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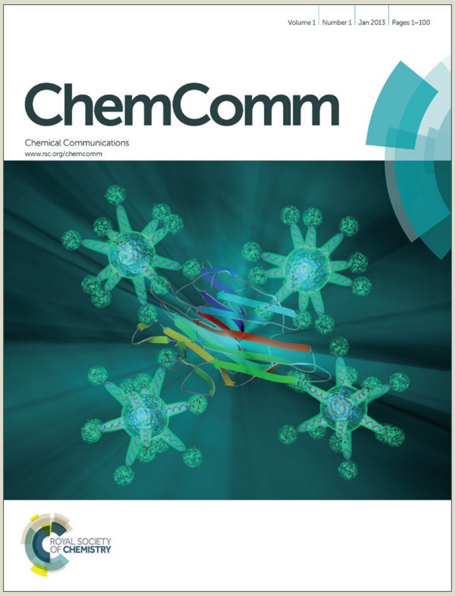

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Cobalt-Catalyzed Chelation Assisted C-H Allylation of Aromatic Amides with Unactivated Olefins†

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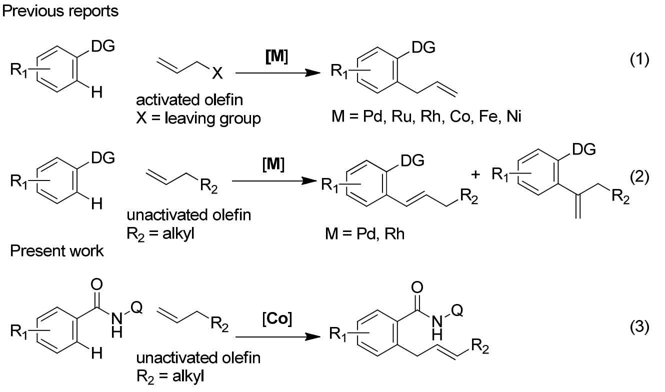
Abstract: The cobalt-catalyzed chelation assisted ortho C-H allylation of aromatic amides with unactivated aliphatic alkenes is reported. The reaction proceeds under air under mild reaction conditions, providing allylated products in good to excellent yields with high *E*-selectivities. This operationally simple method shows a high functional group tolerance.

Transition-metal-catalyzed specific C-C bond formation from ubiquitous C-H bonds is a challenging and attractive method for the synthesis of complex organic molecules, some of which are critical components of pharmaceuticals and functional materials.[1-3] Direct allylation via C-H functionalization is a highly important method and a long standing challenge from the standpoint of its synthetic utility, atom and step economy.[4,5] Numerous examples of allylation reaction have been reported, but all involve the use of activated or prefunctionalized coupling partners, such as allyl halides and phosphates (eq 1, Scheme 1).[6] Compared with the extensively studied oxidative alkenylation of C-H bonds with styrenes and acrylates, unactivated olefins have not been extensively employed in alkenylation reactions, due to concerns regarding their poor reactivity and selectivity.[7] In regard to catalysts, in C-H functionalization with second and third row transition metals, such as Pd, Rh, Ru and Ir a myriad number of examples can be found in the literature,[1,8] but the use of early and earth abundant transition metals in C-H functionalization reactions is still limited. Chemists shifted their focus towards the development of C-H functionalization with inexpensive and earth abundant first row transition metals, such as Co and Ni.[9] It is known that the Co-catalysts are stable in air, inexpensive and have the potential for novel C-H functionalizations.[10] Herein, we report on the first Co-catalyzed allylic type C-H bond functionalization with unactivated alkenes (eq 3, Scheme 1).



