C–H Activation

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Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)–H Bond Alkenylation by Alkynes**

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Abstract: *A method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed C(sp^2)–H bond alkenylation by alkynes was developed. The method shows excellent functional-group tolerance and both internal and terminal alkynes are competent substrates for the coupling. The reaction employs a $Co(OAc)_2{\cdot}4H_2O$ catalyst, $Mn(OAc)_2$ co-catalyst, and oxygen (from air) as a terminal oxidant.*

During the last decade transition-metal-catalyzed C–H bond functionalization methodology has emerged as an important chemistry tool which allows simplification and shortening of synthetic schemes.[1] Within the last years, applications of C–H bond functionalization to the synthesis of natural products and compounds of medicinal interest have emerged, thus showing the maturity of the methodology.[2] However, certain problems are still unsolved. For example, a general functional-group-tolerant method for directed coupling of non-acidic C(sp^2)–H bonds with alkynes has yet to be described. Furthermore, most examples of C(sp^2)–H bond coupling with alkynes feature second-row transition-metal catalysis.[3a–n] Directed alkenylation by employing alkenes is possible.[3o,p]

Following the pioneering work of Murai and co-workers,[3a] a number of groups have reported directed or non-directed reactions of C(sp^2)–H bonds with alkynes catalyzed by second- or third-row transition metals.[3] The use of the more available first-row transition metals has been rare.[4] Only a few examples describe nickel- or cobalt-catalyzed alkyne/C(sp^2)–H bond coupling. Notably, following earlier reports that low-valent cobalt species can activate and functionalize C(sp^2)–H bonds,[5] Yoshikai and co-workers has developed a versatile system for cobalt-catalyzed, imine- and pyridine-directed alkenylation of C(sp^2)–H bonds with internal alkynes.[4f–h,l] Nakao, Hiyama, and co-workers have shown that [Ni(cod)$_2$] catalyzes the coupling of C(sp^2)–H bonds with disubstituted acetylenes,[4d] and Chatani and co-workers has described the nickel-catalyzed reaction of benzoic acid 2-pyridinylmethylamides with internal alkynes.[4e] However, directed coupling of both internal and terminal alkynes with C(sp^2)–H bonds is exceedingly rare.[4m]

We report herein a method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed C(sp^2)–H bond coupling with alkynes. The reaction is successful with terminal and internal alkynes, tolerates a wide range of functional groups on the alkyne and arene, and allows removal of the directing groups. Furthermore, the first use of cobalt catalysis by employing bidentate, monoanionic auxiliaries is demonstrated.

In 2005, we introduced 2-aminoquinoline, picolinamide, and 2-pyridinylmethylamine auxiliaries for palladium-catalyzed C(sp^2)–H and C(sp^3)–H bond functionalization.[6a,b] Subsequently, copper-catalyzed C(sp^2)–H bond sulfenylation, amination, fluorination, and etherification was described.[6c–f] Other groups have extensively used aminoquinoline, picolinamide, and other bidentate monoanionic directing groups for palladium-, ruthenium-, iron-, nickel-, and copper-catalyzed C–H bond functionalization.[7] The near-universal efficiency of these directing groups for transition-metal-catalyzed C–H bond functionalization presumably arises from the substrate acting as a tridentate, dianionic pincer which stabilizes high-valent transition-metal intermediates (Figure 1).[6b,8]

We speculated that 8-aminoquinoline and picolinic acid auxiliaries would promote cobalt-catalyzed *ortho*-alkenylation of C(sp^2)–H bonds since cobalt(III) is known to activate C(sp^2)–H bonds[9] and carbon–carbon multiple-bond insertion into Co^{III}–C bonds has been demonstrated.[10]

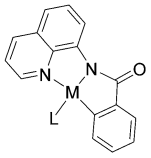

Figure 1. Aminoquinoline directing group.

We decided to use the readily available cobalt(II) acetate catalyst in combination with pivalate as a base. The reaction optimization was carried out with respect to solvent, reaction temperature, and cooxidant (Table 1). The results in entries 1–3 show that the reaction is most efficient in trifluoroethanol as the solvent, presumably because of higher solubility of the cobalt catalyst. The reaction is efficient at temperatures as low as 60 °C (entry 4). Potassium persulfate cannot be used as an oxidant (entry 6), but silver pivalate (entries 1–5) and $Mn(OAc)_2$ (entries 8–10, 12) work well. $Mn(OAc)_2$ was chosen as a cooxidant because of cost considerations. At least 1 equivalent of $Mn(OAc)_2$ is required (entry 9 versus 12). Interestingly, reaction in a degassed solvent affords only traces of the product, thus showing that the presence of oxygen is essential (entries 9 versus 10). Low conversion can be achieved without the $Mn(OAc)_2$ co-catalyst under an atmosphere of oxygen (entry 11). Cobalt(II) acetate tetrahydrate can be used instead of the anhydrous salt without a decrease in the reaction yield. No reaction was observed if $Co(OAc)_2$ was omitted.

