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Cobalt-Catalyzed Bis-alkynylation of Amides via Double C−H Bond Activation

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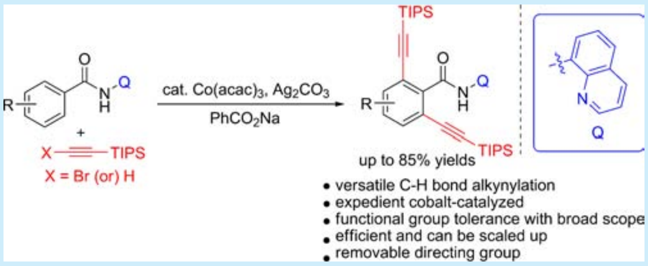
Supporting Information

ABSTRACT: The first example of cobalt-catalyzed selective bis-alkynylation of amides via double C−H bond activation with the directing assistance of a removable bidentate auxiliary is reported. The developed alkynylation strategy is simple, efficient, and tolerant of various functional groups including ether, amine, halides, and heterocyclic motifs. The reaction can be scaled up under mild conditions.



Transition-metal catalyzed direct functionalization of the inert C−H bond has emerged as a powerful strategy for the straightforward synthesis of value-added products with great step economy and low waste production. Over the past decades, considerable efforts have been dedicated toward catalysts based upon precious metals such as Pd, Ru, Rh, and Ir.[1] The replacement of expensive noble metal catalysts by utilizing economical, and environmentally benign first-row transition-metal catalysts is an important paradigm in chemical synthesis. In this regard, earth-abundant first-row late transition metals have been intensely used in C−H bond activation strategy to emulate the selectivity and reactivity of precious-metal catalysts and thus broaden the scope and practical viability.[2] However, their successful application in C−H bond functionalizations still remains at an early stage and can make it difficult to envisage and control catalytic reactivity, as they have a propensity to participate in one-electron chemistry as opposed to classical two-electron transformation ubiquitous in the second- and third-row transition metals.

Alkynes are an exceptionally versatile functional group and are ubiquitous in pharmaceuticals, material science, and other functional compounds.[3] Thus, the development of an efficient strategy for the construction of alkynyl scaffolds is a key motivation in contemporary science and is usually achieved with the Sonogashira cross-coupling reaction between an aryl halide and a terminal alkyne.[4] However, the complementary approach, "inverse Sonogashira coupling" involving the direct alkynylation of inert aryl C−H bonds with easily accessible alkynyl halides, is very attractive and highly desirable in organic synthesis. In this context, alkynylation of unactivated arenes with the assistance of different directing groups has been developed as an efficient protocol to construct C(sp^2)−C(sp) bonds, which was mainly accomplished by Pd-,[5a−d] Ru-,[5e] and Rh-catalysts.[5f,g] A copper-mediated alkynylation of arenes assisted by bidentate amide oxazoline and PIP (2-pyridinyl isopropyl) directing groups has been independently reported by Yu[6a] and Shi,[6b] demonstrating the significant potential of inexpensive, first-row transition metals in C(sp^2)-alkynylation; however, these transformations required a stoichiometric amount of copper salts. More recently, Shi,[7a,b] Li,[7c] and our group[7d] have independently developed a nickel(II)-catalyzed alkynylation of arenes with the directing assistance of a bidentate auxiliary.[2f,8] During the past decade, cobalt catalysts in various oxidation states have been recognized as simple, efficient, and increasingly viable catalysts for C−H bond functionalization.[2d,h,i,2,9] Noteworthy works from the research groups of Kanai,[10] Nakamura,[11] Daugulis,[12] Glorius,[13] Yoshikai,[14] Song,[15] Ackermann,[16] Chang,[17] Ellman,[18] Sundararaju,[19] and others[20] demonstrated the high potential of cobalt catalysts in C−H bond activation reactions. A recent report from Shi[20b] and Ackermann[16g] on the Cp*Co(III)-catalyzed C(sp^2)-alkynylation of pyrimidin-2-yl)-1*H*-indoles with hypervalent iodine(III) reagents and 1-bromoalkyne, respectively, prompted us to disclose our first report on a simple, efficient, air-stable, cobalt(III)-catalyzed C(sp^2)-alkynylation of amides with the directing assistance of a removable 8-aminoquinoline. The present alkynylation strategy has a broad substrate scope and functional group tolerance and can be scaled up under mild conditions. Remarkably, halide groups could be reserved under our reaction conditions and, thus, extend the spectrum for further modification of the products, wherein synthesis of halide-substituted alkyne derivatives using the classical approach, "Sonogashira coupling," is extremely difficult.

