C–H Activation

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Mild Rhodium(III)-Catalyzed C–H Activation and Intermolecular Annulation with Allenes**

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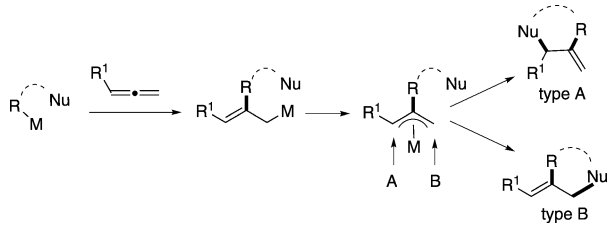
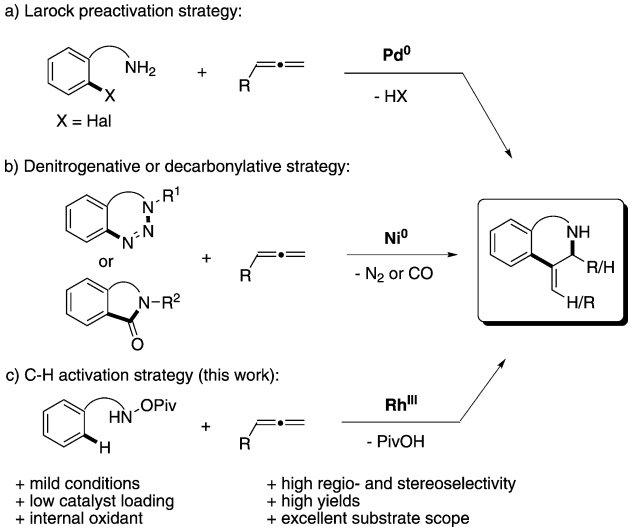
Dedicated to Professor Matthias Beller on the occasion of his 50th birthday

The carbometalation reaction of allenes provides efficient access to highly versatile and reactive π-allyl metal species (Scheme 1).[1] These intermediates can undergo Tsuji–Trost-type substitutions in the presence of external nucleophiles to yield the allylic functionalized products. Intramolecular versions of this reaction lead to interesting carbo- or heterocyclic skeletons, frequently found in pharmaceuticals and materials.[2]



Scheme 1. Carbometalation reaction of allenes.



Scheme 2. Heterocycle synthesis through annulation of allenes.

Pioneered by Larock et al., the heteroannulation of allenes has proven to be a valuable method for the synthesis of a variety of heterocycles (Scheme 2a).[3] However, this method necessitates the use of halogenated starting materials, which require extra synthetic operations thus limiting their availability. Alternatively, methods involving the denitrogenative or decarbonylative coupling of either triazoles[4] or phthalimides[5] with allenes have also been reported, although the limited availability of the precursor is a major concern (Scheme 2b). An enduring objective in synthetic chemistry is to design reaction systems that 1) employ cheap, readily accessible starting materials, 2) proceed under mild conditions, and 3) minimize the production of toxic byproducts. Herein, we disclose a Rh^{III}-catalyzed intermolecular annulation of *N*-pivaloyloxy benzamides with allenes as a straightforward and economical alternative for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones, a biologically important motif widely found in alkaloids and other bioactive compounds.[6]

The past years have witnessed the success of Rh^{III} catalysts in C–H functionalization reactions.[7,8–15] Nevertheless, besides a few other examples such as imines,[8] isocyanates,[9] aldehydes,[10] CO,[11] chloroamines,[12] and most recently arenes,[13] the most versatile coupling partners are activated alkenes[14] and alkynes.[15] Though allenes have been widely applied in transition-metal-catalyzed reactions,[16] the application of this synthetically attractive functional group in C–H activation reactions remains rare.[17]

Previously, we[14l] and others[15h,i] independently reported on Rh^{III}-catalyzed C–H functionalization reactions with alkenes or alkynes proceeding under mild conditions[18] by application of benzhydroxamic acid derivatives as directing groups and internal oxidants.[19] Encouraged by these results, we focused on the oxidative coupling of allenes, which would deliver some interesting heterocycles.

