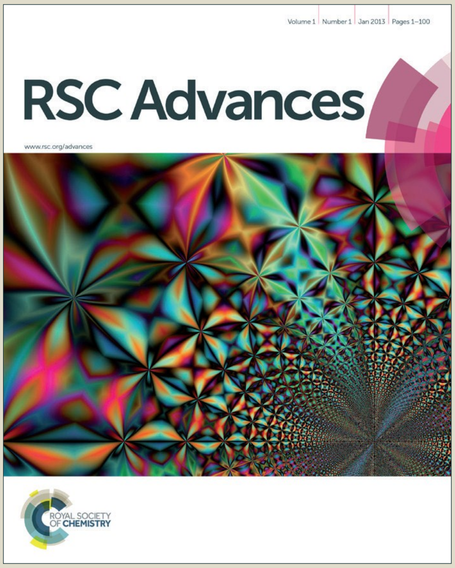
RSC Advances

This article can be cited before page numbers have been issued, to do this please use: P. Anbarasan and V. K. Pandey, *RSC Adv.*, 2016, DOI: 10.1039/C5RA27128B.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA27128B

Journal Name

COMMUNICATION

Copper-catalysed synthesis of trifluoromethyl(hetero)arenes from di(hetero)aryl- λ^3-iodanes‡

Vinay Kumar Pandey, and Pazhamalai Anbarasan[a]

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

An efficient synthesis of trifluoromethylated (hetero)arenes have been achieved through the regioselective copper-catalyzed trifluoromethylation of di(hetero)aryl-λ^3-iodanes employing readily available trifluoromethyltrimethylsilane. The reaction works well for both symmetrical and unsymmetrical di(hetero)aryl-λ^3-iodanes with good regioselectivity and also tolerates diverse functional groups such as bromo, iodo, cyano, nitro, ester, ketone and enolizable ketone.

Trifluoromethylated (hetero)arenes represent a prevalent subunit in agrochemicals, pharmaceuticals and advanced organic materials.[1] The introduction of trifluoromethyl (CF_3) group into the potent organic molecules often drastically alters their physico-chemical properties.[2] Representative examples of trifluoromethylated arenes containing pharmaceutical drugs are shown in Figure 1. However, trifluoromethylated compounds are not found in nature, despite the large abundance of fluorine in earth's crust, because of which the development of practical and new methodologies for the introduction of 'CF_3' group has significantly attracted attention of the scientific community in recent years.[3]

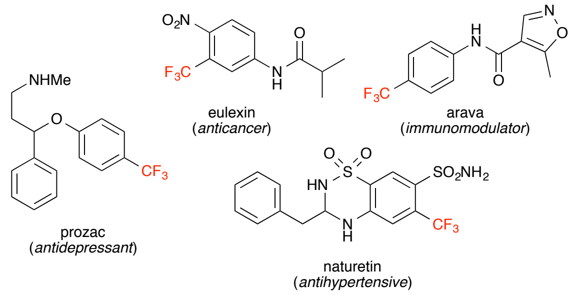
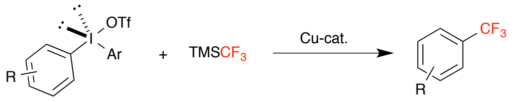


Figure 1. Trifluoromethylated arene containing pharmaceutically important molecules.

Traditionally, synthesis of trifluoromethylated arenes were achieved *via* the Swarts reaction of toluene derivatives, but the utility is rather limited due to the low functional group compatibility and toxicity of the reagent.[4] In recent years, they were replaced with Cu/Pd mediated direct trifluoromethylation of prefunctionalized arenes[5] such as aryl halides[6], arylboron reagents[7], (hetero)arenes[8] using either nucleophilic trifluoromethylating reagent (Ruppert-Prakash reagent)[9] or electrophilic trifluoromethylating reagent[10] (Umemoto's[11] and Togni's reagents[12]). Recently, aryldiazonium salts, an electrophilic arylating reagent were also trifluoromethylated employing super stoichiometric amount of Cu or Ag salts.[13] In general, most of these reactions suffer from high-catalyst loading and harsh reaction conditions. Thus, mild and efficient processes for the introduction of trifluoromethyl group onto aromatic rings are rather highly desirable.

