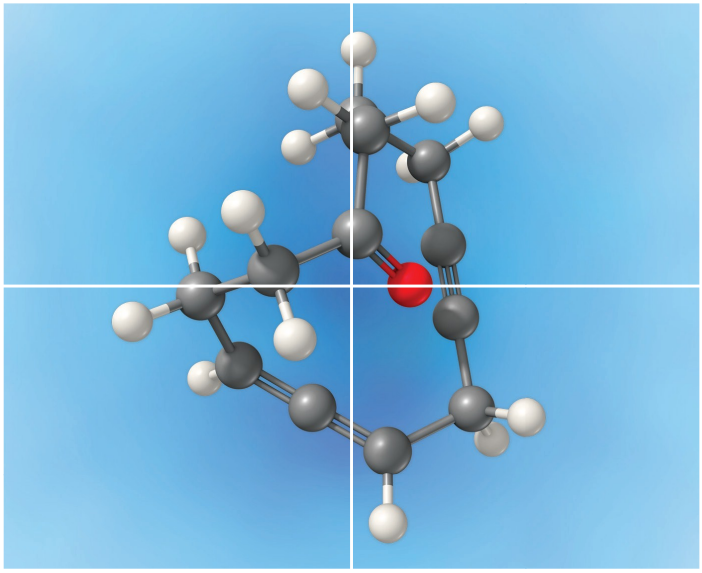
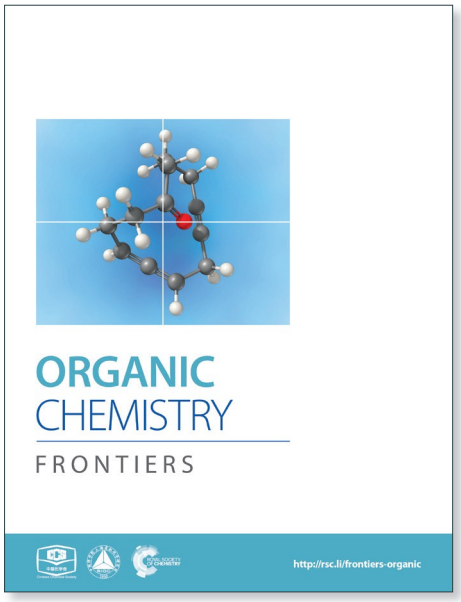
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



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.

ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

Direct Isoperfluoropropylation of Arenediazonium Salts with Hexafluoropropylene†

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Xiaojun Wang,[a,b] Yajun Li,[b] Yuwei Guo,[a,b] Zhentong Zhu,[b,c] Yongming Wu*[b] and Weiguo Cao*[a,b]

An efficient copper-promoted isoperfluoropropylation of aryl diazonium salts is described. The reaction occurs under mild conditions using commercially available hexafluoropropylene (HFP) as a starting material. In addition, a one-pot direct diazotization and isoperfluoropropylation protocol was developed. The method allows facile conversion of various arylamines into isoperfluoropropylarenes with HFP on good functional group compatibility.

Introduction

Incorporating fluorine-containing groups into organic compounds has a significant influence on their physicochemical properties and biological activities. Among various organofluorine molecules, perfluoroalkylarenens play an increasingly important role in pharmaceuticals, agrochemicals and materials due to the low polarizability, high lipophilicity, strong electron-withdrawing nature and prominent metabolic stability of perfluoroalkyl groups.[1] To date, significant progress has been made in introducing trifluoromethyl group into aromatic rings.[2] However, methods for introducing higher analogue of perfluoroalkyl groups (such as C_2F_5, C_3F_7 …) into an aromatic ring are rare.[3] To the best of our knowledge, there are only few methods available for the synthesis of isoperfluoropropylarenes, although these compounds have been widely used in synthesis of pesticides, organocatalysts, and functional materials (Figure 1).[4]

