C–H Activation

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Cobalt-Catalyzed sp^2-C–H Activation: Intermolecular Heterocyclization with Allenes at Room Temperature

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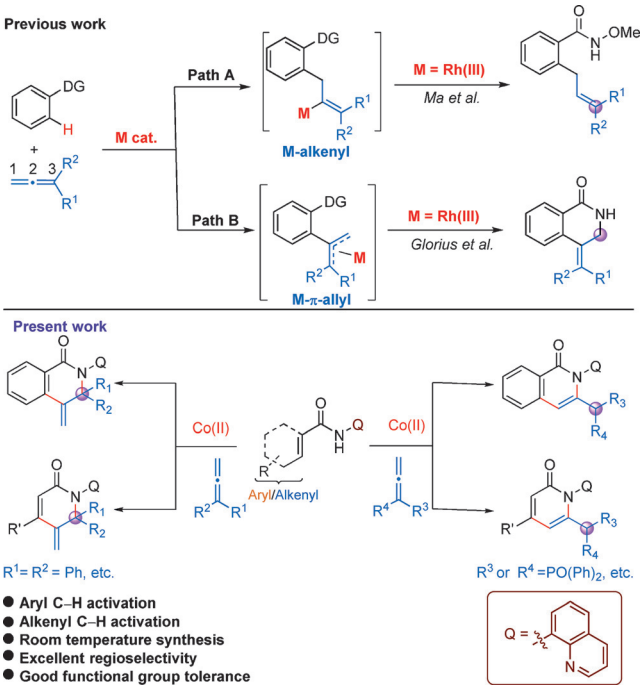
Abstract: *The reactivity of allenes in transition-metal-catalyzed C–H activation chemistry is governed by the formation of either alkenyl–metal (M–alkenyl) or metal–π-allyl intermediates. Although either protonation or a β-hydride elimination is feasible with a M–alkenyl intermediate, cyclization has remained unexplored to date. Furthermore, due to the increased steric hindrance, the regioselectivity for the intramolecular cyclization of the metal–π-allyl intermediate was hampered towards the more substituted side. To address these issues, a unified approach to synthesize a diverse array of biologically and pharmaceutically relevant heterocyclic moieties by cobalt-catalyzed directed C–H functionalization was envisioned. Upon successful implementation, the present strategy led to the regioselective formation of dihydroisoquinolin-1(2H)-ones, isoquinolin-1(2H)-ones, dihydropyridones, and pyridones.*

Allenes have two orthogonal carbon–carbon double bonds and have been explored in a wide variety of metal-catalyzed transformations, including C–H functionalization reactions.[1] The pattern of insertion of an organometallic intermediate R–M with allene is governed by the nature of the metal M and also depends on the steric and electronic nature of the substituents R^1 and R^2. Carbometallation of R–M can take place either on C1 or C2 of the allene, which will lead to either an M–alkenyl or M–π-allyl intermediate, respectively (Scheme 1). Protonation or a β-hydride elimination has previously been explored with an M–alkenyl intermediate by employing rhodium[2] and iridium[3] catalysts.

In a pioneering study, Ma demonstrated the Rh^{III}-catalyzed hydroarylation reaction of allenes proceeding through the protonation of a Rh–alkenyl intermediate (Scheme 1, path A).[4] However, the cyclization pathway leading to biologically and pharmaceutically relevant compounds through an M–alkenyl intermediate has never been realized. Additionally, the M–π-allyl intermediate can undergo Tsuji–Trost type substitutions in the presence of external nucleophiles to afford the functionalized products. In particular, benzamides usually undergo cyclization at the less substituted end of the allene to avoid steric hindrance (M–π-allyl, M = Rh and Pd).[5] Glorius reported the Rh^{III}-catalyzed oxidative annulation of allenes with benzamides, which takes place preferentially at the less hindered side (Scheme 1, path B).[6] In 2010, the groups of Cramer[7] and Takai[8] independently described an imine directed cyclization with allenes. However, regioselective cyclization reactions at the more substituted end of the allene remain unexplored for aryl and alkenylamides. Herein, we report a unified approach for synthesizing versatile heterocycles by controlling the electronic nature of the allene and cobalt catalyst (first-row transition metal) through a directed C–H functionalization (Scheme 1).



