

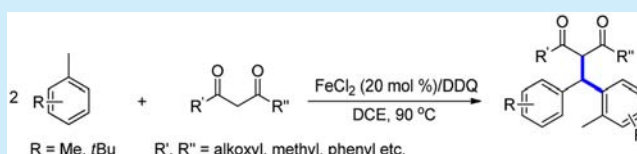
Fe-Catalyzed Double Cross-Dehydrogenative Coupling of 1,3-Dicarbonyl Compounds and Arylmethanes

Kai Yang and Qiuling Song*

Institute of Next Generation Matter Transformation, College of Chemical Engineering, Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, China

S Supporting Information

ABSTRACT: Fe-catalyzed tandem cross-dehydrogenative coupling of the methyl group in arylmethanes with 1,3-dicarbonyl compounds has been developed. The reaction affords one new C(sp³)–C(sp²) bond and one new C(sp³)–C(sp³) bond in a one-pot protocol. Further study suggests that this reaction might start with a Friedel–Crafts-type reaction (cross-dehydrogenative arylation) followed by cross-dehydrogenative coupling with an activated methylene group under mild oxidative conditions.

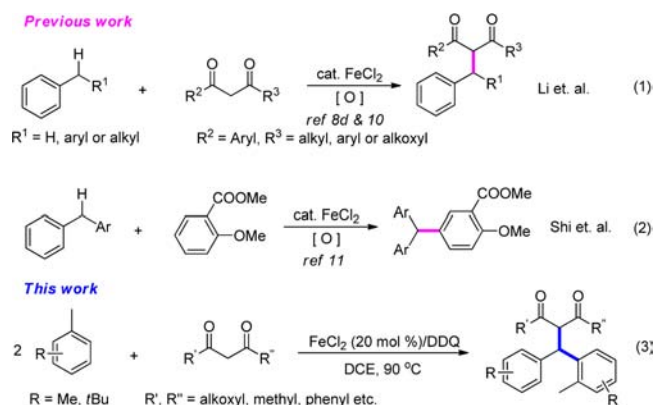


Selective functionalization of C–H bonds for the construction of new C–C bonds has attracted great attention from the synthetic community in the past decade.^{1,2} Through C–H functionalization, preactivation of cheap and readily available starting material could be avoided, thus improving reaction atom-efficiency and shortening synthetic steps, making C–H functionalization potentially applicable in the synthesis of complex molecules. Great progress has been achieved in this area, especially transition-metal-catalyzed C–H functionalization.^{3–7} Among all of the reported transition metals, Fe gets more attention due to its nontoxicity, low cost, and environmentally benign features, which gives Fe-catalyzed C–H activation many advantages over other transition metals.^{1b,8,9} Many research groups greatly contributed to this field; for instance, Li and co-workers reported Fe-catalyzed activation of a benzylic C–H bond with an active dicarbonyl methylene compound to form a new C(sp³)–C(sp³) bond (Scheme 1, eq

1);^{8d,10} Shi et al. described an Fe-catalyzed cross-dehydrogenative arylation between a benzylic C(sp³)–H bond and the arene C(sp²)–H bond (Scheme 1, eq 2).¹¹ However, in these reported examples, only one C–C bond was formed. A cascade or tandem reaction is an easy and efficient way to construct several new bonds in a one-pot protocol; therefore, a tandem cross-dehydrogenative coupling (CDC) is very attractive and desirable. To the best of our knowledge, there is no example for the construction of two new different types of C–C bonds via CDC under Fe-catalyzed reaction. Herein, we disclose the first example of Fe-catalyzed double CDC between two arylmethane molecules and activated dicarbonyl compounds to construct one new C(sp³)–C(sp²) and one new C(sp³)–C(sp³) simultaneously in a tandem pattern.

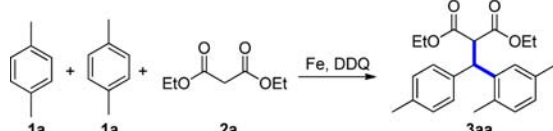
We commenced our study with *p*-xylene (**1a**) and diethyl malonate (**2a**) with FeCl₂ as catalyst under air as a model reaction (Table 1). To our delight, the desired product **3aa** was formed in 36% isolated yield (Table 1, entry 1) with 20 mol % of FeCl₂ and 2.5 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant at 100 °C in a sealed tube. When the oxidant was increased to 3 equiv, the isolated yield of desired product was increased to 52% (Table 1, entry 2); when DDQ was increased to 4 equiv, 68% of desired product was obtained (Table 1, entry 3). Yet 5 equiv of DDQ did not show superiority to 4 equiv of oxidant (Table 1, entry 4), and only 67% of desired product was obtained. Further iron salt screening suggested that FeCl₂ is the best among FeBr₂, Fe(OAc)₂, and FeCl₃ (Table 1, entries 5–7). When the temperature was decreased to 90 °C, surprisingly, 75% of desired product **3a** was obtained, higher than the 100 °C one. Yet when the reaction temperature was dropped to 80 and 70 °C, the isolated yields of desired products were dropped to 60 and 51%, correspondingly (Table 1, entries 8–10). When the