Traditional methods for preparing isoperfluoropropylarenes require to use several isoperfluoropropylation reagents. The most commonly used reagents are isoperfluoropropyl halides, which incorporate isoperfluoropropyl (i-C_3F_7) group into aromatic rings upon treatment with phenols and arylamines *via* Sulfinatodehalogenation reactions[5] or with aryl halides via Ullmann reactions (Scheme 1, path a).[6] On the other hand, a number of isoperfluoropropylmetals (MC_3F_7-i) reagents (such as i-C_3F_7Li, i-C_3F_7MgBr, i-C_3F_7ZnI, $(i\text{-}C_3F_7)_2Hg$, $(i\text{-}C_3F_7)_2Cd$…) have been synthesized, but very few of them are suitable for

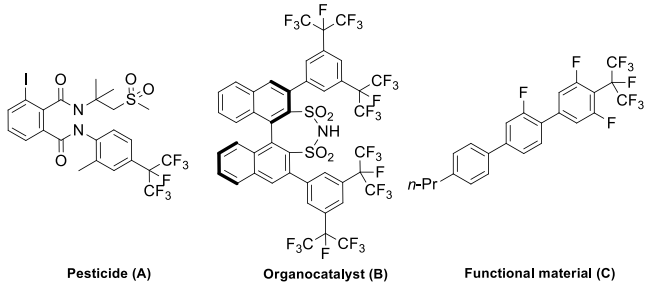
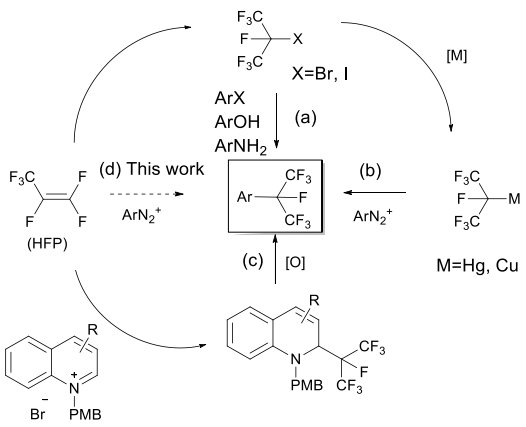


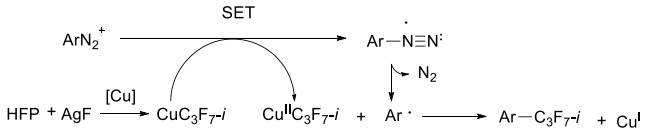
Fig. 1 Isoperfluoropropylated substances.

synthesizing of isoperfluoropropylarenes due to the instability or toxicity.[7] Recently, by using a pre-prepared sensitive i-$C_3F_7Cu(CH_3CN)$ complex that synthesis from isoperfluoropropyl halide with copper in elevated temperature, Chen's group has developed a method of converting arenediazonium salts into isoperfluoropropylarenes (Scheme 1, path b).[3g] Makosza et al. has reported an alternative strategy by introducting i-C_3F_7 into heterocyclic rings using isoperfluoropropyl carbanion generated by HFP and KF. But this method needs an additional oxidation step to obtain aromatic



[a] Department of Chemistry，Shanghai University，99 Shangda Road, Shanghai 200444, China. E-mail: wgcao@staff.shu.edu.cn
[b] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: ymwu@sioc.ac.cn
[c] School of Chemiscal and environmental Engineering, Shanghai Institute of Technology, 100 Haiquan Road, Shanghai 201418, China.
[d] † Electronic Supplementary Information (ESI) available. For ESI See DOI: 10.1039/x0xx00000x

Scheme 1 Methods for synthesis of isoperfluoropropylarenes categoried by-isoperfluoropylation reagents.



