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Cp*-Free Cobalt-Catalyzed C−H Activation/Annulations by Traceless *N,O*-Bidentate Directing Group: Access to Isoquinolines

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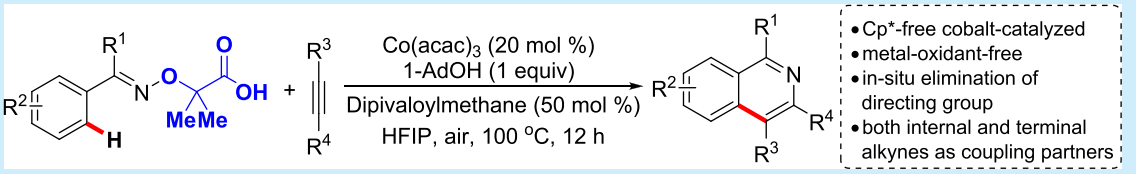
Supporting Information



ABSTRACT: *N,O*-Bidentate directing-enabled, traceless heterocycle synthesis is described via Cp*-free cobalt-catalyzed C−H activation/annulation. The weakly coordinating nature of the carboxylic acid was employed for the preparation of isoquinolines. Meanwhile, the N−O bond of the α-imino-oxy acid can serve as an internal oxidant. Terminal as well as internal alkynes can be efficiently applied to the catalytic system. This operationally simple approach shows a broad substrate scope with the products obtained in good to excellent yields.

Substituted isoquinolines are one of the most important heterocycles, which are frequently found in natural products, pharmaceuticals, chiral ligands, as well as organic materials.[1] Unfortunately, conventional synthetic routes usually suffer from poor functional group tolerance and harsh reaction conditions such as strong acids or high temperature.[2] Hence, it is highly desirable to develop an efficient strategy that exhibits mild conditions and good functional group tolerance.[3] Alternatively, transition-metal-catalyzed C−H bond activation has emerged to be a practical method for the construction of heterocycles in recent years,[4] which provides a complementary approach to obtain isoquinolines. In this context, transition-metal-catalyzed C−H functionalization to furnish isoquinolines has been reported and proven to be an effective method. In general, the practical utility of these transformations relies on precious metal catalysts such as Rh, Pd, and Ru.[5]

From the viewpoint of sustainable development, focus has shifted to the use of environmentally and less expensive transition-metal catalysts for C−H activation.[6] More recently, considerable progress has been accomplished with first-row transition metals to lead to isoquinolines. Among them, the strategy was mainly achieved through monodentate directing groups,[7] whereas examples of utilizing bidentate directing groups remain relatively rare. In 2016, Zhu reported on the demonstration of 2-hydrazinylpyridine-directed (*N,N*-bidentate directing group), traceless synthesis of isoquinolines by cobalt(II) catalyst.[8a] Then, picolinamide as a *N,N*-bidentate directing group for the cobalt-catalyzed selective synthesis of isoquinolines was proposed by Cui.[8b]

However, the above-mentioned strategies mainly employed the L,L-type (i.e., neutral, neutral) bidentate directing groups; the L,X-type (i.e., neutral, anionic) counterparts have not been developed in the area. Notably, pioneering studies have been reported by Yu,[9] who has demonstrated the Pd-catalyzed β-C(sp3)-H iodination and arylation using the L,X-type α-imino-oxy acid auxiliary. Then, a similar auxiliary was applied in the visible-light-promoted C−H functionalization by Studer.[10] Inspired by the aforementioned progress and guided by our previous work,[11] we attempted to explore an efficient method for the preparation of isoquinolines using the cheaper and readily available cobalt salt as the catalyst. Herein a new protocol for Cp*-free cobalt-catalyzed C−H activation/annulation based on a traceless directing group is reported. In the reaction, external metal oxidant was absent due to the fact that the N−O bond of the auxiliary can act as an internal oxidant.[12] Meanwhile, the weakly coordinating carboxyl motif in the *N,O*-bidentate directing group is crucial for the system. The directing group can be removed directly in situ along the catalytic process, which has great potential for streamlining the synthesis of isoquinolines.

