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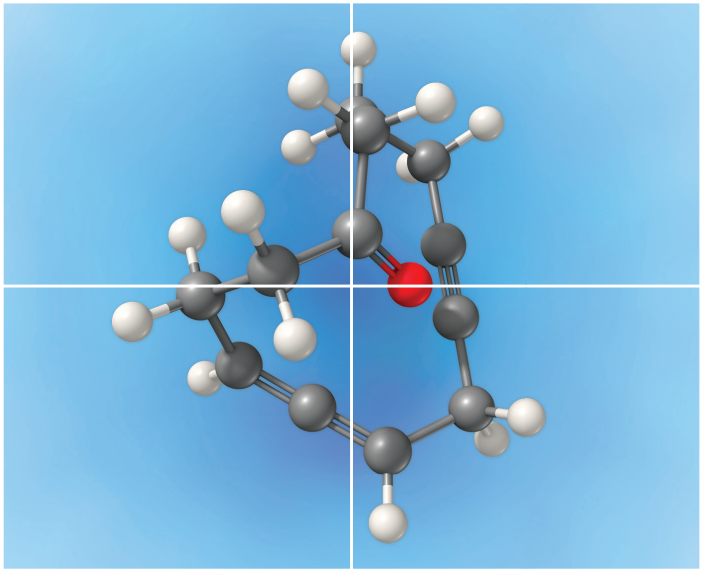

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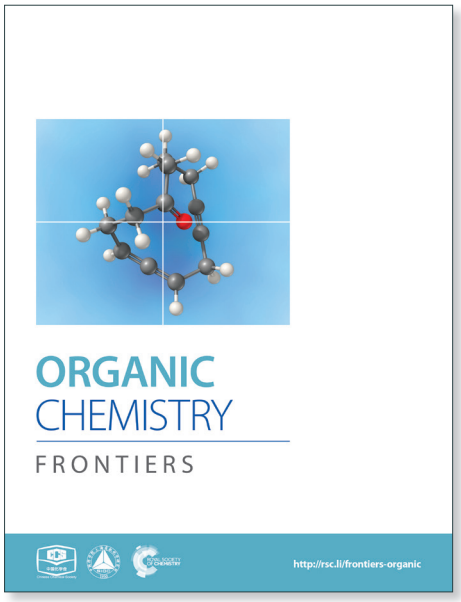

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COMMUNICATION

Synthesis of diaryldifluoromethanes by Pd-catalyzed difluoroalkylation of arylboronic acids

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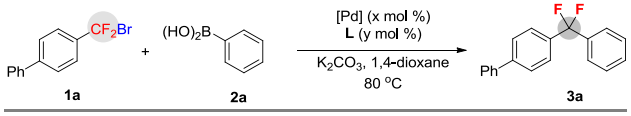
Diaryldifluoromethanes constitute a distinct class of fluorinated compounds in medicinal chemistry. But only limited methods to access such a structural motif have been reported. Herein, we demonstrate the first example of Pd-catalyzed aryldifluoromethylation of arylboronic acids with readily available aryldifluoromethyl bromides. Because of its high efficiency, excellent functional group compatibility, and mild reaction conditions, this protocol provides a facile access to diaryldifluoromethanes. Preliminary mechanistic studies revealed that a Pd(0)L_n-initiated single electron transfer (SET) pathway is involved in the catalytic cycle.

Fluorinated arenes are an important class of structural motif that is found in many pharmaceuticals, agrochemicals, and advanced materials due to the unique properties of fluorine atom and/or the carbon-fluorine bond.[1] As a consequence, substitution of the hydrogen atom(s) in the parent molecules with the fluorine atom(s) is now a common strategy in drug discovery and development.[2] Among the fluorinated arenes, diaryldifluoromethanes, in which the methylene group (CH_2) is replaced by a difluoromethylene group (CF_2), represent a type of appealing compounds because of their important applications in medicinal chemistry. For instance, Ledipasvir, a diaryldifluoromethane containing molecule, is an oral NS5A inhibitor for the treatment of hepatitis C virus (HCV) infection,[3] and has been filed for approval by FDA. To date, however, only limited methods have been reported to access diaryldifluoromethanes. The most common approach to such a fluorinated structural motif relies on deoxyfluorination of carbonyl with dialkylaminosulfurtrifluorides (i.e. DAST or DeoxoFluor).[4] Despite the importance of such a process, to directly introduce a functionalized CF_2 group into organic molecules catalyzed by transitional-metal would be an attractive alternative, as the C-C bond formation catalyzed by transition-metals is a powerful strategy due to its broad substrate scope, high efficiency, and excellent functional-group compatibility. However, compared to transition-metal-catalyzed trifluoromethylation and fluorination of arenes,[5] the difluoroalkylation of arenes through similar strategy has been less studied,[6, 7] although the CF_2 group plays equal important role in medicinal chemistry and material science.[8] To the best of knowledge, there is no successful example that has been reported to prepare diaryldifluoromethanes catalyzed by transition-metal. Therefore, it is highly desirable to develop an efficient reaction to access such a valuable structural motif.

