Directing Groups

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A Simple and Versatile Amide Directing Group for C–H Functionalizations

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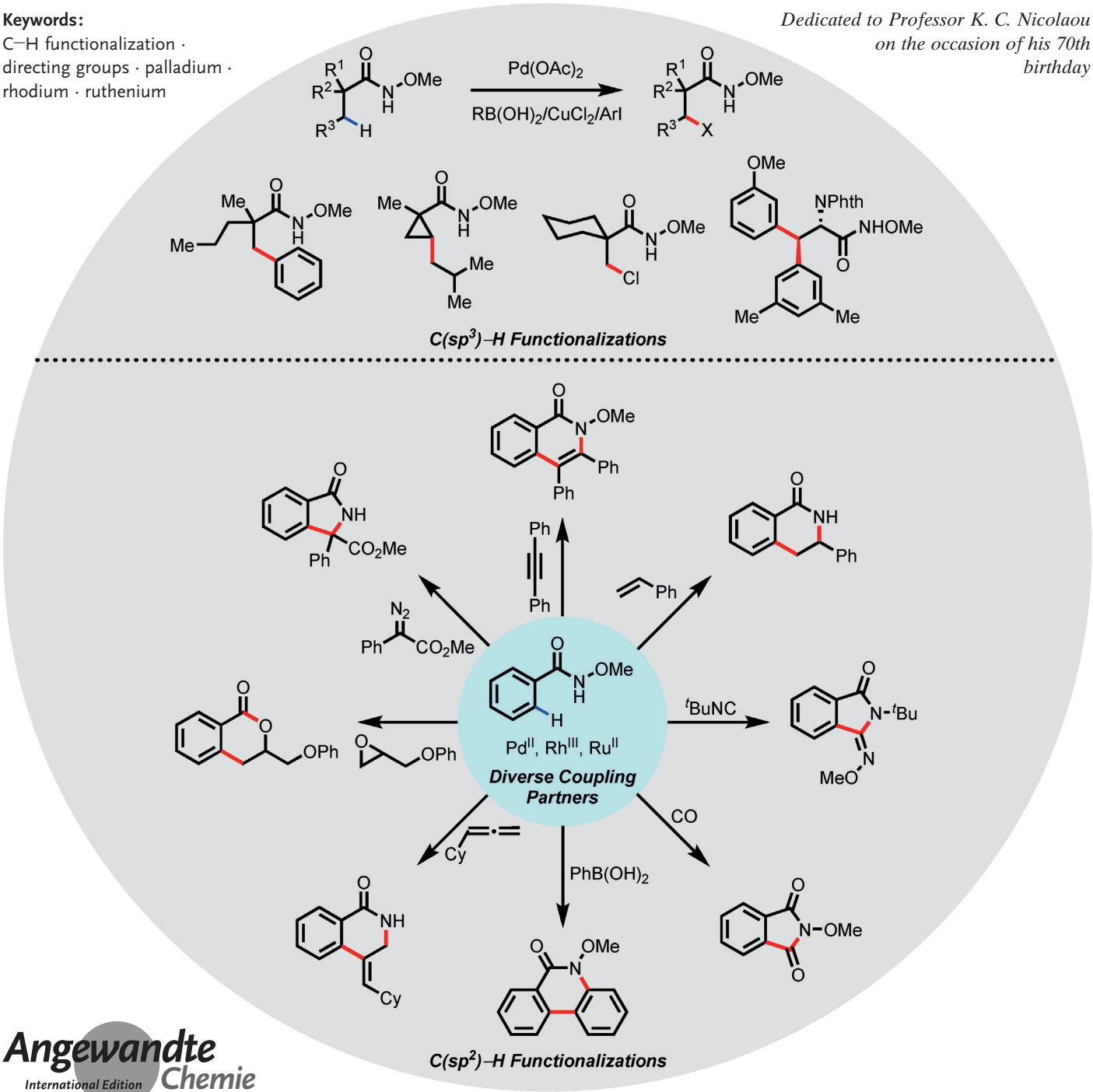
Keywords:
C–H functionalization · directing groups · palladium · rhodium · ruthenium

Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday



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Achieving selective C–H activation at a single and strategic site in the presence of multiple C–H bonds can provide a powerful and generally useful retrosynthetic disconnection. In this context, a directing group serves as a compass to guide the transition metal to C–H bonds by using distance and geometry as powerful recognition parameters to distinguish between proximal and distal C–H bonds. However, the installation and removal of directing groups is a practical drawback. To improve the utility of this approach, one can seek solutions in three directions: 1) Simplifying the directing group, 2) using common functional groups or protecting groups as directing groups, and 3) attaching the directing group to substrates via a transient covalent bond to render the directing group catalytic. This Review describes the rational development of an extremely simple and yet broadly applicable directing group for Pd^{II}, Rh^{III}, and Ru^{II} catalysts, namely the N-methoxy amide (CONHOMe) moiety. Through collective efforts in the community, a wide range of C–H activation transformations using this type of simple directing group have been developed.

From the Contents

1. Introduction

1.1. Regioselectivity

Transition-metal-catalyzed carbon–hydrogen bond (C–H) activation and functionalization has become a prominent area of research within synthetic organic chemistry, and the last decade has witnessed the development of a plethora of transformations that directly functionalize "inert" C–H bonds.[1] The ubiquitous presence of C–H bonds in organic molecules offers overwhelming opportunities for structural modification by C–H activation. On the other hand, achieving site selectivity can be enormously challenging owing to the same reasons that make C–H functionalization so appealing. The fundamental challenge in addressing this issue is to identify parameters that can be used to direct the catalysts to the desired C–H bond. Inspired by enzymatic oxidation chemistry (cytochrome P450 oxygenase),[2] extensive efforts have been dedicated to the development of biomimetic catalysts for selective C–H oxidation through recognition of intrinsic electronic and steric biases.[3] Inevitably, such approaches are challenging to adopt when substrates contain multiple C–H bonds with similar bond strengths and electronic properties. Alternatively, a potentially useful approach is to develop catalytic systems that can distinguish C–H bonds based on their distal and geometric relationship with respect to an existing functional group.[1i] In this context, the interactions between the catalyst and an existing functional group or an installed directing group play a pivotal role in both promoting the C–H activation and controlling the selectivity. To advance this approach, it is essential to develop practical and simple directing groups that are 1) easy to install and remove, 2) small in terms of mass, and 3) coordinate relatively weakly to metal catalysts so that external ligands can coordinate and exert a stronger influence on the metal catalysts, thereby controlling the reactivity, stereoselectivity, and site selectivity. While proximity to a functional group would appear to limit the number of C–H bonds that can be activated, the development of directing groups and ligands to activate distal C–H bonds could drastically expand the scope of this approach as demonstrated recently.[4]

1.2. Reactivity

Historically, directed C–H activation with transition-metal catalysts has predominantly employed strongly coordinating heteroatoms to achieve reactivity through a chelating effect. In this context, pyridines,[5a,b] oxazolines,[5c,d] and imines[5e] are widely used as directing groups [Eq. (1)–(3), Scheme 1]. These directing groups have been shown to be highly efficient at promoting transition-metal-catalyzed C–H cleavage and have found widespread adoption in the literature,[1,5] partly because the cyclometalated intermediates are thermodynamically stable and easy to isolate. However, owing to the thermodynamic stability of the metallacycle complexes formed with strongly coordinating directing groups, at times the functionalization step can be difficult because of a lack of reactivity. One could argue that the relatively poor reactivity of the stable metallacycles significantly hampered the discovery of catalytic conditions for achieving a wide range of C–H functionalizations.[1i] A critical disadvantage of strongly coordinating directing groups also emerges as the field moves forward to develop ligand-controlled and -accelerated C–H activation reactions.[6] The reasons for this are twofold. First, two equivalents of a strongly coordinating substrate could bind to $Pd^{II}X_2$ at the same time, thereby preventing a ligand from binding. Second, a Pd^{II} complex coordinated to an electron-donating ligand and the substrate may not possess the appropriate electronic properties that are required for the cleavage of C–H bonds. In light

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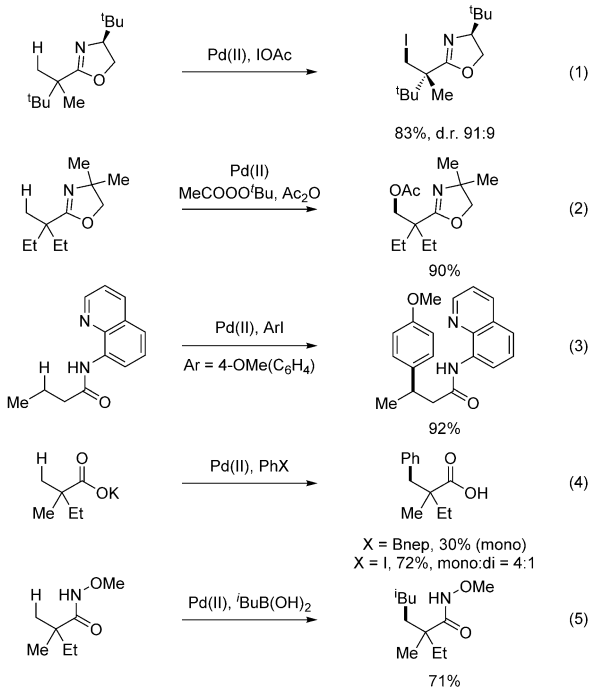
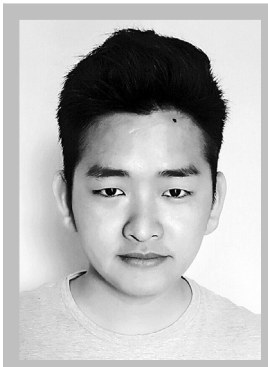


Scheme 1. Evolution of the β-C(sp^3)–H functionalization of aliphatic acids.

of these considerations, our group has systematically developed an alternative approach whereby weakly coordinating directing groups or existing functional groups are used to direct the metalation of C–H bonds. This strategy allows for the formation of less thermodynamically stable metallacycle complexes, which can be more readily functionalized than strongly coordinated complexes, thereby greatly accelerating the discovery of a diverse range of C–H activation transformations. Most importantly, a number of ligands have been discovered to match these weakly coordinating directing groups, leading to C–H activation reactions in which the reactivity is primarily or purely driven by the ligands instead of by the directing group.[6] The extensive development of the *N*-methoxy amide directing group is a prominent example of this approach. The superior reactivity of this directing group and the simplicity of installing and removing this directing group will be discussed in Section 2 (palladium catalysis).

1.3. Synthetic disconnections

For the late-stage diversification of advanced intermediates or final products, it is essential to have different catalysts or strategies that can selectively activate C–H bonds at multiple sites in order to achieve maximum diversity for probing chemical space.[7] On the other hand, achieving selective C–H activation at a single and strategic site proximate to an existing functional group in the presence of multiple C–H bonds is sufficient to provide a powerful and generally useful retrosynthetic disconnection. Indeed, the relationship between existing and newly created functional groups is a cornerstone in retrosynthetic analysis.[8] In this context, it is important that the intended directed C–H activation and functionalization will create commonly encountered structural patterns in synthesis so that the directing group is not a burden, but rather an essential part of the new structural pattern, which constitutes the next level



Ru-Yi Zhu received his B.Sc. in chemistry in 2013 from Peking University for research into the transition-metal-catalyzed activation of inert chemical bonds under the supervision of Prof. Zhang-Jie Shi. In the same year, he moved to The Scripps Research Institute, where he is currently pursuing his Ph.D. on ligand-accelerated Pd^{II}-catalyzed C(sp^3)–H activation reactions under the supervision of Prof. Jin-Quan Yu.

Marcus E. Farmer earned his B.S. in chemistry from the University of South Florida in 2013, where he carried out research under the supervision of Prof. Jon C. Antilla on asymmetric catalysis using chiral phosphoric acids and chiral phosphate metal salts. In the fall of 2013, he began his graduate studies under the supervision of Prof. Jin-Quan Yu and Prof. Phil S. Baran at The Scripps Research Institute, with a focus on ligand development for Pd^{II}-catalyzed C–H activation.

Yan-Qiao Chen received his B.Sc. in chemistry from Cornell University in 2015 where he conducted research in supramolecular catalysis under the supervision of Prof. Chad A. Lewis. He currently is a first-year graduate student in Prof. Jin-Quan Yu's group, developing Pd^{II}-catalyzed C(sp^3)–H activation reactions of unprotected amines using a transient directing group.

Jin-Quan Yu received his B.Sc. in Chemistry from East China Normal University and his M.Sc. from the Guangzhou Institute of Chemistry. In 2000, he obtained his PhD at the University of Cambridge with Prof. J. B. Spencer. After some time as a Junior Research Fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (2004–2007), and finally The Scripps Research Institute, where he is currently Professor of Chemistry. His group studies transition-metal-catalyzed C–H activation.

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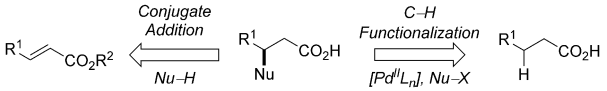
of complexity. With this in mind, our first research project focused on the β-C(sp^3)–H functionalization of aliphatic acids, mirroring the well-established disconnection involving conjugate addition to α,β-unsaturated carboxylic acids (Scheme 2). This Review will systematically reveal the evolution of directing groups for the β-C(sp^3)–H functionalization of aliphatic acids and the advent of a relatively simple



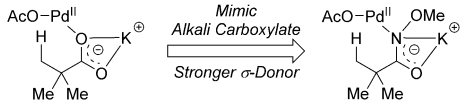
Scheme 2. Different disconnections (conjugate addition vs. C–H functionalization) for the synthesis of β-functionalized aliphatic acids.

and weakly coordinating *N*-methoxy amide directing group (Scheme 3). The utility of this directing group in directed C–H activation of a wide range of substrates with a variety of transition-metal catalysts is also discussed. The compatibility of this directing group with a broad range of substrates, transformations, various metal catalysts (Pd, Rh, and Ru), and mild conditions (room temperature) showcases the efficiency of this weakly coordinating directing group. Most notably, this directing group can cooperate with a ligand to significantly boost the reactivity of C(sp^3)–H activation processes.