We commenced our study by selecting α-imino-oxy acid (**1a**), which was prepared by commercially available starting materials, and diphenylacetylene (**2a**) as model substrates. Optimization studies on the reaction are summarized in Table 1. Initially, the desired product **3aa** was observed in 24% when $Co(acac)_3$ was used as the catalyst in 1,2-dichloroethane (DCE) at 100 °C in air (entry 1). Among the solvents examined, hexafluoroisopropanol (HFIP) exhibited the best transformation, giving the product **3aa** in 56% yield (entries 1−3). Subsequently, alternative cobalt salts including Cp*Co(III) species (entries 4−7) were found to be inferior compared with $Co(acac)_3$, and no product was obtained without the cobalt salt (entry 8). Further investigations (entries 9−12) revealed that 1-adamantane carboxylic acid might act as both a

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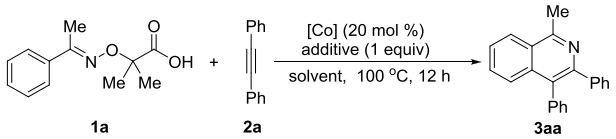
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	[Co] (20 mol %)	additive (1 equiv)	solvent	yield (%)[b]
1	$Co(acac)_3$		DCE	24
2	$Co(acac)_3$		TFE	46
3	$Co(acac)_3$		HFIP	52
4	$Co(acac)_2$		HFIP	35
5	$Co(OAc)_2{\cdot}4H_2O$		HFIP	N.R.
6	$Cp^*Co(CO)I_2$		HFIP	N.R.
7	$[Cp^*Co(MeCN)_3][(SbF_6)_2]$		HFIP	N.R.
8			HFIP	N.R.
9	$Co(acac)_3$	$NaOPiv{\cdot}H_2O$	HFIP	23
10	$Co(acac)_3$	PivOH	HFIP	44
11	$Co(acac)_3$	1-AdOH	HFIP	71
12	$Co(acac)_3$	dipivaloylmethane	HFIP	59
13[c]	$Co(acac)_3$	1-AdOH	HFIP	84
14[d]	$Co(acac)_3$	1-AdOH	HFIP	91

[a]Reaction conditions: substrate **1a** (0.2 mmol), **2a** (1.5 equiv), $Co(acac)_3$ (20 mol %), HFIP (1.0 mL), 1-AdOH (50 mol %), dipivaloylmethane (1 equiv), air atmosphere, 12 h. [b]Isolated yield. [c]1-AdOH (50 mol %), dipivaloylmethane (50 mol %). [d]1-AdOH (1 equiv), dipivaloylmethane (50 mol %). N.R. = no reaction. 1-AdOH = 1-adamantane carboxylic acid.

proton donor and a ligand, whereas dipivaloylmethane might serve as a ligand in the catalytic process, which is beneficial to the system.[13] Therefore, we attempted to adjust the amounts of additives. The product was detected in 91% yield when 1-adamantane carboxylic acid (1 equiv) in conjunction with dipivaloylmethane (0.5 equiv) was added to the reaction (entries 13 and 14). Either elevated or lower temperature was a disadvantage for the reaction activity (see the Supporting Information).

Different directing groups are discussed as follows (see Figure 1). The results indicate that substrate **1a** exhibits a

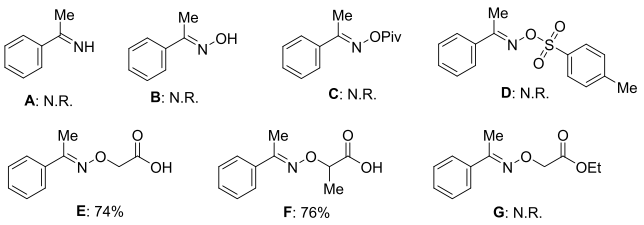
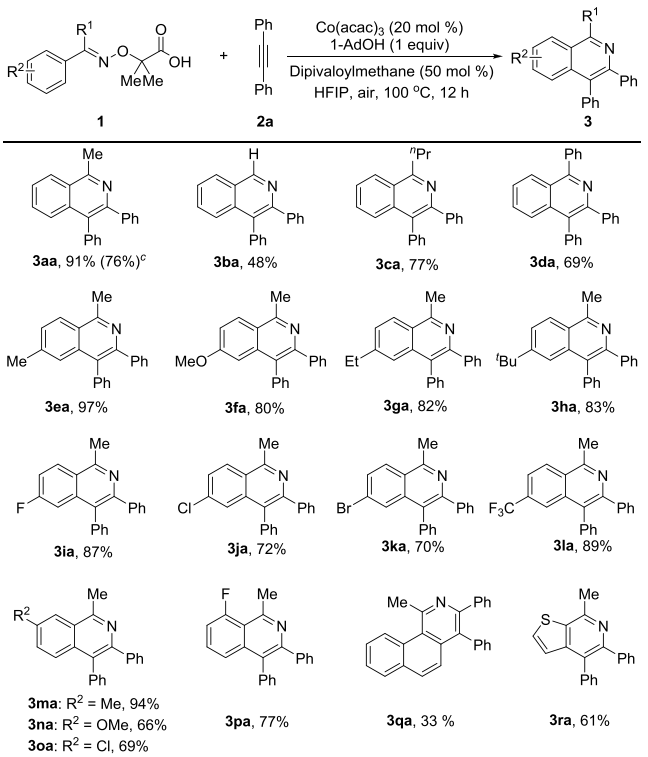


Figure 1. Screening of directing groups for the reaction.

preferable reactivity for the reaction under identical conditions. A series of monodentate directing groups (**A**–**D**) failed to promote the reaction. In contrast, the bidentate coordinating groups **E** and **F** could give **3aa** in moderate yield. Moreover, it seems that increasing the steric bulk of α-imino-oxy acid auxiliary carbon center could facilitate the reaction; however, when the directing group **G** bearing the ethyl ester displaced the auxiliary **E**, the product **3aa** was not detected, further highlighting the unique property of the weakly coordinating carboxyl-directing motif.

