C–H Activation

International Edition: DOI: 10.1002/anie.201504962
German Edition: DOI: 10.1002/ange.201504962

Cobalt(II)-Catalyzed C_{sp^2}–H Alkynylation/Annulation with Terminal Alkynes: Selective Access to 3-Methyleneisoindolin-1-one**

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Abstract: *A highly efficient cobalt(II)-catalyzed alkynylation/annulation of terminal alkynes assisted by an N,O-bidentate directing group is described. This protocol is characterized by wide substrate scope utilizing cheap cobalt catalysts, and offers a new approach to 3-methyleneisoindolin-1-one, which can be converted into an oxadiazine salt in one step. Moreover, the directing group could be removed in three steps.*

In the past decades, transition-metal-catalyzed C–H bond functionalization has emerged as a practical method for the synthesis of value-added molecules because of its high efficiency and atom economy.[1] Remarkable progress has been made in this field and numerous examples have demonstrated the success of such a strategy. In general, the practical utility of these transformations relies on precious metal catalysts such as Rh,[2] Pd,[3] and Ru.[4] As such, it would be advantageous if more-abundant first-row metal catalysts could emulate the reactivity of a noble-metal catalyst and enable comparable catalytic efficacy. Recently, cobalt-catalyzed organic reactions through C–H bond activation have attracted much attention because of low cost, low toxicity, and abundant reserves.[5]

Meanwhile, terminal acetylene chemistry has developed rapidly because of its occurrence in biologically active molecules and functional materials.[6] From the viewpoint of atom and step economy, the direct coupling of C–H bonds with terminal alkynes is more appealing than the traditional Sonogashira coupling reaction because of obviating prefunctionalization of the reactant. Following this strategy, several groups have reported directed coupling reactions of C_{sp^2}–H bonds with terminal alkynes.[7] Su and co-workers reported the palladium-catalyzed alkynylation of heterocycles.[7f] Nevado and co-workers revealed the gold-catalyzed oxidative coupling of arenes with terminal alkynes by the C–H bond activation in 2010.[7c] Copper- and nickel-catalyzed direct alkynylation of azoles and poly-fluoroarenes with terminal alkynes has also been demonstrated by Miura and co-workers recently.[7b] However, the use of highly activated substrates or expensive catalysts restricts its development in organic synthesis chemistry. In contrast, Kanai, Matsunaga, and co-workers have developed a cobalt-catalyzed non-oxidative coupling of C_{sp^2}–H bonds with terminal alkynes.[8] However, the directed cobalt-catalyzed coupling of terminal alkynes with simple arenes by a twofold C–H bond cleavage remains rare.

C–H activation employing simple, but powerful bidentate chelating auxiliaries, has become one of the hottest research areas in organic synthetic methodology since the seminal work of Daugulis and co-workers on the use of the 8-aminoquinoline group in palladium-catalyzed C–H arylation reactions.[9] Subsequently, the conversion of the C–H bond into a new C–X bond (X = C, N, O, halogen, S, B, Si) using a similar bidentate chelation system has made great progress.[10] Among these transformations, the groups of Yu and You independently described copper-mediated coupling reactions of arenes with terminal alkynes using an amide oxazoline and 8-aminoquinoline directing group, respectively, in 2014.[7g,i] Notably, Daugulis and co-workers reported a new method for cobalt(II)-catalyzed, aminoquinoline-directed C_{sp^2}–H bond coupling with terminal alkynes, and six-membered heterocycles, 2-isoquinolin-1-ones, were formed.[11] In this case, for the first time cobalt was used as the catalyst for oxidative C_{sp^2}–H coupling with terminal alkynes by hydroarylation of alkynes. However, to the best of our knowledge, there is no report on the cobalt-catalyzed direct alkynylation of arenes by C–H bond activation. Recently, we also developed a removable bidentate directing group derived from 2-aminopyridine 1-oxide (PyO-amine).[12] Owing to the relatively acidic NH in 2-benzamidopyridine 1-oxide,[13] the N,O-bidentate auxiliary is also believed to facilitate the C–H activation, thus more easily generating a reactive CNO–Co intermediate. We speculated that the use of a PyO directing group might lead to pharmaceutically relevant 3-methyleneisoindolin-1-ones by cobalt-catalyzed C–H alkynylation. While 3-methyleneisoindolin-1-ones are typically prepared from the cyclization of aryl halides under harsh reaction conditions,[14] our approach offers a powerful alternative for accessing these compounds in a direct manner. As part of our interest in the field, we present here the cobalt-catalyzed oxidative alkynylation/annulation of terminal alkynes using an N,O-bidentate auxiliary.

