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Cobalt-Catalyzed Selective Synthesis of Isoquinolines Using Picolinamide as a Traceless Directing Group

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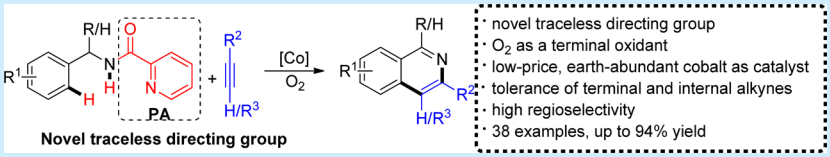
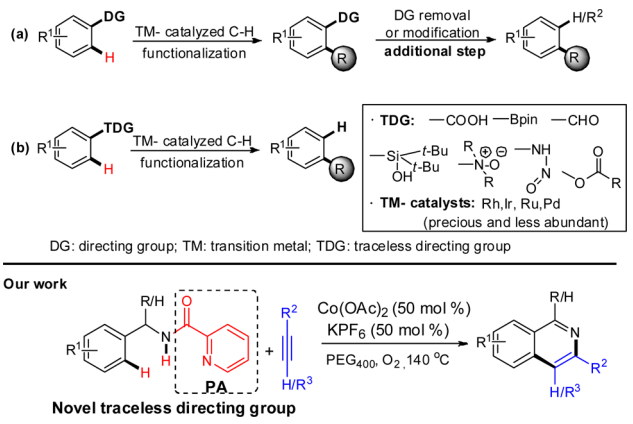
Supporting Information



ABSTRACT: Picolinamide has first been employed as a traceless directing group for the cobalt-catalyzed oxidative annulation of benzylamides with alkynes to synthesize isoquinolines through C−H/N−H bonds activation. Oxygen is used as a terminal oxidant. This protocol exhibits good functional group tolerance and excellent regioselectivity. Both terminal and internal alkynes can be efficiently applied to this catalytic system as substrates.

Transition-metal-catalyzed functional group directed C−H functionalization has emerged as a powerful approach to construct C−C and C−X (X = heteroatom) bonds and represent a state-of-the-art method for the modification of organic molecules in terms of atom and step economy and regioselectivity.[1] In these reactions, the directing groups are essential for acceleration and regioselective control.[2] Nevertheless, this strategy suffers from multichemical steps including removal of directing groups which are not present in the target molecules (Scheme 1). Traceless directing groups, the removal of which does not require additional steps, would be more attractive alternatives. However, the functional groups that can be employed as the traceless directing groups remain relatively rare.[3] Recently, carboxylic acid,[4] *N*-oxide,[5] silicon-tethered,[6] (pinacolato) boron (Bpin),[7] aldehyde,[8] N-nitroso,[9] and acetal[10] have been developed as elegant traceless directing groups for the transition metal (such as Rh, Ir, Ru, and Pt) catalyzed direct C−H functionalization (Scheme 1). Picolinamide as a traceless directing group, in which C−N bond cleavage occurred in one step, remains unprecedented although it has been demonstrated as an effective directing group[11] for C−H functionalization. On the other hand, the isoquinoline framework is an important structural motif found in many natural products,[12] pharmaceuticals[13] and chiral ligands for asymmetric synthesis[14] as well as advanced functional materials.[15] Thus, developing an efficient method to construct such a structure has received considerable attention.[16] Herein we report a cheap and earth abundant cobalt-catalyzed oxidative annulation of benzylamides with alkynes to synthesize isoquinolines through C−H/N−H bond activation. This reaction employs oxygen as an oxidant and picolinamide as a traceless directing group, which exhibits good functional-group tolerance and excellent regioselectivity. Furthermore, both terminal and internal alkynes could be efficiently applied as substrates (Scheme 1).

Scheme 1. Directing Group Assisted Transition-Metal-Catalyzed C−H Functionalization



As an initial attempt, the reaction of benzylamide **1a** with tolane **2a** was chosen as a model reaction for optimization of the various reaction parameters (Table 1). First, the expected product **3a** was obtained in 33% isolated yield in the presence of $Co(OAc)_2{\cdot}4H_2O$ (20 mol %), KPF_6 (20 mol %), and O_2 as an oxidant in PEG-400 at 140 °C for 20 h (Table 1, entry 1). Among a variety of cobalt salts, $Co(OAc)_2{\cdot}4H_2O$ proved to give the optimal result (entries 1−4). Next, solvents, such as DMSO, 1,4-dioxane, and different molecular weight of PEG, were examined and provided inferior results (entries 5−8). Increasing the loading of KPF_6 from 20 to 50 mol % led to an increase in yield from 33% to 43% (entries 1, 9−11). When the amount of KPF_6 was increasing to 1 equiv, the yield of **3a** was slightly improved from 43% to 45% (entry 11). Increasing the

