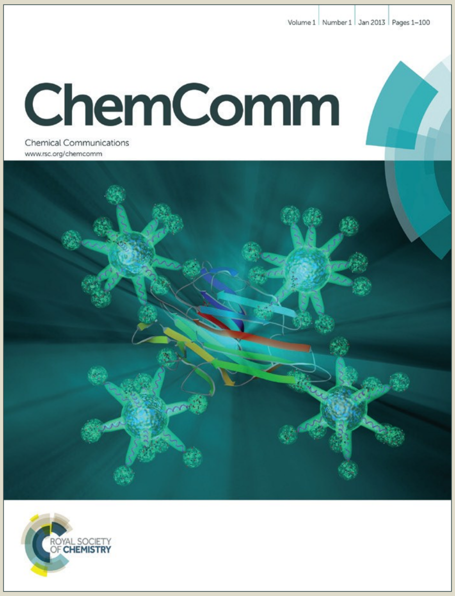
ChemComm

Accepted Manuscript



Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ChemComm

Chemical Communications

www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

ChemComm

COMMUNICATION

Iron-catalyzed synthesis of arylsulfinates through radical coupling reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

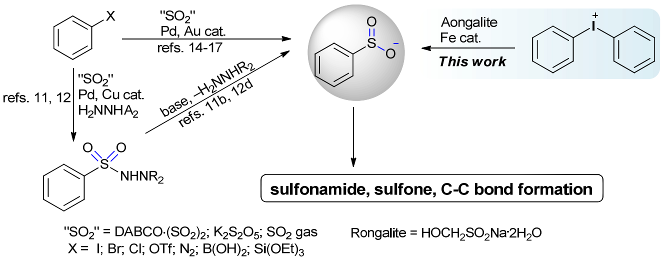
Weixi Zhang, and Meiming Luo*

A novel strategy for installation of sulfonyl fragment into arenes has been accomplished via an iron-catalyzed radical coupling reaction. Arene radicals derived from diaryliodoniums via single electron transfer reaction combine with sulfoxylate anion radical readily generated from commercially available rongalite ($HOCH_2SO_2Na\cdot 2H_2O$) to afford arylsulfinates efficiently at room temperature. In this protocol, a broad range of functional groups are tolerated to give products in good yields.

The importance of the sulfonyl unit ($-SO_2-$) in chemistry cannot be overstated. The compounds containing this moiety such as sulfonamides[1] and sulfones[2] display a broad range of biological activities. Pharmaceutically important examples are often found in therapeutic agents.[3] As such, much attention has been paid for the installation of sulfonyl fragment into organic molecule framework.

In general, two major types of traditional procedures are presented in this field. One of the processes includes the oxidation of sulfides to form corresponding sulfones.[4] This approach often suffers from the preparation of required sulfides, which involves the use of repulsive-smelling thiols.[5] An alternative route focuses on the reactions of sulfonic or sulfinic acid derivatives to afford desired sulfones or sulfonamides through the formation of C–S bond,[6] N–S bond[7] or C–N bond.[8] The difficulties encountered in these methods, however, originate in the preparation of sulfonic or sulfinic acid intermediates,[9] in particular due to the inherent reactivity and regioselectivity biases of electrophilic aromatic substitution. [10]

In response to these limitations, a pioneering work by Willis and co-workers opened a new avenue in this area (Scheme 1). In their work, sulfonyl unit was introduced to arenes through palladium-catalyzed aminosulfonylation of aryl iodides with $DABCO\cdot(SO_2)_2$ and hydrazines to afford *N*-amino-arylsulfonamides.[11] Similar transformations with different substrates to incorporate the sulfonyl moiety were also described by others.[12] If other sulfonyl derivatives are potential targets, however, this approach is always followed by a base-promoted expulsion of expensive hydrazines from *N*-amino-arylsulfonamides to afford arylsulfinates, which can serve as versatile synthetic intermediates for all other sulfonyl derivatives,[11b,12d] and structures arising from C–C bond formation.[13] Hence, a direct catalytic synthesis of arylsulfinates is more facile and desirable approach to incorporate sulfonyl unit into arenes.

