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Free-Radical-Promoted Alkenylation of C(sp^3)-H Bond in Chloroalkane with Cinnamic Acid and *β*-Nitrostyrene

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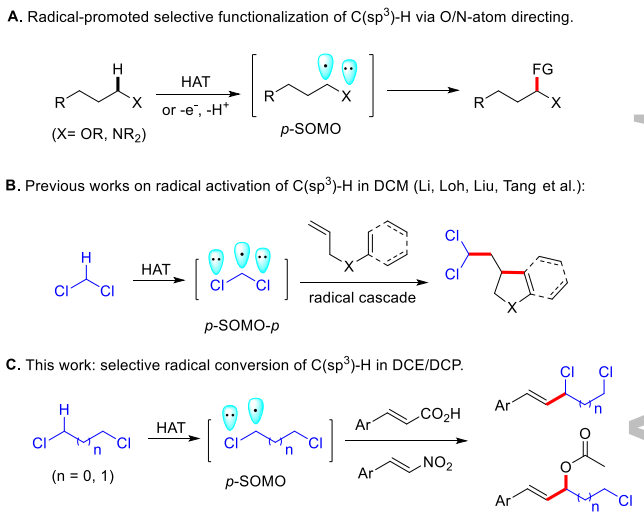
Abstract: We demonstrated herein a free-radical alkenylation of the C(sp^3)-H bond in 1,2-dichloroethane with cinnamic acid and *β*-nitrostyrene. This method not only provides a facile approach to chloroalkylated styrenes, but also would be instructive for halogen-atom directing selective functionalization of inert C(sp^3)-H bond.

Keywords: Free-radical; C-H activation; Decarboxylation; Haloalkane; Cinnamic acid

One of the most atom-economic and valuable transformations in synthetic organic chemistry is the free-radical promoted selective functionalization of C(sp^3)-H bond.[1] As depicted in Scheme 1**A**, considerable advances in site-selective conversion of the C-H bond in amine, ether and alcohol have been achieved in the past decades.[2] In these cases, it is believed that the unique selectivity is dominantly due to bond dissociation energy (BDE) of the C-H bond, polar effect and stability of the radical intermediate.[3] However, the heteroatom-directing effect seems only limited in *N* and *O* atoms. Although halogen-atom might play the similar role, selective activation of the C(sp^3)-H bond in general haloalkane has not been realized so far. Two major factors probably make it challenging. One is the relatively weaker BDE of the carbon-halogen bond than that of C-H bond. And the other is the three full *p*-orbitals (three lone-pairs) of halogen atom that would weaken the *p*-SOMO delocalization. Nevertheless, several examples of this conversion have been achieved in dichloromethane (DCM).[4] The homolytic cleavage of the C-H bond occurred prior to that of the C-Cl bond leading to a more stable Cl_2CH radical (formation enthalpy: ΔH^0_f = 22.3 ± 1.0 kcal/mol) than $ClCH_2$ radical (formation enthalpy: ΔH^0_f = 28.0 ± 0.7 kcal/mol).[5] It might be due to the *p*-SOMO-*p* delocalization in Cl_2CH radical (Scheme 1**B**). Of particular interests are free-radical initiated highly selective functionalization of C(sp^3)-H bond. We began to investigate this conversion with general haloalkanes. Herein we wish to report a free-radical alkenylation of 1,2-dichloroethane (DCE) and 1,3-dichloropropane via selective activation of the inert C(sp^3)-H bond (Scheme 1**C**). To the best of our knowledge, it is the first example of oxidative coupling of DCE with cinnamic acids and/or *β*-nitrostyrenes.[6]

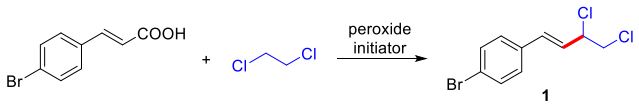


Scheme 1. Free-radical promoted selective functionalization of C(sp^3)-H bond via heteroatom directing.

