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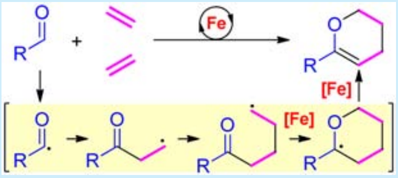
Iron-Catalyzed Convergent Radical Cyclization of Aldehydes with Two Alkenes to 3,4-Dihydropyrans

Leiyang Lv, Hui Xi, Xiaohui Bai, and Zhiping Li*

Department of Chemistry, Renmin University of China, Beijing 100872, China

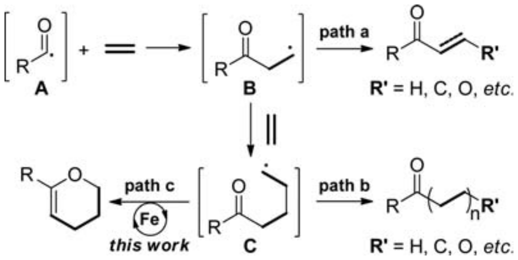
Ⓢ *Supporting Information*

ABSTRACT: A novel convergent radical cyclization of an aldehyde with two alkenes has been developed. With this method, polyfunctionalized 3,4-dihydropyrans are built in an efficient and selective manner. The iron-catalyzed redox radical recombinations are proposed for the formation of a 3,4-dihydropyran skeleton.



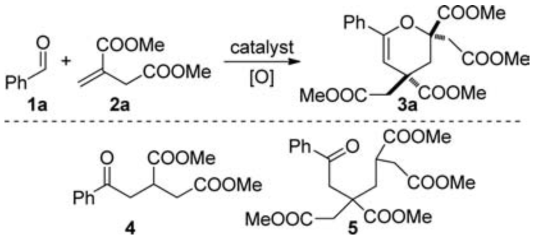
Radical reactions have become an increasingly powerful and attractive tool in chemical synthesis.[1] The control of the selectivity of a free-radical intermediate plays a key role in the success of a desired radical reaction.[2] Intermolecular addition of an acyl radical **A** to unsaturated motifs, such as C═C double bonds, has been previously developed as an efficient and selective method for the synthesis of unsymmetric ketones via intermediate **B** (Scheme 1, path a).[3,4] The propagation of the radical chain of **B** with alkene(s) can also take place to provide the oligomer or polymer (Scheme 1, path b).[5] Although intramolecular radical cyclization represents one of the important strategies for the construction of cyclic compounds, multicomponent convergent radical annulation is an extremely difficult task due to the lack of driving force to cyclization over other competing radical processes. To address the challenge, the Landais[6] and Ryu[7] groups have recently demonstrated a promising strategy for three-component tandem radical annulation by the combination of radical cascades and an ionic process.[8] To the best of our knowledge, convergent radical cyclization involving three-double bonds has never been explored.[9] Herein, we report a novel three-component reaction of aldehydes with two alkenes with the aid of iron catalysis[10] (Scheme 1, path c), which allows for the construction of polyfunctionalized 3,4-dihydropyrans[11] in a one-pot process.

Scheme 1. Intermolecular Addition of Acyl Radicals to C−C Double Bonds



The three-component cyclization was serendipitously discovered from our investigations of the reactions of benzaldehyde **1a** and commercial dimethyl itaconate **2a** (Table 1).[12] The hydroacylation products **4** and **5** were obtained in the presence of di-*tert*-butyl peroxide without a metal catalyst (entry 1). Surprisingly, a three-component radical annulation product **3a** was observed when a metal catalyst was used (entries 2−13). The

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	[O]	**3a**[b] (%)	**4**; **5**[b] (%)
1		(t-BuO)$_2$		8; 25 (1:1)
2	FeCl$_2$	(t-BuO)$_2$	87 (2.2:1)	3; 0
3	FeCl$_3$	(t-BuO)$_2$	85 (2.2:1)	4; 0
4	FeBr$_2$	(t-BuO)$_2$	79 (1.6:1)	13; 0
5	Fe(OAc)$_2$	(t-BuO)$_2$	72 (1.9:1)	10; 0
6	Fe(acac)$_2$	(t-BuO)$_2$	70 (2.1:1)	9; 0
7	CuCl$_2$	(t-BuO)$_2$	44 (1.2:1)	16; 13 (1:1)
8	CuCl	(t-BuO)$_2$	55 (1.0:1)	18; 14 (1:1)
9	CuBr$_2$	(t-BuO)$_2$	53 (1.1:1)	18; 12 (1:1)
10	MnCl$_2$	(t-BuO)$_2$	12 (0.9:1)	19; 28 (1:1)
11	MnBr$_2$	(t-BuO)$_2$	10 (1.0:1)	10; 27 (1:1)
12	CoBr$_2$	(t-BuO)$_2$	5 (1.0:1)	30; 26 (1:1)
13	FeCl$_2$	PhCOOO*t*Bu	50 (2.2:1)	15; 0
14	FeCl$_2$	(PhCOO)$_2$		
15	FeCl$_2$			

