Heterocycles

International Edition: DOI: 10.1002/anie.201605900
German Edition: DOI: 10.1002/ange.201605900

A Copper-Catalyzed Decarboxylative Amination/Hydroamination Sequence: Switchable Synthesis of Functionalized Indoles

Tian-Ren Li, Bei-Yi Cheng, Ya-Ni Wang, Mao-Mao Zhang, Liang-Qiu Lu, and Wen-Jing Xiao*

Abstract: *A copper-catalyzed decarboxylative amination/hydroamination sequence of propargylic carbamates with various nucleophiles is described for the first time. It features an earth-abundant metal catalyst, mild reaction conditions, and high efficiency. Further treatments of the resultant key intermediates using an acid or a base in one pot enable the controllable and divergent synthesis of two types of functionalized indoles. Moreover, experiments to demonstrate the synthetic potential of this methodology are performed.*

The development of new methodologies which enable facile access to valuable heterocycles remains a subject of intensive research in chemical sciences. In this context, the construction of the indole scaffold, a nitrogen-containing heterocyclic motif prevalent in numerous natural products and pharmaceutical agents, is still under active investigation.[1,2] In the past decade, transition-metal-catalyzed sequential reactions of aniline-bearing propargyl alcohols and their derivatives have been demonstrated to be a highly efficient and fruitful strategy for constructing functionalized indoles (Figure 1).[2–5]

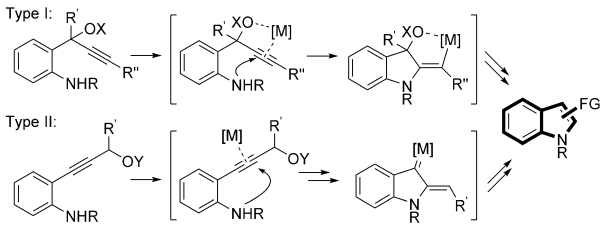


Figure 1. Pervious work on transition-metal-catalyzed sequential reactions for the synthesis of functionalized indoles. [M] = metal complex with Pt, Au, Rh, Pd, Ag, etc.; X = H, Me, or Ac; Y = H, Me, or CO_2Et. FG = functional group.

For example, in 2007, Fensterbank, Malacria, and co-workers reported an elegant example of a platinum-catalyzed intramolecular hydroamination/aza-Cope rearrangement/aromatization sequence to afford either 3-acetoxy- or 3-methoxy-2-homoallyl indoles.[3a] In 2010, the group of Chan reported an impressive method for producing 3-aryl-2-vinyl and 2-hydroxymethyl indoles, where a cationic gold(I) catalyst was used to promote either an intramolecular hydroamination/dehydration or S_N2' substitution sequence.[3b] Recently, Tang et al. developed several prominent sequential reactions to achieve functionalized indoles via either rhodium(I) or platinum(II) carbene intermediates.[3g,4b] Despite these impressive advances, many methods usually involve intramolecular processes with precisely designed substrates and/or frequently employ precious metals as the reaction catalysts. Therefore, it is highly desirable to develop an alternative route to structurally diverse indoles with earth-abundant metals as the catalyst.

Because of the pioneering work from the groups of Murahashi[5a] and Godfrey[5b] in 1994, the catalytic transformation of propargylic esters by a highly active copper allenylidene species (Figure 2) has been identified as a powerful tool to introduce productive alkyne functional groups.[6] However, copper-catalyzed sequential transformations via this key intermediate remain underdeveloped. In 2010, the group of Nishibayashi disclosed the first example of a copper-catalyzed sequential propargylic amination/Diels–Alder reaction.[7] Recently, Hu and co-workers successfully developed a few reactions of propargylic esters with substrates bearing two nucleophilic components.[8] These transformations have nicely demonstrated the potential of the copper allenylidene intermediate in the construction of heterocyclic architectures.[7,8] As part of our continuing efforts on heterocycle synthesis,[9] we recently designed a new propargyl carbamate

