Journal of Fluorine Chemistry 131 (2010) 1108–1112

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Decarboxylative trifluoromethylation of aryl halides using well-defined copper–trifluoroacetate and –chlorodifluoroacetate precursors

Kristen A. McReynolds [a], Robert S. Lewis [a], Laura K.G. Ackerman [a], Galyna G. Dubinina [a], William W. Brennessel [b], David A. Vicic [a,*]

[a] Department of Chemistry, University of Hawaii, 2545 McCarthy Mall, Honolulu, HI 96822, United States
[b] The X-ray Crystallographic Facility, Department of Chemistry, University of Rochester, Rochester, NY 14627, United States

ARTICLE INFO

Article history:
Received 17 March 2010
Received in revised form 15 April 2010
Accepted 20 April 2010
Available online 28 April 2010

Keywords:
Trifluoromethylation
Organometallic
Copper

ABSTRACT

New synthetic routes to (NHC)copper–trifluoroacetate and –chlorodifluoroacetate complexes were developed (NHC = *N*-heterocyclic carbenes) so baseline reactivity patterns could be established for the decarboxylative trifluoromethylation of organic halides. In the presence of aryl halides, loss of CO_2 from these new precursors occurred at 160 °C concurrent with the formation of aryl–CF_3.

1. Introduction

The catalytic trifluoromethylation of non-activated organic halides represents a long-standing goal in organometallic chemistry [1–10]. The ability to introduce a trifluoromethyl group into a molecule of interest at a late stage of a synthesis using mild conditions alleviates the need to carry the fluorine functional group through potentially incompatible synthetic procedures, thereby eliminating potential side-reactions and raising overall yields. The development of a catalytic procedure that is wide in scope would powerfully impact the ability to synthesize new materials, drugs, pesticides, agrichemicals, and fluorous tags [11–16].

Motivated by the intense commercial and scientific interest in trifluoromethylation reactions, several key studies have highlighted some of the problematic steps of catalysis [1–4,17]. Perhaps most well-documented is the difficulty in reductive elimination of Ar-CF_3 from low valent Group 10 metal centers, which poses a serious challenge to the development of new catalysts for the trifluoromethylation of aryl bromides and chlorides [1,4,17]. Another area of concern is the lack of a convenient and inexpensive source of the trifluoromethyl group. Electrophilic sources of CF_3 like [(*S*-trifluoromethyl)dibenzothiophene][BF_4] (**1**, Chart 1) are commercially available, and this reagent has been used in a trifluoromethylation reaction catalytic in palladium [18]. Silyl reagents like Et_3Si–CF_3 (**2**) and Me_3Si–CF_3 (**3**) have been used extensively to stoichiometrically trifluoromethylate metal halides [1–4,19], and the former reagent has even been employed in a catalytic reaction using copper and activated aryl iodides [20]. These trifluoromethylsilyl reagents tend to be liquids, easy to handle, with by-products that are readily removed at the end of reactions. However, unless new protocols are developed that can lower the price of these reagents, the utility of trifluoromethylsilyl reagents in large-scale synthesis may be limited. Chart 1 shows that the costs of **1**, **2**, and **3** are exceedingly high (all prices are derived from the largest quantities available in the 2009–2010 Aldrich catalogue). Trifluoromethyl iodide (**4**), another reagent used to trifluoromethylate organic halides [21,22], is cheaper, but clearly more cost effective trifluoromethylating reagents are needed.

Compounds **5**–**8** (Chart 1) are much cheaper alternatives to reagents **1**–**3**. The use of the methyl acetates **5** and **6** as trifluoromethyl sources is well-documented [23–30], however all of the known decarboxylation procedures generate extraneous methyl halide which complicates the development of any *catalytic* cross-coupling procedure with these reagents. We propose that commercial chlorodifluoroacetic acid (**7**) should be a better trifluoromethyl source than **5** or **6** for both cost reasons and for the fact that the by-products of a catalytic reaction involving **7** could be readily handled. We have found no reports of the use of (**7**) as a reagent in a decarboxylative method for forming aryl–CF_3 products. Finally, trifluoroacetic acid (**8**) represents perhaps the most convenient, inexpensive, and readily available source of the trifluoromethyl group for coupling to organic halides. Moreover, it

* Corresponding author.
E-mail address: vicic@hawaii.edu (D.A. Vicic).