Scheme 1. Overview of the work.

Recently, cobalt catalyzed C–H activation has gained much interest, and excellent reports in this area have come from the groups of Nakamura,[9] Kanai,[10] Yoshikai,[11] Ackermann,[12] Daugulis,[13] and others.[14] Based on the prior success of allene interaction with organometallic intermediates,[5,15] benzamide was employed as the model substrate for cobalt-catalyzed sp^2-C–H activation. Anchoring cobalt in close proximity to benzamide and stabilizing the metallacycle for the allene insertion was planned using the bidentate chelator 8-aminoquinoline.[16] The allene was expected to interact with the cobaltacycle intermediate generated by facile C–H activation of benzamide.

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A combination of benzamide (**1a**) and phenylallene was reacted with readily available $Co(acac)_2$ at room temperature. After optimization (see Supporting Information), we were delighted to observe the formation of dihydroisoquinolin-1(2*H*)-one (**2a**) as the major isomer (5:1 regioisomers, as observed by ^{1}H NMR), the structure of which was confirmed by X-ray crystallography. Detailed optimization revealed that the use of $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant and $NaOPiv{\cdot}H_2O$ as the base in trifluoroethanol was crucial for obtaining good yields of **2a** (for crystallographic data, see Ref. [18]). The reaction showed a high regioselectivity for the heterocyclization at the more substituted side, which proceeded through a Co–π-allyl intermediate. This is in sharp contrast with the Rh^{III}-catalyzed C–H activation reactions,[6] in which reductive elimination took place predominantly at the less sterically hindered side. We attribute this difference in selectivity to the smaller ionic radius of cobalt compared to rhodium. Subsequently, a broad range of electron-poor and electron-rich aromatic substrates were investigated (**2b–p**, Table 1). Several valuable functional groups such as methoxy (**2d**), fluoro (**2e**), chloro (**2f**), and bromo (**2g**) groups were tolerated at different positions of **1,** providing ample opportunity for further derivatization of the products. Meta-substituted benzamides resulted in complicated mixtures of regioisomers with phenylallene.

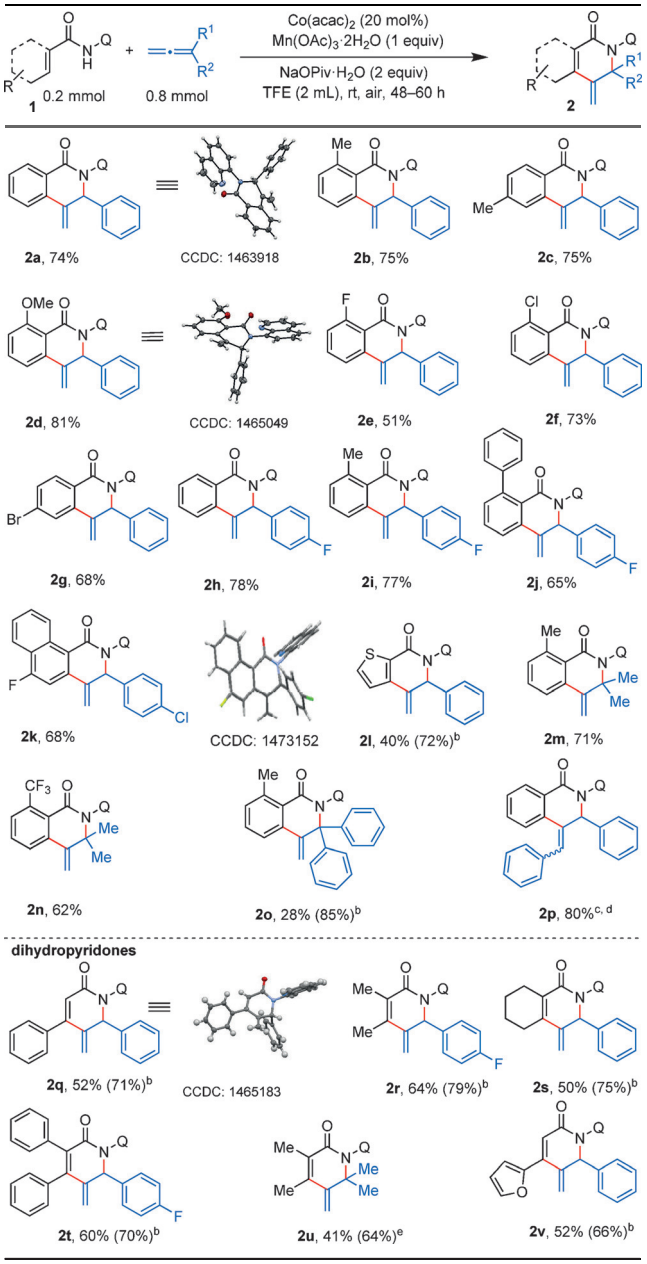
The reaction was also applicable to 2-biphenyl and 1-naphthyl derivatives, which provided the corresponding highly functionalized products **2j** and **2k** in synthetically useful yields. The structure of **2k** was confirmed by X-ray crystallography. Interestingly, the same regioselectivity was observed for sterically demanding 1,1-dimethylallene (**2m** and **n**) and 1,1-diphenyl substituted allene (**2o**), which furnished the corresponding dihydroisoquinolin-1(2*H*)-ones in good yields. Notably, 1,3-diphenylallene provided the product **2p** in excellent yield.