As part of systematic study on transition-metal-catalyzed reactions for the direct introduction of fluorinated moieties into organic molecules,[7, 9] herein we describe the first example of synthesis of diaryldifluoromethanes through Pd-catalyzed cross-coupling between readily available aryldifluoromethyl bromides and arylboronic acids. The notable advantages of this protocol are its mild reaction conditions, excellent functional group compatibility, and operational simplicity, thus providing a facile access to a range of diaryldifluoromethanes of interest in drug discovery and development. Furthermore, to demonstrate the usefulness of this method, the late-stage aryldifluoromethylation of bioactive molecules has also been performed.

Initial studies focused on the Pd-catalyzed cross-coupling reaction of phenylboronic acid **2a** with the readily available 4-(bromodifluoromethyl)-1,1′-biphenyl **1a**[10] in the presence of a variety of phosphine ligands (Table 1, entries 1-8). It was found that the choice of phosphine ligand was very critical to the reaction efficiency, and the bulky ligand cataCXium AHI [PAd_2(*n*-Bu) HI][11] was the optimal one, providing difluoromethylenated product **3a** in 83% yield (determined by ^{19}F NMR, Table 1, entry 6). This is probably because of formation of an active T-shaped palladium complex (Ph)(CF_2Ar)Pd[PAd_2(*n*-Bu)] that benefits the reductive elimination.[12] While, only poor yield (27%) of **3a** was obtained when XantPhos, which was previously demonstrated to be an excellent bisphosphine ligand for reductive elimination from fluoroalkyl palladium complexes,[7c, 13] was employed (Table 1, entry 8). Encouraged by these results, several reaction parameters were examined to further optimize the reaction conditions (Table 1, entries 9-15, for details, see Supporting Information). It revealed that K_2CO_3, 1,4-dioxane, and $Pd(OAc)_2$ were the optimal choices, leading to compound **3a** in the best yield (91% upon isolation) when the ratio of Ligand/Pd was decreased from 2/1 to 1/1 (Table 1, entry 10). Other bases, solvents, or palladium catalysts either afforded lower yields or showed no activity. The absence of palladium catalyst or ligand failed to provide desired product, thus demonstrating that a Pd(0/II) catalytic cycle is involved in the reaction (Table 1, entries 16 and 17).

Table 1. Representative results for optimization of Pd-catalyzed cross-coupling of **1a** with **2a**[a]

