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Direct Synthesis of Quinolines via Co(III)-Catalyzed and DMSO-Involved C−H Activation/Cyclization of Anilines with Alkynes

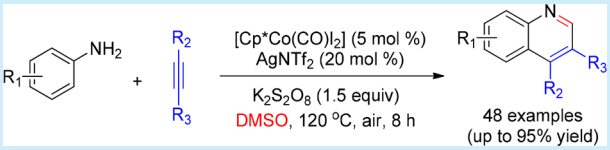
Xuefeng Xu,[†] Yurong Yang,[‡] Xu Zhang,*[,†] and Wei Yi*[,‡]

[†]College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang 473061, China

[‡]Key Laboratory of Molecular Clinical Pharmacology & Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 511436, China

Supporting Information

ABSTRACT: A unique Co(III)-catalyzed and DMSO-involved C−H activation/cyclization of simple, cheap, and easily available anilines with alkynes for direct and highly efficient synthesis of privileged quinolines with exclusive regioselectivity and broad substrate/functional group tolerance and in good to excellent yields, where DMSO was employed as both the solvent and the C_1 building block of quinoline products, is reported. Mechanistic experiments revealed that the versatile reaction might employ the 2-vinylbenzenamine species as the active intermediate.

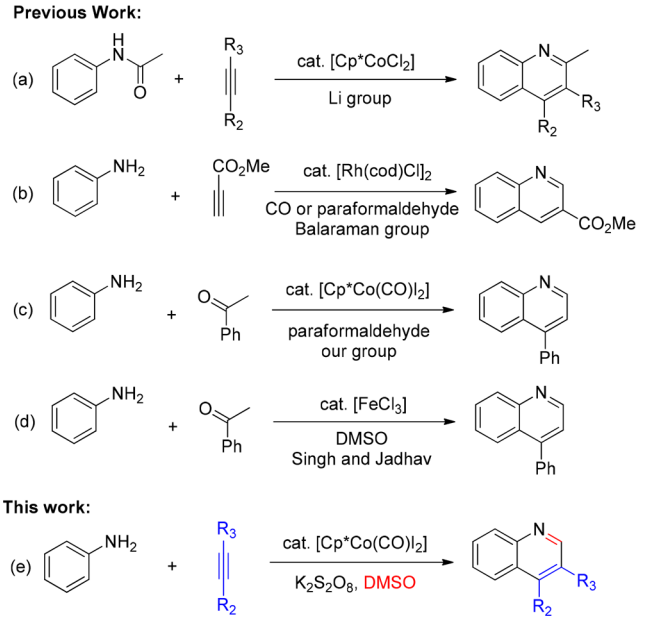


Quinoline represents a ubiquitous structural motif that is found in a broad range of biologically active compounds and pharmaceuticals.[1] Recognizing the great importance of quinoline and its derivatives, the development of efficient methods toward their synthesis has attracted considerable attention. As a result, a number of named reactions have been developed, such as Skraup,[2] Doebner−von Miller,[3] Conrad−Limpach,[4] Pfitzinger,[5] and Friedländer concentration syntheses.[6] However, by reviewing these classical procedures, they still suffer from harsh conditions, corrosive reagents, and a limited substrate scope. Alternatively, a recently popular C−H bond functionalization strategy has emerged as one of the most powerful tools for the step- and atom-economical construction of quinoline framework. Indeed, numerous versatile protocols have been disclosed by second-row transition metals such as Rh, Ru, Pd, Au, Ag, etc.[7] Despite this compelling progress, it would be ideal to directly build the quinoline motif via earth-abundant and inexpensive first row transition-metal-catalyzed C−H bond functionalization strategy in view of green and sustainable chemistry. In this regard, a few seminal examples have been reported.[8]

Recently, cobalt-catalyzed C−H functionalization has gained significant attention due to its distinctive properties, including abundance and inexpensiveness, outstanding reactivity and selectivity, and excellent substrate/functional group tolerance.[9] In general, the assistance of a proximal directing group (DG) is typically required for achieving the cobalt-catalyzed C−H bond activation.[9,10] However, the DG cannot be removed simultaneously in C−H activation reactions and thus often leaves a chemical trace in the final products, limiting their structural diversity.