Diaryl-λ^3-iodanes have emerged as an alternative and efficient electrophilic arylating agent in modern organic synthesis for the C-C and C-heteroatom bond forming transformations,[14] since they are readily accessible from simple arenes. Very recently, Qing and co-workers reported the copper mediated trifluoromethylation of diaryl-λ^3-iodanes.[15] However, this method requires a stoichiometric amount of copper catalyst, thus there is a great in developing general and catalytic method for the regioselective trifluoromethylation of diaryl-λ^3-iodanes.[16] Owing to the potential of trifluoromethylated aromatic compounds and based on our continued interest in the synthesis of fluorinated organics and use of diaryl-λ^3-iodanes,[17] herein we reveal the elegant copper-catalyzed regioselective trifluoromethylation of diaryl-λ^3-iodanes employing readily available trifluoromethyltrimethylsilane, $TMSCF_3$.



Scheme 1. An approach to direct trifluoromethylation of di(hetero)aryl-λ^3-iodanes.

For our initial studies, we chose symmetrical diphenyl-λ^3-iodane **1a** as model substrate, which was synthesized from

---

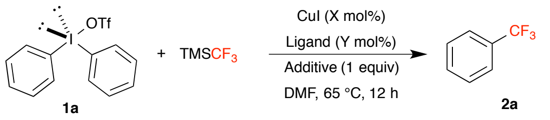
[a] *Department of Chemistry, Indian Institute of Technology Madras, Chennai – 600036, India. E-mail: anbarasansp@iitm.ac.in*

Electronic Supplementary Information (ESI) available: Experimental methods, optimization, characterizations data, ^{19}F NMR and GCMS spectra. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5RA27128B

readily available benzene and iodine under oxidative conditions.[18] The reaction of 1 equivalent of **1a** and 2 equivalents of TMSCF$_3$ in presence of 20 mol% of CuI in DMF at various temperature did not afford any detectable amount of trifluoromethylbenzene **2a**, in ^{19}F NMR (Table 1). To our delight, addition of 1 equivalent of CsF to release the CF$_3$-anion from TMSCF$_3$ promoted the expected reaction to furnish the product **2a** in 50% yield, based on ^{19}F NMR (Table 1, entry 2). Subsequently, screening of various additives revealed that KF is best promoter for the present trifluoromethylation with 75% yield (Table 1, entries 3-5). On the other hand, no trifluoromethylation of **1a** with TMSCF$_3$ and KF was observed in the absence CuI (Table 1, entry 6). This revealed that the present trifluoromethylation indeed was catalyzed by CuI and promoted by KF.

Table 1. Direct trifluoromethylation of diphenyl-λ^3-iodanes.[a]

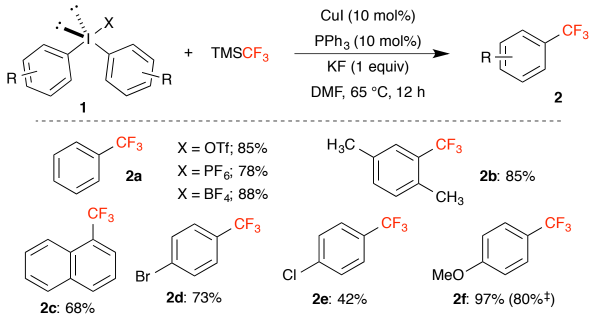


Entry	X (mol%)	Ligand (Y mol%)	Additive	Yield (%)[b]
1	20	-	-	0
2	20	-	CsF	50
3	20	-	KF	75
4	20	-	TBAF	15
5	20	-	^{t}BuOK	7
6	-	-	KF	0
7	10	-	KF	65
8	10	PPh$_3$ (10)	KF	85
9	10	P(*o*-Tolyl)$_3$ (10)	KF	88
10	10	X-Phos (10)	KF	91
11	10	Bipy (10)	KF	48
12	10	Phen (10)	KF	71
13	10[c]	PPh$_3$ (10)	KF	10
14	10[d]	PPh$_3$ (10)	KF	6
15[e]	10	PPh$_3$ (10)	KF	20

[a] Reaction conditions: **1a** (50 mg, 0.115 mmol, 1 equiv), TMSCF$_3$ (0.23 mmol, 2 equiv), CuI (X mol%), ligand (Y mol%), additive (1 equiv), DMF, 65 °C, 12 h; [b] All are ^{19}F NMR yields; [c] Cu(OTf)$_2$ is used; [d] Cu(CH$_3$CN)$_4$BF$_4$ is used; [e] at room temperature.