Scheme 2 Proposed mechanism of Sandmeyer isoperfluoropropylation of diazonium salts

heterocyclic compounds (Scheme 1, path c).[8]

Recently, novel Sandmeyer-type trifluoromethylation,[9] trifluoromethylthiolation[10] and difluoromethylthiolation[11] of arenediazonium salts have been reported. Generally, the mechanism of the Sandmeyer reaction is believed to proceed via radical intermediates.[9a, 9c, 9d, 11, 12] It is plausible that a single-electron transfer (SET) from Cu(I) species to the diazonium group forms a diazo radical and Cu(II) intermediate. The resulting diazo radical then releases nitrogen to form an aryl radical, which further reacts with Cu(II) intermediate to generate final trifluoromethylated (trifluoromethylthiolation / difluoromethylthiolation) products. The trifluoromethylating Sandmeyer reactions were discovered nearly simultaneously by the groups of Fu, Gooβen and Wang in 2013.[9a-c] In the above examples, the CF_3 source is Umemoto's reagent in Fu's method and Ruppert-Prakash reagent ($TMSCF_3$) in Gooβen's protocal and Wang's protocols. By the fluoroform-derived $CuCF_3$, Grushin's group also had realized trifluoromethylation of arenediazonium salts in aqueous.[9d] Despite the progress in the Sandmeyer-type fluoroalkylation, the known routes to isoperfluoropropylarenes are still rely mainly on toxic isoperfluoropropyl halides agents. So it is urgent to develop the alternative solutions for more practical ways. Serveal attempts for isoperfluoropropylation of aryl iodides or arynes have been made by using MC_3F_7-*i* derived from *i*-C_3F_7H, $TMSC_3F_7$-*i* or isoperfluoropropyl halides, but the effects are unsatisfactory.[3d, 3e, 13] In sight of the rare successful examples introducing *i*-C_3F_7 into aromatic rings and inspaired that fluoroalkylmetals may act as the key intermediate in Sandmeyer fluoroalkylation, we hypothesized that isoperfluoropropyl copper species could be generated in situ in the presence of isoperfluoropropyl silver reagent and cuprous salt, which may react with arenediazonium to form the isoperfluoropropylated compounds (Scheme 2).

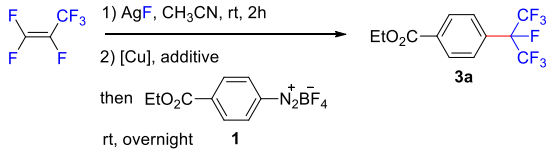
It is worth noting that HFP is the starting material for the synthesis of isoperfluoropropyl halides and isoperfluoropropylmetals reagents, which act as the isoperfluoropropylation reagents (*vide supra*). According to literature,[14] when silver fluoride is introduced into a solution of HFP in acetonitrile, a reasonably stable isoperfluoropropyl silver reagent was formed. Considering both Stability and toxicity of the isoperfluoropropylmetals, we envisioned isoperfluoropropyl silver could act as the ideal agent for introducing *i*-C_3F_7 into aromatic rings. In fact, we have recently reported that this reagent is active for isoperfluoropropylation of arylboronic acids.[15] Inspired by this result, we aimed to explore the possibility for isoperfluoropropylation of arenediazonium salts directly from HFP, an inexpensive and readily available agent (Scheme 1, path d).

Results and discussion

The reaction of 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**1**) with isoperfluoropropyl silver reagent derived from HFP in the presence of copper or copper salt had been investigated (Table 1). Direct reaction of **1** with isoperfluoropropyl silver reagent generated in situ at room temperature resulted no desired product, ethyl 4-isoperfluoropropyl-benzoate (**3a**) (Table 1, entry 1). Under the identical conditions, when copper powder (1.6 equivalent) was added, **3a** was formed in 30% yield after 24 hours (based on ^{19}F NMR analysis) (entry 2). This result indicated that the copper was essential for the formation of the desired product. Other copper species were screened (entries 3-9) and the results suggested that cuprous iodide was the best choice, affording **3a** in 77% yield. It was also found that the addition of phosphines or nitrogens ligands had a disadvantageous impact on the reaction (entry 9-15).