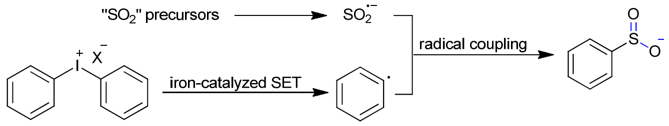


Scheme 1. Catalytic synthesis of arylsulfinates.

Only a few catalyzed sulfinations of arenes have been exploited to date (Scheme 1). The existing protocols involve the palladium-catalyzed reactions of aryldiazonium with H_2 and SO_2 gas under high pressure,[14] aryl halides with $DABCO\cdot(SO_2)_2$ or $K_2S_2O_5$ in the presence of phosphine ligands.[15,16] Besides, arylsulfinates could be prepared through the reaction of arylboronic acids with $DABCO\cdot(SO_2)_2$ or $K_2S_2O_5$ using palladium or gold catalyst.[17] While significant progress has been made, these documented examples in which sulphur dioxide undergoes the required insertions into metal-carbon bonds can only be accomplished in the presence of palladium or gold catalysts. Generally, the requirements of ligands or difficult-to-handle phosphine ones and excess additives were found to be inevitable. From the sustainability perspective, a novel catalytic sulfination with more environmental friendly conditions has remained an elusive goal.

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China;
E-mail: luomm@scu.edu.cn

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

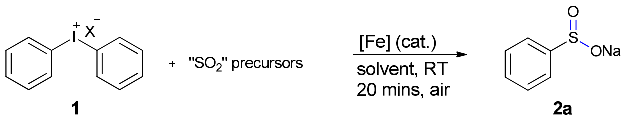


Scheme 2. Proposed iron-catalyzed radical coupling reaction for the synthesis of arylsulfinates.

In this respect, development of processes employing iron catalysts for catalytic sulfination presents substantial interest. Given its environmentally benign character, iron catalysts represent an attractive alternative to other commonly used transition metals in organic synthesis.[18] As single-electron transfer reagents,[19] iron catalysts play an important role in many radical reactions.[20] It was postulated that aryl radicals could be delivered from stable and non-toxic aryl diaryliodoniums in the presence of $FeCl_2$.[21] Meanwhile, the direct coupling of two radicals was believed to be a powerful and concise approach for bond formations.[22] Hence, we envisioned that if a proper sulfoxylate anion radical $SO_2^{\cdot -}$ species could be in-situ generated, arylsulfinates could be formed through iron-catalyzed radical coupling reaction between sulfoxylate anion radical and phenyl radical (Scheme 2). Pleasingly, commercially available and cheap sulfoxylate anion radical precursors such as $Na_2S_2O_4$ or rongalite ($HOCH_2SO_2Na{\cdot}2H_2O$) have been reported to yield anion radical $SO_2^{\cdot -}$.[23] Based on these observations, we herein describe a novel catalytic strategy which would allow the efficient and facile incorporation of sulfonyl unit into arenes to afford arylsulfinates through radical coupling reaction.

The feasibility of the proposed chemistry was first examined using diphenyliodonium triflate, iron salts and a few sulfoxylate anion radical precursors (Table 1). To our delight, the desired product was observed in the systems of $Na_2S_2O_4$ or rongalite with $FeCl_2$ (Table 1, entries 2 and 3). The reaction proceeded quite quickly at room temperature, and complete consumption of the iodonium was observed in 20 minutes. Remarkably, conducting the reaction without a catalyst at 40 ^{o}C also resulted in 28% yield of product (Table 1, entry 4). Copper catalysts were not active in this transformation (Table 1, entries 5 and 6). Interestingly, $FeCl_3$ which can not initiate the radical reaction of diaryliodonium promoted the reaction significantly (Table 1, entry 7). A $FeCl_3$ loading of 30 mol% gave better product yield (Table 1, entry 9). We next investigated the effect of counteranion in diphenyliodonium salt (Table 1, entries 9-11). The results showed that higher yields were obtained when using diphenyliodonium salt with tetrafluoroborate anions (Table 1, entry 10). Further screening a variety of solvents showed that the reaction proceeded most efficiently in DMF/MeCN (1:1) (Table 1, entries 12-17). It should be noted that the reaction was performed in air without the need of inert atmosphere. Meanwhile, it is also noteworthy that anhydrous conditions are not necessary for this radical coupling reaction because water brought into the system by rongalite showed little impact on the reaction yield.

