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

Liene Grigorjeva and **Olafs Daugulis***
Department of Chemistry, University of Houston, Houston, TX 77204-5003, USA

Abstract

We have developed a method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed sp^2 C-H bond alkenylation by alkynes. Method shows excellent functional group tolerance and both internal and terminal alkynes are competent substrates for the coupling. The reaction employs $Co(OAc)_2*4H_2O$ catalyst, $Mn(OAc)_2$ cocatalyst, and oxygen from air as a terminal oxidant.

Keywords

Alkenes; C-H Activation; Alkynes; Cobalt

During the last decade, transition-metal catalyzed C-H bond functionalization methodology has emerged as an important chemistry tool that allows simplification and shortening of synthetic schemes.[1] Within last years, applications of C-H bond functionalization to synthesis of natural products and compounds of medicinal interest have emerged, 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 sp^2 C-H bonds with alkynes has yet to be described. Furthermore, most examples of sp^2 C-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,[3a] a number of groups have reported directed or non-directed reactions of sp^2 C-H bonds with alkynes catalyzed by second- or third row transition metals.[3] Use of more available first-row transition metals has been rare.[4] Only few examples describe nickel- or cobalt-catalyzed alkyne/sp^2 C-H bond coupling. Notably, following earlier reports that low-valent cobalt species can activate and functionalize sp^2 C-H bonds,[5] Yoshikai has developed a versatile system for cobalt-catalyzed, imine- and pyridine-directed alkenylation of sp^2 C-H bonds with internal alkynes.[4f–h,l] Nakao and Hiyama have shown that $Ni(cod)_2$ catalyzes coupling of sp^2 C-H bonds with disubstituted acetylenes.[4d] Chatani has described nickel-catalyzed reaction of benzoic acid 2-pyridinylmethylamides with internal alkynes.[4e] However, directed coupling of both

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*Fax: (+1)713-743-2709, olafs@uh.edu.

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internal and terminal alkynes with sp^2 C-H bonds is exceedingly rare.[4i,m] We report here a method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed sp^2 C-H bond coupling with alkynes. The reaction succeeds with terminal and internal alkynes, tolerates a wide range of functional groups on alkyne and arene, and allows for a removal of directing groups. Furthermore, 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 sp^2 and sp^3 C-H bond functionalization.[6a,b] Subsequently, copper-catalyzed sp^2 C-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, 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 that 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 sp^2 C-H bonds since Co(III) is known to activate sp^2 C-H bonds[9] and carbon-carbon multiple bond insertion into Co(III)-C bonds has been demonstrated.[10]

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

The reaction scope with respect to aminoquinoline amides is presented in Table 2. The reactions are successful for both electron-rich (entries 5, 7) and electron-poor (entries 2–4, 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) showing compatibility of reaction conditions with heterocycles. Reaction headspace volume is important as 1 equiv 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, with free alcohol moiety (entry 1), ester (entry 6), silyl (entry 7), cyclopropyl (entry 8), and protected amine (entry 9) compatible with reaction conditions. Terminal alkynes with either aromatic (entry 3) or large substituents (entries 4,

7) afford products as a single regioisomers. Terminal alkynes with smaller substituents (entries 6, 8 and 9) as well as unsymmetric internal alkynes (entry 5) form regioisomer 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.

Picolinamide directing group can be used (Scheme 2), allowing functionalization of benzyl- and naphthylamine derivatives. Picolinamide of 1-naphthylamine was reacted with 2-butyne in the presence of catalytic $Co(OAc)_2*4H_2O$ to afford the non-cyclized alkenylation product **6** in moderate yield. Similarly, 1-methylbenzylamine picolinamide reacted with 2-butyne to give cyclized product **8** in 44% yield. As shown before[6] picolinamidedirected reactions are less efficient affording lower yields of products, requiring higher temperatures, and longer reaction times.

The advantage of aminoquinoline and picolinamide directing groups lies in the possibility of their removal, affording useful functionalized products (Scheme 3). Base hydrolysis of **8** removes picolinamide, giving trimethylisoquinoline **9**. Aminoquinoline directing group can be removed by treatment with CAN at room temperature. Cleavage of directing group is accompanied by oxidation of the double bond, affording ketolactone **10** in moderate yield.