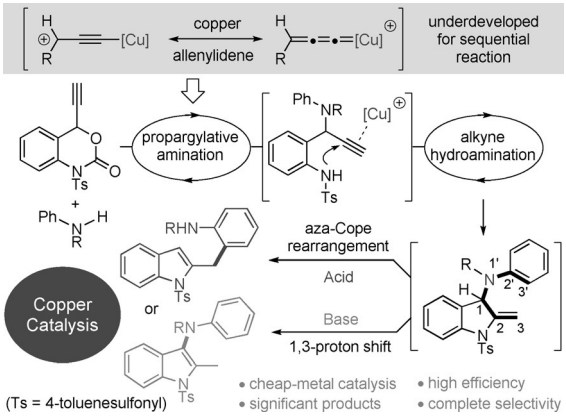


Figure 2. Proposal of this work: Copper-catalyzed sequential reaction for the switchable synthesis of functionalized indoles.

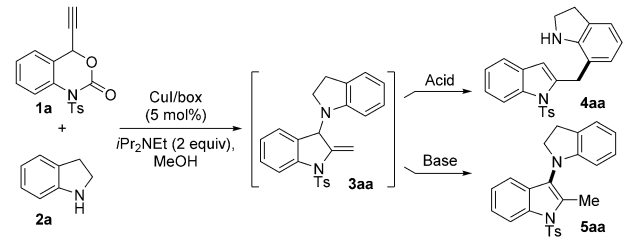
[*] T.-R. Li, B.-Y. Cheng, Y.-N. Wang, M.-M. Zhang, Prof. Dr. L.-Q. Lu, Prof. Dr. W.-J. Xiao
Key Laboratory of Pesticide & Chemical Biology Ministry of Education, College of Chemistry, Central China Normal University
152 Luoyu Road, Wuhan, Hubei 430079 (China)
E-mail: luliangqiu@mail.ccnu.edu.cn
Prof. Dr. W.-J. Xiao
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin) (China)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201605900.

reagent (Figure 2)[10] and hypothesized that in the presence of a copper catalyst, this reagent could undergo an intermolecular decarboxylative amination reaction to generate a propargylamine through a reactive copper allenylidene species. If successful, an intramolecular alkyne hydroamination process would afford the pivotal 3-aminoindoline intermediate, from which two different indole derivatives are expected, either by a one-pot, acid-mediated aza-Cope rearrangement or a base-mediated 1,3-proton shift.

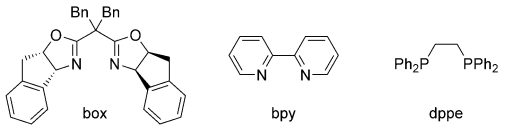
We initially chose the propargylic carbamate **1a** and indoline **2a** as model substrates to examine the feasibility of the proposal and optimize reaction conditions (Table 1).

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



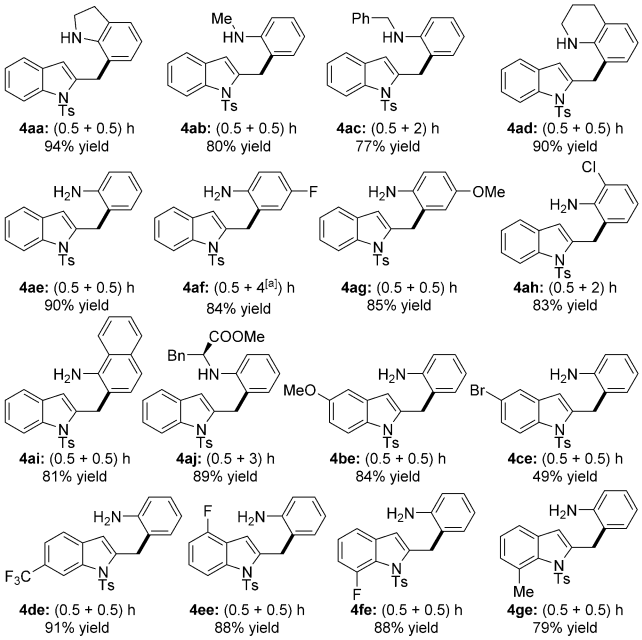
Entry	Change from the standard reaction conditions	Yield [%] 3aa	4aa	5aa
1	none	97	–	–
2	bpy instead of box	55	–	–
3	dppe instead of box	34	30	–
4	$Cu(OAc)_2$ instead of CuI	64	–	–
5	$Cu(OTf)_2$ instead of CuI	80	–	–
6	Cs_2CO_3 instead of iPr_2NEt	complex mixture		
7[b]	TFA added when **1a** consumed	–	88	–
8[b]	$BF_3{\cdot}Et_2O$ added when **1a** consumed	–	94	–
9[c]	Cs_2CO_3 added when **1a** consumed	–	–	86