[a] Reaction conditions: **1a** (1.5 mmol), **2a** (0.3 mmol), catalyst (2.5 mol %), [O] (0.75 mmol), PhCl (1.0 mL), 115 °C, 3 h, under N$_2$. [b] Reported yields are based on **2a** and determined by ^{1}H NMR using an internal standard; diastereomeric ratios are given in parentheses.

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catalyst screening showed that simple iron salts efficiently promoted the formation of **3a**, accompanied by a small amount of **4** (entries 2−6). Copper catalysts led to moderate yields of the desired product **3a** and substantial amounts of **4** and **5** (entries 7−9). Manganese and cobalt catalysts were less effective, resulting in the formation of more side products **4** and **5** (entries 10−12). The efficiency of this transformation was affected by the choice of oxidant (entries 13 and 14). The starting materials were recovered when the reaction was carried out in the absence of oxidant (entry 15). It is worth mentioning that the iron catalyst also had an effect on the diastereoselectivity of the transformation, and a ca. 2:1 ratio of the diastereoisomers of **3a** was achieved by various iron catalysts. These results indicated that the iron catalyst was likely involved in the cyclization step of the convergent radical cyclization.

The generality of the transformation was subsequently investigated under the optimized conditions. To our delight, a variety of α-substituted acrylates **2** reacted smoothly with benzaldehyde **1a** to give the corresponding 3,4-dihydropyrans **3** in synthetically useful yields (Figure 1). In contrast, methyl acrylate could not undergo the convergent radical cyclization, which suggested that the substituent at the α position of acrylate was necessary for the annulation. We hypothesized that the in situ generated tertiary carbon radicals were the key intermediates for the three-component cascade reactions. It is interesting to note that the diastereoselectivity of the radical cyclization is dependent on the steric bulk of both R^1 and R^2. Up to a 10:1 diastereomeric ratio of **3l** was achieved when R^1 was *tert*-butyl and R^2 was phthalimide group. The absolute configuration of the major diastereomer of **3j** was confirmed by X-ray diffraction analysis as shown in Figure 2.

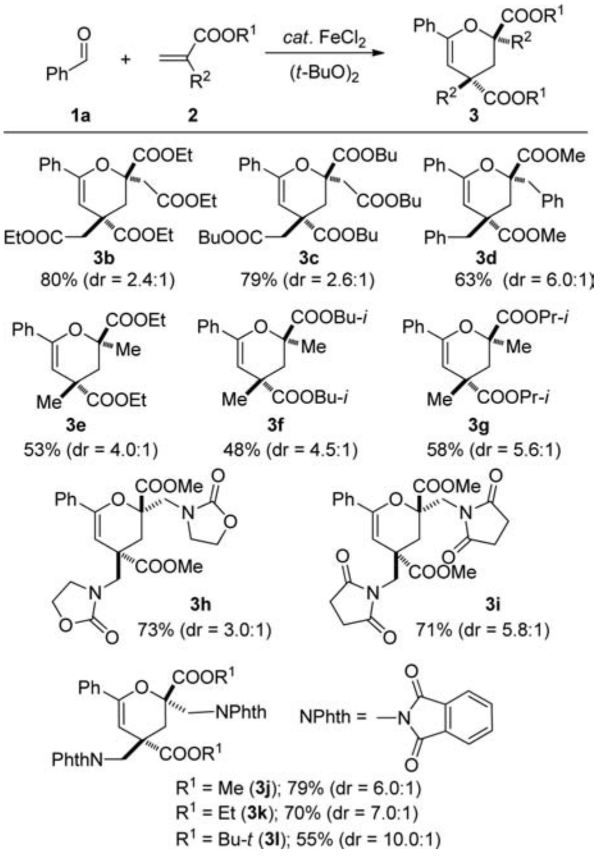


Figure 1. Scope of alkene **2**: **1a** (1.5 mmol), **2** (0.3 mmol), FeCl$_2$ (2.5 mol %), (*t*-BuO)$_2$ (0.75 mmol), PhCl (1.0 mL), 115 °C, 3 h, under N$_2$; reported yields are the isolated yields; diastereomeric ratios of **3** are given in parentheses.