Gratifyingly, the reaction was not restricted to aromatic amides. Olefinic carboxamides under the same conditions provided the expected dihydropyridones. As shown in Table 1, the heterocyclization of cinnamic acid amide with phenylallene afforded the corresponding dihydropyridone (**2q**) through alkenyl sp^2 C–H activation. Evidently, irrespective of the steric demand in arylallene and 1,1-dimethylallene, both allenes provided the corresponding dihydropyridones (**2q–v**) in good yields (Table 1).

Variation of the electronic properties of the allene has the potential to change their reactivity patterns. Interestingly, changing the allene partner from aryl allene to an electron deficient allene such as allenyl phosphonate led to the formation of isoquinolinones (**3a–j**) or pyridone **3k** as the sole products with aryl or alkenyl amides, respectively (Table 2; for crystallographic data, see Ref. [18]). As expected, 1-phenyl-substituted allenyl phosphonate also provided the same regioisomeric product **3j** with excellent yield (Table 2). In addition to aryl amides, heterocyclic derivatives like thiophene (**3g**) and quinoline (**3h**) were also compatible. After evaluating the scope with allenylphosphonates, other allenes were tested under the optimal reaction conditions. In the case of cyclohexylallene, the desired isoquinolinone (**3l**) and pyridones (**3m–p**) were obtained as the major regioisomeric products. Alkenyl amides gave the corresponding pyridone products with methoxyallene (**3q–s**) in moderate yields. These differences in the yield and regioselectivity of the products may be due to the back donation of lone pair electrons from the oxygen atom of the allene (Table 2).