We initially examined the Rh^{III}-catalyzed coupling reaction of *N*-methoxybenzamide (**1**)[20] with cyclohexylallene (**3a**) in the presence of a substoichiometric amount of CsOAc in MeOH.[14l] However, no desired product was observed (Table 1, entry 1). To our delight, the application of **2a** as the substrate at room temperature resulted in the formation of 3,4-dihydroisoquinolin-1(2*H*)-one **4aa** in 62% yield (entry 2).

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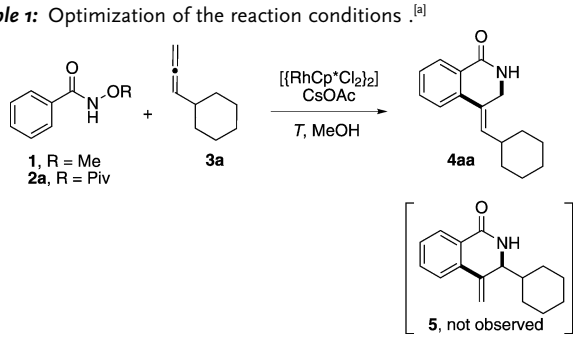
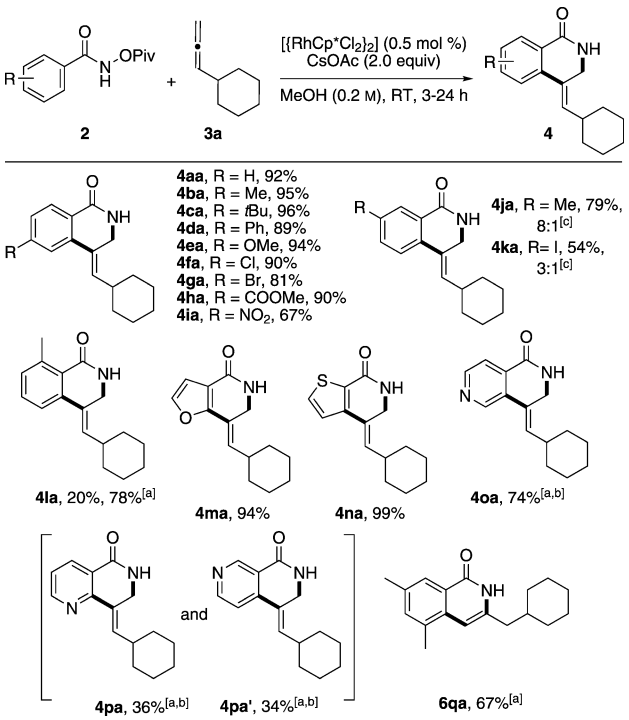
Table 1: Optimization of the reaction conditions .[a]



Entry	Substrate	[{RhCp*Cl_2}$_2$] [mol%]	CsOAc [equiv]	Allene **3a** [equiv]	Yield[b] [%]
1[c]	**1**	2.5	0.3	2.0	0
2	**2a**	2.5	0.3	2.0	62
3	**2a**	0.5	0.3	2.0	64
4	**2a**	0.25	0.3	2.0	19
5	**2a**	0	0.3	2.0	0
6	**2a**	0.5	2.0	2.0	92 (78)[d]
7	**2a**	0.5	2.0	1.1	56

[a] Reaction conditions: **1** or **2a** (0.4 mmol), allene **3a**, [{RhCp*Cl_2}$_2$], CsOAc, MeOH (2 mL), RT, 16 h. [b] Yields of isolated products; ratio of **4aa** to other isomers: >99:1 based on GC–MS analysis. [c] 60°C. [d] 4 mmol scale based on **2a**.