We initially focused our investigation on the cobalt-catalyzed cross-coupling of 2-benzamidopyridine 1-oxide (**1a**) with phenylacetylene (**2a**). To our delight, the desired product, (*Z*)-2-(1-benzylidene-3-oxoisoindolin-2-yl)pyridine 1-oxide (**3aa**), was obtained in 28% yield in the presence of

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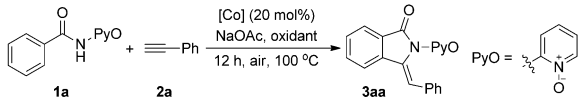
[**] We are grateful to the National Natural Science Foundation of China (No. 21272217) for financial support of this work.

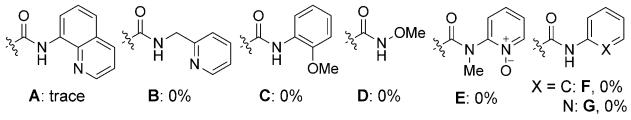
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504962.

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant	Yield [%]
1	$Co(OAc)_2{\cdot}4H_2O$	Ag_2O	28
2	$Co(OAc)_2{\cdot}4H_2O$	AgOAc	61
3[b]	$Co(OAc)_2{\cdot}4H_2O$	AgOAc	70
4[c]	$Co(OAc)_2{\cdot}4H_2O$	AgOAc	72
5	$[Co(acac)_2]$	AgOAc	70
6	$[Co(acac)_3]$	AgOAc	67
7	$CoC_2O_4{\cdot}4H_2O$	AgOAc	79
8[c,d]	$CoC_2O_4{\cdot}4H_2O$	AgOAc	85
9	none	AgOAc	n.r.

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol, 3 equiv), [Co] (20 mol%), NaOAc (1 equiv), oxidant (1 equiv), DMSO (1 mL), under air, 12 h. Yield are t hose of the isolated product. [b] AgOAc (2 equiv). [c] $Na_2C_2O_4$ was used instead of NaOAc. [d] $CoC_2O_4{\cdot}4H_2O$ (5 mol%), **1a** (0.15 mmol), **2a** (0.18 mmol, 1.2 equiv). acac = acetylacetonate, DMSO = dimethylsulfoxide, n.r. = no reaction.