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), CuI (5 mol%), ligand (6 mol%), and iPr_2NEt (0.4 mmol, 2.0 equiv) in MeOH (2 mL) at ambient temperature for 0.5 h. Yield is that of isolated product. [b] Stirred at 65 °C for 0.5 h after 10 equiv of acid were introduced. [c] Stirred at 65 °C for 2 h after 2 equiv of base were introduced. TFA = trifluoroacetic acid.



Upon evaluating various reaction parameters, we determined that the combination of CuI and a bisoxazoline ligand (box) in methanol can efficiently catalyze the propargylative amination/alkyne hydroamination sequence at ambient temperature, thus furnishing 3-aminoindoline **3aa** in 97% yield (entry 1). Replacement of the box ligand with the nitrogen-containing ligand 2,2′-dipyridyl (bpy) adversely affected the reaction efficiency (entry 2). Reaction with the bidentate phosphine ligand 1,2-bis(diphenylphosphanyl)ethane (dppe) provided a mixture of indole and indoline products (entry 3). We observed that CuI was superior to other copper catalyst precursors (entries 4 and 5) and that the use of the inorganic base Cs_2CO_3 only resulted in a complex mixture. As expected, after the introduction of either the Brønsted acid TFA or Lewis acid $BF_3{\cdot}Et_2O$ to the reaction system when the substrate **1a** was consumed, the aza-Cope rearrangement of **3aa** did indeed occur, and readily afforded the final indole product **4aa** in 88 and 94% yield, respectively (entries 7 and 8). When Cs_2CO_3 was added instead of the acid, the 1,3-proton-transfer process also proceeded well. Another indole product, **5aa**, was given in 86% yield (entry 9). The structures of the indole products **4aa** and **5aa** were definitively confirmed by X-ray analysis.[11]

Having identified the optimal reaction conditions, we probed the generality of this methodology for divergent indole synthesis. As illustrated in Scheme 1, various 2-*ortho*-

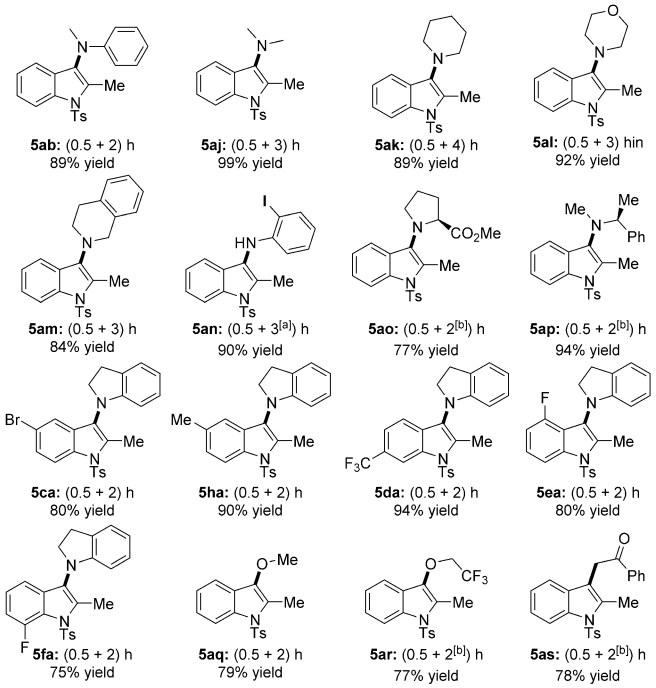


Scheme 1. Indole synthesis by copper-catalyzed sequential reactions and acid-mediated aza-Cope rearrangements. Reaction conditions A: see entry 8 in Table 1. Yield is that of the isolated product. [a] 110 °C in toluene instead of 65 °C in methanol.