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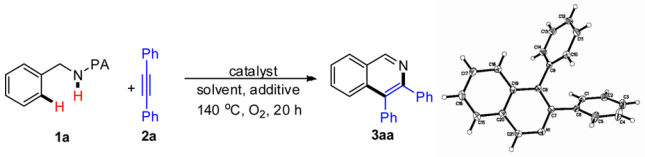
Table 1. Optimization of the Reaction Conditions[a]



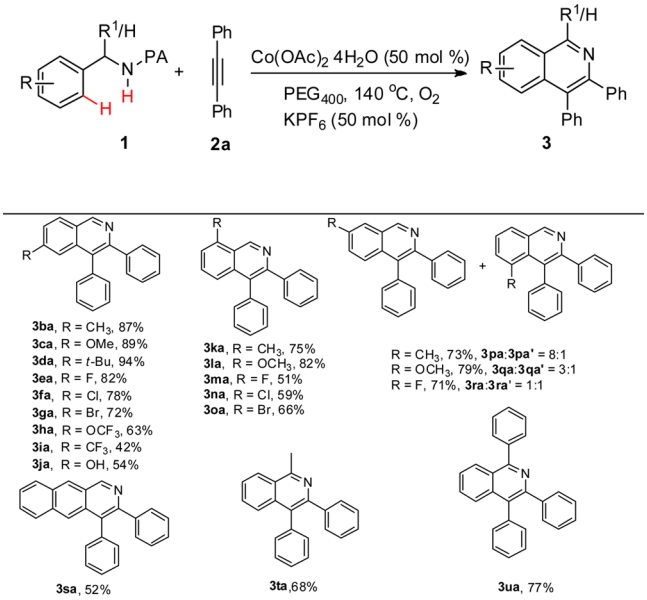
entry	catalyst (mol %)	solvent	additive (mol %)	yield (%)[b]
1	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-400	KPF_6 (20)	28
2	$Co(acac)_2$ (20)	PEG-400	KPF_6 (20)	10
3	$CoCl_2$ (20)	PEG-400	KPF_6 (20)	15
4	$CoSO_4$ (20)	PEG-400	KPF_6 (20)	n.r.
5	$Co(OAc)_2{\cdot}4H_2O$ (20)	DMSO	KPF_6 (20)	12
6	$Co(OAc)_2{\cdot}4H_2O$ (20)	1,4-dioxane	KPF_6 (20)	n.r.
7	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-200	KPF_6 (20)	18
8	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-600	KPF_6 (20)	21
9	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-400	KPF_6 (30)	33
10	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-400	KPF_6 (40)	39
11	$Co(OAc)_2{\cdot}4H_2O$ (20)	PEG-400	KPF_6 (50)/ (100)[c]	43/45[c]
12	$Co(OAc)_2{\cdot}4H_2O$ (30)	PEG-400	KPF_6 (50)	64
13	$Co(OAc)_2{\cdot}4H_2O$ (40)	PEG-400	KPF_6 (50)	72
14	$Co(OAc)_2{\cdot}4H_2O$ (50)	PEG-400	KPF_6 (50)	89
15	$Co(OAc)_2{\cdot}4H_2O$ (60)	PEG-400	KPF_6 (50)	91

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), solvent (1.0 mL), 140 °C under O_2 (1 atm), 20 h. [b]Isolated yields. [c]1 equiv of KPF_6.

catalyst loading from 20 to 50 mol % significantly enhanced this reaction (entries 1, 12−14), while further increasing the loading of the catalyst to 60 mol % could not obviously improve the reaction efficiency (entry 15).

