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Iron-Catalyzed Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone

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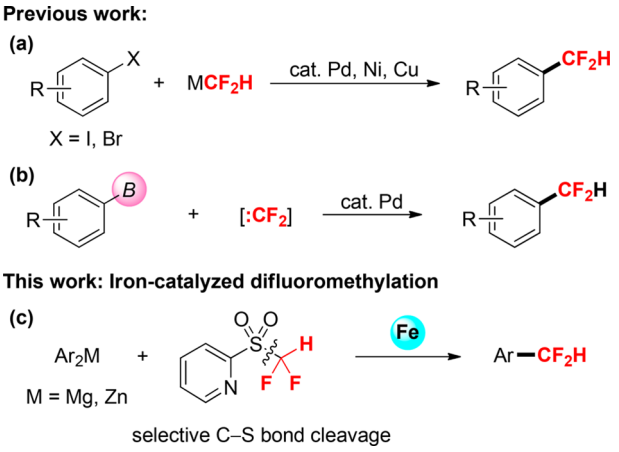
Supporting Information

ABSTRACT: We report the first iron-catalyzed difluoromethylation of arylzincs with difluoromethyl 2-pyridyl sulfone via selective C−S bond cleavage. This method employs the readily available, bench-stable fluoroalkyl sulfone reagent and inexpensive iron catalyst, allowing facile access to structurally diverse difluoromethylated arenes at low temperatures. The experiment employing a radical clock indicates the involvement of radical species in this iron-catalyzed difluoromethylation process.

There has been an increasing awareness of the use of fluorine atom(s) to alter the biological properties of organic molecules. The fluorinated molecules often possess superior lipophilicity, bioavailability, and metabolic stability (compared to their nonfluorinated counterparts) and therefore have great potentials in the areas of pharmaceuticals, agrochemicals, and life sciences.[1] As a result of the extensive presence of hydrogen bonding in biological systems and their indispensable role in achieving various physiological functions, the use of the difluoromethyl group (CF_2H) as a structural mimic to the hydroxyl group in bioactive molecules attracts considerable attentions.[2,3]

However, conventional methods for direct introduction of a difluoromethyl group onto arenes are limited[4] and often suffer from harsh reaction conditions, and poor functional group compatibility.[5] Several radical strategies have been developed to incorporate CF_2H group, such as radical difluoromethylation of heteroarenes,[6] difluorination of benzylic C−H bonds[7] and decarboxylative fluorination of α-fluoroarylacetic acids.[8] Recently, transition-metal-mediated difluoromethylation reactions have been demonstrated as a viable approach for direct difluoromethylation.[4,9,10] Most of the reported reaction modes feature a cross-coupling between aryl halides with difluoromethyl trimethylsilane (Me_3SiCF_2H),[9a,c−e] tributyl(difluoromethyl)stannane[9b] or various difluoromethyl metal reagents (L_nMCF_2H, M = Zn and Ag) (Scheme 1a).[10a,d−f] Furthermore, the palladium-catalyzed reaction between arylborons and difluorocarbene sources has proved to be a useful complementary approach (Scheme 1b).[10b,c,g] In contrast, the reaction of arylmetal reagents (ArM) and XCF_2H (X = heteroatom) via direct CF_2H transfer has been scarcely explored,[10h,i] probably as a result of the low boiling point and limited accessibility of XCF_2H (X = I, Br, Cl).[11] Furthermore, XCF_2H (X = I, Br, Cl) are known to be readily deprotonated and produce difluorocarbene species, which add additional uncertainty to the desired reaction pathway.[10g,12] Herein, we report a new strategy for the aromatic difluoromethylation through the cross-coupling between difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H) and arylzinc reagents via C−S bond cleavage (Scheme 1c).