Table 1: Optimization of reaction conditions[a]

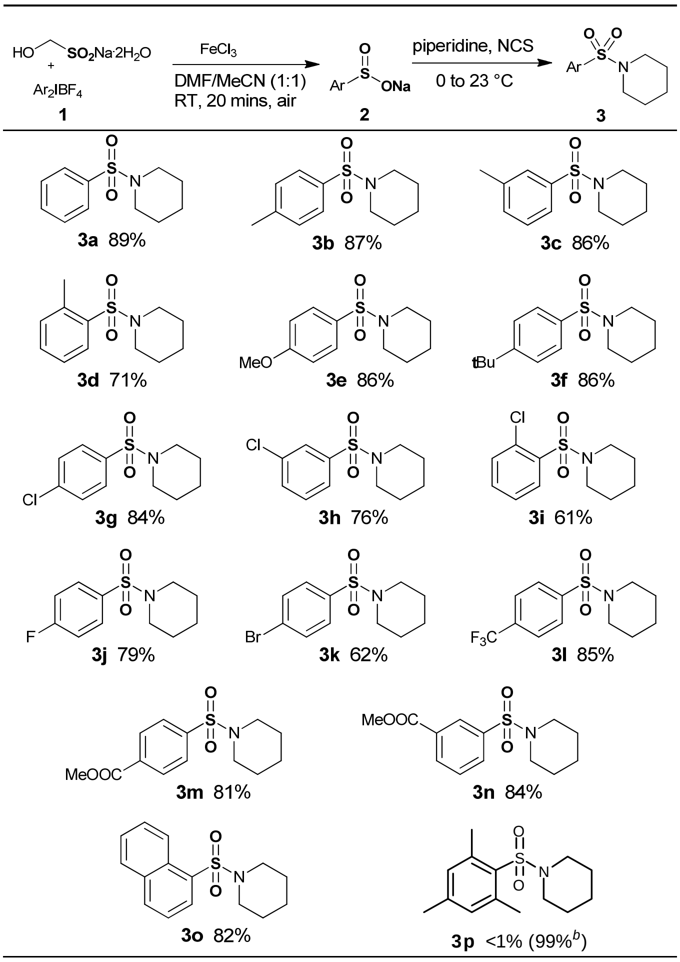


entry	X	"SO_2"	catalyst (mol%)	solvent	yield (%)[b]
1	OTf	$Na_2S_2O_5$	$FeCl_2$ (15)	DMF	-
2	OTf	$Na_2S_2O_4$	$FeCl_2$ (15)	DMF	37
3	OTf	rongalite	$FeCl_2$ (15)	DMF	54
4[c]	OTf	rongalite	-	DMF	28
5	OTf	rongalite	$CuCl_2$ (15)	DMF	trace
6	OTf	rongalite	CuCl (15)	DMF	trace
7	OTf	rongalite	$FeCl_3$ (15)	DMF	63
8	OTf	rongalite	$FeCl_3$ (20)	DMF	67
9	OTf	rongalite	$FeCl_3$ (30)	DMF	76
10	BF_4	rongalite	$FeCl_3$ (30)	DMF	86
11	OTs	rongalite	$FeCl_3$ (30)	DMF	81
12[d]	BF_4	rongalite	$FeCl_3$ (30)	DMF/DCM	89
13[d]	BF_4	rongalite	$FeCl_3$ (30)	DMF/THF	65
14[d]	BF_4	rongalite	$FeCl_3$ (30)	DMF/EtOH	84
15[d]	**BF_4**	**rongalite**	**$FeCl_3$ (30)**	**DMF/MeCN**	**99**
16[e]	BF_4	rongalite	$FeCl_3$ (30)	DMF/MeCN	92
17[f]	BF_4	rongalite	$FeCl_3$ (30)	DMF/MeCN	95

[a] Reaction conditions: iron salt, diphenyliodonium salt (0.3 mmol), "SO_2" precursors (1.5 equiv), solvent (1.0 mL), RT, 20 mins under air; [b] HPLC yield relative to an internal standard; [c] Reaction temperature is 40 °C and reaction time is 1 hours; [d] Solvent ratio: 1:1; [e] Solvent ratio: 2:1; [f] Solvent ratio: 1:2.

