Organic Letters

Letter

pubs.acs.org/OrgLett

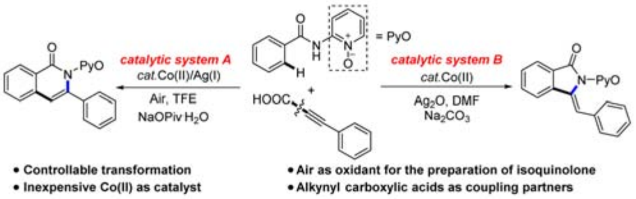
Cobalt(II)-Catalyzed Decarboxylative C−H Activation/Annulation Cascades: Regioselective Access to Isoquinolones and Isoindolinones

Xin-Qi Hao,[†] Cong Du,[†] Xinju Zhu, Peng-Xiang Li, Jia-Heng Zhang, Jun-Long Niu,[*] and Mao-Ping Song[*]

College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, P. R. China

Supporting Information

ABSTRACT: A new cobalt(II)-catalyzed decarboxylative C−H activation/annulation of benzamides and alkynyl carboxylic acids has been described. Alkynyl carboxylic acids were first employed as the coupling partners using inexpensive Co$(OAc)_2 \cdot 4H_2O$ as the catalyst. This method enables a switchable cyclization to isoquinolones and isoindolinones with excellent selectivity. Moreover, a catalytic amount of Ag_2O was adopted as co-catalyst and O_2 (from air) as a terminal oxidant for the preparation of isoquinolones.



- Controllable transformation
- Inexpensive Co(II) as catalyst
- Air as oxidant for the preparation of isoquinolone
- Alkynyl carboxylic acids as coupling partners

In the past decades, transition-metal-catalyzed C−H functionalization has continued to expand and has proven to be an effective strategy for the construction of various organic frameworks.[1] Despite tremendous advancements, C−H functionalization with controllable transformation is still a long-standing challenge.[2] The exploration of a switchable strategy for the synthesis of valuable compounds from simple chemicals is attractive, as it allows a diversity-oriented access to complex molecules without redesigning synthetic routes. Isoquinolones and isoindolinones have been widely investigated as important structural motifs in a variety of natural drugs and pharmaceuticals.[3] Unfortunately, the preparation of isoquinolones and isoindolinones often requires different starting materials and synthetic routes, which is cost-ineffective.[4] Thus, it is highly desirable to develop an innovative methodology to obtain these heteroarenes from common starting materials in a controllable way.

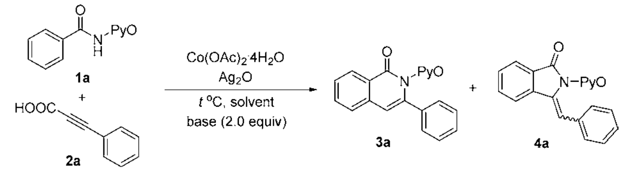
On the other hand, carboxylic acid derivatives have been widely investigated in organic synthesis as the coupling partners, owing to their ubiquity, easy storage, and inexpensiveness.[5] In this context, a large number of catalytic decarboxylative C−H activations have been developed that are mainly dominated by Pd catalyst.[6] Recently, the first-row metals, such as Cu, Co, Ni, showed comparable activities for decarboxylation reactions as disclosed by Ge,[7] Lu,[8] and others.[9] However, most strategies relied on the employment of substrates containing special structures or electronic effects, such as benzoxazole and indole. To overcome these limitations, Shi has demonstrated Cu-catalyzed decarboxylative coupling reaction of unactivated arenes with 2-thiophenecarboxylic acid.[10] Also, Zhang discovered Cu-catalyzed decarboxylative coupling reaction of C_{sp2}−H bond or C_{sp3}−H bond with 3-phenylpropiolic acid.[11] Despite this great success, to our knowledge, Co(II)-catalyzed decarboxylative C−H functionalization with unactivated C_{sp2}−H bond has not been achieved.

As a representative of earth-abundant first-row metal, cobalt has exhibited versatile and comparable efficiency in C−H functionalization.[12] Meanwhile, cobalt catalysis showed prominent activity with alkynes.[13,14] Based on our previous work on cobalt-catalyzed C_{sp2}−H functionalization.[13e,15] we herein report a protocol for cobalt-catalyzed decarboxylation C−H activation with regiodivergent access to isoquinolones and isoindolinones. Notable features of the current method include (i) unprecedented cobalt(II)-catalyzed decarboxylation for unactivated C_{sp2}−H bond, (ii) regiodivergent access to isoquinolones and isoindolinones with excellent selectivity, (iii) operational convenience with O_2 (from air) as a terminal oxidant for isoquinolones under mild conditions.