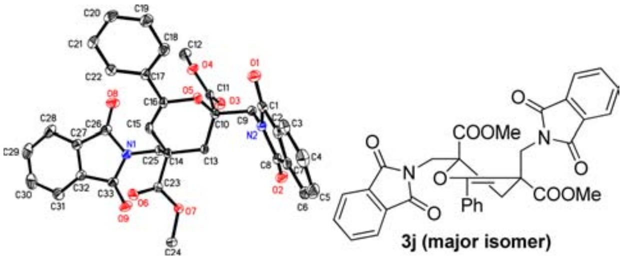


Figure 2. X-ray diffraction of the major diastereomer of **3j**.

The scope of the aldehydes was also examined (Figure 3). The electron-rich aldehydes, such as anisyl aldehyde and *p*-tolualdehyde, afforded the products **3m** and **3n** in moderate yields, while the aldehydes with a halogen atom reacted smoothly with **2a** to afford the products **3o**−**q** in excellent yields. However, the strongly electron-withdrawing group (CN) on the phenyl ring of benzaldehyde eroded the efficiency of this transformation and **3r** was obtained in 52% yield. Furthermore, other aromatic aldehydes such as thiophene-2-carbaldehyde and 2-naphthaldehyde were also well applicable for the present transformation. Unfortunately, aliphatic aldehydes did not give the convergent radical cyclization products under the same reaction conditions.

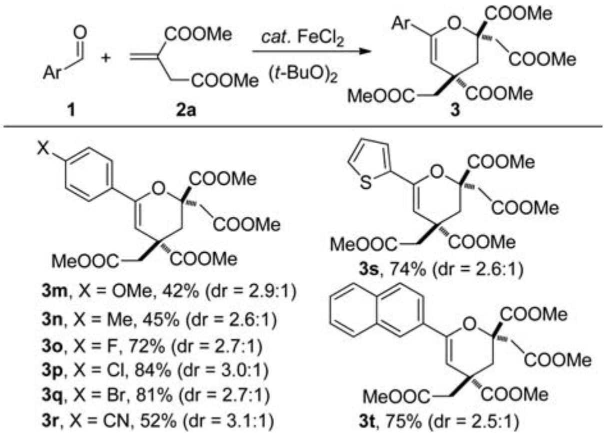
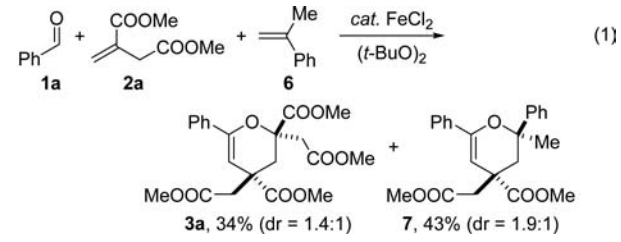
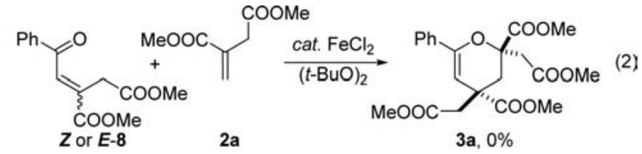


Figure 3. Scope of aldehyde **1**: **1** (1.5 mmol), **2a** (0.3 mmol), FeCl$_2$ (2.5 mol %), (*t*-BuO)$_2$ (0.75 mmol), PhCl (1.0 mL), 115 °C, 3−4 h, under N$_2$; reported yields are the isolated yields; diastereomeric ratios of **3** are given in parentheses.

Given the success of the cycloaddition of benzaldehydes **1** with α-substituted acrylates **2**, we hypothesized that the [2 + 2 + 2] cycloaddition from three different components might be realized by the introduction of the second alkene, which alone could not be transformed into the cyclic product under the standard reaction conditions. To our delight, the cross three-component cycloaddition product **7** was obtained in 43% yield as the major product for the reaction of **1a**, **2a**, and α-methylstyrene **6** eq 1.

As mentioned in Scheme 1, a linear cascade reaction path was initially proposed for the cyclization. Alternatively, hetero-Diels−Alder reaction[11d] could also explain the formation of the 3,4-dihydropyrans. Accordingly, α,β-unsaturated ketone **8** was synthesized and used to react with alkene **2a** eq 2. The [4 + 2]





cycloaddition product **3a** was not observed under the standard reaction conditions. This result ruled out the possibility that **3a** was formed through the hetero-Diels−Alder reaction.

