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Letter

Cobalt-Catalyzed Regioselective Carboamidation of Alkynes with Imides Enabled by Cleavage of C−N and C−C Bonds

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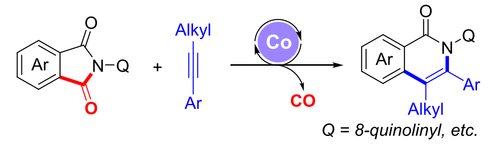
ABSTRACT: Through the oxidative addition of cobalt into the N−C(O) bond of phthalimide and the subsequent decarbonylation, we describe an efficient cobalt-catalyzed intermolecular decarbonylative carboamidation of alkynes. High regioselectivities have been achieved for unsymmetrical alkynes (including aryl−alkyl or aryl−aryl) to deliver polysubstituted isoquinolones. To facilitate step economy, a three-component decarbonylative carboamidation of alkynes with phthalic anhydrides and amines has been demonstrated using the current cobalt catalysis.

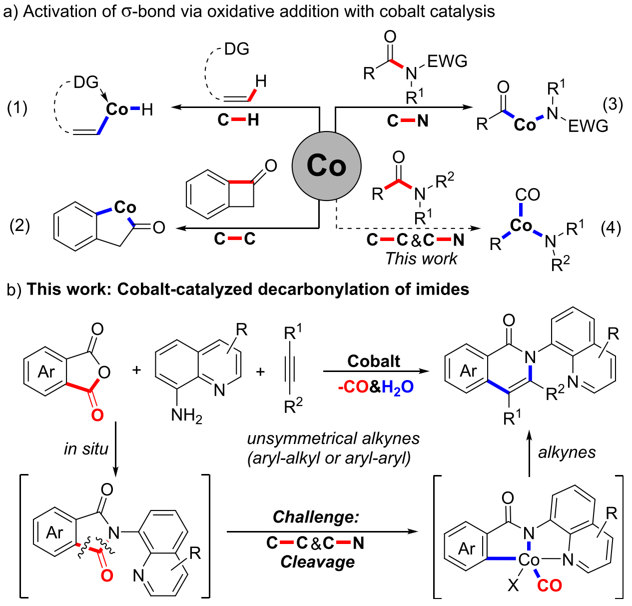


- Oxidative addition of cobalt into the N-C(O) bond and then decarbonylation
- Three-component carboamidation of alkynes
- Regioselectivity control

The activation of σ-bonds via oxidative addition with transition metals is a fundamental step in organometallic chemistry. Therefore, the development of novel transition metal catalytic systems for facilitating such a process is one of the leading edge efforts in catalysis.[1] Compared with the widely used noble metals, the earth-abundant first-row transition metals have gained particular attention in recent years owing to their relatively lower cost and toxicity[2a,b,c] as well as greater sustainability. Among them, cobalt catalysis has emerged as a powerful tool and substantial progress has been achieved in this area.[2d,e] For example, cobalt-catalyzed C(sp^2)−H activation via oxidative addition has been well established (Scheme 1a, eq 1).[3,4] However, the oxidative addition of cobalt with C−C bonds is generally limited to strained rings, such as benzocyclobutenones[5a] and methylenecyclopropanes,[5b,c] and others[6] (Scheme 1a, eq 2). Furthermore, the C−N activation of amide under cobalt catalysis is rare. In 2017, Danoun and co-workers described the first cobalt-catalyzed activation of N-Boc-amides (twisted amides) to form esters for the first time[7] (Scheme 1a, eq 3). Despite advances in the transition metal catalyzed decarbonylation of amide,[8] the cobalt-catalyzed decarbonylative coupling of imides requiring both C−N and C−C bond cleavages remains undiscovered (Scheme 1a, eq 4).