Scheme 1. Transition-Metal Catalyzed Reactions To Access Difluoromethyl Arenes



The cross-couplings via the activation of C−S bond are challenging as a result of the inertness of the C−S bond to engage in the oxidation addition by transition metals.[13] In addition, the regioselectivitive cleavage of C−S bonds of unsymmetrical sulfones is challenging. Recently, progresses have been made in the field of transition-metal (palladium, nickel, cobalt, or iron)-catalyzed C−C bond formation via C−S bond cleavage.[14] We have developed a bench-stable, readily available and cost-effective reagent, difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H, **1**), and established that **1** can accomplish *gem*-difluoroolefination[15] and formal nucleophilic halodifluoromethylation of carbonyl compounds,[16a,b] as well as can serve as difluoroalkanesulfinate precursor.[16c,d] Inspired by recent success by using difluoromethyl heterocyclic sulfones as a precursor to generate difluoromethyl radical through C−S bond cleavage,[17] we attempted the cross-coupling between 2-PySO_2CF_2H and arylmetal reagents catalyzed by the inexpensive and environmentally benign iron catalyst.[18] Although iron-catalyzed $C(sp^2)-C(sp^3)$ cross coupling using aryl Grignard reagents or arylzinc reagents with alkyl electrophiles

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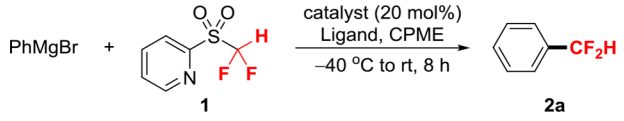
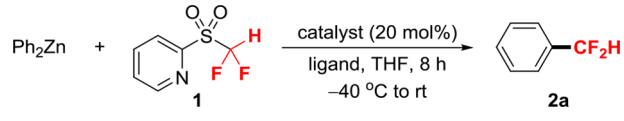
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand (equiv)	**2a**, yield (%)[b]
1[c]	$Fe(acac)_3$	TMEDA (8.0)	trace
2[c]	–	TMEDA (8.0)	0
3	$Fe(acac)_3$	TMEDA (2.0)	25
4[d]	$Fe(acac)_3$	TMEDA (2.0)	16
5[e]	$Fe(acac)_3$	TMEDA (2.0)	trace
6	$FeBr_3$	TMEDA (2.0)	0
7	$FeCl_3$	TMEDA (2.0)	0
8	$FeBr_2$	TMEDA (2.0)	21
9	$Fe(acac)_3$	TMBDA (2.0)	19
10[f]	$Fe(acac)_3$	TMBDA (0.4)	44

[a]Reaction conditions: **1** (0.3 mmol), PhMgBr (0.45 mmol), catalyst (20 mol %), CPME (cyclopentyl methyl ether) (2.0 mL), −40 °C to rt, 8 h. [b]Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [c]rt. [d]−40 °C. [e]0 °C to rt. [f]Anisole (2.0 mL) was used as solvent.

Table 2. Screening of the Reaction Conditions[a]



entry	catalyst	ligand (equiv)	**2a**, yield (%)[b]
1	$Fe(acac)_3$	TMEDA (1.5)	61
2	$Fe(acac)_3$	TMEDA (0)	0
3	$Fe(acac)_3$	TMEDA (0.4)	21
4	$Fe(acac)_3$	TMEDA (1.0)	48
5	$Fe(acac)_3$	TMEDA (2.0)	94
6[c]	$Fe(acac)_3$	TMEDA (2.0)	95

[a]Reaction conditions: **1** (0.3 mmol), Ph_2Zn (0.45 mmol), catalyst (20 mol %), THF (2.0 mL), −40 °C to rt, 8 h. [b]Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [c]2 h.

has been known,[13,19] to the best of our knowledge, the iron-catalyzed aromatic difluoromethylation has never been previously reported.