anilinemethyl indoles were produced in good to high yields through a copper-catalyzed sequential reaction followed by a BF_3-mediated aza-Cope rearrangement. In addition to various secondary anilines (**4aa**–**ad**: 77–94% yields), primary anilines with different substituents on the benzene ring also participated in this one-pot reaction, thus affording the corresponding products in 81–90% yields (**4ae**–**ai**). In the case of electron-deficient 4-fluoroaniline as the substrate, a higher temperature was needed to promote the rearrangement process (**4af**). A chiral amino-acid-derived secondary amine, methyl *N*-phenyl phenylalaninate, also served as an efficient substrate, thus producing the corresponding indole product **4aj** in 89% yield. Moreover, we surveyed the scope of the propargylic carbamates in this transformation. For instance, variation of the propargylic carbamates, including the substituent position on the benzene ring and its electronic character, was compatible with the reaction conditions A, thus yielding the final products with generally high reaction efficiencies (**4be**–**ge**). Because of the significance of fluorine

substitution in biological, pharmaceutical, and materials science,[12] propargylic carbamates bearing either CF_3 or fluorine groups were tested under the present reaction conditions. To our delight, the corresponding fluoro-containing indoles were produced in high yields (**4de**: 91%, **4ee**: 88%, **4fe**: 88%).

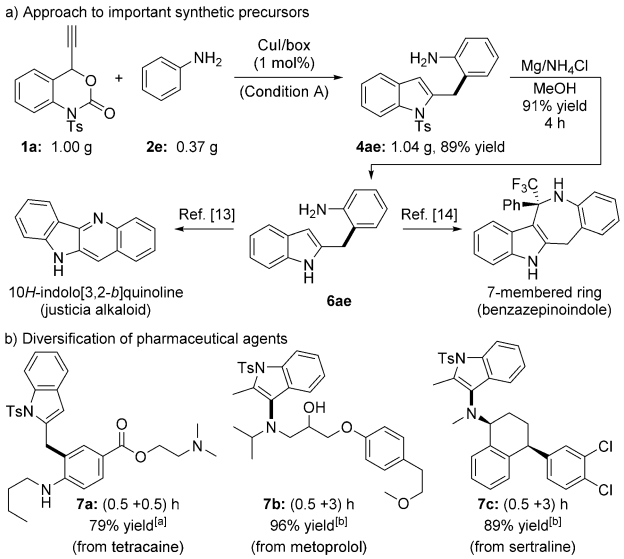
In parallel, we examined the generality of the copper-catalyzed sequential reaction followed by a base-promoted 1,3-proton shift process. As shown in Scheme 2, many amine



Scheme 2. Indole synthesis by the copper-catalyzed sequential reactions and base-mediated 1,3-proton shift. Reaction conditions B: see entry 9 in Table 1. Yield is that of the isolated product. [a] nBu$_4$NCl and $NaHCO_3$ at ambient temperature, instead of Cs_2CO_3 at 65 °C. [b] KOtBu, instead of Cs_2CO_3.

nucleophiles, including aromatic *N*-methyl aniline and aliphatic secondary amines, were suitable for this transformation. A wide range of structurally diverse 3-aminoindole products were achieved in 84–99% yields (**5ab** and **5aj**–**am**). 2-Iodoaniline was also tested for the one-pot sequential reaction, and the indole product **5an** was synthesized in 90% yield at ambient temperature when Cs_2CO_3 was replaced with nBu$_4$NCl and $NaHCO_3$.[10] Chiral secondary amines were also efficient substrates for this transformation, thus affording the corresponding indole derivatives in high yields (**5ao**: 77%, **5ap**: 94%). In addition, the reactivity of various propargylic carbamates were explored and an array of 3-aminoindoles with different substitutions were prepared in 75–94% yields (**5ca**–**fa** and **5ha**). In addition to amines, we were pleased to find that other nucleophiles, such as methanol, trifluoroethanol, and an acetophenone-derived enamine, can participate in this reaction efficiently, thus delivering the corresponding indole products in good yields (**5aq**–**as**).