To overcome the aforementioned limitation, one recent emerging strategy to develop an innovative bifunctional-directing group (BDG) which acts as both a DG and a basic component of products has attracted much attention. For example, in 2015, the Li group reported a beautiful Co(III)-catalyzed redox-neutral annulative coupling of amides with alkynes for synthesis of quinolines, in which the acetamino group was used as the versatile BDG (Scheme 1a).[11] Afterward, the Balaraman group revealed a rhodium-catalyzed C−H activation strategy which employed unprotected anilines and

Scheme 1. Quinoline Synthesis via Transition Metal-Catalyzed C−H Annulation of Anilines with Alkynes/Ketones



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electron-deficient alkynes to build quinoline products, where CO gas or paraformaldehyde was employed as one carbon source (Scheme 1b).[12] Recently, our group has also described a similar Co(III)-catalyzed C−H activation strategy for one-pot construction of a quinoline framework (Scheme 1c).[13] Very recently, Singh and Jadhav described an elegant $FeCl_3$-catalyzed oxidative annulation promoted by $K_2S_2O_8$ involving anilines, aryl ketones, and DMSO as a methine equivalent giving direct access to 4-arylquinolines (Scheme 1d).[14] Compared to paraformaldehyde, indeed, DMSO is more feasible due to its rather low cost, relative stability, and low toxicity. However, in sharp contrast with that using DMSO as the precursor for the introduction of various functional groups such as the sulfonyl group,[15] formyl group,[16] methylthio,[17] and cyano substituents,[18] the examples that employed DMSO as a one carbon source to directly construct heterocyclic compounds still remain underexplored.[14,19]

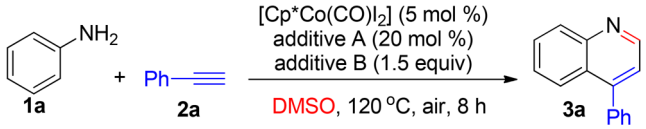
Motivated by the aforementioned information and in continuation of our interest in transition-metal-catalyzed C−H functionalization, we herein report, for the first time, a Co(III)-catalyzed and DMSO-involved C−H activation/cyclization of anilines with alkynes for one-pot synthesis of quinolines, in which DMSO was employed as both the solvent and the C_1 building block of quinoline products (Scheme 1e).

We initiated our studies by testing different reaction conditions for the desired synthesis of quinoline **3a** (Table 1). To our delight, the anticipated **3a** was smoothly detected in DMSO and isolated with 64% yield, when simple aniline (**1a**) and phenylacetylene (**2a**) were employed as model substrates, and Cp*CoI_2(CO), $AgSbF_6$, and $K_2S_2O_8$ were selected as the catalytic system (Table 1, entry 1). Encouraged by this finding, we next investigated the effects of additives for this reaction optimization. As shown in entries 2−12, the brief screening displayed that employing both $AgNTf_2$ and $K_2S_2O_8$ as co-additives was optimal, giving the product **3a** in 85% isolated yield (entry 5). The control experiments demonstrated that the omission of either the catalyst or cocatalytic additives led to a significant decrease in the product yield (entries 11−14). Finally, changing Cp*$Co(CO)I_2$ to other well-known cobalt species also obviously inhibited the process (entries 15−17).

With the optimal reaction conditions in hand, the scope of the reaction with respect to various anilines was evaluated initially (Scheme 2); the results showed that the reaction proceeded smoothly to give the desired products in high yields, and the electronic and steric effects of the substituents on the anilines had no obvious influence on the efficiency of the reaction. For example, anilines bearing the either electron-donating (Me, *t*-Bu) or electron-withdrawing (F, Br) substituents at the *ortho*-position all showed good compatibility, and the corresponding products **3b−e** were obtained in 77−82% yields. Similarly, *meta*- and *para*-substituted anilines also successfully afforded the corresponding quinoline products **3f−3r** with excellent yields (up to 91%). It was worth emphasizing that, for *meta*-substituted anilines, the sole regioisomer was detected, in which the C−H activation reaction exclusively occurred at a less-hindered *ortho*-position. Notably, the polyaromatic naphthalene substrates were also well tolerated with the Co(III)-catalyzed system as exemplified by the successful synthesis of **3s**. Finally, large-size aminoglutethimide and 4-morpholinobenzenamine were also viable substrates, providing the desired products **3t** and **3u** in 71% and 85% yields, respectively.