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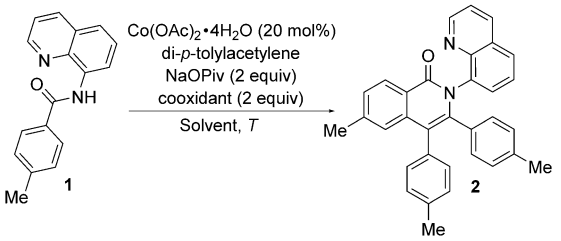
Table 1: Optimization of reaction conditions.[a]



Entry	*T* [°C]	*t* [h]	Solvent	Cooxidant	**2**/**1**
1[b,c]	150	12	DMF	AgOPiv	<1:99
2[b,c]	150	12	*o*-$Cl_2C_6H_4$	AgOPiv	1:2 (33%)[h]
3[b,c]	150	12	CF_3CH_2OH	AgOPiv	>99:1 (63%)[h]
4	60	12	CF_3CH_2OH	AgOPiv	>99:1 (65%)[h]
5[b]	25	12	CF_3CH_2OH	AgOPiv	1:4 (16%)[h]
6	60	12	CF_3CH_2OH	$K_2S_2O_8$	<1:99
7[d]	60	2	CF_3CH_2OH	$PhI(OAc)_2$	1:1 (11%)[h]
8	60	16	CF_3CH_2OH	$Mn(OAc)_2$	5:1 (79%)[h]
9[e]	80	2	CF_3CH_2OH	$Mn(OAc)_2$	1:2 (63%)[h]
10[e,f]	80	12	CF_3CH_2OH	$Mn(OAc)_2$	<1:99
11[g]	80	18	CF_3CH_2OH	O_2	1:1 (50%)[h]
12[d]	80	2	CF_3CH_2OH	$Mn(OAc)_2$	10:1 (87%)[h]

[a] Amide 0.1 mmol, solvent 0.7 mL. Conversions were determined by ^1H NMR analysis. [b] $Co(OAc)_2$ catalyst. [c] Cooxidant: 0.8 equiv. [d] Cooxidant: 1 equiv [e] Cooxidant: 0.5 equiv. [f] Deoxygenated solvent. [g] Reaction vessel pressurized with O_2. [h] Yield of **2** determined by NMR spectroscopy using 1,1,2-trichloroethane as an internal standard in parentheses. DMF = *N*,*N*-dimethylformamide, Piv = pivalate.

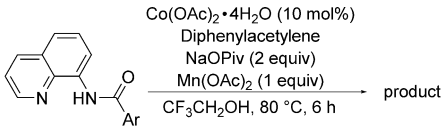
The reaction scope with respect to aminoquinoline amides is presented in Table 2. The reactions are successful for both electron-rich (entries 5 and 7) and electron-poor (entries 2–4, and 6) amides. Various functionalities, such as bromide (entry 3), nitro (entry 4), and iodide (entry 6) are tolerated. Furanecarboxylic and thiophenecarboxylic acids are reactive (entries 8 and 9), thus showing the compatibility of reaction conditions with heterocycles. The reaction headspace volume is important as 1 equivalent of O_2 is consumed in the reaction.

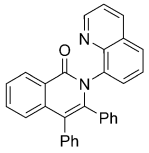
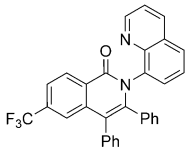
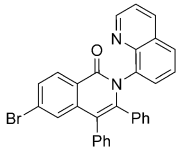
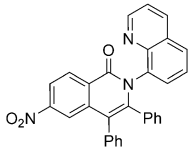
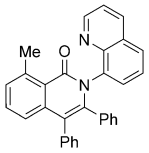
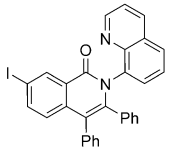
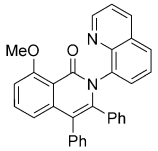
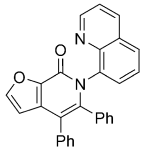
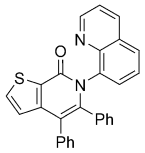
The reaction scope with respect to alkynes is presented in Table 3. The reaction is remarkably functional-group tolerant, wherein a free alcohol moiety (entry 1), ester (entry 6), silyl (entry 7), cyclopropyl (entry 8), and protected amine (entry 9) are compatible with the reaction conditions. Terminal alkynes with either aromatic (entry 3) or large substituents (entries 4 and 7) afford products as single regioisomers. Terminal alkynes with smaller substituents (entries 6, 8, and 9) as well as unsymmetric internal alkynes (entry 5) form regioisomeric mixtures. However, selectivities are reasonably good, ranging from about 6:1 for ethyl propiolate (entry 6) to 14:1 for phenylmethylacetylene (entry 5).

