C–H Activation

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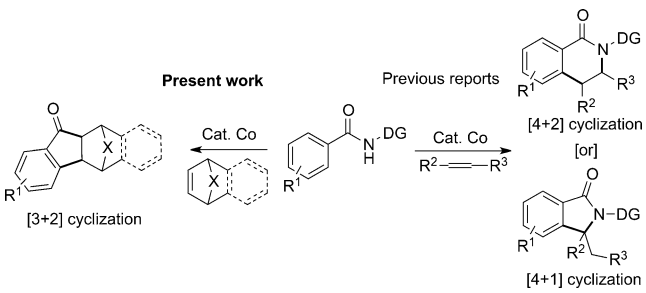
Diastereoselective [3+2] Annulation of Aromatic/Vinylic Amides with Bicyclic Alkenes through Cobalt-Catalyzed C–H Activation and Intramolecular Nucleophilic Addition

*Parthasarathy Gandeepan, Pachaiyappan Rajamalli, and Chien-Hong Cheng**

Abstract: *A highly diastereoselective method for the synthesis of dihydroepoxybenzofluorenone derivatives from aromatic/vinylic amides and bicyclic alkenes is described. This new transformation proceeds through cobalt-catalyzed C–H activation and intramolecular nucleophilic addition to the amide functional group. Transition-metal-catalyzed C–H activation reactions of secondary amides with alkenes usually lead to [4+2] or [4+1] annulation; to the best of our knowledge, this is the first time that a [3+2] cycloaddition is described in this context. The reaction proceeds under mild conditions and tolerates a wide range of functional groups. Mechanistic studies imply that the C–H bond cleavage may be the rate-limiting step.*

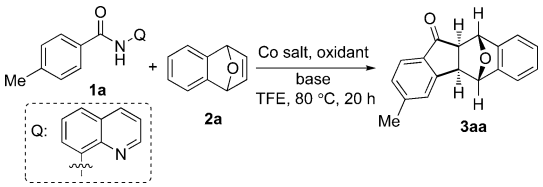
Transition-metal-catalyzed C–H bond functionalization reactions have become an essential method for the synthesis of functionalized organic compounds.[1,2] Although the use of noble metals, including Pd, Rh, Ru, and Ir, has been dominating the field of C–H activation,[3] cobalt-catalyzed C–H activation reactions[4,5] have also received much interest because cobalt is earth-abundant and therefore less expensive than noble metals. Moreover, owing to its unique reactivity and functional-group tolerance, the use of cobalt catalysts for C–H activation provides a complementary method to noble-metal catalysis.

Recently, the groups of Daugulis,[6] Ackermann,[7] and others[8] have shown that air-stable commercially available Co^{II}/Co^{III} salts can be used to functionalize aromatic/vinylic $C(sp^2)$–H bonds with alkynes/alkenes. Cobalt-catalyzed C–H activation reactions of amides with alkenes afforded the [4+2] or [4+1] annulation products (Scheme 1). Considering the hypothesis that these reactions proceed through directing group (DG) assisted C–H activation, alkene insertion, and



Scheme 1. Cobalt-catalyzed C–H activation and annulation reactions of amides with alkenes.

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



Entry	Co salt (mol%)	Oxidant (equiv)	Base	Yield[b] [%]
1	$Co(OAc)_2$ (20)	Ag_2CO_3 (2)	K_2CO_3	58
2	$Co(OAc)_2$ (30)	Ag_2CO_3 (2)	K_2CO_3	78
3	$Co(OAc)_2$ (40)	Ag_2CO_3 (2)	K_2CO_3	95 (91)
4	$[CoCp^*(CO)I_2]$ (40)	Ag_2CO_3 (2)	K_2CO_3	39
5	$Co(OAc)_2$ (40)	AgOAc (2)	K_2CO_3	30
6	$Co(OAc)_2$ (40)	$Mn(OAc)_2$ (2)	K_2CO_3	trace
7	$Co(OAc)_2$ (40)	$Mn(OAc)_3{\cdot}2H_2O$ (2)	K_2CO_3	18
8	$Co(OAc)_2$ (40)	Ag_2CO_3 (1)	K_2CO_3	69
9	$Co(OAc)_2$ (40)	Ag_2CO_3 (2)	KOAc	55
10	–	Ag_2CO_3 (2)	K_2CO_3	–
11	$Co(OAc)_2$ (40)	–	K_2CO_3	trace

