynes) using mainly palladium(II) salts as catalyst [8-10]. Palladium complexes with N-heterocyclic carbene (NHC) ligands have since been showcased as highly efficient catalysts for this reaction [11-14].

Alternative catalytic systems based on salts or complexes of other noble metals, such as platinum [15-17], gold [18,19], or rhodium [20], as well as of non-noble, electrophilic metals [21-26] have also been successfully employed. Finally, an even greater number of catalysts have been proposed over the years to promote alkyne hydroarylation in an intramolecular fashion [1-7]. In such reactions, often simply termed cyclisation reactions, the arene and the alkyne are linked through a tether, the nature of which can range from simple alkyl groups to ether, amino, ester or amido groups; depending on the nature and length of the tether, different kinds of unsaturated poly(hetero)cyclic compounds can be conveniently synthesized.

Recently, the unique ability of gold centres to activate C–C triple bonds towards nucleophilic attack has clearly emerged in the literature [27-34]. In the light of the above, it is surprising that the number of studies on the use of gold species as catalysts for alkyne hydroarylation is still quite limited. A substantial number of reports on the intramolecular cyclisation of arenes with tethered alkyne moieties using gold(I) or, to a lesser extent, gold(III) catalysts can be found in the literature [35-46]; however, only one additional example, beyond the two early reports by Reetz and Sommer [18] and by Shi and He [19], of gold-catalysed intermolecular hydroarylation has been described, albeit concerning 2-substituted oxazoles as the reaction partner [47]. Investigations on the intramolecular variant have focused mainly on the nature of the aromatic moiety that adds to the alkyne, and on the nature and/or length of the tether, whereas concerning the alkyne moiety, only terminal, electron-rich alkyne groups (propargylic moieties in most instances) were employed, with very few exceptions [36,40,44]. Finally, concerning the nature of the employed catalysts, simple gold salts or phosphino complexes of gold(I) were utilized in the majority of cases, although in recent years an increasing number of studies have been dealing with the application of NHC complexes of gold for these and related reactions [48-53].

We have an ongoing interest in the development of novel catalysts for the hydroarylation of alkynes and have extensively investigated the ability of palladium(II) complexes with chelating N-heterocyclic dicarbene ligands to promote this reaction [12-14]. Recently, we have extended our interest in the organometallic chemistry of such ligands to group 11 metals, in particular gold(I) and gold(III) centers [54-56]. In the present contribution we would like to assess the catalytic efficiency of such gold complexes with NHC ligands for the hydroarylation of alkynes.

Results and Discussion

We recently reported on the synthesis of dinuclear gold(I) complexes with bridging dicarbene ligands [55], as well as on the preparation of the corresponding dinuclear gold(III) analogues, which are obtained from the former upon oxidation with bromine [54]. Complexes **I**–**V** were now tested as catalysts in standard intermolecular hydroarylation reactions, together with two mononuclear gold complexes previously reported in the literature, namely complexes **VI** (also termed IPrAuCl) [57] and **VII** (also termed $IPrAuBr_3$) [58] (Figure 1).

The standard reaction between pentamethylbenzene and ethyl propiolate (Scheme 2) was initially taken as the benchmark for catalyst evaluation. Initial attempts were performed at room

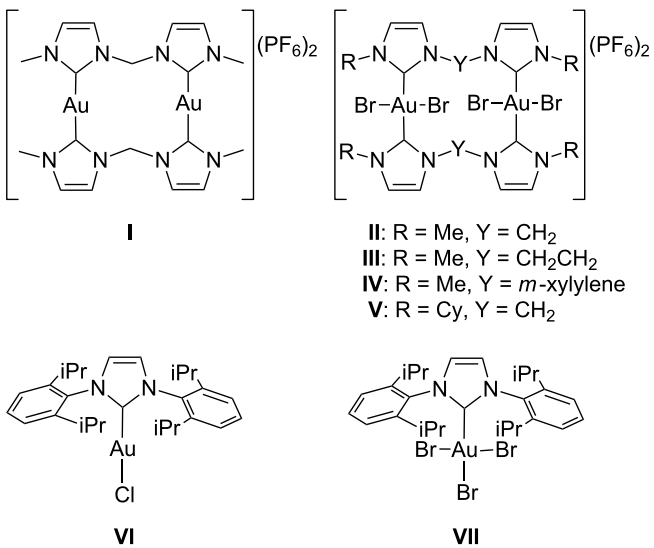
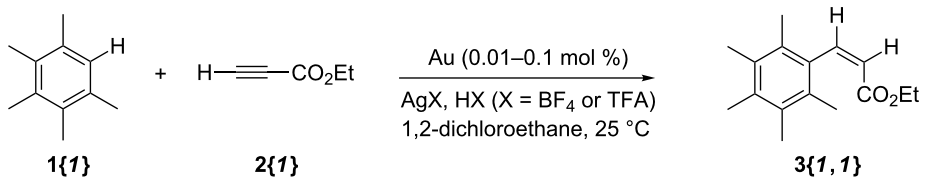


Figure 1: Gold(I) and gold(III) NHC complexes employed as catalysts in this study.



Scheme 2: Hydroarylation of ethyl propiolate with pentamethylbenzene.

temperature (25 °C) with very low levels of complex **II** as catalyst (0.005 mol %) by using trifluoroacetic acid (HTFA) or HBF_4 as acidic medium plus 0.02 mol % AgTFA or $AgBF_4$, respectively, as co-catalyst to remove bromides from the coordination sphere of the gold centres, thereby liberating coordination sites at the metal and boosting its electrophilicity.

The obtained results established that the complex was inactive when HTFA was employed as the acidic medium, whereas 20% yield of the desired product **3{*1*,*1*}** was obtained after 18 h with HBF_4. Consequently, a screening of the catalytic efficiency of the various complexes was carried out with the latter acidic medium; the amount of catalyst was increased tenfold (to 0.1 mol % Au) in order to achieve faster reaction rates, whereas the amount of employed $AgBF_4$ co-catalyst was always stoichiometrically equivalent to the amount of bromide in the employed complex. It should be mentioned that under these reaction conditions neither $AgBF_4$ nor HBF_4 promote the reaction, as previously demonstrated by us in investigations on related palladium(II) catalysts for the same reaction [13]. The conversion curves obtained with the various catalysts are reported in Figure 2.

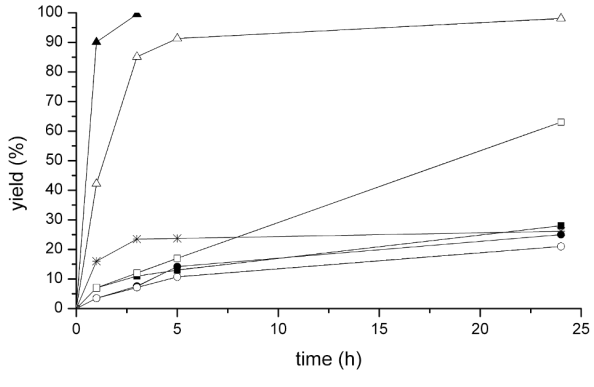


Figure 2: Yield in **3{*1*,*1*}** versus time diagram for the reaction of pentamethylbenzene and ethyl propiolate catalysed by complexes **II**–**VII** and $KAuBr_4$ at room temperature in HBF_4 and with added $AgBF_4$: complex **II** (black squares); complex **III** (circles); complex **IV** (squares); complex **V** (black circles); complex **VI** (black triangles); complex **VII** (triangles); $KAuBr_4$ (asterisks). Reaction conditions: 1 equiv arene, 1 equiv alkyne, 1 equiv tetrafluoroboric acid, 0.1 mol % Au, 0.1–0.4 mol % $AgBF_4$, 1,2-dichloroethane, 25 °C.

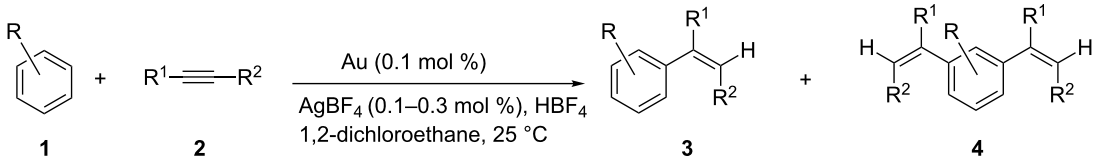
As expected, the dinuclear dicarbene gold(I) complex **I** was found to be inactive for the reaction, as the NHC ligands saturate the coordination sphere of the gold(I) centres. On the other hand, the dinuclear dicarbene gold(III) complexes **II**–**V**, for which 4 equiv of $AgBF_4$ with respect to the complex were added, turned out to be active. All dinuclear complexes exhibited very similar initial activity in the first few hours of reaction. This observation indicates that the reactivity of the complexes is not hampered by steric effects, as complexes with ligands of widely different steric bulk, such as **II** and **V**, exhibit similar performance. On the other hand, the complexes deactivate with time at different rates, depending on the nature of the employed dicarbene ligand. Complex **IV** turned out to be the catalyst most resistant to deactivation.

When catalysts **VI**, **VII** and $KAuBr_4$ were employed together with the corresponding amount of $AgBF_4$ co-catalyst, higher initial activities compared to the dinuclear dicarbene gold(III) catalysts were recorded. However, whereas $KAuBr_4$ was very quickly and completely deactivated, catalysts **VI** and **VII** retained their activity, highlighting the importance of the NHC ligand in stabilizing the catalytically active species. Catalyst **VI** (IPrAuCl) was particularly efficient and able to effect over 90% yield in just 1 h with complete selectivity for the hydroarylation product. Remarkably, compared to the palladium(II) complexes with chelating N-heterocyclic dicarbene ligands previously investigated by us as catalysts for the same reaction under identical reaction conditions [13], complex **VI** exhibits higher catalytic activity and complete selectivity for the insertion of only one alkyne molecule into the aromatic C–H bond, whereas the palladium(II) complexes predominantly yielded the product deriving from the insertion of two alkyne molecules. The catalytic efficiency of complexes **VI** and **VII** was evaluated with other arene and alkyne substrates under the same reaction conditions and the results are reported in Table 1.