Scheme 1 Reaction of C-H bonds with olefins

The quest for selective allylation with unactivated terminal olefins started with aromatic amides that contain an 8-aminoquinoline directing group, which is unexceptionally promising tool for use in C-H functionalizations.[11] The reaction started by treating **1a** with 1-octene (**2a**) in the presence of $Co(OAc)_2.4H_2O$ (20 mol%) as a catalyst and Ag_2CO_3 (1 equivalent) as an oxidant, in dichloroethane (DCE) at 120 °C for 24 h (entry 1, Table 1). Interestingly, the allylated product **3aa** was produced in the form of a mixture of E/Z isomers in good yield (77%) with the E-isomer being favored. It was gratifying to learn that the allylated product was produced in the presence of air instead of Heck type vinylated or branched alkenylated product (eq 2 in Scheme 1).[7] However, some amount of starting material (86% conversion of **1a**) remained after the reaction. This interesting result prompted us to further investigate suitable conditions for achieving an improved yield. Optimization studies were started by surveying a series of potential solvents, including toluene, DMF and $PhCF_3$. In toluene, good yield were obtained, along with other unidentified byproducts (entry 2, Table 1). The yield decreased in the case of $PhCF_3$ and DMF was found to be

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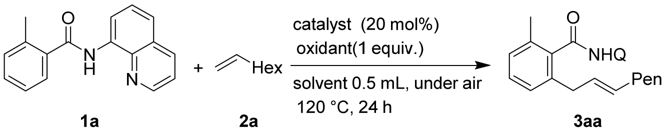
ineffective (entries 3 and 4, Table 1). In order to improve the yield of **3aa** and completely convert **1a**, the concentrations of reactants and catalyst loading were examined in separate experiments. Yields were decreased when the reactants were diluted and varying the amount of catalyst loading had a negligible effect on the reaction (see the SI). The use of 2 equivalents of Ag_2CO_3, however, resulted in a 100% consumption of starting material, but product yield was lowered to 63% (entry 5, Table 1). Several silver salts, including AgOAc, AgOBz, AgOTf, AgF and $AgNO_3$ were screened (entries 6-10, Table 1) instead of Ag_2CO_3, among the screened salts, AgOAc was found to be effective and **3aa** was obtained in 62% yield with a 64% conversion of **1a**. Other silver salts had no effect. However, none of these modifications had a dramatic effect on the yield in the reaction or on the conversion of **1a**. Other cobalt catalysts, including $CoBr_2$ and $Co(acac)_2$ were also examined, but were not effective (entries 11 and 12, Table 1). Next, the reaction was conducted at different temperatures, 100 °C, 80 °C and room temperature (see the SI). No reaction was observed when the reaction was run at rt and **3aa** was produced in low yield at 80 °C. When the reaction was carried out at 100 °C, **3aa** was produced in 69% yield with a 73% conversion of **1a**. Gratifyingly, 2 equivalents of Ag_2CO_3 at 100 °C for 12 h gave **3aa** in 83% yield with a 94% conversion of **1a** (entry 14, Table1). The reaction was found to be clean with no other detectable byproducts shown on TLC and crude ^1H NMR.

With these optimization conditions in hand, we next evaluated the scope of the reaction with respect to the alkene being used. Several other unactivated terminal alkenes were explored in order to expand the scope of the reaction (Table 2). Some olefins, such as 1-hexene (**2b**), allylbenzene (**2c**) and allylcyclohexane (**2d**) were examined, and all were observed to react well with **3ab**, **3ac** and **3ad** being produced in excellent yields, 76%, 85% and 72% isolated yields, respectively. We next focused on the functionalized terminal olefins to evaluate the feasibility of the reaction. The reaction of **1a** with 5-hexen-1-ol (**2e**), 5-hexenyl acetate (**2f**) and methyl -5-hexenoate (**2g**) gave **3ae**, **3af** and **3ag** in 65%, 85% and 65% yields, respectively, indicating that the reaction tolerated different types of functional groups. Our attention then focused on the sterically demanding branched alkenes, **2h** and **2i**. The reaction of **1a** with 3-methylhexene (**2h**) gave the products in a total yield of 55% with a 2.8:1 ratio of a mixture of **3ah** (E/Z=3.4:1) and **3ah'**. The reaction with vinylcyclohexane (**2i**) produced a total yield of 69% with a mixture of **3ai** and **3ai'** in the ratio of 3.2:1. In both cases, allylated products were the major isomer. 1,6-Heptadiene (**2j**) also reacted efficiently with **1a** to provide a mixture of mono- and di-coupled products, **3aj** and **3aj'** in 62% (E/Z=23:1) and 6% yields, respectively.