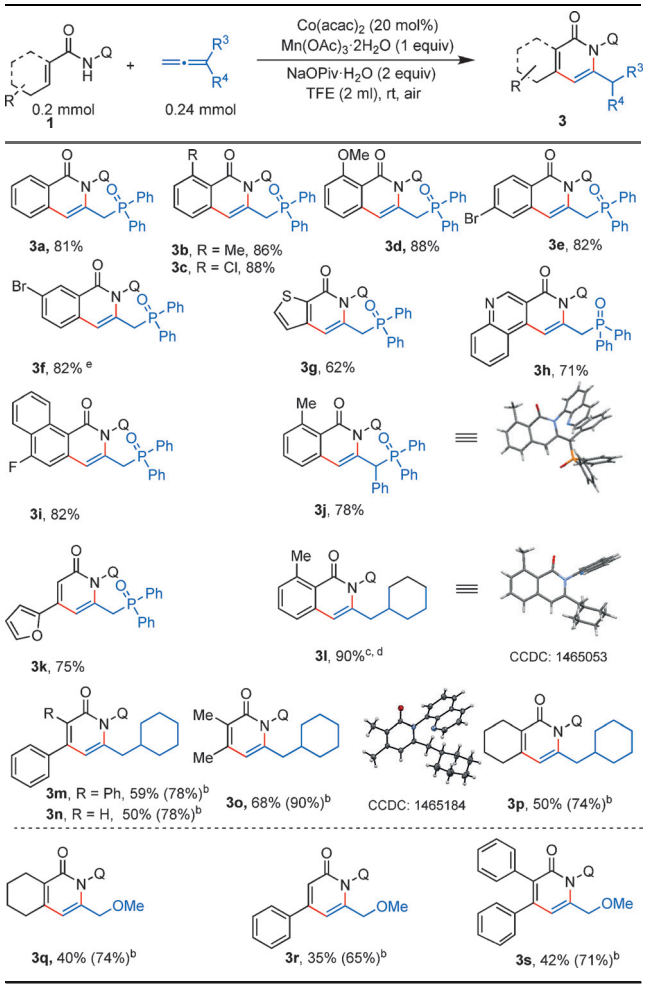
To study the scalability of the present method, the reaction of **1b** with allenylphosphonate was performed in the gram scale and **3b** was isolated in 67% yield (1.3 g, Scheme 2). To demonstrate the synthetic utility of the

Table 1: Synthesis of dihydroisoquinolin-1(2*H*)-ones and dihydropyridones.[a]

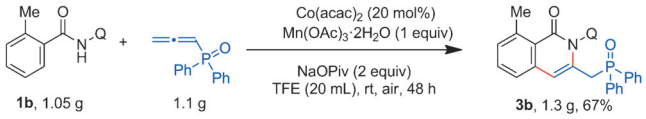


[a] Reaction conditions: **1** (0.2 mmol), allene (0.8 mmol), $Co(acac)_2$ (20 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (0.2 mmol), $NaOPiv{\cdot}H_2O$ (0.4 mmol), TFE (2 mL), 48–60 h, rt, isolated yield for combined two isomers (5:1 regioisomers determined by crude ^{1}H NMR). [b] brsm (based on recovered starting material) yield, [c] 2:1 (*E*/*Z*) ratio, [d] determined by crude ^{1}H NMR analysis, [e] 2:1 regioisomers.

Table 2: Synthesis of isoquinolin-1(2*H*)-ones and pyridones.[a]



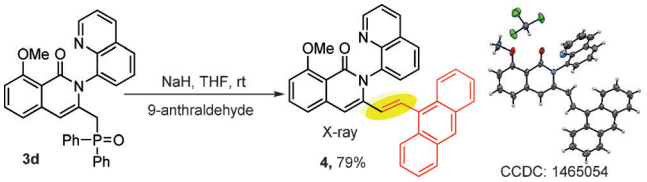
[a] Reaction conditions: **1** (0.2 mmol), allene (0.24 mmol), $Co(acac)_2$ (20 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (0.2 mmol), $NaOPiv{\cdot}H_2O$ (0.4 mmol), TFE (2 mL), 24–60 h, rt, isolated yield. [b] brsm yield, [c] 2:1 regioisomers, [d] determined by crude ^1H NMR analysis, [e] 4:1 regioisomers, [f] 10:1 regioisomers.