With the optimal conditions in hand, we first investigated the substrate scope of this reaction between various substrate **1** derivatives and diphenylacetylene **2a**. As shown in Scheme 1, a wide variety of functionalized α-imino-oxy acids were tolerated by the cobalt catalyst to give the desired product **3**.

Scheme 1. Co(III)-Catalyzed Synthesis of Isoquinoline Derivative[a,b]



[a]Reaction conditions: substrate **1a** (0.2 mmol), **2a** (1.5 equiv), $Co(acac)_3$ (20 mol %), 1-AdOH (1 equiv), dipivaloylmethane (50 mol %), HFIP (1.0 mL), air atmosphere, 12 h. [b]Isolated yield. [c]Yield of 1 mmol scale.

The yield of product decreased (**3aa**–**3da**) when methyl was replaced by hydrogen, *n*-propyl, or phenyl. The para-substituted α-imino-oxy acids bearing both electron-donating and electron-withdrawing groups were compatible with the

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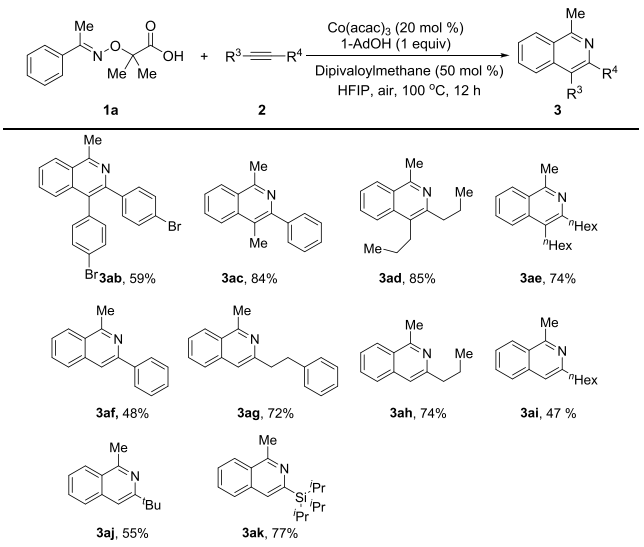
optimized reaction conditions, thus affording the corresponding products in 70−97% yields (**3ea**−**3ja**). Substitution on the meta position allowed C−H activation to take place exclusively on the less hindered position (**3ma**−**3oa**); in particular, **3ma** was generated in an excellent yield of 94%. When a sterically hindered *ortho*-fluoro-substituted α-imino-oxy acid was employed, the corresponding product **3pa** was obtained in 77% yield. Meanwhile, the **1q** derived from a bicyclic system was smoothly converted to the corresponding benzo[*h*]-isoquinoline **3qa**. In addition, the heteroarene α-imino-oxy acid was compatible in this transformation of **3ra** with 61% yield.

Subsequently, the scope of the reaction with respect to alkynes was examined, and experimental results are illustrated in Scheme 2. In general, both terminal and internal alkynes

Scheme 2. Substrate Scope for Alkynes[a,b]

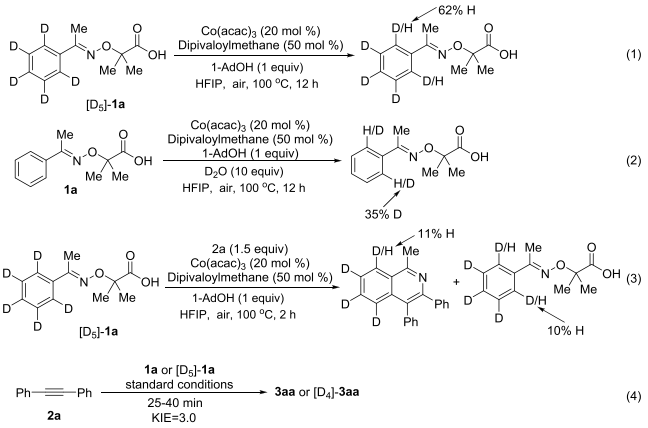


[a]Reaction conditions: substrate **1a** (0.2 mmol), **2a** (1.5 equiv), $Co(acac)_3$ (20 mol %), 1-AdOH (1 equiv), dipivaloylmethane (50 mol %), HFIP (1.0 mL), air atmosphere, 12 h. [b]Isolated yield.