With the optimized reaction conditions in hand, we first investigated the scope of benzylamides (Scheme 2). To our delight, a remarkably broad range of benzylamides was tolerated. Tolane **2a** could react efficiently with benzylamides **1** bearing both electron-donating and -withdrawing groups, delivering the targeted products **3** in moderate to excellent yields. Generally, benzylamides with electron-withdrawing groups gave lower yields than those with electron-donating groups. For instance, benzylamides with the electron-donating groups at the *para* position, such as Me−, MeO−, and *tert*-Bu− promoted this transformation smoothly. The desired products (**3ba**−**3da**) were obtained in excellent yields (87%−94%). Benzylamides substituted by electron-withdrawing groups, such as X− (Cl−, F−, Br−), CF_3O−, and CF_3− also reacted with **2a**, giving the corresponding products in 42−82% yields (**3ea**−**3ia**). *para*-Hydroxyl benzylamide also could react with **2a** and give the desired product in 54% yield (**3fa**). Next the *ortho*-substituted benzylamides had been investigated. The corresponding annulated products were given in moderate to good yields (**3ka**−**3oa**). The steric hindrance of *ortho*-substitution had no significant effect on the reaction efficiency. In the case of *meta*-substituted substrates (**3pa**−**3ra**), a regioisomeric

Scheme 2. Scope of the Benzylamides[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.125 mmol), KPF_6 (0.125 mmol), PEG-400 (1.0 mL), 140 °C under O_2 (1 atm), 20 h.

mixture was obtained in good yields (71%−79%). Higher regioselectivity (**3pa:3pa′** = 8:1) was provided for *meta*-methyl benzylamide than *meta*-F benzylamide (**3ra:3ra′** = 1:1) perhaps due to the steric hindrance. When 2-naphthamide was used as the substrate, **3sa** could be isolated in 52% yield. Importantly, *α*-substituted substrates, such as *α*-methyl and phenyl benzylamines, proceeded smoothly with tolane, allowing facile access to 1,3,4-trisubstituted isoquinolines **3ta** and **3ua** in good yields.

Subsequently, we investigated the scope of alkynes (Scheme 3). The annulative coupling between **1a** and various symmetric diarylacetylenes bearing electron-donating (CH_3−, CH_3O−) or electron-withdrawing (F−, Cl−, CF_3−, EtOOC−) groups at the *para* or *meta* position afforded the corresponding products in 55−79% yields (**3ab**−**3ak**). However, no desired product was obtained for *ortho*-substituted tolanes, such as CH_3−, CH_3O− groups, probably due to the steric effect. The reaction of dialkyl-substituted alkynes also reacted smoothly, affording the corresponding product in 87−91% yield (**3al, 3am**). To our surprised, the terminal arynes (**2n**−**2p**) displayed good reactivity as well with high regioselectivity (**3an**−**3ao**). Unsymmetrical internal alkynes with one phenyl group such as 1-phenyl-1-propyne (**2q**), 1-phenyl-1-butyne (**2r**), and 1-phenyl-1-hexyne (**2s**) also efficiently gave products (**3aq**−**3as**) in good yields with excellent regioselectivity. The configuration of **3aq** was confirmed by single-crystal X-ray diffraction. Unsymmetrical internal aryl alkynes with two aryl groups, such as methyl-4-((4-nitrophenyl)ethynyl)benzene, were tested as substrate, giving a regioisomeric mixture (**3at:3at′** = 1:1) in 72% total yield.

To gain insights into the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 4). Two parallel reactions of **1a** and **1a-d$_5$** were conducted under the standard reaction conditions and were terminated after 30 min. The KIE (KH/KD) is 1.1, indicating that C−H bond activation might not be involved as the rate-determining step. Furthermore, a

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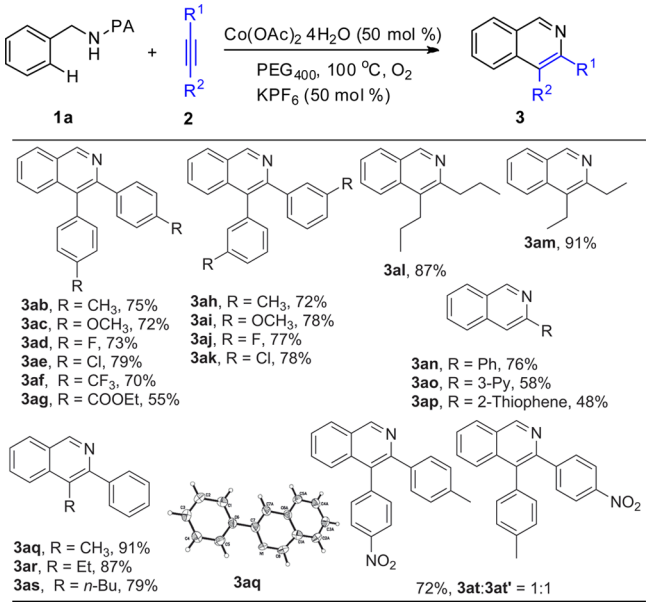
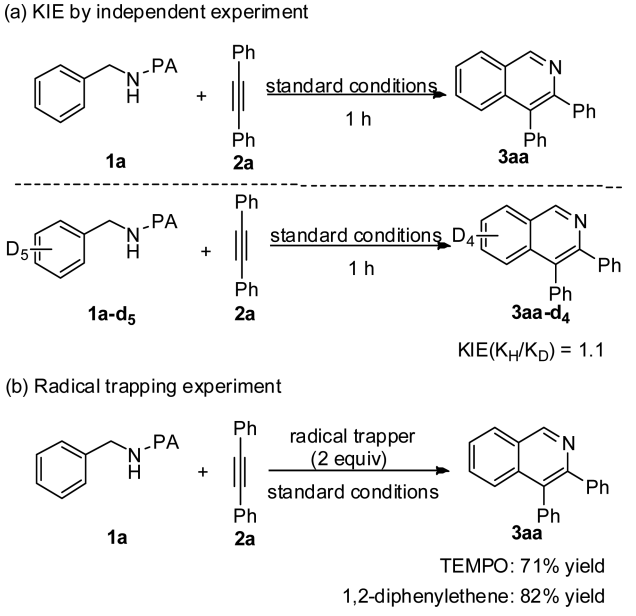
Scheme 3. Scope of Symmetrical and Unsymmetrical Alkynes[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.125 mmol), KPF_6 (0.125 mmol), PEG-400 (1.0 mL), 140 °C under O_2 (1 atm), 20 h.