The scope of alkynes was next examined (Scheme 3). A wide variety of phenyl-functionalized *terminal* alkynes bearing various substituents either at the *ortho*-, *meta*-, or *para*- position on the benzene ring all gave the corresponding products with excellent regioselectivity and in moderate to excellent yields (68−95%) (**4a−4p**). Both electron-donating (Me, OMe, Et, *n*-Pr, *t*-Bu, $N(CH_3)_2$) and -withdrawing (F, Cl, Br, I, CF_3) groups that attached at the benzene ring part of alkynes were all well tolerated. Interestingly, the phenyl group of alkynes could also be extended to the heteroaryl moiety, such as 2-ethynylfuran, 2-ethynylthiophene, and 3-ethynylpyridine substituents, deliver-

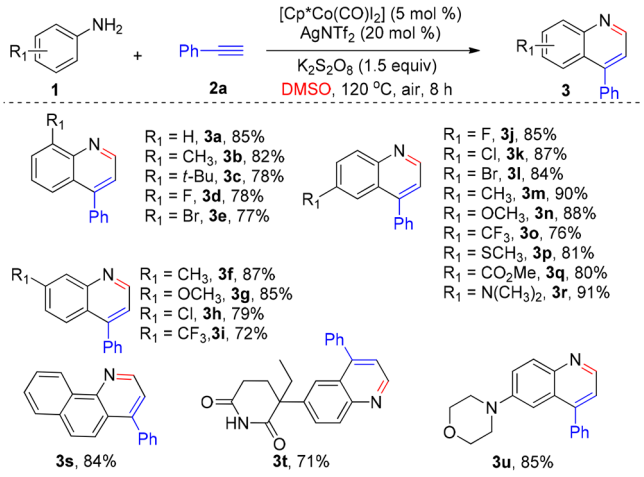
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive A	additive B	yield (%)[b]
1	Cp*$Co(CO)I_2$	$AgSbF_6$	$K_2S_2O_8$	64
2	Cp*$Co(CO)I_2$	AgOAc	$K_2S_2O_8$	32
3	Cp*$Co(CO)I_2$	AgOTf	$K_2S_2O_8$	54
4	Cp*$Co(CO)I_2$	Ag_2CO_3	$K_2S_2O_8$	0
5	Cp*$Co(CO)I_2$	$AgNTf_2$	$K_2S_2O_8$	85
6	Cp*$Co(CO)I_2$	$AgNTf_2$	$(NH_4)_2S_2O_8$	0
7	Cp*$Co(CO)I_2$	$AgNTf_2$	$Na_2S_2O_8$	40
8	Cp*$Co(CO)I_2$	$AgNTf_2$	H_2O_2	0
9	Cp*$Co(CO)I_2$	$AgNTf_2$	TBHP	35
10	Cp*$Co(CO)I_2$	$AgNTf_2$	DTBP	37
11	Cp*$Co(CO)I_2$	$AgNTf_2$	–	0
12	Cp*$Co(CO)I_2$	–	$K_2S_2O_8$	34
13	–	$AgNTf_2$	$K_2S_2O_8$	21
14	–	–	$K_2S_2O_8$	0
15	$Co(OAc)_2$	$AgNTf_2$	$K_2S_2O_8$	17
16	$Co(acac)_2$	$AgNTf_2$	$K_2S_2O_8$	0
17	CoI_2	$AgNTf_2$	$K_2S_2O_8$	62

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Cp*$Co(CO)I_2$ (5.0 mol %), additive A (20 mol %), additive B (1.5 equiv), DMSO (2 mL), 120 °C, 8 h, reaction kettle in air. [b]Isolated yield after chromatography.

Scheme 2. Scope of Aniline[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), Cp*$Co(CO)I_2$ (5.0 mol %), $AgNTf_2$ (20 mol %), $K_2S_2O_8$ (1.5 equiv), DMSO (2 mL), 120 °C, 8 h, reaction kettle in air, isolated yield after chromatography.