Our study began with the iron-catalyzed difluoromethylation using phenylmagnesium bromide as a model substrate, and the results are shown in Table 1. It was quickly identified that the use of $Fe(acac)_3$ as the catalyst and *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA) as the ligand allowed the difluoromethylation of phenylmagnesium bromide (Table 1, entry 1). The control experiment established that the iron catalyst is required to achieve the desired difluoromethylarene **2a** (entry 2). Higher yields were obtained by slow addition of phenylmagenesium bromide to a solution of 2-$PySO_2CF_2H$ and $Fe(acac)_3$ at −40 °C (entry 3). The effect of the reaction temperature was also briefly investigated (entries 3−5). Other iron salts and diamine-based ligands are less efficient for the current transformation (entries 6−9). Although the use of anisole as the solvent and the addition of substoichiometric amounts of *N,N,N′,N′*-tetramethylbutane-1,4-diamine (TMBDA) improved the yield to 44% (entry 10), attempts to further increase the yield were unsuccessful (for details, see Supporting Information (SI)). As a result of the highly reactive nature of Grignard reagents, a consumption of 2-$PySO_2CF_2H$ was observed even in absence of iron catalyst with the attack of Grignard reagents to 2-$PySO_2CF_2H$, which explains the low efficiency of the overall process. We then turned our attention to the milder arylzinc reagents to diminish the undesired reaction pathways.

It turned out that the use of diphenyl zinc (Ph_2Zn) in the current $Fe(acac)_3$-catalyzed difluoromethylation gave much better results (Table 2). Varying the amounts of TMEDA proved to have a remarkable influence on the reaction efficiency, as indicated in entries 1−6. TMEDA has proved to be an effective ligand in the iron-catalyzed cross-coupling reactions, and the requirement of excess amount of TMEDA (2.0 equiv) is likely owing to the coordination of TMEDA to iron species and Zn reagents.[19a,20] The reaction time can be shortened to 2 h (entry 6), without substantially decreasing product formation. It is noteworthy that other difluoromethyl heterocyclic sulfone reagents that we examined provided inferior yields under the same reaction conditions (see SI). Under our optimized conditions, the desired difluormethylated product **2a** was obtained in 95% yield with 20 mol % $Fe(acac)_3$ and 2.0 equiv TMEDA.

To demonstrate the substrate scope of this iron-catalyzed difluoromethyaltion protocol, a range of arylzincs were coupled with 2-$PySO_2CF_2H$ under the optimal conditions (Table 3). Arylzincs with ortho-substituent gave inferior yields (**2d** and **2e**), whereas reactions with *meta*- and *para*-substituted arylzincs gave excellent yields (**2b** and **2c**, **2f**−**2i**). We found that electron-neutral (**2e**−**2h**), -rich (**2j**-**2n**), and -poor (**2n**−**2s**) arylzinc reagents were all viable in the current iron-catalyzed difluoromethylation. 1,3-Propanediol acetal-bearing substrate was also successfully difluoromethylated to give product **2t** in moderate yield. Furthermore, aryzinc reagent bearing C═C double bond (**2u**) are also amenable to this reaction. The cross-coupling reaction proceeds smoothly with substrates bearing a range of heterocyclic motifs, such as pyridine (**2v**−**2x**), morpholine (**2x**), benzofuran (**2y**), thiophene (**2z**), carbazole (**2aa**), and indole (**2ab**). This method can also be used for difluoromethylation of L-menthol derivative (**2ac**). It is notable that this iron-catalyzed difluoromethylation reaction performs efficiently in gram-scale experiments. We have conducted the iron-catalyzed difluoromethylation on an 8.0 mmol scale without obvious decrease of product yield, affording the corresponding difluoromethylated product in good yields (**2m**, **2n**, **2v**). This additional advantage makes the present method more attractive for large-scale preparation of difluoromethylated arenes.

To gain more mechanistic insights into the current iron-catalyzed difluoromethylation reaction, the radical inhibiting experiments were performed. It was found that the reaction is completely suppressed by the addition of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and 1,4-benzoquinone (BQ), and the addition of 1,4-dinitrobenzene, a single electron transfer (SET) inhibitor, led to the substantial inhibition (Scheme 2a), which suggests that the involvement of a SET process and radical intermediates is likely during the reaction. The radical clock experiment employing **1b** as a substrate produced cyclized product **3b** in 47% yield (Scheme 2b). The reaction of Ph_2Zn with 2-$PySO_2CF_2D$ generated the deuterated (difluoromethyl)-benzene **2a′**, without deuterium scrambling (Scheme 2c). This result suggests that an alternative mechanism involves deprotonation and elimination of sulfinate (a difluorocarbene pathway) is unlikely. Taken together, these results suggest that carbon-centered radicals are generated by a SET pathway.