Optimization studies on the *ortho* C−H bond alkynylation are summarized in Table 1. We began our investigation using 2-chloro-*N*-(quinolin-8-yl)benzamide (**1a**) as a model substrate and (triisopropylsilyl)ethynyl bromide **2** as a coupling reagent in the presence of Co(acac)$_3$ (10 mol %), PhCO$_2$Na (0.2 equiv),

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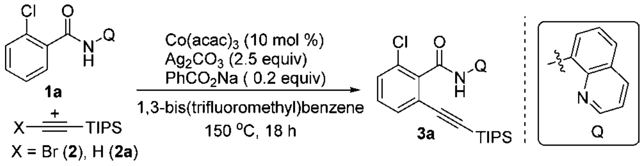
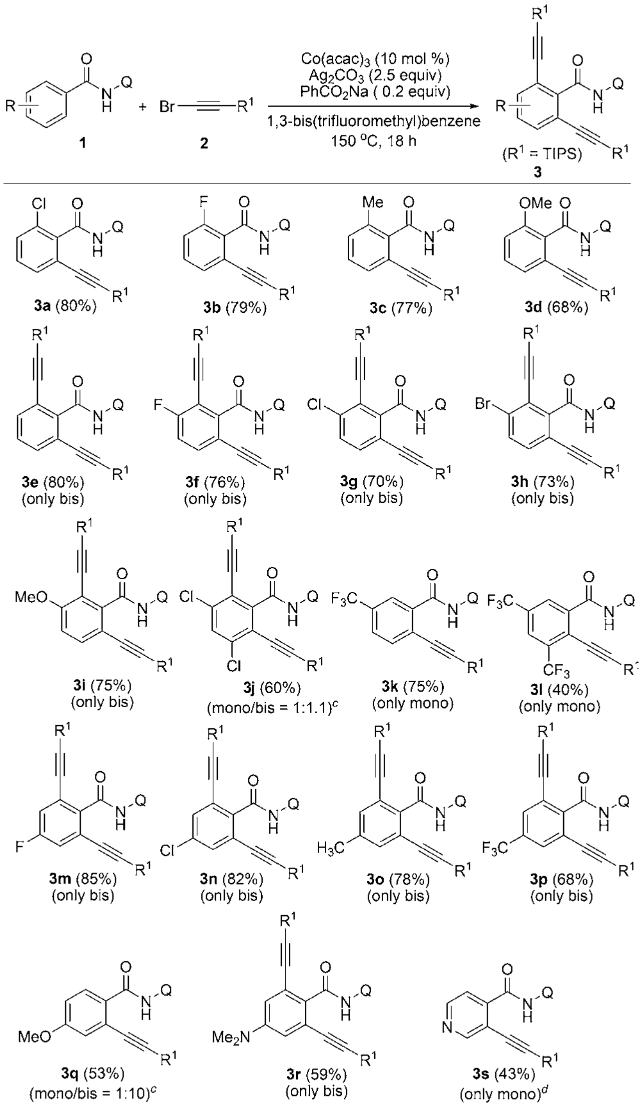
Table 1. Optimization of the Reaction Conditions[a]