2. Palladium Catalysis

Our early investigations into the use of organometallic reagents as coupling partners in C–H functionalization (e.g. organotin[9] and organoboron reagents[10,11a]) prompted us to extend their applications to simple substrates such as carboxylic acids. The *ortho*-C(sp^2)–H coupling of benzoic acids and aryl acetic acids with organoboron compounds proceeded in high yields;[11] however, the coupling of the β-C(sp^3)–H bonds in aliphatic acids with organoboron compounds was inefficient owing to the homocoupling of the organometallic reagents prior to C–H activation.[11a] Considering the utility and availability of aryl and alkyl boronic acids, we set out to overcome this limitation. We reasoned that while the weakly coordinating potassium carboxylate is capable of directing C–H activation, the side reaction of the aryl or alkyl boronic acid with Pd^{II} is more facile. Therefore, we needed to slightly increase the binding strength of the directing group to sequester the Pd^{II} more efficiently.

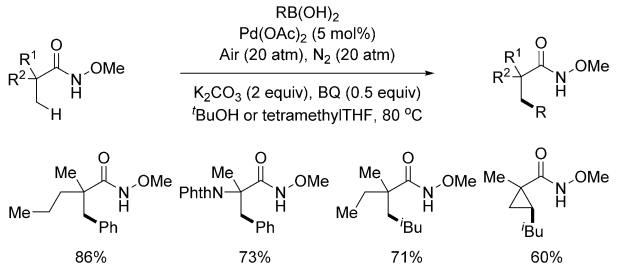
Based on structural information regarding the coordination of alkali metal carboxylates to Pd^{II},[11,12] we proposed that the alkali metal carboxylate coordinates to Pd^{II} as a neutral σ-donor in the transition state (Scheme 3). We therefore envisioned that a more Lewis basic carboxylate mimetic could bind to Pd^{II} more efficiently, minimizing homocoupling background reactions of boronic acid derivatives in Pd^{II}/Pd^0 catalytic manifolds. At the same time, we hoped that the carboxylate mimetic could adopt a similar coordination mode to facilitate the C–H insertion step. We envisioned that an



Scheme 3. Rational design of the *N*-methoxy amide directing group from alkali metal carboxylate directing groups.

acidic amide moiety could be deprotonated to form an imidate structure similar to the alkali metal carboxylate. From a brief search of the literature, we noticed that *O*-methyl hydroxamic acid had been used as a masked ester in synthesis.[13a,b] Furthermore, a few examples of *ortho* lithiation using this chelating group had also been reported.[13c,d] We reasoned that the well-balanced acidity would allow us to generate an imidate structure under mildly basic conditions. Such an imidate is anticipated to have a slightly improved coordinating ability to Pd^{II} compared to an alkali metal carboxylate. It is also believed that the sp^2 hybridization of the coordinating atom is beneficial for minimizing the dihedral angle between Pd^{II} and the target C–H bond in the desired transition state.[14] The coordination via the anionic nitrogen atom of the amide could also be responsible for this enhanced reactivity as supported by X-ray analysis of an isolated intermediate.[18,19] The facile installation and removal of the *N*-methoxy amide directing group, as recently demonstrated in β-C(sp^3)–H arylation, is also an important practical advantage.[27]

With this in mind, we tested the *N*-methoxy amide directing group for the coupling of β-C(sp^3)–H bonds with organoboronic acids in 2008 (Scheme 4). To our delight, this directing group enabled the β-C(sp^3)–H alkylation of carboxylate derivatives with alkyl boronic acids. This work established the first method for C(sp^3)–H/C(sp^3)–B cross-



Scheme 4. Pd^{II}-catalyzed C(sp^3)–H cross-coupling with aryl (alkyl) boronic acids using the *N*-methoxy amide directing group (Yu et al., **2008**).[15] BQ = benzoquinone, tetramethylTHF = 2,2,5,5-tetramethyltetrahydrofuran.

coupling.[15] Notably, this coupling reaction allowed the use of pressurized air as the sole oxidant in this Pd^{II}/Pd^0 catalytic cycle.

The utility of this directing group was further examined by our group in the same year to effect an intramolecular C(sp^2)–H amidation and an intermolecular C(sp^3)–H chlorination by Pd^{II}/Pd^0 catalysis (Scheme 5).[16] The success of these two reactions hinged on the use of the *N*-methoxy

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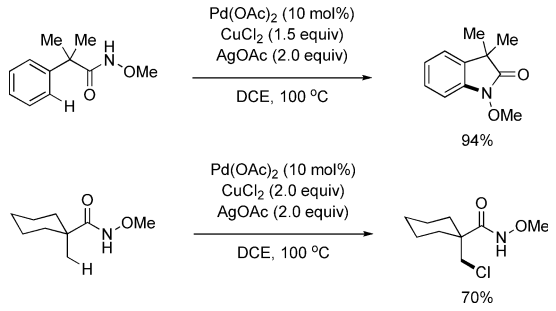
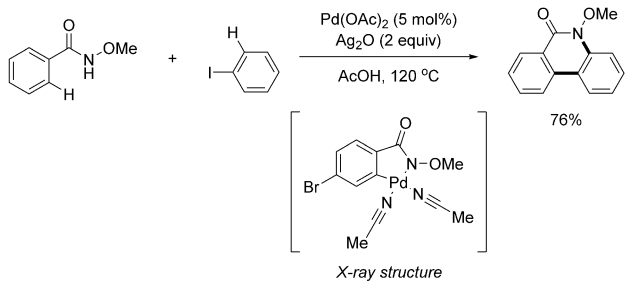


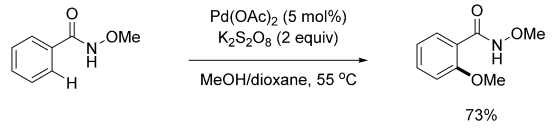
Scheme 5. Pd^{II}-catalyzed $C(sp^2)$–H amidation and $C(sp^3)$–H chlorination by Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Yu et al., **2008**).[16] DCE = 1,2-dichloroethane.



Scheme 7. Pd^{II}-catalyzed dual $C(sp^2)$–H activation by Pd^{II}/Pd^{IV} and Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Wang et al., **2011**).[18a]

amide and suggested that this directing group might be generally applicable to both $C(sp^2)$–H and $C(sp^3)$–H activation.

In 2009, Wang and co-workers reported an efficient $C(sp^2)$–H alkoxylation reaction using the *N*-methoxy amide directing group in the presence of a strong external oxidant. This reaction was proposed to proceed through a Pd^{II}/Pd^{IV} catalytic cycle owing to the need for a strong oxidant to promote the transformation (Scheme 6).[17] Interestingly,

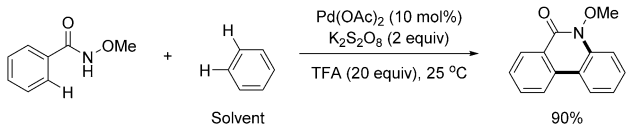


Scheme 6. The first Pd^{II}-catalyzed $C(sp^2)$–H alkoxylation by Pd^{II}/Pd^{IV} catalysis using the *N*-methoxy amide directing group (Wang et al., **2010**).[17]

when screening oxidants for the direct $C(sp^2)$–H methoxylation of benzoic acid using this directing group, they found that $PhI(OAc)_2$ only gave trace amounts of the oxidation products. Considering the structural similarity between oximes and the imidate form of the *N*-methoxy amide, it was surprising to the authors that no product was formed with this oxidant, even though this oxidant is commonly used in oxime-directed C–H oxidations.[5e] This result exemplifies the fact that the *N*-methoxy amide does not behave in the same way as oxime directing groups and should not necessarily be considered to be kin to these strongly coordinating directing groups. After further screening, Wang and co-workers achieved the direct alkoxylation of benzoic acid derivatives utilizing the *N*-methoxy amide directing group in a Pd^{II}/Pd^{IV} catalytic system with $K_2S_2O_8$ as the bystanding oxidant.

In 2011, the Wang group further showcased the robustness of this directing group with a variety of redox cycles by combining a directed Pd^{II}/Pd^{IV} $C(sp^2)$–H arylation with an intramolecular Pd^{II}/Pd^0 $C(sp^2)$–H amidation to provide phenanthridinones from benzoic acid derivatives and aryl iodides (Scheme 7).[18a] Notably, a stable five-membered Pd^{II} metallacycle was obtained after C–H cleavage, which revealed the *N*-methoxy amide coordinating as an anionic donor. However, in the transition state for the C–H activation step, the *N*-methoxy amide may also coordinate to the Pd^{II} catalyst as a neutral (L type) directing group in the form of an imidate as shown for a related acidic amide directing group (Scheme 3).[19] Subsequent isomerization of the directing group from an imidate to a more stable amide structure could account for the formation of this palladacycle. Very recently, Bhanage and co-workers reported a similar approach by replacing aryl iodides with aryl diazonium salts that were generated in situ by the diazotization of anilines in the presence of *tert*-butyl nitrite (^{t}BuONO).[18b]

In the same year, Cheng and co-workers developed an alternative strategy for the synthesis of phenanthridinones that is based on the oxidative coupling of *N*-methoxy benzamide derivatives and arene solvents (Scheme 8).[20]



Scheme 8. Pd^{II}-catalyzed triple $C(sp^2)$–H activation by Pd^{II}/Pd^{IV} and Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Cheng et al., **2011**).[20] TFA = trifluoroacetic acid.

Whereas the arene had to be used as the solvent for this reaction, the conditions were surprisingly mild, providing the desired products after three separate $C(sp^2)$–H activations at room temperature. The efficiency of the *N*-methoxy amide directing group is uniquely demonstrated by this reaction as it enables three C–H activations at such a mild temperature. Together, these two methods developed in 2011 provide rapid access to phenanthridinone derivatives.

Also in 2011, the groups of Brooker-Milburn and Lloyd-Jones published a collaborative paper disclosing the tandem $C(sp^2)$–H olefination/Wacker oxidation and $C(sp^2)$–H carbonylation of *N*-methoxy benzamides (Scheme 9).[21a] The observation of a subsequent intramolecular Wacker oxidation after an initial $C(sp^2)$–H olefination reaction is worth mentioning. This is in stark contrast to other acidic amide directed olefinations of the time, as cyclization through conjugate addition typically occurred after $C(sp^2)$–H activation. Notably, this is also in contrast to the rhodium systems (discussed below) that had been disclosed with this directing

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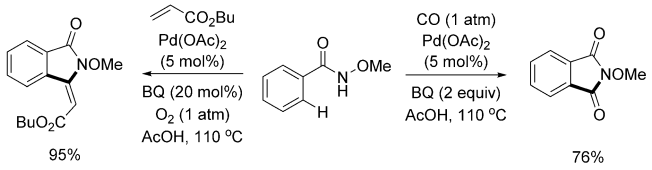
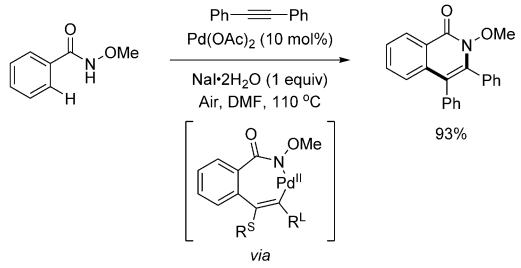


Scheme 9. Pd^{II}-catalyzed $C(sp^2)$–H olefination and carbonylation by Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Lloyd-Jones, Booker-Milburn et al. and Wang et al., **2011**).[21a,b]

group, which provided solely the olefination product (Scheme 26). Simultaneously, Wang and co-workers reported the $C(sp^2)$–H olefination of *N*-methoxy benzamides to afford isoindolinones.[21b]

Huang and co-workers also introduced internal alkynes as coupling partners to synthesize isoquinolinones by Pd^{II}/Pd^0 catalysis (Scheme 10).[22] Interestingly, the examination of

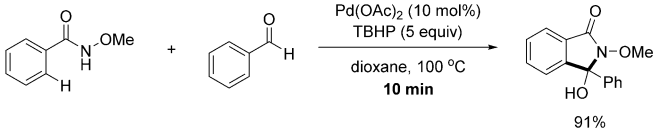


Scheme 10. Pd^{II}-catalyzed $C(sp^2)$–H annulation with internal alkynes by Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Huang et al., **2012**).[22] DMF = dimethylformamide, R^S = small group, R^L = large group.

additives showed that alkali metal salts were beneficial to this reaction. Among these salts, $NaI{\cdot}2H_2O$ was the most effective additive. Notably, atmospheric air was the sole oxidant in this reaction to oxidize Pd^0 and regenerate the Pd^{II} catalyst. Finally, it was determined that this reaction favored the formation of products wherein the large group on an unsymmetric alkyne is positioned adjacent to the nitrogen atom.

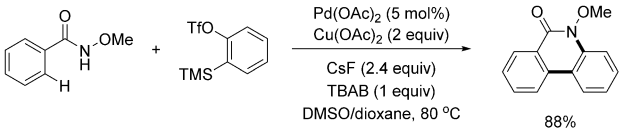
Another beautiful example of palladium catalysis was described by Zhao and co-workers, who achieved the $C(sp^2)$–H acylation of *N*-methoxy benzamides with aldehydes as the coupling partners in 2013 (Scheme 11).[23a] Subsequent cyclization afforded hydroxy-substituted isoindolones. Both aromatic and aliphatic aldehydes could be employed, indicating a broad coupling partner scope. Notably, mechanistic studies revealed that a radical process is likely to be involved as adding a radical scavenger shut down the reaction. In 2016, Zhang and co-workers disclosed a similar reaction in which a large excess of a toluene derivative served as a precursor to benzaldehyde for this transformation.[23b]

Inspired by the annulation reactions of internal alkynes, the groups of Jeganmohan[24a] and Xu[24b] independently reported a Pd^{II}-catalyzed $C(sp^2)$–H activation reaction with



Scheme 11. Pd^{II}-catalyzed $C(sp^2)$–H annulation with aldehydes using the *N*-methoxy amide directing group (Zhao and Huang et al., **2013**).[23a] TBHP = *tert*-butyl hydroperoxide.

arynes and the *N*-methoxy amide as the directing group to afford phenanthridinone derivatives (Scheme 12).