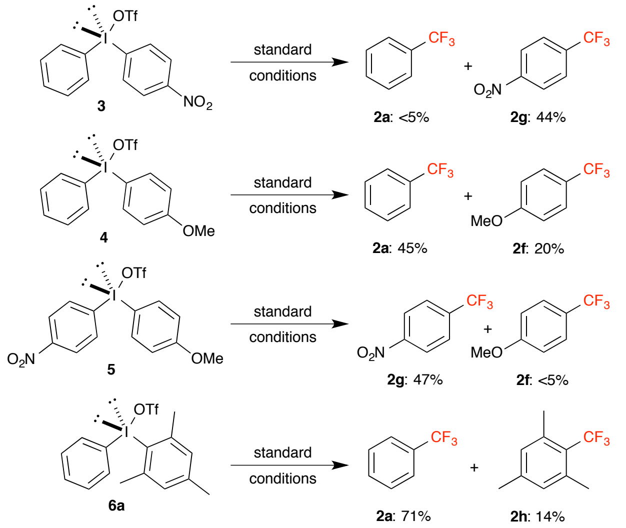
Next, decreasing the catalyst loading to 10 mol% gave the product **2a** in low yield (65%, Table 1, entry 7). To improve the efficiency of the reaction with low catalyst loading, various phosphorous and nitrogen based ligands were examined. Reactions in the presence of electron rich phosphine ligands (PPh$_3$, P(*o*-Tolyl)$_3$ and X-Phos) afforded the product **2a** in excellent yield (Table 1, entries 8-10). In contrast, nitrogen based ligands did not improve the outcome of the present trifluoromethylation (Table 1, entries 11-12). Considering the efficiency and cost of phosphine ligands, PPh$_3$ was chosen as suitable ligand for further investigation. Screening of other copper salts such as Cu(OTf)$_2$ and Cu(CH$_3$CN)$_4$BF$_4$ gave the product in very low yield (~10%, Table 1, entries 13-14). Similar decrease in yield (20%) was observed when the temperature was reduced to room temperature (Table 1, entry 15). Finally, entry 8 in Table 1 was chosen as optimal reaction conditions for the further exploration of substrates scope.

Having achieved the optimal reaction condition for the copper-catalyzed trifluoromethylation, scope and limitation of various symmetrical diaryl-λ^3-iodanes **1** was investigated. As shown in Scheme 2, diverse substituted trifluoromethylbenzenes **2** were achieved in moderate to excellent yield. Initial screening of non-coordinating counterion like PF$_6$-anion and BF$_4$-anion gave the product **2a** in comparable yield. Electron deficient halo-substituted trifluoromethylbenzene **2d** and **2e** were synthesized in good yield from corresponding symmetrical diaryl-λ^3-iodanes. Similarly, electron rich methoxy substituted trifluoromethylbenzene **2f** was achieved in 80% isolated yield. Interestingly, the present reaction conditions also tolerate the sterically demanding *ortho*-substituted diaryl-λ^3-iodanes and led to the formation of **2b** and **2c** in 85% and 68% yield, respectively.



Scheme 2. Copper-catalyzed trifluoromethylation of symmetrical diaryl- λ^3-iodanes.