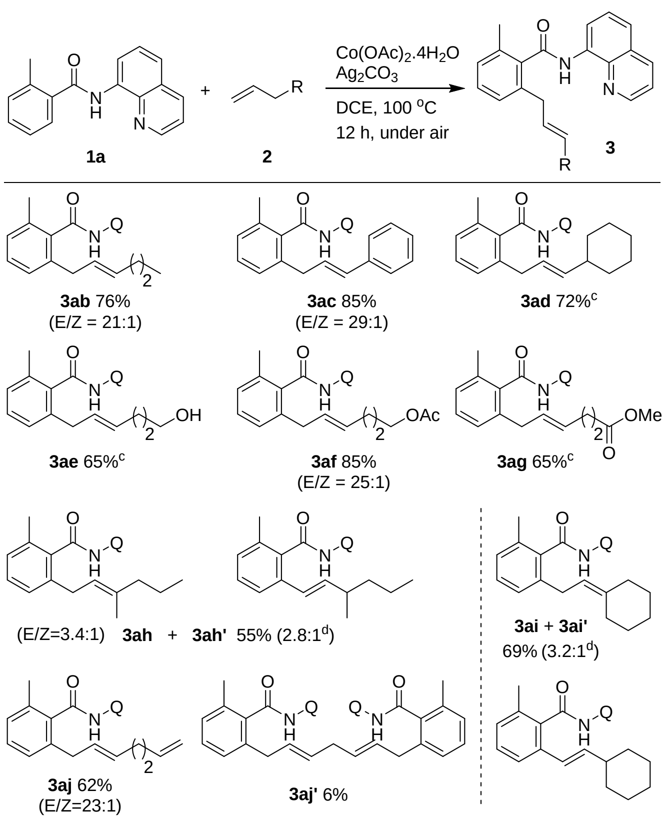
Table 1 Optimization of reaction conditions[a]



entry	catalyst	oxidant	solvent	yields (%) (3aa/1aa)[b]
1	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	DCE	77/14
2	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	Toluene	76/trace
3	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	DMF	9/22
4[c]	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	$PhCF_3$	55/13
5[d]	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	DCE	63/0
6[d]	$Co(OAc)_2 \cdot 4H_2O$	AgOAc	DCE	62/36
7[d]	$Co(OAc)_2 \cdot 4H_2O$	AgOBz	DCE	messy
8[d]	$Co(OAc)_2 \cdot 4H_2O$	AgOTf	DCE	0/0
9[d]	$Co(OAc)_2 \cdot 4H_2O$	AgF	DCE	0/97
10[d]	$Co(OAc)_2 \cdot 4H_2O$	$AgNO_3$	DCE	trace/trace
11	$CoBr_2$	Ag_2CO_3	DCE	0/25
12	$Co(acac)_2$	Ag_2CO_3	DCE	10/37
13[d, e]	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	DCE	56/0
14[d, f]	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3	DCE	83/6 (79/3)

[a] All reactions involved treating **1a** (0.15 mmol), **2a** (0.3 mmol) in a solvent (0.5 mL) in the presence of the cobalt catalyst (0.03 mmol) and oxidant (0.15 mmol) for 24 h otherwise stated. [b] Yields were determined by ^1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. Values given in the parentheses are yields of isolated product and starting material (**1a**). [c] The reaction was carried at 150 °C. [d] Oxidant (0.3 mmol) was used. [e] The reaction was carried oud for 12 h. [f] The reaction was carried at 100 °C for 12 h.