The catalytic activity of the complexes remained high also with less substituted substrates, complex **VI** being systematically superior to complex **VII**. The selectivity of the reaction was, however, hampered by the formation of significant amounts of products deriving from the addition of two molecules of alkyne to the arene (product type **4**), which was invariably recorded

when more than one C–H group was available for reaction. Other by-products that were observed on using Pd catalysis, such as, e.g., products of double-bond isomerisation or deriving from insertion of more than one alkyne molecule into the same arene C–H bond, were however never detected with Au catalysts. Only in the case of *p*-xylene was the reaction again fully

Table 1: Hydroarylation of alkynes using gold NHC catalysts: screening of different arenes and alkynes.[a]



2{*1*} R^1 = H; R^2 = CO_2Et
2{*2*} R^1 = Ph; R^2 = CO_2Et
2{*3*} R^1 = H; R^2 = *n*-Bu

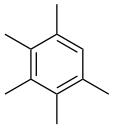
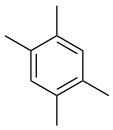
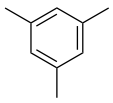
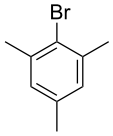
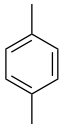
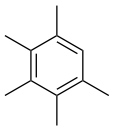
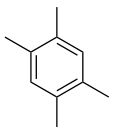
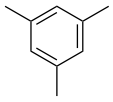
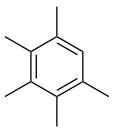
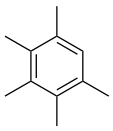
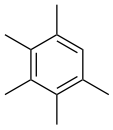
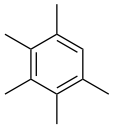
Catalyst	Arene	Alkyne	Time (h)	Arene conversion, % (alkyne conversion)	Yield (%)[b]			
VI	 **1{*1*}**	**2{*1*}**	1 3	90 (90) >99 (>99)	**3{*1,1*}**	90 >99		
VI	 **1{*2*}**	**2{*1*}**	1 5	68 (94) 72 (100)	**3{*2,1*}**	42 44	**4{*2,1*}**	26 28
VI	 **1{*3*}**	**2{*1*}**	1 5	72 (95) 74 (98)	**3{*3,1*}**	49 50	**4{*3,1*}**	23 24
VI	Br  **1{*4*}**	**2{*1*}**	5	35 (38)	**3{*4,1*}**	32	**4{*4,1*}**	3
VI	 **1{*5*}**	**2{*1*}**	1 5	20 (20) 45 (45)	**3{*5,1*}**	20 45	**4{*5,1*}**	0 0
VII	 **1{*1*}**	**2{*1*}**	1 5	43 (43) 91 (91)	**3{*1,1*}**	43 91		
VII	 **1{*2*}**	**2{*1*}**	1 5	18 (19) 58 (72)	**3{*2,1*}**	17 45	**4{*2,1*}**	1 13

Table 1: Hydroarylation of alkynes using gold NHC catalysts: screening of different arenes and alkynes.[a] (continued)

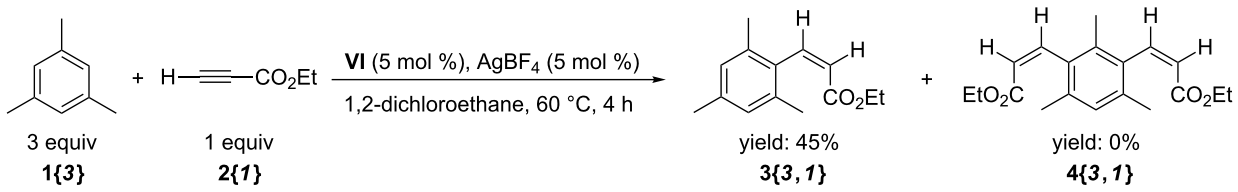
VII	 **1{*3*}**	**2{*1*}**	1 5	66 (86) 71 (93)	**3{*3,1*}**	46 50	**4{*3,1*}**	20 22
VI	 **1{*1*}**	**2{*2*}**	1 5	23 (23) 58 (58)	**3{*1,2*}**	23 58		
VI	 **1{*1*}**	**2{*3*}**	5	0	**3{*1,3*}**	0		
VI	 **1{*1*}**	**2{*1*}**	5	51 (51)[c]	**3{*1,1*}**	51		
VI	 **1{*1*}**	**2{*1*}**	48	15 (15)[d]	**3{*1,1*}**	15		

[a]Reaction conditions: 1 equiv arene, 1 equiv alkyne, 1 equiv tetrafluoroboric acid, 0.1 mol % Au, 0.1 or 0.3 mol % $AgBF_4$, 1,2-dichloroethane, 25 °C. [b]The yield was determined by ^1H NMR spectroscopy. [c]Reaction performed with trifluoroacetic acid. [d]Reaction performed without acid.

selective, albeit sluggish. Variations of the alkyne substrate made it apparent that electron-rich alkynes, such as 1-hexyne, are not viable substrates for this reaction, and that electron-poor, internal alkynes react only scarcely under these conditions.

The high catalytic activity of complex **VI** prompted us to evaluate its efficiency also under less acidic conditions. Hydroarylation of ethyl propiolate with pentamethylbenzene run with 0.1% **VI** and 0.1% AgTFA in HTFA yielded 51% pure monohydroarylated product after 5 h. On the other hand, the reaction run with 0.1% **VI** and 0.1% $AgBF_4$ under neutral conditions yielded only 15% product after 48 h. Thus, the nature and amount of acid have a very strong influence on catalytic efficiency, as in the case of catalysis by palladium(II) NHC complexes [13]; in contrast to Pd, though the catalyst remains slightly active even under neutral conditions. This result was expected, as in early examples of the use of gold catalysts for intermolecular alkyne hydroarylations the reaction was invariably done without acid addition, although much more forceful conditions (larger amount of catalyst, higher temperature, longer reaction times) were applied [18,19,47]. In order to have a closer comparison between the catalytic efficiency of **VI** and that of the previously employed gold(I) catalysts, such as $AuCl(PPh_3)$, we subjected complex **VI** to the same catalytic test performed by Reetz and Sommer with the phosphino complex (Scheme 3) [18]. The catalytic test performed with catalyst **VI** resulted in the exclusive formation of the hydroarylation product in 45% yield. Catalyst $AuCl(PPh_3)$ was reported instead to produce, under the same reaction conditions, the hydroarylation product in 56% yield, together with 28% yield of the product deriving from insertion of two alkyne molecules into two C–H bonds of mesitylene [18]. Thus, it can be stated that catalyst **VI** is apparently less active but more selective under these neutral reaction conditions.

Finally, we preliminarily investigated the capability of complexes **VI** and **VII** to act as catalysts for intramolecular alkyne hydroarylation reactions. As mentioned in the Introduction, gold salts and complexes have been extensively employed for intramolecular cyclisations of this kind [35-46], but in most instances only terminal pendant alkynes have been employed as reacting groups. Furthermore, to the best of our knowledge substrates with amido tethers between the aryl and the alkyne,



Scheme 3: Hydroarylation experiment with catalyst **VI** under neutral conditions.

such as substrates **5** (Scheme 4), have never been reported to undergo cyclisation with gold catalysts, whereas there are examples of the use of palladium catalysts with these substrates leading to different products in dependence on the reaction conditions: reaction under neutral conditions produces the 5-*exo-dig* cyclisation product **6** [59], whereas in the presence of an acid the 6-*endo-dig* product **7** is formed [60]. Thus, we set out to evaluate the reactivity of substrates **5** with catalysts **VI** and **VII**.

Under neutral conditions the reaction gave no yield in the desired cyclised product and the substrate was recovered unchanged in all cases. Therefore, we moved to investigate the reaction in the presence of trifluoroacetic acid, using a reaction protocol previously employed by Fujiwara for running analogous reactions with palladium(II) catalysts [60]. The results are reported in Table 2.

Catalyst **VII** was completely inactive even under acidic conditions with substrate **5**{*2*}, whereas with substrate **5**{*1*} it reacted sluggishly forming complex product mixtures containing also the 6-*endo-dig* cyclisation product **7**{*2*}. On the other hand, with complex **VI** moderate to very good conversions of the substrates were obtained, but the main reaction product was invariably the product of hydration of the triple bond **8**, whereas the 6-*endo-dig* cyclisation product **7** was present in minor amounts. Gold(I) NHC complexes such as **VI** are known to be extremely efficient catalysts for alkyne hydration [61], hence it

Table 2: Intramolecular alkyne hydroarylation under acidic conditions.[a]

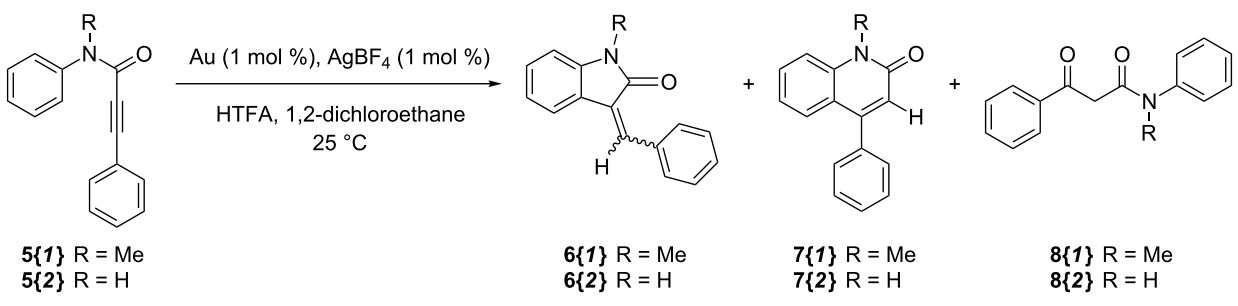
Substrate	Catalyst	Conversion (%)[b]	Yield (%)[b]			
5{*1*}	**VI**	89	**7**{*1*}	12	**8**{*1*}	78
5{*1*}	**VII**	31	**7**{*1*}	10	**8**{*1*}	-
5{*2*}	**VI**	54	**7**{*2*}	7	**8**{*2*}	47
5{*2*}	**VII**	0	**7**{*2*}	0	**8**{*2*}	0

[a]Reaction conditions: 1 equiv substrate, 20 equiv trifluoroacetic acid, 1 mol % Au, 1 mol % $AgBF_4$, 1,2-dichloroethane, room temperature, 24 h. [b]The conversion and the yields were determined by ^1H NMR spectroscopy.

can be expected that alkyne hydration by traces of water may become a serious competitive reaction despite the low concentration of water in the reaction mixture. On the basis of the above, it can be hypothesised that in order to steer the reaction towards the hydroarylation product, more activating, hence electron-donating substituents should be installed on the aryl ring. Experiments towards this goal are currently underway.

Conclusion

In conclusion, we have demonstrated that gold complexes with N-heterocyclic carbenes are active catalysts for alkyne hydroarylations under acidic conditions. Mononuclear complexes appear more active than dinuclear ones, and gold(I) complexes are more active and selective than analogous gold(III) complexes. Under neutral reaction conditions, mononuclear gold(I) NHC complexes appear less active but more selective than the



Scheme 4: Intramolecular cyclisation through hydroarylation investigated in this work.

corresponding triphenylphosphine complexes. Finally, tests performed on the intramolecular hydroarylation of substrates **5**{*1*} and **5**{*2*} indicate that the reaction does not take place under neutral conditions, whereas under acidic conditions products of alkyne hydration by traces of water present in the reaction mixture are mainly formed, together with low yields of the 6-*endo*-*dig* cyclisation product. Possibly the installation of an electron-donating group on the aryl ring will improve the efficiency of the hydroarylation process.

Experimental

All manipulations were carried out using standard Schlenk techniques under an atmosphere of dry argon or dinitrogen. The reagents were purchased at Sigma–Aldrich or Merck as high-purity products and generally used as received. All solvents were dried by standard procedures and distilled under dinitrogen prior to use. Complexes **I** [55], **II**–**V** [54] and **VII** [58], as well as substrates **5**{*1*} and **5**{*2*} [59] were prepared according to literature procedures. NMR spectra were recorded on a Bruker Avance 300 MHz (300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C); chemical shifts (δ) are reported in units of parts per million (ppm) relative to the residual solvent signals.

Catalytic tests. General procedure for the intermolecular hydroarylation: In a 100 mL three-necked, round-bottomed flask were placed the arene (13.2 mmol), the Au complex (0.013 mmol for mononuclear complexes, 0.0065 mmol for dinuclear complexes) and $AgBF_4$ (0.013 mmol to 0.052 mmol, depending on the Au complex employed). The flask was evacuated and filled with argon, after which the acid (13.2 mmol) and 1,2-dichloroethane (the quantity necessary to reach a total volume of 6.3 mL) were added. Finally, the alkyne (13.2 mmol) was introduced, and the flask was placed in a water bath thermostated at 25 °C and vigorously stirred. Aliquots of the reaction mixture (around 0.2 mL) were periodically withdrawn from the reactor and analysed by ^{1}H NMR.

General procedure for the intramolecular hydroarylation: In a Schlenck tube were placed the substrate (1.00 mmol), the Au complex (0.010 mmol) and $AgBF_4$ (0.010 mmol). The flask was evacuated and filled with argon, after which 1,2-dichloroethane (2 mL) and trifluoroacetic acid (1.5 mL, 20 mmol) were added. The resulting mixture was vigorously stirred at room temperature for 24 h. The reaction mixture was subsequently poured into a saturated aqueous NaCl solution (20 mL) and neutralized with a saturated aqueous $NaHCO_3$ solution. The residual substrate and products were extracted into diethyl ether (20 mL). The resulting ethereal solution was washed with a saturated aqueous NaCl solution (10 mL) and water (10 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was analysed by ^{1}H NMR.