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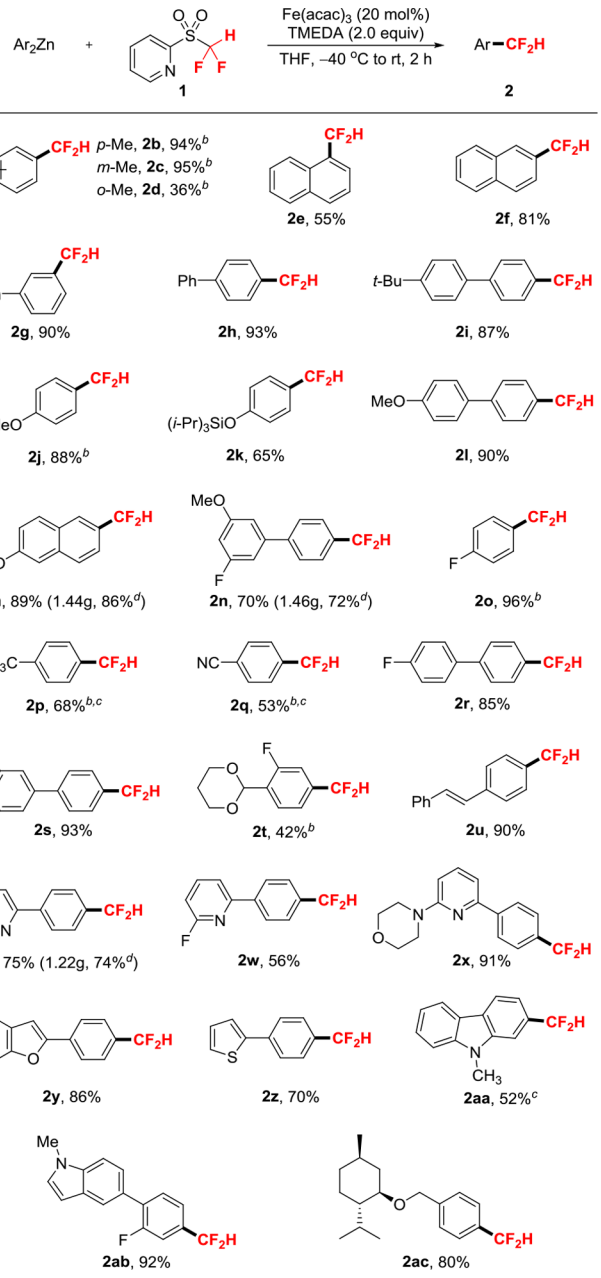
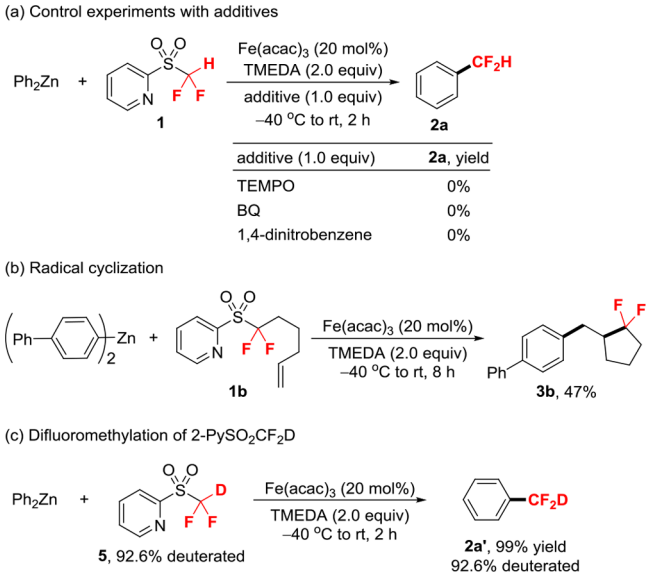
Table 3. Scope of Iron-Catalyzed Cross-Coupling of Arylzinc Reagents with 2-$PySO_2CF_2H$[a,b]



