Cobalt-Catalyzed Addition of Azoles to Alkynes
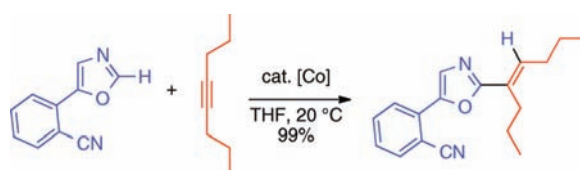
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ABSTRACT

A ternary catalytic system consisting of a cobalt salt, a diphosphine ligand, and a Grignard reagent promotes *syn*-addition of an azole C(2)−H bond across an unactivated internal alkyne with high chemo-, regio-, and stereoselectivities under mild conditions. Mechanistic experiments suggest that the reaction involves oxidative addition of the oxazolyl C−H bond to the cobalt center, alkyne insertion into the Co−H bond, and reductive elimination of the resulting diorganocobalt species.

Aromatic heterocycles represent ubiquitous structural motifs found in a broad range of functional molecules including pharmaceuticals and photo- and electroactive materials. Consequently, the development of efficient preparative methods for densely functionalized heteroarenes has attracted considerable attention from synthetic chemists. In this context, C−C bond-forming reactions through activation of heteroaromatic C−H bonds are particularly attractive.[1] While rhodium has been among the most versatile metals for such transformations,[1a] its lighter homologue, cobalt, has rarely been exploited for catalytic elaboration of heteroaromatic[2] and aromatic[3] C−H bonds regardless of its attractiveness

because of its much lower cost.[4] Here we report that a cobalt complex serves as an efficient catalyst for activation of a C(2)−H bond of an azole derivative followed by insertion of an unactivated internal alkyne.[5] The reaction occurs under mild conditions to afford a trisubstituted olefin with excellent *cis*-stereoselectivity and makes a useful addition to the rapidly expanding repertoire of methods for direct functionalization of azole heterocycles.[6−12]

Our study began with the reaction of benzoxazole **1a** and 4-octyne **2a**.[7a,b] Screening of catalysts generated from cobalt

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salts, ligands, and reducing agents led us to find that the combination of CoBr$_2$ (10 mol %), bis[(2-diphenylphosphino)phenyl] ether (DPEphos, 10 mol %), and Me$_3$SiCH$_2$MgCl (100 mol %) serves as an effective ternary catalytic system to afford the alkenylated product **3aa** ($E/Z > 99$:1) in 75% yield at 20 °C (Table 1, entry 1). Addition of pyridine (40

Table 1. Cobalt-Catalyzed Addition of Benzoxazole to 4-Octyne[a]
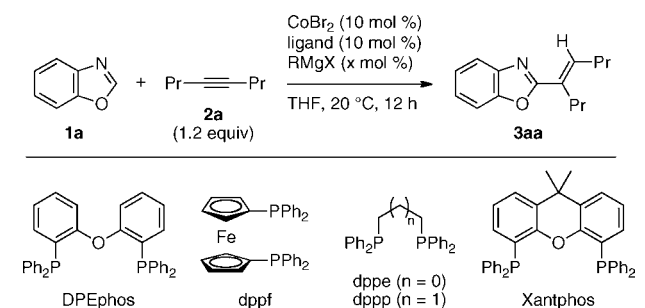
entry	ligand	RMgX (x mol %)	yield (%)[b]
1	DPEphos	Me$_3$SiCH$_2$MgCl (100)	(75)
2[c]	DPEphos	Me$_3$SiCH$_2$MgCl (100)	(86)
3[c]	DPEphos	Me$_3$SiCH$_2$MgCl (50)	(82)
4[d]		Me$_3$SiCH$_2$MgCl (50)	75
5	dppf	Me$_3$SiCH$_2$MgCl (50)	57
6	dppe	Me$_3$SiCH$_2$MgCl (50)	2
7	dppp	Me$_3$SiCH$_2$MgCl (50)	2
8	Xantphos	Me$_3$SiCH$_2$MgCl (50)	5
9[e]	PPh$_3$	Me$_3$SiCH$_2$MgCl (50)	7
10	DPEphos	MeMgCl (50)	16
11	DPEphos	iPrMgBr (50)	9
12	DPEphos	tBuCH$_2$MgBr (50)	46