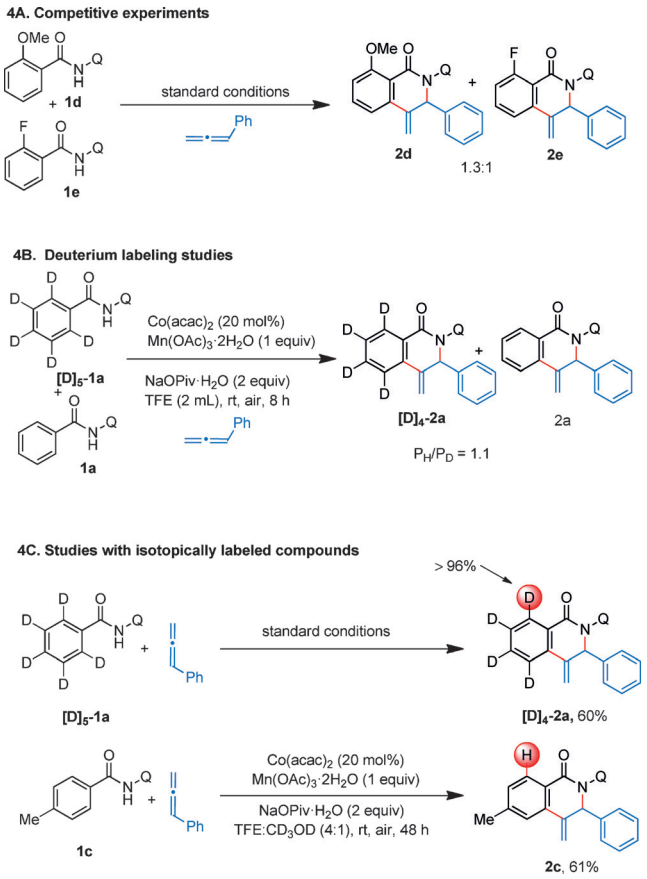
Scheme 2. Gram scale synthesis of dihydroisoquinolin-1(2*H*)-ones.

isoquinolin-1(2*H*)-one products, a Horner–Wittig[17] reaction was performed with **3d**. The reaction of the stabilized phosphonate carbanion with 9-anthraldehyde resulted in the formation of olefin **4** with excellent *E*-selectivity. The structure of **4** was confirmed by X-ray crystallography (Scheme 3; for crystallographic data, see Ref. [18]).

The mechanism of the reaction was studied in detail using intermolecular competition and deuterium labeling experiments. The kinetic investigation of the reaction with benzamide **1a** suggested a first-order rate dependence (see Supporting Information) with respect to **1a**. When a 1:1 mixture of *o*-methoxybenzamide **1d** and *o*-fluorobenzamide



Scheme 3. Application: Horner–Wittig reaction.

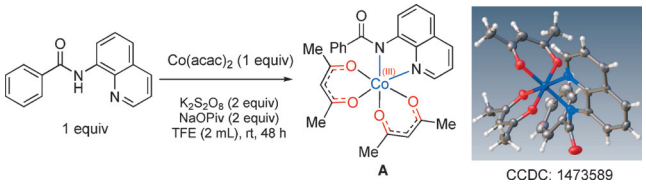


Scheme 4. Preliminary mechanistic investigation.

1e was subjected to the standard conditions, a 1:1.3 mixture of products was obtained, which suggests that electrophilic cobaltation is unlikely (Scheme 4A). An intermolecular competition between **1a** and **$[D]_5$-1a** gave a product distribution value of 1.1 $\{[P_H/P_D]\}$ (Scheme 4B). This value indicates that C–H bond cleavage might not be involved in the rate-limiting step. Furthermore, no D/H exchange was observed when **$[D]_5$-1a** was treated with phenylallene under standard conditions. Similarly, no deuterium incorporation in the product **2c** was observed when **1c** was treated with isotopically labelled CD_3OD as a cosolvent. These results suggest that the C–H cobaltation step is irreversible (Scheme 4C).

Considering our preliminary mechanistic studies and literature precedent, we propose the mechanism shown in Scheme 6A. In accordance with the known coordination properties of Co^{III} with arenes, we hypothesize that the catalytic reaction starts with a Co^{III} species. To support the

formation of an active Co^{III} complex, we reacted benzamide **1a** with $Co(acac)_2$ in the presence of $K_2S_2O_8$ at room temperature, upon which we observed the formation of Co^{III} intermediate **A** (Scheme 5; for crystallographic data, see Ref. [18]), which was confirmed by X-ray crystallography. We were delighted to observe the formation of the key intermediate **B** along with **A**, when **1c** was used instead of **1a** under the same conditions. The formation of intermediate **B** can be proposed based on high-resolution mass spectrometry (HRMS) and ^1H NMR studies (see Supporting information).