Scheme 12. Pd^{II}-catalyzed $C(sp^2)$–H annulation with arynes by Pd^{II}/Pd^0 catalysis using the *N*-methoxy amide directing group (Jeganmohan et al. and Xu et al., **2014**).[24a,b] DMSO = dimethyl sulfoxide, TBAB = tetra-*n*-butylammonium bromide.

A significant challenge for C–H functionalization is the robust control of positional selectivity. The use of a weakly coordinating directing group to control the selectivity would seem, at the fundamental level, problematic with the majority of medicinally important heterocyclic substrates as the strongly coordinating heteroatoms can interfere with the catalyst, leading to either poisoning or undesired selectivity. To overcome this limitation when using this directing group, we envisioned that this acidic amide directing group could serve as an acetate surrogate to assist the aerobic oxidation of Pd^0 to Pd^{II}, thereby anchoring the catalyst and enabling the cleavage of proximal C–H bonds despite the presence of Lewis basic heterocycles. We anticipated that the key to this approach was to deprive the reaction conditions of any external anions and to use a Pd^0 precatalyst. With this idea in mind, in 2014, we developed an aerobic $C(sp^2)$–H annulation with isocyanides and the *N*-methoxy amide directing group that effectively overcomes catalyst poisoning by heterocycles and overrides the commonly observed positional selectivity dictated by heterocycles. The success of this reaction with pyridine-containing substrates demonstrates that the interference from heterocycles in C–H functionalization methods can be overcome by carefully choosing the directing group and reaction conditions (Scheme 13).[25]

Later, we found that this strategy could be applied to olefinic C–H activation. Unlike for β-olefinic C–H activation, the same five-membered cyclometalation intermediates are involved as in directed aromatic C–H activation. For the first time, it was observed that a palladium catalyst selectively cleaved the α-olefinic C–H bonds of α,β-unsaturated olefins, which is due to the special reaction mechanism (Scheme 14).[26] A range of 4-imino-β-lactams were readily synthesized with this method. Notably, when the α-position of

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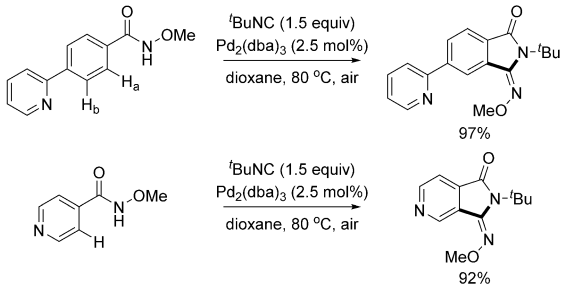
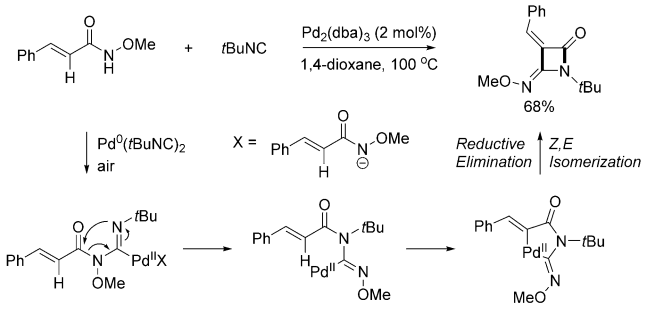


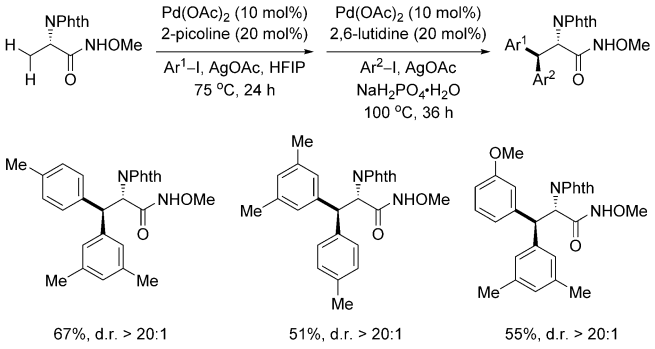
Scheme 13. Pd^{II}-catalyzed $C(sp^2)$–H annulation with isocyanide using the *N*-methoxy amide directing group (Dai and Yu et al., **2014**).[25] dba = dibenzylideneacetone.



Scheme 14. Mechanism of the Pd^{II}-catalyzed $C(sp^2)$–H annulation with isocyanide using the *N*-methoxy amide directing group (Dai and Yu et al., **2016**).[26] dba = dibenzylideneacetone.

the α,β-unsaturated olefin is blocked, activation of the β-C–H bond can be achieved.

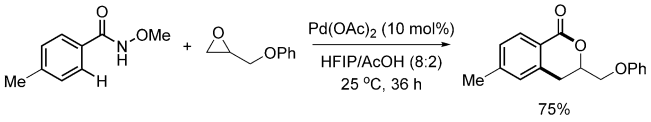
Whereas exploiting the C–H activation reactivity solely driven by the directing group has proven to be productive in developing a variety of transformations, it is crucial for the field to achieve C–H activation reactions in which the reactivity is enabled by the ligands. This is of great importance as both enantioselectivity and regioselectivity can potentially be controlled by catalytic amounts of ligands. In a first attempt to address this, a ligand-controlled β-$C(sp^3)$–H mono- or diarylation of alanine derivatives with an acidic amide ($CONHAr_F$, $Ar_F = 4\text{-}CF_3(C_6F_4)$) as the directing group was developed by our group in 2014.[6g] However, the directing group utilized in this approach was rather difficult to remove when attached to bulky substrates, such as the products arising from diarylation. To enhance the practicality of this method, we developed conditions and ligands that would enable us to utilize the *N*-methoxy amide auxiliary for this transformation as it is far easier to remove (Scheme 15).[27] The facile removal of the *N*-methoxy amide to provide the corresponding ester or acid proceeds with quantitative yield and complete retention of chirality, demonstrating the usefulness of this directing group. A range of β-(hetero)aryl alanine derivatives were rapidly assembled through $C(sp^3)$–H activation by utilizing this method. The *N*-methoxy amide can also activate the secondary benzylic $C(sp^3)$–H bonds of phenylalanine derivatives when the ligand is exchanged. A series of β,β′-homo/hetero-diaryl alanine



Scheme 15. Ligand-controlled Pd^{II}-catalyzed $C(sp^3)$–H arylation of α-amino acids by Pd^{II}/Pd^{IV} catalysis using the *N*-methoxy amide directing group (Yu et al., **2015**).[27] HFIP = hexafluoro-2-propanol, 2,6-lutidine = 2,6-dimethylpyridine, 2-picoline = 2-methylpyridine.

derivatives were thus obtained in a one-pot fashion. Afterwards the *N*-methoxy amide was easily converted into the methyl ester with full retention of chirality.

In 2015, Kanai and co-workers reported the first example of Pd^{II}-catalyzed $C(sp^2)$–H functionalization with epoxides under very mild conditions by using a pyridyl directing group. Interestingly, they found that the *N*-methoxy amide directing group can also be used in this reaction (Scheme 16).[28] Several 3-substituted isochroman-1-ones were synthesized through C–H alkylation with epoxides and subsequent intramolecular condensation.



Scheme 16. Pd^{II}-catalyzed $C(sp^2)$–H annulation with epoxides using the *N*-methoxy amide directing group (Kanai et al., **2015**).[28] HFIP = hexafluoro-2-propanol.

It is clear that the *N*-methoxy amide directing group has found great utility in palladium catalysis, with significant contributions to heterocycle synthesis by $C(sp^2)$–H annulation with various coupling partners. Both Pd^{II}/Pd^0 and Pd^{II}/Pd^{IV} catalytic cycles have been shown to be compatible with this directing group, demonstrating the versatility of this auxiliary for a variety of catalytic processes. As the ligand effects for this directing group begin to become clear, many new transformations may become possible with palladium catalysis. Given the versatility of this directing group, it is unsurprising that it has also gained popularity in C–H activation reactions with other metal catalysts as discussed below.

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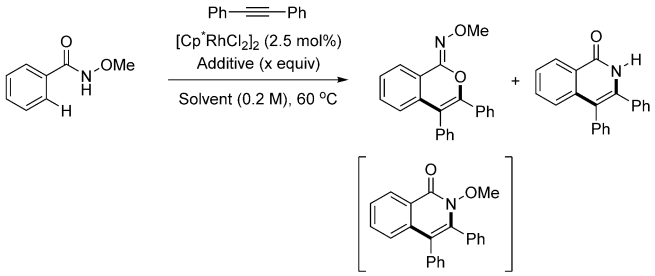
3. Rhodium Catalysis

3.1. Rhodium(III)-Catalyzed C(sp^2)–H Activation with Alkynes

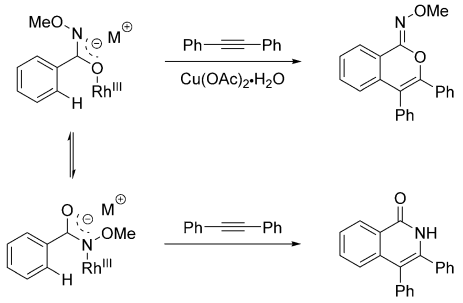
Owing to its simplicity and finely tuned coordination strength, the *N*-methoxy amide directing group has also been widely adopted in the field of rhodium-catalyzed C–H activation. The first Rh^{III}-catalyzed C(sp^2)–H activation utilizing the *N*-methoxy amide was disclosed by Fagnou and Guimond in 2010 and enabled the synthesis of nitrogen-containing heterocycles through annulation with alkynes (Table 1).[29] Their initial choice of conditions was influenced by previously developed methods for Rh^{III}-catalyzed C(sp^2)–H annulations with alkynes using other directing groups,[30–32] but they found that when utilizing the *N*-methoxy amide directing group, a mixture of products was obtained. Initially, the minor product was misassigned as the C–N cyclization product. This side product was later correctly identified by Huang[22] to arise from C–O cyclization with retention of the N–OMe moiety (Table 1), which has significant mechanistic implications. Intriguingly, the O-cyclized product appears to be formed through direct reductive elimination from a Rh^{III} center, forging the C–O bond, which is consistent with an alkali metal carboxylate type coordination mode (Scheme 3). It is likely that in the case of C–O bond reductive elimination, the Rh^{I} is oxidized by $Cu(OAc)_2 \cdot H_2O$ to regenerate the Rh^{III} catalyst and close the catalytic cycle. Meanwhile, the desired isoquinolone product was obtained by C–N bond formation, after which the Rh^{I} was oxidized to Rh^{III} by N–O bond cleavage. Recognizing this, $Cu(OAc)_2 \cdot H_2O$ was replaced with redox-innocent CsOAc to improve the selectivity, and the isoquinolone was formed cleanly in high yields. This result indicated that the *N*-methoxy amide directing group could act as an internal oxidant in the absence of an external oxidant. With optimized reaction conditions in hand, a range of benzoic acid derivatives and internal alkynes were employed to afford isoquinolones. It is interesting to note that in the presence of an appropriate external oxidant, Pd^{II}/Pd^{0} catalysis provided the product of C–N bond formation without cleaving the N–OMe bond (Scheme 10), whereas Rh^{III}/Rh^{I} catalysis yielded the side product of C–O bond formation.[22] It is likely that Pd^{II} favors coordination by the nitrogen atom of the directing group, whereas Rh^{III} equilibrates between Rh–O and Rh–N bound isomers (Scheme 17). Notably, this newly established system has proven to be very general in rhodium and ruthenium catalysis.

Table 1: The first Rh^{III}-catalyzed C(sp^2)–H annulation with internal alkynes using the *N*-methoxy amide directing group (Guimond and Fagnou et al., **2010**).[29]



Entry	Solvent	Additive (*x* equiv)	Yield [%][a] (O + N) – CP[c]	Ratio (O/N) – CP[c]
1	DMF	$Cu(OAc)_2 \cdot H_2O$ (2)	89	1:1.1
2	DMF	CsOAc (2)	38	1:20
3	MeOH	CsOAc (2)	97 (92)[b]	1:20
4	MeOH	CsOAc (0.3)	97 (90)[b]	1:20

[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product. [c] CP = Cyclized product. Cp* = pentamethylcyclopentadienyl.



Scheme 17. Different coordination modes in rhodium catalysis with the *N*-methoxy amide directing group.[29]

In 2011, Glorius and co-workers explored the reactivity of a related *N*-pivaloyloxy amide directing group (Scheme 26), and the Fagnou group later applied this directing group to their annulation reaction with internal alkynes.[33] Although the reaction conditions when using the *N*-methoxy amide were fairly mild to begin with, the authors set out to modify the nature of the directing group to obtain improved conditions that would enable lower catalyst loadings and improved substrate scope. They reasoned that using hydroxamic acids bearing better leaving groups or groups that could better stabilize intermediates of the catalytic cycle would be beneficial to the reaction. To ensure that the *N*-pivaloyloxy amide directing group was optimal, a series of hydroxamic acid derivatives were synthesized and examined under the standard conditions to shed light on the reaction mechanism (Table 2). Although most of the directing groups were efficient for coupling with diphenylacetylene, only the O-carboxylate-based directing groups were effective with both internal diarylalkynes and less reactive internal dialkylalkynes. The increased reactivity might arise from the better leaving group ability and the interaction of the carbonyl oxygen lone pair with the rhodium catalyst. With the enhanced *N*-pivaloyloxy amide directing group, the reaction can be conducted with lower rhodium catalyst loadings (as low as 0.5 mol%) and at room temperature; furthermore, the substrate scope of terminal and internal alkynes was significantly improved (Scheme 18).

A systematic mechanistic study was carried out to elucidate the reaction mechanism of this annulation reaction.