With the optimized conditions in hand, we then evaluated the scope of the reaction by transforming the produced arylsulfinates to the corresponding sulfonamides in view of the importance of the functionality and for convenience of product characterization. As shown in Table 2, electron-rich, -neutral and -deficient diaryliodonium salts were competent substrates and the crude arylsulfinates could be used without isolation to afford sulfonamides through reported method.[15] Firstly, the sulfonyl unit was easily introduced to arenes with electron-donating group under standard conditions (**3b**-**3f**). Sulfonamdies containing bromo, chloro and fluoro substituents could also be prepared through this mild reaction in good yields (**3g**-**3k**). Substrates with electron-withdrawing groups such as ester and trifluoromethyl reacted smoothly to give the corresponding sulfonamides in 81-85% yields (**3l**-**3n**). With the present protocol, incorporation of sulfonyl unit in naphthalene went successfully and product **3o** was obtained in 85% yield. For sterically hindered **3d** and **3i**, modest yields of 71% and 61% were obtained respectively. A further increase in the steric bulk on the arenes accompanied by formation of trace amount of 2,4,6-trimethylsulfonamide (**3p**) under standard conditions. However, 99% yield of 2,4,6-trimethylsulfinate (**2p**) could be detected by HPLC. This result indicated that steric hindrance retarded the reaction of 2,4,6-trimethylsulfinate with *N*-chloroamine rather than the sulfination process.

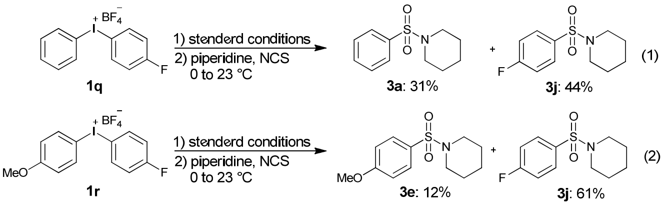
Table 2: Scope of diaryliodonium salts[a]



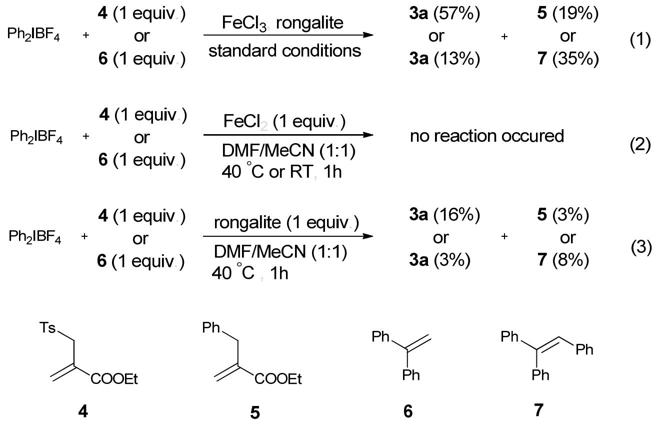
[a] Reaction conditions: $FeCl_3$ (30 mol%), diaryliodonium salt (0.3 mmol), $NaSO_2CH_2OH{\cdot}2H_2O$ (0.45 mmol), solvent (1.0 mL), RT, 20 mins under air. [b] $NaSO_2CH_2OH{\cdot}2H_2O$ (0.6 mmol) was used, 40 mins. HPLC yield of 2,4,6-trimethylsulfinate (**2p**) relative to an internal standard.