were compatible with the reaction. The diphenylacetylene derivative **2b** could also smoothly perform and gave the product **3ab** in moderate yield. For the unsymmetrical internal alkyne, it could afford 84% of **3ac** with exclusive regioselectivity. Similarly, dialkyl (**2d** and **2e**) alkynes reacted smoothly to give corresponding isoquinolines in 85 and 74% yields. When terminal alkynes were employed, the corresponding cyclization products were furnished with moderate to good yields, yet with relatively high regioselectivities (**3af**−**3ag**). Meanwhile, chain alkynes were also compatible with the reaction conditions and gave the corresponding products (**3ah**, **3ai**). Moreover, we observed that triisopropylsilylacetylene was a suitable alkyne, yielding an isoquinoline that can be subsequently functionalized (**3ak**).

Additional experiments were performed to probe the mechanism of the reaction (Scheme 3). The competition experiment between **1e**/**1f** and **2a** was performed and revealed the preferred reaction for electron-rich **1e** (**1e**/**1f** = 1.43; see the SI). Meanwhile, under an atmosphere of Ar, the yield of product decreased significantly; even the cobalt salt loading increased to 1 equiv, suggesting that oxygen most likely changes the coordination environment for the generation of a

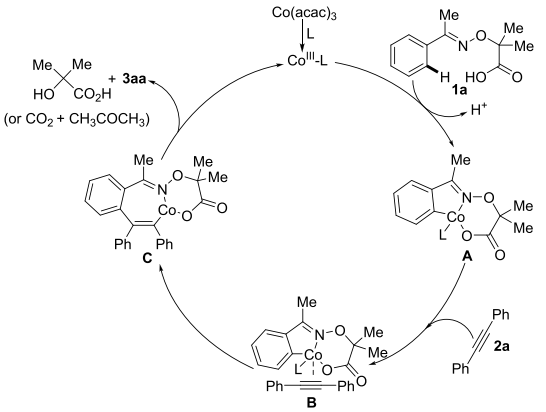
Scheme 3. Mechanistic Studies



more reactive cobalt catalytic center during the catalytic process[8a] (see the SI). Furthermore, significant H/D exchanges could be detected in the reactions of both isotopically labeled substrates [D_5]-**1a** and **1a**/D_2O under standard reaction conditions without **2a** (Scheme 3, eqs 1 and 2). Additionally, we also conducted the reaction of [D_5]-**1a** with **2a** for 2 h under standard reaction conditions; the existence of 11% H/D exchange in product [D_4]-**3aa** (Scheme 3, eq 3) was observed. The previously described experiments of H/D exchange indicate that the C−H cleavage process might be reversible. A kinetic isotope effect (KIE) value of 3.0 was observed between **1a** or [D_5]-**1a** and **2a** in the parallel experiments (Scheme 3, eq 4), which indicates that Co-catalyzed C−H bond cleavage might be involved in the rate-limiting step. Then, a KIE (1.4) was observed in the competitive reaction of **1a** and [D_5]-**1a** with **2a** (see the SI).

On the basis of the above mechanistic studies and related reports,[8,9,14] a plausible Co(III)/Co(I) catalytic cycle is illustrated in Scheme 4. Initially, $Co(acac)_3$ undergoes ligand

Scheme 4. Plausible Reaction Mechanism



exchange to generate a catalytically active species. Then, coordination of the substrate **1a** to the catalytically active species and subsequent cyclometalation by C−H bond cleavage provide intermediate **A**. Alkyne **2a** is then coordinated to the Co(III) center of intermediate **A** to provide intermediate **B**. Then, coordinative insertion of the carbon−carbon triple bond into the C−Co bond of intermediate **B** results in the seven-membered cobaltacyclic intermediate **C**. Finally, intermediate **C** might undergo intramolecular sub-

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stitution, leading to product **3aa** and side product 2-hydroxyisobutyric acid (or the release of side product CO_2 and acetone)[15] along with the regeneration of the catalytically active species for a new catalytic cycle.

In summary, we described an efficient cobalt-catalyzed C−H activation/annulation of α-imino-oxy acids with terminal as well as internal alkynes. Meanwhile, a strategy based on a traceless oxidizing directing group was successfully utilized for the process. The weakly coordinating nature of the carboxylic acid plays a crucial role in the synthesis of isoquinolines. The reaction exhibits a broad substrate scope, with the products obtained in good yields. Further applications of the directing group strategy in other related types of C−H functionalization and detailed mechanistic studies are actively ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00866.

Experimental procedures and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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