Based on the fact that aminoquinoline ligand stabilizes transition metals in high oxidation states, it is likely that the reaction proceeds via Co(III) intermediate **11** formed by oxidation of $Co(OAc)_2$ in the presence of aminoquinoline amide ligand (Scheme 4). Insertion of alkyne into cobalt-aryl bond would provide **12**. Alternative mechanism with cobalt acetylide intermediate is unlikely since (1) internal alkynes are reactive, and (2) terminal alkynes form product as a mixture of two isomers. Compound **12** could directly reductively eliminate **13**, or Co(III) could be protonated to give **14** which could oxidatively cyclize to give **13**. Formation of intermediate **14** is plausible since picolinamide of 1-naphthylamine reacts to form non-cyclic **6** (Scheme 2). To distinguish between those pathways, **14** was heated with $Co(OAc)_2$ and $Mn(OAc)_2$ at 60 °C. Complex reaction mixture was obtained and formation **13** was not observed, thus excluding 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 sp^2 C-H bonds. The reaction employs $Co(OAc)_2*4H_2O$ catalyst, $Mn(OAc)_2$ cocatalyst, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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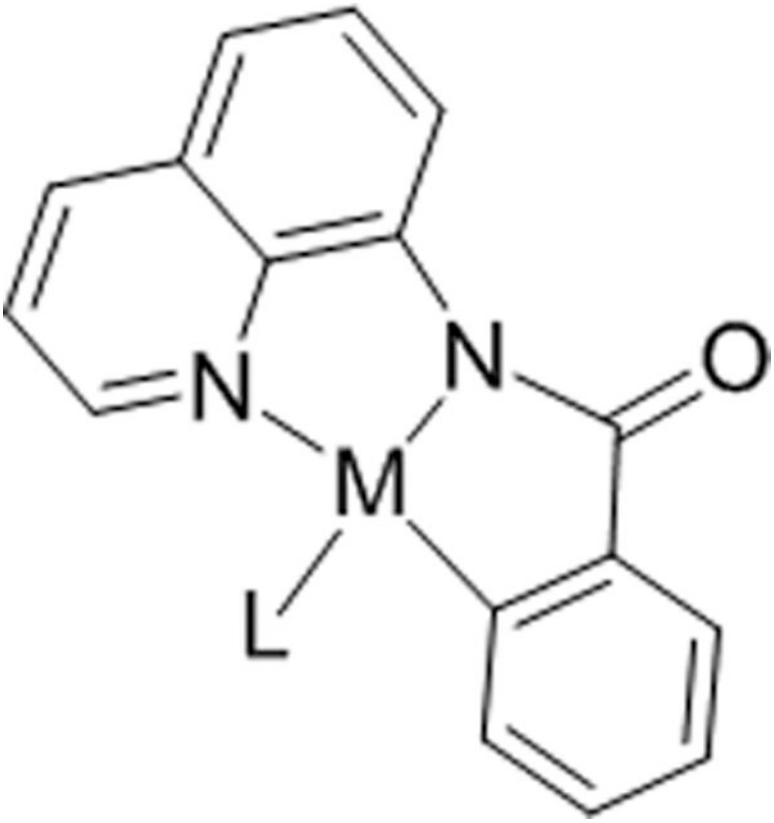
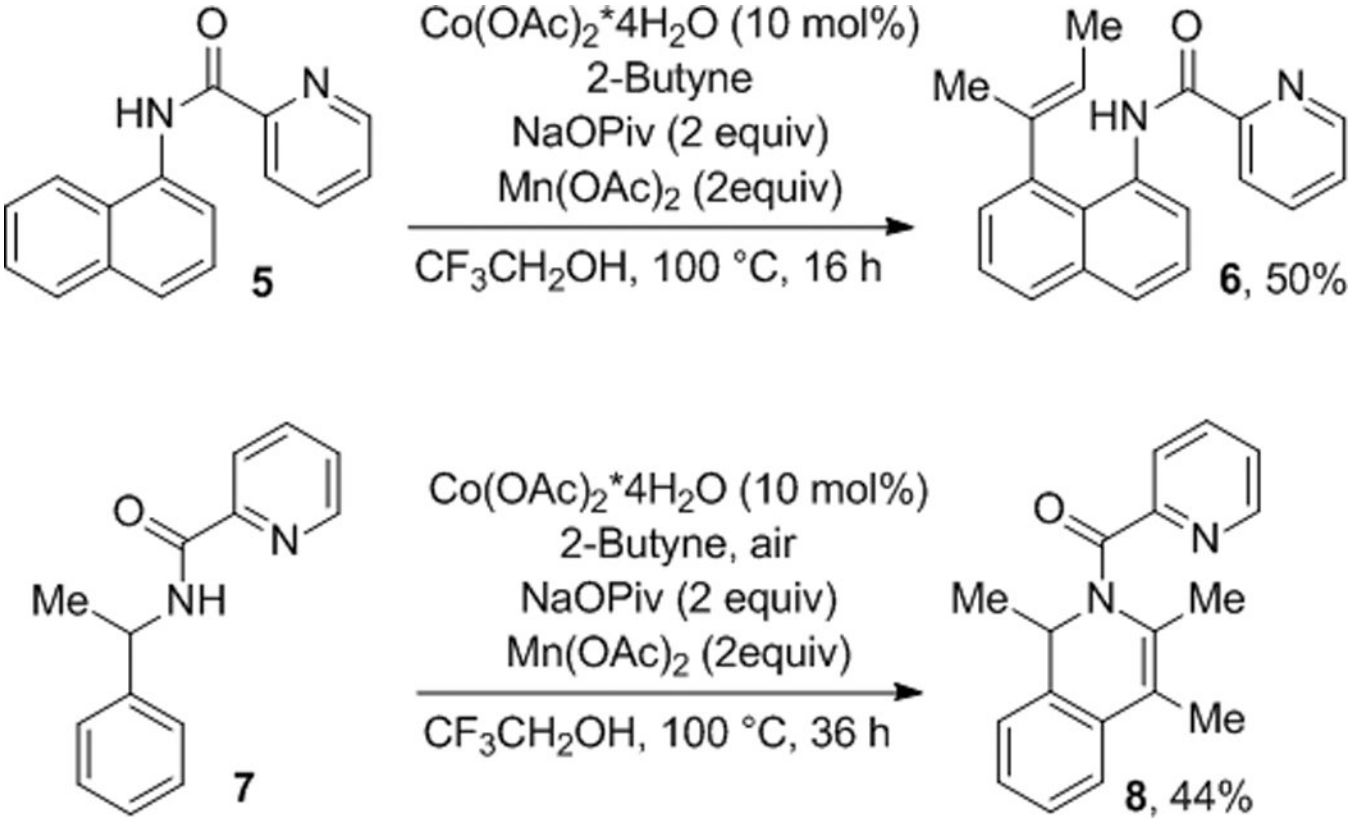
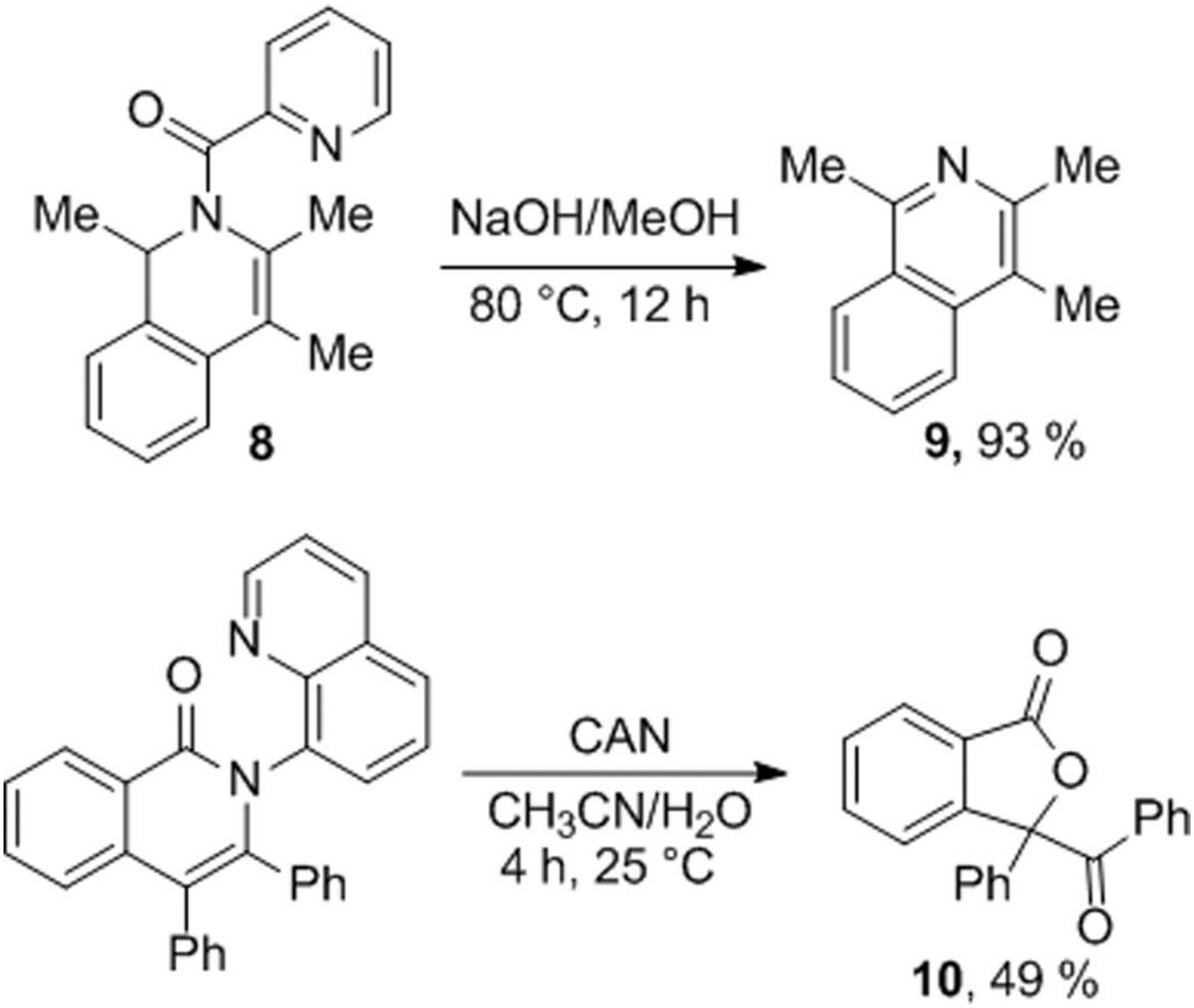