To investigate the chemoselectivity of this radical coupling reaction, intramolecular competition experiments with diaryliodonium salts bearing two different aryl substituents were carried out. As shown in Scheme 3, sulfonamides **3a** and **3j** were obtained in 31% and 44%, respectively (eq. 1, Scheme 3). As more electron-donating methoxy-group was introduced, the yield of **3j** increased to 61% and **3e** was obtained in 12% (eq. 2, Scheme 3). It suggested that the electron-poor arenes were more favorable compared with more electron-rich arenes in this radical reaction. Similar result was reported in other radical reactions of diaryliodonium salts.[24]

To verify the pathway of this protocol, further investigation were performed (for details, see ESI, pp. 5-7). Phenyl radical trapping agent allylsulfone **4**[25] and 1,1-diphenylethylene **6**[26] were subjected to controlled experiments respectively (Scheme 4). In addition to **3a**, the corresponding allylation product **5** or triphenylethylene **7** were obtained under the standard conditions (Scheme 4, equation 1). This evidence showed that the generation of aryl radical from diaryliodonium through single electron transfer was involved in this process.



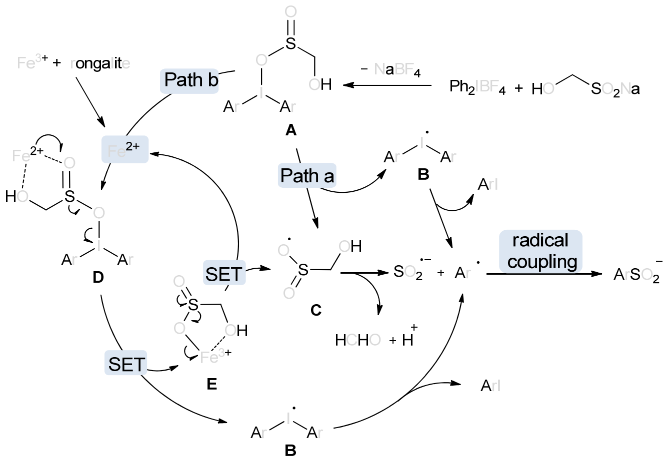
Scheme 3. Intramolecular competition experiments.



Scheme 4. Controlled experiments.

Besides, Fe^{3+} was found to be reduced to Fe^{2+} by rongalite in this reaction (for details, see SI, pp. 5). Therefore, we initially reasoned that the in-situ generated Fe^{2+} might initiate the aryl radicals from diaryliodoniums as postulated in literature.[21] To our surprise, however, no expected **5** or **7** was detected in the presence of 1 equivalent $FeCl_2$ (Scheme 4, equation 2), indicating that $FeCl_2$ could not promote the formation of aryl radicals from diaryliodoniums. On the contrary, small amount of **5** or **7** could be obtained in the reaction of diaryliodonium and rongalite without any iron species (Scheme 4, equation 3), demonstrating that rongalite itself was able to react with diaryliodonium to generate aryl radicals. These intriguing results suggested that the radical coupling reaction was not initiated by iron catalyst alone. It was more reasonable to assume that the initial interaction between diaryliodonium and rongalite was crucial to this radical reaction, and iron catalyst facilitated the reaction.

Based on the above experiments, plausible mechanisms that rationalize the observed results are shown in Scheme 5. It starts from the reaction of diaryliodonium and rongalite to form intermediate **A** which undergoes reactions in two pathways a and b in the presence or absence of iron catalyst. In path a without the iron catalyst, the homolysis of I-O bond in intermediate **A** under heating generates iodanyl radical **B** and radical **C**. Subsequent fragmentation of **B** gives aryl iodide and aryl radical concomitantly.[25] Meanwhile, intermediate **C** decomposes to the sulfoxylate anion radical $SO_2^{\cdot-}$[23a,23b] which couples with aryl radical immediately to yield the desired arylsulfinates. In path b with the iron catalyst, complexation of the in-situ generated Fe^{2+} with **A** leads to the cyclic five-membered intermediate **D** in which an intramolecular single electron transfer from Fe^{2+} facilitates the formation of radical



Scheme 5. Proposed mechanism.