On the other hand, catalytic multicomponent reaction, due to its rapid construction of multiple new bonds in one step, has received much attention over the past decades.[9] We envisioned phthalimide derivatives could be formed in situ from the condensation of phthalic anhydrides with amines (Scheme 1b). Subsequently, the aryl-cobalt intermediate generated from activating its C−N and C−C bonds will undergo migratory insertion into alkynes to give substituted isoquinolones (Scheme 1b). The challenges for this strategy include the following: (a) facile CO insertion into the C−Co bond makes it difficult to dissociate CO from cobalt;[10,11] (b) competitive decarbonylative homocoupling[12] and protolysis[13] due to production of water in the three-component reaction; (c) regiocontrol in the carboamidation of unsymmetrical alkynes.

Scheme 1. Activation of σ-Bond via Cobalt Catalysis



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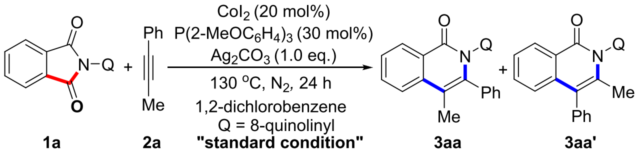
Herein, we report a cobalt-catalyzed intermolecular decarbonylative carboamidation of alkynes to form substituted isoquinolones (Scheme 1b).

The two-component decarbonylative carboamidation of alkyne **2a** with phthalimide derivative **1a** was initially investigated (Table 1). After careful evaluation of the reaction conditions, isoquinolone **3aa** was formed in 92% yield with 14:1 (**3aa**/**3aa′**) regioselectivity using CoI_2/$P(2\text{-}MeOC_6H_4)_3$ as the metal/ligand combination and Ag_2CO_3 as the oxidant (entry 1). Control experiments were subsequently conducted to understand the role of each reagent. In the absence of the cobalt catalyst or Ag_2CO_3, no desired product was observed (entries 2–3). Both the reactivity and regioselectivity decreased in the absence of $P(2\text{-}MeOC_6H_4)_3$ (entry 4). Interestingly, the reaction did not proceed with Co^0 precursors (entries 5–6). The use of a Co^I or Co^{II} precursor, such as $Co(PPh_3)_3Cl$ and $Co(dppe)Cl_2$, slightly lowered the yields (entries 7–8) (see Table S1). Probably due to the lack of available coordination sites, the employment of high valent $Cp^*Co(CO)I_2$ as the catalyst precursor gave only an 8% yield of **3aa** (entry 9). Other monodentate phosphine ligands, such as PPh_3 or $P(2\text{-furyl})_3$, led to inferior results (entries 10–11). The bidentate ligand Xantphos could also promote this transformation but in slightly diminished yield (entry 12). The use of Ag_2O instead of Ag_2CO_3 as the oxidant also gave isoquinolone **3aa** in a good yield (entry 13). However, the use of either AgOAc or TBHP as the oxidants significantly inhibited the reaction, thus suggesting both the oxidant and silver ion are important for generating the active intermediate (entries 14–16).

Table 1. Selected Optimization Studies[a]