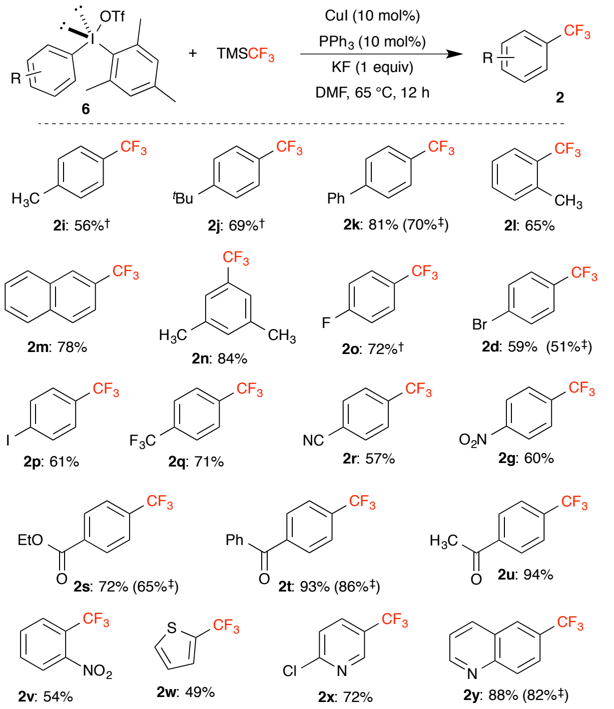
Although the developed trifluoromethylation of symmetrical diaryl-λ^3-iodanes has shown significant scope, synthesis of highly electronically rich and deficient aryl containing symmetrical diaryl-λ^3-iodanes are rather difficult.[18] On the other hand, synthesis of unsymmetrical diaryl-λ^3-iodanes is relatively easier, but the regioselective functionalization is a potential problem.[19] Hence, we focused our attention on the trifluoromethylation of unsymmetrical diaryl-λ^3-iodanes employing the optimized conditions. At first, we synthesized electronically and sterically different diaryl-λ^3-iodanes (**3**-**6**) and subjected under the copper-catalyzed trifluoromethylation conditions. Reaction of diaryl-λ^3-iodane **3** containing electronically neutral (Ph) and deficient (4-NO$_2$Ph) aryl moiety afforded the trifluoromethylated product **2g** as predominant product (Scheme 3). On the other hand, ~2:1 mixture of trifluoromethylated products **2a** and **2f** were observed with unsymmetrical diaryl-λ^3-iodane **4**, where electronically neutral aryl moiety was trifluoromethylated faster than electron rich aryl moiety. Next, trifluoromethylation of nitro and methoxy substituted aryl containing unsymmetrical diaryl-λ^3-iodane **5** gave product **2g** as major product. Interestingly, sterically different phenyl and mesityl substituted diaryl-λ^3-iodane **6a** afforded benzotrifluoride (**2a**) as major product along with minor amount of mesityl trifluoromethylated product **2h** (Scheme 3). These results show that regioselective trifluoromethylation of unsymmetrical diaryl-λ^3-iodanes mainly depends on the electronic and steric factor of aryl groups; specifically, trifluoromethylation is preferred at electron deficient and sterically less hindered aryl moiety.



Scheme 3. Regioselective trifluoromethylation of 3-6.

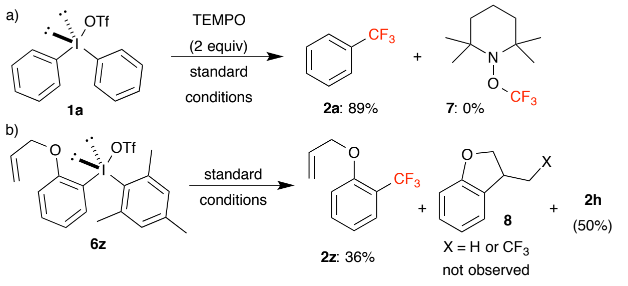
After the successful study of regioselective trifluoromethylation of unsymmetrical diaryl-λ^3-iodanes, we focused our attention on the generality of the regioselective trifluoromethylation of various unsymmetrical diaryl-λ^3-iodanes having mesityl as constant blocker. Various electronically and sterically diverse unsymmetrical diaryl-λ^3-iodanes having mesityl group were regioselectively trifluoromethylated in good to excellent yield under the optimized conditions, along with ~5-10% of **2h** (Scheme 4). Simple alkyl and aryl substituted phenyl containing unsymmetrical diaryl-λ^3-iodanes furnished the expected products **2i-k**, **2m** and **2n** in ~60-84% yield, among them **2k** was isolated in 70% yield. *Ortho*-trifluoromethyltoluene **2l** was achieved in 65% yield from corresponding unsymmetrical diaryl-λ^3-iodane. Readily functionalizable and reactive fluoro, bromo and iodo substituted unsymmetrical diaryl-λ^3-iodanes were well tolerated under the optimized conditions to afford the corresponding benzotrifluorides (**2o**, **2d** and **2p**) in moderate to good yield. Interestingly, the present trifluoromethylation is highly compatible with reactive functional groups such as trifluoromethyl, nitrile, nitro, ester, ketone and enolizable ketone and led to the corresponding benzotrifluorides (**2q-2v**) in ~55-94% yield, wherein **2s** and **2t** were isolated in 65% and 86% yield, respectively. Furthermore, thiophen-2-yl, 2-chloropyridin-5-yl and quinol-6-yl, heteroaromatic substituted unsymmetrical diaryl-λ^3-iodanes were successfully trifluoromethylated in good yield and regioselectivity. These studies revealed that the present optimized condition is applicable for regioselective trifluoromethylation of both symmetrical and unsymmetrical diaryl-λ^3-iodanes in high yield.