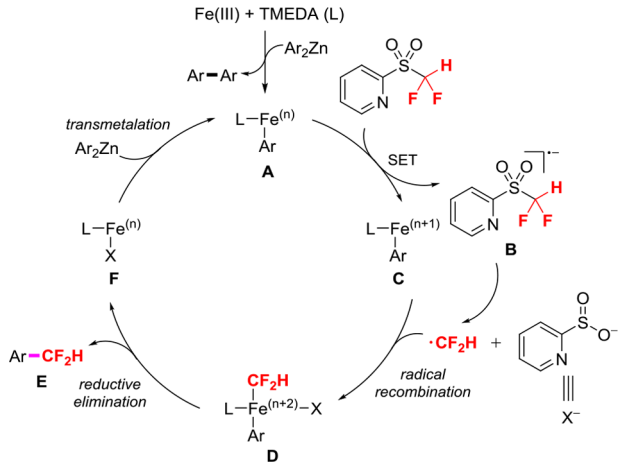
[a]Reaction condition: **1** (0.8 mmol), Ar_2Zn (1.2 mmol, 1.5 equiv), $Fe(acac)_3$ (20 mol %), THF, −40 °C to rt, 2 h, isolated yield. [b]Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [c]Ar_2Zn (1.6 mmol, 2.0 equiv). [d]8.0 mmol scale; isolated yields are shown in parentheses.

Although the exact mechanism of the reaction remains elusive, on the basis of previous investigation[18,19b,21] and the above observations, an outline of a possible mechanism for iron-catalyzed difluoromethylation of arylzinc reagents with 2-$PySO_2CF_2H$ is illustrated in Scheme 3. The catalytic cycle commences with the formation of a reduced iron species **A**, which is generated from the reduction of the $Fe(acac)_3$ precatalyst with an arylzinc reagent in the presence of TMEDA. Electron transfer between the catalytically active iron species **A** and 2-$PySO_2CF_2H$ affords the radical anion **B**, the fragmentation of which produces a difluoromethyl radical that

Scheme 2. Mechanistic Investigations



Scheme 3. Proposed Mechanism



undergoes recombination with iron complex **C** to produce the intermediate **D**. The subsequent reductive elimination delivers the desired product **E** and rendered the low-valent iron species **F**. The catalytically active iron species **A** is then regenerated through the transmetalation between **F** and Ar_2Zn to close the catalytic cycle.

In summary, we have developed the first iron-catalyzed difluoromethylation of arylzincs with 2-$PySO_2CF_2H$. This new approach employs bench-stable and readily available fluoroalkylation reagent that allows the difluoromethylation to proceed under mild reaction conditions with the cost-effective iron catalyst. The current method is complementary to the well-established difluoromethylation of aryl halides and represents a valuable addition to the synthetic toolbox for organofluorine chemistry. Our study not only provides a new aromatic difluoromethylation protocol but also gives new insights into the new reactivity of fluoroalkyl sulfones under transition metal catalysis. Further study in this direction is underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b11976.

Experimental procedures and characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (e) Liu, Q.; Ni, C.; Hu, J. *Natl. Sci. Rev.* **2017**, *4*, 303.

(2) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. (b) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 9325 , and references therein.

(3) (a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (b) Gouverneur, V.; Müller, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: From biophysical aspects to clinical applications*; Imperial College Press: London, 2012.

(4) For recent reviews, see: (a) Chen, B.; Vicic, D. *Top. Organomet. Chem.* **2014**, *52*, 113−142. (b) Ni, C.; Zhu, L.; Hu, J. *Huaxue Xuebao* **2015**, *73*, 90. (c) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2015**, *21*, 12836. (d) Lu, Y.; Liu, C.; Chen, Q.-Y. *Curr. Org. Chem.* **2015**, *19*, 1638. (e) Xu, P.; Guo, S.; Wang, L.; Tang, P. *Synlett* **2014**, *26*, 36. (f) Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017**, *6*, 139. (g) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. - Eur. J.* **2017**, *23*, 14676.