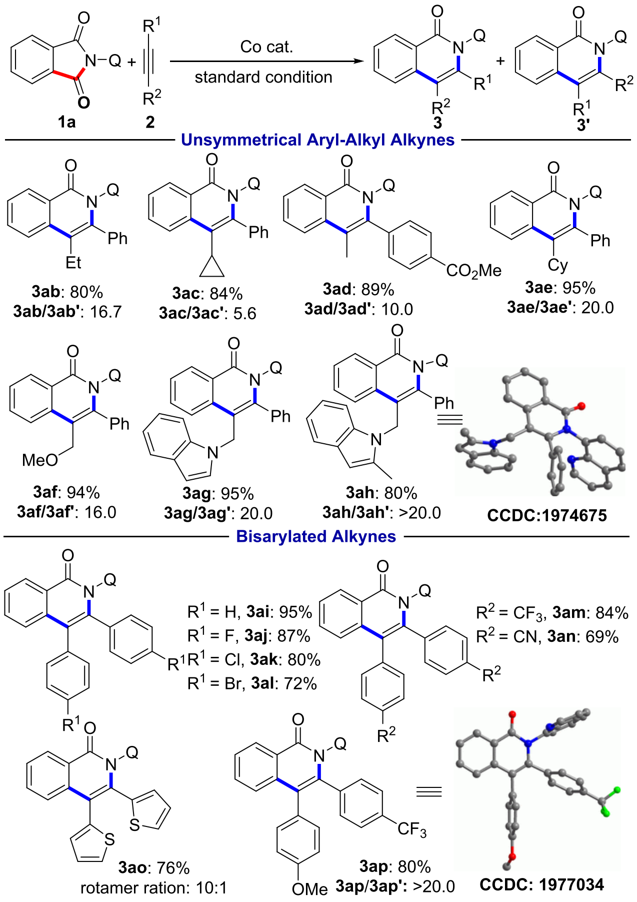


entry	deviation from standard condition	3aa/3aa′	yield (3aa)[b]
1	***none***	**14.3**	***92%***[c]
2	without CoI_2	–	NR
3	without Ag_2CO_3	–	NR
4	without $P(2\text{-}MeOC_6H_4)_3$	4.0	28%
5	$Co(PMe_3)_4$ instead of CoI_2	–	NR
6	$Co_2(CO)_8$ instead of CoI_2	–	NR
7	$Co(PPh_3)_3Cl$ instead of CoI_2	8.9	61%
8	$Co(dppe)Cl_2$ instead of CoI_2	5.7	56%
9	$Cp^*Co(CO)I_2$ instead of CoI_2	–	8%
10	PPh_3 instead of $P(2\text{-}MeOC_6H_4)_3$	5.6	35%
11	$P(2\text{-furyl})_3$ instead of $P(2\text{-}MeOC_6H_4)_3$	3.7	33%
12	Xantphos instead of $P(2\text{-}MeOC_6H_4)_3$	5.0	80%
13	Ag_2O instead of Ag_2CO_3	8.3	86%[c]
14	AgOAc instead of Ag_2CO_3	–	14%
15	TBHP instead of Ag_2CO_3	–	NR
16	AgOAc and TBHP instead of Ag_2CO_3	8.0	52%

[a] All reactions were performed on 0.10 mmol scale. See Supporting Information for full details. [b] Determined by ^1H NMR analysis. [c] Isolated yield.

With the optimal conditions in hand, the substrate scope for the Co-catalyzed carboamidation of alkynes with phthalimides was investigated (Scheme 2). A variety of unsymmetrical aryl–alkyl alkynes underwent carboamidation smoothly to deliver isoquinolone derivatives (**3aa**–**3af**) with high yields and regioselectivities. Cyclopropyl, ester, and alkoxy groups were well tolerated. For aryl–alkyl alkynes bearing indoles, good yields and excellent regioselectivities were observed (**3ag**–**3ah**). The regioselectivity for this unsymmetrical alkyne carboamidation was confirmed by X-ray analysis of **3ah**. A series of symmetrical diarylacetylenes were also compatible with this protocol, giving the corresponding products in good to excellent yields (**3ai**–**3an**). A heterocycle, such as thiophene, was well tolerated under the cobalt catalysis (**3ao**). It is interesting to note that, in the case of the unsymmetrical aryl–aryl alkyne with a slight difference in the electronic property of the two aryl substituents, the annulation delivered 3,4-diaryl substituted isoquinolone **3ap** with excellent regioselectivity (>20:1).