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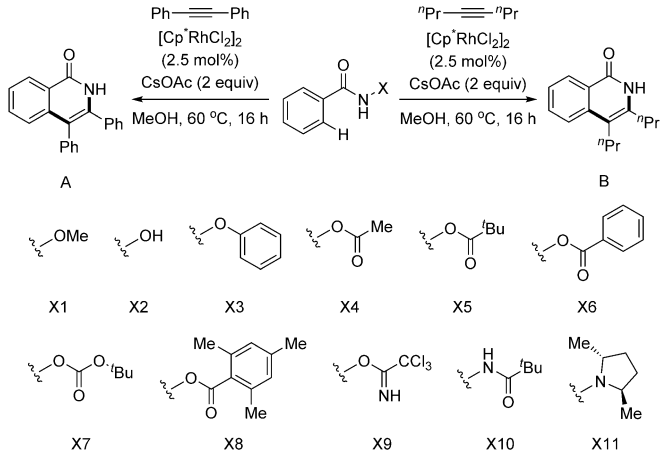
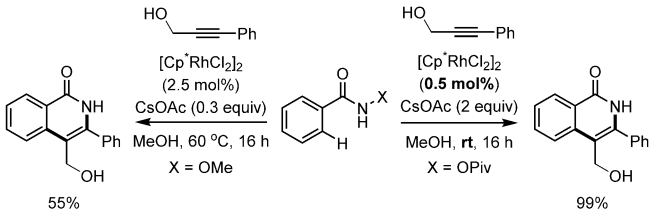
Table 2: Directing group optimization (Guimond and Fagnou et al., **2011**).[33]



X	Yield A [%][a]	Yield B [%][a]	X	Yield A [%][a]	Yield B [%][a]
1	90	12	7	86	63
2	52	n.d.	8	78	63
3	74	14	9	0	n.d.
4	93	77	10	0	n.d.
5	98	85	11	0	n.d.
6	97	85			

[a] Determined by ^{1}H NMR spectroscopy using trimethoxybenzene as the internal standard. n.d. = not determined.

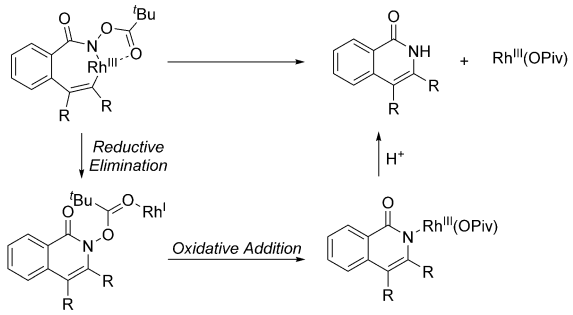
First, they conducted the reaction of *N*-methoxy benzamide and diphenylacetylene under the standard reaction conditions in deuterated methanol to partial conversion. The unreacted benzamide and the product were isolated and analyzed by



Scheme 18. Direct comparison of a previously reported system and the newly designed system (Guimond and Fagnou et al., **2011**).[33]

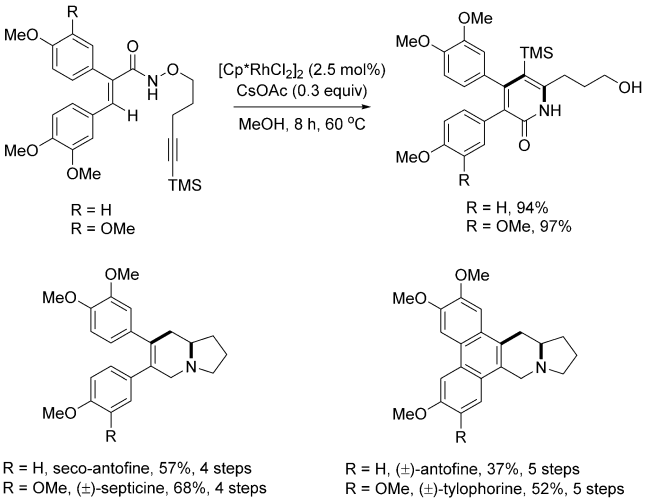
^{1}H NMR spectroscopy to probe for deuterium incorporation. They found no deuterium incorporation in either of the compounds, which indicated that the C–H activation step was irreversible or that the following step was extremely fast relative to the C–H bond cleavage. Next, by measuring the initial rates of substrate and deuterated substrate in parallel for the *N*-methoxy and *N*-pivaloyloxy amide directing groups, a large KIE value for the *N*-pivaloyloxy amide directed C–H activation was observed, which is consistent with the conclusion that the C–H activation step was the rate-limiting step. In contrast, there was no kinetic isotope effect for the *N*-methoxy amide directing group. With these insights and DFT calculations, a stepwise mechanism was proposed to account for the C–N bond formation and N–O bond cleavage by way of a Rh^{III}/Rh^{I} catalytic cycle (Scheme 19).

Subsequently, Park and co-workers tethered the alkyne coupling partner to the substrate so as to construct indolizidine scaffolds by Rh^{III}-catalyzed intramolecular C(sp^2)–H



Scheme 19. A stepwise mechanism for the N–O bond cleavage (Guimond and Fagnou et al., **2011**).[33]

activation and annulation (Scheme 20).[34] This tethering approach enabled the total synthesis of (±)-antofine, (±)-septicine, and (±)-tylophorine.



Scheme 20. Rh^{III}-catalyzed intramolecular C(sp^2)–H annulation with alkynes and application in total synthesis (Park et al., **2012**).[34] TMS = trimethylsilyl.

In 2012, Glorius and co-workers made use of Rh^{III}-catalyzed C(sp^2)–H annulation with alkynes and their newly developed *N*-pivaloyloxy amide directing group and employed an alkynyl MIDA boronate as the coupling partner to synthesize heterocyclic boronic acids (Scheme 21).[35] Interestingly, the MIDA group was crucial for the reaction to proceed. One limitation of the substrate scope was that internal alkynyl MIDA boronates failed to provide any product. The heterocyclic boronic acid products could be arylated by Pd^0-catalyzed Suzuki cross-couplings.

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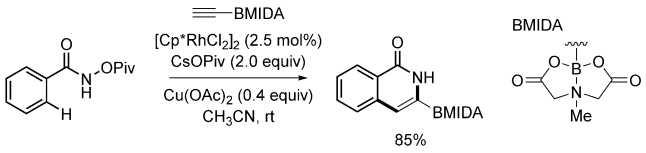
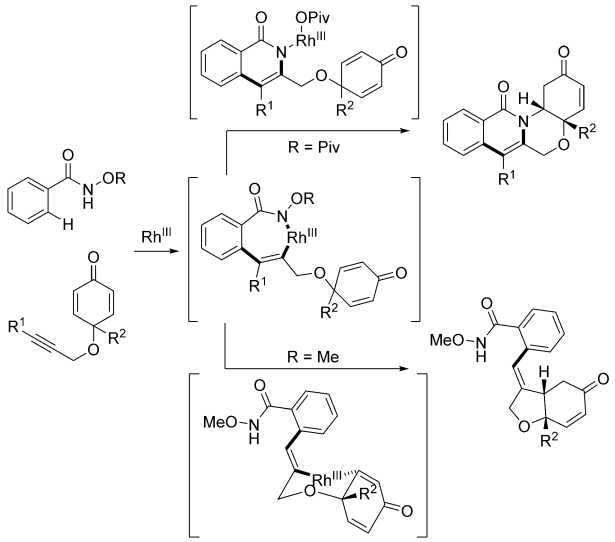


Scheme 21. Rh^{III}-catalyzed C(sp^2)–H annulation with alkyne MIDA boronates using the *N*-pivaloyloxy amide directing group (Glorius et al., **2012**).[35]

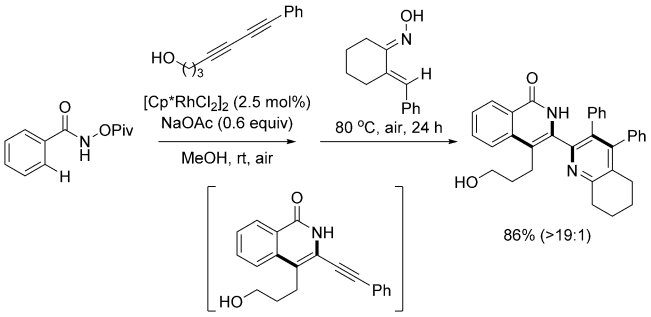
Intrigued by Fagnou's and Park's work, Lin and co-workers cleverly engineered a 1,6-enyne coupling partner to react with the *N*-methoxy benzamide or the *N*-pivaloyloxy benzamide to afford hydrobenzofurans and isoquinolones, respectively (Scheme 22).[36] The steric congestion of the cyclohexadienone motif from R^2 suppressed the direct Michael addition between the benzamide and the coupling



Scheme 22. Rh^{III}-catalyzed C(sp^2)–H annulation with 1,6-enynes using the *N*-methoxy or *N*-pivaloyloxy amide directing group (Tian and Lin et al., **2014**).[36]

partner. The different reactivities were due to the coordination difference of the *N*-pivaloyloxy and *N*-methoxy directing groups. For the *N*-pivaloyloxy benzamide, the chelation effect allowed for direct C–N bond reductive elimination followed by an intramolecular conjugate addition of the N–Rh bond to form the product. However, the weaker coordination ability of the *N*-methoxy benzamide led to protonation and gave an opened vinyl Rh^{III} intermediate. Subsequently, the C–Rh bond added across the cyclohexadienone in a Michael addition type process to afford the corresponding product.

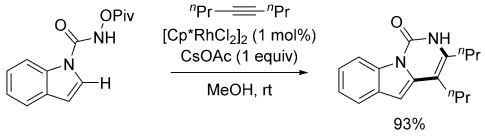
In 2014, Glorius and co-workers explored the reactivity of 1,3-diynes in Rh^{III}-catalyzed C(sp^2)–H activation of *N*-pivaloyloxy benzamides to synthesize diverse bisheterocycles.[37] The challenges encountered when utilizing 1,3-diynes as coupling partners were the control of chemoselectivity, regioselectivity, and mono/diselectivity. Gratifyingly, they found that the *N*-pivaloyloxy benzamide could be coupled with both symmetric and nonsymmetric 1,3-diynes with good to excellent selectivities to afford bisisoquinolones. Using a *N*-pivaloyloxy benzamide/1,3-diyne ratio of 1:1 under milder conditions, a high degree of monoselectivity was achieved. Further, the mono-annulated product was subjected to many other substrates under Rh^{III} catalysis and converted into various nonsymmetric bisheterocycles. This method could be adapted to a one-pot procedure to rapidly obtain diverse bisheterocycles (Scheme 23). Based on the observations of the authors, it appears that the regioselectivity of the migratory insertion was strongly affected by the hybridization



Scheme 23. Rh^{III}-catalyzed C(sp^2)–H annulation with 1,3-diynes using the *N*-pivaloyloxy amide directing group (Glorius et al., **2014**).[37]

of the carbon atom and the coordination ability of the substituents, with the order of preference for groups to remain in the position adjacent to the heteroatom of the heterocycles being alkynyl and isoquinolonyl, phenyl, and finally alkyl groups.

Utilizing *N*-pivaloyloxy urea as the directing group, Cui and co-workers were able to functionalize the 2-position of indoles and pyrroles with various alkynes by adopting similar conditions to those developed by Fagnou and co-workers (Scheme 24).[38]



Scheme 24. Rh^{III}-catalyzed C(sp^2)–H annulation with alkynes using the *N*-pivaloyloxy amide directing group (Cui et al., **2014**).[38]

In 2015, Ma and co-workers reported an elegant method for the formation of tetrasubstituted allenes by applying 2-alkynyl carbonates as coupling partners in Rh^{III}-catalyzed C(sp^2)–H activation reactions of *N*-methoxy benzamides. The rational design of the coupling partner was based on the hypothesis that a leaving group attached adjacent to the alkynyl moiety might allow for β-elimination after alkyne insertion to afford the allene. Among several screened leaving groups, carbonate was found to be the optimal choice presumably because it is also a suitable directing group for

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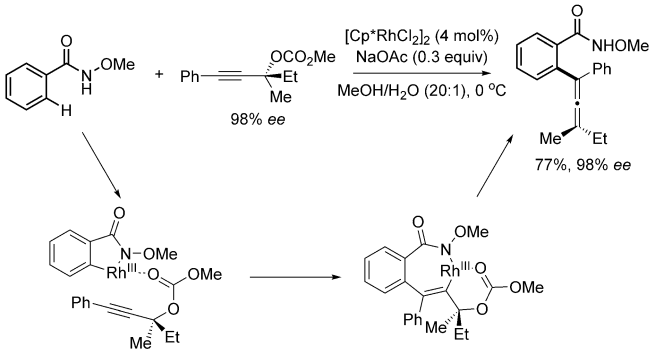
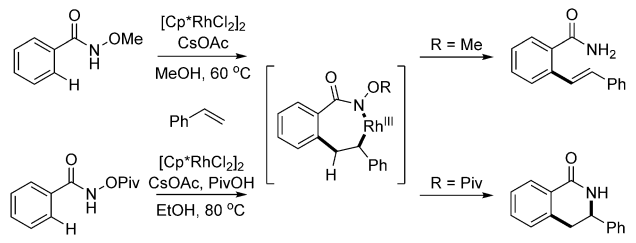
steering the regioselectivity during alkyne insertion and orienting the Rh^{III} center *syn* to the carbonate leaving group so as to facilitate the *syn* β-oxygen elimination. Notably, only tertiary propargylic carbonates could be used in this reaction. As the alkyne insertion and the *syn* β-oxygen elimination steps are stereospecific, enantioenriched coupling partners could be employed to form chiral tetrasubstituted allenes by chirality transfer (Scheme 25).[39]



Scheme 25. Rh^{III}-catalyzed C(sp^2)–H activation with tertiary propargylic carbonates using the *N*-methoxy amide directing group (Ma et al., **2015**).[39]

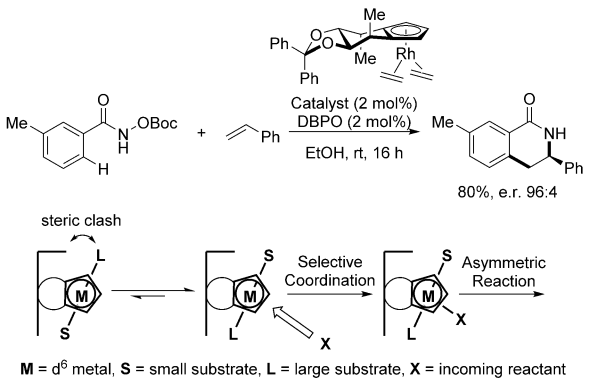
3.2. Rhodium(III)-Catalyzed C(sp^2)–H Activation with Alkenes

Glorius and co-workers reported a Rh^{III}-catalyzed C(sp^2)–H olefination using the *N*-methoxy amide moiety as the directing group and internal oxidant under a similar set of conditions as those developed for the coupling of alkynes.[40] The different reactivities of the *N*-methoxy amide and *N*-pivaloyloxy amide groups are rather interesting (Scheme 26). Presumably, coordination of the pivaloyl carbonyl group to the rhodium center influences the reaction towards direct reductive elimination to form a C–N bond followed by subsequent N–O bond cleavage. The lack of this secondary binding to the Rh catalyst when using the *N*-methoxy amide appears to influence the reaction towards the product arising from β-hydride elimination. It is likely that in contrast to the bidentate *N*-pivaloyloxy amide directing group, the monodentate *N*-methoxy amide directing group releases Rh^{III}, allowing for rotation about the C–C bond and β-hydride elimination. However, the chelating effect from the *N*-pivaloyloxy amide directing group prevented the release of Rh^{III}, a requisite for β-hydride elimination, thereby promoting the alternate reductive elimination pathway. In both cases, the N–O bond serves as the internal oxidant for this reaction.