0022-1139/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.04.005

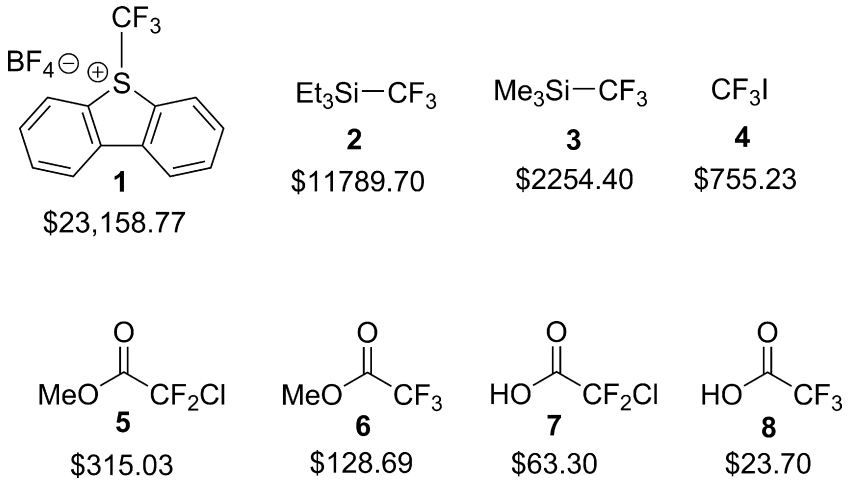


Chart 1. Price per mole of various trifluoromethyl sources. The total cost of using **5**–**7** would also be affected by the need for a fluoride source to either generate a trifluoromethyl group [24,25,28] or facilitate decarboxylation [30,38].

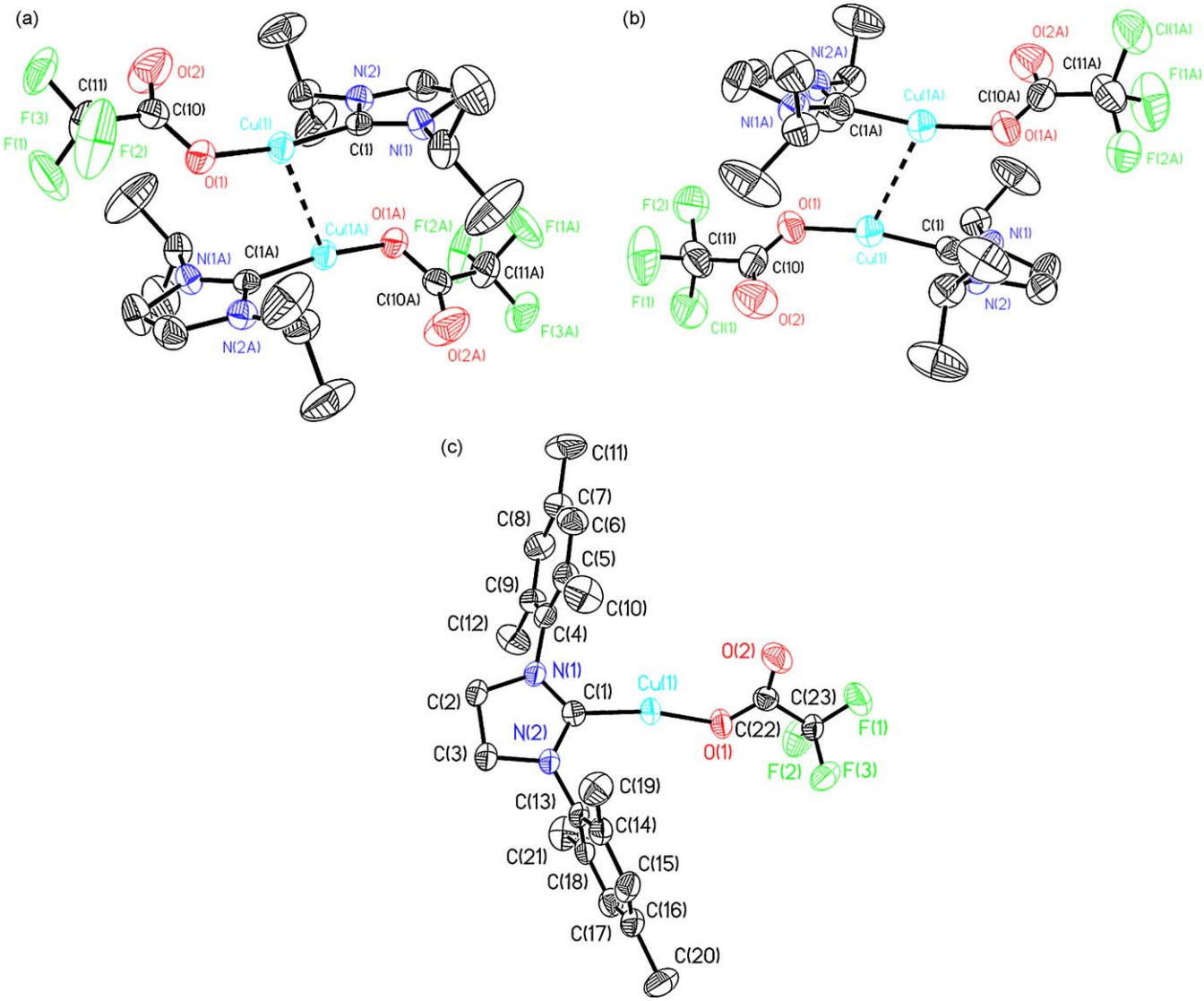
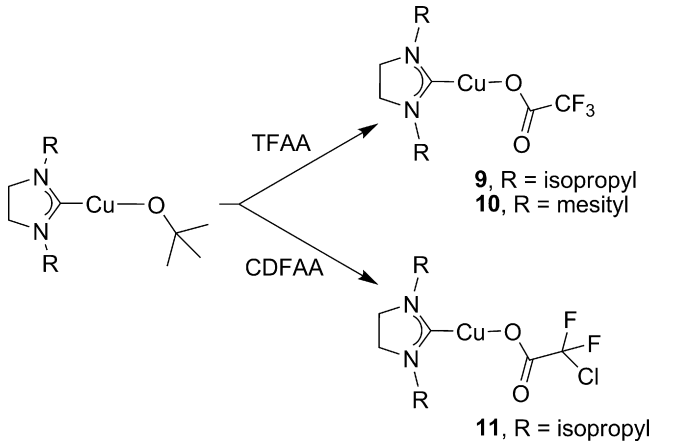