Figure 1.
Aminoquinoline Directing Group.

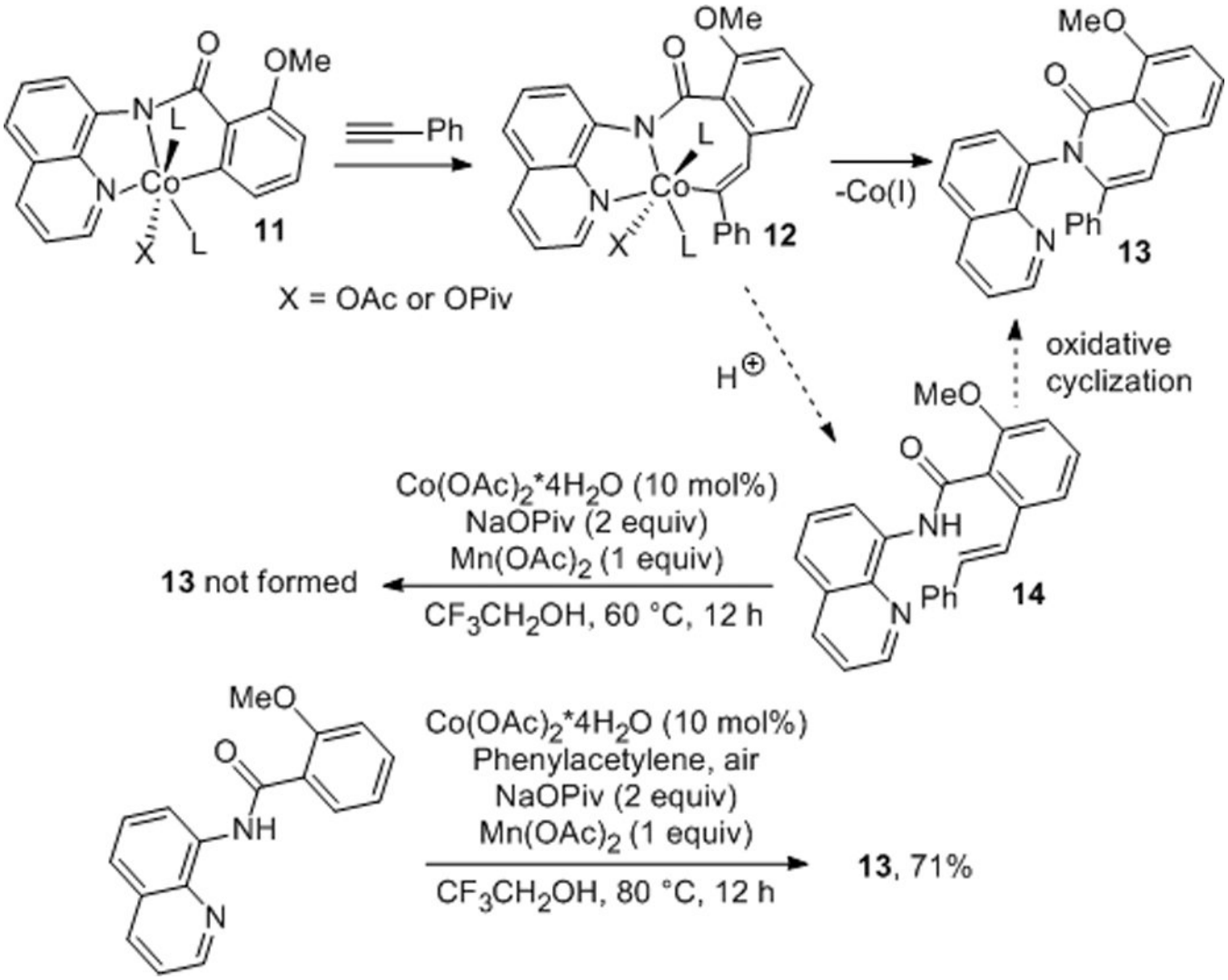
Scheme 1.
Cyclization with Vinyl Amide.