To further study the possible reaction mechanisms for the convergent radical cyclization, an olefinic ketone **9a** was synthesized and reacted with benzaldehyde **1a** (Figure 4). To our satisfaction, the expected 3,4-dihydropyran product **10a** was obtained in 67% yield under the standard reaction conditions, which indicated the 6-*endo-trig* cyclization is possible. Importantly, the addition and decomposed products **11** and **12a** were generated without an iron catalyst, which further demonstrated the iron catalyst is essential for the cyclization. **D** and **E**[13] are two possible intermediates for the formation of **10a**, **11**, and **12a**. In order to distinguish between a radical and a cation species, we synthesized olefinic ketones **9** bearing different substituents and investigated their reactivities of the cyclization (Figure 5). The corresponding 3,4-dihydropyrans **10b−d** (R = COOMe, Ph, Me) were obtained by the reactions of **9b−d** with **1a**. The results suggested that carbon cation intermediates were unlikely because the intermediates with phenyl and methyl should be more easily oxidized to a cation than one with an ester substituent.[14]

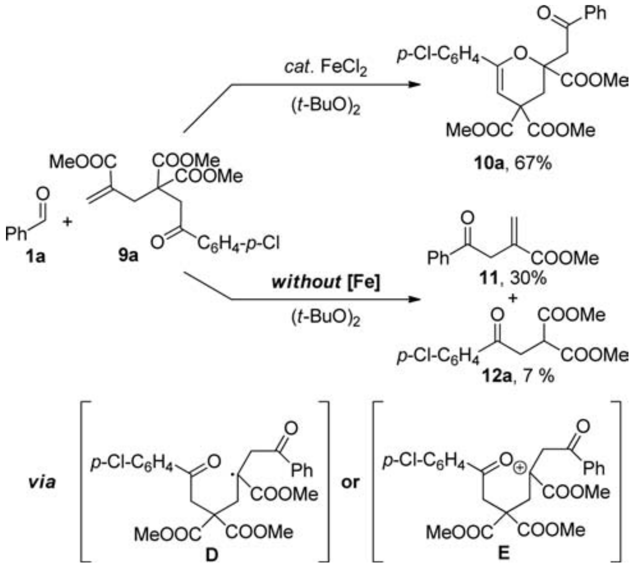


Figure 4. Reactions of **9a** and **1a**.

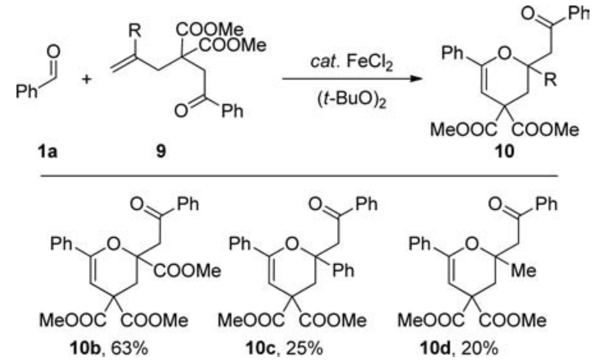
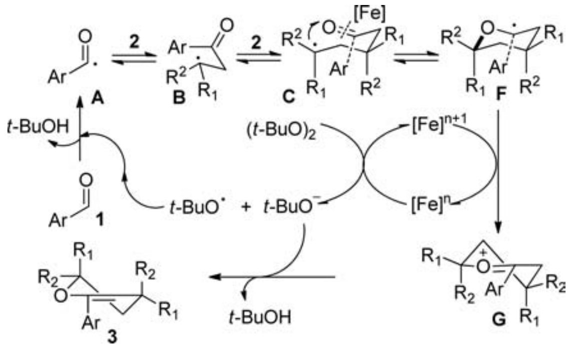


Figure 5. Bimolecular reactions: **1a** (1.5 mmol), **9** (0.3 mmol), $FeCl_2$ (2.5 mol %), $(t\text{-BuO})_2$ (0.75 mmol), PhCl (1.0 mL), 115 °C, 3−4 h, under N_2; reported yields are the isolated yields.

Scheme 2. Tentative Reaction Mechanism



On the basis of our results and the literature, a tentative reaction pathway was proposed for the iron-catalyzed convergent radical cyclization (Scheme 2). Acyl radical **A** was generated by hydrogen abstraction of aldehyde **1**. The sequential radical addition of **A** to two C═C double bonds leads to the intermediate **C**. The coordination of the carbonyl to the Lewis acid (iron catalyst in this case) changes the FMOs of the carbonyl and a decrease of the HOMO energy, thus leading to a better interaction with the SOMO of the radical. Consequently, it is feasible for **C** to proceed via the 6-*endo-trig* addition to give the radical intermediate **F**.[15] Then **F** is irreversibly oxidized by iron catalyst to give the oxonium cation **G**.[16] Finally, deprotonation of **G** delivered the convergent radical cyclization product **3**.