Fig. 1. Solid-state structures of [(SI*i*Pr)Cu(trifluoroacetate)] **9** (a), [(SI*i*Pr)Cu(chlorodifluoroacetate)] **11** (b), and [(SIMes)Cu(trifluoroacetate)] **10** (c). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) for **10**: Cu(1)–O(1) 1.842(4); Cu(1)–C(1) 1.875(6); C(22)–C(23) 1.555(9). Selected bond angles (°): O(1)–Cu(1)–C(1) 168.2(2); C(22)–O(1)–Cu(1) 130.1(4); O(1)–C(22)–C(23) 109.6(5). Crystallographic data (excluding structure factors) for compounds **9**–**11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 769523–769525, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].



Scheme 1. Preparation of new (*N*-heterocyclic carbene)copper–trifluoroacetate and –chlorodifluoroacetate complexes. TFAA, trifluoroacetic acid; CDFAA, chlorodifluoroacetic acid.

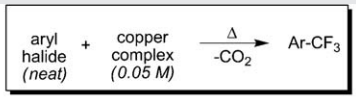
is well-known that heating copper salts with sodium trifluoroacetate leads to a decarboxylation reaction and the formation of a trifluoromethyl source that can be trapped with various organic substrates [31–37], including aryl halides [34–36]. However, trifluoromethylation of aryl halides under these conditions required temperatures above 150 °C and super-stoichiometric amounts of copper.