In our search for the effect of solvents on selectivity, 2,2,2-trifluoroethanol (TFE) was beneficial to produce isoquinolone (**3a**) (see the Supporting Information for single-crystal X-ray diffraction data), and *N*,*N*-dimethylformamide (DMF) was helpful in obtaining isoindolinone (**4a**) with excellent *Z* selectivity. Inspired by the preliminary results, the effects of bases, catalyst loadings, and temperature were investigated (Table 1). Isoquinolone (**3a**) was initially investigated, which showed that the transformation was hypersensitive to the amount of Ag_2O (Table 1, entries 1−5). Employing 0.5 equiv of Ag_2O significantly improved the yield (80%) and selectivity (100%) (Table 1, entry 2), with no decreased performance observed for 10 mol % Ag_2O loading (Table 1, entry 3). Additionally, an improved yield was observed when a lower amount of Co catalyst was utilized (Table 1, entry 4). Further optimization showed that the amount of Ag_2O could be reduced to 5% without affecting the efficiency (Table 1, entry

Received: June 6, 2016
Published: July 20, 2016

Table 1. Optimization of the Reaction Conditions[a]



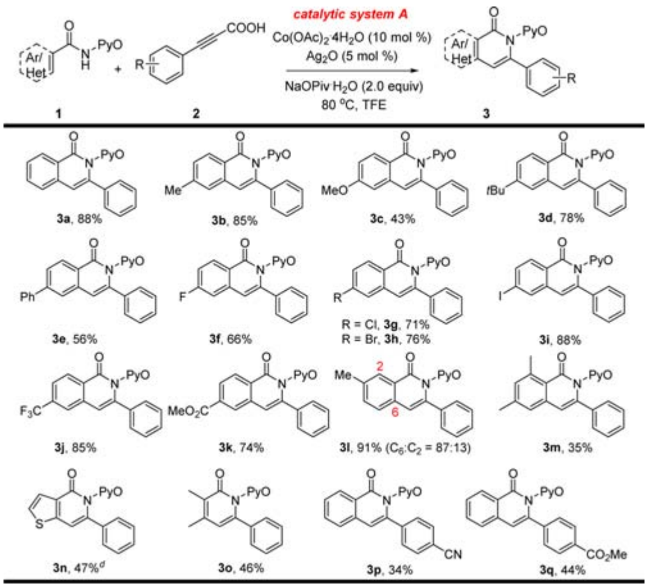
entry	solvent	base	Ag_2O (mol %)	yield[b] (%) [3a:4a(Z):4a(E)][c]
1[d]	TFE	$NaOPiv·H_2O$	100	54 (25/63/12)
2[d]	TFE	$NaOPiv·H_2O$	50	80 (100/0/0)
3[d]	TFE	$NaOPiv·H_2O$	10	80 (100/0/0)
4	TFE	$NaOPiv·H_2O$	10	88 (100/0/0)
5	**TFE**	**$NaOPiv·H_2O$**	**5**	**88 (100/0/0)**
6[e]	DMF	$NaOPiv·H_2O$	100	62 (3/94/3)
7[e,f]	DMF	$NaOPiv·H_2O$	100	66 (3/96/1)
8[e,f]	DMF	$Na_2C_2O_4$	100	50 (7/91/2)
9[e,f]	DMF	Na_2CO_3	100	67 (2/96/2)
10[e,f]	DMF	Cs_2CO_3	100	12 (6/92/2)
11[f]	**DMF**	**Na_2CO_3**	**150**	**74 (2/98/0)**

[a]Reaction conditions: substrate **1a** (0.15 mmol), **2a** (2.0 equiv), $Co(OAc)_2·4H_2O$ (10 mol %), base (2.0 equiv), Ag_2O (100 mol %), solvent (1.0 mL), air atmosphere, 12 h, 80 °C. [b]Isolated yield. [c]The ratio was determined by ^1H NMR analysis. [d]$Co(OAc)_2·4H_2O$ (20 mol %). [e]**2a** (1.5 equiv). [f]100 °C. PyO = 2-aminopyridine 1-oxide.