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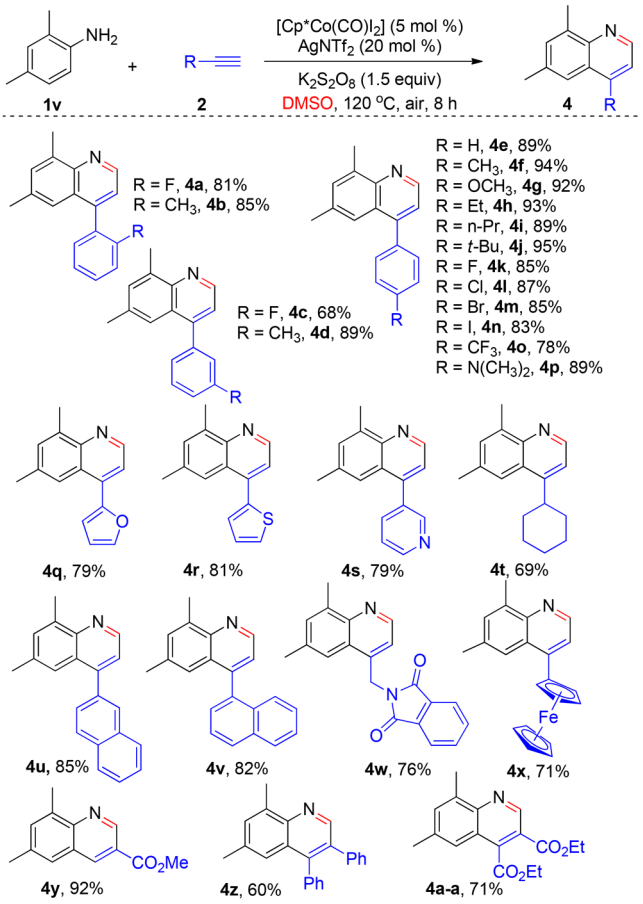
Scheme 3. Scope of Alkynes[a]

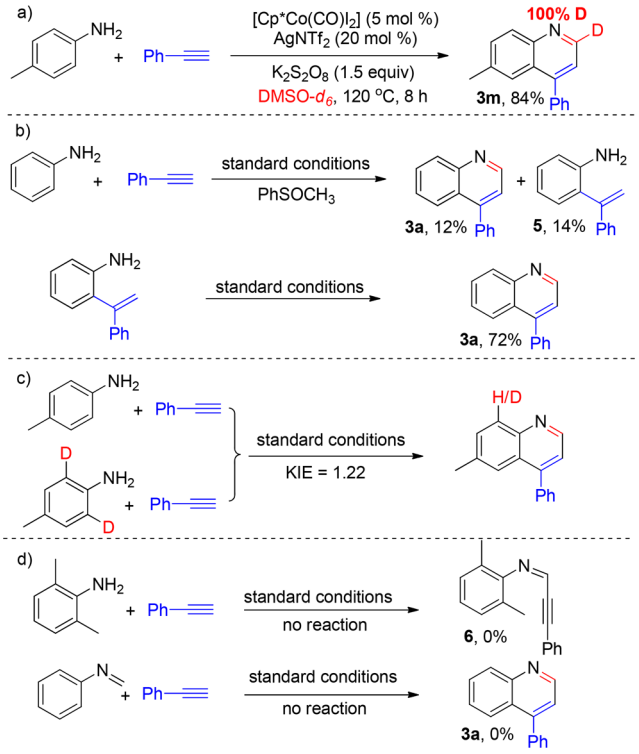


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Cp*Co(CO)I_2 (5.0 mol %), $AgNTf_2$ (20 mol %), $K_2S_2O_8$ (1.5 equiv), DMSO (2 mL), 120 °C, 8 h, reaction kettle in air, isolated yield after chromatography.

ing the corresponding quinoline products in good yield (for **4q**, 79%; **4r**, 81%; and for **4s**, 79%). It should be noted that the substituted acetylenes, such as cyclohexylacetylene (**1t**), ethynylnaphthalene (**1u**–**v**), *N*-porargylphthalimide (**1w**), and ethynylferrocen (**1x**), could be accommodated in the catalytic system, thus giving their corresponding products **4s**–**x** in moderate to good yields. This methodology could be extended to internal alkynes as well. For example, the reaction of **1v** with 1,2-diphenylethyne or diethyl but-2-ynedioate worked well in DMSO to deliver the expected products **4z** and **4a**–**a** in 60% and 71% yields, respectively.