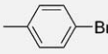
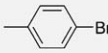
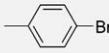
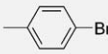
While the use of "ligandless" copper salts as decarboxylation catalysts for **5**–**8** would be most practical in terms of catalyst choice, the study of well-defined ligated copper complexes may provide added insight into controlling reactivity. Such a study would be extremely helpful for understanding the nature and facility of the rate limiting step in the decarboxylation of trifluoroacetic acetate, which is known to occur at temperatures around 150 °C with copper salts [34–36]. The goal of this work is to begin to address the structure/reactivity relationships of well-defined LCu-carboxylates (*i.e.* to determine if ligands can lower the decarboxylation temperature) by developing routes to new copper complexes of **7** and **8**, and to demonstrate the proof-in-principle that indeed these well-defined complexes can be used for the trifluoromethylation of organic halides.

2. Results and discussion

We chose to investigate the use of *N*-heterocyclic carbenes (NHCs) as ligands in the decarboxylation reactions, as it was recently reported that [(NHC)Cu–CF_3] complexes could readily trifluoromethylate aryl iodides [2,3] and bromides [3]. We found the most reliable method to prepare the new (NHC)copper–trifluoroacetate and –chlorodifluoroacetate complexes was to add the corresponding acid to an equivalent amount of [(NHC)Cu(O^tBu)] complex as outlined in Scheme 1. These new copper carboxylate complexes show diagnostic ^{19}F NMR signals at about −76 ppm for the trifluoroacetate and −61 ppm for the chlorodifluoroacetate derivatives. The compounds are stable under an inert atmosphere and crystallize as colorless plates. X-ray crystal structures of **9**–**11** have been obtained, and the ORTEP diagrams are shown in Fig. 1. Interestingly, X-ray analysis reveals that the SI*i*Pr complexes **9** and **11** (SI*i*Pr = 1,3-di-*i*-propylimidazolin-2-ylidene) exist as dimers in the solid-state with Cu–Cu contacts (2.870 and 2.869 Å, respectively), whereas the SIMes derivative **10** (SIMes = 1,3-dimesitylimidazolin-2-ylidene) exists as a monomer. Analyses of the solid-state structures of **9** and **11** were complicated by the common rotational disorders involving CX_3 bonds, but fortunately no disorder was observed for **10**. Selected bond lengths and angles for this SIMes derivative are provided in Fig. 1.

Table 1
Trifluoromethylations at 160 °C mediated by well-defined copper acetate derivatives and "ligandless" copper salts.



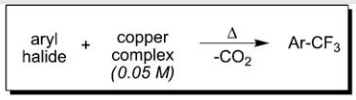
Entry	Aryl Halide	Metal Complex	Time (h)	Yield of Ar-CF_3 (%)
1		(SI*i*Pr)Cu(TFA)	24	64
2		(SIMes)Cu(TFA)	4	20
3		(SI*i*Pr)Cu(CDFA) + 10 equiv CsF	4	19
4		CuI + 2 equiv CF_3CO_2Na	24	0
5		(SI*i*Pr)Cu(TFA)	24	64
6		(SIMes)Cu(TFA)	4	5
7		(SI*i*Pr)Cu(CDFA) + 10 equiv CsF	4	2
8		CuI + 2 equiv CF_3CO_2Na	24	0

Yields were measured by ^{19}F NMR relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields based on copper as the limiting reagent and are an average of two runs. TFA, trifluoroacetate; CDFA, chlorodifluoroacetate.

With the new well-defined copper complexes in hand, the reactivity towards the loss of CO_2 was explored (Table 1). Temperatures of 160 °C were required to achieve decarboxylation, and when the thermolysis of [(SI*i*Pr)Cu(TFA)] was performed in neat phenyl iodide, 64% of trifluorotoluene was obtained (Table 1, entry 1). [(SIMes)Cu(TFA)] and [(SI*i*Pr)Cu(CDFA)] afforded less trifluoromethylated product from phenyl iodide (20 and 19%, respectively, entries 2 and 3). Significantly, all three complexes outperformed the use of "ligandless" copper iodide plus two equivalents of sodium trifluoroacetate under these conditions, which yielded no detectable product by GC/MS or NMR spectroscopy (entry 4). Performing the decarboxylation reactions in neat 4-bromotoluene (entries 5–8) led to similar yields of trifluoromethylated product for [(SI*i*Pr)Cu(TFA)] but substantially lower yields for [(SIMes)Cu(TFA)] and [(SI*i*Pr)Cu(CDFA)]. While the yields in Table 1 are modest at best, they represent improvements in conditions from previous reports of decarboxylative trifluoromethylations using sodium trifluoroacetate as a trifluoromethyl source [34–36]. In these previous studies, trifluoromethylations all proceeded in amide-based solvents with super-stoichiometric amounts of copper relative to aryl halide [34–36].