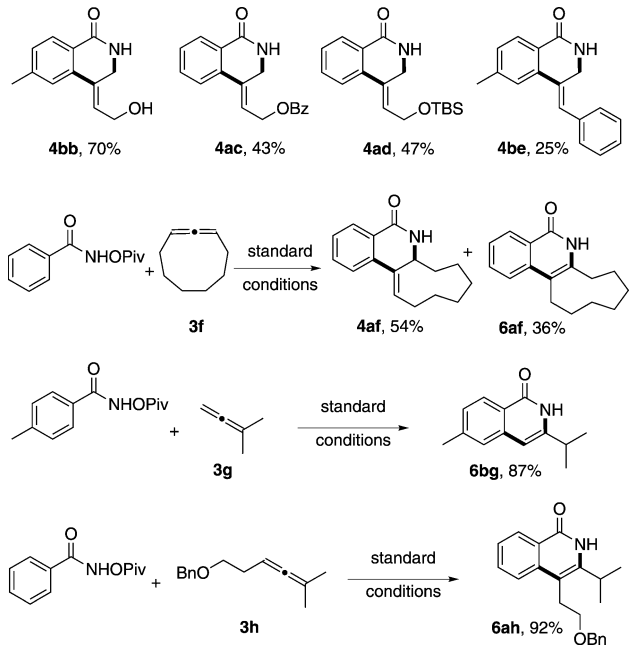
Scheme 3. Rh^{III}-catalyzed annulation of *N*-pivaloyloxyarene amides **2** with cyclohexylallene (**3a**). General reaction conditions: **2** (0.4 mmol), **3a** (0.8 mmol), [{RhCp*Cl_2}$_2$] (0.5 mol%), CsOAc (0.8 mmol), MeOH (2 mL), RT. [a] [{RhCp*Cl_2}$_2$] (2.5 mol%). [b] 40°C. [c] Ratio of **4** to other isomers .

It should be noted that **4aa** was the only isomer detected, indicating a highly regio- and stereoselective reaction. The newly formed exocyclic double bond allows for further functionalization (vide infra). Gratifyingly, comparable catalytic activity was achieved with a much lower catalyst loading (0.5 mol% of dimer) (entries 3 and 4). Omission of Rh^{III} completely shut down the reactivity, demonstrating its importance (entry 5). We also found that increasing the CsOAc loading to 2 equiv considerably accelerated the reaction and improved the yield to 92%.[15i,21] Notably, this procedure is practical and scalable as 78% yield was obtained when the reaction was conducted on a 4.0 mmol scale. Attempts to lower the allene loading failed and the yield decreased significantly (entry 7).

Intriguingly, the regioselectivity of the C–N bond-formation step (Scheme 1, type B) was in sharp contrast with that observed in other preactivation strategies (Scheme 1, type A),[3–5,17] wherein the nucleophilic attack or reductive elimination predominantly occurred at the more substituted end of the π-allyl metal intermediate. This unique feature might arise from the steric hindrance of the Cp* ligand, and the complete reversal of the selectivity may also benefit from the rather mild conditions of this reaction.

The optimized reaction conditions were applicable to a broad range of electron-poor and -rich aromatic substrates (Scheme 3). Many valuable functional groups such as methoxy (**4ea**), ester (**4ha**), chloro (**4fa**), bromo (**4ga**), iodo (**4ka**), and nitro (**4ia**) were well tolerated, providing ample opportunity for further derivatization of the products. In the reactions of *meta*-substituted substrates, good regioselectivity favoring activation of the less hindered C–H bond was observed (**4ja** and **4ka**). The *ortho* substituent retarded the reaction, possibly because of steric interference. However, when the catalyst loading was simply increasedto 2.5 mol%, the corresponding product **4la** was obtained in 78% yield. As another strong point, heterocycles are very well tolerated, leading to valuable products. Electron-rich heterocycles like furan **2m** and thiophene **2n**, which could potentially be oxidized under oxidative conditions, gave the cyclized products in excellent yields. It is worth mentioning that the C–H activation took place exclusively at the α position of the furan when **2m** was employed. Owing to the prevalence of pyridine in natural products and pharmaceuticals, the direct C–H functionalization of pyridine represents a challenging but attractive method. We were pleased to find that nicotinic (**2p**) and isonicotinic acid (**2o**) derivatives are suitable substrates providing the corresponding products in good yields under slightly modified conditions.[22] A 1:1 mixture of regioisomers **4pa** and **4pa′** was observed when a nicotinic acid derivative was applied. It is surprising that the 3,5-dimethylbenzamide derivative, in which both of the *ortho* positions are potentially shielded, was found to react readily. However, an unusual regioselectivity of the allene partner was observed in this case, and the 3-substituted isoquinolone **6qa** was obtained in 67% yield, implying that the reaction outcome is sensitive to the steric properties of the arene partner.