Scheme 1. Transition-Metal-Catalyzed C–C Bond Formation Reaction between a Benzylic C–H Bond and an Activated C–H Bond



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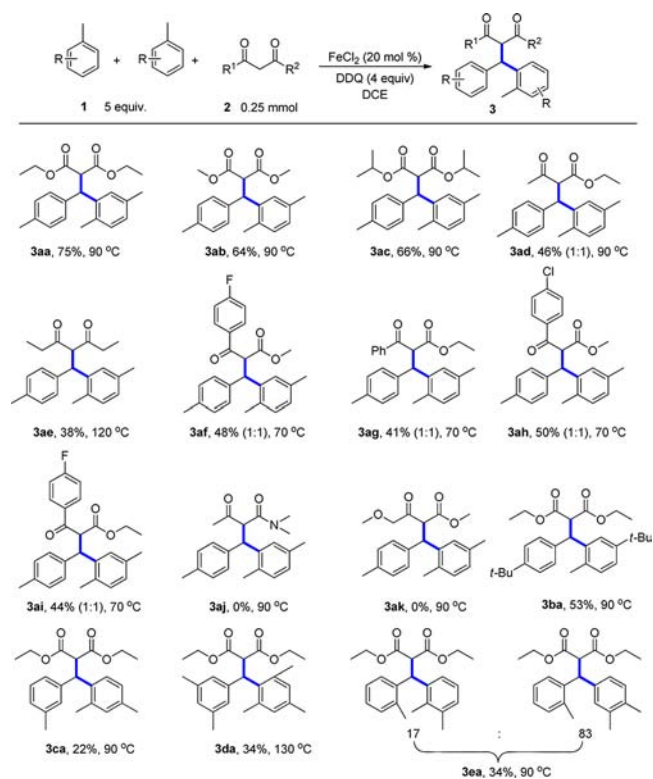
Table 1. Optimization of the Reaction Conditions^a


entry	catalyst (mol %)	oxidant (equiv)	solvent	temp (°C)	time (h)	yield (%) ^b
1	FeCl ₂ (20)	DDQ (2.5)	DCE	100	24	36
2	FeCl ₂ (20)	DDQ (3)	DCE	100	24	52
3	FeCl ₂ (20)	DDQ (4)	DCE	100	24	68
4	FeCl ₂ (20)	DDQ (5)	DCE	100	24	67
5	FeBr ₂ (20)	DDQ (4)	DCE	100	24	29
6	Fe(OAc) ₂ (20)	DDQ (4)	DCE	100	24	trace
7	FeCl ₃ (20)	DDQ (4)	DCE	100	24	40
8	FeCl₂ (20)	DDQ (4)	DCE	90	24	75
9	FeCl ₂ (20)	DDQ (4)	DCE	80	24	60
10	FeCl ₂ (20)	DDQ (4)	DCE	70	24	51
11	FeCl ₂ (10)	DDQ (4)	DCE	90	24	52
12	FeCl ₂ (20)	DDQ (4)	CH ₂ Cl ₂	90	24	61 ^c
13	FeCl ₂ (20)	DDQ (4)	CHCl ₃	90	24	trace
14	FeCl ₂ (20)	DDQ (4)	dioxane	90	24	0
15	FeCl ₂ (20)	DDQ (4)	CH ₃ CN	90	24	0
16	FeCl ₂ (20)	DDQ (4)	DMSO	90	24	0
17	FeCl ₂ (20)	DDQ (4)	DMF	90	24	0
18	FeCl ₂ (20)	TBHP (70%) (4)	DCE	90	24	0
19	FeCl ₂ (20)	DTBP (4)	DCE	90	24	0
20	FeCl ₂ (20)	K ₂ S ₂ O ₈ (4)	DCE	90	24	0

^aReaction conditions: diethyl malonate (0.25 mmol), *p*-xylene (5 equiv), Fe salt (20 mol %), DDQ, in corresponding solvent (1 mL) in a sealed tube under air. ^bIsolated yield. ^cGC yield.