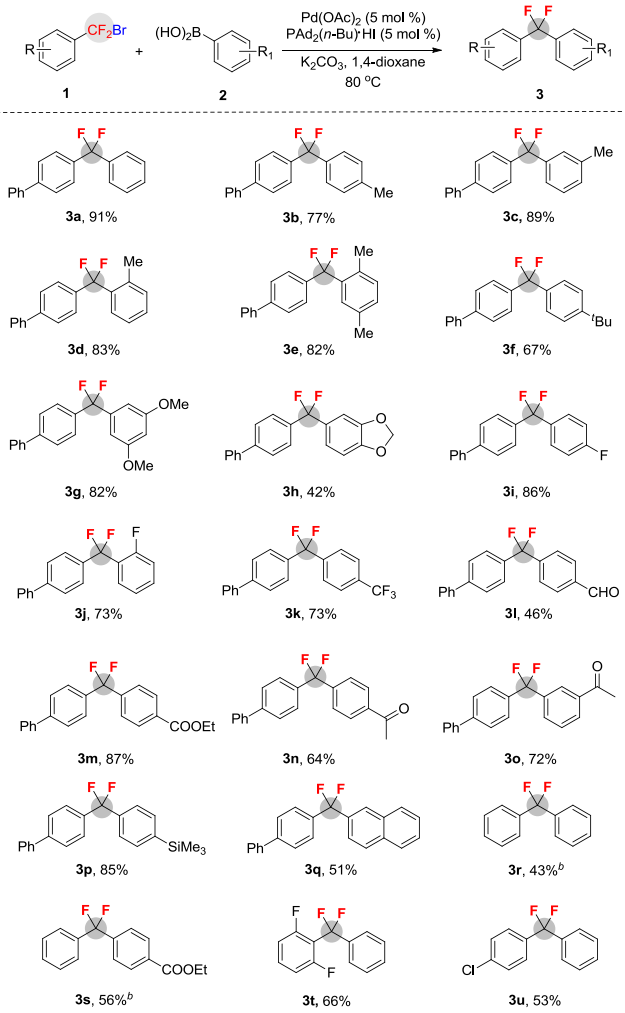


Entry	[Pd](x)	L(y)	3a,Yield (%)[b]
1	$Pd(OAc)_2$ (5)	PPh_3 (10)	27
2	$Pd(OAc)_2$ (5)	P(*o*-OMePh)$_3$ (10)	4
3	$Pd(OAc)_2$ (5)	PCy_3 ·HBF_4 (10)	39
4	$Pd(OAc)_2$ (5)	P*t*-Bu_3 ·HBF_4 (10)	15
5	$Pd(OAc)_2$ (5)	CyJohnPhos (10)	8
6	$Pd(OAc)_2$ (5)	PAd_2(*n*-Bu) ·HI (10)	83
7	$Pd(OAc)_2$ (5)	DPPE (10)	8
8	$Pd(OAc)_2$ (5)	XantPhos (10)	27
9	$Pd(OAc)_2$ (5)	PAd_2(*n*-Bu) ·HI (7.5)	89
10	$Pd(OAc)_2$ (5)	PAd_2(*n*-Bu) ·HI (5)	97(91)
11	$Pd(PPh_3)_4$ (5)	PAd_2(*n*-Bu) ·HI (5)	trace
12	$Pd_2(dba)_3$ (2.5)	PAd_2(*n*-Bu) ·HI (5)	34
13	$Pd_2(Allyl)_2Cl_2$ (2.5)	PAd_2(*n*-Bu) ·HI (5)	56
14	$Pd(PPh_3)_2Cl_2$ (2.5)	PAd_2(*n*-Bu) ·HI (5)	trace
15	$PdCl_2$(dppp) (2.5)	PAd_2(*n*-Bu) ·HI (5)	14
16	$Pd(OAc)_2$ (5)	none	NR
17	none	PAd_2(*n*-Bu) ·HI(5)	NR

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), K_2CO_3 (2.0 equiv), 1,4-dioxane (2 mL), 8 h. [b]Determined by ^{19}F NMR using $PhCF_3$ as an internal standard and number in parenthesis is isolated yield.

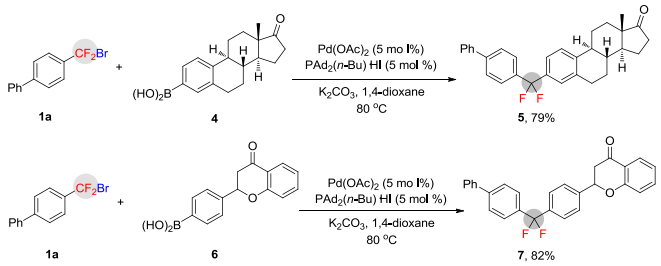
Upon the identification of viable reaction conditions, the substrate scope of this transformation was tested and the representative results are illustrated in Table 2. Overall, aromatic boronic acids with either electron-rich or electron-deficient substituents underwent the present cross-coupling process with aryldifluoromethyl bromide **1a** in moderate to high yields. A variety of important functional groups, such as the formyl, alkoxycarbonyl, enolizable ketone, and trimethylsiyl groups, were tolerated quite well (**3l-p**). The sterically hindered *ortho*-tolyboronic acid and its derivative were excellent substrates, and the cross-coupling with **1a** proceeded with high efficiency (**3d** and **3e**). Furthermore, other aryldifluoromethyl bromides were also applicable to the reaction and moderate yields were obtained (**3r-u**). However, it should be mentioned that in the cases of reactions of phenyldifluoromethyl bromide **1b** with arylboronic acids, significant amount of $PhCF_2H$ was observed under standard conditions. We supposed that the formation of $PhCF_2H$ was ascribed to the reaction of solvent with $PhCF_2$· radical that was generated from **1b** with Pd/PAd_2(*n*-Bu)/Base. To our delight, when 1.0 equiv of H_2O was added to the reaction, moderate yields of **3r** and **3s** were obtained. However, the role of H_2O in this reaction remains uncertain. Notably, arylchloride was also compatible with the reaction conditions, thus providing a good opportunity for downstream transformations (**3u**).