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N-Heterocyclic carbene–palladium catalysts for the direct arylation of pyrrole derivatives with aryl chlorides

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Abstract

New Pd–NHC complexes have been synthesized and employed for palladium-catalyzed direct arylation of pyrrole derivatives by using electron-deficient aryl chlorides as coupling partners. The desired coupling products were obtained in moderate to good yields by using 1 mol % of these air-stable palladium complexes. This is an advantage compared to the procedures employing air-sensitive phosphines, which have been previously shown to promote the coupling of aryl chlorides with heteroarenes.

Introduction

N-Heterocyclic carbenes (NHC) have emerged as an important class of ligands in the development of homogeneous catalysis [1-9]. Such ligands, which are electronically and sterically tunable, and which generally form thermally stable compounds with different metal ions, are strong σ-donors. These qualities have rendered N-heterocyclic carbene ligands as classical substitutes to phosphines in organometallic catalysis [10-14]. This is especially true for palladium-catalyzed coupling reactions. Pd–NHC catalysts [15] have proven to be excellent alternatives to catalytic systems involving palladium associated to tertiary phosphine ligands [16-19].

The introduction of aryl groups at C2 or C5 positions of pyrroles is an important research area in organic synthesis as such motives are known to be present in several bioactive molecules, such as Atorvastatin, which is used for lowering

blood cholesterol, Fendosal, which is an anti-inflammatory agent, or Tanaproget, which is a progesterone-receptor agonist (Figure 1).

The palladium-catalyzed direct arylation of various heteroaromatics including pyrroles by a C–H bond activation using aryl halides has met great success in recent years, allowing the synthesis of a wide variety of arylated heteroaromatics in only one step [20-25]. However, there are still limitations for these reactions in terms of aryl halide or heteroaromatic tolerance. Up to now, very few examples of palladium-catalyzed direct arylations of pyrroles by using aryl chlorides have been reported, [26,27]. Daugulis and co-workers recently described the arylation of pyrrole derivatives with a variety of aryl chlorides using 5 mol % of $Pd(OAc)_2$ associated to 10 mol % of Cy_2P-*o*-biphenyl as the catalyst [26]. However, in most cases, such couplings were performed with aryl bromides or iodides [28-39].

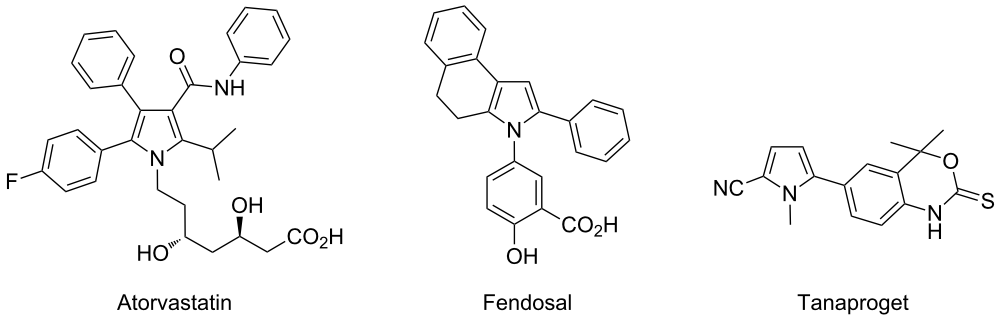
The influence of mono- or diphosphines as ligands for the palladium-catalyzed coupling of heteroarenes with aryl halides through a C–H bond activation has been largely explored. On the other hand, the influence of carbene ligands for such couplings remains largely unexplored [40-47]. Quite congested *N*-heterocyclic carbene–palladium catalysts have been employed by Fagnou and co-workers to promote intramolecular direct arylations of arenes [40]. A few examples of couplings of aryl bromides and iodides employing Pd–NHC complexes have also been reported [41-45]. For example, Sames and co-workers described the use of imidazolylidene carbene ligands for the Pd-catalyzed direct arylation of pyrroles or indoles using bromobenzene and aryl iodides [42]. They observed that an important steric demand on the carbene ligand led to better results. Recently, the use of palladium(II) acetate complexes bearing both a phosphine and a carbene ligand, was reported by Lee and co-workers for the direct arylation of imidazoles with some aryl chlorides [46]. However, to our knowledge, *N*-heterocyclic carbene ligands have not yet been employed for the palladium-catalyzed direct arylation of pyrroles with aryl chlorides. As carbene ligands have proved to be very useful for several palladium-catalyzed reactions involving aryl chlorides, we decided to explore their potential for the direct 2- or 5-arylation of pyrrole derivatives.

Results and Discussion

First, a range or Pd–NHC complexes employing a variety of carbene ligands was prepared (Scheme 1). The deviations from the accustomed structures of palladium–NHC complexes can be attributed to steric rather than to electronic factors [48]. The use of quite congested carbene ligands has been found to be required for the palladium-catalyzed direct arylation of pyrroles, indoles, benzothiophene [42,45] or arenes [40]. Therefore, we employed carbenes bearing relatively bulky N-substituents. The reaction of $Pd(OAc)_2$ with the corresponding benzimidazolium halides in DMSO at 60–110 °C gave **1**–**9** in 53–87% yields (Scheme 1). The geometry of these complexes was not defined, as no crystals suitable for X-ray analysis could be obtained.

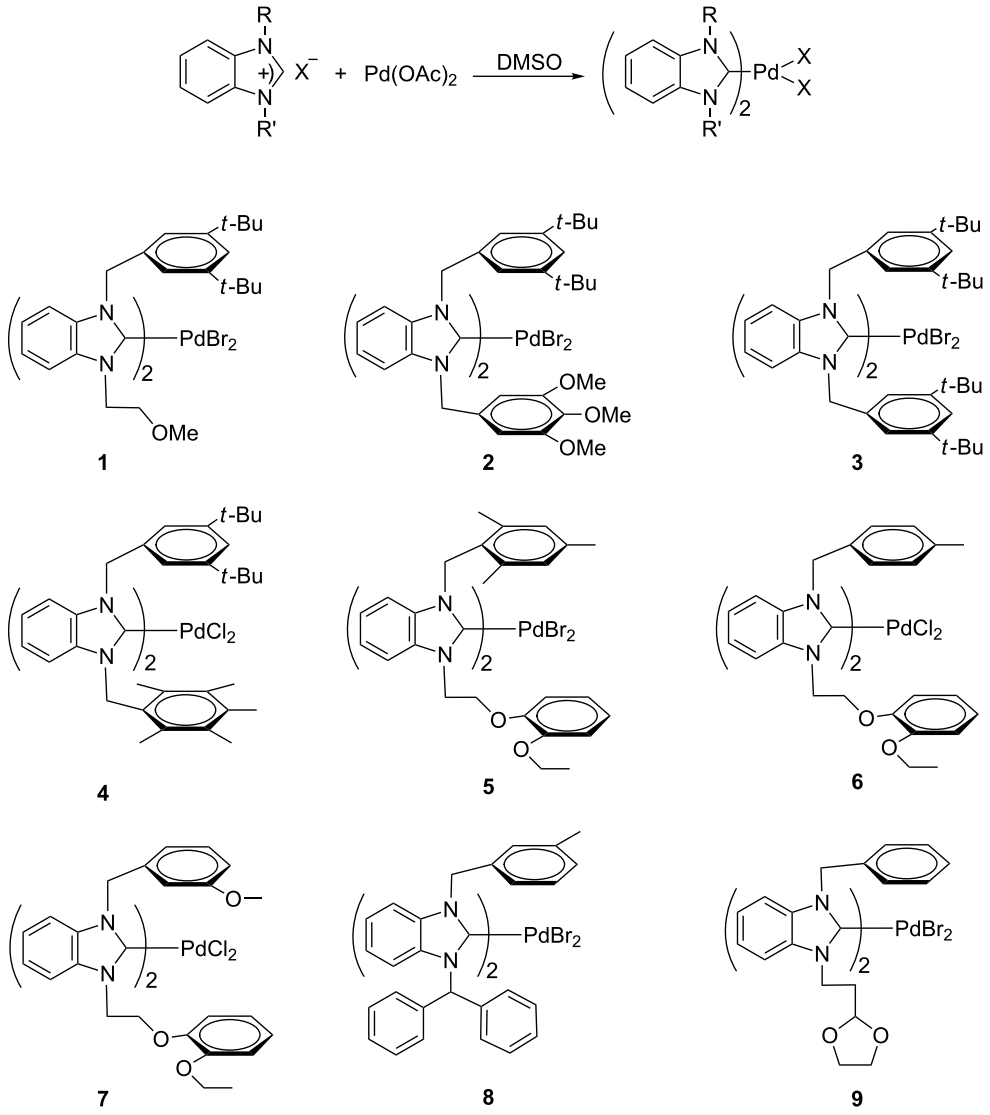
Arylation with Pd–NHC complexes

We initially examined the direct 5-arylation of 1-methylpyrrole-2-carboxaldehyde (**10**) with 4-chlorobenzonitrile (**11**) using these nine Pd–NHC complexes. We had previously observed that with this pyrrole derivative a high yield of 89% could be obtained in the presence of only 0.5 mol % of a triphosphine associated to $Pd(OAc)_2$ as the catalyst [27]. With complexes **2**, **3**, **8** and **9**, a high conversion of 4-chlorobenzonitrile (**11**) and good yields of the coupling product **16** were obtained (Table 1, entries 1–9). Then, in order to confirm this trend, 2-chlorobenzonitrile (**12**) and 4-(trifluoromethyl)chlorobenzene (**13**) were reacted with 1-methylpyrrole-2-carboxaldehyde (**10**) by using this library of complexes (Table 1, entries 10–27). Again, complexes **2**, **8** and **9** were found to be effective catalysts for this transformation, and led to a high conversion of 2-chlorobenzonitrile (**12**) to give **17** in 55–60% yield (Table 1,



Atorvastatin Fendosal Tanaproget

Figure 1: Examples of pyrrole-containing bioactive compounds.



Scheme 1: Synthesis of Pd–NHC complexes.

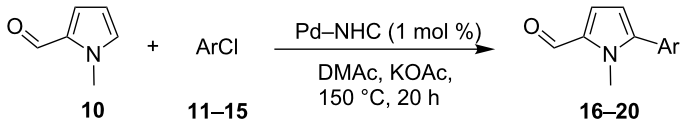
entries 10–18). For 4-(trifluoromethyl)chlorobenzene (**13**), the best results were obtained with catalysts **2** and **8** to give **18** in 76% and 74% yields, respectively (Table 1, entries 20 and 26). Then, the reactivity of 4-chlorobenzaldehyde (**14**) and 4-chloroacetophenone (**15**) was examined by using complexes **2**, **8** and **9**. For both substrates the best yields of products **19** and **20** of 41% and 50% were obtained with complex **8** (Table 1, entries 28–33).

The reactivity of 2-acetyl-1-methylpyrrole (**21**) was similar to 1-methylpyrrole-2-carboxaldehyde (**10**, Table 2). Complexes **8** and **9** promoted an almost complete conversion of 2- and 4-chlorobenzonitrile, and of 4-(trifluoromethyl)chlorobenzene to give the desired coupling products **22**–**24** in good yields. On the other hand, low to moderate yields were obtained with complexes **1**, **4** and **6**.