catalyst loading was reduced to 10 mol %, only 52% of the desired product was obtained (Table 1, entry 11). Solvent and oxidant screening indicated that dichloroethane (DCE) and DDQ are the best choices (Table 1, entry 8), while other solvents, such as CH₂Cl₂, chloroform, dioxane, MeCN, dimethylsulfoxide (DMSO), dimethylformamide (DMF), and other oxidants, like *tert*-butyl hydroperoxide (TBHP) (70% in aqueous solution), di-*tert*-butyl peroxide (DTBP), and K₂S₂O₈, were not effective in this transformation (Table 1, entries 12–20). After sufficient screening, the optimal condition eventually emerged as toluene derivative **1a** (5 equiv), malonate **2a** (0.25 mmol), FeCl₂ (20 mol %), DDQ (4 equiv), and DCE (1 mL) at 90 °C under air.

With the optimized conditions available, we explored the substrate scope (Scheme 2). As shown in Scheme 2, **1a** works very well with a variety of dicarbonyl compounds **2** under standard conditions to afford moderate to good yields of desired products (Scheme 2, **3aa–3ai**): 1,3-diester (**2a–c**), 1,3-diketone (**2e**), and β -keto esters (**2d**, **2f–i**) were all found to react smoothly with *p*-xylene to afford corresponding desired products, and the substituents on the aromatic rings of aryl β -keto esters survived well (Scheme 2, **2f**, **2h**, and **2i**). Dialkyl **2e** was also a suitable dicarbonyl substrate to smoothly generate the desired product (Scheme 2, **3ae**). Besides, **1a**, *p*-*tert*-butyl toluene (**1b**), *m*-xylene (**1c**), mesitylene (**1d**), and *o*-xylene (**1e**) were all good candidates for this reaction, although **3ca** was obtained only in 22% yield and **3da** needs a higher temperature to process smoothly. For **1e**, two regioisomers were obtained with a total isolated yield of 34% under the

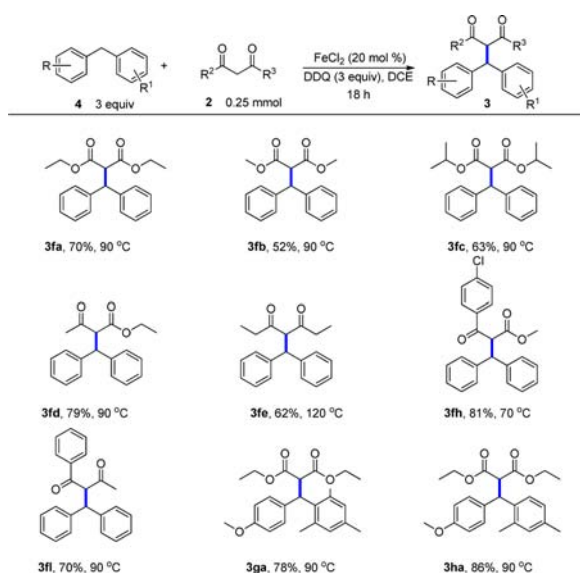
Scheme 2. Tandem Cross-Dehydrogenative Coupling of 1,3-Dicarbonyl Compounds with Aryl Methanes^a

^aReaction conditions: toluene derivatives **1** (1.25 mmol), 1,3-dicarbonyl compounds **2** (0.25 mmol), FeCl₂ (20 mol %), DDQ (1 mmol), DCE (1 mL) in air in a sealed tube, corresponding temperature, 24 h. Isolated yield based on **2**. The ratio of the two diastereomers is given in the parentheses.

standard conditions. Yet surprisingly, if amide **2j** was used or ether ester **2k** was involved in the reaction, no desired products were formed (Scheme 2, **3aj** and **3ak**).