entry	reaction conditions	yield (%)[b]
1	toluene used a solvent	31
2	PhF used a solvent	43
3	1,4-dioxane used a solvent	n.r.
4	standard conditions (using **2**)	80
5	without $PhCO_2Na$	52
6	NaOAc instead of $PhCO_2Na$	47
7	without Ag_2CO_3	6
8	AgOAc instead of Ag_2CO_3	55
9	$AgSbPF_6$ instead of Ag_2CO_3	n.r.
10	at 80 °C	28
11	without [Co] cat.	nr
12	$Co(OAc)_2$ used as [Co] source	63
13	$CoCl_2$ used as [Co] source	trace
14	$CoBr_2$ used as [Co] source	trace
15	$[Cp^*Co(C_6H_6)][PF_6]_2$	n.r.
16	standard conditions (using **2a**)	28

[a] Reaction conditions: Condition A: **1a** (0.1 mmol), $Co(acac)_3$ (0.01 mmol), Ag_2CO_3 (0.25 mmol), **2** (0.12 mmol), sodium benzoate (0.02 mmol), and 1,3-bis(trifluoromethyl)benzene (1 mL) heated at 150 °C for 18 h under argon. [b] Isolated yields.

Scheme 1. Cobalt-Catalyzed Alkynylation of Amides: Scope of Amides[a,b]

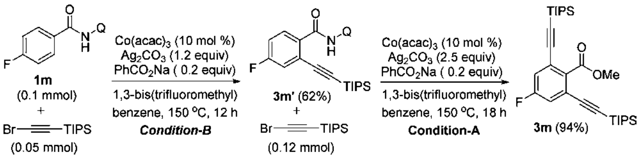


[a] Reaction conditions: **1** (0.1 mmol), $Co(acac)_3$ (0.01 mmol), Ag_2CO_3 (0.25 mmol), **2** (0.12 mmol (**1a**−**1d**) or 0.25 mmol (**1e**−**1s**)), $PhCO_2Na$ (0.02 mmol), and 1,3-bis(trifluoromethyl)benzene (1 mL) heated at 150 °C for 18 h under argon. [b] Isolated yields. [c] The ratio of mono- and bis-alkynylation products is based upon the individual isolated yields. [d] In the absence of $PhCO_2Na$.

and Ag_2CO_3 as the oxidant in toluene heated at 150 °C (bath temperature) for 18 h to yield the expected product **3a** in 31% isolated yield (Table 1, entry 1). The solvent dependency of the same reaction was carried out (Table 1, entries 1−4), and we found that the reaction proceeds efficiently in 1,3-bis(trifluoromethyl)benzene compared to other solvents to afford **3a** in an isolated yield of 80% (Table 1, entry 4).[21] Notably, the efficiency of the reaction was significantly affected in the absence of $PhCO_2Na$ (Table 1, entry 5) and clearly revealed the coordination of the 8-aminoquinolylamide to the cobalt complex followed by a ligand exchange that was accelerated by the base.[22] By lowering the temperature we obtained the product in lower yield (Table 1, entry 10), and no reaction was observed in the absence of the cobalt catalyst (Table 1, entry 11). Among a variety of different cobalt complexes, $Co(acac)_3$ proved to give optimal results (Table 1, entries 4, 12−15). Gratifyingly, ethynyltriisopropylsilane (**2a**) was also effective for this alkynylation reaction and gave **3a** in lower yield (28%) under optimal conditions (Table 1, entry 16). Notably, no (or trace) alkynylation was observed in the absence of an oxidant.[23]