We then examined the possibility of one-pot protocol of this reaction by using in situ generated arenediazonium salt from

Table 1 Optimization of the reaction conditions of isoperfluoropropylation of arenediazonium salts[a]



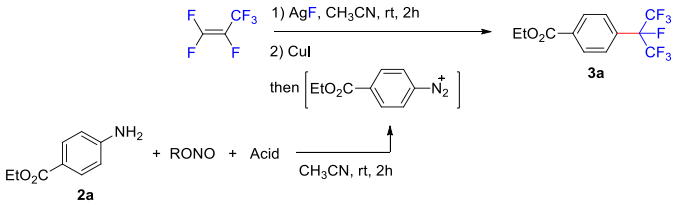
Entry	[Cu]	Additive	Yield[b](%)
1	-	-	0
2	Cu	-	30
3	$CuBr_2$	-	27
4	CuCl	-	46
5	CuSCN	-	29
6	CuCN	-	15
7	CuOTf●2MeCN	-	19
8	CuI	-	77
9	CuI●$P(OEt)_3$	-	51
10	CuI	$P(o\text{-tol})_3$[c]	48
11	CuI	biPy	24
12	CuI	TMEDA	12
13	CuI	BPhen[d]	23
14	CuI	PPh_3	8
15	CuI	Xantphos[e]	59

[a] Reaction conditions: HFP (excess, balloon, 1 atm), AgF (0.2 mmol), [Cu] (0.16 mmol), additive (0.16 mmol), **1** (0.1 mmol), CH_3CN (1.5 + 1.0 mL), under N_2 atmosphere. [b] Yield determined by ^{19}F NMR analysis versus $PhCF_3$ as an internal standard. [c] $P(o\text{-tol})_3$ = Tris(o-tolyl)phosphine. [d] Bphen = Bathophenanthroline. [e] 0.4 equivalent.

corresponding anilines instead of pre-prepared arenediazonium tetrafluoroborates. The solution of diazonium salt generated from the reaction of ethyl 4-aminobenzoate (**2a**) and tert-butyl nitrite in acetonitrile was added into the solution containing isoperfluoropropyl silver reagent generated in situ and cuprous iodide. However, the isoperfluoropropylated product (**3a**) was not found (Table 2, entry 1). Fortunately, when sulfuric acid was added in the diazotization step, the desired product was obtained in 52% yield based on ^{19}F NMR spectroscopy (entry 2),[3g, 9c, 16] implying that the counterions of arenediazonium salts had a significant impact in this reaction. Further study indicated that when p-toluenesulfonic acid (*p*TSA) was employed, the product yield was improved to 75% (entry 6), while other acids had less effect (entry 3-5). In addition, the use of isopropyl nitrite reduced the yield to 64% (entry 7). It was found that this reaction was sensitive to the amount of tert-butyl nitrite, extra tert-butyl nitrite may had a negative effect on the reaction (entry 9).

After established this one-pot diazotization and isoperfluoropropylation method, we explored the scope of the reaction with various arylamines (Scheme 3). It showed that the aromatic amines bearing either electron-donating or -withdrawing groups reacted smoothly to form the corresponding isoperfluoropropylarenes in moderate to good yields. The method is compatible with a broad array of functional groups, including ether, ester, amide, keto, cyano, and nitro etc. Substrates containing fluoro, chloro, bromo or iodo substituents (**3l**-**3r**) were well tolerated which might be of potential for further transformation. Remarkably, oxidation sensitive vinyl group also tolerated the reaction conditions (**3h**). Although *i*-C_3F_7 is a very bulky group, the anilines bearing *ortho*- substitutents, such as iodo and bulky phenyl,