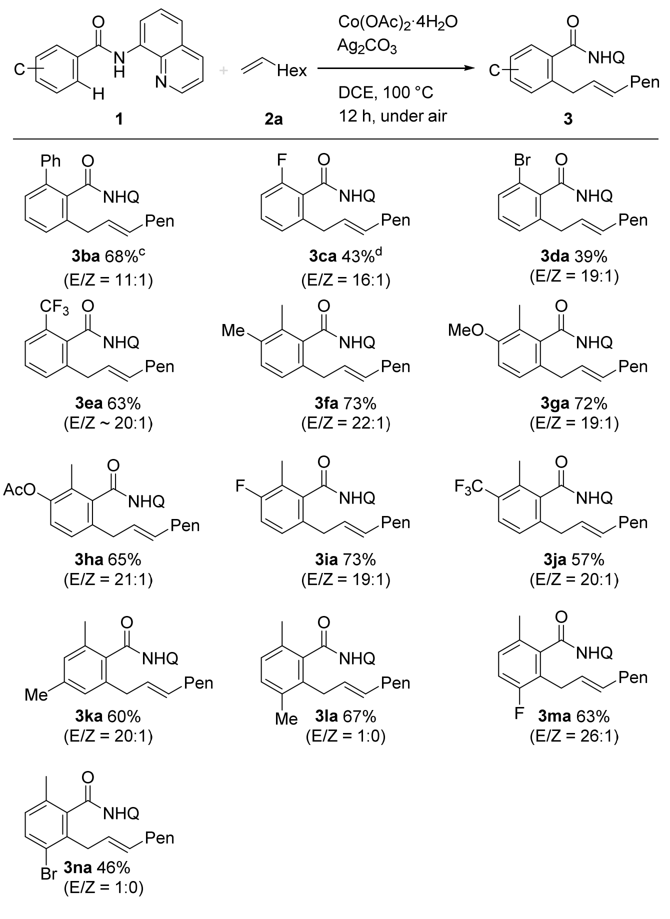
Table 2 Alkene scope[a, b]



[a] All reactions involved treating **1a** (0.15 mmol), alkene **2** (0.3 mmol) in the presence of $Co(OAc)_2.4H_2O$ (0.03 mmol) and Ag_2CO_3 (0.3 mmol) in DCE for 12 h, unless otherwise stated. [b] The cited yields are for isolated products. [c] E/Z ratio was not calculated due to the overlapping of the NMR peaks. [d] Only the E-isomer was obtained.

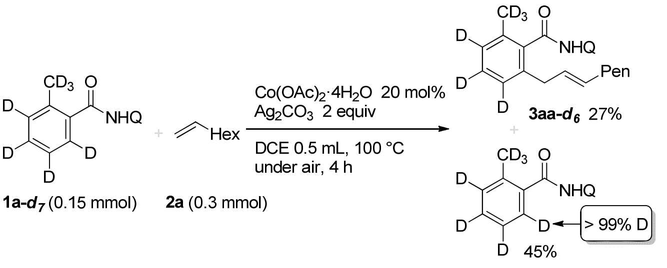
Table 3 summarizes the generality of the allylation reaction with substituted benzamides (**1b**-**1n**). The reaction of *o*-phenyl, *o*-fluoro, *o*-bromo and *o*-trifluoromethyl-substituted benzamides with 1-octene (**2a**) under optimized reaction conditions provided the expected allylated products. Next, *ortho*-methyl-substituted benzamides with other functional groups were examined in order to check the functional group tolerance of the reaction. An benzamide substituted with an electron-donating group, such as 2,3-dimethyl (**1f**), 2-methyl-3-methoxy (**1g**), 2-methyl-3-acetoxy (**1h**) reacted efficiently to give **3fa**, **3ga** and **3ha** in 73%, 72% and 65% yields, respectively. Amides with an electron-withdrawing substituent, such as 2-methyl-3-fluoro (**1i**) and trifluoromethyl benzamide (**1j**) also reacted with **2a** to afford **3ia** and **3ja**. As shown in the reaction of 2,5-dimethyl (**1l**), 2-methyl-5-fluoro (**1m**), and 2-methyl-5-bromo-substituted benzamides (**1n**), the reaction was not sensitive to steric hindrance. The reaction shows a high functional group compatibility.