5), and thus, the optimized conditions to product isoquinolone (**3a**) were established. Compared with previous work on Co(II)-catalyzed annulations,[13] our strategy employed O_2 (from air) as the oxidant, which avoided the use of stoichiometric metal oxidant and was operationally convenient. Next, the reaction conditions for isoindolinone were optimized (**4a**). Various Co(II) salts and oxidants were screened to reveal that $Co(OAc)_2·4H_2O$ and Ag_2O were the optimal choice, affording the isoindolinone (**4a**) in 62% yield (Table 1, entry 6). A slightly improved yield was observed when the temperature was elevated to 100 °C (Table 1, entry 7). Among a variety of bases evaluated, Na_2CO_3 gave the highest yield (Table 1, entries 8−10). The yield and selectivity could be further increased when 2.0 equiv of **2a** and 1.5 equiv Ag_2O were employed (Table 1, entry 11). It was noteworthy that both isoquinolone (**3a**) and isoindolinone (**4a**) were readily accessible via catalytic transformations using same starting materials.

With the optimized conditions in hand, the feasibility of this protocol to synthesize isoquinolones (**3**) was first investigated (Scheme 1). A variety of substituted benzamides could proceed smoothly with high selectivity to afford the corresponding isoquinolones (**3**). In general, *ortho*-, *para*-, and *meta*-substituted benzamides exhibited similar reactivities under the catalytic system. The halogen (F, Cl, Br, I)-substituted benzamides were tolerated as well, providing opportunity for further potential transformations. The trifluoromethyl-substituted benzamide gave a similar yield compared to the methyl-substituted benzamide (**3b**, **3j**), indicating the electronic effect had negligible influence on the transformation. For *meta*-substituted benzamides, the reaction mainly occurred at the less hindered *ortho*-position (**3l**). The protocol was also appropriate with *ortho*-substituted benzamide (**3m**). Importantly, 3-thiophenecarboxamide and *α,β*-unsaturated amide were converted into the corresponding products **3n** and **3o** in moderate yields. Unfortunately, the reaction of 3-phenylpropiolic acid bearing electron-donating functional groups, such as methyl and methoxyl, did not occur. According to the previous literature,[13c] electron-donating groups substituted with 3-phenylpropiolic acid may inhibit the reaction to some extent. Likewise, 3-phenylpropiolic acid bearing electron-donating functional groups (e.g., methyl, methoxyl) could not generate the desired products under standard conditions. Nevertheless, the ones bearing electron-withdrawing groups could be successfully utilized in this transformation, and the products were obtained in relatively low yields (**3p**, **3q**).

Scheme 1. Co(II)-Catalyzed Synthesis of Isoquinolone Derivatives[a]−[c]

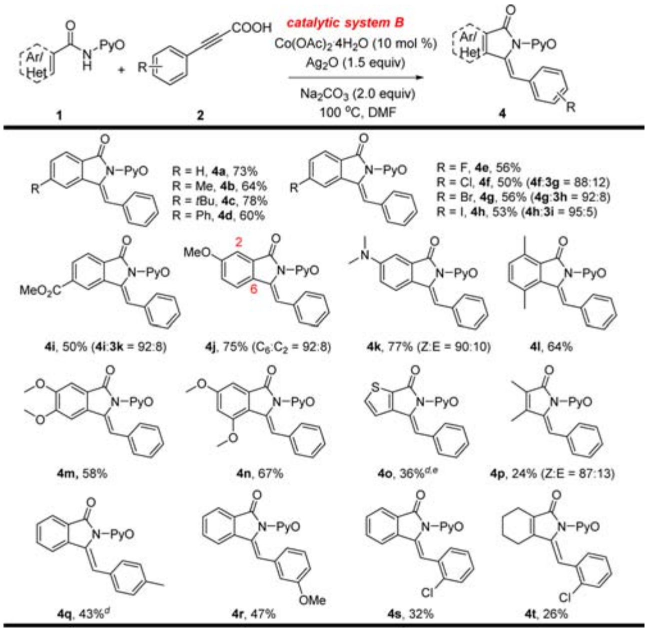


[a]Catalytic system A: substrate **1** (0.15 mmol), **2** (2.0 equiv), $Co(OAc)_2·4H_2O$ (10 mol %), $NaOPiv·H_2O$ (2.0 equiv), Ag_2O (5 mol %), TFE (1.0 mL), air atmosphere, 80 °C, 12 h. [b]Isolated yields. [c]The ratio was determined by ^1H NMR analysis; if not mentioned, the ratio (**3**/**4**) was greater than 20:1. [d]$Co(OAc)_2·4H_2O$ (20 mol %).