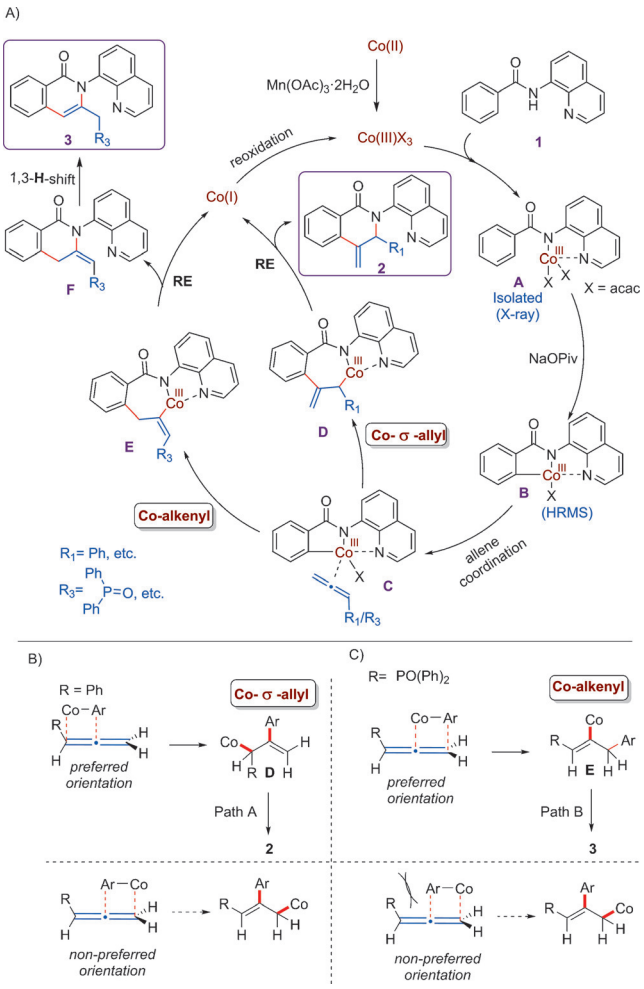


Scheme 5. Isolation of intermediate A.

Coordinative insertion of the double bond of an allene into a C–Co bond of intermediate **C** affords the seven membered cobaltacycle intermediate **D** or **E,** depending on the electronic nature of the allene. Carbocobaltation of allenes is known to proceed through the addition of aryl to the central carbon of the allene to produce a Co–π-allyl complex. For R = Ph, insertion with the more electron-rich double bond is favored and can account for the selective formation of the stable Co–σ-allyl complex **D** (Scheme 6B). Reductive elimination of intermediate **D** gives cyclized product **2** and regenerates the Co^{III} species after oxidation of Co^{I} with $Mn(OAc)_3{\cdot}2H_2O$.

In contrast, when either electron-poor allenes or sterically hindered allenes were employed, carbocobaltation of intermediate **C** takes place through a different pathway (Co–alkenyl) leading to **E** (Scheme 6C). Reductive elimination of **E** leads to **F**, which undergoes a 1,3-hydrogen shift, which provides the corresponding isoquinolin-1(2*H*)-ones or pyridones **3**.

In conclusion, we have reported a heterocyclization reaction of (hetero) arylamides and alkenylamides with allenes under operationally simple conditions at room temperature. Variation of the electronic properties of the allenes changed the reactivity pattern for the regioselective cyclization with aryl/alkenyl C–H activation using an inexpensive and commercially available cobalt catalyst. A novel and efficient synthesis of cobalt-catalyzed intermolecular heterocyclization for the synthesis of dihydroisoquinolin-1(2*H*)-ones, isoquinolin-1(2*H*)-ones, dihydropyridones, and pyridones through either M–alkenyl or M–π-allyl intermediates was developed. This reaction features high regioselectivity and impressive substrate scope for both the coupling partners.



Scheme 6. Proposed reaction mechanism.

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