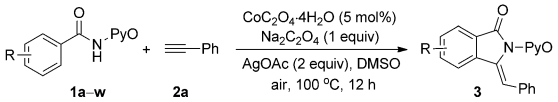


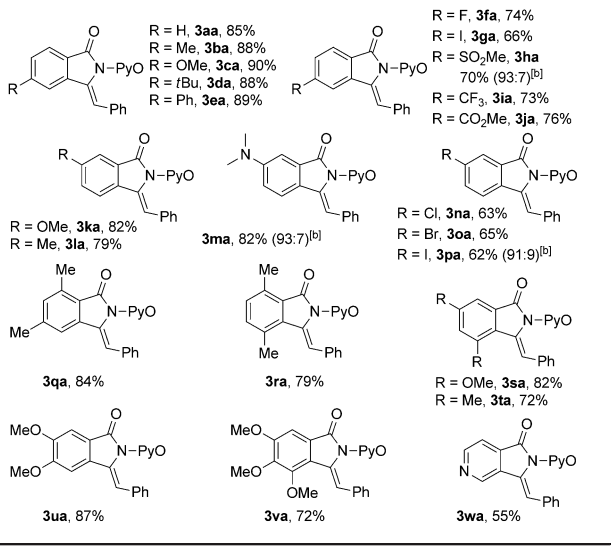
20 mol% of $Co(OAc)_2{\cdot}4H_2O$, 1 equivalent of Ag_2O, and 1 equivalent of NaOAc in DMSO at 100 °C after 12 hours (Table 1, entry 1). The structure of **3aa** was further confirmed by an X-ray crystallographic analysis.[15] Among a broad range of oxidants surveyed (see the Supporting Information), silver and manganese salts provided the desired product, with AgOAc delivering a superior yield (entry 2). Increasing the amount of AgOAc was beneficial for the reaction (entry 3). After an extensive screening of bases (see the Supporting Information), $Na_2C_2O_4$ was chosen as the base because it led to a slightly higher yield (entry 4). Next, the effect of various cobalt catalysts was investigated (entries 5–7), and it showed that this reaction could be promoted by either cobalt(II) or cobalt(III) salts. Among them, $CoC_2O_4{\cdot}4H_2O$ proved to be an effective catalyst (entry 7). The initially employed solvent, DMSO, was found to be more effective compared to other solvents (see the Supporting Information). To our delight, the reaction still proceeded smoothly with 1:1.2 ratio of **1a** and **2a**, even when the catalyst loading was reduced to 5 mol% (entry 8). The formation of the homocoupling product of **2a** was not observed. No reaction occurred in the absence of cobalt salts (entry 9).

Moreover, it seems that the 2-aminopyridine 1-oxide auxiliary has an unparalleled reactivity for this transformation, since a series of other bidentate coordinating groups (**A**–**C**; Table 1) failed to promote the alkynylation of the arenes. Moreover, di-, tri-, and tetrapeptide directing groups reported by Yu and co-workers did not work in the reaction.[10e] The products were also not obtained when the structurally similar, but monodentate groups **D**–**G** were used, thus revealing the unique property of the catalysis system.

We next tested the reaction scope with the respect to 2-aminopyridine 1-oxide amides (**1**). As summarized in Table 2,

Table 2: Scope with respect to the aromatic amides.[a]



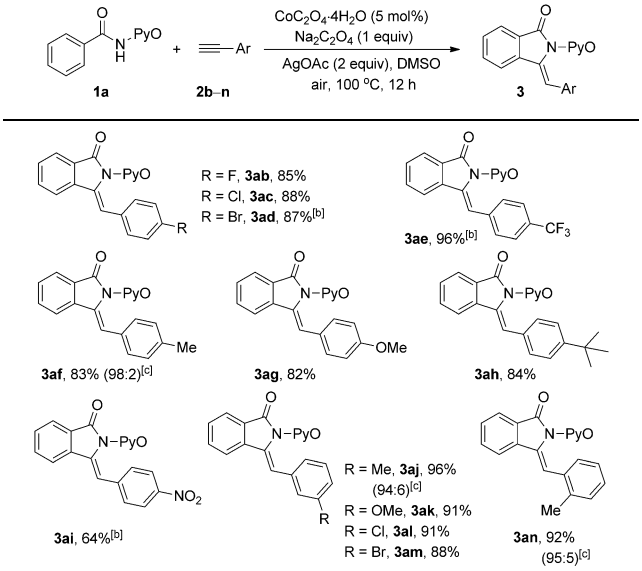


[a] Reaction conditions: **1** (0.15 mmol), **2a** (0.18 mol, 1.2 equiv), $CoC_2O_4{\cdot}4H_2O$ (5 mol%), $Na_2C_2O_4$ (1 equiv), AgOAc (2 equiv), DMSO (1 mL), 100 °C, air, 12 h. [b] The *Z*/*E* ratio was determined by ^1H NMR analysis.

the reaction system could tolerate a variety of substituents, including methyl, methoxy, *tert*-butyl, trifluoromethyl, phenyl, *N*,*N*-dimethyl, ester, halogen, and sulfonyl groups, at different positions on the arenes. In general, the aryl substrates with electron-donating groups in the *para*-position afforded higher yields (**3ba**–**ea**) compared to those bearing electron-withdrawing groups (**3fa**–**ja**). For *meta*-substituted amides, the selective alkynylation took place at the less hindered position (**3ka**–**pa**). The functional groups in the *ortho*-position of arenes did not inhibit the transformation and provided the desired products in good yields (**3qa**–**ra**). The reaction of di- and trisubstituted amides with **2a** proceeded to give the target products in good yields (**3sa**–**va**). Moreover, the protocol was also appropriate with heterocyclic substrates under the reaction conditions (**3wa**). The compatibility of halogen groups, especially the iodo group on the aromatic ring, is a significant feature which remains difficult for Sonagashira reactions.