[a] All reactions were carried out using **1a** (80 mg, 0.30 mmol), **2a** (48 mg, 0.33 mmol), Co catalyst, base (0.6 mmol), and oxidant in TFE (3.0 mL) at 80°C for 20 h. [b] Yields were determined by ^1H NMR analysis of the crude reaction mixture using mesitylene as the internal standard. Values given in parentheses refer to the yields of isolated products.

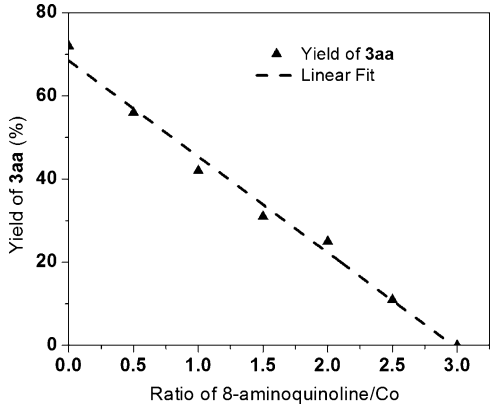


Figure 1. Effect of the concentration of 8-aminoquinoline on the yield of **3aa**.

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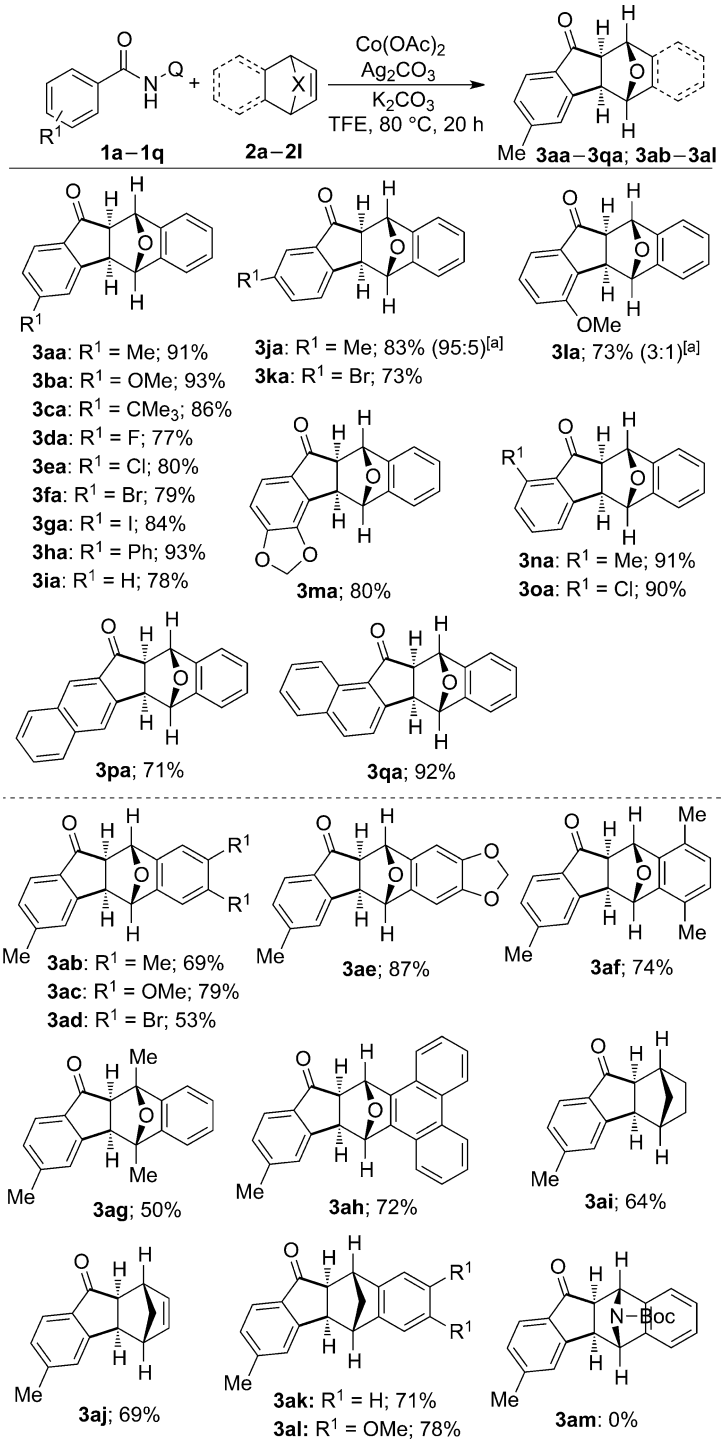
reductive elimination/β-hydride elimination, we envisioned that the intermediate C–Co bond that is formed after alkene insertion could be used for intramolecular nucleophilic addition to an amide carbonyl group, which could lead to the [3+2] annulation product.[9] Very recently, Kanai et al. reported the [3+2] annulation of *N*-carbamoyl indoles and alkynes to form pyrroloindolones using $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ as the catalyst.[10] The transformation was limited to indole substrates with a tertiary amide nitrogen atom. [3+2] Annulation reactions of amide and alkenes have not been reported. Herein, we disclose the first [3+2] annulation of aromatic/vinylic amides with bicyclic alkenes by cobalt-catalyzed C–H activation. [3+2] Annulations of secondary amides with alkynes/alkenes are highly challenging under transition-metal catalysis because the more favorable C–N bond-forming [4+2]/[4+1] cyclization reactions compete.