Next, preliminary mechanistic investigations were carried out on the optimized reaction. Since many of the copper-catalyzed transformations were proposed to involve radical species,[13b, 13c, 20] influence of radical scavenger and radical clock probe experiments were envisioned to validate whether the radical species are formed in the present trifluoromethylation conditions.



Scheme 4. Regioselective trifluoromethylation of unsymmetrical diaryl-λ^3-iodanes. All are ^{19}F NMR yields. In all the cases ~5-10% of 2h was observed. †~20% of 2h was observed. ‡isolated yield.

Trifluoromethylation of **1a** in the presence of excess of TEMPO under the standard conditions gave the product **2a** in 89% yield (Scheme 5a), which is similar to the yield obtained in Table 1. The formation of either TEMPO-CF_3 **7** or TEMPO-Ph was not observed, as determined by ^{1}H , ^{19}F NMR and GCMS analysis of the crude reaction mixture. Even formation of **7** was not observed with $TMSCF_3$ and TEMPO in the absence of **1a** under the standard conditions.



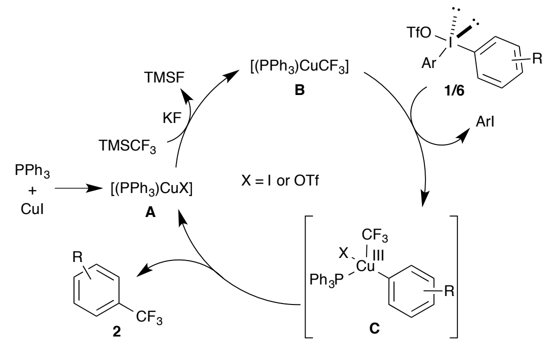
Scheme 5. Mechanistic investigation.

To rule out the formation of aryl radical species, allylether substituted diaryl-λ^3-iodane **6z**, radical clock probe, was subjected under the standard conditions. The trifluoromethylated product **2z** was formed in 36% yield along with 50% of **2h**, whereas cyclization product **8** was not observed, as determined by NMR and GCMS. The increased

View Article Online
DOI: 10.1039/C5RA27128B

yield of **2h** and diminished yield of **2z** were possibly due to the high electron rich nature of allyloxyphenyl moiety. These observations are not in support of the generation of radical species in the present reaction conditions. Next, to probe insights into the mechanism of copper-catalyzed trifluoromethylation, ^{31}P NMR and ^{19}F NMR studies were conducted. Unfortunately, all these studies did not afford any valuable information about the mechanism (see Supporting information).

Thus, based on the observation and copper-catalyzed cross-coupling reaction,[20-21] we postulated the following mechanism for the copper-catalyzed trifluoromethylation of symmetrical and unsymmetrical diaryl-λ^3-iodanes **1**/**6**. The active copper complex **A**, generated from Cu(I) and PPh_3, on reaction with $TMSCF_3$ in the presence of KF would form the CF_3-bound copper species **B**. Formation of copper species **C** could be explained through the oxidation of **B** with diaryl-λ^3-iodanes **1**/**6**. Finally, reductive elimination of benzotrifluorides **2** from **C** would afford the active copper species **A** to continue the catalytic cycle.