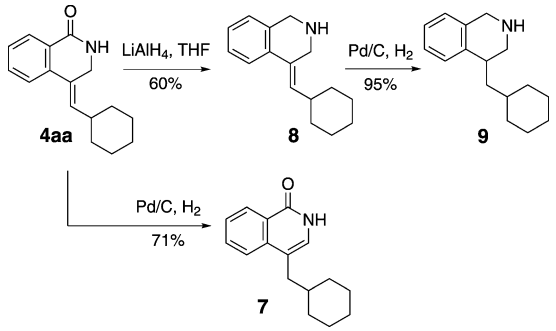
The substrate scope was further extended to include a wide variety of mono- and multisubstituted allenes (Scheme 4). Monosubstituted allenes bearing hydroxy (**4bb**), ester (**4ac**), and silyl ether (**4ad**) functional groups can be smoothly transformed into the desired products. In accordance with previous observations,[3–5,17] an allene with an



Scheme 4. Rh^{III}-catalyzed annulation of *N*-pivaloyloxy benzamides with different allenes **3**. For general reaction conditions, see Scheme 3.

aromatic substituent gave a lower yield (**4be**). The use of 1,3-disubstituted allene **3f** furnished the tricyclic structure **4af** in 54% yield, however, together with the disubstituted isoquinolone product **6af** (36% yield). The 1,1-disubstituted allene **3g** can also be employed as an efficient coupling partner, affording isoquinolone **6bg** in 87% yield. In this case, the regioselectivity of the allene was controlled by steric factors thus yielding a product similar to **6qa**. It is impressive that even the 1,1,3-trisubstituted allene **3h** can participate in this reaction, giving dialkyl-substituted isoquinolone **6ah** as the sole isomer in excellent yield. Notably, the more sterically demanding *i*Pr group was installed at the 3-position rather than the 4-position, which stands in contrast to the typical selectivity observed with unsymmetrical dialkyl alkyne coupling partners.

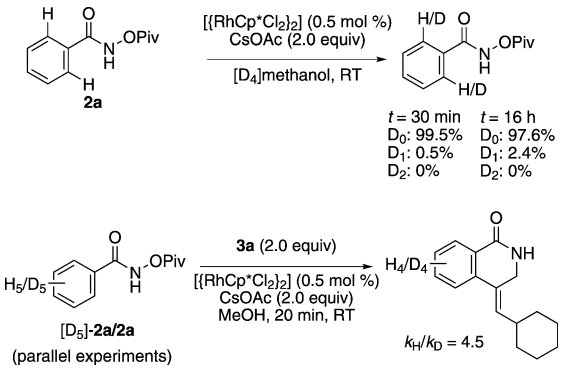
Importantly, the exocyclic double bond provides additional opportunities for elaborating the products (Scheme 5). For example, two subsequent reduction steps allowed the construction of the 4-substituted tetrahydroisoquinoline **9**, a very valuable skeleton in drugs and biologically active



Scheme 5. Derivatization of 3,4-dihydroisoquinolin-1(2*H*)-one **4aa**.

compounds.[23] In addition, the double bond could also be isomerized into the cycle to yield the 4-substituted isoquinolone **7** by a simple operation.