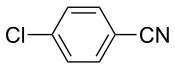
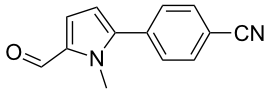
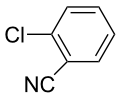
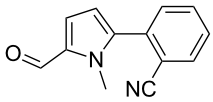
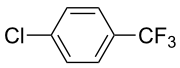
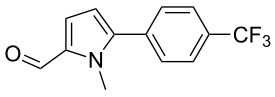
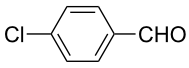
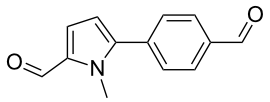
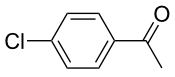
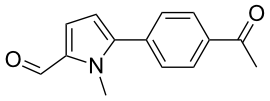
Methyl 1-methylpyrrole-2-carboxylate (**25**) also reacts with 4-chlorobenzonitrile (**11**) to give **26** in good yields with catalysts **2**, **8** and **9** (Table 3). No significant decarboxylation of the pyrrole derivative was observed in the course of this reaction.

Three aryl chlorides have also been coupled with 1-methylpyrrole (**27**, Table 4). A large excess of 1-methylpyrrole (**27**) was employed (4 equiv) in order to avoid the formation of 2,5-diarylated pyrroles. From 2- and 4-chlorobenzonitrile, **28** and **29**

Table 1: Direct arylation of 1-methylpyrrole-2-carboxaldehyde (**10**) with chlorobenzene derivatives.[a]



10 **11–15** **16–20**

Entry	ArCl	Pd–NHC	Product	Conv. (%)[b]	Yield (%)[b]
1	 **11**	**1**	 **16**	68	57
2		**2**		99	**87**
3		**3**		99	**83**
4		**4**		69	61
5		**5**		64	57
6		**6**		46	36
7		**7**		45	37
8		**8**		80	**72**
9		**9**		74	**65**
10	 **12**	**1**	 **17**	63	23
11		**2**		78	**60**
12		**3**		38	11
13		**4**		45	33
14		**5**		32	7
15		**6**		32	5
16		**7**		26	20
17		**8**		65	**58**
18		**9**		67	**55**
19	 **13**	**1**	 **18**	100	56
20		**2**		98	**76**
21		**3**		100	34
22		**4**		100	32
23		**5**		86	8
24		**6**		77	40
25		**7**		100	28
26		**8**		98	**74**
27		**9**		98	21
28	 **14**	**2**	 **19**	11	2
29		**8**		70	**41**
30		**9**		74	38
31	 **15**	**2**	 **20**	24	9
32		**8**		73	**50**
33		**9**		74	47

[a]Reaction conditions: Pd–NHC (0.01 mmol), aryl chloride (1 mmol), 1-methylpyrrole-2-carboxaldehyde (**10**, 2 mmol), KOAc (2 mmol), DMAc (3 mL), 20 h, 150 °C. [b]Determined by GC and NMR.

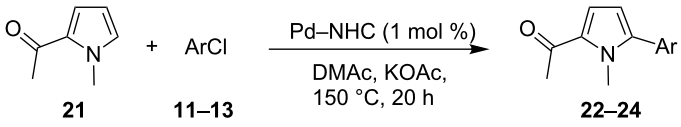
were obtained in high yields in the presence of complexes **8** and **9**. On the other hand, the formation of several side-products was observed during the coupling of 4-(trifluoromethyl)chlorobenzene (**13**) with this pyrrole derivative, and **30** was obtained in low yields (Table 4, entries 11–15).

Finally, the reactivity of 1-phenylpyrrole (**31**) with two aryl chlorides was examined (Table 5). Again, good yields in **32** were obtained with complexes **2**, **8** and **9** for the coupling with 4-chlorobenzonitrile (**11**). 4-Chloroacetophenone (**15**) also gave **33** in good yields with complexes **8** and **9**.

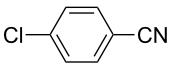
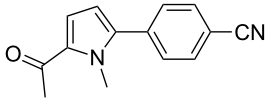
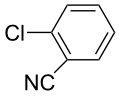
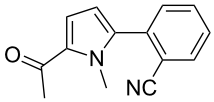
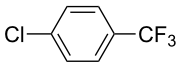
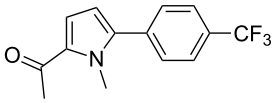
Conclusion

In summary, we have demonstrated that the regioselective C2 or C5 direct arylation of a range of pyrrole derivatives using electron-deficient aryl chlorides can be promoted by *N*-heterocyclic carbene ligands associated to palladium. So far, the reason for the influence of the nature of the carbene ligand on such

Table 2: Direct arylation of 2-acetyl-1-methylpyrrole (**21**) with chlorobenzene derivatives.[a]

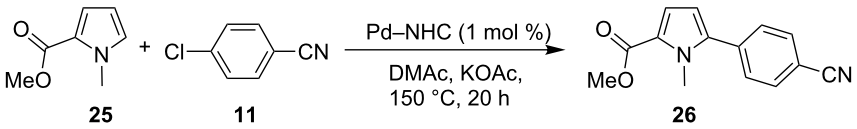


21 **11–13** **22–24**

Entry	ArCl	Pd–NHC	Product	Conv. (%)[b]	Yield (%)[b]
1		**1**		58	54
2		**4**		64	61
3		**6**		79	45
4		**7**		77	71
5		**8**		98	**85**
6	**11**	**9**	**22**	99	**85**
7		**1**		62	38
8		**4**		71	59
9		**8**		94	**78**
10	**12**	**9**	**23**	90	**78**
11		**1**		79	21
12		**4**		80	42
13		**8**		92	**77**
14	**13**	**9**	**24**	95	**76**

[a]Reaction conditions: Pd–NHC (0.01 mmol), aryl chloride (1 mmol), 2-acetyl-1-methylpyrrole (2 mmol), KOAc (2 mmol), DMAc (3 mL), 20 h, 150 °C. [b]Determined by GC and NMR.

Table 3: Direct arylation of methyl 1-methylpyrrole-2-carboxylate (**25**) with 4-chlorobenzonitrile (**11**).[a]



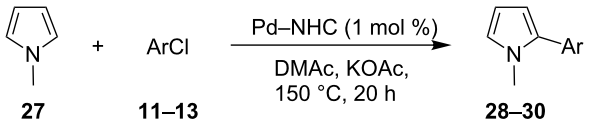
25 **11** **26**

Entry	Pd–NHC	Conv. (%)[b]	Yield (%)[b]
1	**1**	52	32
2	**2**	94	**78**
3	**4**	58	27
4	**5**	69	51
5	**6**	66	47
6	**7**	61	49
7	**8**	98	**83**
8	**9**	97	**81**

[a]Reaction conditions: Pd–NHC (0.01 mmol), 4-chlorobenzonitrile (**11**, 1 mmol), methyl 1-methylpyrrole-2-carboxylate (**25**, 2 mmol), KOAc (2 mmol), DMAc (3 mL), 20 h, 150 °C. [b]Determined by GC and NMR.

couplings remains unclear. However, the presence of bulky N-substituents on the benzimidazole ring, such as 3,5-di-*tert*-butylbenzyl (**1**–**4**) or benzhydryl (**8**), appears to be favorable; whereas, 2-(2-ethoxy)phenoxyethyl substituent (**5**–**7**) generally led to lower yields. The presence of a 2-(2-ethyl)-1,3-dioxalane as N-substituent (**9**) was also found to be profitable. To our knowledge, these are the first examples of direct arylations of pyrroles by using aryl chlorides as the coupling partners and Pd-N-heterocyclic carbene complexes as the catalyst. Finally, as the major by-products are AcOK associated to HBr instead of metallic salts, this procedure is environmentally more attractive than the classical coupling procedures.

Table 4: Direct arylation of 1-methylpyrrole (**27**) with chlorobenzene derivatives.[a]

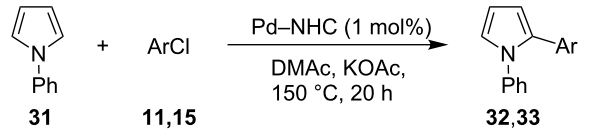


27 **11–13** **28–30**

Entry	ArCl	Pd–NHC	Product	Conv. (%)[b]	Yield (%)[b]
1		**1**		56	50
2		**4**		75	70
3	Cl–⟨⟩–CN	**6**	N–⟨⟩–CN	44	39
4		**7**		68	63
5	**11**	**8**	**28**	94	**83**
6		**9**		96	**90**
7		**1**		78	74
8		**4**		81	70
9	Cl, NC	**8**	N, NC	94	**88**
10	**12**	**9**	**29**	92	**83**
11		**2**		94	31
12		**3**		91	27
13	Cl–⟨⟩–CF_3	**4**	N–⟨⟩–CF_3	89	39
14		**8**		96	29
15	**13**	**9**	**30**	97	25

[a]Reaction conditions: Pd–NHC (0.01 mmol), aryl chloride (1 mmol), 1-methylpyrrole (**27**, 4 mmol), KOAc (2 mmol), DMAc (3 mL), 20 h, 150 °C.
[b]Determined by GC and NMR.

Table 5: Direct arylation of 1-phenylpyrrole (**31**) with chlorobenzene derivatives.[a]



31 **11,15** **32,33**

Entry	ArCl	Pd–NHC	Product	Conv. (%)[b]	Yield (%)[b]
1		**1**		81	71
2		**2**		90	85
3		**4**		80	73
4	Cl–⟨⟩–CN	**5**	N, Ph–⟨⟩–CN	85	79
5		**6**		86	74
6	**11**	**7**	**32**	87	81
7		**8**		98	**89**
8		**9**		98	**88**
9		**2**		87	55
10	Cl, O	**8**	N, Ph, O	92	86
11	**15**	**9**	**33**	99	76

[a]Reaction conditions: Pd–NHC (0.01 mmol), aryl chloride (1 mmol), 1-phenylpyrrole (**31**, 4 mmol), KOAc (2 mmol), DMAc (3 mL), 20 h, 150 °C.
[b]Determined by GC and NMR.

Experimental

The reaction of benzimidazolium halide (2 equiv) with $Pd(OAc)_2$ in DMSO according to Scheme 1 led to the formation of the desired complexes of Pd(II) in 53–87% yield. The crude product was recrystallized from a dichloromethane/diethyl ether mixture 1:3 at room temperature, which afforded

the corresponding crystals. The new complexes were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis techniques, which support the proposed structures.

As described in [49], the air and moisture-stable palladium-carbene complexes (**1–9**) were soluble in halogenated solvents and insoluble in nonpolar solvents. Palladium complexes exhibit a characteristic $\nu_{(NCN)}$ band typically at 1407–1477 cm^{-1}. The formation of the Pd–NHC complexes was confirmed by the absence of the ^{1}H NMR resonance signal of the acidic benzimidazolium C2–H. The ^{13}C NMR spectra of Pd–NHC complexes exhibit a resonance signal in the 181.2–183.6 ppm range ascribed to the carbenic carbon atom, which is consistent with the reported values for Pd–NHC complexes [43]. NMR data showed that complexes **2** and **4**–**7** were *cis*/*trans* mixtures.

General procedure for the preparation of the palladium–NHC complexes

As described in [50], to a solution of benzimidazolium salts (10 mmol) in DMSO (5 mL) was added palladium(II) diacetate (5 mmol) under argon, and the resulting mixture was stirred at room temperature for 2 h, then at 60 °C for 4 h, at 80 °C for 2 h and finally at 110 °C for 2 h. Volatiles were removed in vacuo, and the residue was washed twice with THF (5 mL). The complex was crystallized from dichloromethane/diethyl ether 1:3 at room temperature.