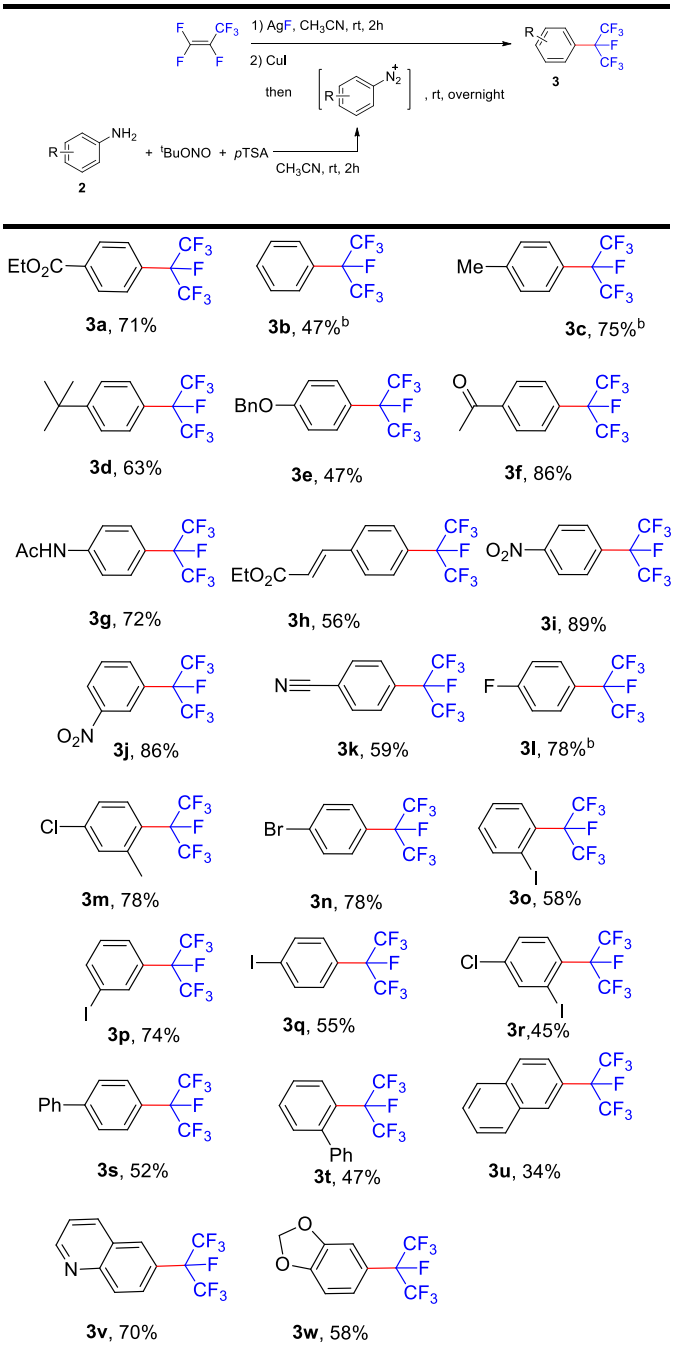
Table 2: Optimization of the reaction conditions of one-pot diazotization and isoperfluoropropylation[a]



Entry	Acid	RONO	Yield[b] (%)
1	-	^{t}BuONO	0
2	H_2SO_4 (98.3%)	^{t}BuONO	52
3	CF_3COOH	^{t}BuONO	67
4	CH_3SO_3H	^{t}BuONO	71
5	CF_3SO_3H	^{t}BuONO	58
6	*p*TSA	^{t}BuONO	75
7	*p*TSA	^{i}PrONO	64
8	*p*TSA	^{t}BuONO[c]	57
9	*p*TSA	^{t}BuONO[d]	66

[a] Reaction conditions: HFP (excess, balloon, 1 atm), AgF (0.2 mmol), CuI (0.16 mmol), **2a** (0.1 mmol), RONO (0.12 mmol), acid (0.15 mmol), CH_3CN (1.5 mL + 1.5 mL), under N_2 atmosphere. [b] Yield determined by ^{19}F NMR analysis versus $PhCF_3$ as an internal standard. [c] 1.0 equiv. ^{t}BuONO. [d] 1.35 equiv. ^{t}BuONO.

Scheme 3 Scope of the reaction[a]



[a] Reaction conditions: HFP (excess, balloon, 1 atm), AgF (0.6 mmol), CuI (0.48 mmol), **2** (0.3 mmol), ^{t}BuONO (0.36 mmol), *p*TSA (0.45 mmol), CH_3CN (3 mL+3 mL). Yield of isolated product given. [b] Yield determined by ^{19}F NMR analysis versus $PhCF_3$ as an internal standard.

gave the corresponding products **3p** and **3t** in yields comparable to that obtained in the reactions with the para-substituted analogues (**3q** and **3s**). In addition, substrates with unprotected carbonyl functionalities afforded desired products in good yields (**3f** and **3g**) and various heterocycles were also isoperfluoropropylated successfully (**3v**, **3w**). However, *ortho*-nitroaniline failed to generate isoperfluoropropylated product, probably due to the coordination of the ortho nitro group to the metal center.