[a] Reaction was carried out on a 0.3 mmol scale. [b] GC yield. Values in parentheses refer to isolated yields. [c] Pyridine (40 mol %) was added. [d] CoCl$_2$(DPEphos) (10 mol %) was used as the precatalyst. [e] PPh$_3$ (20 mol %) was used.

mol %) as an additive slightly improved the product yield to 86% (entry 2). The amount of Me$_3$SiCH$_2$MgCl could be reduced to 50 mol % without decreasing the catalytic activity (entry 3), while the reaction became very sluggish with 30−40 mol % of Me$_3$SiCH$_2$MgCl and stopped with further

decrease. The use of a preformed cobalt−phosphine complex CoCl$_2$(DPEphos) as the precatalyst gave a similar catalytic activity (entry 4). While low-valent cobalt complexes are well-known to catalyze cyclotrimerization of alkynes,[13] no such product was detected in these experiments.

The use of other bidentate phosphine ligands resulted in much lower yields of **3aa**, but dppf was moderately effective (entries 5−8). Monodentate ligands such as PPh$_3$ were also ineffective (entry 9). Replacement of Me$_3$SiCH$_2$MgCl with other Grignard reagents uniformly reduced the product yield, although neopentylmagnesium bromide was moderately effective (entries 10−12).[14] As for the metal precatalyst, CoBr$_2$ was the best among other common cobalt salts (e.g., CoCl$_2$, CoI$_2$, Co(acac)$_3$), and other metal salts (e.g., Fe, Ni, Ru, Rh, Pd) were entirely ineffective under otherwise identical conditions.[15]

The present reaction was applicable to a variety of (benz)oxazole derivatives, as illustrated in Figure 1. Benzoxazoles
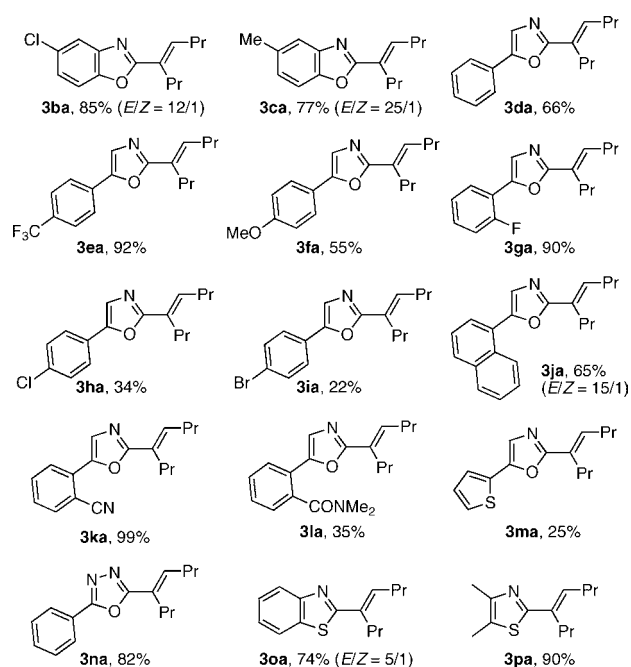
Figure 1. Scope of azoles. Unless otherwise noted, the reaction was performed under the conditions described in Table 1, entry 3, and E/Z ratio of the product was >99/1. For **3da−3ia**, 100 mol % of Me$_3$SiCH$_2$MgCl was used. For **3oa** and **3pa**, Xantphos (10 mol %) and toluene were used as the ligand and the solvent, respectively, and the reaction was performed at 60 °C.