Furthermore, aminoquinoline vinylamides are reactive (Scheme 1). Thus, cinnamic acid aminoquinoline amide was treated with 2-butyne and the cyclization product was isolated in 75% yield.

The picolinamide directing group can be used (Scheme 2), thus allowing functionalization of benzyl- and naphthylamine derivatives. The picolinamide of 1-naphthylamine (**5**) was reacted with 2-butyne in the presence of catalytic $Co(OAc)_2{\cdot}4H_2O$ to afford the noncyclized alkenylation product

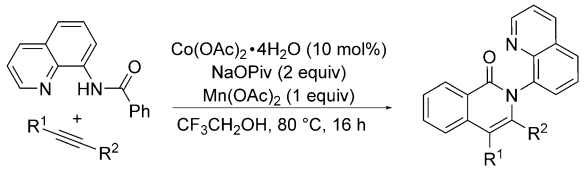
Table 2: Reaction scope with respect to arylamides.[a]



Entry	Ar	Product	Yield [%]
1	C_6H_5		78
2	4-$CF_3C_6H_4$		70
3	4-BrC_6H_4		73
4	4-$NO_2C_6H_4$		78
5	2-MeC_6H_4		86
6	3-IC_6H_4		84
7[b]	2-$MeOC_6H_4$		74
8[c]	2-furyl		81
9[d]	2-thienyl		86

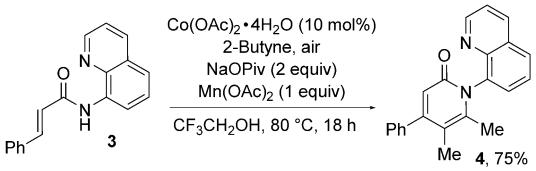
[a] Amide 0.5 mmol, CF_3CH_2OH 5 mL, air. Yields are those of the isolated products. Please see the Supporting Information for details. [b] Time: 18 h. [c] Time: 16 h. [d] Time: 20 h.

Table 3: Reaction scope with respect to alkynes.[a]

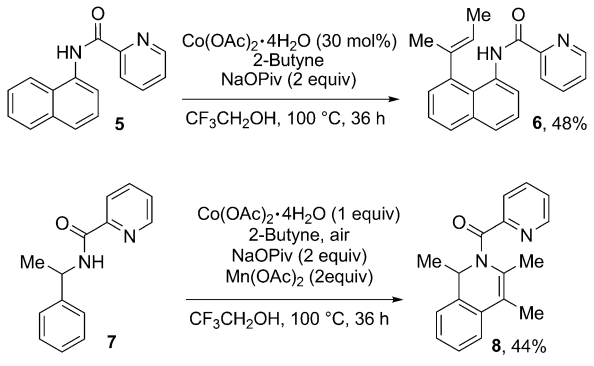


Entry	R^1	R^2	Yield [%]
1	CH_2OH	CH_2OH	95
2	Me	Me	96
3	H	Ph	95
4	H	*t*Bu	73
5[b]	Me	Ph	95
6[c]	H	CO_2Et	82
7	H	TIPS	64
8[d]	H	cyclopropyl	84
9[e]	H	CH_2NPhth	93

[a] Amide 0.5 mmol, CF_3CH_2OH 5 mL, alkyne 1.2 equiv, air. Yields are those of isolated products. Please see the Supporting Information for details. [b] Isolated as a 14:1 mixture of isomers. [c] Minor isomer (13%) also isolated. [d] Isolated as a 13:1 mixture of isomers. [e] Isolated as a 7:1 mixture of isomers; reaction time: 18 h. TIPS = triisopropylsilyl.



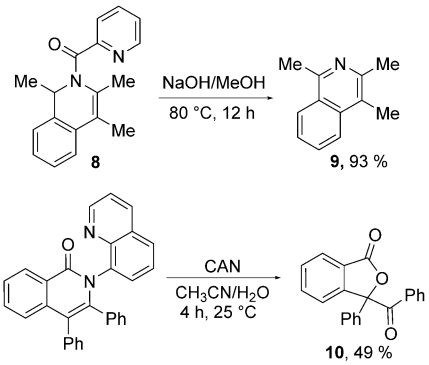
Scheme 1. Cyclization with vinyl amide.