Dibromo-bis[1-(3,5-di-*tert*-butylbenzyl)-3-(2-methoxyethyl)benzimidazol-2-ylidene]palladium(II) (1): Yield: 0.29 g, 87%; mp 172–174 °C; ^{1}H NMR ($CDCl_3$, δ) 1.29 (t, J = 7.0 Hz, 4H, $NCH_2CH_2OCH_3$), 1.31 (t, J = 7.0 Hz, 4H, $NCH_2CH_2OCH_3$), 1.33 (s, 36H, $NCH_2C_6H_3(C(CH_3)_3$-3,5), 2.63 (s, 6H, $NCH_2CH_2OCH_3$), 5.10 (s, 4H, $NCH_2C_6H_3(C(CH_3)_3$-3,5)), 6.89–7.6 (m, 14H, NC_6H_4N and $NCH_2C_6H_3(C(CH_3)_3$-3,5)); ^{13}C NMR ($CDCl_3$, δ) 31.5 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 34.8 ($NCH_2C_6H_3(C(CH_3)_3$-3,5)), 35.0 ($NCH_2CH_2OCH_3$), 41.0 ($NCH_2C_6H_3(C(CH_3)_3$-3,5)), 48.3 ($NCH_2CH_2OCH_3$), 58.8 ($NCH_2C_6H_3(C(CH_3)_3$-3,5)), 111.1, 111.2, 121.7, 122.3, 122.7, 122.9, 134.2, 134.6, 151.1, 151.3 (NC_6H_4N and $NCH_2C_6H_3$-$(C(CH_3)_3$-3,5)), 183.6 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1407; Anal. calcd for $C_{50}H_{68}N_4PdBr_2$: C, 60.58; H, 6.91; N, 5.65; found: C, 60.47; H, 6.94; N, 5.63.

***cis/trans*-Dibromo-bis[1-(3,5-di-*tert*-butylbenzyl)-3-(3,4,5-trimethoxybenzyl)benzimidazol-2-ylidene]palladium(II) (2):** Yield: 0.29 g, 87%; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, δ) 1.16, 1.21 (s, 36H, $NCH_2C_6H_3(C(CH_3)_3$-3,5), 3.66, 3.80, 3.81, 3.86 (s, 18 H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5), 5.32, 5.37 (s, 4H, $NCH_2C_6H_3(C(CH_3)_3$-3,5), 5.74, 5.79 (s, 4H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5), 6.09–7.39 (m, 18H, NC_6H_4N, $NCH_2C_6H_3(C(CH_3)_3$-3,5 and $NCH_2C_6H_2(OCH_3)_3$-3,4,5); ^{13}C NMR ($CDCl_3$, δ) 31.2, 31.3 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 31.4, 31.7, 34.7, 34.8 ($NCH_2C_6H_2(OCH_3)_3$-3,4,5), 41.0, 41.1 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 53.2, 53.9 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 56.3, 56.4 ($NCH_2C_6H_2(OCH_3)_3$-3,4,5), 104.4, 104.8, 111.8, 112.4, 121.1, 121.3, 123.4, 129.9, 130.4, 133.1, 133.5, 133.9, 134.3, 134.4, 134.7, 137.7, 151.2, 151.5, 153.5, 153.7 (NC_6H_4N, $NCH_2C_6H_3(C(CH_3)_3$-3,5 and $NCH_2C_6H_2(OCH_3)_3$-3,4,5), 181.2 and 182.3 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1447; Anal. calcd for $C_{64}H_{80}N_4O_6PdBr_2$: C, 60.64; H, 6.36; N, 4.42; found: C, 60.57; H, 6.54; N, 4.45.

Dibromo-bis[1,3-bis(3,5-di-*tert*-butylbenzyl)benzimidazol-2-ylidene]palladium(II) (3): Yield: 0.27 g, 82%; mp 248–250 °C; ^{1}H NMR ($CDCl_3$, δ) 1.18 (s, 72H, $NCH_2C_6H_3(C(CH_3)_3)$-3,5), 5.80 (s, 8H, $NCH_2C_6H_3(C(CH_3)_3$-3,5), 6.14–7.48 (m, 20H, NC_6H_4N and $NCH_2C_6H_3(C(CH_3)_3$-3,5); ^{13}C NMR ($CDCl_3$, δ) 31.4 ($NCH_2C_6H_3(C(CH_3)_3)$-3,5), 41.02 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 53.9 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 111.6, 112.2, 121.3, 121.5, 122.3, 122.8, 133.4, 134.4, 134.6, 151.1, 151.2 (NC_6H_4N and $NCH_2C_6H_3(C(CH_3)_3$-3,5)), 182.5 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1477; Anal. calcd for $C_{74}H_{100}N_4PdBr_2$: C, 67.75; H, 7.68; N, 4.27; found: C, 67.72; H, 7.64; N, 4.27.

***cis/trans*-Dichloro-bis[1-(3,5-di-*tert*-butylbenzyl)-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazol-2-ylidene]palladium(II) (4):** Yield: 0.27 g, 82%; mp 310–312 °C; ^{1}H NMR ($CDCl_3$, δ) 1.27, 1.29 (s, 36 H, $NCH_2C_6H_3(C(CH_3)_3$-3,5)), 2.20, 2.23, 2.24, 2.29, 2.30, 2.34 (s, 30H, $NCH_2C_6(CH_3)_5$-2,3,4,5,6), 5.30 and 5.40 (s, 4H, $NCH_2C_6(CH_3)_5$-2,3,4,5,6), 5.53, 5.54 (s, 4H, $NCH_2C_6H_3(C(CH_3)_3$-3,5)), 6.04–7.55 (m, 14H, NC_6H_4N and $NCH_2C_6H_3(C(CH_3)_3$-3,5)); ^{13}C NMR ($CDCl_3$, δ) 31.3, 31.4 ($NCH_2C_6H_3(C(CH_3)_3$-3,5), 41.0, 41.1 ($NCH_2C_6H_3(C(CH_3)_3$-3,5)), 17.1, 17.2, 17.3, 17.6, 17.7, 17.8 ($NCH_2C_6(CH_3)_5$-2,3,4,5,6), 51.2, 51.3 ($NCH_2C_6(CH_3)_5$-2,3,4,5,6), 51.5, 51.6 ($NCH_2C_6H_3(C(CH_3)_3$-3,5)), 111.2, 111.4, 111.8, 121.3, 121.5, 122.0, 122.5, 122.7, 122.8, 128.5, 128.6, 132.9, 133.0, 134.3, 134.4, 134.5, 134.6, 134.8, 134.9, 135.1, 151.0, 151.1 (NC_6H_4N and $NCH_2C_6H_3(C(CH_3)_3$-3,5)), 182.4, 182.5 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1451; Anal. calcd for $C_{68}H_{84}N_4PdCl_2$: C, 71.97; H, 7.46; N, 4.94; found: C, 71.92; H, 7.64; N, 4.97.

***cis/trans*-Dibromo-bis[1-(2,4,6-trimethylbenzyl)-3-(2-(2-ethoxy)phenoxyethyl)benzimidazol-2-ylidene]palladium(II) (5):** Yield: 0.33 g; 81%; mp 238–240 °C; ^{1}H NMR ($CDCl_3$, δ) 1.23, 1.39 (t, J = 7.0 Hz, 6H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 2.29, 2.34, 2.35, 2.36 (s, 18H, $NCH_2C_6H_2(CH_3)$-2,4,6), 3.89, 4.01 (q, J = 7.0 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 4.81, 4.83 (t, J = 5.9 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 5.39, 5.41 (t, J = 5.9, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 6.03, 6.13 (s, 4H, $NCH_2C_6H_2(CH_3)$-2,4,6), 6.80–7.77 (m, 20H, NC_6H_4N,

NCH_2CH_2-$OC_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_2(CH_3)$-2,4,6); ^{13}C NMR ($CDCl_3$, δ) 15.1, 15.3 ($NCH_2CH_2OC_6H_4$-(OCH_2CH_3)-2), 21.0, 21.1, 21.2, 21.3 ($NCH_2C_6H_2(CH_3)$-2,4,6), 48.0, 48.1 ($NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 50.1, 50.6 ($NCH_2CH_2O$-$C_6H_4(OCH_2CH_3)$-2), 64.0, 64.1 ($NCH_2CH_2O$-$C_6H_4(OCH_2CH_3)$-2), 67.8, 67.9 ($NCH_2C_6H_2(CH_3)$-2,4,6), 111.3, 111.5, 112.8, 113.3, 120.7, 120.9, 121.4, 122.9, 128.0, 129.4, 129.6, 134.6, 135.7, 138.4, 138.6, 138.9, 148.0, 148.5, 148.6 ($NC_6H_4NNCH_2CH_2$-$OC_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_2(CH_3)$-2,4,6), 182.2, 182.3 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1448; Anal. calcd for $C_{54}H_{60}N_4O_4PdBr_2$: C, 59.21; H, 5.52; N, 5.12; found: C, 59.27; H, 5.54; N, 5.13.

***cis/trans*-Dichloro-bis[1-(2-(2-ethoxy)phenoxyethyl)-3-(4-methylbenzyl)benzimidazol-2-ylidene] palladium(II) (6):** Yield: 0.32 g, 66%; mp 235–237 °C; ^1H NMR ($CDCl_3$, δ) 1.43, 1.45 (t, J = 6.9 Hz, 6H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 2.29, 2.35 (s, 6H, $NCH_2C_6H_4(CH_3)$-4), 3.98, 4.03 (q, J = 7.0 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 4.57, 4.82 (t, J = 5.0 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 5.27, 5.42 (t, J = 5.0 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 5.97, 6.15 (s, 4H, $NCH_2C_6H_4(CH_3)$-4), 6.68–8.56 (m, 24H, NC_6H_4N, NCH_2CH_2O-$C_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_4(CH_3)$-4); ^{13}C NMR ($CDCl_3$, δ) 15.0, 15.1 ($NCH_2CH_2OC_6H_4$-(OCH_2CH_3)-2), 21.1, 21.2 ($NCH_2C_6H_4(CH_3)$-4), 48.1, 48.3 ($NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 52.1, 52.2 ($NCH_2CH_2O$-$C_6H_4(OCH_2CH_3)$-2), 64.0, 64.1 ($NCH_2CH_2OC_6H_4$-$(OCH_2CH_3)$-2), 68.3, 68.6 ($NCH_2C_6H_4(CH_3)$-4), 110.8, 111.1, 112.2, 112.8, 113.1, 120.7, 120.9, 121.2, 123.0, 123.1, 127.6, 127.7, 127.8, 129.3, 129.5, 132.6, 134.1, 135.6, 137.4, 137.6, 148.0, 148.4, 148.6 ($NC_6H_4NNCH_2CH_2O$-$C_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_4(CH_3)$-4), 182.0, 182.1 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1407; Anal. calcd for $C_{50}H_{52}N_4O_4PdCl_2$: C, 63.19; H, 5.52; N, 5.90; found: C, 63.18; H, 5.50; N, 5.93.

***cis/trans*-Dichloro-bis[1-(2-(2-ethoxy)phenoxyethyl)-3-(3-methoxybenzyl)benzimidazo-2-ylidene]palladium(II) (7):** Yield: 0.22 g, 53%; mp 205–207 °C; ^1H NMR ($CDCl_3$, δ) 1.43, 1.45 (t, J = 7.0 Hz, 6H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 3.66, 3.75 (s, 6H, $NCH_2C_6H_4(OCH_3)$-3), 3.97, 4.03 (q, J = 7.0 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2)), 4.60, 4.83 (t, J = 5.6 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 5.29, 5.43 (t, J = 5.7 Hz, 4H, $NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 6.01, 6.18 (s, 4H, $NCH_2C_6H_4(OCH_3)$-3), 6.67–7.86 (m, 24H, NC_6H_4N, NCH_2CH_2O-$C_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_4(OCH_3)$-3); ^{13}C NMR ($CDCl_3$, δ) 15.0, 15.3 ($NCH_2CH_2OC_6H_4$-(OCH_2CH_3)-2), 48.0, 48.3 ($NCH_2CH_2OC_6H_4(OCH_2CH_3)$-2), 52.3, 52.4 ($NCH_2C_6H_4(OCH_3)$-3), 55.5, 55.7 ($NCH_2CH_2O$-$C_6H_4(OCH_2CH_3)$-2), 63.9, 64.0 ($NCH_2CH_2OC_6H_4$-$(OCH_2CH_3)$-2), 68.3, 68.6 ($NCH_2C_6H_4(OCH_3)$-3), 112.3, 113.1, 114.7, 120.0, 120.7, 120.9, 123.1, 123.2, 129.8, 134.0, 134.1, 135.6, 137.0, 137.3, 148.0, 148.4, 160.0, 160.3 (NC_6H_4N NCH_2CH_2O-$C_6H_4(OCH_2CH_3)$-2, $NCH_2C_6H_4(OCH_3)$-3), 182.0, 182.2 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1444; Anal. calcd for $C_{50}H_{52}N_4O_6PdCl_2$: C, 61.14; H, 5.34; N, 5.70; found: C, 61.21; H, 5.37; N, 5.73.