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bearing 5-chloro and 5-methyl substituents underwent addition reaction to **2a** as smoothly as the parent benzoxazole **1a** to give the products **3ba** and **3ca** in ca. 80% yield. 5-Aryl oxazole derivatives also participated in the reaction and afforded the corresponding alkenylated products **3da**–**3ma** in moderate to excellent yields. The substrates bearing electron-withdrawing groups such as 4-trifluoromethyl and 2-fluoro groups gave the products **3ea** and **3ga**, respectively, in ca. 90% yields. On the other hand, the reaction became sluggish with a 4-methoxy group to give the product **3fa** in 55% yield. Neither extending the reaction time nor increasing the reaction temperature improved the yield. The reaction became even more sluggish when the substrate bore a chloro or bromo substituent. Thus, the products **3ha** and **3ia** were obtained in modest yields. Note that the C–Cl and C–Br bonds remained entirely intact under the reaction conditions, and the unreacted starting materials were recovered. The reaction tolerated the presence of cyano and amide functional groups and afforded the addition products **3ka** and **3la** in 99 and 35% yields, respectively. A thienyl-substituted oxazole also underwent the reaction albeit with a modest reactivity (see **3ma**).

An oxadiazole derivative also participated in the reaction at room temperature and afforded the product **3na** in 82% yield. Furthermore, (benzo)thiazoles underwent addition reaction to 4-octyne under modified conditions using Xantphos instead of DPEphos to afford the products **3oa** and **3pa** in good yields. Imidazoles did not participate in the reaction under the present conditions but underwent decomposition to unidentifiable products.

Figure 2 summarizes the results of cobalt-catalyzed addition of (benz)oxazole derivatives to a variety of alkynes.
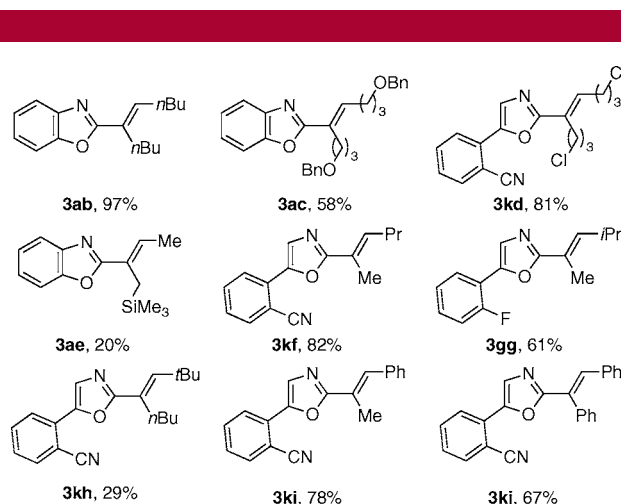

Figure 2. Scope of alkynes. Unless otherwise noted, the reaction was performed under the conditions described in Table 1, entry 3, and the *E/Z* ratio of the product was >99/1. For **3kd**, **3kf**, **3gg**, **3kh**, **3ki**, and **3kj**, the reaction was performed at 80 °C. For **3ae**, 1,4-bis(trimethylsilyl)but-2-yne was used as the alkyne. **3kf** is the major regioisomer (regioselectivity was 2:1).

Symmetrical aliphatic alkynes participated smoothly in the reaction and afforded the addition products **3ab**, **3ac**, and **3kd** in good to excellent yields with excellent stereoselec-

tivity (*E/Z* > 99:1). Benzyl ethers and C(sp³)–Cl bonds were tolerated well (see **3ac** and **3kd**). Interestingly, the reaction of 1,4-bis(trimethylsilyl)but-2-yne was accompanied by desilylation of one of the Me₃Si groups and gave the product **3ae** in a modest yield. The reaction of an unsymmetrical aliphatic alkyne required heating to 80 °C and resulted in regioselective C–C bond formation. While a moderate regioselectivity of 2:1 was observed for the reaction of 2-hexyne (see **3kf**), 4-methyl-2-pent-2-yne and 2,2-dimethyloct-3-yne underwent exclusive C–C bond formation at the less hindered carbon atoms (see **3gg** and **3kh**). Arylalkynes also gave the addition products **3ki** and **3kj** in good yields, while terminal alkynes did not participate in the reaction.