To demonstrate the synthetic utility of these methods, we performed a gram-scale reaction of **1a** and **2e** while simultaneously reducing the catalyst loading to 1 mol%. To our delight, no erosive effect on the reaction efficiency was observed (Scheme 3a, **4ae**: 89%). Additionally, 2-aniline-



Scheme 3. Synthetic utility of methodology. [a] Reaction conditions A. [b] Reaction conditions B, where Cs_2CO_3 was replaced with KOtBu.

methyl indole **6ae**, an important precursor in the total synthesis of the natural alkaloid 10*H*-indolo[3,2-*b*]quinoline,[13] was obtained in 91% yield through a reductive detosylation step.[14] Note that this compound can also be converted into a useful benzazepinoindoles through a catalytic asymmetric Pictet–Spengler reaction.[15] In addition, we chose three commercially available prescribed drugs: tetracaine, metoprolol, and sertraline, as a platform to further demonstrate the potential of this copper-catalyzed sequential reaction, as diversification of commercial drugs is well accepted to be a fruitful approach to pharmaceutical candidate discovery.[16] Subjecting these drug molecules to our standard reaction conditions, we successfully synthesized medicinally relevant compounds **7a**–**c** in high yields (Scheme 3b).

A plausible mechanism for the reaction of the propargylic carbamates **1** and nucleophiles **2** has been proposed to illustrate the pathway to the key indoline intermediates **3**.[17] As depicted in Figure 3, the copper catalyst initially reacts with **1** to generate the copper acetylide complex **A** in the presence of iPr$_2$NEt. Subsequently, the decarboxylation reaction of **A** followed by a protonation process generates the copper allenylidene complex **B** and its resonance structure **C**. The capture of this reactive species with **2**, followed by an iPr$_2$NEt-mediated proton shift of **D**, results in the intermediate **E** and regenerates the copper catalyst.[8a,18] In the second catalytic cycle, the copper catalyst can act as a π acid to activate the alkyne competent in complex **F**,[3h,19] thus yielding the intermediate **G** through an intramolecular alkyne hydroamination reaction. Finally, **3** is produced after

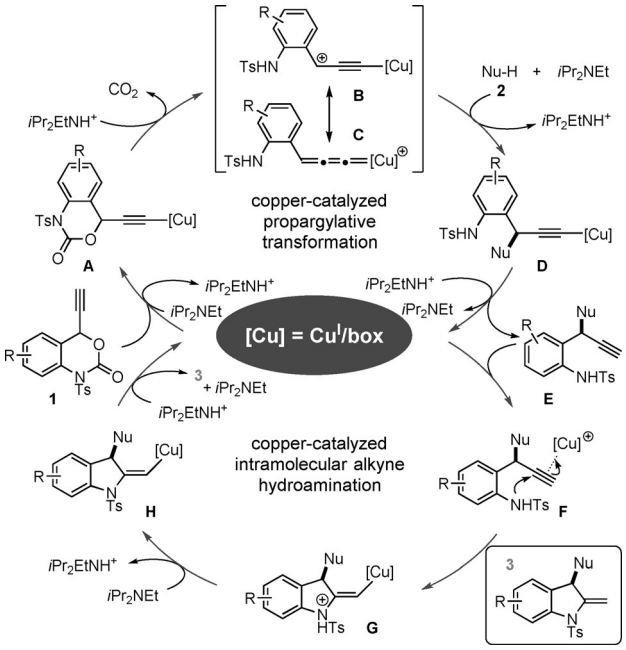


Figure 3. Proposed mechanism to generate the key indoline intermediate **3**.