Table 3 Benzamide scope [a, b]



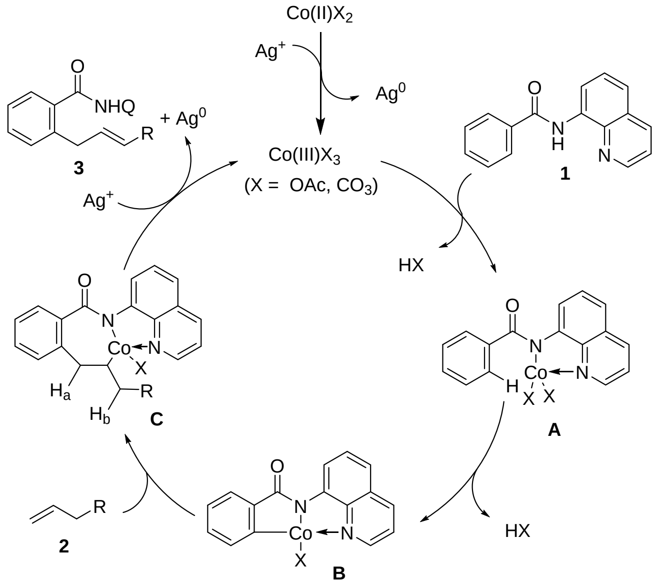
[a] All reactions involved treating **1** (0.15 mmol), **2a** (0.3 mmol) in the presence of $Co(OAc)_2.4H_2O$ (0.03 mmol) and Ag_2CO_3 (0.3 mmol) in DCE (0.5 mL) for 12 h. [b] The cited yields are for isolated products. [c] The reaction was carried out at 120 °C. [d] 27% of starting material (**1c**) was recovered.

A deuterium labeling experiment with amide **1a-*d*$_7$** with 1-octene (**2a**) indicated that no H/D exchange was detected in the recovered **1a-*d*$_7$**. This result indicates that the C-H bond cleavage step is irreversible.[10a,10d]



Scheme 2 Deuterium labeling experiment

Scheme 3 shows a plausible mechanism for the present allylation reaction. The mechanism is proposed based on our observations and previous literature reports.[10] In the first step, Ag^+ oxidizes Co(II) to a Co(III) species,[10d] which is critical for the present reaction to proceed. The coordination of **1** to the Co(III) species gives **A**, the acetate mediated abstraction of the ortho proton leads to the generation of the 5-membered cobaltacycle **B**. The insertion of the double bond of the alkene (**2**) into C-Co bond in **B** provides the 7-membered cobaltacycle **C**. The subsequent β-hydride elimination and oxidation by Ag^+ leads to the production of the allylated product **3** with the regeneration of the active Co(III) species. Based on product formation, it is assumed that β-hydride elimination with H_a leading to the formation of vinylated products is not possible, due to the rigid 7-membered metallocycle which is formed by the strong coordination of the 8-aminoquinoline group. Alternatively, a single bond rotation leads to a syn coplanar C-Co and C-H_b allows β-hydride elimination to form the allylated products **3**.



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Scheme 3 Plausible mechanism

In summary, we report herein the $Co(OAc)_2.4H_2O$ catalyzes *E*-selective allylation reactions with unactivated olefins on ortho C-H bonds of benzamides. The reaction proceeds in the presence of air under mild reaction conditions. It allows an efficient route to allylation with unactivated alkenes, also has a wide functional group tolerance. Detailed mechanistic studies are currently underway in our laboratory.

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