Scheme 26. Rh^{III}-catalyzed C(sp^2)–H olefination using the *N*-methoxy or *N*-pivaloyloxy amide directing group (Glorius et al., **2011**).[40]

Despite the plethora of Rh^{III}-catalyzed C(sp^2)–H functionalization reactions developed over the past few years, asymmetric variants are rare. This is partly due to the difficulty associated with incorporating an effective chiral ligand in rhodium catalysis. Considering the strong coordination of cyclopentadienyl (Cp) ligands to rhodium, Cramer and co-workers reasoned that a suitable chiral Cp ligand might effectively control the spatial arrangement of reactants around the rhodium center. Confirming this idea, in 2012, they reported the first example of using a class of C_2-symmetric Cp ligands that enable the synthesis of chiral dihydroquinolones based on Glorius' and Fagnou's pioneering work on Rh^{III}-catalyzed C(sp^2)–H annulation with alkenes using the *N*-methoxy or *N*-pivaloyloxy amide directing group.[41] Several key features of these ligands are crucial for the observed enantioselectivity (Scheme 27). For instance,



Scheme 27. The first asymmetric Rh^{III}-catalyzed C(sp^2)–H olefination enabled by chiral Cp ligands using the *N*-*tert*-butoxycarbonyloxy amide directing group (Cramer et al., **2012**).[41] DBPO = dibenzoyl peroxide.

the tethered alkyl groups serve as a back wall that restricts the approach of the reactant, while the locked axial methyl groups serve as side walls that orient the substrates to avoid steric clash. Thus the substrate is oriented in a fixed conformation with the olefin reactant approaching only from one side, resulting in selective coordination of the olefin and high enantioselectivity.

At the same time, Rovis and co-workers reported a rhodium-catalyzed enantioselective coupling of benzamides and alkenes by artificial metalloenzyme catalysis (Scheme 28).[42] Unlike with other chiral ligands, the highly optimized chiral environments within enzymes provide the distinct advantage of increased reactivity and selectivity. However, their structures are usually tailored to specific biochemical reactions, which limits their reaction scope. To overcome this drawback, Rovis and co-workers engineered a variant of Streptavidin with carboxylate residues inside, which works in concert with a biotinylated rhodium(III)

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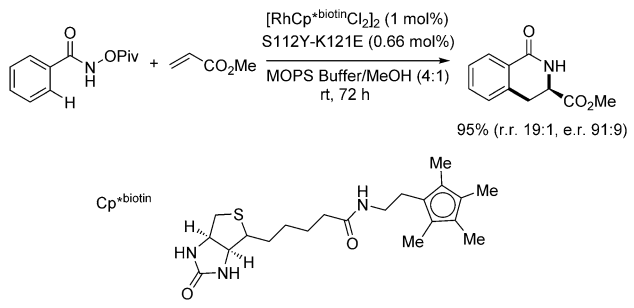
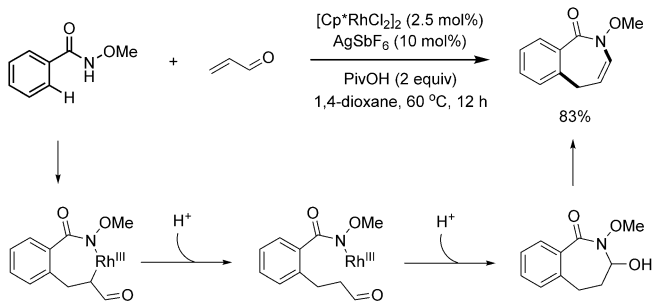


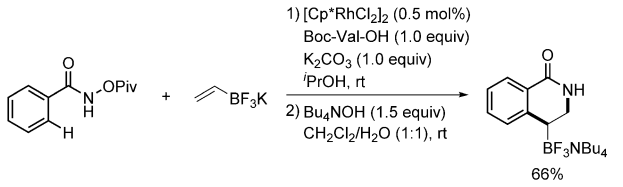
Scheme 28. The first asymmetric Rh^{III}-catalyzed C(sp^2)–H olefination enabled by biotinylated chiral Cp ligands using the *N*-pivaloyloxy amide directing group (Rovis et al., **2012**).[42]



Scheme 30. Rh^{III}-catalyzed C(sp^2)–H annulation with α,β-unsaturated aldehydes and ketones using the *N*-methoxy amide directing group (Glorius et al., **2013**).[44]

complex to promote C(sp^2)–H activation. The installation of a glutamic or aspartic acid group at a specific position inside the chiral cavity of the metalloenzyme provided accelerated reactivity (nearly 100 fold), increased regioselectivity, and excellent enantioselectivity (up to 93:7 e.r.).

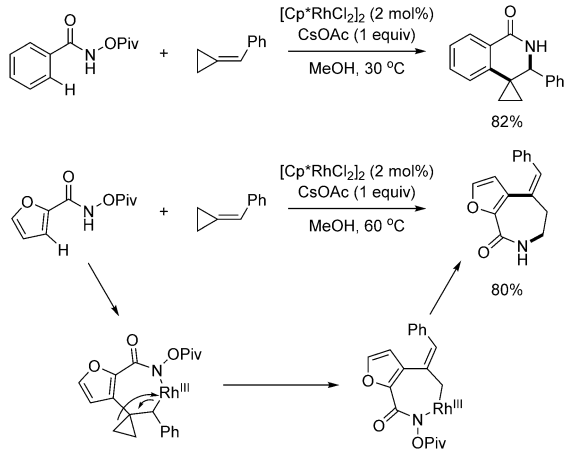
In a very interesting example, Molander and co-workers used potassium vinyltrifluoroborate as the olefin partner in Rh^{III}-catalyzed C(sp^2)–H activation to afford regioisomerically complementary substitution patterns compared to those obtained with other alkenes in related reactions (Scheme 29).[43] The unusual regioselectivity is likely governed by the electronic properties of potassium vinyltrifluoroborate. The boron substituent could be further converted into a hydroxy group.



Scheme 29. Rh^{III}-catalyzed C(sp^2)–H olefination with potassium vinyltrifluoroborate using the *N*-pivaloyloxy amide directing group (Molander et al., **2013**).[43]

The Rh^{III}-catalyzed annulation of benzamides is one of the most efficient ways to build five- and six-membered azaheterocycles. However, in 2012, larger rings had not yet been synthesized through this methodology. In 2013, Glorius and co-workers disclosed a rhodium-catalyzed method to effectively construct seven-membered azepinones by using α,β-unsaturated aldehydes and ketones as the coupling partners to react with the *N*-methoxy benzamide (Scheme 30).[44] To gain insight into the mechanism of this reaction, the hemiaminal intermediate was independently synthesized under standard reaction conditions at room temperature. This intermediate was treated separately with each individual component of the reaction conditions, and it was found that only the rhodium catalyst and/or the silver species yielded the dehydration product. In the proposed mechanism, the Rh^{III} catalyst undergoes protonolysis rather than β-hydride elimination after alkene insertion. The formed Rh–N bond can intramolecularly add across the carbonyl group, delivering a cyclorhodated intermediate, which subsequently undergoes protonolysis to afford the seven-membered hemiaminal. Dehydration of the hemiaminal produces the final product. This method was applied to the synthesis of the homoprotoberberine natural product framework.

In 2013, Cui and co-workers employed highly strained methylenecyclopropanes in Rh^{III}-catalyzed C(sp^2)–H activation using the *N*-pivaloyloxy amide directing group to prepare a variety of spirocyclic dihydroisoquinolines (Scheme 31).[45]



Scheme 31. Rh^{III}-catalyzed C(sp^2)–H olefination with methylenecyclopropanes using the *N*-pivaloyloxy amide directing group (Cui et al., **2013**).[45]

Interestingly, when *N*-pivaloyloxy furan-2-carboxamide was used, an unexpected rearrangement occurred to provide the seven-membered azepinone scaffold.

In 2013, Rovis and co-workers systematically studied the directing group effect on Rh^{III}-catalyzed intramolecular C(sp^2)–H activation with alkenes tethered to the substrate.[46] Three distinct pathways are possible depending on both the directing group and the reaction conditions. After intramolecular alkene insertion, protonolysis, β-hydride elimination, or reductive elimination provide access to different structural scaffolds (Table 3). With the *N*-methoxy amide directing group, protonolysis and β-hydride elimination are

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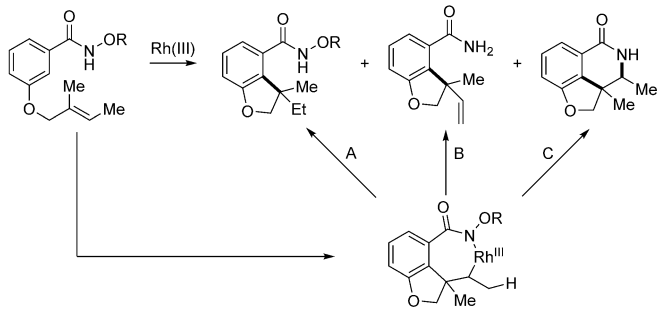
Table 3: The effect of the directing group on Rh^{III}-catalyzed intramolecular $C(sp^2)$–H olefination (Rovis et al., **2013**).[46]

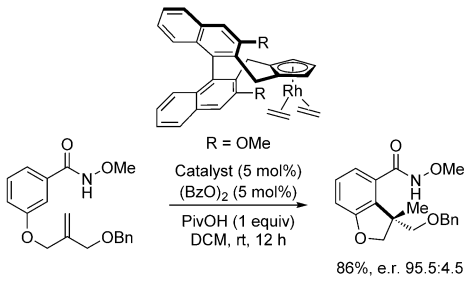


Entry	R	Conditions[a]	Ratio (A/B/C)	Conv.[b] [%]
1	Me	A, 17 h	71:29:0	53
2	Piv	A, 17 h	0:0:100	61
3	Me	B, 2 h	0:100:0	100
4	Piv	B, 12 h	0:22:78	100

[a] A: $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (1 mol%), PivOH (1 equiv), DCE (0.2 M), 80 °C; B: $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOAc (2 equiv), MeOH (0.2 M), RT. [b] Conversion determined by ^1H NMR spectroscopy.

the preferred pathways, whereas with the *N*-pivaloyloxy amide directing group, the reaction favors reductive elimination to form a C–N bond. The rationale for the observed selectivity is analogous to that for the simple systems previously discussed (Scheme 26). Glorius and co-workers later also developed a mild and efficient method for the synthesis of fused oligocyclic lactam skeletons through path C.[47a] Recently, closely related work on the synthesis of arylated spirocycles by Rh^{III}-catalyzed $C(sp^2)$–H activation coupled to an intramolecular Heck-type reaction was published by Chabaud and Guillou (path B).[47b]

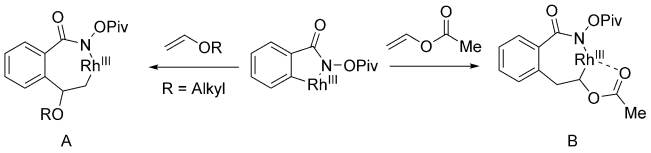
Shortly after the report on Rh^{III}-catalyzed intramolecular $C(sp^2)$–H olefination by Rovis and co-workers, Cramer et al. further expanded their chiral Cp ligand class by introducing a sterically tunable biaryl backbone to render the reaction enantioselective (Scheme 32).[48] Tuning the size of the R group on the biaryl backbone enabled an enantioselective hydroarylation of tethered alkenes, providing enantioenriched dihydrobenzofurans. For the hydroarylation reaction, the *meta*-alkoxy group served as a secondary directing group,



Scheme 32. Asymmetric intramolecular Rh^{III}-catalyzed $C(sp^2)$–H olefination using the *N*-methoxy amide directing group enabled by chiral Cp ligands (Cramer et al., **2014**).[48] Bz = benzoyl, DCM = dichloromethane.

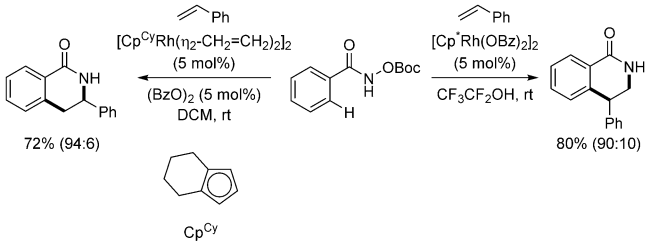
thereby enabling activation of the more hindered *ortho*-$C(sp^2)$–H bond. The ability to modularly tune the steric properties of this Cp ligand should, in principle, allow for a plethora of other enantioselective transformations in combination with C–H activation to be realized.