protonation of the intermediate **H**, accompanied by the regeneration of the active copper catalyst. The key indoline intermediate, that is, **3aa**, can be isolated and its structure has been unambiguously established by X-ray analysis.[11]

In summary, we have successfully developed an unprecedented copper-catalyzed decarboxylative amination/hydroamination sequence of propargylic carbamates with N-, O-, and C-centered nucleophiles. Variation of the reaction condition allows the switchable synthesis of two types of functionalized indoles with high efficiencies and complete chemoselectivities. This process has been successfully employed in the formal synthesis of the natural alkaloid 10*H*-indolo[3,2-*b*]quinolone, and its utility has been further demonstrated by the derivatization of some prescribed drugs.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (NO. 21232003, 21472057 and 21572074) and other financial supports (NO. 201422, CCNU15A02007 and 2015CFA033) for support of this research.

Keywords: alkynes · copper · hydroamination · indoles · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 12422–12426
Angew. Chem. **2016**, *128*, 12610–12614

[1] For select reviews on the importance of indoles, see: a) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761–793; b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; *Angew. Chem.* **2009**, *121*, 9786–9824; c) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620–6662.

[2] For select reviews on indole synthesis, see: a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; b) K. Krüger née Alex, A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153–2167; c) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2010**, *111*, PR215–PR283; d) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195–7210; e) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929–3968.

[3] For examples with the type I propargyl alcohols and their derivatives as substrates by precious metal catalysis, see: a) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2007**, *46*, 1881–1884; *Angew. Chem.* **2007**, *119*, 1913–1916; b) P. Kothandaraman, W. Rao, S. J. Foo, P. W. H. Chan, *Angew. Chem. Int. Ed.* **2010**, *49*, 4619–4623; *Angew. Chem.* **2010**, *122*, 4723–4727; c) P. Kothandaraman, S. R. Mothe, S. S. M. Toh, P. W. H. Chan, *J. Org. Chem.* **2011**, *76*, 7633–7640; d) C. Chowdhury, B. Das, S. Mukherjee, B. Achari, *J. Org. Chem.* **2012**, *77*, 5108–5119; e) D. Susanti, F. Koh, J. A. Kusuma, P. Kothandaraman, P. W. H. Chan, *J. Org. Chem.* **2012**, *77*, 7166–7175; g) X. Li, H. Li, W. Song, P.-S. Tseng, L. Liu, I. A. Guzei, W. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 12905–12908; *Angew. Chem.* **2015**, *127*, 13097–13100; an example via Cu catalysis, see: h) H. Li, X. Li, H.-Y. Wang, G. N. Winston-McPherson, H. J. Geng, I. A. Guzeic, W. Tang, *Chem. Commun.* **2014**, *50*, 12293–12296.

[4] For examples with the type II propargyl alcohols and their derivatives as substrates, see: a) I. Ambrogio, S. Cacchi, G. Fabrizi, *Org. Lett.* **2006**, *8*, 2083–2086; b) D. Shu, W. Song, X. Li, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 3237–3240; *Angew. Chem.* **2013**, *125*, 3319–3322; c) D. Shu, G. N. Winston-McPherson, W. Song, W. Tang, *Org. Lett.* **2013**, *15*, 4162–4165; d) S. Cacchi, G. Fabrizi, A. Goggiamani, C. Molinaro, R. Verdiglione, *J. Org. Chem.* **2014**, *79*, 401–407.

[5] For pioneering work, see: a) Y. Imada, M. Yuasa, I. Nakamura, S.-I. Murahashi, *J. Org. Chem.* **1994**, *59*, 2282; b) J. D. Godfrey, Jr., R. H. Mueller, T. C. Sedergran, N. Soundararajan, V. J. Colandrea, *Tetrahedron Lett.* **1994**, *35*, 6405.