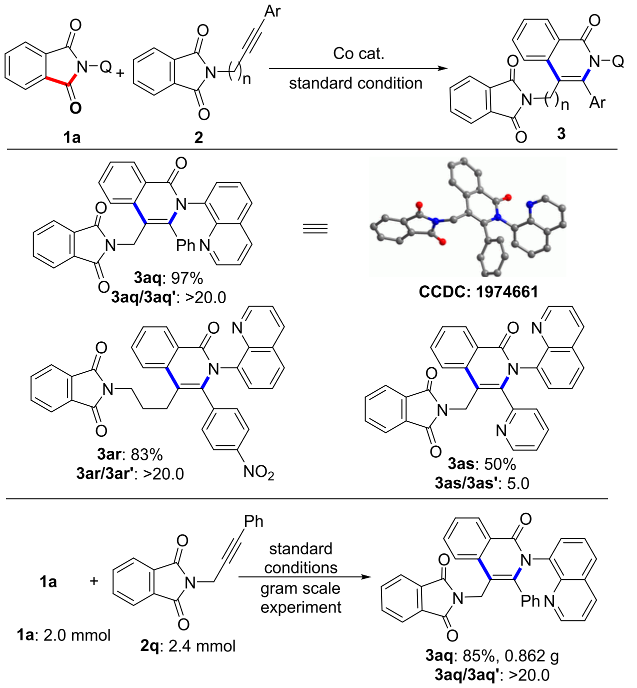
Scheme 2. Scope of the Alkynes[a]



[a] Isolated yield of the major regioselective isomer.

Next, selective decarbonylative annulation of phthalimide derivatives with alkynes that also bear phthalimides groups, which are widely embedded in pharmaceuticals and biologically active molecules such as thalidomide[14] were tested (Scheme 3). Selective C–N activation in the presence of four amide bonds on two structurally similar substrates (**1a** and **2q**–**2s**) may pose a challenge for the cobalt catalysis. Satisfactorily, the tested alkynes were compatible with this protocol, providing isoquinolones bearing phthalimide groups in high yields and regioselectivities (>20:1, **3aq**–**3ar**). Furthermore, isoquinolone **3as** with multiple *N*-heterocycles was isolated in moderate yield and regioselectivity. To demonstrate the scalability of this methodology, the reaction

Scheme 3. Selective Activation Among Four Amide Bonds[a]

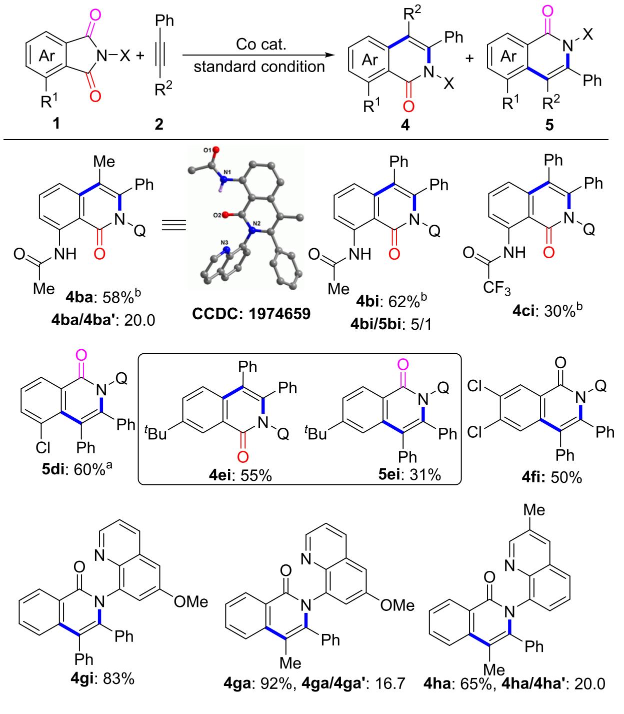


[a]Isolated yield of the major regioselective isomer.

of **1a** with **2q** was successfully performed on 2.0 mmol of starting materials, which afforded 0.862 g of **3aq** (85% yield).