In 2014, Marsden and co-workers studied the behavior of electron-rich alkenes in Rh^{III}-catalyzed $C(sp^2)$–H activation.[49] Vinyl ether was found to be a convenient acetylene equivalent to enable the synthesis of 3,4-unsubstituted isoquinolones. Based on their observations, the authors claimed that electronic factors favored formation of intermediate A by migration of rhodium to the more electron-rich carbon atom of the enol ether. However, the regioselectivity was reversed when coordinating groups were present, possibly owing to directing effects from the OAc group (Scheme 33).



Scheme 33. Rationale for the regioselectivity observed with electron-rich alkenes in Rh^{III}-catalyzed $C(sp^2)$–H olefination using the *N*-pivaloyloxy amide directing group (Marsden et al., **2014**).[49]

The regioselectivity of the insertion step of styrene derivatives in Rh^{III}-catalyzed $C(sp^2)$–H olefination is generally determined by intrinsic substrate control. However, Cramer and co-workers reported a Cp ligand controlled



Scheme 34. Cp ligand controlled regiodivergent Rh^{III}-catalyzed $C(sp^2)$–H olefination using the *N-tert*-butoxycarbonyloxy amide directing group (Cramer et al., **2014**).[50]

route that enables the regiodivergent synthesis of 3- and 4-aryl dihydroisoquinolones (Scheme 34).[50]

In 2014, Wang and co-workers utilized a modified terminal olefin for the Rh^{III}-catalyzed $C(sp^2)$–H allylation of *N*-methoxy benzamides (Scheme 35).[51] When $R^1 = R^2 = H$ or Me, the *E*/*Z* ratio for the product was generally greater than 20:1. However, when R^1 or R^2 was an alkyl or aryl group and the other one a hydrogen atom, the *E*/*Z* ratio became modest. A tentative mechanism was proposed that implicated a β-oxygen elimination for the release of CO_2 after alkene insertion.

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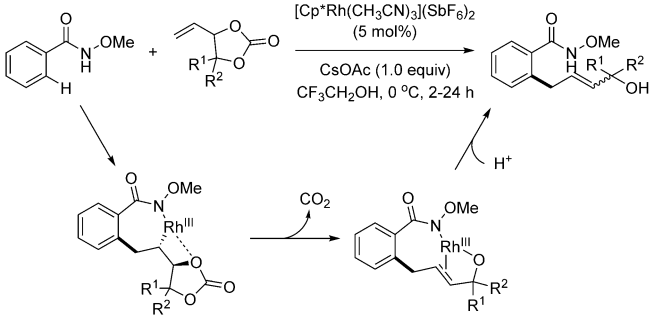
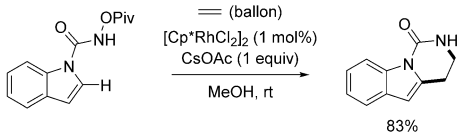


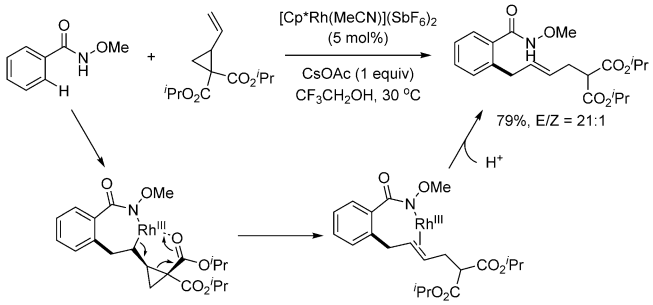
Scheme 35. Rh^{III}-catalyzed $C(sp^2)$–H allylation with 4-vinyl-1,3-dioxolan-2-ones using the *N*-methoxy amide directing group (Wang et al., **2014**).[51]

By using the *N*-pivaloyloxy urea directing group, Cui and co-workers were able to functionalize the 2-position of indoles and pyrroles with a variety of alkenes under similar conditions as those used by Fagnou and Glorius (Scheme 36).[38] Impressively, ethylene gas could be used as a coupling partner in this reaction.



Scheme 36. Rh^{III}-catalyzed $C(sp^2)$–H annulation with alkenes using the *N*-pivaloyloxy amide directing group (Cui et al., **2014**).[38]

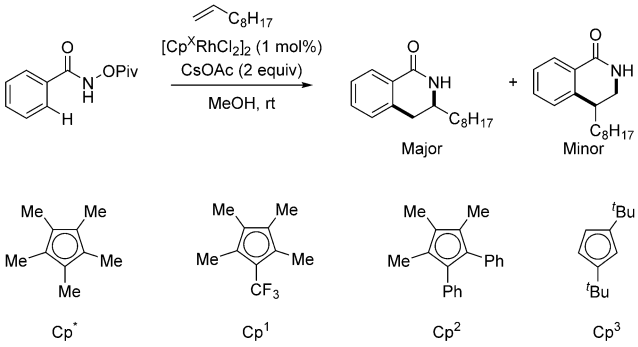
More recently, Wang and co-workers employed a versatile vinylcyclopropane in *N*-methoxy amide directed Rh^{III}-catalyzed $C(sp^2)$–H activation to obtain allylated products (Scheme 37).[52] Tuning the steric bulk of the ester led to good *E*/*Z* selectivity. The reaction pathway likely involves a β-carbon elimination to open the cyclopropane ring.



Scheme 37. Rh^{III}-catalyzed $C(sp^2)$–H allylation with vinylcyclopropanes using the *N*-methoxy amide directing group (Wang et al., **2015**).[52]

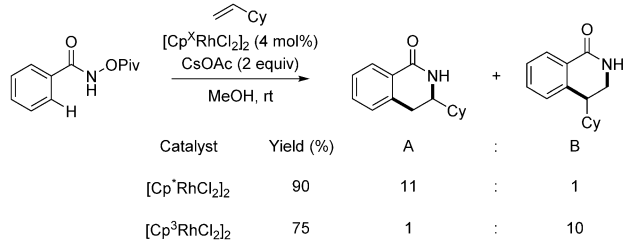
Although alkene insertion into the C–Rh bond derived from $C(sp^2)$–H activation provides numerous useful reactions, when dealing with sterically less demanding terminal alkenes, such as 1-decene, the regioselectivity is commonly problematic. Recently, Rovis and co-workers creatively designed a bulky di-*tert*-butyl-substituted cyclopentadienyl ligand to enable the regioselective synthesis of dihydroisoquinolones.[53] This Cp ligand significantly improved the regioselectivity for migratory insertion compared to the commonly employed Cp* ligand and other Cp ligands (Table 4). Meanwhile, the regioselectivity for the $C(sp^2)$–H activation step decreased for *meta*-substituted substrates, which was explained by the uneven distribution of steric bulk in the Cp^3 ligand. When bulky vinylcyclohexane was used, the alternate regioisomer B was obtained with good selectivity (Scheme 38).

Table 4: Cp ligand design for regioselective Rh^{III}-catalyzed $C(sp^2)$–H annulation with alkyl-substituted terminal alkenes using the *N*-pivaloyloxy amide directing group (Rovis et al., **2015**).[53]



Entry	Catalyst	Yield[a] [%]	Regioselectivity
1	$[Cp^*RhCl_2]_2$	90	2.4:1
2	$[Cp^1RhCl_2]_2$	85	2.4:1
3	$[Cp^2RhCl_2]_2$	82	12:1
4	$[Cp^3RhCl_2]_2$	92	15:1

[a] Determined by ^1H NMR spectroscopy.



Scheme 38. Rh^{III}-catalyzed $C(sp^2)$–H annulation with vinylcyclohexane and different catalysts using the *N*-pivaloyloxy amide directing group (Rovis et al., **2015**).[53]

Based on the work of Glorius and Fagnou, Xu and co-workers extended the alkene scope to quinones to synthesize dibenzo[*b*,*d*]pyran-6-ones (Scheme 39).[54] The *N*-methoxy amide directing group was crucial for the Rh^{III}-catalyzed $C(sp^2)$–H activation. The authors used iodosylbenzene to oxidize hydroquinones to quinones in situ.

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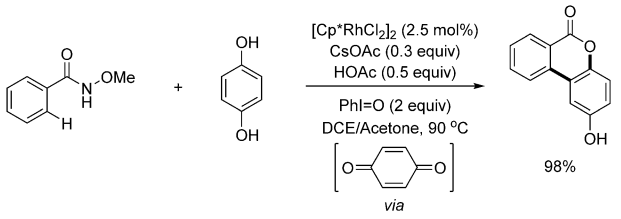
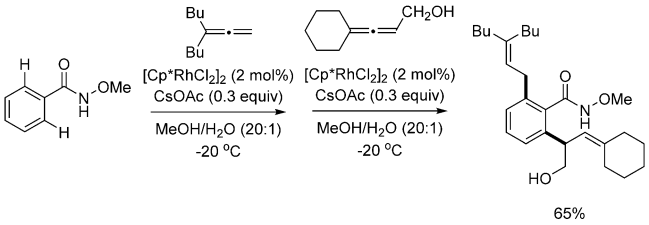


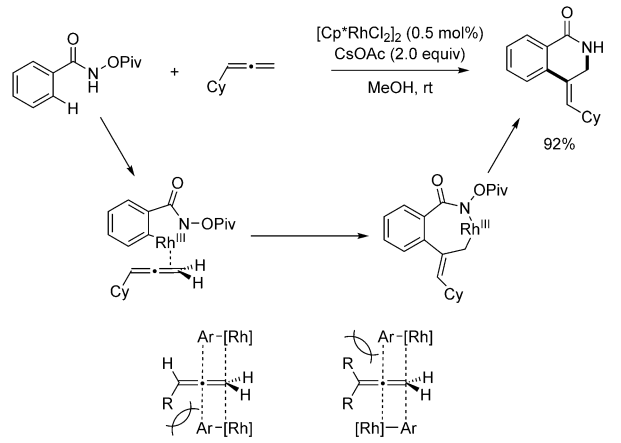
Scheme 39. Rh^{III}-catalyzed $C(sp^2)$–H annulation with hydroquinones using the *N*-methoxy amide directing group (Xu et al., **2015**).[54]



Scheme 41. Stepwise Rh^{III}-catalyzed $C(sp^2)$–H annulation with allenes using the *N*-methoxy amide directing group (Ma et al., **2012**).[56]

3.3. Rhodium(III)-Catalyzed C(sp^2)–H Activation with Allenes

Until 2012, only alkynes and alkenes had been shown to be efficient coupling partners in Rh^{III}-catalyzed $C(sp^2)$–H activation with both the *N*-methoxy and *N*-pivaloyoxy amide directing groups, but not their allene counterparts. To address this shortcoming, Glorius and co-workers explored the reactivity of allenes with these two prevalent directing groups and Rh^{III} catalysts (Scheme 40).[55] Surprisingly, the

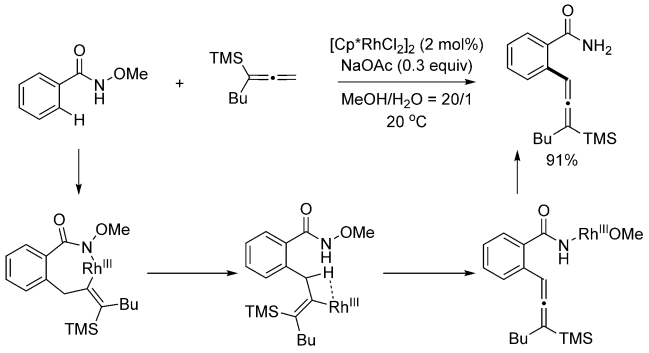


Scheme 40. Rh^{III}-catalyzed $C(sp^2)$–H annulation with allenes using the *N*-pivaloyloxy amide directing group and a rationale for the regioselectivity of the insertion step (Glorius et al., **2012**).[55]

desired product was not observed when *N*-methoxy benzamide was reacted with cyclohexylallene under standard conditions. Fortunately, the *N*-pivaloyloxy amide was able to give the allene insertion product. For monosubstituted allenes, the regioselectivity was determined as depicted in Scheme 40. However, for sterically more congested allenes, different regioselectivities were obtained.

Simultaneously, Ma and co-workers exploited Rh^{III}-catalyzed $C(sp^2)$–H activation reactions with 1,1-disubstituted and trisubstituted allenes using the *N*-methoxy amide directing group (Scheme 41).[56] A slight modification of the reaction conditions enabled the use of the *N*-methoxy amide directing group in this reaction, and the regioselectivity for migratory insertion was consistent with Glorius' result for sterically hindered allenes. However, with the *N*-methoxy amide directing group, protonolysis occurred after allene insertion instead of direct reductive elimination, allowing for redox-neutral catalysis. Notably, this reaction is highly monoselective, enabling the stepwise allylation of benzoic acids.

Ma and co-workers serendipitously discovered that when simply changing one of the substituents of 1,1-disubstituted allenes to a TMS group, the reaction pathway for the Rh^{III}-catalyzed $C(sp^2)$–H activation with 1,1-disubstituted allenes was completely changed (Scheme 42).[57] Interestingly, these



Scheme 42. Rh^{III}-catalyzed $C(sp^2)$–H allenylation with allenylsilanes using the *N*-methoxy amide directing group (Ma et al., **2013**).[57] TMS = trimethylsilyl.

allenes behaved like terminal olefins in related reactions. After allene insertion, the Rh^{III} intermediate underwent β-H elimination rather than protonolysis or reductive elimination to afford trisubstituted allenylsilanes by Rh^{III}/Rh^{I} catalysis.

Shortly after Glorius and Ma had established Rh^{III}-catalyzed $C(sp^2)$–H activation with allenes, Cramer and co-workers set out to find suitable chiral Cp ligands to render the insertion step of this reaction enantioselective (Scheme 43).[58] By tuning the size of the R group on the biaryl backbone of the modified Cp ligand, they achieved the enantioselective allylation of benzamides.