Subsequently, the applicability of this protocol to establish isoindolinones (**4**) was investigated (Scheme 2). A wide range of benzamides (**1**) were explored, delivering the corresponding isoindolinones (**4**) in moderate to good yields. In general, the substituted benzamides bearing electron-donating groups at the *para*-position obtained higher yields (**4a−d**) compared to those bearing electron-withdrawing groups at the same position (**4e−i**). Similar to catalytic system A, the reaction of *meta*-substituted benzamides mainly occurred at the less hindered *ortho*-position (**4j,k**). The disubstituted amides could proceed smoothly to afford the desired products (**4l−n**). Moreover, the heterocyclic substrate and *α,β*-unsaturated amide were compatible with the current catalytic system, furnishing the desired products **4o** and **4p** in moderate yields. The transformations of 3-phenylpropiolic acid bearing electron-donating groups and electron-withdrawing groups both proceeded smoothly to generate the corresponding products (**4q−t**) in relatively low yields.

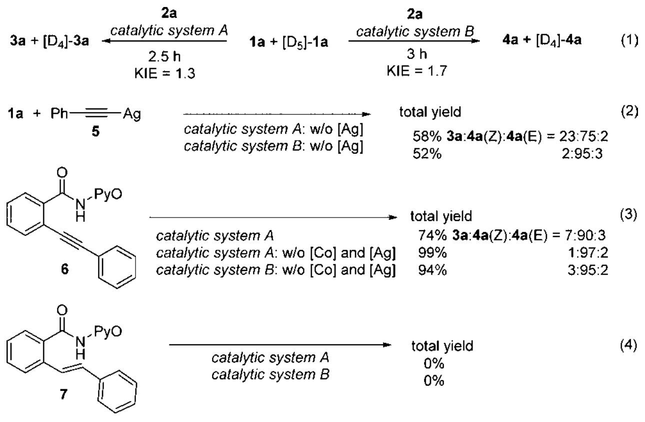
To explore the plausible reaction pathway, a sequence of control experiments was carried out (Scheme 3). No desired product could be obtained in the absence of $Co(OAc)_2·4H_2O$ or Ag_2O under both catalytic system A and B, which indicates that both the $Co(OAc)_2·4H_2O$ and Ag_2O were necessary for

Scheme 2. Co(II)-Catalyzed Synthesis of Isoindolinone Derivatives[a]–[c]



[a] Catalytic system B: substrate **1** (0.15 mmol), **2** (2.0 equiv), Co(OAc)$_2$·4H$_2$O (10 mol %), Na$_2$CO$_3$ (2.0 equiv), Ag$_2$O (1.5 equiv), DMF (1.0 mL), air atmosphere, 100 °C, 12 h. [b] Isolated yields. [c] The ratio was determined by ^{1}H NMR analysis; if not mentioned, the ratio (**4**:**3**) was greater than 20:1 and the ratio (*Z*/*E*) was greater than 20:1. [d] Co(OAc)$_2$·4H$_2$O (20 mol %). [e] 120 °C.