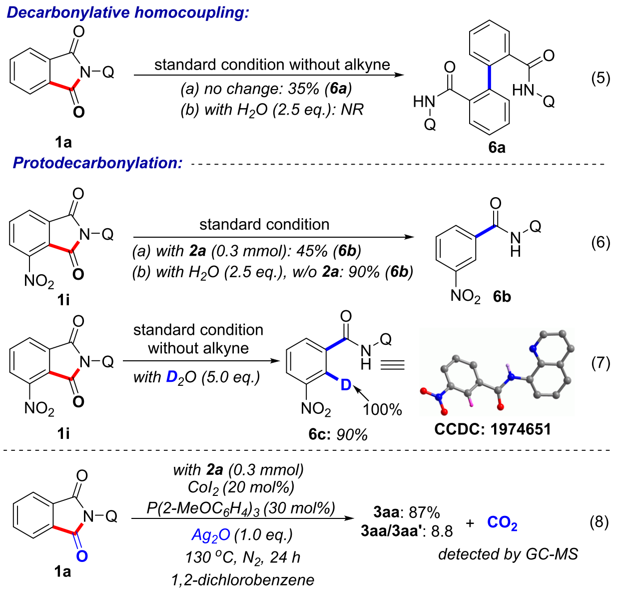
After exploring the scope of the alkynes, an array of phthalimide derivatives were examined (Scheme 4). 3-Amino substituted phthalimides are prevalent motifs in drugs[15] and fluorescent probes;[16a−c] thus, it would be of interest to modify the substrates of such motifs. The regioselective annulations of 3-amino substituted phthalimides **1b** and **1c** were successfully demonstrated. Moreover, it was found that the free NH on **1b** and **1c** plays an important role in the regiocontrol, because formation of its tautomer may hinder the oxidative addition of the adjacent carbonyl moiety with cobalt.[16a,b,d] The reaction of 3-chlorophthalimide **1d** with alkyne **2i** afforded cycloadduct **5di** in 60% yield, the product of which is difficult to synthesize via C−H activation owing to steric hindrance.[17] Phthalimides such as **1e**, **1f**, **1g**, **1h** were also compatible with the process, providing the corresponding products **4ei**, **4fi**, **4gi**, **4ga**, **4ha** in acceptable yields. 8-Amino-5-methoxyquinoline (MQ) can be used instead of 8-aminoquinoline for its ease of cleavage.[18]

Scheme 4. Scope of the Phthalimides[a]



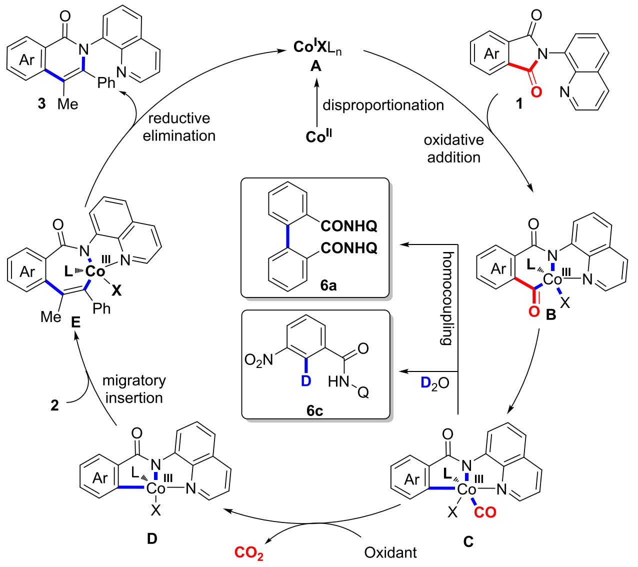
[a]Isolated yield of the major regioselective isomer. [b]$PhCF_3$ as the solvent.

Mechanistically, we sought to probe the aryl−cobalt intermediates resulting from the oxidative addition of a low-valent cobalt into the N−C(O) bond of imides and the subsequent decarbonylation (eqs 5−8). Interestingly, the decarbonylative homocoupling product **6a** can be obtained in 35% yield in the absence of alkynes.[12] The addition of stoichiometric H_2O prevents the formation of **6a** (eq 5). When **1i** and **2a** were treated with the standard conditions, the corresponding cyclization product was not detected, and instead, decarbonylative product **6b** was obtained in 45% yield. The use of external water as an additive gave product **6b** in 90% yield (eq 6). Full incorporation of deuterium at the site of decarbonylation (**6c**) in the presence of D_2O suggested that water was the proton source for this reaction (eq 7).[13] To gain insight into the role of the oxidant, the gas phase of the reaction mixture was analyzed by GC-MS (eq 8). Silver oxide (Ag_2O) was used instead of Ag_2CO_3 to avoid the background decarboxylation of Ag_2CO_3 (eq 8). Carbon dioxide (CO_2) was detected as the major gas component, which suggested that the oxidant played a role as a CO scavenger in the cobalt-catalyzed decarbonylation.