Initially we chose (*E*)-3-(4-bromophenyl)acrylic acid and DCE as the model substrate to optimize the reaction conditions (Table 1). We started with a series of peroxides, and TBPA was found more effective

than others to afford the desired product **1** (entries 1-4). Then temperature was monitored (entries 5 and 6). An elevated temperature cound not give a better yield. Next an array of metal and or metal salts were screened (entries 7-14). As a result, low yields of the products were obtained with or not the initiators (entry 15). Subsequently, we examined the concentration of the reactants (entries 16-18). To our delight, the yield increased to 42% by using 5 mL of DCE as the solvent. Interestingly, decreasing the amounts of TBPA to 2 equivalents gave a better yield rather than 3 equivalents (entries 19-21). Furthermore, addition of a catalytic Cu_2O led to a similar result (entry 22). Finally, a mixed solvent cound not accelerate the reaction (entry 23). The decarboxylative methylation would occur in *t*-BuOH, which might undergo an addition and decarboxylation reaction of the methyl radical with cinnamic acid.[7] It's worth noting that only *E*-alkenes were observed in all cases.[8]

Table 1. Modification of the typical reaction conditions.[a]

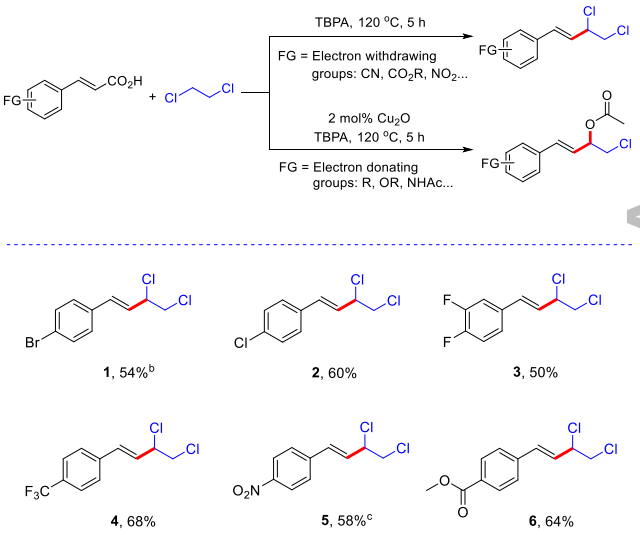


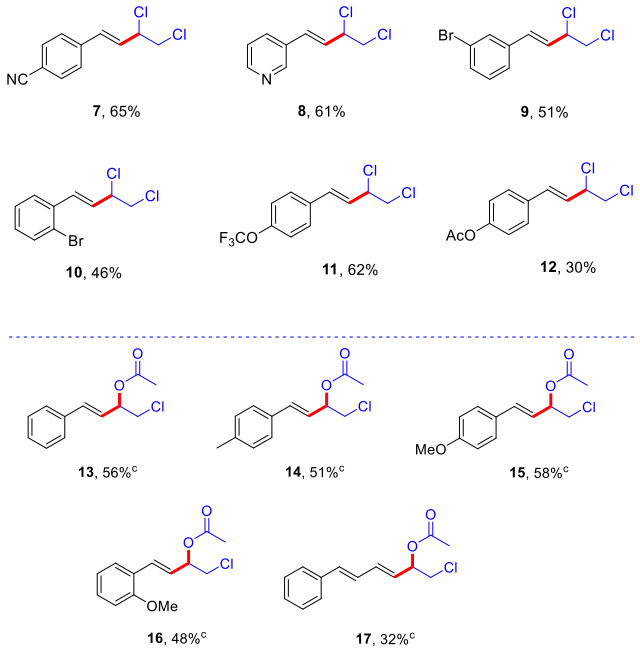
entry	peroxide (equiv.)	catalyst (mol%)	solvent (mL)	T (°C)	**1** %[b]
1	DTBP (3)	Cu_2O (5)	2	120	-
2	TBHP (3)	Cu_2O (5)	2	120	-
3	DCP (3)	Cu_2O (5)	2	120	-
4	TBPA (3)	Cu_2O (5)	2	120	30
5	TBPA (3)	Cu_2O (5)	2	130	18
6	TBPA (3)	Cu_2O (5)	2	110	21
7	TBPA (3)	Cu (5)	2	120	12
8	TBPA (3)	CuCl (5)	2	120	15
9	TBPA (3)	CuI (5)	2	120	16
10	TBPA (3)	CuF_2 (5)	2	120	13
11	TBPA (3)	$Cu(acac)_2$ (5)	2	120	15
12	TBPA (3)	$Cu(OAc)_2$ (5)	2	120	10
13	TBPA (3)	$FeCl_2$ (5)	2	120	-
14	TBPA (3)	$AgNO_3$ (5)	2	120	-
15	TBPA (3)	-	2	120	16
16	TBPA (3)	-	3	120	23
17	TBPA (3)	-	5	120	42
18	TBPA (3)	-	7	120	41
19	TBPA (2)	-	5	120	54
20	TBPA (1.5)	-	5	120	30
21	TBPA (1.75)	-	5	120	38
22	TBPA (2)	Cu_2O (2)	5	120	53
23[c]	TBPA (2)	-	5	120	35