Scheme 2.
Picolinamide Directing Group.



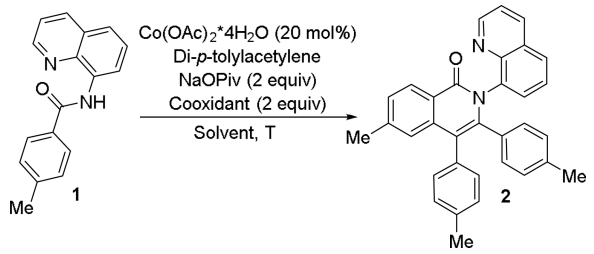
Scheme 3.
Directing Group Removal.



Scheme 4.
Mechanistic Considerations.

Table 1

Optimization of Reaction Conditions.[a]



Entry	T, °C	Time, h	Solvent	Cooxidant	Ratio 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.

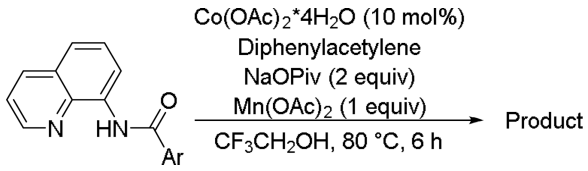
[f] Deoxygenated solvent.

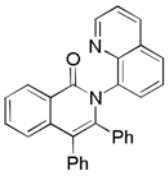
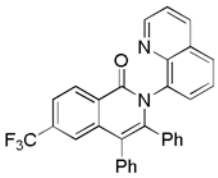
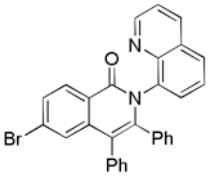
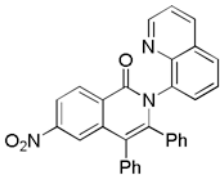
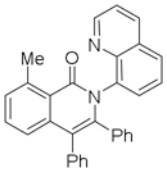
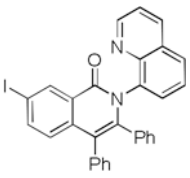
[g] Reaction vessel pressurized with O_2.