Conclusions

In summary, we have developed a copper-promoted isoperfluoropropylation reaction for converting arylamines to isoperfluoropropylarenes and heteroarenes by using the readily accessbile hexafluoropropylene as starting meterial. The transformation can proceed in a one-pot protocol forming isoperfluoropropylarenes from aromatic amines with good functional group tolerance. This method provides an attractive approach to valuable isoperfluoropropylarenes. Further investigations on the synthetic application and the mechanism of the transformation are currently underway in our laboratory.

Experimental section

Typical procedure for the direct isoperfluoropropylation of arenediazonium salts with hexafluoropropylene

In a nitrogen-filled glove box, an oven-dried 20 mL crimp cap vessel (**1**) with Teflon-coated stirrer bar was charged with silver fluoride (76.2 mg, 0.60 mmol) and was brought under an atmosphere of dry nitrogen. To this vessel, 3 mL of anhydrous acetonitrile and hexafluoropropylene (balloon, excess) were added, and the mixture was stirred at room temperature under ordinary pressure in the dark until silver fluoride precipitate is disappeared. This process takes about two hours and the isoperfluoropropyl silver is generated. In the process of this reaction, in a nitrogen-filled glove box, an oven-dried 20 mL crimp cap vessel (**2**) with Teflon-coated stirrer bar was charged with p-toluenesulfonic acid (77.4 mg, 0.45 mmol) and was brought under an atmosphere of dry nitrogen. To this vessel, **2a** (49.5mg, 0.3 mmol), 3 mL of anhydrous acetonitrile and tert-butyl nitrite (37.1 mg, 0.36 mmol) were added. The reaction mixture was stirred at ambient temperature for 2 h to generate the corresponding diazonium salt. After these procedures, the reaction mixtures in crimp cap vessels (**1**) and (**2**) was added in sequence *via* syringe into an third oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar charging with cuprous iodide (91.4 mg, 0.48 mmol) under nitrogen. The new reaction mixture was stirred at ambient temperature for overnight. The resulting mixture was diluted with Et_2O (10 mL), then filtered through a short pad of celite and rinsed with diethyl ether. The resulting organic solution was add into water (10 mL) and extracted by ethyl Et_2O (3×10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was further purified by flash chromatography on silica gel to give the desired product.

Acknowledgements

This work was supported by the National Basic Research Program of China (2012CB821600) and the National Natural Science Foundation of China (No. 21172239).

Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2004; (*b*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (*c*) K. Mueller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*d*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475.

2 For selective reports, see: (*a*) F. Swart, *Bull. Acad. R. Belg.*, 1892, **24**, 309; (*b*) V. C. R. McLoughlin and J. Thrower, *Tetrahedron*, 1969, **25**, 5921; (*c*) C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu and J. C. Xiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 1896; (*d*) D. A. Nagib and D. W. C. Macmillan, *Nature*, 2011, **480**, 224; (*e*) A. Zanardi, M. A. Novikov, E. Martin, J. B. Buchholz and V. V. Grushin, *J. Am. Chem. Soc.*, 2011, **133**, 20901; (*f*) L. Chu and F. L. Qing, *J. Am. Chem.Soc.*, 2012, **134**, 1298; (*g*) Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 2955; (*h*) S. Seo, J. B. Taylor and M. F. Greaney, *Chem. Commun.*, 2013, **49**, 6385; (*i*) Z. Gonda, S. Kovács, C. Wéber, T. Gáti, A. Mészáros, A. Kotschy and Z. Novák, *Org. Lett.*, 2014, **16**, 4268; (*j*) M. Shang, S. Z. Sun, H. L. Wang, B. N. Laforteza, H. X. Dai and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2014, **53**, 10439; (*k*) X. Li, J. Zhao, L. Zhang, M. Hu, L. Wang and J. Hu, *Org. Lett.*, 2015, **17**, 298; (*l*) J. Zheng, J. H. Lin, X. Y. Deng and J. C. Xiao, *Org. Lett.*, 2015, **17**, 532.