Considering the remarkably broad substrate scope displayed by the Co(III) catalytic system, we performed a series of control experiments to probe the possible reaction mechanism (Scheme 4). Initially, by using DMSO-d_6 to replace DMSO, the deuterated product **3m** was formed in 84% yield with more than 99% incorporation of deuterium (Scheme 4a), which provided clear evidence that DMSO was not only used as the solvent but also acted as the C_1 in this reaction. Further, when the reaction was performed in methylphenylsulfoxide under otherwise identical conditions (Scheme 4b, above), both product **3a** and 2-vinylbenzenamine species **5** were isolated in 12% and 14% yield, respectively, suggesting that **5** might be employed as an active intermediate for this transformation. To further confirm this, the treatment of 2-styrylphenylamine with DMSO under the standard conditions was carried out. As

Scheme 4. Mechanistic Studies



predicted, the product **3a** was obtained smoothly in 72% yield (Scheme 4b, below). Moreover, the kinetic isotope effect was measured to shed more light on the C–H activation process (Scheme 4c), and a small value for the kinetic isotope effect (KIE = 1.22) was monitored from two independent, side-by-side experiments, revealing that the C–H bond cleavage was unlikely involved in the turnover limiting step. No reaction was observed when 2,6-dimethylaniline and *N*-methyleneaniline were respectively employed as the substrate with the reaction of phenylacetylene (Scheme 4d).

On the basis of our experimental results and previous reports, a plausible catalytic cycle is depicted in Scheme 5. First, the active cationic Co(III) catalyst is generated upon treatment of Cp*Co(Co)I_2 with $AgNTf_2$, which coordinated with aniline, followed by the EAS pathway and then *ortho*-metalation to afford the intermediate **A**. More polarized carbon–cobalt in intermediate **A** should favor 1,2-regioselective insertion[20] of an alkyne leading to intermediate **B**. In the presence of $K_2S_2O_8$, the DMSO is activated by $K_2S_2O_8$ to give **C**, which couples with **B** to produce the intermediate **D**. Subsequently, **D** is oxidized to give an imine species **E** with the elimination of HSMe, followed by Co–C migratory insertion to provide the intermediate **F**. Finally, protonolysis of **F** delivers the final product **3a** with the release of the active Co(III) catalyst.

In conclusion, we have developed the first example of Co(III)-catalyzed and DMSO-involved C–H activation/cyclization of anilines with alkynes for direct and highly efficient synthesis of privileged quinolines, in which DMSO was employed as both the solvent and the C_1 building block. Experimental investigations revealed that this transformation might be initiated with the C–H activation process and use 2-vinylbenzenamine species as the active intermediate. Considering the simple, cheap, and easily available starting materials, the valuable structures of the products, mild reaction conditions, exclusive regioselectivity, and excellent substrate/

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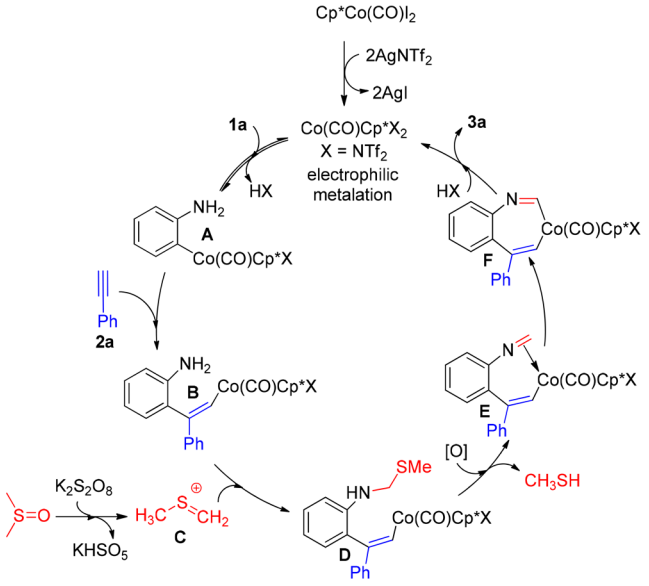
Scheme 5. Plausible Catalytic Cycle



functional group tolerance, we believe that the reaction should have potential wide synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03673.

Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yiwei@gzhmu.edu.cn.
*E-mail: zhangxuedu@126.com.

ORCID

Xu Zhang: 0000-0002-3588-3240
Wei Yi: 0000-0001-7936-9326

Notes

The authors declare no competing financial interest.

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