[a] Conditions: cinnamic acid (1 equiv., 0.2 mmol), DCE (as solvent), heat (measured temperature of oil bath), sealed tube, 5 h., unless otherwise noted. [b] Isolated yield. [c] Solvent (4 mL of DCE and 1 mL of *t*-BuOH). DTBP= Di-*tert*-butyl peroxide; TBHP= *tert*-Butyl hydroperoxide; DCP= Dicumyl peroxide; TBPA= *tert*-Butyl peroxyacetate.

With the information in hand, we then evaluated the substrate scope (Table 2). It was found that various cinnamic acids yielded the corresponding products smoothly. A series of (*E*)-(3,4-dichlorobut-1-en-1-yl)benzenes were isolated as the major products with electron-deficient aryl substituted cinnamic acids (**1**-**12**). Gratifyingly, (*E*)-3-(pyridin-3-yl)acrylic acid afforded the expected product in 61% yield (**8**). In addition, cinnamic acids containing the aromatic cores with substituents in different positions affected the yield slightly (**9** and **10**). (*E*)-3-(4-(trifluoromethoxy)phenyl)acrylic acid gave a 62% yield of the product while (*E*)-3-(4-acetoxyphenyl)acrylic acid only afforded a yield of 30% (**11** and **12**). It indicated that the electron density of the aromatic core in cinnamic acids might play a critical role in this reaction. In order to investigate the electronic effect, a set of cinnamic acids with electron-rich arenes were examined (**13**-**17**). To our surprise, a series of (*E*)-1-chloro-4-arylbut-3-en-2-yl acetates (**13**-**16**) were isolated as the major products with these type of cinnamic acids. Furthermore, (2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid also yielded the corresponding product **17**. In these cases, a catalytic amount of Cu_2O (2 mol%) could improve the yields. Low conversion of the starting materials were often found in the cases of **10**, **12** and **17**, which resulted in relatively low yields of the corresponding products. Finally, we had also evaluated bromo and iodo and even fluoroalkanes. But all failed. The former two kinds of haloalkanes gave a mass involving dehalogenative products. And only low yield of decarboxylative methylation products was isolated with fluoroalkanes.

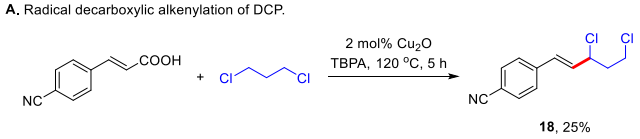
Table 2. Decarboxylative coupling of cinnamic acids with DCE.[a]