Scheme 6. Plausible mechanism.

In conclusion, an efficient copper-catalyzed trifluoromethylation of symmetrical and unsymmetrical diaryl-λ^3-iodanes have been developed for the synthesis of diverse trifluoromethylated (hetero)arenes in good yield and regioselectivity. The optimized reaction tolerates various reactive functional groups like bromo, iodo, cyano, nitro, ester, ketone and enolizable ketone.

Notes and references

‡ We thank Council of Scientific & Industrial Research (CSIR) (Project No. 02(0092)/12/EMR-II) for financial support and Department of Science and Technology (DST) (Project No. SR/S1/OC-48/2012) for sponsoring Gas Chromatography. VKP thanks CSIR for a fellowship.

1 (a) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (c) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH Verlag GmbH, Weinheim, 2013.

2 (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (c) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.

3 (a) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; (b) G. K. Prakash and M. Mandal, *J. Fluorine Chem.*, 2001, **112**, 123; (c) J.-A. Ma and D. Cahard, *J. Fluorine Chem.*, 2007, **128**, 975; (d) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (e) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (f) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475.

4 J. H. Simons and C. J. Lewis, *J. Am. Chem. Soc.*, 1938, **60**, 492.

5 (a) P. Chen and G. Liu, *Synthesis*, 2013, **45**, 2919; (b) X.-F. Wu, H. Neumann and M. Beller, *Chem. Asian J.*, 2012, **7**, 1744; (c) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le and S. Roy, *Tetrahedron*, 2011, **67**, 2161.

6 (a) A. Maleckis and M. S. Sanford, *Organometallics*, 2014, **33**, 2653; (b) X. Li, J. Zhao, L. Zhang, M. Hu, L. Wang and J. Hu, *Org. Lett.*, 2015, **17**, 298; (c) T. Ruhl, W. Rafique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056; (d) M. G. Mormino, P. S. Fier and J. F. Hartwig, *Org. Lett.*, 2014, **16**, 1744; (e) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adan, P. Novak and V. V. Grushin, *J. Org. Chem.*, 2013, **78**, 11126; (f) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nature Chem.*, 2013, **5**, 941; (g) H. Kondo, M. Oishi, K. Fujikawa and H. Amii, *Adv. Synth. Catal.*, 2011, **353**, 1247; (h) T. Knauber, F. Arikan, G.-V. Roschenthaler and L. J. Gooßen, *Chem. –Eur. J.*, 2011, **17**, 2689; (i) M. Oishi, H. Kondo and H. Amii, *Chem. Commun.*, 2009, 1909; (j) Z. Gonda, S. Kovacs, C. Weber, T. Gati, A. Meszaros, A. Kotschy and Z. Novak, *Org. Lett.*, 2014, **16**, 4268; (k) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng and K.-W. Huang, *Organometallics*, 2011, **30**, 3229.

7 (a) S. Arimori and N. Shibata, *Org. Lett.*, 2015, **17**, 1632; (b) P. Ivashkin, G. Lemonnier, J. Cousin, V. Gregoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. –Eur. J.*, 2014, **20**, 9514; (c) H. Serizawa, K. Aikawa and K. Mikami, *Org. Lett.*, 2014, **16**, 3456; (d) S. R. Dubbaka, M. Salla, R. Bolisetti and S. Nizalapur, *RSC Adv.*, 2014, **4**, 6496; (e) M. Presset, D. Oehlrich, F. Rombouts and G. A. Molander, *J. Org. Chem.*, 2013, **78**, 12837; (f) Y. Li, L. Wu, H. Neumann and M. Beller, *Chem. Commun.*, 2013, **49**, 2628; (g) P. Novak, A. Lishchynskyi and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2012, **51**, 7767; (h) B. A. Khan, A. E. Buba and L. J. Goo√üen, *Chem. –Eur. J.*, 2012, **18**, 1577.