Table 2. Pd-catalyzed aryldifluoromethylation of arylboronic acids **2** with aryldifluoromethyl bromides **1**[a]



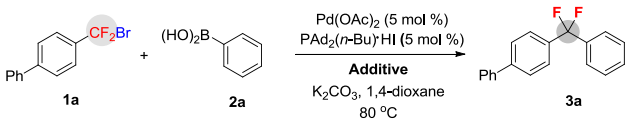
[a]Reaction conditions (unless otherwise specified): **1** (0.4 mmol, 1.0 equiv), **2** (0.6 mmol, 1.5 equiv), K_2CO_3 (2.0 equiv), 1,4-dioxane (4 mL), 8 h. All reported yields are isolated yields. [b]1.0 equiv of H_2O was used.

The importance and usefulness of this method can also be highlighted by late-stage aryldifluoromethylation of bioactive molecules. As shown in Scheme 1, treatment of estrone-derived arylboronic acid **4** with the difluoroalkyl bromide **1a** afforded difluoroalkylated compound **5** with high efficiency (79%). Similarly, the flavanone-derived arylboronic acid **6** also led to its corresponding difluoroalkylated product **7** in high yield (82%). In view of the fact that CF_2 can functionalize as a bioisostere of the oxygen atom or carbonyl group,[14] and leads to profound changes in physical and biological properties of CF_2 containing molecules,[8] we view these transformations as a highly valuable opportunity for application in drug discovery and development.



Scheme 1 Late-Stage functionalization for synthesis of biologically active molecules

To gain some mechanistic insights into the present reaction, radical inhibition experiments were conducted (Scheme 2). Significant decrease of the yields were observed when an electron transfer (ET) inhibitor (1, 4-dinitrobenzene) was added to the reaction mixture of **1a** and **2a** in the presence of $Pd(OAc)_2$ (5 mol %), $PAd_2(n\text{-Bu})\cdot HI$ (5 mol %), and K_2CO_3 in dioxane.[15] Thus, these preliminary studies demonstrate that a single electron transfer (SET) pathway via a aryldifluoromethyl radical is involved in the catalytic cycle.

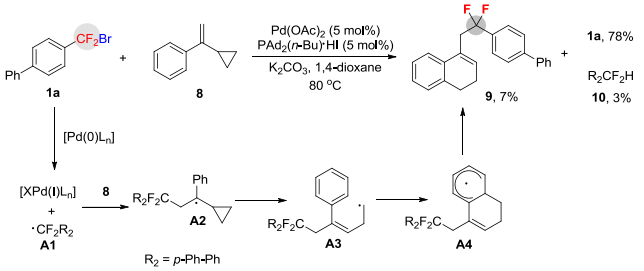


Additive	**3a**, yield (%)
none	97
1,4-dinitrobenzene (0.2 equiv)	36
1,4-dinitrobenzene (1.0 equiv)	6

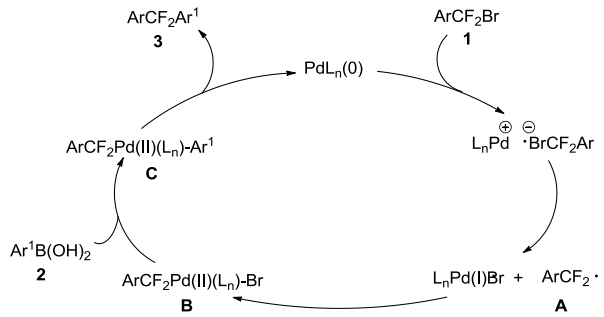
Scheme 2 Radical inhibition experiments

To confirm that a free aryldifluoromethyl radical was generated during the reaction, a radical clock experiment was conducted (Scheme 3). When compound **8**[16] was treated with **1a** under standard conditions, a ring-expanded product **9** was formed in 7% yield (determined by ^{19}F NMR) along with 3% yield of protonated product **10** and 78% of starting material **1a** unreacted. This finding demonstrated that a free radical was indeed generated during the reaction.