In 2013, Ma and co-workers combined the robustness of Rh^{III}-catalyzed $C(sp^2)$–H activation with the *N*-methoxy amide directing group and the versatile reactivity of allenes to disclose a cascade $C(sp^2)$–H activation with allenols to provide 2,5-dihydrofuran derivatives (Scheme 44).[59]

More recently, Ma and co-workers exploited 1,6-allenenes as coupling partners in Rh^{III}-catalyzed $C(sp^2)$–H activation with the *N*-pivaloyloxy amide directing group to construct eight-membered lactams (Scheme 45).[60]

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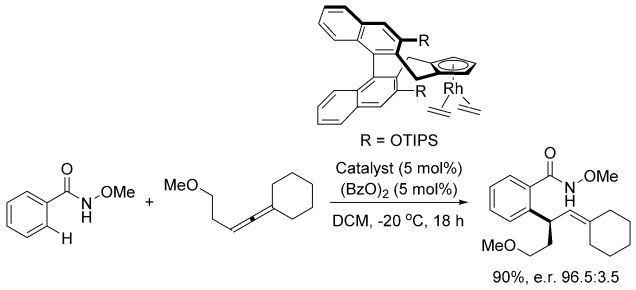
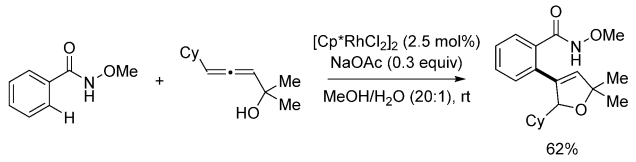
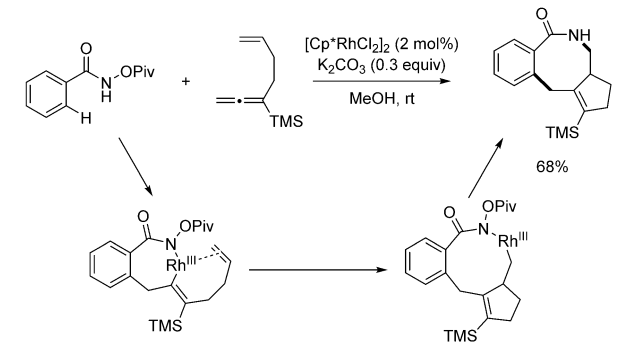


Scheme 43. Asymmetric Rh^{III}-catalyzed $C(sp^2)$–H allenylation using the *N*-methoxy amide directing group enabled by a chiral Cp ligand (Cramer et al., **2013**).[58]



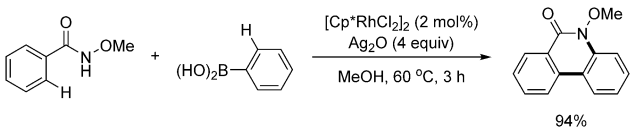
Scheme 44. Rh^{III}-catalyzed $C(sp^2)$–H activation with allenols using the *N*-methoxy amide directing group (Ma et al., **2013**).[59] Cy = cyclohexyl.



Scheme 45. Rh^{III}-catalyzed $C(sp^2)$–H activation with 1,6-allene-enes using the *N*-pivaloyloxy amide directing group (Ma et al., **2015**).[60]

3.4. Rhodium(III)-Catalyzed $C(sp^2)$–H Cross-Coupling with Organometallic Reagents

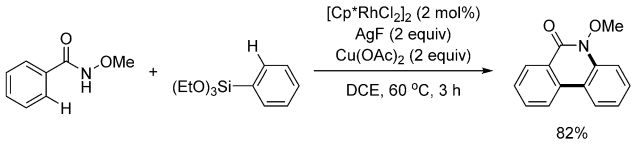
Although Pd-catalyzed couplings of C–H bonds with organometallic reagents have been extensively studied since 2005,[9–11] analogous transformations with Rh^{III} catalysts have not been fully established. In 2012, Cheng and co-workers reported a rare example of such a catalytic transformation for the preparation of phenanthridinones through a Rh^{III}-catalyzed $C(sp^2)$–H coupling of aryl boronic acids using the *N*-methoxy amide directing group. The reaction proceeded by Rh^{III}/Rh^{I} catalysis in a similar fashion to that of Pd^{II}/Pd^{0} redox catalysis (Scheme 46).[61] Ag_2O was used as the external oxidant to enable the dual $C(sp^2)$–H activation. Interestingly, the product arising from C–N reductive elimination was the sole product, unlike in the original report by Fagnou, wherein C–N and C–O reductive elimination proceeded in the presence of an external oxidant. The KIE values were measured by conducting intermolecular KIE experiments



Scheme 46. Rh^{III}-catalyzed $C(sp^2)$–H cross-coupling with aryl boronic acids using the *N*-methoxy amide directing group (Cheng et al., **2012**).[61]

for both the substrate and the coupling partner in parallel and used to determine that the first C–H activation was the rate-limiting step.

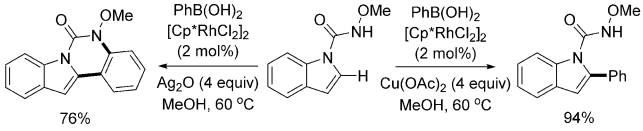
Having developed Rh^{III}-catalyzed $C(sp^2)$–H activation reactions and cross-couplings with organoboronic acids and *N*-methoxy benzamides, Cheng and co-workers further showcased that aryl silanes serve as efficient coupling partners in the same catalytic system to provide a complementary method for phenanthridinone synthesis (Scheme 47).[62] AgF



Scheme 47. Rh^{III}-catalyzed $C(sp^2)$–H cross-coupling with aryl silanes using the *N*-methoxy amide directing group (Cheng et al., **2013**).[62]

was used to promote the transmetalation of the aryl silanes and may serve a secondary role as an external oxidant.

Based on Cheng's work on Rh^{III}-catalyzed $C(sp^2)$–H cross-couplings of benzoic acids with aryl boronic acids utilizing the *N*-methoxy amide directing group, Cui and co-workers expanded the substrate scope from benzoic acids to indoles by attaching the directing group to the nitrogen atom of the indole. By switching the external oxidant, they were able to obtain either 2-arylated products or the products of a subsequent cyclization (Scheme 48).[63]



Scheme 48. Rh^{III}-catalyzed $C(sp^2)$–H cross-coupling with aryl boronic acids using the *N*-methoxy amide directing group (Cui et al., **2014**).[63]

In 2015, Cheng and co-workers expanded the coupling partner scope to organotin compounds by reporting the Rh^{III}-catalyzed $C(sp^2)$–H vinylation of *N*-methoxy benzamides with vinyl stannanes. As the directing group also acts as an internal oxidant, no external oxidant was required (Scheme 49).[64]

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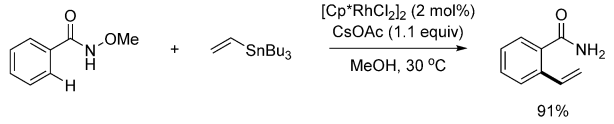
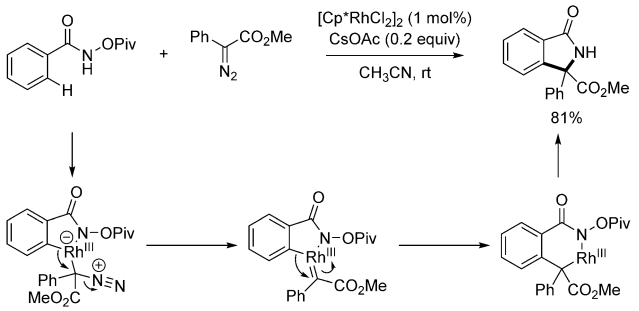


Scheme 49. Rh^{III}-catalyzed $C(sp^2)$–H vinylation with vinyl stannanes using the *N*-methoxy amide directing group (Cheng et al., **2015**).[64]

3.5. Rhodium(III)-Catalyzed $C(sp^2)$–H Activation with Diazo Compounds

As diazo compounds are versatile coupling partners in transition-metal-catalyzed $C(sp^2)$–H activation, Rovis and co-workers examined the reactivity of donor/acceptor diazo compounds in Rh^{III}-catalyzed $C(sp^2)$–H activation with the *N*-pivaloyloxy amide directing group (Scheme 50).[65] A range



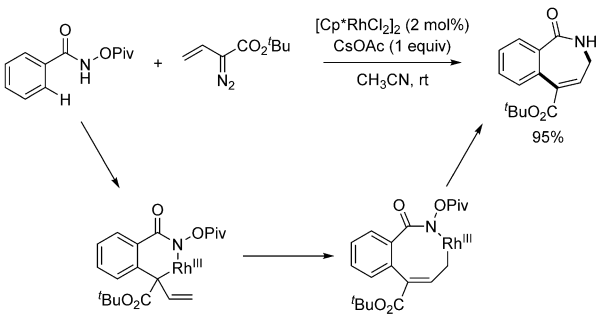
Scheme 50. Rh^{III}-catalyzed $C(sp^2)$–H annulation with diazo compounds using the *N*-pivaloyloxy amide directing group (Rovis et al., **2013**).[65]

of γ-lactams could be formed using this method. The mechanism features the generation of a rhodium carbenoid, which can undergo 1,1-migratory insertion to form the six-membered rhodacyclic intermediate. Wing-Yiu Yu and co-workers also reported a similar reaction with an *N*-acetoxy amide directing group.[66]

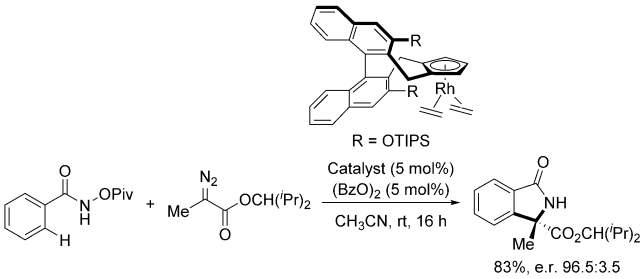
Following Rovis' work on Rh^{III}-catalyzed $C(sp^2)$–H annulation with diazo compounds, in 2013, Cui and co-workers developed a cascade reaction for the synthesis of seven-membered azepinones by using vinyl diazo compounds as the coupling partners (Scheme 51).[67] The reaction pathway is likely to involve a 1,3-allyl migration after diazo insertion.

Being interested in further investigating the ability of their chiral Cp ligands to enable enantioselective transformations, the Cramer group reinvestigated the annulation reaction with diazo compounds (Scheme 52).[68] Notably, the substituent on the ester group had a significant impact on the enantioselectivity. In terms of enantioselectivity, alkyl-substituted diazo compounds performed better than their aryl-substituted counterparts. After optimization of the ligand structure by tuning the R groups, a series of enantiomerically enriched isoindolones could be obtained according to this method.

After Rovis and co-workers had reported the Rh^{III}-catalyzed $C(sp^2)$–H activation of benzoic acid derivatives with diazo compounds, Cui et al. expanded the substrate

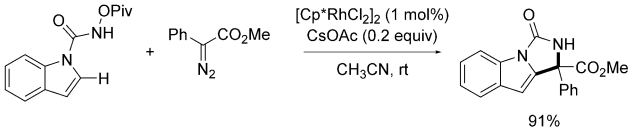


Scheme 51. Rh^{III}-catalyzed $C(sp^2)$–H annulation with vinyl diazo compounds using the *N*-pivaloyloxy amide directing group (Cui et al., **2013**).[67]



Scheme 52. Rh^{III}-catalyzed $C(sp^2)$–H annulation with diazo compounds using the *N*-pivaloyloxy amide directing group enabled by a chiral Cp ligand (Cramer et al., **2014**).[68] Bz = benzoyl.

scope to indoles and pyrroles, functionalizing the 2-position with many diazo compounds by attaching the directing group to the indole or pyrrole nitrogen atom as they had done previously (Scheme 53).[38]



Scheme 53. Rh^{III}-catalyzed $C(sp^2)$–H annulation with diazo compounds using the *N*-pivaloyloxy amide directing group (Cui et al., **2014**).[38]

In an attempt to expand the coupling partner scope for Rh^{III}-catalyzed $C(sp^2)$–H activation with diazo compounds, Cui and co-workers found that the in situ generation of diazo compounds through the reaction of ketones and hydrazine in the presence of excess MnO_2 could expand the scope to donor/donor diazo compounds (Scheme 54).[69] Both aryl alkyl ketones and diaryl ketones were employed to afford isoindolinones.

In 2015, Yi and co-workers described the reaction between *N*-methoxy benzamides and an α-diazotized Meldrum's acid derivative by Rh^{III}-catalyzed $C(sp^2)$–H activation, providing access to *N*-methoxy isoquinolinediones (Scheme 55).[70]

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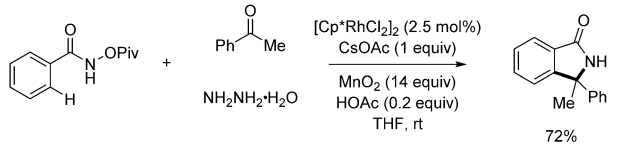
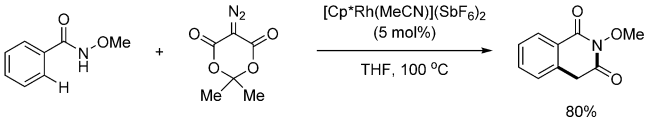


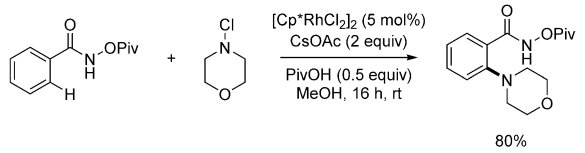
Scheme 54. Rh^{III}-catalyzed C(sp^2)–H annulation with diazo compounds generated in situ using the *N*-pivaloyloxy amide directing group (Cui et al., **2015**).[69]



Scheme 55. Rh^{III}-catalyzed C(sp^2)–H annulation with α-diazotized Meldrum's acid using the *N*-methoxy amide directing group (Xu and Yi et al., **2015**).[70]

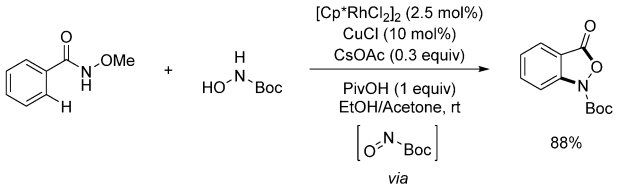
3.6. Rhodium(III)-Catalyzed C(sp^2)–H Amination

In 2012, Glorius and co-workers reported an elegant C–H amination reaction that is enabled by the *N*-pivaloyloxy amide directing group and rhodium catalysis under mild conditions (Scheme 56).[71] A series of six-membered heterocyclic amines were converted into mono-aminated benzoic acid derivatives. However, the scope appeared to be limited to cyclic amines as only one acyclic amine was used and gave the corresponding product in low yield. The deuterium incorporation observed in the absence of an aminating reagent showed that Rh^{III}-catalyzed C–H cleavage is efficient and reversible, whereas no deuterium was incorporated in both the starting material and the product when the model reaction was conducted in deuterated MeOH. This finding indicated that C–N bond formation was significantly faster than the C–H activation step. A large KIE value was measured upon subjecting a 1:1 ratio of benzamide and the corresponding deuterated benzamide to the standard reaction conditions. The proposed plausible mechanism involves an electrophilic amination process after the C–H activation step by redox-neutral catalysis.