8 (a) S. Zhong, A. Hafner, C. Hussal, M. Nieger and S. Brase, *RSC Adv.*, 2015, **5**, 6255; (b) M. Wu, X. Ji, W. Dai and S. Cao, *J. Org. Chem.*, 2014, **79**, 8984; (c) J. Xie, X. Yuan, A. Abdukader, C. Zhu and J. Ma, *Org. Lett.*, 2014, **16**, 1768; (d) F. Sladojevich, E. McNeill, J. Borgel, S.-L. Zheng and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3712; (e) G. Shi, C. Shao, S. Pan, J. Yu and Y. Zhang, *Org. Lett.*, 2015, **17**, 38; (f) S. Seo, J. B. Taylor and M. F. Greaney, *Chem. Commun.*, 2013, **49**, 6385; (g) L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei and Z.-J. Shi, *Org. Lett.*, 2013, **15**, 10; (h) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95.

9 (a) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683; (b) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513.

10 S. Barata-Vallejo, B. Lantano and A. Postigo, *Chem. –Eur. J.*, 2014, **20**, 16806.

11 C. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 6580.

12 J. Charpentier, N. Fruh and A. Togni, *Chem. Rev.*, 2015, **115**, 650.

13 (a) D. L. Browne, *Angew. Chem., Int. Ed.*, 2014, **53**, 1482; (b) A. Lishchynskyi, G. Berthon and V. V. Grushin, *Chem. Commun.*, 2014, **50**, 10237; (c) G. Danoun, B. Bayarmagnai, M. F. Grunberg and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2013, **52**, 7972; (d) 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.

View Article Online
DOI: 10.1039/C5RA27128B

14 (a) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed.*, 2009, **48**, 9052; (b) S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.*, 2015, **137**, 1416; (c) L. Chan, A. McNally, Q. Y. Toh, A. Mendoza and M. J. Gaunt, *Chem. Sci.*, 2015, **6**, 1277; (d) I. Sokolovs, D. Lubriks and E. Suna, *J. Am. Chem. Soc.*, 2014, **136**, 6920.

15 J.-Y. Yang, X.-H. Xu and F.-L. Qing, *J. Fluorine Chem.*, 2015, **180**, 175.

16 J. R. Bour, N. M. Camasso and M. S. Sanford, *J. Am. Chem. Soc.*, 2015, **137**, 8034.

17 (a) V. K. Pandey and P. Anbarasan, *J. Org. Chem.*, 2014, **79**, 4154; (b) P. Saravanan and P. Anbarasan, *Adv. Synth. Catal.*, 2015, **357**, 3521.

18 (a) M. D. Hossain, Y. Ikegami and T. Kitamura, *J. Org. Chem.*, 2006, **71**, 9903; (b) M. Bielawski, D. Aili and B. Olofsson, *J. Org. Chem.*, 2008, **73**, 4602.

19 B. Wang, J. W. Graskemper, L. Qin and S. G. DiMagno, *Angew. Chem., Int. Ed.*, 2010, **49**, 4079.

20 A. I. Konovalov, A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2014, **136**, 13410.

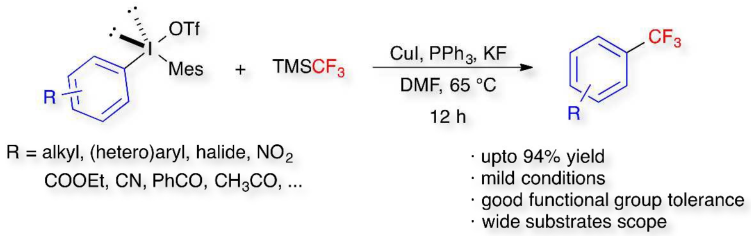
21 N. Nebra and V. V. Grushin, *J. Am. Chem. Soc.*, 2014, **136**, 16998.

View Article Online
DOI: 10.1039/C5RA27128B

Table of contents

Copper catalysed synthesis of trifluoromethyl(hetero)arenes from di(hetero)aryl- λ^3-indanes

Vinay Kumar Pandey, Pazhamalai Anbarasan*



Efficient regioselective copper-catalyzed trifluoromethylation of symmetrical and unsymmetrical diaryl-λ^3-iodanes have been achieved for the synthesis of trifluoromethyl(hetero)arenes in good yield.