In conclusion, we have demonstrated a novel iron-catalyzed convergent radical cyclization of an aldehyde with two alkenes. A variety of multifunctional 3,4-dihydropyran derivatives have been efficiently synthesized. In addition, potential intermediates have been designed to probe the possible reaction pathways with a radical process being the most reasonable one. This mechanistic information has broad synthetic implications, especially using 6-*endo-trig* cyclization for the construction of pyrans. Further studies on the mechanism, diastereoselectivity control, and applications of the convergent radical cyclization are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhipingli@ruc.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Studer, A.; Curran, D. P. *Nat. Chem.* **2014**, *6*, 765−773. (b) Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014**, *47*, 3459−3470. (c) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018−5022. (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.

(2) (a) Zhang, J.; Jiang, J.; Xu, D.; Luo, Q.; Wang, H.; Chen, J.; Li, H.; Wang, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1231−1235. (b) Cheng, J.-K.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 42−45. (c) Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klussmann, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8737−8740.

(3) For reviews, see: (a) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563−1574. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1−35. (c) Franke, R.; Selent, D.; Borner, A. *Chem. Rev.* **2012**, *112*, 5675−5732. (d) Brennfuhrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133.

(4) For selected recent examples, see: (a) Faulkner, A.; Scott, J. S.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 7224−7230. (b) Luo, J.-Y.; Hua, H.-L.; Chen, Z.-S.; Zhou, Z.-Z.; Yang, Y.-F.; Zhou, P.-X.; He, Y.-T.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2014**, *50*, 1564−1566. (c) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690−2694. (d) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2256−2259. (e) Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *Chem. - Eur. J.* **2011**, *17*, 4307−4312. (f) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592−596. (g) Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 10154−10157. (h) Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *J. Org. Chem.* **1994**, *59*, 850−853.

(5) (a) Fusano, A.; Sumino, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 2114−2117. (b) Miura, K.; Tojino, M.; Fujisawa, N.; Hosomi, A.; Ryu, I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2423−2425. (c) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187−1189.

(6) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662−12663.

(7) Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 1006−1008.

(8) (a) Xie, Y.; Guo, S.; Wu, L.; Xia, C.; Huang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 5900−5904. (b) Du, P.; Li, H.; Wang, Y.; Cheng, J.; Wan, X. *Org. Lett.* **2014**, *16*, 6350−6353. (c) Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658−2661. (d) Godineau, E.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2008**, *73*, 6983−6993. (e) Godineau, E.; Schäfer, C.; Landais, Y. *Org. Lett.* **2006**, *8*, 4871−4874. For a review, see: (f) Godineau, E.; Landais, Y. *Chem. - Eur. J.* **2009**, *15*, 3044−3055.

(9) For the radical cyclization involving two double bonds and one triple bond, see: Tsuchii, K.; Doi, M.; Hirao, T.; Ogawa, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3490−3493.

(10) For selected reviews, see: (a) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170−3387. (b) Jia, F.; Li, Z. *Org. Chem. Front.* **2014**, *1*, 194−214. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314. (d) Correa, A.; Garcia Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108−1117. (e) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254.

(11) (a) Clarke, P. A.; Ermanis, K. *Curr. Org. Chem.* **2013**, *17*, 2025−2037. (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059−3061. (c) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588.

(12) (a) Lv, L.; Lu, S.; Guo, Q.; Shen, B.; Li, Z. *J. Org. Chem.* **2015**, *80*, 698−704. (b) Lv, L.; Shen, B.; Li, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 4164−4167. (c) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756−10759.

(13) Nguyen, V.-H.; Nishino, H. *Tetrahedron Lett.* **2004**, *45*, 3373−3377.

(14) Naredla, R. R.; Klumpp, D. A. *Chem. Rev.* **2013**, *113*, 6905−6948.

(15) (a) Liu, D.; Tang, S.; Yi, H.; Liu, C.; Qi, X.; Lan, Y.; Lei, A. *Chem. - Eur. J.* **2014**, *20*, 15605−15610. (b) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981−19984. For a recent review, see: (c) Liu, D.; Liu, C.; Lei, A. *Chem. - Asian J.* **2015**, DOI: 10.1002/asia.201500326.

(16) (a) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 4884−4887. (b) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497−7500. (c) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949−1952.