B and intermediate **E**. Subsequently, another intramolecular single electron transfer to Fe^{3+} occurs immediately in **E** to form **C** and regenerates Fe^{2+}. Finally, the coupling between aryl radical and $SO_2^{\cdot-}$, which are in-situ generated from **B** and **C** though the same way as in path a, affords the corresponding arylsulfinates.

In summary, we have designed and successfully developed the first iron-catalyzd methodology for the installation of sulfonyl unit into arenes. The important feature of this novel strategy is furnishing arylsulfinates though very efficient radical coupling reaction which is accomplished via iron-catalyzed reaction between readily available rongalite and diaryliodoniums salts. The reaction proceeds fast at room temperature to afford a number of arylsulfinates in modest to excellent yields under air without the need of any ligands and additives. The importance of the sulfonyl scaffold would render this protocol attractive for both synthetic and medicinal chemistry. Meanwhile, the reaction mechanism is proposed. The utilization of other aryl radical precursors in this novel radical coupling approach is undergoing.

We gratefully acknowledge the National Natural Science Foundation of China (21321061, 21072134 and J1103315/J0104) for financial support, and the Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University for NMR and MS measurements.

Notes and references

1 D. A. Smith, R. M. Jones, *Curr. Opin. Drug Discovery Dev.*, **2008**, *11*, 72.
2 R. Ettari, E. Nizi, M. E. Di Francesco, M.-A. Dude, G. Pradel, R. Vicik, T. Schirmeister, N. Micale, S. Grasso, M. Zappala, *J. Med. Chem.,* **2008**, *51*, 988.
3 (a) J. Drew, *Science,* **2000**, *287*, 1960; (b) P. Tfelt-Hansen, P. D. Vries, P. R. Saxena, *Drugs,* **2000**, *60*, 1259;
4 For selected examples, see: (a) K. Schank, *The Chemistry of Sulfones and Sulfoxides*, Wiley, New York, **1988**, Chapter 7; (b) D. Antonow, T. Marrafa, I. Dawood, T. Ahmed, M. R. Haque, D. E. Thurston, G. Zinzalla, *Chem. Commun.,* **2010**, *46*, 2289.
5 For selected examples, see: (a) D. Baranano, J. F. Hartwig, *J. Am. Chem. Soc.*, **1995** , *117*, 2937; (b) V. P. Reddy, A. V. Kumar, K. Swapna, K. R. Rao, *Org. Lett.,* **2009**, *11*, 1697.
6 For selected examples, see: (a) S. Cacchi, G. Fabrizi, A. Goggiamani, L. M. Parisi, R. Bernini, *J. Org. Chem.,* **2004**, *69*, 5608; (b) N. Umierski, G. Manolikakes, *Org. Lett.*, **2013**, *15*, 188.
7 For selected examples, see: (a) X. D. Tang, L. B. Huang, C. R. Qi, X. Wu, W. Q. Wu, H. F. Jiang, *Chem. Commun.*, **2013**, *49*, 6102; (b) W. X. Zhang, J. Y. Xie, B. Rao, M. M. Luo, *J. Org. Chem.*, **2015**, *80*, 3504.
8 For selected examples, see: (a) P. Qu, C. Sun, J. Ma, F. Li, *Adv. Synth. Catal.*, **2014**, *356*, 447; (b) S.-Y. Moon, J. Nam, K. Rathwell, W.-S. Kim, *Org. Lett.,* **2014**, *16*, 338.
9 J. R. DeBergh, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.*, **2013**, *135*, 10638
10 R. J. Cremlyn, *Chlorosulfonic Acid: A Versatile Reagent*; Royal Society of Chemistry: Cambridge, **2002**, pp. 7–21.