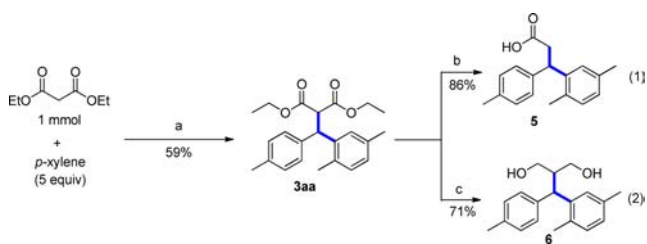
For the mechanism of the novel tandem reaction, we hypothesize that cross-dehydrogenative arylation of two arylmethane molecules should be performed first to afford diaryl methylene compounds, which further couples with 1,3-dicarbonyl compounds to generate desired products. To verify our hypothesis, diphenylmethane **4** was directly treated with 1,3-diester **2** under the standard conditions. The desired product **3fa** was obtained just as we expected. After simple modification (Table S2, Supporting Information), such as reduction of the amount of diaryl compounds and DDQ, compound **3fa** was obtained in 70% yield (Scheme 3, **3fa**). Further exploration showed that diaryl compounds could react with various dicarbonyl compounds, for instance, 1,3-diester (**2a–c**), 1,3-diketone (dialkyl **2e** or alkyl aryl **2l**), β -keto ester (alkyl **2d** and aryl **2h**), to afford corresponding products in good yields. In contrast to Li's method, which mainly focused on 3-oxo-3-phenylpropanoate (β -keto ester) and no alkyl β -keto ester, dialkyl 1,3-diketone, or 1,3-diester involved, our method widely expanded the substrate scope of dicarbonyl compounds. At the same time, DDQ has many advantages over peroxide, which Li and co-workers used in their method in terms of safety; therefore, our work could be a complementary strategy to Li's method.

To illustrate the further synthetic utility of this novel method, desired product **3aa**, which was made from a scaled-up reaction

Scheme 3. Alkylation of Diaryl C–H Bonds with 1, 3-Dicarbonyl Compounds^a

^aReaction conditions: toluene derivatives **4** (0.75 mmol), 1,3-dicarbonyl compounds **2** (0.25 mmol), FeCl₂ (20 mol %), DDQ (0.75 mmol), DCE (1 mL) in air in a sealed tube, corresponding temperature, 18 h. Isolated yield based on **2**.

(1 mmol, based on 1,3-diethyl ester **2a**), was treated with sodium hydroxide in MeOH/H₂O. After being acidified by acetic acid, eventually acid **5**, a key intermediate for the synthesis of hexahydropyrroloisoquinoline compounds, which are useful for the treatment of histamine H₃ receptor- and serotonin-mediated disease,¹² was easily obtained from readily available starting materials in two steps (Scheme 4, eq 1). Acid

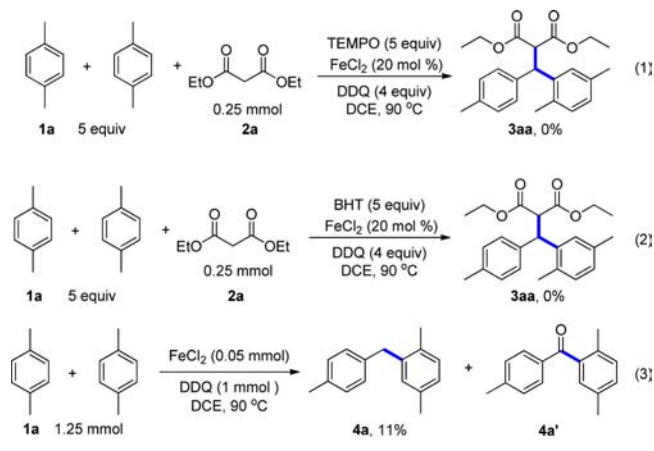
Scheme 4. Synthetic Utility of the Current Method^a

^aReaction conditions: (a) FeCl₂ (20 mol %), DDQ (4 equiv), DCE, 90 °C; (b) (1) NaOH (3 equiv), 90 °C, 18 h, MeOH (2 mL), H₂O (1 mL); (2) AcOH (2 mL), 90 °C, 12 h; (c) LiAlH₄, THF.

5 was difficult to access by other methods. When **3aa** was applied with LiAlH₄ in THF, 1,3-diol **6**, which is a very useful building block in organic synthesis, was formed in 71% yield (Scheme 4, eq 2).

Several control experiments were conducted to get further insights into the reaction mechanism. First, radical trapping experiments were carried out by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) with **1a** and **2a** under the standard conditions. As shown in Scheme 2, the reactions were totally inhibited by TEMPO and BHT, suggesting a radical pathway might be involved in this reaction (Scheme 5, eqs 1 and 2). When *p*-xylene was used under the standard conditions, 11% of cross-dehydrogenative arylation product (dimer) **4a** was obtained