Scheme 2. Picolinamide directing group.

6 in moderate yield. Similarly, the 1-methylbenzylamine-derived picolinamide **7** reacted with 2-butyne to give the cyclized product **8** in 44% yield. As shown before,[6] picolinamide-directed reactions are less efficient, thus affording lower yields of products, and requiring higher temperatures and longer reaction times.

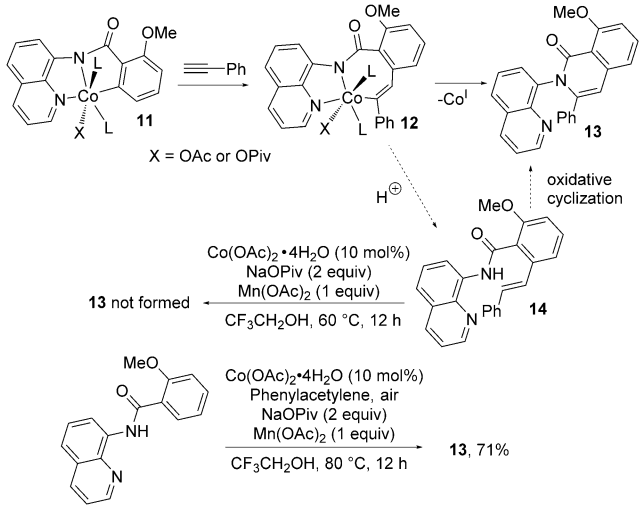
The advantage of aminoquinoline and picolinamide directing groups lies in the possibility of their removal, which affords useful functionalized products (Scheme 3). The



Scheme 3. Directing-group removal. CAN = ceric ammonium nitrate.

base hydrolysis of **8** removes picolinamide to give the trimethylisoquinoline **9**. The aminoquinoline directing group can be removed by treatment with CAN at room temperature, and cleavage of the directing group is accompanied by oxidation of the double bond, thus affording the ketolactone **10** in moderate yield.

Based on the fact that the aminoquinoline ligand stabilizes transition metals in high oxidation states, it is likely that the reaction proceeds via the cobalt(III) intermediate **11**, which is formed by oxidation of $Co(OAc)_2$ in the presence of aminoquinoline amide ligand (Scheme 4). Insertion of the alkyne



Scheme 4. Mechanistic considerations.

into the cobalt–aryl bond would provide **12**. An alternative mechanism with the cobalt acetylide intermediate is unlikely since 1) internal alkynes are reactive, and 2) terminal alkynes form an isomeric mixture of products. The compound **12** could directly reductively eliminate to give **13**, or cobalt(III) could be protonated to give **14** which could oxidatively cyclize to give **13**. Formation of **14** is plausible since the picolinamide of 1-naphthylamine reacts to form the noncyclic **6** (Scheme 2). To distinguish between those pathways, **14** was heated with $Co(OAc)_2$ and $Mn(OAc)_2$ at 60°C. A complex reaction

mixture was obtained and formation of **13** was not observed, thus excluding the intermediacy of **14**.

In conclusion, we have developed a highly general, functional-group-tolerant method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed coupling of alkynes with $C(sp^2)$–H bonds. The reaction employs a $Co(OAc)_2 \cdot 4H_2O$ catalyst, $Mn(OAc)_2$ co-catalyst, and oxygen (from air) as a terminal oxidant. Future directions of the work involve mechanistic studies of the transformation and attempts to isolate reaction intermediates.

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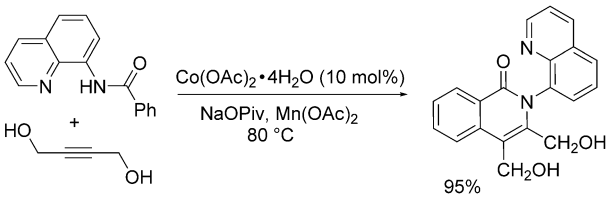
Communications

C–H Activation

L. Grigorjeva,
O. Daugulis* ——— ■■■■–■■■■

Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)–H Bond Alkenylation by Alkynes



In the air: Excellent functional-group tolerance is observed in the title reaction, and both internal and terminal alkynes are competent substrates for the coupling. The reaction employs $Co(OAc)_2 \cdot 4H_2O$ as the catalyst, $Mn(OAc)_2$ as the co-catalyst, and oxygen (from air) as the terminal oxidant. Piv = pivalate.