Subsequently, a wide range of terminal alkynes were explored in the cobalt-catalyzed alkynylation of **1a** (Table 3). We were pleased to find that aryl alkynes possessing both electron-donating groups and electron-withdrawing groups underwent the transformation smoothly. The alkynes with electron-withdrawing groups such as fluoro, chloro, bromo, and trifluoromethyl in the *para*-position of the phenyl ring (**3ab**–**ae**) were more effective than those containing electron-donating groups, including methyl, methoxy, and *tert*-butyl (**3af**–**ah**). Interestingly, alkynes bearing *meta*-substituted arenes showed good reactivity compared to those having the same substituents on the *para*-position (**3aj**–**am**). The

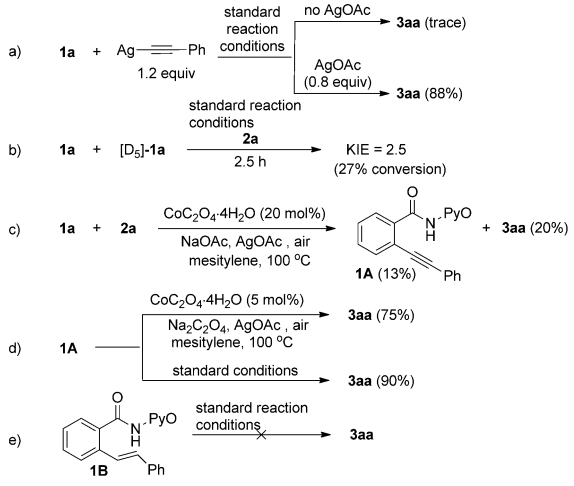
Table 3: Scope with respect to the alkynes.[a]



[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.18 mmol, 1.2 equiv), $CoC_2O_4{\cdot}4H_2O$ (5 mol%), $Na_2C_2O_4$ (1 equiv), AgOAc (2 equiv), DMSO (1 mL), 100 °C, air, 12 h. [b] 1 equiv of **2** (0.15 mmol) was used. [c] The *Z*/*E* ratio was determined by ^{1}H NMR analysis.

alkyne bearing a nitro moiety was also tolerated under the optimized reaction conditions, albeit in a moderate yield (**3ai**). The alkyne bearing an *ortho*-substituted arene gave the corresponding product in 91% yield (**3an**). Unfortunately, the internal alkynes and aliphatic alkynes were unsuccessful in achieving their corresponding products.

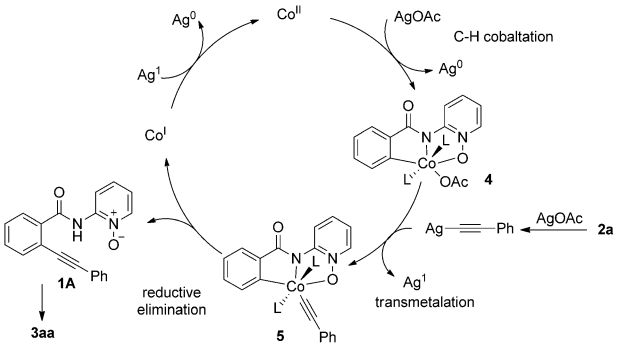
Additional control experiments were performed to probe the mechanism of the reaction. The observations were listed in Scheme 1. The addition of extra AgOAc was essential to afford the desired product (Scheme 1a). Only a trace amount of **3aa** was observed in the absence of AgOAc. These facts revealed that the silver salt is the terminal oxidant, and the silver acetylide intermediate might be involved in the