Dibromo-bis[1-(3-methylbenzyl)-3-(benzhydryl)]benzimidazol-2-ylidene]palladium(II) (8): Yield: 0.35 g, 60%; mp 230–232 °C; ^1H NMR ($CDCl_3$, δ) 2.12 (3-$CH_3C_6H_5$), 5.72 (s, 2H, (3-CH_3)(C_6H_5)-CH_2), 6.74–7.79 (m, 19H, $CH(C_6H_5)_2$, C_6H_4 and 3-$CH_3C_6H_5$); ^{13}C NMR ($CDCl_3$, δ) 21.3 (3-(CH_3)(C_6H_5)), 52.0 (3-(CH_3)(C_6H_5)-CH_2), 67.5 ($CH(C_6H_5)$, 112.4, 123.6, 125.5, 128.6, 128.7, 128.9, 129.1, 133.4, 133.8, 134.9, 135.9, 136.1, 137.6, 138.0, 138.2, 138.4 (3-(CH_3)(C_6H_5), $CH(C_6H_5)$ and C_6H_4), 183.5 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1412; Anal. calcd for $C_{56}H_{46}N_4Br_2Pd$: C, 64.60; H, 4.45; N, 5.38; found: C, 64.58; H, 4.49; N, 5.46.

Dibromo-bis[1-(benzyl)-3-(2-(2-ethyl)-1,3-dioxalane)]benzimidazol-2-ylidene]palladium(II) (9): Yield: 0.31 g, 62%; mp 282–284 °C; ^1H NMR ($CDCl_3$, δ) 2.27 (m, 2H, NCH_2CH_2CH), 3.83 and 3.99 (t, 4H, J = 6.6 Hz, $NCH_2CH_2CHO_2CH_2CH_2$), 5.01 (m, 3H, NCH_2CH_2CH and NCH_2CH_2CH), 6.01 (s, 2H, (C_6H_5)-CH_2), 7.0–7.92 (m, 9H, (C_6H_5)CH_2 and C_6H_4); ^{13}C NMR ($CDCl_3$, δ) 33.7 (NCH_2CH_2CH), 40.8 (NCH_2CH_2CH), 64.9 ($NCH_2CH_2CHO_2CH_2CH_2$), 101.6 ($NCH_2CH_2CHO_2CH_2CH_2$), 101.9, 111.3, 112.2, 123.7, 128.3, 128.5, 128.8, 128.9, 133.9, 134.4, 136.6 ($C_6H_5CH_2$ and C_6H_4), 181.7 (Pd-$C_{carbene}$); IR (cm^{-1}) $\nu_{(CN)}$: 1408; Anal. calcd for $C_{38}H_{40}O_4N_4PdBr_2$: C, 51.69; H, 4.57; N, 6.35; found: C, 51.60; H, 4.61; N, 6.37.

General Procedure for direct arylations

As described in [47], in a typical experiment, the aryl chloride (1 mmol), heteroaryl derivative (2 or 4 mmol) (see Table 1–5) and KOAc (2 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. The Pd complex (0.01 mmol, see Table 1–5) and DMAc (3 mL) were added, and the Schlenk tube was purged several times with argon. The Schlenk tube was placed in a preheated oil bath at 150 °C, and the reaction mixture was stirred for 20 h. Then, the reaction mixture was analysed by gas chromatography to determine the conversion of the aryl chloride. The solvent was removed by heating of the reaction vessel under vacuum and the residue was charged directly onto a silica-gel column. The products were eluted by using an appropriate ratio of diethyl ether and pentane.

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Complete σ* intramolecular aromatic hydroxylation mechanism through O_2 activation by a Schiff base macrocyclic dicopper(I) complex

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Full Research Paper

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Abstract

In this work we analyze the whole molecular mechanism for intramolecular aromatic hydroxylation through O_2 activation by a Schiff hexaazamacrocyclic dicopper(I) complex, $[Cu^I_2(bsH2m)]^{2+}$. Assisted by DFT calculations, we unravel the reaction pathway for the overall intramolecular aromatic hydroxylation, i.e., from the initial O_2 reaction with the dicopper(I) species to first form a Cu^ICu^{II}-superoxo species, the subsequent reaction with the second Cu^I center to form a μ-η^2:η^2-peroxo-Cu^{II}_2 intermediate, the concerted peroxide O–O bond cleavage and C–O bond formation, followed finally by a proton transfer to an alpha aromatic carbon that immediately yields the product $[Cu^{II}_2(bsH2m\text{-}O)(\mu\text{-}OH)]^{2+}$.

Introduction

Bearing in mind the key role of dioxygen in biology, in particular toward Cu and Fe metal centers, being involved in the catalytic cycle of proteins, including dinuclear copper-active sites, such as hemocyanin, tyrosinase and catechol oxidases [1-7], either transporting or activating O_2, its comprehension is still underway. Efforts in biomimetics have been made to understand the interaction of such prototypical metalloenzymes with dinuclear Cu^I complexes with molecular O_2 [8-10], in particular by modifying the nature of the ligands bonded to the metals [11-14]. On the other hand, a hot topic is still to unravel, either experimentally or by calculations, which of the side-on μ-η^2:η^2-peroxo and bis(μ-oxo) isomeric $Cu_2O_2^{2+}$ cores are present, and in the case that they exist, to study the feasibility of their interconversion [15-19], tuning either the metallic complex or the reaction conditions [20-23]. Moreover, both $Cu_2O_2^{2+}$ cores have been proposed to be the active species in the aromatic hydroxylation process. Indeed, this question still remains controversial [24-26].

Among the recent studies in the field of oxidation of Cu systems, tyrosinase model systems that selectively produce aromatic hydroxylation products [27-32] and methane monooxygenase (MMO) models that yield stable aliphatic hydroxylation compounds [33,34] are the subject of interest, and both aliphatic and aromatic hydroxylations have been analyzed theoretically. In particular, there are detailed studies of pMMO complexes [35,36], showing why they are suitable for the conversion of methane to methanol [37]. On the other hand, several theoretical studies have analyzed the inter- and intramolecular hydroxylation of aromatic rings [38-46]. Most of these studies agree that the aromatic hydroxylation takes place through a peroxo group side-on to the Cu_2O_2 core.

Although from the hexaazamacrocyclic dinuclear Cu^I complex $[Cu^I_2(bsH2m)]^{2+}$ (**a**) [14] the μ-phenoxo-μ-hydroxo product $[Cu^{II}_2(bsH2m\text{-}O)(\mu\text{-}OH)]^{2+}$ (**g**) was characterized experimentally, it was not possible to trap or detect any intermediate in the path from **a** + O_2 → **g**. Here, by means of density functional theory (DFT) calculations, we search for the whole reaction pathway (Figure 1). The results are compared with those obtained in a similar previous study in which the hexaazamacrocyclic ligand used (H3m) was more flexible [40]. Crystallographic data on related copper compounds by using the same ligand suggest that complex **a** may present many conformations of rather similar energy [47]; however, the optimized geometries of similar complexes was found to be in perfect agreement with the X-ray structures [40,48-56].

Computational details

All geometry optimizations, as described in [40], were performed with the Gaussian03 package [57], by using the B3LYP functional [58-60] and the standard 6-31G(d) basis set [61,62]. The geometries obtained at the B3LYP/6-31G(d) level were used to perform single-point energy calculations with a larger basis set, the 6-311G(d,p) basis set [63], and the same functional (B3LYP/6-311G(d,p)//B3LYP/6-31G(d)). Intrinsic reaction pathways were calculated to confirm that the located transition states connected the expected minima. Analytical Hessians were computed to determine the nature of all the stationary points we located, and to calculate zero-point energies (ZPEs) and thermodynamic properties at 298 K.

For open-shell states, the geometry optimizations were performed within the broken-symmetry unrestricted methodology, while for the closed-shell singlet states the restricted

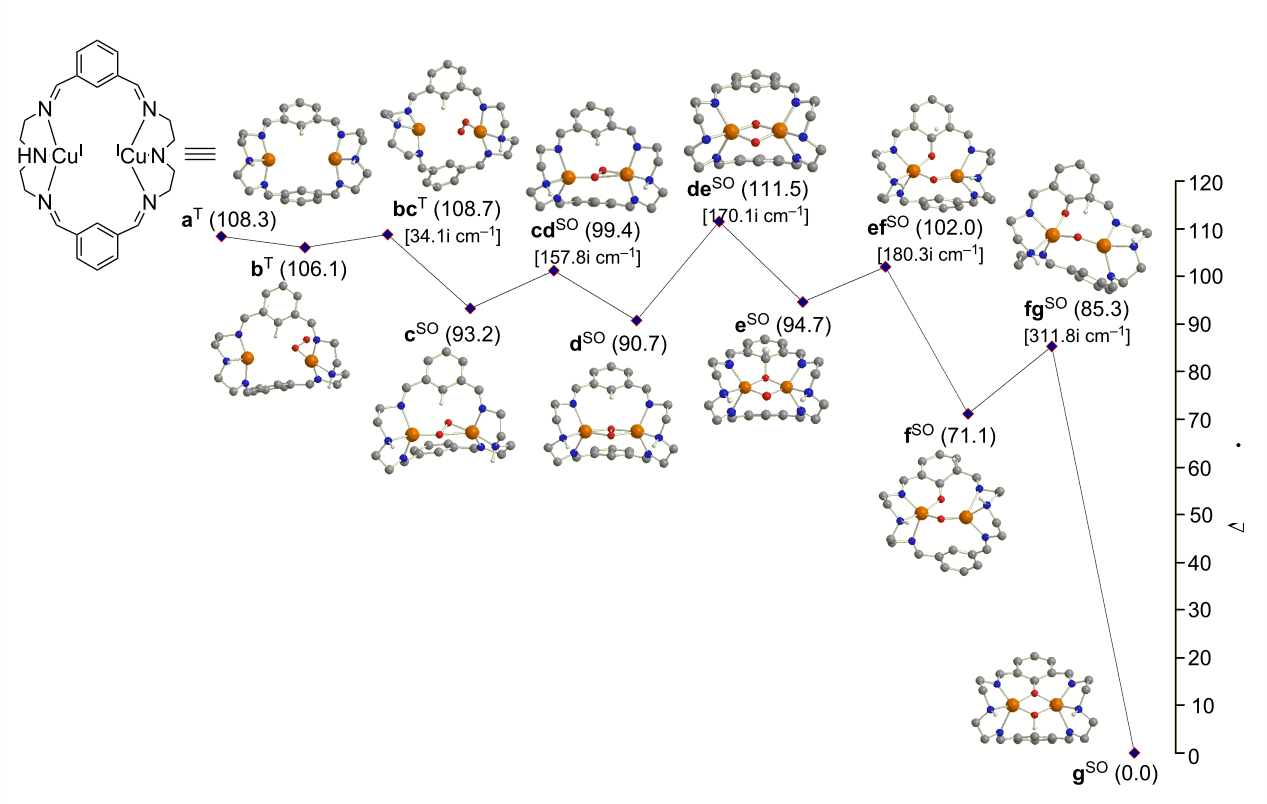


Figure 1: Stationary points located along the reaction path of the aromatic hydroxylation mechanism (some H atoms omitted for clarity). Gibbs energies relative to the product (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindexes SO (open-shell singlet) and T (triplet) refer to the multiplicity of the ground state.

formalism was used. Theoretical treatment of biradical singlet species requires multiconfigurational or multireference methods due to strong static electron correlation. Unfortunately, these methods can only be applied to relatively small systems because computationally they are extremely demanding. As an alternative, we have used the unrestricted UB3LYP method in broken symmetry (BS, using GUESS = MIX) [64]. This method improves the modeling of biradical singlet states at the expense of introducing some spin contamination from higher spin states [65-73].