[6] For a recent reviews, see: a) D.-Y. Zhang, X.-P. Hu, *Tetrahedron Lett.* **2015**, *56*, 283–295; for recent examples, see: b) W. Shao, H. Li, C. Liu, C.-J. Liu, S.-L. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 7684–7687; *Angew. Chem.* **2015**, *127*, 7794–7797; c) K. Nakajima, M. Shibata, Y. Nishibayashi, *J. Am. Chem. Soc.* **2015**, *137*, 2472–2475.

[7] a) G. Hattori, Y. Miyake, Y. Nishibayash, *ChemCatChem* **2010**, *2*, 155–158.

[8] a) C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu, X.-P. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 9585–9588; b) F.-L. Zhu, Y.-H. Wang, D.-Y. Zhang, J. Xu, X.-P. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10223–10227; *Angew. Chem.* **2014**, *126*, 10387–10391; c) D.-Y. Zhang, L. Shao, J. Xu, X.-P. Hu, *ACS Catal.* **2015**, *5*, 5026–5030; d) Z.-T. Liu, Y.-H. Wang, F.-L. Zhu, X.-P. Hu, *Org. Lett.* **2016**, *18*, 1190–1193; e) L. Shao, Y.-H. Wang, D.-Y. Zhang, J. Xu, X.-P. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 5014–5018; *Angew. Chem.* **2016**, *128*, 5098–5102.

[9] Select work from our group, see: a) L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Acc. Chem. Res.* **2012**, *45*, 1278–1293; b) T.-R. Li, F. Tan, L.-Q. Lu, Y. Wei, Y.-N. Wang, Y.-Y. Liu, Q.-Q. Yang, J.-R. Chen, D.-Q. Shi, W.-J. Xiao, *Nat. Commun.* **2014**, *5*, 5500; c) Y. Wei, L.-Q. Lu, T.-R. Li, B. Feng, Q. Wang, W.-J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2016**, *55*, 2200–2204; *Angew. Chem.* **2016**, *128*, 2240–2244; d) Q. Wang, X.-T. Qi, L.-Q. Lu, T.-R. Li, Z.-G. Yuan, K. Zhang, B.-J. Li, Y. Lan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2016**, *55*, 2840–2844; *Angew. Chem.* **2016**, *128*, 2890–2894; e) Q. Wang, T.-R. Li, L.-Q. Lu, M.-M. Li, K. Zhang, W.-J. Xiao, *J. Am. Chem. Soc.* **2016**, *138*, 8360–8363.

[10] Please see the Supporting Information for details.

[11] CCDC 1482135 (**3aa**), 1482130 (**4aa**), and 1482136 (**5aa**) contain the supplementary crystallographic data for this paper. These

data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[12] For select reviews, see: a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; b) V. A. Petrov in *Fluorinated Heterocyclic Compounds: Synthesis Chemistry, and Applications*, Wiley, Hoboken, **2009**.
[13] a) T.-L. Ho, D.-J. Jou, *Helv. Chim. Acta* **2002**, *85*, 3823 – 3827; b) G.-V. Subbaraju, J. Kavitha, D. Rajasekhar, J.-I. Jimenez, *J. Nat. Prod.* **2004**, *67*, 461 – 462.
[14] J.-A. May, B. Stoltz, *Tetrahedron* **2006**, *62*, 5262 – 5271.
[15] X.-J. Li, D. Chen, H.-R. Gu, X.-F. Lin, *Chem. Commun.* **2014**, *50*, 7538 – 7541.
[16] Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, *Science* **2015**, *349*, 62 – 66.
[17] Please see the Supporting Information for control experiments to shed light on the proposed reaction mechanism.
[18] a) R. J. Detz, M. M. E. Delville, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3777 – 3780; *Angew. Chem.* **2008**, *120*, 3837 – 3840; b) G. Hattori, H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem. Int. Ed.* **2008**, *47*, 3781 – 3783; *Angew. Chem.* **2008**, *120*, 3841 – 3843; c) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chem. Eur. J.* **2011**, *17*, 5921 – 5930.
[19] H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem. Int. Ed.* **2007**, *46*, 2295 – 2298; *Angew. Chem.* **2007**, *119*, 2345 – 2348.

Received: June 17, 2016
Published online: September 4, 2016