Scheme 1. Control experiments.

reaction. The presence of the radical quencher, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 1 equiv), did not suppress product formation (see the Supporting Information), thus indicating the radical pathway might be ruled out. In the reaction of **1a** and [D_5]-**1a** with **2a**, a kinetic isotope effect (KIE) of 2.5 was obtained, thus suggesting that C–H bond cleavage of the arenes is the rate-limiting step (Scheme 1b). Notably, the *ortho*-alkynyl benzamide **1A** was obtained in a yield of 13%, along with the annulation product **3aa** in 20% yield, when 20 mol% of $CoC_2O_4{\cdot}4H_2O$ was used as catalyst and mesitylene was chosen as a solvent (Scheme 1c). Moreover, **1A** could be transformed into **3aa** when mesitylene is employed as the solvent (Scheme 1d). Then **1A** and **1B** were synthesized respectively, and **1A** was transformed into **3aa** smoothly under the standard reaction conditions, while **1B** did not provide the product under the current conditions (Scheme 1d,e). These observations suggest that **1A** might be an intermediate in the reaction.

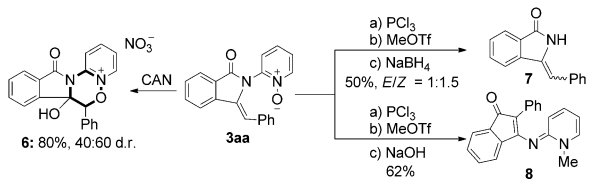
On the basis of the above facts, the reaction mechanism with a cobalt acetylide intermediate is more likely compared to that of the cobalt-catalyzed alkenylation proposed by Grigorjeva and Daugulis,[11] since 1) internal alkynes are not reactive in our reaction system; 2) six-membered heterocycles (2-isoquinolin-1-ones) are not formed; 3) **1A** rather than **1B** could be obtained in the coupling of **1a** with **2a**. Moreover, **1A** was transformed into **3aa** smoothly under the standard reaction conditions, while **1B** was failed to afford the product in the process; 4) the fact that the reaction went smoothly when silver acetylide was used as a coupling partner indicates that the reaction proceeds by cobalt-catalyzed alkynylation. The reaction pathway is proposed in Scheme 2. With the help



Scheme 2. Proposed mechanism.

of AgOAc, the cobalt(II) complex is oxidized to a high-valent cobalt(III) species (**4**), along with C–H bond activation. The silver acetylide is transferred to **4** to furnish the essential intermediate **5**. The *ortho*-alkynyl amide **1A** is obtained by reductive elimination, and then intramolecular annulation delivers **3aa**.

Oxadiazines were found to be ideal drug motifs for Alzheimer's disease because of their toxicological and pharmacokinetic profiles.[16] In our case, we found that the oxadiazine salt **6** could be directly synthesized from **3aa** in one step.[15] We also attempted the removal of the PyO group.



Scheme 3. Transformation of the cyclization product **3aa**. CAN = ceric ammonium nitrate, Tf = trifluoromethanesulfonyl.

As shown in Scheme 3, the deoxygenation of **3aa** followed by treatment with MeOTf and reduction by $NaBH_4$ produced the isomers **7** (*Z* and *E*) in moderate yield. 2-Phenylindenone (**8**) could be obtained under a similar reaction sequence when NaOH was employed instead of $NaBH_4$.[15]

In conclusion, we have disclosed a highly active transformation for cobalt-catalyzed alkynylation/annulation of terminal alkynes through the use of a PyO directing group. The protocol is simple, and suitable for various aromatic amides with a catalyst loading as low as 5 mol%. In the process of the transformation, AgOAc was shown to serve as the terminal oxidant. Moreover, the oxadiazine salt can be synthesized in one step, and the directing group can be removed, thus presenting a unique approach to the design of valuable molecules.

Keywords: C–H activation · annulations · cobalt · ligand design · nitrogen oxides

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10012–10015
Angew. Chem. **2015**, *127*, 10150–10153

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Received: June 1, 2015
Published online: July 14, 2015