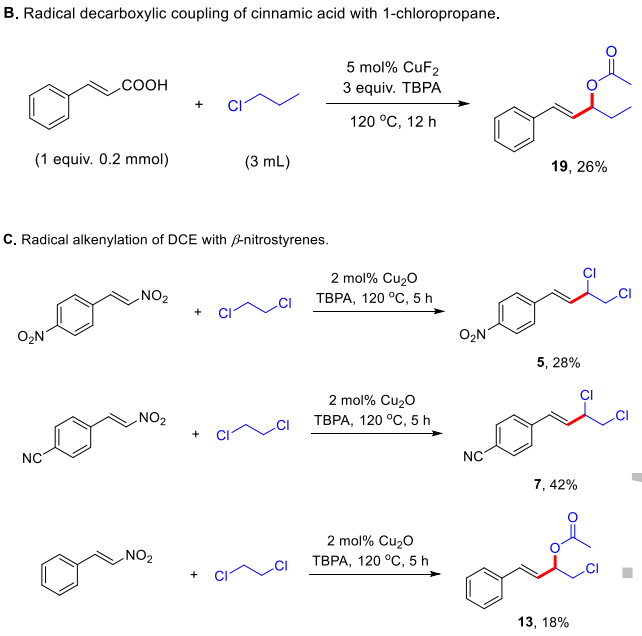




[a] Conditions: cinnamic acid (1 equiv., 0.2 mmol), DCE (5 mL), TBPA (2 equiv., 0.4 mmol), 120 °C (measured temperature of oil bath), sealed tube, 5 h., unless otherwise noted. [b] Isolated yield. [c] Cu_2O (2 mol%, 0.004 mmol).

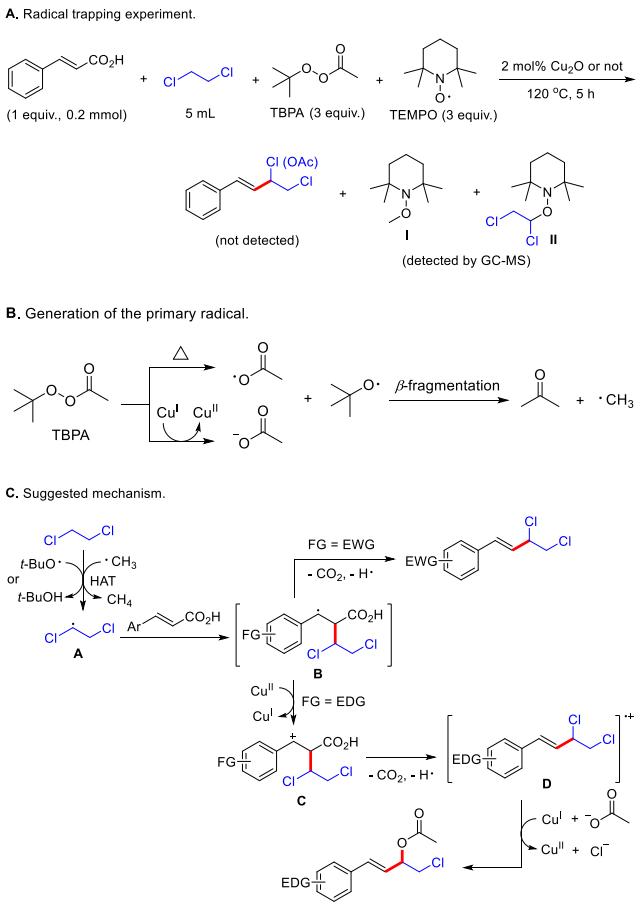
Next, we also examined other chloroalkanes and coupling partners (Scheme 2). As depicted in Scheme 2**A**, reaction of (*E*)-3-(4-cyanophenyl)acrylic acid with 1,3-dichloropropane afforded the expected product **18** in 25% yield. The relatively low yield might be due to the solvent effect, which affected the efficiency of reaction critically. It's noteworthy that 26% yield of (*E*)-1-phenylpent-1-en-3-yl acetate **19** can be isolated from a relatively complex system given by radical coupling reaction of cinnamic acid with 1-chloropropane (Scheme 2**B**). Although the yield is relatively low, this example suggested that highly site-specific functionalization of the C(sp^3)-H bond in more general haloalkanes could be realized in the future. Additionally, *β*-nitrostyrenes also could be utilized as the effective coupling partners in this system (Scheme 2**C**). Furthermore, we had carefully studied the effect of copper salts in both electron-rich and electron-poor aryl-substituted cinnamic acids. And we found that the copper salts affected the electron-defficient acids little. But the electron-rich acids and *β*-nitrostyrene substrates would give a more complex system without the copper salts. And we proposed that the copper salts might accelerate the single-electron oxidation of the radical adduct and therefore a nuclophilic substitution occurred with electron-rich substrates.