Scheme 5. Control Experiments under Standard Conditions

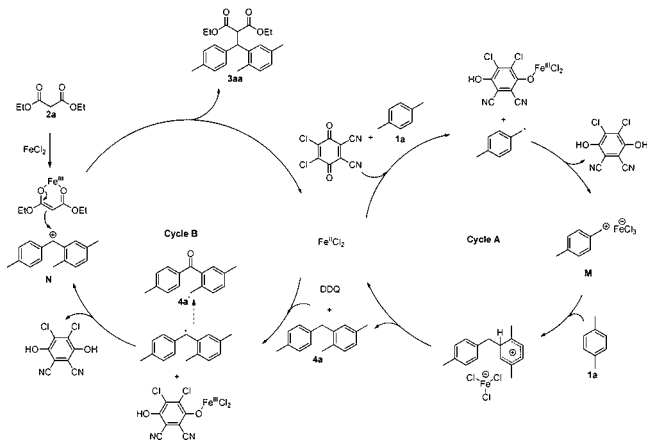


with its corresponding oxidized product **4a'** (Scheme 5, eq 3), and the two compounds **4a** and **4a'** were also detected in the model reaction under the standard conditions (Figure S1, Supporting Information). Interestingly, Shi and co-workers mentioned one similar reaction in their cross-dehydrogenative arylation of a benzylic compound with an electron-rich arene, in which the benzylic compound and electron-rich arene are the same: mesitylene was dimerized into product at 150 °C for 36 h with TON = 11. Compared to our condition, their's was very harsh and needs a very long reaction time.¹¹

Further kinetic study was also conducted under various reaction times: when the reaction was conducted at the standard condition of 15 min, GC yield of product **3aa** was 20%, 30 min was 27%, and 1 and 2 h gave the same GC yields of product with 36%. This revealed that the reaction was initiated by SET process very quickly, yet later, it was slowed. Since dimer **4a** and its corresponding oxidized compound **4a'** were both detected besides the desired product **3aa** under the standard conditions (Table S1, Supporting Information) and no dimerization of 1,3-diketone product was ever detected, based on the previous literature report^{3c,11,13} and our observations, as well as the above experimental results, we gave a proposed mechanism: the reaction was initiated by FeCl₂-catalyzed SET oxidation of one arylmethane molecule to generate a benzylic cation **M**, a subsequent Friedel–Crafts-type process with another molecule of arylmethane, and further proton abstraction of hydroquinone to afford dimer **4a** (cycle A), which served as a new benzylic compound and started a new cycle (cycle B) to generate a new benzyl cation **N**; the new cation **N** reacted with iron-chelated the 1,3-dicarbonyl compound to produce the desired product **3aa** (Scheme 6).

In conclusion, a novel Fe-catalyzed double C–C bond formation via a tandem CDC of dicarbonyl compounds with arylmethanes has been developed under mild conditions. This novel reaction has many advantages with double C–H activation in a one-pot protocol to generate two new types of C–C bonds. Substrate scope exploration suggested that this method was complementary to the existing method in terms of safer oxidant and wider substrate functionalities. Further investigation on the mechanism, scope, and synthetic application of this reaction are ongoing in our laboratory.

Scheme 6. Proposed Mechanism



■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: qsong@hqu.edu.cn. Fax: 86-592-6162990.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293–1314. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (d) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588–5598. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74–100. (f) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219–9280.
- (2) (a) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369–375. (c) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129–133. (d) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215–220.
- (3) For Cu-catalyzed: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811. (b) Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1446–1450. (c) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558–5562. (d) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446–3449. (e) Zhang, G.; Miao, J.; Zhao, Y.; Ge, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8318–8321. (f) Yan, H.; Lu, L.; Rong, G.; Liu, D.; Zheng, Y.; Chen, J.; Mao, J. *J. Org. Chem.* **2014**, *79*, 7103–7111.
- (4) For Pd-catalyzed: (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. (b) Cho, S. H.; Hwang, S. J.; Chang, S. J. *Am. Chem. Soc.* **2008**, *130*, 9254–9256. (c) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169–6173. (d) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1926–1929.
- (5) For Au-catalyzed: Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811.

(6) For Zn-catalyzed: Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504–2507.

(7) For Ni-catalyzed: (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733–1736. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740.

(8) (a) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497–7500. (b) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002–6004. (c) Wu, W.; Su, W. *J. Am. Chem. Soc.* **2011**, *133*, 11924–11927. (d) Pan, S.; Liu, J.; Li, Y.; Li, Z. *Chin. Sci. Bull.* **2012**, *57*, 2382–2386. (e) Ratnikov, M. O.; Xu, X.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 9475–9479.

(9) (a) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560. (b) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633–13635. (c) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638–3641. (d) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868–3871. (e) Jia, F.; Li, Z. *Org. Chem. Front.* **2014**, *1*, 194–214.

(10) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505–6507.

(11) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817–3820.

(12) Apodaca, R.; Barbier, A. J.; Carruthers, N. I.; Gomez, L. A.; Keith, J. M.; Lovenberg, T. W.; Wolin, R. L. Patent Appl. WO2006138604 (A1), 2006.

(13) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893–15895.