To gain insight into the mechanism, deuteration experiments and a kinetic isotope effect (KIE) study were conducted (Scheme 6). In contrast to our previous observation,[12a] no obvious deuterium incorporation was detected

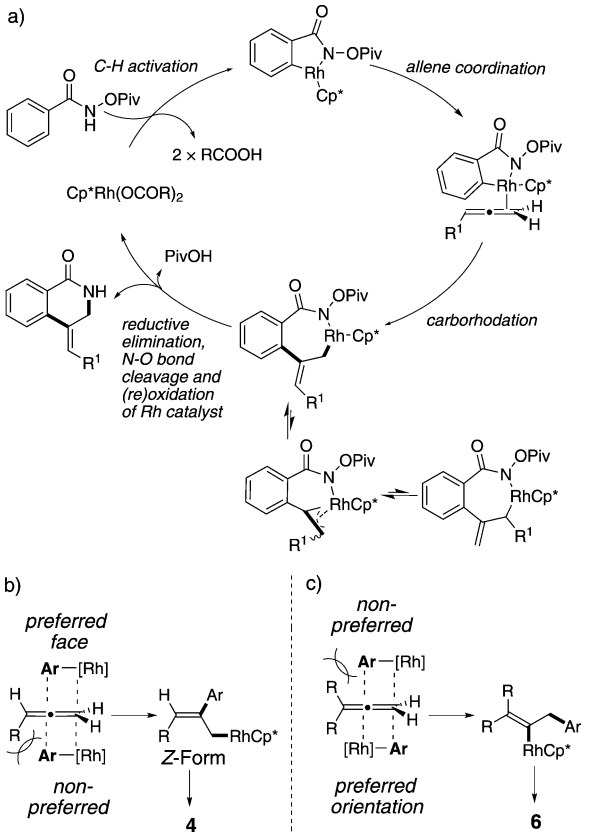


Scheme 6. Deuteration experiments and the study of kinetic isotope effect.

when the reaction was carried out in $[D_4]$methanol in the absence of the allene. This may be attributed to the low catalyst loading and the absence of the reactive proton source PivOH. A primary KIE value of 4.5 was observed, clear evidence that C–H bond cleavage is the rate-determining step.

On the basis of these experiments and literature precedent,[14l,15h,i,24] we propose the mechanism shown in Scheme 7. C–H activation is the rate-determining step and may follow a concerted metalation/deprotonation (CMD) pathway. In standard cases, the carborhodation of allene is governed by electronic factors and a C–C bond is formed with the central carbon atom of the allene moiety. The seven-membered rhodacycle could slowly isomerize to other allylic species. Nevertheless, a reductive elimination occurring preferentially at the less hindered carbon affords the product with an exocyclic double bond. The Rh^{III} catalyst is regenerated by the cleavage of the N–O bond (Scheme 7a). The attack from the sterically less encumbered face of the allene may account for the formation of the *Z* product (Scheme 7b). When more-substituted allenes or sterically hindered aromatic amide derivatives are used, the regioselectivity of the insertion step is reversed, suggesting that steric interference outweighs the electronic factors in these cases (Scheme 7c). In addition, the observation that the regioselectivity of the allene was influenced by the steric effect of the arene (**6qa**) clearly demonstrates that the allene was inserted into the Rh–C bond rather than the Rh–N bond.

In summary, we have developed a novel and efficient Rh^{III}-catalyzed intermolecular annulation of benzamide derivatives with allenes for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones. This reaction features high regio- and stereoselectivity, impressive substrate scope for both coupling partners, and excellent functional group tolerance. Moreover,



Scheme 7. Plausible reaction mechanism and rationale for the regio- and stereoselectivity. a) Proposed mechanism. b) Rationale for obtaining the *Z* form of the double bond (facial selectivity). c) Rationale for the obtained regioselectivity when sterically congested allenes or arenes were used (positional selectivity).

the reaction proceeds under mild conditions at low catalyst loading and does not require external oxidants. Furthermore, we have demonstrated that the products can be easily transformed into other biologically important skeletons. We expect this new protocol to complement existing preactivation methods and to evoke more C–H activation reactions using allenes as coupling partners.

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