The Co-catalyzed amide $C(sp^2)$–H bond activation/[3+2] annulation reaction was optimized with 4-methyl-*N*-(quinolin-8-yl)benzamide (**1a**) and 7-oxabenzonorbornadiene (**2a**) as the substrates. After significant screening efforts, we found that the reaction of **1a** (0.3 mmol) and **2a** (0.33 mmol) in the presence of $Co(OAc)_2$ (0.12 mmol), Ag_2CO_3 (0.6 mmol), and K_2CO_3 (0.6 mmol) in 2,2,2-trifluoroethanol (TFE) at 80 °C for 20 hours gave the desired product **3aa** in 91 % yield after isolation (Table 1, entry 3). The product was thoroughly characterized by ^1H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry (HRMS), and single-crystal X-ray diffraction.[11] The product yield and NMR analysis of the crude product mixture both suggested that the reaction is highly diastereoselective. The choice of oxidant, base, and solvent is crucial for the success of this transformation (see the Supporting Information for details on the optimization studies). Control experiments revealed that no product was formed in the absence of either $Co(OAc)_2$ or Ag_2CO_3. Furthermore, we replaced the quinolyl (Q) moiety by many other groups, but none of them were equally effective (see the Supporting Information, Table S5). The reaction required a high catalyst loading (40 mol %), and we speculate that the 8-aminoquinoline (AQ) that is released during the reaction probably reduces the catalytic activity of the Co catalyst by coordinating to the metal. To confirm this notion, we performed the reaction of **1a** and **2a** under the optimized reaction conditions with additional AQ (Table S6). The yield of product **3aa** indeed decreased with an increase in the amount of AQ (Figure 1).



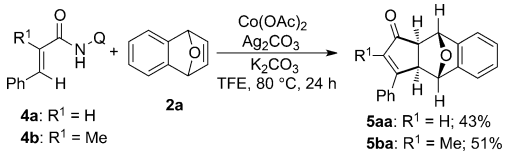
Scheme 2. Scope of the reaction. Reaction conditions: **1** (0.3 mmol), **2** (0.33 mmol), $Co(OAc)_2$ (0.12 mmol), Ag_2CO_3 (0.6 mmol), and K_2CO_3 (0.6 mmol) in TFE at 80 °C for 20 h. Yields of isolated products are given. [a] The regioisomeric ratio was determined by ^1H NMR analysis and is given in parentheses; the major isomer is shown. Boc = *tert*-butoxycarbonyl.