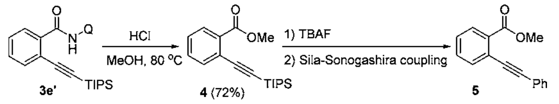
With an optimized catalytic system in hand (Table 1), we set out to probe its versatility in the C(sp^2)-alkynylation of various substituted amides. The developed synthetic methodology is general and has a broad substrate scope. As shown in Scheme 1, the present cobalt-catalyzed alkynylation is compatible with various benzamides containing an electron-rich or deficient substituent, affording the expected alkynylated products in good to excellent yields. Alkynylation of *ortho*-substituted benzamides (**1a**−**d**) containing a range of functional groups, such as alkyl, methoxy, fluoro, and chloro, survived and gave the mono-alkynylation products (**3a**−**3d**) in good yields (up to 80%). Bis-alkynylated amides are the precursors of conjugated polymers by oxidative coupling on catalysts such as with the Cp*Ru catalyst, as the alkyne groups cannot interact intramolecularly. However, selective bis-alkynylation of unactivated C−H bonds of benzamide (**1**) through a double C−H activation strategy is difficult and rather rare, as it often tends to afford a mixture of both mono- and bis-alkynylated amides. Gratifyingly, our optimal conditions gave the bis-alkynylated product as a single product with complete selectivity (**3e**−**3i**, **3m**−**3p**, and **3r**). Notably, with 3-bromo-*N*-(quinolin-8-yl)benzamide (**1h**), the alkynylation occurred at a sterically hindered position and yielded bis-alkynylation as a major product in 73% isolated yield. However, the electron-deficient 3-(CF_3)-substituted amides (**1k**−**1l**) underwent the reaction smoothly and gave mono-alkynation as a single product with moderate yields (75% of **3k** and 40% of **3l**), perhaps because of the combination of both steric hindrance (in case of **1l**) and strong electron deficiency. It is noteworthy that the synthetically valuable halide substituents could be reserved under our reaction conditions and can extend the spectrum for further modification of the products, wherein synthesis of halide-substituted alkyne derivatives using the classical approach, the Pd-catalyzed "Sonogashira coupling," is extremely difficult. In this regard, benzamides bearing halides such as chloro, bromo groups (**1a**, **1g**–**h**, **1j**, and **1n**) proceeded efficiently and yielded the corresponding alkynylated products in good yields under our catalytic conditions. To our delight, a challenging heteroaromatic amide (**1s**) selectively gave the corresponding mono-alkynylated product in good yield (**3s** in 43% isolated yield) in the absence of $PhCO_2Na$. Selective mono-alkynylation and sequential bis-alkynylation were achieved successfully under conditions B and A, respectively (Scheme 2).

Scheme 2. Sequential Bis-alkynylation of 1m



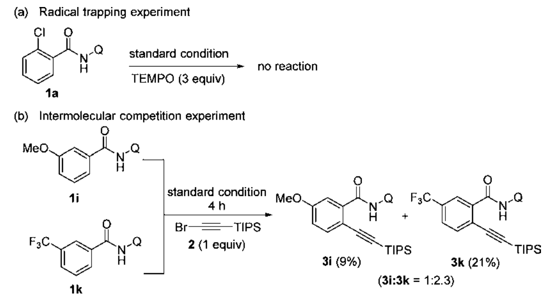
The removal of the directing bidentate auxiliary (8-aminoquinonyl group) was easily accomplished under mild reaction conditions.[7d] Subsequently, the chemoselective removal of the TIPS group was achieved under standard reaction conditions, with further conversion to a phenyl group to yield **5** in 72% overall yield through the Pd-catalyzed Sila–Sonogashira coupling reaction (Scheme 3).[24]