We next explored the effect of switching to a 1:1 mixture of aryl halide and *N*,*N*-dimethylacetamide (DMA) solvent, as DMA is known to solvate copper salts [39]. The solvent effects were dramatic for "ligandless" copper iodide precursor, which in this

Table 2
Solvent effects for trifluoromethylations at 160 °C mediated by well-defined copper acetate derivatives and "ligandless" copper salts.



Entry	Aryl Halide/Solvent	Metal Complex	Time (h)	Yield of Ar-CF_3 (%)
1	I : DMA (1:1)	CuI + 2 equiv CF_3CO_2Na	24	48
2	Br : DMA (1:1)	CuI + 2 equiv CF_3CO_2Na	24	73
3	I : DMA (1:1)	(SI*i*Pr)Cu(TFA)	10	56
4	Br : DMA (1:1)	(SI*i*Pr)Cu(TFA)	10	59
5	I : DMA (1:1)	(SIMes)Cu(TFA)	24	29
6	Br : DMA (1:1)	(SIMes)Cu(TFA)	24	55
7	I : DMA (1:1)	(SI*i*Pr)Cu(CDFA) + 10 equiv CsF	4	27
8	Br : DMA (1:1)	(SI*i*Pr)Cu(CDFA) + 10 equiv CsF	4	2
9	I : DMA (1:1)	CuI + 1.1 equiv diphenylacetylene + 2 equiv CF_3CO_2Na	24	20
10	Br : DMA (1:1)	CuI + 1.1 equiv diphenylacetylene + 2 equiv CF_3CO_2Na	24	33

Yields were measured by ^{19}F NMR relative to 1,3-dimethyl-2-fluorobenzene as an internal standard. Yields based on copper as the limiting reagent and are an average of two runs.

mixture of solvents afforded yields of 48 and 73% of trifluoromethylated product from phenyl iodide and 4-bromotoluene, respectively (Table 2, entries 1 and 2 vs. Table 1, entries 4 and 8). These yields are on par with what has previously been reported for solvated copper salts in amide-based solvents [34–36]. Notably, the yields of product using DMA solvated copper iodide surpassed that of all the new copper complexes **9**–**11** for the 4-bromotoluene substrate. Solvent effects were less pronounced for **9**–**11** (Table 2, entries 3–8), which are inherently much more homogeneous in aryl halide solution. The addition of diphenylacetylene inhibited the trifluoromethylations relative to "ligandless" copper iodide (Table 2, entries 9 and 10 vs. 1 and 2) which is important because it suggests that decarboxylations may be tunable though ligand design. DFT studies may aid in this regard, especially if it can be determined whether bound DMA facilitates or inhibits the decarboxylation reactions. Finally, an unusual trend was observed in which the trifluoromethylation of 4-bromotoluene proceeded in higher yields than for phenyl iodide for a number of entries (Table 2, entries 2, 4, 6, 10). This electronic effect, and how it may be of relevance to the mechanism of these copper-catalyzed decarboxylative trifluoromethylations, is currently under further investigation.

3. Conclusion

Here we report the first decarboxylative trifluoromethylation of aryl halides using well-defined copper–trifluoroacetate and –chlorodifluoroacetate precursors. The successful syntheses of **9**–**11** permitted the baseline reactivity studies outlined in Tables 1 and 2. In aryl halide solvent, the ligated copper complexes **9**–**11** outperformed "ligandless" copper iodide. However, in DMA solvent, the ligated copper complexes did not afford any enhancement of yields over the known decarboxylation chemistry of copper salts. With these new complexes and data in hand, we can now begin to systematically explore the effects of additives and ligand modifications on the facility and scope of decarboxylative trifluoromethylations with the ultimate goal of performing reactions catalytic in copper.