Scheme 2. Free-radical promoted selective functionalization of C(sp^3)-H bond in chloroalkanes.

Finally, mechanistic studies were carried out to get insight into the details of this process (Scheme 3). As demonstrated in Scheme 3**A**, a radical trapping experiment showed that no desired product was observed by loading a radical scavenger TEMPO. Furthermore, radical adducts **I** and **II** were detected by GC-MS, which indicated that the methyl radical as well as the 1,2-dichloroethyl radical might be the active intermediates in this process. Based upon the previous literatures[9] and the above results, we proposed a possible mechanism for this reaction (Scheme 3**B** and 3**C**). Thermal homolysis of TBPA would generate acetic and *tert*-butoxy radicals. Alternatively, single-electron reduction of TBPA by Cu(I) would afford acetic anion and *t*-BuO radical. Then *β*-fragmentation of *tert*-butoxy radical gave acetone and methyl radical. Hydrogen-atom-transfer (HAT) from chloroalkane to *tert*-butoxy or methyl radical occurred to form radical A, which then added to the carbon-carbon double bond leading to radical **B**. Subsequently, decarboxylation followed by HAT of **B** would yield (*E*)-(3,4-dichlorobut-1-en-1-yl)arene if the substituents on the arene are electron-withdrawing groups. While the substituents are electron-donating groups, one electron oxidation of **B** by Cu(II) leading to a benzyl cation **C** would be faster than decarboxylation. And then a radical cation **D** would be formed by decarboxylation and HAT of **C**. Allyl nucleophilic substitution followed by single electron reduction would yield the final product.



Scheme 3. Mechanistic studies.

In summary, a free-radical alkenylation of the C(sp^3)-H bond in DCE with cinnamic acids and/or *β*-nitrostyrenes was developed. It allows a convenient access to a variety of chloroalkylated styrenes, which are valuable building blocks by diverse late-stage transformations. Besides, the results of 1-chloropropane and 1,3-dichloropropane indicated that site-specific HAT of the C(sp^3)-H bond in haloalkane via halogen-atom direction would be possible. Continuous investigations in this field are ongoing in this lab.

Experimental Section

General procedure: A mixture of cinnamic acids (1 equiv., 0.2 mmol) and TBPA (2 equiv., 0.4 mmol) was heated in DCE (5 mL) under reflux at 120 °C (measured temperature of oil bath) for about 5 h in a sealed tube. After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography to afford the desired product.

Acknowledgements

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References

[1] For selected recent reviews on C(sp^3)−H functionalization, see: a) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; b) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.* **2011**, *50*, 3362; c) J. L. Roizen, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; d) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.* **2013**, *52*, 11726; e) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.* **2014**, *53*, 74; f) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754; g) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.* **2017**, *117*, 9016. For selected recent reviews on general C-H functionalization, see: h) J. Le Bras and J. Muzart, *Chem. Rev.* **2011**, *111*, 1170; i) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; j) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; k) X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.* **2013**, *42*, 3253; l) L. Yang and H. Huang, *Chem. Rev.* 2015, **115**, 3468; m) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.* **2015**, *115*, 1622; n) R. Narayan, K. Matcha, A. P. Antonchick, *Chem. Eur. J.* **2015**, *21*, 14678; o) Q.-Z. Zheng and N. Jiao, *Chem. Soc. Rev.* **2016**, *45*, 4590; p) K. Murakami, S. Yamada, T. Kaneda and K. Itami, *Chem. Rev.* **2017**, *117*, 9302; q) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754; r) D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925; s) H. Sterckx, B. Morel, B. U. W. Maes, *Angew. Chem. Int. Ed.* **2019**, *58*, 7946.