On the basis of these results, a plausible reaction mechanism was proposed (Scheme 4). The reaction is initiated by a $[PdL_n(0)]$-promoted SET pathway to generate aryldifluoroalkyl radical ($ArCF_2\bullet$) **A**. **A** subsequently reacts with $L_nPd(I)Br$ to produce Pd(II)-complex **B**. After transmetalation, a key intermediate **C** would be generated. As the final step of the catalytic cycle, reductive elimination of **C** affords diaryldifluoromethanes **3**. However, for the detailed reaction mechanism remains a subject to be studied.



Scheme 3 Radical clock experiment.



Scheme 4 Proposed reaction mechanism

Conclusions

In conclusion, we have demonstrated the first example of palladium-catalyzed aryldifluoromethylation of arylboronic acids with readily available aryldifluoromethyl bromides. The utility of $PAd_2(n\text{-Bu})\cdot HI$ is critical for the reaction efficiency. The reaction proceeds under mild reaction conditions with excellent functional group compatibility. Thus, these transformations provide a facile route for application in medicinal chemistry. Mechanistic studies revealed that a $[Pd(0)L_n]$ promoted SET pathway via a free fluoroalkyl radical is involved in the reaction. Further studies to uncover the reaction mechanism as well as other derivative reactions are now in progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available:Detailed experimentalprocedures, and analytical data for all new compounds. See DOI: 10.1039/b000000x/.

1 For selected reviews, see: (a) B. E. Smart, *J. Fluorine Chem.*,2001, **109**, 3; (b) P. Maienfisch, and R. G. Hall, *Chimia.*, 2004, **58**, 93; (c) Special issue on "Fluorine in the Life Sciences", *ChemBioChem.*, 2004, **5**, 557; (d) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308.

2 For selected reviews, see: (a) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (b) J.-P. Begue and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992; (c) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (d) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (e) S.

Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
3 J. O. Link, J. G. Taylor, L. Xu, M. Mitchell, H. Guo, H. Liu, D. Kato, T. Kirschberg, J. Sun, N. Squires, J. Parrish, T. Keller, Z.-Y. Yang, C. Yang, M. Matles, Y. Wang, K. Wang, G. Cheng, Y. Tian, E. Mogalian, E. Mondou, M. Cornpropst, J. Perry and Desai, M. C, *J. Med. Chem.*, 2014, **57**, 2033.
4 For selected examples of difluorination of carbonyl group with fluorinated reagents, see: (a) W. J. Middleton and E. M. Bingham, *J. Org. Chem.*, 1980, **45**, 2883; (b) G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. Cheng, *J. Org. Chem.*, 1999, **64**, 7048; (c) D. Solas, R. L. Hale and D. V. Patel, *J. Org. Chem.*, 1996, **61**, 1537. (d) S. Kobayashi, A. Yoneda, T. Fukuhara and S. Hara, *Tetrahedron.*, 2004, **60**, 6923; (e) T. Umemoto, R. P. Singh, Y. Xu and N. Saito, *J. Am. Chem. Soc.*, 2010, **132**, 18199; (f) A. L'Heureux, F. Beaulieu, C. Bennett, D. R. S. Clayton, F. LaFlamme, M. Mirmehrabi, S. Tadayon, D. Tovell and M. Couturier, *J. Org. Chem.*, 2010, **75**, 3401.
5 For selected reviews, see: (a) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (b) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (c) C. Hollingworth and V. Gouverneur, *Chem. Commun.*, 2012, **48**, 2929; (d) T. Besset, C. Schneider and D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048. (e) F.-L. Qing, *Chin. J. Org. Chem.*, 2012, **32**, 815; (f) X. Wang, Y. Zhang and J. Wang, *Sci. Sin. Chim.*, 2012, **42**, 1417.
6 For transition-metal-catalyzed difluoroalkylation, see: (a) K. Araki and M. Inoue, *Tetrahedron*, 2013, **69**, 3913; (b) S. Ge, W. Chaladj and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4149.
7 For our contribution to transition-metal-catalyzed difluoroalkylation, see: (a) Z. Feng, F. Chen and X. Zhang, *Org. Lett.*, 2012, **14**, 1938; (b) Z. Feng, Y.-L. Xiao and X. Zhang, *Org. Chem. Front.*, 2014, **1**, 113; (c) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem. Int. Ed.*, 2014, **53**, 1669; (d) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230; (e) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 9909; (f) Y.-B. Yu, G.-Z. He and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 10457; (g) Y.-L. Xiao, B. Zhang, Z. Feng, and X. Zhang, *Org. Lett.*, 2014, **16**, 4822.
8 For selected reviews, see: (a) X.-L. Qiu, X.-H. Xu and F.-L. Qing, *Tetrahedron*, 2010, **66**, 789; (b) N. A. Meanwell, *J. Med.Chem.*, 2011, **54**, 2529. For selected papers, see: (c) C. S. Burgey, K. A. Robinson, T. A. Lyle, P. E. J. Sanderson, S. Dale Lewis, B. J. Lucas, J. A. Krueger, R. Singh, C. Miller-Stein, R. B. White, B. Wong, E. A. Lyle, P. D. Williams, C. A. Coburn, B. D. Dorsey, J. C. Barrow, M. T. Stranieri, M. A. Holahan, G. R. Sitko, J. J. Cook, D. R. McMasters, C. M. McDonough, W. M. Sanders, A. A.Wallace, F. C. Clayton, D. Bohn, Y. M. Leonard, T. J. Jr. Detwiler, J. J. Jr. Lynch, Y. Yan, Z. Chen, L. Kuo, S. J. Gardell, J. A. Shafer and J. P. Vacca, *J. Med. Chem.*, 2003, **46**, 461; (d) J. Li, S. Y. Chen, B. J. Murphy, N. Flynn, R. Seethala, D. Slusarchyk, M. Yan, P. Sleph, H. Zhang, W. G. Humphreys, W. R. Ewing, J. A. Robl, D. Gordon and J. A. Tino, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4072; (e) C. L. Lynch, C. A. Willoughby, J. J. Hale, E. J. Holson, R. J. Budhu, A. L. Gentry, K. G. Rosauer, C. G. Caldwell, P. Chen, S. G. Mills, M. MacCoss, S. Berk, L. Chen, K. T. Chapman, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. J. Siciliano, M. A. Cascieri, A. Carella, G. Carver, K. Holmes, W. A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller and E. A. Eminic, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 119.
9 (a) C.-Y. He, S. Fan and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 12850; (b) X. Zhang, S. Fan, C.-Y. He, X. Wan, Q.-Q. Min, J. Yang and Z.-X. Jiang, *J. Am. Chem. Soc.*, 2010, **132**, 4506; (c) S. Fan, F. Chen and X. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 5918; (d) Z. Chen, C.-Y. He, Z. Yin, L. Chen and X. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 5813.
10 J. He and C. U. Pittman, *Synth. Commun.*, 1999, **29**, 855.
11 (a) A. Ehrentraut, A. Zapf and M. Beller, *Synlett*, 2000, 1589; (b) A. Zapf, A. Ehrentraut and M. Beller, *Angew. Chem., Int. Ed.*, 2000, **39**, 4153.
12 A. G. Sergeev, A. Spannenberg and M. Beller, *J. Am. Chem. Soc.*, 2008, **130**, 15549.
13 (a) V. V.Grushin and W. J. Marshall, *J. Am. Chem. Soc.*, 2006, **128**, 12644; (b) V. I. Bakhmutov, F. Bozoglian, K. Gómez, G. González, V. V. Grushin, S. A. Macgregor, E. Martin, F. M. Miloserdov, M. A. Novikov, J. A. Panetier and L. V. Romasho, *Organometallics*, 2012, **31**, 1315.
14 (a) C. M. Blackburn, D. A. England and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 930; (b) G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc. Perkin Trans. I*, 1984, 1119; (c) T. Kitazume and T. Kamazaki, *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science: Tokyo, 1998.
15 For related radical inhibition experiments studies, see: (a) X.-T. Huang and Q.-Y. Chen, *J. Org. Chem.*, 2001, **66**, 4651; (b) R. N. Loy and M. S. Sanford, *Org. Lett.*, 2011, **13**, 2548.
16 J. E. Baldwin, *Chem. Rev.*, 2003, **103**, 1197.