4. Experimental procedures

4.1. General considerations

All manipulations were performed using standard Schlenk and high-vacuum techniques [40] or in a nitrogen-filled dry box, unless otherwise noted. Solvents were distilled from Na/benzophenone or CaH_2. All reagents were used as received from commercial vendors unless otherwise noted. ^1H NMR spectra were recorded at ambient temperature on a Varian Oxford 300 MHz spectrometer and referenced to residual proton solvent peaks. ^{19}F spectra were recorded on the Varian Oxford spectrometer operating at 282 MHz and were referenced to $CFCl_3$ set to zero. A Rigaku SCXMini diffractometer was used for X-ray structure determinations. $[(SIiPr)Cu(O^tBu)]_2$ and $[(SIMes)Cu(O^tBu)]$ were synthesized according to previously published procedures [2,3].

4.1.1. General procedure to prepare the [(NHC)Cu] complexes 9–11

1 mmol of CF_3COOH was added to solution of corresponding $[(NHC)Cu(O^tBu)]$ (1 mmol) in 10 ml THF and the resulting solution was stirred for 2 h at room temperature. The solvent was then evaporated on a high vac line and the residue was washed with 10 ml of pentane, filtered, and dried under vacuum.

4.1.2. [(1,3-Di-i-propylimidazolin-2-ylidene)copper(trifluoroacetate)] (9)

Yield: 75%. ^1H NMR (CD_2Cl_2): δ 1.25 (d, J = 6.7 Hz, 12H), 3.51 (s, 4H), 4.33 (hept., J = 6.7 Hz, 2H). ^{13}C NMR (THF-d_8): δ 21.6, 44.1, 52.9, 159.9, 197.9. The CF_3 carbon was not observed. ^{19}F NMR (CD_2Cl_2): δ −75.7 (s, 3F).

4.1.3. [(1,3-Dimesitylimidazolin-2-ylidene)copper(trifluoroacetate)] (10)

Yield: 82%. ^1H NMR (CD_2Cl_2): δ 2.32 (s, 6H, *para*-CH_3), 2.34 (s, 12H, *ortho*-CH_3), 3.99 (s, 4H, CH_2-CH_2), 7.02 (s, 4H, Ar-H). ^{13}C (THF-d_8): δ 203.1, 139.3, 136.7, 136.6, 130.5, 52.0, 21.3, 18.3. (Note: the carbon resonances belonging to the trifluoroacetate ligand were not observed.) ^{19}F NMR (CD_2Cl_2): δ −75.9 (s, 3F).

4.1.4. [(1,3-Di-i-propylimidazolin-2-ylidene)copper(chlorodifluoroacetate)] (11)

Yield: 86%. ^1H NMR (THF-d_8): δ 1.26 (d, J = 6.7 Hz, 12H), 3.56 (br s, 4H), 4.39 (sept, J = 6.8 Hz, 2H). ^{13}C NMR (THF-d_8): δ 21.5, 44.0, 52.9. ^{19}F NMR (THF-d_8): δ 61.4 (s,2F).

4.2. General procedure for the decarboxylative cross-coupling reactions

All samples were prepared in J-Young NMR tubes in a nitrogen-filled glovebox. 0.04 mmol of the copper complex was dissolved in 0.8 ml of the desired solvent to give a 0.05 M solution. Sodium trifluoroacetate or cesium fluoride was added, if necessary, as described in Tables 1 and 2. Then 20 μl of 2-fluoro-1,3-dimethylbenzene was added as the internal standard. The resulting solutions were degassed via three freeze–pump–thaw cycles on a high-vacuum line and then heated to the desired temperature in a silicon oil bath. Reactions were monitored by ^{19}F NMR spectroscopy. Yields based on copper complex as the limiting reagent.

Acknowledgement

D.A.V. thanks the Office of Basic Energy Sciences of the U.S. Department of Energy (DE-FG02-07ER15885) for support of this work.