Scheme 3. Diversification of Alkylated Amides



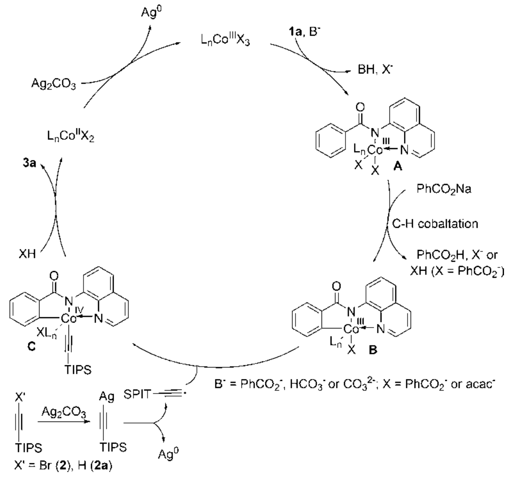
We have also successfully shown the scalability of this catalytic protocol under mild conditions. In this regard, the present cobalt-catalyzed alkynylation was tested for gram-scale synthesis of **3a** (4.0 mmol scale), and it worked excellently with an expected alkynylated product (**3a**) in 72% yield.[25] The reaction performed in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; 3 equiv) was completely inhibited, indicating that the radical reaction pathway could be involved in the catalytic cycle (Scheme 4a). In addition, competitive experiments performed with an electron-rich and deficient amide using (triisopropylsilyl)ethynyl bromide **2** showed that alkynylation is favored with an electron-deficient substrate (Scheme 4b).[25] This finding showed that the acidity of the *ortho* C–H bond is important. A similar trend was also observed in previously reported $C(sp^2)$-alkynylation.[7c,d] Importantly, the requirement of the oxidant is essential for the success of the alkynylation, and no alkynylated products were observed when $AgSbF_6$ (Table 1, entry 9) was used, indicating the classical electrophilic-type C–H bond activation mechanism by the cationic cobalt(III) complex can be ruled out.[9,20b]

Scheme 4. Mechanistic Studies



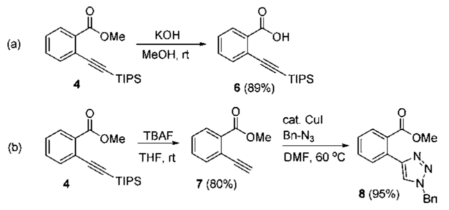
On the basis of these experiments and previous reports,[20b,26] a plausible catalytic cycle is outlined in Scheme 5. The first step of the catalytic reaction is the coordination of the amide **1a** to the Co(III) followed by the base assisted or carboxylate assisted C–H bond cobaltation leading to complex **B**. The attack of an *in situ* generated alkyne radical into complex **B** gives the intermediate **C**, which undergoes reductive elimination to give **3a** and generates the Co(II) species. The oxidation of Co(II) to Co(III) by silver salts further continues the catalytic cycles. Notably, ethynyltriisopropylsilane (**2a**) was also effective for this alkynylation reaction and yielded **3a** in lower yield (28%) under optimal conditions (Table 1, entry 16).

Scheme 5. Plausible Mechanism



The synthetic utility of the versatile cobalt-catalyzed alkynylation was also demonstrated by further diversification of the products (Schemes 3 and 6).

Scheme 6. Removal of Directing Group and Click Reaction of Alkynylated Amide



In conclusion, we have reported the first example of expedient cobalt-catalyzed selective bis-alkynylation of $C(sp^2)$–H bonds of amides through a double C–H bond activation strategy using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group. The present *ortho*-alkynylation has a broad substrate scope as well as functional group tolerance and can thereby be scaled up in gram-scale synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00095.

> Details on experimental procedures, characterization data of all compounds and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(21) Further screening using common solvents, including apolar arenes (*o*-xylene and PhCl) or polar DMF, DMSO, DMA, DCE, and CF_3CH_2OH, proved ineffective in the C−H bond alkynylation.

(22) Other bases such as NaOAc, CsOAc, Li_2CO_3, Na_2CO_3, K_2CO_3, and Cs_2CO_3 proved ineffective, and less formation (up to ∼30%) of **3a** was observed under optimal conditions.

(23) Despite the use of economical cobalt catalysts, often an expensive silver salt is required for reoxidation of Co(II) to Co(III) and *in situ* generation of an alkynyl radical. Other oxidants such as Ag_2O, $AgSO_2CF_3$, AgOAc, Ag_3PO_4, and AgOC(O)CF_3 did not improve the yield of the alkynylated product **3a** under optimal conditions (see the Table 1, entries 8−9).

(24) Compound **3e′** (yield = 45%) was prepared under condition B.

(25) See the Supporting Information.

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