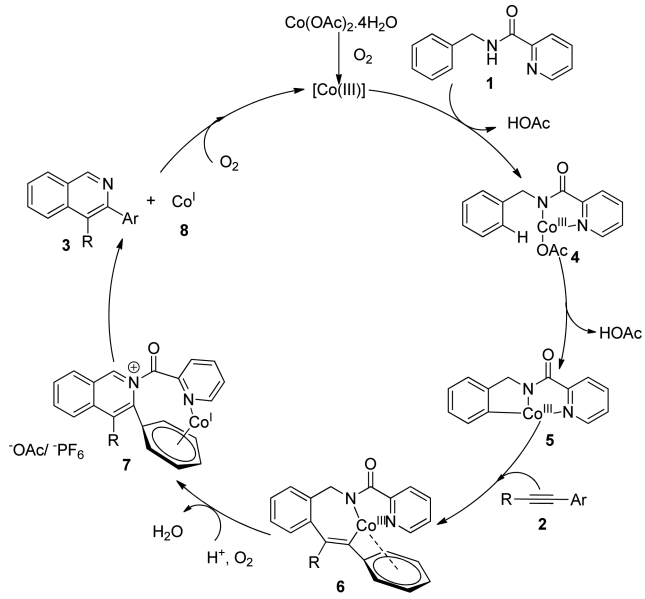
Scheme 4. Mechanistic Studies



radical trapping experiment carried out using TEMPO and 1,2-diphenylethene under standard reaction conditions. The reaction was not obviously inhibited, which suggested that the radical process could be ruled out.

In accordance with the mechanistic studies and literature,[17] a plausible reaction mechanism is depicted in Scheme 5. The reaction is initiated by Co(III) species generated *in situ* by the aid of oxygen from Co(II) species. Then coordination of the benzylamide **1** with the cobalt center followed by ligand exchange with the concomitant generation of HOAc gives the intermediate **4**, which undergoes reversible cyclomatalation to give the intermediate **5** probably via a concerted metalation–deprotonation (CMD) mechanism. Then, coordination and insertion of intermediate **5** with alkyne **2** gives a seven-membered intermediate **6**, which undergoes reductive elimination and dehydrogenation with the aid of oxygen to afford isoquinolinium salt **7**. Then the C–N bond cleavage gives isoquinoline product **3** and the Co(I) species **8**, which was subsequently oxidated by oxygen into the active Co(III) species for the next catalytic cycle.

Scheme 5. Plausible Reaction Mechanism



In summary, we developed a cobalt-catalyzed annulation of benzylamides with alkynes to synthesize isoquinolines by using picolinamide as a traceless directing group. This protocol features a wide substrate scope: not only internal aryl/aliphatic alkynes but also terminal alkynes can efficiently be applied in this reaction which show good tolerance to functional groups and excellent regioselectivity. Furthermore, oxygen was used as the sole oxidant instead of a metal oxidant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00702.

Experimental details and procedures (PDF)
Crystallographic information for compound **3aa** (CIF)
Crystallographic information for compound **3aq** (CIF)

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Notes

The authors declare no competing financial interest.

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