(5) (a) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, *1973*, 787. (b) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(6) (a) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

(7) (a) Xu, P.; Guo, S.; Wang, L.; Tang, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5955. (b) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494.

(8) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 2648.

(9) (a) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (b) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (c) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014**, *1*, 774. (d) Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984. (e) Bour, J. R.; Kariofillis, S. K.; Sanford, M. S. *Organometallics* **2017**, *36*, 1220.

(10) (a) Gu, Y.; Leng, X.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405. (b) Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44. (c) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. *Org. Lett.* **2016**, *18*, 4384. (d) Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536. (e) Serizawa, H.; Ishii, K.; Aikawa, K.; Mikami, K. *Org. Lett.* **2016**, *18*, 3686. (f) Aikawa, K.; Serizawa, H.; Ishii, K.; Mikami, K. *Org. Lett.* **2016**, *18*, 3690. (g) Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918. (h) Sheng, J.; Ni, H.-Q.; Bian, K.-J.; Li, Y.; Wang, Y.-N.; Wang, X.-S. *Org. Chem. Front.* **2018**, DOI: 10.1039/C7QO00934H. (i) Fu, X.-P.; Xiao, Y.-L.; Zhang, X. *Chin. J. Chem.* **2018**, *36*, 143.

(11) Cao, P.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 737.

(12) (a) Guiadeen, D.; Kothandaraman, S.; Yang, L.; Mills, S. G.; MacCoss, M. *Tetrahedron Lett.* **2008**, *49*, 6368. (b) Ni, F.; Li, J. *Synthesis* **2012**, *44*, 3598. (c) Ruhl, T.; Rafique, W.; Lien, V. T.; Riss, P. J. *Chem. Commun.* **2014**, *50*, 6056.

(13) Denmark, S. E.; Cresswell, A. J. *J. Org. Chem.* **2013**, *78*, 12593.

(14) (a) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674. (b) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (c) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 5042. (d) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, *4*, 280.

(15) (a) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444. (b) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J. *Chem. - Eur. J.* **2014**, *20*, 7803. (c) Gao, B.; Zhao, Y.; Hu, J.; Hu, J. *Org. Chem. Front.* **2015**, *2*, 163.

(16) (a) Zhao, Y.; Gao, B.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 5790. (b) Miao, W.; Ni, C.; Zhao, Y.; Hu, J. *Org. Lett.* **2016**, *18*, 2766. (c) Zhao, Y.; Zhang, L.; Xu, G.; Zheng, J.; Hu, J. *Sci. China Chem.* **2011**, *41*, 1833. (d) Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2559.

(17) (a) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743. (b) Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X.-Q.; Song, M.-P. *Chem. Commun.* **2016**, *52*, 13413. (c) Rong, J.; Ni, C.; Wang, Y.; Kuang, C.; Gu, Y.; Hu, J. *Huaxue Xuebao* **2017**, *75*, 105.

(18) For selected reviews: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (c) Bolm, C. *Nat. Chem.* **2009**, *1*, 420. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (e) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170. (f) Bedford, R. B. *Acc. Chem. Res.* **2015**, *48*, 1485. (g) Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *ACS Catal.* **2016**, *6*, 1640. (h) Guérinot, A.; Cossy, J. *Top. Curr. Chem.* **2016**, *374*, 49−74. (i) Fürstner, A. *ACS Cent. Sci.* **2016**, *2*, 778.

(19) For selected examples: (a) Lin, X.; Zheng, F.; Qing, F.-L. *Organometallics* **2012**, *31*, 1578. (b) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132.

(20) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794. (c) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364. (d) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (e) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078. (f) Ito, S.; Fujiwara, Y.-i.; Nakamura, E.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4306. (g) Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496.

(21) (a) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078. (b) Adams, C. J.; Bedford, R. B.; Carter, E.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Huwe, M.; Cartes, M. Á.; Mansell, S. M.; Mendoza, C.; Murphy, D. M.; Neeve, E. C.; Nunn, J. *J. Am. Chem. Soc.* **2012**, *134*, 10333.