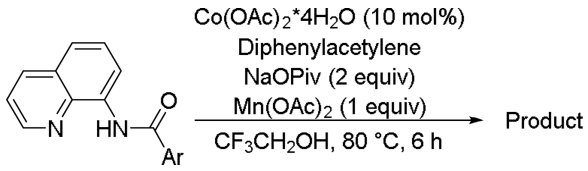
[h] NMR yield of **2** using 1,1,2-trichloroethane as internal standard in parentheses.

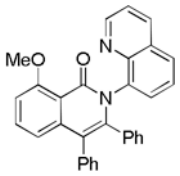
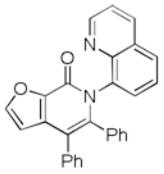
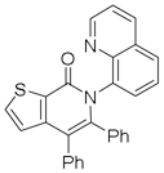
Table 2

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-$BrCC_6H_4$		73
4	4-$NO_2C_6H_4$		78
5	2-MeC_6H_4		86
6	3-IC_6H_4		84



Entry	Ar	Product	Yield, %
7[b]	2-MeOC$_6$H$_4$		74
8[c]	2-furyl		81
9[d]	2-thiophenyl		86

[a] Amide 0.5 mmol, CF_3CH_2OH 5 mL, air. Yields are isolated yields. Please see Supporting information for details.

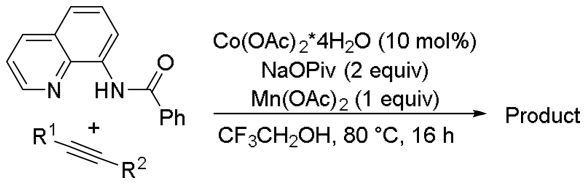
[b] Time: 18 h.

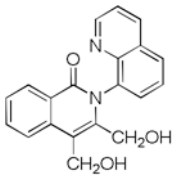
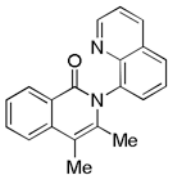
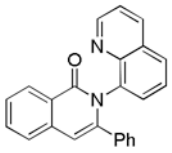
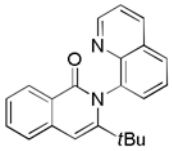
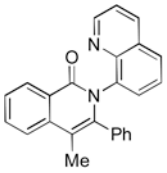
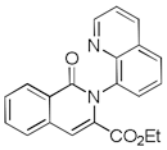
[c] Time: 16 h.

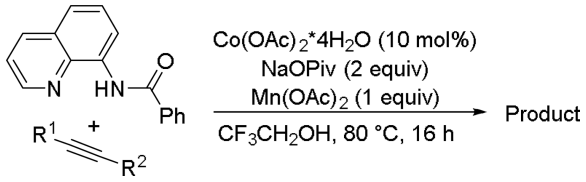
[d] Time: 20 h.

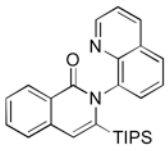
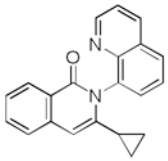
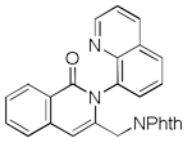
Table 3

Reaction Scope with Respect to Alkynes [a]



Entry	R^1, R^2	Product	Yield, %
1	CH_2OH CH_2OH		95
2	Me Me		96
3	H Ph		95
4	H *t*Bu		73
5[b]	Ph Me		95
6[c]	CO_2Et H		82



Entry	R^1, R^2	Product	Yield, %
7	TIPS H		64
8[d]	cyclopropyl H		84
9[e]	CH_2 NPhth H		93

[a] Amide 0.5 mmol, CF_3CH_2OH 5 mL, alkyne 1.2 equiv, air. Yields are isolated yields. Please see Supporting information for details.

[b] Isolated as 14/1 isomer mixture.

[c] Minor isomer (13%) also isolated.

[d] Isolated as 13/1 isomer mixture.

[e] Isolated as 7/1 isomer mixture, reaction time: 18 h.