Solvent effects including contributions of non-electrostatic terms have been estimated in single-point calculations on the gas-phase-optimized structures, based on the polarizable continuous solvation model (PCM) with CH_3CN as a solvent [74,75], i.e., the same solvent used experimentally.

The relative Gibbs energies reported in this work include energies computed using the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) method together with solvent effects obtained at the B3LYP/6-31G(d) level, and zero-point energies, thermal corrections, and entropy effects calculated at 298 K with the B3LYP/6-31G(d) method.

Results and Discussion

Bearing in mind the easy transformation of **a** to **g**, done at low temperature and atmospheric pressure [14], the coordination of O_2 gives as a result the formation of a Cu^ICu^{II}-superoxo species **b** switching the singlet ground state to a triplet, in a barrierless process checked by means of several reaction coordinate linear transits between one or both oxygen atoms and the Cu atoms. The rotation of about 180° of the O_2 moiety in order to facilitate that the non-bonded oxygen atom points towards the still free Cu atom costs just 2.6 kcal·mol^{-1}, evolving to the μ-η^1:η^2-peroxo isomer **c** with an energetic stabilization of 12.9 kcal·mol^{-1} with respect to the preceding complex **b**. Furthermore, this step also requires change to a biradical singlet ground state, although the triplet state is only 1 kcal·mol^{-1} higher as a result of the long distance between both Cu atoms that allocate both unpaired electrons [76,77]. To achieve the μ-η^2:η^2-peroxo-Cu^{II}_2 isomer **d** only the formation of Cu–O is necessary, the later step having a barrier of 6.2 kcal·mol^{-1} to overcome. Before the formation of this peroxo intermediate **d** the side-on Cu^ICu^{II}-superoxo isomeric species was not located, probably due the higher rigidity that is imposed by the Schiff bases bsH2m with respect to the similar, previously described system H3m [40].

The two possible routes from **d** to **e** (C–O bond formation) corresponding to the attacks on the two phenyl rings are basically identical, and consequently, only one of them has been analyzed. This step leads to the cleavage of the O–O bond and consists of a direct and concerted attack on the closest carbon atom of the aromatic ring to form species **e** through a barrier of 20.8 kcal·mol^{-1}. In an alternative route in Figure 2, the μ-η^2:η^2-peroxo-Cu^{II}_2 intermediate **d** might evolve first to the closed-shell singlet bis(μ-oxo)-Cu^{III}_2 isomer (**h**), but this bis(μ-oxo) species is 20.0 kcal·mol^{-1} higher in energy with respect to the peroxo form [40]. Apart from the high instability with respect to the peroxo intermediate, from **d** it is necessary to overcome a barrier of 22.3 kcal·mol^{-1}, which rules out the role of **h** in the reaction pathway **a**→**g**. However, as reported by Cramer [11,12,78], it is necessary to point out that the equilibrium μ-η^2:η^2-peroxo/bis(μ-oxo) is artificially displaced towards the peroxo species by hybrid functionals, such as the B3LYP functional, due to unbalanced correlation corrections [11,12]. In spite of that, previous calculations agree in considering that the μ-η^2:η^2-peroxo species is the active species in the hydroxylation process studied here [38-40,79,80].

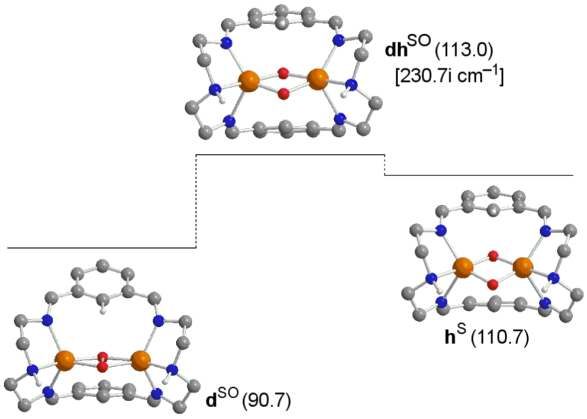


Figure 2: Computed structures of the potential equilibrium between the peroxo and bis-μ-oxo intermediates (some H atoms omitted for clarity). Gibbs energies relative to product **g** (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindexes SO (open-shell singlet) and S (closed-shell singlet) refer to the multiplicity of the ground state.

This step from **d** to **e** corresponds to the beginning of the so-called σ* electrophilic mechanism described for *ortho*-hydroxylation towards phenolate [5]. It is worth noting that in the next reaction step, the aromatic H atom in the activated C–H bond of **e** is transferred as a proton to one neighboring aromatic carbon. Amazingly this step requires only 7.3 kcal·mol^{-1}. It is necessary to point out that this small barrier comes in part from the breaking of the nearest Cu–O to this proton, which facilitates the electronic arrangement. Finally, overcoming a barrier of 14.2 kcal·mol^{-1} the product is reached when transferring the proton to the other oxygen and rebuilding the broken Cu–O bond.

There are different parallel reactions and competitive intermediates that might be present in the reaction pathway. In Figure 3 the **f**→**g** step is compared with the migration of the hydrogen to the nearest nitrogen first, and then this nitrogen atom easily throws it to the oxygen bonded to the aromatic ring overcoming a barrier of 2.8 kcal·mol^{-1} in the **i**→**g** step. However, the upper barrier of 27.3 kcal·mol^{-1} of the step **f**→**i** in the **f**→**g** process in Figure 3 must be compared to 14.2 kcal·mol^{-1} of step **f**→**g** in Figure 1. Thus the migration to the nitrogen atom first is discarded.

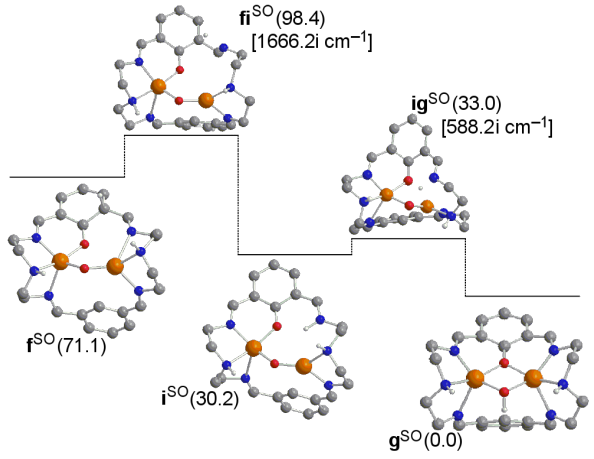


Figure 3: Computed structures for a potential alternative pathway **f**→**g** of the σ* mechanism (some H atoms omitted for clarity). Gibbs energies relative to product **g** (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindex SO (open-shell singlet) refers to the multiplicity of the ground state.

In Figure 4, from species **e** the donation of the hydrogen atom to the oxygen bonded to the aromatic carbon would be possible through a barrier of 25.2 kcal·mol^{-1}, thus extremely disfavored with respect to 7.3 kcal·mol^{-1} when migrating this hydrogen to one alpha aromatic carbon in the **e**→**f** step in Figure 1. Then, if this alternative mechanism is taken into account, the subsequent formation of the product from intermediate **j** requires 11.8 kcal·mol^{-1}. However, in Figure 5 it is shown that species **j** can evolve towards species **i** overcoming a negligible barrier of 0.2 kcal·mol^{-1}. From the Gibbs energies obtained in these alternative pathways, one can conclude that the role played by species **i** and **j** in the whole reaction mechanism is irrelevant.

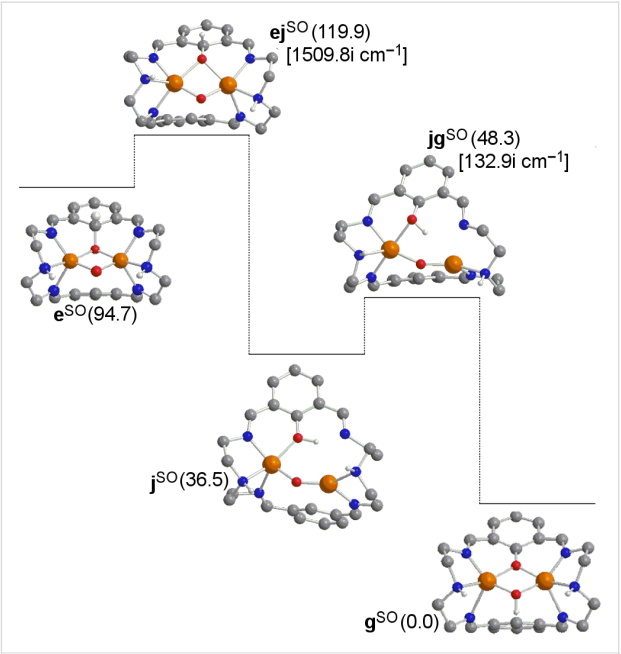


Figure 4: Computed structures for a potential alternative pathway **e**→**g** of the σ* mechanism (some H atoms omitted for clarity). Gibbs energies relative to product **g** (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindexes SO (open-shell singlet) and T (triplet) refer to the multiplicity of the ground state.

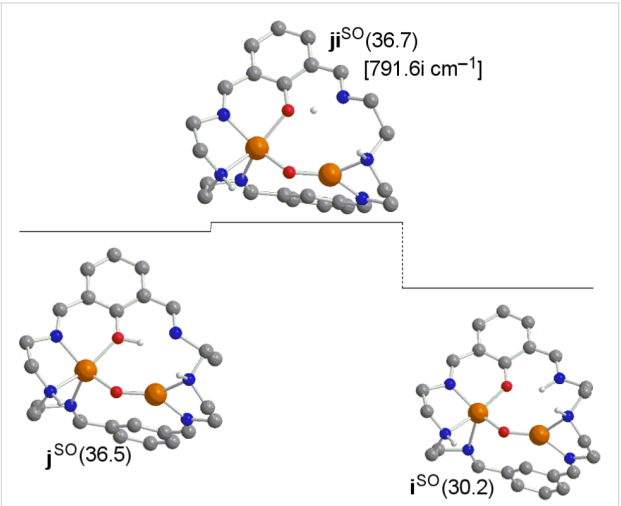


Figure 5: Computed structures for a potential alternative pathway **j**→**i** of the σ* mechanism (Gibbs energies in kcal·mol^{-1}). Superindex SO (open-shell singlet) refers to the multiplicity of the ground state.

After the formation of the C–O bond in species **e**, the previously described ligand H3m showed that the other aromatic ring could assist the aromatic proton transfer to the nearer oxygen atom with an upper barrier of only 1.4 kcal·mol^{-1} [40]. However, for bsH2m the distance between the two aromatic rings is always too large for them to help each other. Indeed bsH2m is significantly more rigid, and this factor reduces the degrees of free rotation. However, the upper barrier for bsH2m is only 7.3 kcal·mol^{-1}. Thus, the most favored mechanism might change depending on the nature of the chains between the N atoms of the hexaaza ligand. However, the affinity of the peroxo species **d** to interact with either of the aromatic rings is the key factor that decides whether the intramolecular hydroxylation will take place or not [13-26].