[2] For selected reviews, see: a) S. Zhang, F. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937-1949; b) X. Shang, Z.-Q. Liu, *Acta. Chim. Sin.* **2015**, *73*, 1275-1282; c) M. K. Lakshman, P. K. Vuram, *Chem. Sci.* **2017**, *8*, 5845; d) S.-R. Guo, P. S. Kumar, M. Yang, *Adv. Synth. Catal.* **2017**, *359*, 2-25.

[3] a) Tedder, J. M. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401; b) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553; c) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969; d) X.-S. Xue, P. Ji, B. Zhou, J.-P. Cheng, *Chem. Rev.* **2017**, *117*, 8622; e) D. Šakić, H. Zipse, *Adv. Synth. Catal.* **2016**, *358*, 3983.

[4] a) Y. Tian, Z.-Q. Liu, *RSC Adv.* **2014**, *4*, 64855; b) M.-Z. Lu, T.-P. Loh, *Org. Lett.* **2014**, *16*, 4698; c) Y. Liu, J.-L. Zhang, R.-J. Song, J.-H. Li, *Org. Chem. Front.* **2014**, *1*, 1289; d) Y. Liu, J.-L. Zhang, R.-J. Song, J.-H. Li, *Eur. J. Org. Chem.* **2014**, 1177; e) X. Li, J. Xu, Y. Gao, H Fang, G. Tang, Y. Zhao, *J. Org. Chem.* **2015**, *80*, 2621; f) Y. Liu, R.-J. Song, S. Luo, J.-H. Li, *Org. Lett.* **2018**, *20*, 212.

[5] Y.-R. Luo, Handbook of Bond Dissociation Energies in Organic Compounds, CRC Press, Boca Raton, 2002.

[6] For a review on decarboxylation of C-H with cinnamic acid, see: a) A. J. Borah, G. Yan, *Org. Biomol. Chem.* **2015**, *13*, 8094; For selected examples of alkenylation of C-H with cinnamic acid and *β*-nitrostyrene, see: b) Z. Cui, X. Shang, X.-F. Shao, Z.-Q. Liu, *Chem. Sci.* **2012**, *3*, 2853-2858; c) Y.-J, Jang, Y.-K. Shih, J.-Y. Liu,

W.-Y. Kuo, C.-F. Yao, *Chem. Eur. J.* **2003**, *9*, 2123; d) J.-F. Xue, S.-F. Zhou, Y.-Y. Liu, X. Pan, J.-P. Zou, O. T. Asekun, *Org. Biomol. Chem.* **2015**, *13*, 4896; For a recent example of C-C bond formation with DCE, see: e) Z. Wang, J. Yin, F. Zhou, Y. Liu, J. You, *Angew. Chem., Int. Ed.* **2019**, *58*, 254; f) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486.

[7] Z. Xu, C. Yan, Z.-Q. Liu *Org. Lett.* **2014**, *16*, 5670.

[8] For a discussion of the *E*/*Z* selectivity, see: L. Zhang, Z. Hang, Z.-Q. Liu *Angew. Chem. Int. Ed.* **2016**, *55*, 236-239.

[9] For reviews on decarboxylative C-C/C-X bond formation, see: a) L. J. Gooßen, N. Rodríguez and K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120; b) N. Rodríguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030-5048; c) R. Shang, L. Liu, *Sci. China Chem.* **2011**, *54*, 1670-1687; d) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671-2678; e) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Andy Hor, X. Liu, *Chem. Soc. Rev.* **2015**, *44*, 291-314; f) J. Xuan, Z.-G. Zhang, W.-J. Xiao, *Angew. Chem. Int. Ed.*, **2015**, *54*, 15632-15641; g) Y. Wei, P. Hu, M. Zhang, W. Su, *Chem. Rev.* **2017**, *117*, 8864-8907.

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