Scheme 56. Rh^{III}-catalyzed C(sp^2)–H amination using the *N*-pivaloyloxy amide directing group (Glorius et al., **2012**).[71]

The groups of Zhang and Xu reported a unique hydroxyamidation method by using *N*-hydroxycarbamates as amidating reagents under synergistic Rh/Cu catalysis with *N*-methoxy benzamide substrates (Scheme 57).[72] CuCl (10 mol%) was essential for the reaction to proceed. The authors speculated that the Cu^{I} species catalyzed the oxidation of the *N*-hydroxycarbamate to the nitrosocarbonyl compound, which then acted as an electrophile and reacted with the rhodacycle derived from Rh^{III}-catalyzed C(sp^2)–H activation. The C–Rh bond added across the N=O bond, which was followed by protonolysis and intramolecular condensation to furnish benzo[*c*]isoxazol-3(1*H*)-ones in good yields.

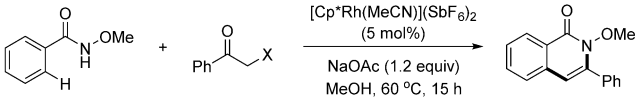


Scheme 57. Rh^{III}-catalyzed C(sp^2)–H hydroxyamidation using the *N*-methoxy amide directing group (Xu and Zhang et al., **2015**).[72]

3.7. Rhodium(III)-Catalyzed C(sp^2)–H Activation with Other Coupling Partners

In 2014, Glorius and co-workers first introduced α-halide and pseudohalide ketones as terminal alkyne equivalents to accomplish the synthesis of nitrogen heterocycles by Rh^{III}-catalyzed C(sp^2)–H activation of *N*-methoxy benzamides.[73] Among the (pseudo)halides screened (Table 5), Cl, OTs, and OMs were effective. The authors proposed a mechanism involving Rh^{III}-catalyzed Grignard-type C–H alkylation, intramolecular condensation, and dehydration.

Table 5: Rh^{III}-catalyzed C(sp^2)–H annulation with α-(pseudo)halo ketones using the *N*-methoxy amide directing group (Glorius et al., **2014**).[73]



Entry	X	Yield[a] [%]
1	Br	10[b]
2	Cl	62
3	OTs	86
4	OMs	86
5	OBz	0

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy.

In the same year, Loh and co-workers first used a hypervalent iodine reagent in Rh^{III}-catalyzed C(sp^2)–H activation with the *N*-pivaloyloxy amide directing group to achieve the *ortho* alkynylation of benzoic acid derivatives (Scheme 58).[74] Notably, the reaction was highly monoselective and compatible with many functional groups on the benzamides. However, the alkyne scope was limited to those containing very sterically hindered groups (TIPS and ^{t}Bu). It is possible that this hypervalent iodine reagent might behave like an internal alkyne during the alkyne insertion step.

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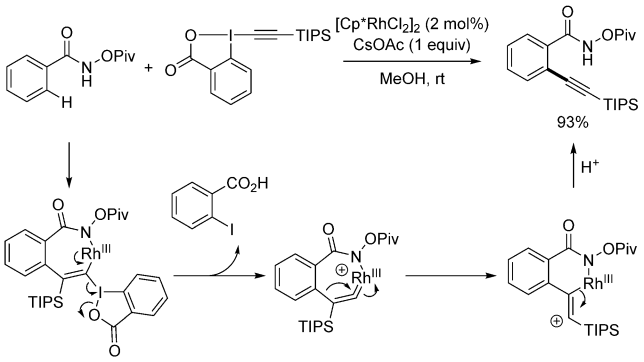
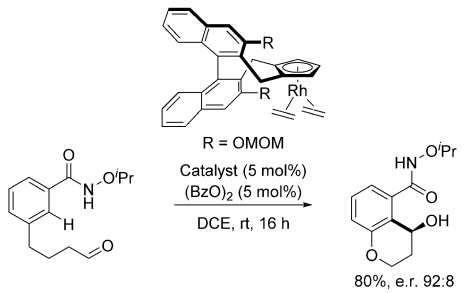


Scheme 58. Rh^{III}-catalyzed $C(sp^2)$–H alkynylation using the *N*-pivaloyloxy amide directing group (Loh et al., **2014**).[74]

In 2015, Cramer and co-workers further showcased the versatility of their chiral Cp ligands by achieving an intramolecular Rh^{III}-catalyzed $C(sp^2)$–H activation with tethered aldehydes to afford hydroxychromanes with moderate to good enantioselectivity (Scheme 59).[75]

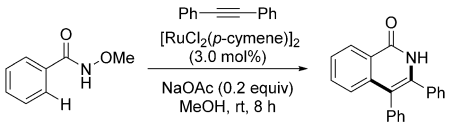


Scheme 59. Intramolecular Rh^{III}-catalyzed $C(sp^2)$–H annulation with aldehydes using the *N*-isopropoxy amide directing group (Cramer et al., **2015**).[75] MOM = methoxymethyl.

Since the first demonstration that the simple *N*-methoxy amide is an efficient directing group for Pd^{II}-catalyzed C–H activation, a plethora of Rh^{III}-catalyzed $C(sp^2)$–H activation reactions using the *N*-methoxy or related pivaloyloxy amide directing group have been developed within the last five years. However, to date, this directing group has only been shown to be effective for $C(sp^2)$–H activation with rhodium catalysis. It is likely that future efforts utilizing this directing group will be directed towards expanding its applicability to the activation of $C(sp^3)$–H bonds, as already demonstrated in palladium catalysis.[15,16,27]

4. Ruthenium Catalysis

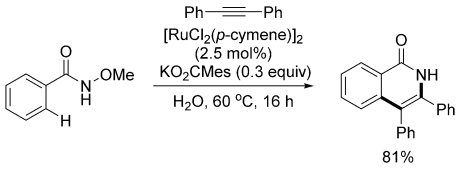
Ru^{II} catalysts have also been found to catalyze C–H activation reactions through redox chemistry analogous to that of Pd^{II}/Pd^0 and Rh^{III}/Rh^I catalysis. Wang and co-workers reported the first example of using a less-expensive ruthenium catalyst to prepare isoquinolones by annulation of alkynes with *N*-methoxy benzamides (Scheme 60).[76] The reaction conditions and substrate scope are similar to those of



Scheme 60. The first Ru^{II}-catalyzed $C(sp^2)$–H annulation with internal alkynes using the *N*-methoxy amide directing group (Wang et al., **2011**).[76] *p*-cymene = 4-isopropyltoluene.

the corresponding rhodium-catalyzed reactions. However, when *meta*-substituted benzamide substrates are used, a noticeable amount of the regioisomer that is due to activation of the more hindered $C(sp^2)$–H bond was commonly observed. Especially when the substituent was an electronegative heteroatom, such as oxygen or bromine, the unusual regioisomer became dominant. The observed selectivity was proposed to be due to the C–H bond acidity or Ru–C bond stability.

Also in 2011, Ackermann and co-workers, following their own extensive studies on Ru^{II}-catalyzed C–H activation,[77] further showcased the robustness of the alkyne annulation reaction with H_2O as the reaction medium in the presence of a sterically hindered carboxylate salt, KO_2CMes (Scheme 61).[78] In the presence of this additive, free hydroxamic acid could be directly used as the directing group. The combination of carboxylate assistance with the *N*-methoxy amide directing group in ruthenium-catalyzed $C(sp^2)$–H functionalization has enabled mild and environmentally friendly reaction conditions, providing facile access to isoquinolone derivatives. Similar regioselectivity was also observed for *meta*-substituted substrates, indicating the generality of this trend.



Scheme 61. Ru^{II}-catalyzed $C(sp^2)$–H annulation with internal alkynes using the *N*-methoxy amide directing group (Ackermann et al., **2011**).[78] Mes = mesityl.

By mimicking Rh^{III}-catalyzed $C(sp^2)$–H olefination, Wang and co-workers showed that ruthenium catalysts are also capable of catalyzing olefination reactions with the *N*-methoxy amide directing group (Scheme 62).[79] In reactions with acrylate derivatives, similar reactivity as for rhodium catalysis was observed. However, the cyclized products were formed when styrene or cyclic alkenes were used, indicating that there is indeed a difference in reactivity between rhodium and ruthenium catalysis. For *meta*-substituted substrates, the usual regioselectivity was also observed with ruthenium catalysis.

After extensive studies on Ru^{II}-catalyzed $C(sp^2)$–H functionalization with alkynes and alkenes, allenes were also successfully employed by the Ackermann group in 2015,

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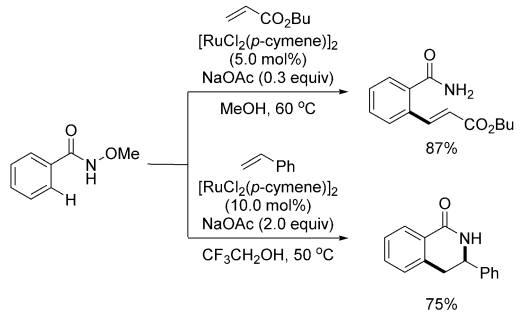
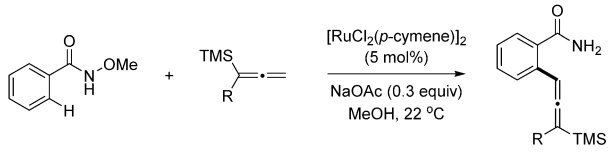


Scheme 62. Ru^{II}-catalyzed C(sp^2)–H activation with alkenes using the *N*-methoxy amide directing group (Wang et al., **2011**).[79]

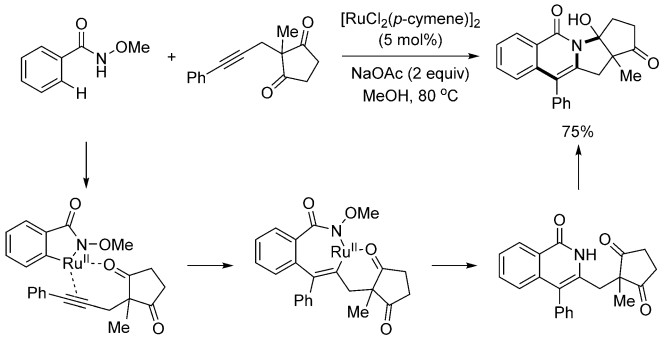
albeit with relatively limited allene scope compared to those of the corresponding rhodium-catalyzed processes (Scheme 63).[80] Notably, the reaction became sluggish when



Scheme 63. Ru^{II}-catalyzed C(sp^2)–H allenylation with allenylsilanes using the *N*-methoxy amide directing group (Ackermann et al., **2015**).[80]

the R substituent was a methyl, cyclopropyl, benzyl, or phenyl group. The bulky TMS group was also crucial for this reaction, and its replacement with a *tert*-butyl substituent resulted in lower yields.

In 2016, Chegondi and co-workers reported a carbonyl-assisted reverse regioselective cascade reaction for the synthesis of complex molecules by Ru^{II}-catalyzed C(sp^2)–H annulation of *N*-methoxy benzamides with 2-acetylenic ketones (Scheme 64).[81] The weak intermolecular coordination of the carbonyl group to the Ru^{II} center sets up the regioselectivity for the alkyne insertion. Subsequent reductive elimination and reoxidation of the catalyst followed by



Scheme 64. Ru^{II}-catalyzed C(sp^2)–H annulation with 2-acetylenic ketones using the *N*-methoxy amide directing group (Chegondi et al., **2016**).[81]

intramolecular nucleophilic attack of the amide on the carbonyl group delivered the final product.

Whereas Ru^{II}-catalyzed reactions using the *N*-methoxy or *N*-pivaloyloxy directing groups are still underdeveloped at present, it is reasonable to anticipate further advances in this direction owing to its lower cost. Though it may be naive, the question remains as to how generally ruthenium, in combination with the *N*-methoxy or *N*-pivaloyloxy directing group, can replace the more expensive rhodium catalysts that have been used so extensively in the literature. Furthermore, the discovery of reactivity that diverges from rhodium catalysis might be of even greater interest.

5. Conclusion

One of the most appealing features of directed C–H activation is that C–H activation can occur highly selectively at a strategically desired position despite the presence of multiple C–H bonds with similar electronic and steric environments. To render this approach broadly useful, the design of simple, effective, and broadly applicable directing groups is crucial. In this Review, we have described the early studies of the coordination mode of alkali metal carboxylates with Pd^{II} catalysts in carboxylate-directed C–H activation, and how this understanding provided insight that enabled the development of the *N*-methoxy amide directing group. A plethora of examples of various C–H activation transformations catalyzed by an array of metal catalysts showcase the extraordinary versatility of the *N*-methoxy amide and closely related directing groups. It is most exciting that this simple directing group can cooperate with pyridine-type ligands to promote the activation of C(sp^3)–H bonds with Pd^{II} catalysts. We eagerly anticipate the further exploitation of this directing group towards the development of truly practical C–H activation reactions.

Acknowledgements

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