Indeed, intermediates found here are also very different from those found in an aliphatic hydroxylation reaction studied by Holthausen [39]. Thus, in terms of comparison, to broaden the scope of this study, in Figure 6 the study of a different mechanism starting from species **b** was envisaged. Intermediate **l** represents a valid option as a potential reactive intermediate for the direct attack to the aromatic ring by one of the oxygen atoms. The formation of **l** requires that a barrier of only 2.6 kcal·mol^{-1} higher in energy with respect to the formation of species **c** be overcome. And species **l** is 2.0 kcal·mol^{-1} less stable with respect to species **c**. However, although species **l** needs to overcome a barrier of only 11.0 kcal·mol^{-1} to create a C–O bond after the interaction of an oxygen atom with an aromatic ring, the upper barrier from species **b** to the product **g** requires 43.6 kcal·mol^{-1}, which is 38.2 kcal·mol^{-1} higher than the upper barrier of the reaction pathway in Figure 1. Thus, the aliphatic hydroxylation scheme is not reproducible here, and thus we can confirm that the aromatic rings play a key role in intramolecular aromatic hydroxylation reactions through O_2 activation.

In Figure 7 the attack on the aromatic ring from species **c** instead of species **d** is displayed. This alternative mechanism reveals an upper energy barrier of 24.5 kcal·mol^{-1} instead of the 18.3 kcal·mol^{-1} described in the mechanism in Figure 1. Thus, the reactivity towards the aromatic rings of the intermediate trans-peroxo (**c**) is worse with respect to the intermediate with a peroxo core (**d**). Finally, comparison of the Gibbs energy profiles of Figure 1 in the present work with those in reference [40], show that energy barriers present in the H3m reaction mechanism [40] are somewhat lower than those found in the more rigid bsH2m ligand, and therefore, the $[Cu^{I}_2(H3m)]^{2+}$ catalyst is expected to be slightly more efficient than the $[Cu^{I}_2(bsH2m)]^{2+}$ one.

Bearing in mind that Mayer Bond Order (MBO) theory gives insight into the strength of the bonds [81-89], MBOs between two atoms A and B were calculated through Equation 1 [90,91], where S is the atomic orbital overlap matrix and P is the density matrix. The sums run over the basis set functions belonging to a given atom A or B.

$$B_{AB}=2\sum_{\mu\in A}\sum_{\upsilon\in B}\left[\left(P^{\alpha}S\right)_{\mu\upsilon}\left(P^{\alpha}S\right)_{\upsilon\mu}+\left(P^{\beta}S\right)_{\mu\upsilon}\left(P^{\beta}S\right)_{\upsilon\mu}\right] \quad (1)$$

A first glance at Table 1 shows that the in study of the **d**→**e** step in complexes containing bsH2m and H3m ligands, the MBOs are quite similar. There is a slight difference between the MBOs of the new O–C bond in **e** in the transition state **de**, with values of 0.069 and 0.122 for the $[Cu^{I}_2(bsH2m)]^{2+}$ and $[Cu^{I}_2(H3m)]^{2+}$ systems, respectively. This might help to explain why the

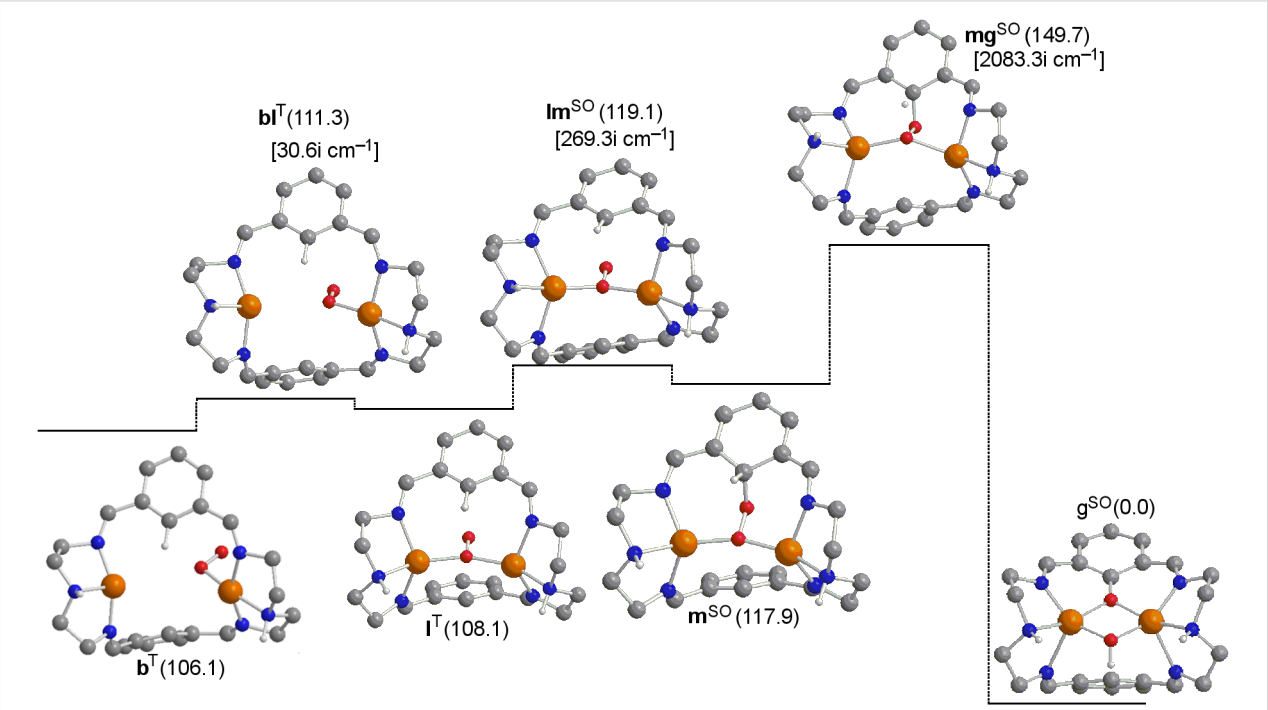


Figure 6: Computed structures for a potential alternative pathway **b**→**g** of the σ* mechanism (some H atoms omitted for clarity). Gibbs energies relative to product **g** (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindexes SO (open-shell singlet) and T (triplet) refer to the multiplicity of the ground state.

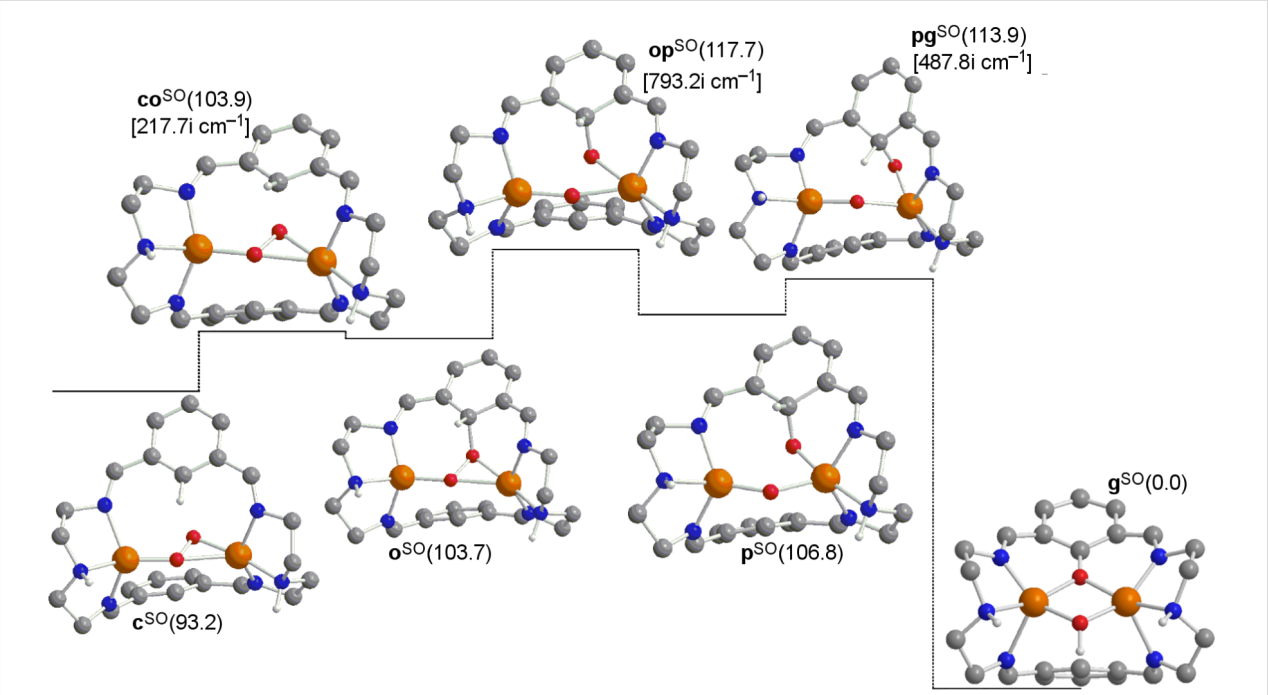


Figure 7: Computed structures for a potential alternative pathway **c**→**g** of the σ* mechanism (some H atoms omitted for clarity). Gibbs energies relative to product **g** (in kcal·mol^{-1}) in solution are given in parentheses. Calculated imaginary frequencies for transition structures are given in brackets. Superindex SO (open-shell singlet) refers to the multiplicity of the ground state.

Table 1: MBOs for **d**→**e** step for the $[Cu^{I}_2(H3m)]^{2+}$ and the $[Cu^{I}_2(bsH2m)]^{2+}$ catalysts.

	Intermediate	Cu1–O1	Cu1–O2	Cu2–O1	Cu2–O2	O1–O2	O2–C
$[Cu^{I}_2(bsH2m)]^{2+}$	**d**	0.401	0.382	0.403	0.382	0.889	0.015
	de	0.644	0.629	0.684	0.657	0.416	0.069
	e	0.558	0.386	0.801	0.462	0.027	0.856
$[Cu^{I}_2(H3m)]^{2+}$	**d**	0.391	0.378	0.391	0.379	0.878	0.017
	de	0.640	0.678	0.640	0.678	0.412	0.122
	e	0.505	0.822	0.395	0.614	0.040	0.843

barrier for the $[Cu^{I}_2(H3m)]^{2+}$ system is lower than for $[Cu^{I}_2(bsH2m)]^{2+}$ by 8.8 kcal·mol^{-1}. However, the differences between the MBOs are small, but this study of the MBOs is not meaningless because it confirms that structurally both systems are similar. On the other hand, to explain the **d**→**e** step the O···C distance in the peroxo intermediate **d** is key, being 2.601 Å for $[Cu^{I}_2(bsH2m)]^{2+}$ but 2.350 Å for $[Cu^{I}_2(H3m)]^{2+}$, which explains why for the latter system the energy barrier for the **d**→**e** step is lower. Indeed, for the $Cu^{I}_2(bsH2m)]^{2+}$ system this step displays the upper barrier of the overall reaction pathway **a**→**g**.

Conclusion

To sum up, the intramolecular hydroxylation of a Schiff base hexaazamacrocyclic dicopper(I) complex (**a**) by means of O_2 to finally yield the μ-phenoxo-μ-hydroxo product (**g**) occurs thanks to a σ*-mechanism that proceeds through a μ-η^2:η^2-peroxo species. Bearing in mind the DFT calculations for the full reaction pathway, it is feasible to explain why it is difficult to characterize experimentally any intermediate, particularly for two reasons: first the lack of high energy barriers, and second the cascade of the energy decay to the product. Furthermore, we provide a detailed analysis of potential alternative reaction pathways to reach product (**g**) [40]; however, these different explored paths between intermediates, in all cases, involve higher energy barriers or are not feasible. Finally, comparison of the reaction mechanisms involving hexaazamacrocyclic bsH2m and H3m ligands indicates that the energy barriers present in the H3m reaction mechanism are somewhat lower than those found in the more rigid bsH2m ligand.

Supporting Information

Supporting Information File 1

Complete computational methods used and xyz coordinates; ChemDraw and full 3D drawings of all stationary points found.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-63-S1.pdf]

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