In order to gain insight into the reaction mechanism, several mechanistic experiments were performed. First, unlike the cobalt-catalyzed carbometalation reactions,[5] quenching the reaction of **1a** and **2a** with D₂O did not cause deuteration of either the product or the recovered starting material.[16] In accordance with this observation, the reaction of deuterated benzoxazole **1a**-*d* with **2a** gave the corresponding deuterated adduct **3aa**-*d* in 43% yield (Scheme 1a). It

Scheme 1. Mechanistic Experiments
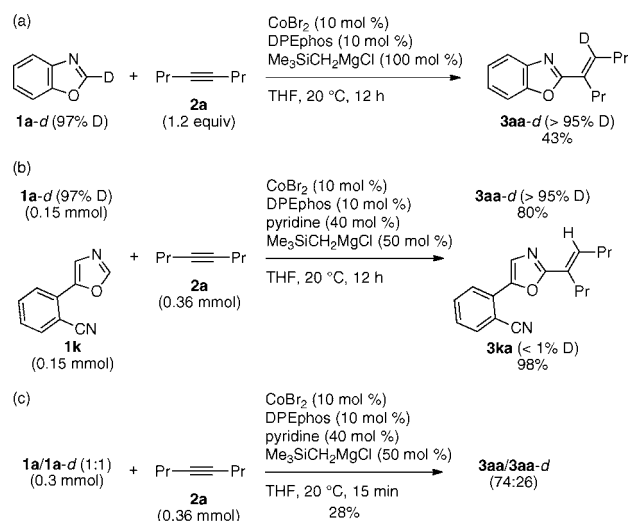
was notable that the reaction was apparently slower than that of parent benzoxazole (see Table 1, entry 1). In addition, the reaction of an equimolar mixture of **1a**-*d* and the oxazole **1k** with **2a** afforded **3aa**-*d* and **3ka** in 80 and 98% yields, respectively, without causing H/D crossover (Scheme 1b). These results clearly demonstrate that the aryl group and the hydrogen (deuterium) atom in the product molecule are derived from the same reactant molecule. Finally, a competitive reaction of an equimolar mixture of **1a** and **1a**-*d* with **2a**, which was quenched at an early stage of the reaction, gave a mixture of **3aa** and **3aa**-*d* in 28% yield with a ratio

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of 74:26 (Scheme 1c). Thus, a kinetic isotope effect of ca. 2.8 is indicated for the C−H bond cleavage step.

The above experimental results suggest that the present reaction does not involve either electrophilic metalation[17] or deprotonation of the oxazole substrate.[18,19] We consider that the reaction is likely to involve oxidative addition of the oxazolyl C−H bond to the cobalt center,[20,21] insertion of the alkyne into the Co−H bond in a *syn*-fashion, and reductive elimination of the resulting alkenyl(oxazolyl)cobalt intermediate,[7] while other mechanistic possibilities involving a radical process may not be fully excluded.[22] This mechanism allows one to rationalize the origin of the regioselectivity observed for the products such as **3gg** and **3kh** in terms of the preference of the cobalt center to avoid steric repulsion during the alkyne insertion step. While the identity of the catalytically active cobalt species remains elusive at this stage, the necessity of a larger amount of the Grignard reagent than required for the reduction of Co(II) to Co(0) (20 mol %) and the significant influence of the Grignard reagent on the catalytic activity (see Table 1) suggest possible involvement of an organocobalt(0)ate species as the reactive species.[23]

In summary, we have demonstrated that a cobalt/diphosphine/Grignard ternary catalytic system allows alkenylation of an azole C(2)−H bond with an unactivated internal alkyne under mild conditions with high chemo-, regio-, and stereoselectivities. The catalytic activity of cobalt complexes toward C−H bonds being rather unexplored,[2,3,24] extension of the present chemistry could lead to cost-effective methods for the functionalization of other classes of C−H bonds.[4]

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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