3 (*a*) H. Morimoto, T. Tsubogo, N. D. Litvinas and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2011, **50**, 3793; (*b*) Q. Qi, Q. Shen and L. Lu, *J. Am. Chem. Soc.*, 2012, **134**, 6548; (*c*) N. D. Litvinas, P. S. Fier and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 536; (*d*) A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2013, **135**, 12584; (*e*) Y. Zeng and J. Hu, *Chem. - Eur. J.*, 2014, **20**, 6866; (*f*) M. G. Mornino, P. S. Fier and J. F. Hartwig, *Org. Lett.*, 2014, **16**, 1744; (*g*) D. F. Jiang, C. Liu, Y. Guo, J. C. Xiao and Q. Y. Chen, *Eur. J. Org. Chem.*, 2014, 6303.

4 (*a*) M. Tohnishi, H. Nakao, T. Furuya, A. Seo, H. Kodama, K. Tsubata, S. Fujioka, H. Kodama, T. Hirooka and T. Nishimatsu, *J. Pestic. Sci.*, 2005, **30**, 354; (*b*) A. Conte and H. Kuehne, US 20070185058, 2007; (*c*) J. Guin, C. Rabalako and B. List, *Angew. Chem. Int. Ed.*, 2012, **51**, 8859; (*d*) O. Kazuo, JP 2007308483, 2007.

5 W. Y. Huang and F. H. Wu, *Isr. J. Chem.*, 1999, **39**, 167.

6 J. Hassan, M. Se´vignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.

7 (*a*) R. D. Chambers, W. K. R. Musgrave and J. Savory, *J. Chem. Soc.*, 1962, 1993; (*b*) W. T. Miller and M. B. Freedman, *J. Am. Chem. Soc.*, 1963, **85**, 180; (*c*) P. E. Aldrich, E. G. Howard, W. J. Linn, W. J. Middleton and W. H. Sharkry, *J. Org. Chem.*, 1963, **28**, 184; (*d*) B. L. Dyatkin, S. R. Sterlin, B. I. Martynov, E. I. Mysov and I. L. Knunyants, *Tetrahedron*, 1971, **27**, 2843; (*e*) H. Lange and D. Naumann, *J. Fluoroine Chem.*, 1984, **26**, 1.

8 R. Loska and M. Makosza, *J. Org. Chem.*, 2007, **72**, 1354.

9 (*a*) J. J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z. J. Liu, X. Lu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 8436; (*b*) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 10330; (*c*) G. Danoun, B.

10 Bayarmagnai, M. F. Grünberg and L. J. Gooßen, *Angew. Chem. Int. Ed.*, 2013, **52**, 7972; (*d*) A. Lishchynskyi, G. Berthon and V. V. Grushin, *Chem. Commun.*, 2014, **50**, 10237.
11 G. Danoun, B. Bayarmagnai, M. F. Grünberg and L. J. Gooßen, *Chem. Sci.*, 2014, **5**, 1312.
12 J. Wu, Y. Gu, X. Leng and Q. Shen, *Angew. Chem. Int. Ed.*, 2015, **54**, 7648.
13 (*a*) J. K. Kochi, *J. Am. Chem. Soc.*, 1957, **79**, 2942; (*b*) C. Galli, *Chem. Rev.*, 1988, **88**, 765.
14 H. Kato, K. Hirano, D. Kurauchi, N. Toriumi and M. Uchiyama, *Chem. - Eur. J.*, 2015, **21**, 3895.
15 W. T. Miller, Jr. and R. J. Burnard, *J. Am. Chem. Soc.*, 1968, **90**, 7367.
16 Y. Li, X. Wang, Z. Zhu, Y. Guo, Y. Wu and Y. Gong, *Chem. Commun.*, 2016, **52**, doi: 10.1039/C5CC07616A.
17 B. Bayarmagnai, C. Matheis, E. Risto and L. J. Goossen, *Adv. Synth. Catal.*, 2014, **356**, 2343.