References

[1] G.G. Dubinina, W.W. Brennessel, J.L. Miller, D.A. Vicic, Organometallics 27 (2008) 3933–3938.
[2] G.G. Dubinina, H. Furutachi, D.A. Vicic, J. Am. Chem. Soc. 130 (2008) 8600–8601.
[3] G.G. Dubinina, J. Ogikubo, D.A. Vicic, Organometallics 27 (2008) 6233–6235.
[4] V.V. Grushin, W.J. Marshall, J. Am. Chem. Soc. 128 (2006) 12644–12645.
[5] V.V. Grushin, W.J. Marshall, J. Am. Chem. Soc. 128 (2006) 4632–4641.
[6] D.M. Wiemers, D.J. Burton, J. Am. Chem. Soc. 108 (1986) 832–834.
[7] Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, E. Chikami, Chem. Pharmaceut. Bull. 18 (1970) 2334–2339.
[8] Y. Kobayashi, K. Yamamoto, T. Asai, M. Nakano, I. Kumadaki, J. Chem. Soc. Perkin Trans. 1 (1980) 2755–2762.
[9] Y. Kobayashi, K. Yamamoto, I. Kumadaki, Tetrahedron Lett. 20 (1979) 4071–4072.
[10] F. Cottet, M. Schlosser, Eur. J. Organic Chem. (2002) 327–330.
[11] D.P. Curran, Science 321 (2008) 1645–1646.
[12] M. Zanda, New J. Chem. 28 (2004) 1401–1411.
[13] P. Jeschke, ChemBioChem 5 (2004) 570–589.
[14] M. Schlosser, Angew. Chem. Int. Ed. 45 (2006) 5432–5446.
[15] S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330.
[16] H.-J. Boehm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Mueller, U. Obst-Sander, M. Stahl, ChemBioChem 5 (2004) 637–643.
[17] D.A. Culkin, J.F. Hartwig, Organometallics 23 (2004) 3398–3416.
[18] X. Wang, L. Truesdale, J.-Q. Yu, J. Am. Chem. Soc. 132 (2010) 3648–3649.
[19] F.L. Taw, B.L. Scott, J.L. Kiplinger, J. Am. Chem. Soc. 125 (2003) 14712–14713.
[20] M. Oishi, H. Kondo, H. Amii, Chem. Commun. (2009) 1909–1911.
[21] V.C.R. McLoughlin, Thrower, J. Tetrahedron 25 (1969) 5921–5940.
[22] T.S. Lin, Y.S. Gao, J. Med. Chem. 26 (1983) 598–601.
[23] Q. Chen, J. Duan, Tetrahedron Lett. 34 (1993) 4241–4244.
[24] J. Duan, D. Su, Q. Chen, J. Fluorine Chem. 61 (1993) 279–284.
[25] J.-X. Duan, D.-B. Su, J.-P. Wu, Q.-Y. Chen, J. Fluorine Chem. 66 (1994) 167–169.
[26] J.G. MacNeil Jr., D.J. Burton, J. Fluorine Chem. 55 (1991) 225–227.
[27] W.L. Mitchell, P. Ravenscroft, M.L. Hill, L.J.S. Knutsen, B.D. Judkins, R.F. Newton, D.I.C. Scopes, J. Med. Chem. 29 (1986) 809–816.
[28] D. Su, J. Duan, Q. Chen, Tetrahedron Lett. 32 (1991) 7689–7690.
[29] D. Su, J. Duan, A. Yu, Q. Chen, J. Fluorine Chem. 65 (1993) 11–14.
[30] B.R. Langlois, N. Roques, J. Fluorine Chem. 128 (2007) 1318–1325.
[31] Y. Chang, C. Cai, Chin. Chem. Lett. 16 (2005) 1313–1316.
[32] Y. Chang, C. Cai, Huaxue Shiji 27 (2005) 453–455.
[33] Y. Chang, C. Cai, J. Fluorine Chem. 126 (2005) 937–940.
[34] K. Matsui, E. Tobita, M. Ando, K. Kondo, Chem. Lett. (1981) 1719–1720.
[35] G.E. Carr, R.D. Chambers, T.F. Holmes, D.G. Parker, J. Chem. Soc. Perkin Trans. I (1988) 921–926.
[36] Y. Chang, C. Cai, Jingxi Huagong 22 (2005) 311–313.
[37] Y. Chang, C. Cai, Tetrahedron Lett. 46 (2005) 3161–3164.
[38] L. Jablonski, J. Joubert, T. Billard, B.R. Langlois, Synlett (2003) 230–232.
[39] P. Lemoine, P. Herpin, Acta Crystallogr. Sect. B B36 (1980) 2772–2774.
[40] D.A. Vicic, G.D. Jones, Experimental methods & techniques: basic techniques, in: R.H. Crabtree, D.M.P. Mingos (Eds.), Comprehensive Organometallic Chemistry III, Elsevier, 2006.