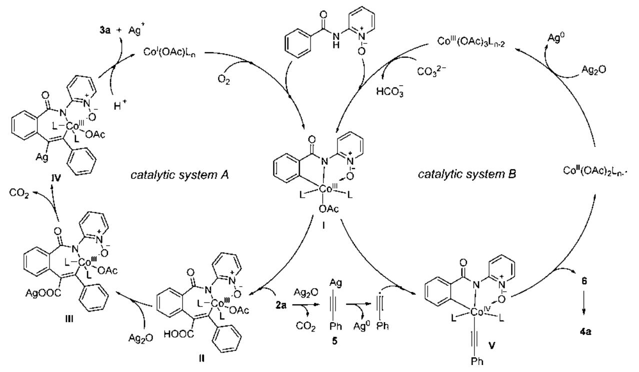
Scheme 3. Mechanistic Studies



the formation of **3a** and **4a** (see the SI). When the reaction was performed in the absence of bases, the yield under catalytic system B was decreased to 66% and the reaction was even completely inhibited under catalytic system A, which shows the importance of bases (see the SI). When the reactions were performed under argon atmosphere, only a trace amount of product was obtained under catalytic system A, while a lower yield was observed under catalytic system B, which reveals that O$_2$ serves as the terminal oxidant under catalytic system A and Ag$_2$O as the main oxidant under catalytic system B (see the SI). In the reactions of **1a** and [D$_5$]-**1a** with **2a** under both catalytic systems A and B, the kinetic isotope effects (KIE) (1.3 and 1.7) were obtained, respectively (Scheme 3, eq 1). The addition of a radical quencher, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-diisopropyl-4-methylphenol (BHT), totally suppressed the reactions under catalytic system A. The reactions under catalytic system B could proceed with additional TEMPO and was totally inhibited with additional BHT. These facts demonstrate that a radical pathway may proceed under either catalytic system A and B (see the SI). Replacement of **2a** and Ag$_2$O with silver phenylacetylide **5** led to the main product **4a** under both catalytic systems A and B, indicating that silver phenylacetylide **5** might be involved in the formation of **4a** (Scheme 3, eq 2). Moreover, compound **6** could be transformed into **4a** without Co(OAc)$_2$·4H$_2$O and Ag$_2$O (Scheme 3, eq 3), while **7** did not provide the product **3a** or **4a** under either catalytic system A and B, suggesting that **6** might be an intermediate for the formation of **4a** (Scheme 3, eq 4).

On the basis of the above control experiments and relevant reports,[13] a plausible mechanism for catalytic systems A and B is proposed in Scheme 4. Initially, cobalt salt was oxidized to Co(III) species, which allowed the C$_{sp2}$—H activation to form the intermediate **I** for both catalytic systems A and B. Alkyne insertion of intermediate **I** with **2a** afforded intermediate **II**, which reacted with Ag$_2$O through an acid—base reaction to generate silver carboxylate **III**. Subsequent protodecarboxylation of intermediate **III** generated intermediate **IV**,[16] followed by protonation and reductive elimination to liberate **3a** and regenerate the active catalyst.[17] On the other hand, The protodecarboxylation of **2a** with Ag$_2$O produced alkyne radical, which attacked the Co(III) intermediate **I** to give intermediate **V**. The alkynylated product **6** is obtained by reductive elimination followed by intramolecular annulation to furnish product **4a** and regenerate Co(III) in the presence of Ag$_2$O oxidant.

Scheme 4. Proposed Reaction Mechanism



In conclusion, a new Co(OAc)$_2$·4H$_2$O-catalyzed decarboxylative C—H activation for an unactivated C$_{sp2}$—H bond was disclosed. The strategy could afford isoquinolones or isoindolinones divergently with excellent selectivity via two proposed catalytic systems. Meanwhile, this protocol enables operational convenience with good tolerance of various aromatic amides. Furthermore, isoquinolones could be successfully implemented under air atmosphere with a catalytic amount of Ag$_2$O as the co-catalyst. This novel methodology may provide insight into the development of cobalt-catalyzed C—H functionalization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01632.

Experimental procedures and spectral data for new compounds (PDF)
Single-crystal X-ray diffraction data for compound **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: niujunlong@zzu.edu.cn.
*E-mail: mpsong@zzu.edu.cn.

Author Contributions

[†]X.-Q.H. and C.D. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work described in this paper was supported by the National Natural Science Foundation of China (Nos. 21502173, 21272217), Outstanding Young Talent Research Fund of Zhengzhou University (No. 1521316002).

■ REFERENCES

(1) For selected reviews of C−H functionalizations, see: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (f) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

(2) (a) Li, B.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1125. (b) Su, Y.; Zhou, H.; Chen, J.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Org. Lett.* **2014**, *16*, 4884. (c) Zhang, X.; Si, W.; Bao, M.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**, *16*, 4830. (d) Du, W.; Gu, Q.; Li, Z.; Yang, D. *J. Am. Chem. Soc.* **2015**, *137*, 1130. (e) Kang, D.; Hong, S. *Org. Lett.* **2015**, *17*, 1938.

(3) (a) Botero Cid, H. M.; Tränkle, C.; Baumann, K.; Pick, R.; Mies-Klomfass, E.; Kostenis, E.; Mohr, K.; Holzgrabe, U. *J. Med. Chem.* **2000**, *43*, 2155. (b) Pettit, G. R.; Ducki, S.; Eastham, S. A.; Melody, N. *J. Nat. Prod.* **2009**, *72*, 1279.

(4) (a) Sivakumar, G.; Vijeta, A.; Jeganmohan, M. *Chem. - Eur. J.* **2016**, *22*, 5899 and references cited therein.