With the optimized reaction conditions in hand, we examined the scope of this new [3+2] amide/alkene annulation reaction. As shown in Scheme 2, a variety of amides with substituents at the *para*, *meta*, or *ortho* position of the aryl ring were tolerated, and gave the corresponding products **3aa**–**3qa** in good yields. The 3-methoxy-substituted benzamide gave the product that results from activation of the sterically more hindered C–H bond as the major regioisomer (**3la**). Similarly, a methylenedioxy-substituted benzamide gave **3ma** as a single isomer by activation of the sterically more hindered C–H bond. These selectivities

are probably due to the interaction of the neighboring oxygen atom with the cobalt center during the cyclometalation step.[12]

The reaction worked well with *ortho*-substituted amides (**1n**, **1o**) to give the expected products in excellent yields (**3na** and **3oa**). Both 2-naphthyl and 1-naphthyl amides also reacted smoothly with **1a** under the optimized reaction conditions to give the cycloaddition products **3pa** and **3qa** in 71% and 92% yield, respectively. Aside from the variation of the amide substrate, different bicyclic alkene coupling partners were also examined. A variety of 7-oxabenzonorbornadienes (**2b**–**2h**) were effectively coupled with **1a** to afford the respective polycyclic indenone derivatives **3ab**–**3ah** in good to excellent yields. The reaction also proceeded well with norbornene, norbornadiene, and benzonorbornadienes to give the corresponding [3+2] cycloaddition products in good yields (**3ai**–**3al**). Unfortunately, azabicyclic alkene **2m** failed to give the desired product under the standard reaction conditions.

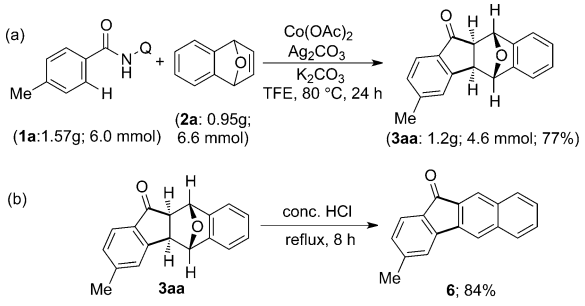
To further expand the scope of the reaction with regard to amides, we examined the compatibility of the reaction with vinylic substrates (Scheme 3). The reactions of cinnamamide



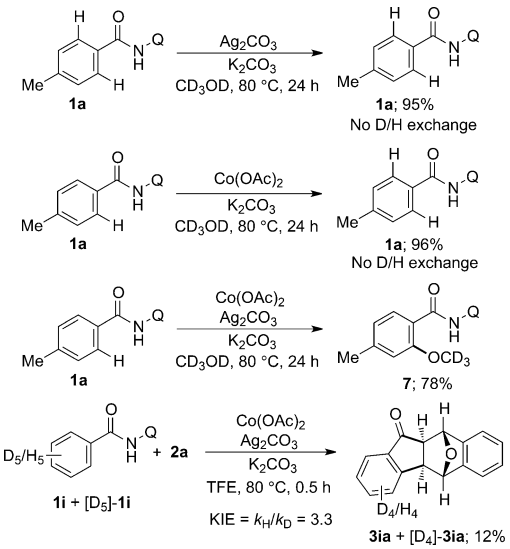
Scheme 3. Reactions with vinylic amides. Reaction conditions: **4** (0.3 mmol), **2a** (0.33 mmol), $Co(OAc)_2$ (0.12 mmol), Ag_2CO_3 (0.6 mmol), and K_2CO_3 (0.6 mmol) in TFE at 80 °C for 24 h. Yields of isolated products are given.

4a and α-methylcinnamamide **4b** with **2a** under the optimized reaction conditions smoothly provided the expected products, **5aa** and **5ba**, in 43% and 51% yield, respectively (Scheme 3).