11 (a) B. Nguyen, E. J. Emmet, M. C. Willis, *J. Am. Chem. Soc.,* **2010**, *132*, 16372; (b) C. S. Richards-Taylor, D. C. Blakemore, M. C. Willis, *Chem. Sci.*, **2014**, *5*, 222.
12 For selected examples, see: **(**a) S. Ye, J. Wu, *Chem. Commun.*, **2012**, *48*, 7753; (b) S. Ye, J. Wu, *Chem. Commun.*, **2012**, *48*, 10037; (c) D. Q. Zheng, Y. Y. An, Z. H. Li, J. Wu, *Angew. Chem., Int. Ed.,* **2014**, *53*, 2451; (d) Y. Luo, X. Pan, C. Chen, L. Yao, J. Wu, *Chem. Commun.*, **2015**, *51*, 180; (e) X. Wang, L. Xue, Z. Wang, *Org. Lett.,* **2014**, *16*, 4056; (f) W. Li, H. Li, P. Langer, M. Beller, X. Wu, *Eur. J. Org. Chem.,* **2014**, 3101.
13 (a) G.-W. Wang, T. Miao, *Chem. Eur. J.,* **2011**, *17*, 5787; (b) B. Rao, W. Zhang, L. Hu, M. Luo, *Green Chem.*, **2012**, *14*, 3436; (c) X. Zeng, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.,* **2011**, *133*, 17638; (d) H. Rao, L. Yang, Q. Shuai, C.-J. Li, *Adv. Synth. Catal*., **2011**, 353 , 1701.
14 G. Pelzer, W. Keim, *J. Mol. Catal. A,* **1999**, *139*, 235.
15 A. Shavnya, S. B. Coffey, A. C. Smith, V. Mascitti, *Org. Lett.*, **2013**, *15*, 6226.
16 E. J. Emmett, B. R. Hayter, M. C. Willis, *Angew. Chem., Int. Ed.,* **2014** , *53*, 10204.
17 (a) M. W. Johnson, S. W. Bagley, N. P. Mankad, R. G. Bergman, V. Mascitti, F. D. Toste, *Angew. Chem., Int. Ed.*, **2014**, *53*, 4404. (b) A. S. Deeming, C. J. Russell, M.C. Willis, *Angew. Chem., Int. Ed., DOI: 10.1002/anie.201508370*
18 (a) C. Bolm, J. Legros, J. L. Paih, L. Zani, *Chem. Rev.*, **2004**, *104*, 6217; (b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.,* **2008**, *41*, 11, 1500.
19 (a) Z. Li, L. Cao, C.-J. Li, *Angew. Chem., Int. Ed.* **2007**, *46*, 6505; (b) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie, J.-H. Li, *Angew. Chem., Int. Ed.,* **2013**, *52*, 3638; (c) H.-R. Wu, H.-Y Huang, C.-L. Ren, L. Liu, D. Wang, C.-J. Li, *Chem. Eur. J.*, **2015**, *21*, 16744.
20 (a) W. Du, L. Tian, J. Lai, X. Huo, X. Xie, X. She, S. Tang, *Org. Lett.*, **2014**, *16*, 2470; (b) L. Lv, H. Xi, X. Bai, Z. Li, *Org. Lett.,* **2015**, *17*, 4324.
21 M. Z. Lu, T. P. L, *Org. Lett.*, **2014**, *16*, 4698.
22 (a) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem., Int. Ed.*, **2015**, *54*, 1625; (b) J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu, A. Lei, *Angew. Chem., Int. Ed.*, **2015**, *54*, 6604; (c) J. L. Jeffrey, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2015**, *137*, 8404.
23 (a) C. Wakselman, M. Tordeux, J.-L. Clavel, B. J. Langlois, Chem. Soc., Chem. Commun., **1991**, 993; (b) B.-N. Huang, F.-H. Wu, C.-M. Zhou *J. Fluor. Chem.,* **1995**, 75, 1; (c) S. Kotha, P. Khedkar, *Chem. Rev.,* **2012**, *112*, 1650
24 (a) J. Wen, R. Zhang, S. Chen, J. Li, J. Zhang, X. Yu, *J. Org. Chem.*, **2012**, *77*, 766; (b) J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang, Y. Zhao, *J. Org. Chem.*, **2013**, *78*, 8176.
25 A. Baralle, L. Fensterbank, J. Goddard, C. Ollivier, *Chem. Eur. J.*, **2013**, *19*, 10809.
26 D. H. R. Barton, J.-P. Finet, C. Giannotti, F. Halley, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 241-249.