A proposed catalytic cycle is depicted in Scheme 5. First, Co(II) is disproportionated to active Co(I) species **A**.[19] Through an oxidative addition process, Co(I) species **A** activates the C−N bond of imides to form Co(III) intermediate **B** (from the perspective of ring strained, N−C activation precedes C−C activation; see the Supporting Information for details). A subsequent decarbonylation leads

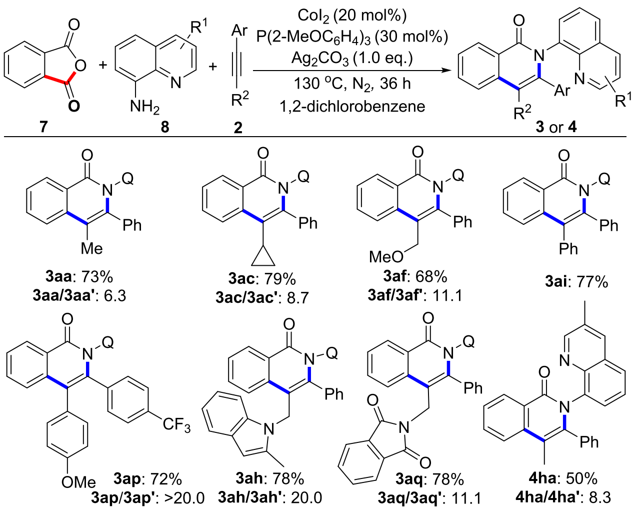
Scheme 5. Proposed Mechanism



to the cobalt complex **C**. As a CO scavenger, the addition of an external oxidant facilitates the formation of active intermediate aryl-Co **D**. In the presence of alkyne **2**, intermediate **D** undergoes coordination and migratory insertion of the alkyne to afford seven-membered cobaltacycle **E**. A final reductive elimination produces the isoquinolone products and regenerates Co(I) catalyst **A**. In the absence of alkyne **2**, aryl-cobalt **C** undergoes a homocoupling pathway to yield compound **6a**[12] or protolysis to yield compound **6c**.[13]

A three-component decarbonylative carboamidation was accomplished by the use of bulk chemicals phthalic anhydride **7**, 8-aminoquinoline **8**, and alkynes **2** (Scheme 6). Overall, this three-component protocol cleaves four existing bonds while creating three additional new bonds in one pot. Gratifyingly, under the standard reaction conditions, a series of representative isoquinolones were obtained in moderate to high yields (**3aa**, **3ac**, **3af**, **3ai**, **3ap**, **3ah**, **3aq**, **4ha**). Compared with the traditional C−H activation strategy, this three-component reaction provides a more convenient alternative to access such cyclic products.[17]

Scheme 6. Three-Component Decarbonylative Carboamidation of Alkynes[a]



[a] Isolated yield of major regioselective isomer.

In summary, we have described an efficient Co-catalyzed intermolecular decarbonylative carboamidation of alkynes via the cleavage of C−N and C−C bonds of imides. The migratory insertion of aryl−cobalt species with unsymmetrical alkynes (including aryl−alkyl or aryl−aryl) occurs in high regiocontrol to deliver polysubstituted isoquinolones. A three-component Co-catalyzed decarbonylative carboamidation of alkynes with phthalic anhydrides and amines has been also demonstrated to increase step economy. Further application of this strategy to other amide decarbonylations and detailed mechanistic investigations are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00875.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **3ap**, **3ah**, **3aq**, and **4ba** (PDF)

Accession Codes

CCDC 1974651, 1974659, 1974661, 1974675, and 1977034 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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