To examine the scalability of the present method, the reaction of **1a** and **2a** was performed on gram scale, giving product **3aa** in 77% (1.2 g) yield after isolation (Scheme 4a). A synthetic application of product **3aa** was also demonstrated. Treatment of **3aa** with concentrated HCl smoothly afforded fluorenone **6** in 84% yield (Scheme 4b).



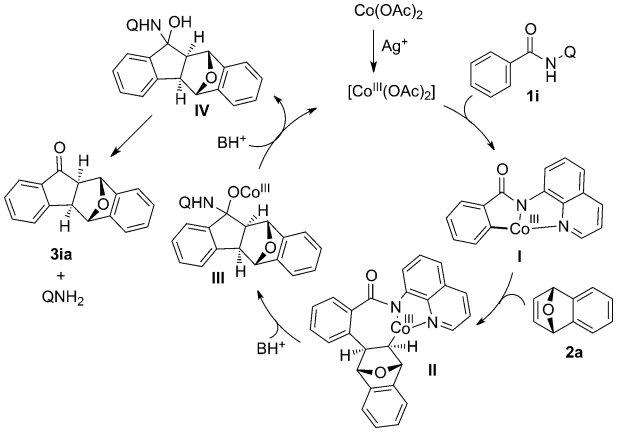
Scheme 4. Gram-scale synthesis and further transformation of product **3aa**.



Scheme 5. Mechanistic studies.

Next, we conducted a series of experiments to determine the mechanism of the reaction (Scheme 5). In a deuterium/hydrogen exchange experiment with **1a** under the standard reaction conditions using CD_3OD as the solvent, no D/H exchange was observed in the absence of either $Co(OAc)_2$ or Ag_2CO_3. However, the *ortho*-methoxylation product **7** was obtained in 78% yield under the standard reaction conditions.[13] These results suggest that the C–H activation is probably catalyzed by a Co^{III} species that is formed in situ from Co^{II} by oxidation with Ag^+.[14] Finally, an intermolecular kinetic isotopic effect (KIE, k_H/k_D) of 3.3 was determined for the reaction of **1i** and [D_5]-**1i** with **2a**. These results indicate that the C–H bond cleavage is involved in the first irreversible step in the catalytic cycle.[15]

Based on our experimental studies and previous reports, a plausible catalytic cycle is proposed in Scheme 6. The catalytic reaction is likely initiated by the oxidation of Co^{II} to Co^{III} by Ag^+.[14] Then, coordination of the amide substrate to the Co^{III} complex and subsequent cyclometalation by C–H bond cleavage provide intermediate **I**. Coordination of the bicyclic alkene to the Co center of **I** followed by insertion



Scheme 6. Proposed reaction mechanism.

generates intermediate **II** with a seven-membered ring. Intramolecular nucleophilic addition of the C–Co bond to the amide carbonyl group followed by protodemetalation and elimination of AQ provides the final ketone product and regenerates the catalytically active Co^{III} species. It is noteworthy that the insertion of 7-oxabenzonorbornadiene (**2a**) into intermediate **I** to give **II** generally occurs only at the *exo* face of **2a**, resulting in the observed stereochemistry.[16] Furthermore, intermediate **II** features no suitable β-hydrogen atoms for elimination to give an olefination product,[7] and the combined steric hindrance of the AQ moiety and bicyclic alkene **2a** prevents the direct reductive elimination to a six-membered lactam.[6]

In summary, we have developed a cobalt-catalyzed [3+2] cycloaddition of aromatic/vinylic secondary amides with bicyclic alkenes. The reaction proceeds by coordination-assisted C–H activation, alkene insertion, and intramolecular nucleophilic addition. The transformation works well under mild reaction conditions and features a broad substrate scope. Mechanistic studies suggest that a high-valent cobalt catalyst might be involved in the C–H bond cleavage. Detailed mechanistic studies and the application of this unique reaction to other substrates are currently in progress in our laboratory.

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Keywords: alkenes · amides · annulation · C–H activation · cobalt

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