(5) (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (b) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (c) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022. (d) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (e) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.

(6) For selected examples of Pd-catalyzed decarboxylation, see: (a) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (b) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174. (c) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (d) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564.

(7) Yang, K.; Zhang, C.; Wang, P.; Zhang, Y.; Ge, H. *Chem. - Eur. J.* **2014**, *20*, 7241.

(8) (a) Yang, K.; Wang, P.; Zhang, C.; Kadi, A. A.; Fun, H.-K.; Zhang, Y.; Lu, H. *Eur. J. Org. Chem.* **2014**, *2014*, 7586. (b) Yang, K.; Chen, X.; Wang, Y.; Li, W.; Kadi, A. A.; Fun, H.-K.; Sun, H.; Zhang, Y.; Li, G.; Lu, H. *J. Org. Chem.* **2015**, *80*, 11065.

(9) For selected examples, see: (a) Yu, L.; Li, P.; Wang, L. *Chem. Commun.* **2013**, *49*, 2368. (b) Wang, C.; Wang, S.; Li, H.; Yan, J.; Chi, H.; Chen, X.; Zhang, Z. *Org. Biomol. Chem.* **2014**, *12*, 1721. (d) Chen, L.; Ju, L.; Bustin, K. A.; Hoover, J. M. *Chem. Commun.* **2015**, *51*, 15059. (e) Crawford, J. M.; Shelton, K. E.; Reeves, E. K.; Sadarananda, B. K.; Kalyani, D. *Org. Chem. Front.* **2015**, *2*, 726. (f) Patra, T.; Nandi, S.; Sahoo, S. K.; Maiti, D. *Chem. Commun.* **2016**, *52*, 1432.

(10) Zhao, S.; Liu, Y.-J.; Yan, S.-Y.; Chen, F.-J.; Zhang, Z.-Z.; Shi, B.-F. *Org. Lett.* **2015**, *17*, 3338.

(11) Zhang, J.; Li, D.; Chen, H.; Wang, B.; Liu, Z.; Zhang, Y. *Adv. Synth. Catal.* **2016**, *358*, 792.

(12) For recent reviews on Co-catalyzed C−H bond functionalization, see: (a) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (b) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948. (c) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498. (d) Wei, D.; Zhu, X.; Niu, J.-L.; Song, M.-P. *ChemCatChem* **2016**, *8*, 1242.

(13) For recent selected examples of Co(II)-catalyzed C−H functionalizations with alkynes, see: (a) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209. (b) Kalsi, D.; Sundararaju, B. *Org. Lett.* **2015**, *17*, 6118. (c) Planas, O.; Whiteoak, C. J.; Company, A.; Ribas, X. *Adv. Synth. Catal.* **2015**, *357*, 4003. (d) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990. (e) Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 10012. (f) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *ACS Catal.* **2016**, *6*, 551. (g) Mei, R.; Wang, H.; Warratz, S.; Macgregor, S. A.; Ackermann, L. *Chem. - Eur. J.* **2016**, *22*, 6759.

(14) For recent selected examples of Co(III)-catalyzed C−H functionalizations with alkynes, see: (a) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424. (b) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (c) Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 15525. (d) Lu, Q.; Vásquez-Céspedes, S.; Gensch, T.; Glorius, F. *ACS Catal.* **2016**, *6*, 2352. (e) Sen, M.; Emayavaramban, B.; Barsu, N.; Premkumar, J. R.; Sundararaju, B. *ACS Catal.* **2016**, *6*, 2792. (f) Zhang, S.-S.; Liu, X.-G.; Chen, S.-Y.; Tan, D.-H.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Wang, H. *Adv. Synth. Catal.* **2016**, *358*, 1705. (g) Landge, V. G.; Jaiswal, G.; Balaraman, E. *Org. Lett.* **2016**, *18*, 812.

(15) (a) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272. (b) Guo, X.-K.; Zhang, L.-B.; Wei, D.; Niu, J.-L. *Chem. Sci.* **2015**, *6*, 7059. (c) Zhang, L.-B.; Zhang, S.-K.; Wei, D.; Zhu, X.; Hao, X.-Q.; Su, J.-H.; Niu, J.-L.; Song, M.-P. *Org. Lett.* **2016**, *18*, 1318.

(16) Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5710.

(17) Certain steps of catalytic cycle A may involve a radical pathway; see ref 13b,c.