Iron(II)-Catalyzed Trifluoromethylation of Potassium Vinyltrifluoroborates

Andrew T. Parsons, **Todd D. Senecal**, and **Stephen L. Buchwald**[*]
Department of Chemistry, Room 18-490, Massachusetts Institute of Technology Cambridge, MA 02139 (USA)

Abstract
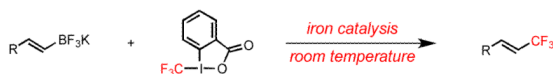
An iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates has been developed. The reactions proceed under mild conditions and provide E/Z selectivities of > 95:5 for 2-aryl and -heteroarylvinyl substrates. Experimental observations suggest that the reaction does not proceed through a transmetallation of the RBF$_3$K to the iron catalyst.

Keywords

The incorporation of fluorinated functional groups in pharmaceutical and agrochemical molecules has had a significant impact on the discovery and development of biologically active compounds.[1,2] Due to its metabolic stability, lipophilicity, and electron-withdrawing character,[3] use of the trifluoromethyl (CF$_3$) substituent has gained considerable attention in recent years. New methods for direct C–CF$_3$ bond-formation have had a prominent presence in current literature, highlighting the importance of this transformation.[4,5] Efforts in our lab have focused on the development of new fluorination[6] and trifluoromethylation[7] reactions through the use of transition metal catalysis and promotion. Herein, we report a facile method to access vinyl–CF$_3$ functional groups through an iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates (**1**) using Togni's reagent **2**[8] (eq 1).
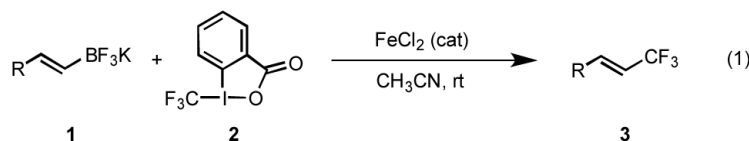
Recently, we reported an oxidative trifluoromethylation of terminal olefins, providing rapid access to allyl–CF$_3$ containing products of type **4**.[9,10] During the course of our studies, we observed **5**, a side product resulting from chloride counterion transfer from CuCl to the olefin substrate subsequent to C–CF$_3$ bond formation (Figure 1, A). We hypothesized several possible intermediates (summarized as **6**) leading to the formation of both **4** and **5**.

[*]Fax: (+1) 617-253-329 sbuchwal@mit.edu.

After consideration of these possibilities, we surmised that regioisomeric products (i.e. vinyl–CF$_3$ containing molecules) might be accessed through a similar type of reactive intermediate. Toward this end, we sought to bias the presumed product-forming step through the use of a functionalized vinyl substrate such as a vinylboron reagent (Figure 1, B). Thus, trifluoromethylation of **7** would lead to formation of intermediate **6d**. Loss of the boron-based functional group would result in the generation of the desired vinyl–CF$_3$ containing product.

We commenced our studies by examining the trifluoromethylation of styryl–BX$_n$ reagents with **2** using various metal catalysts. During our preliminary studies, we discovered that both copper(I)[11] and iron(II) chloride provided a satisfactory yield of product **3a** (Table 1, entries 1-4). Due to the low cost and cleaner reaction profile, we continued our studies using catalytic FeCl$_2$ by examining various vinylboron reagents (Table 1, entries 2-4). Interestingly, the E/Z product ratio varied significantly depending on the identity of styryl–BX$_n$ reagent employed. We felt that these variations suggest that our proposed intermediate **6d** is formed en route to the vinyl–CF$_3$ products since isomerization would be difficult to explain if the olefin remained intact throughout the course of the reaction. The ratios of E/Z isomers may be dependent on the rate of elimination of the boron-based leaving group, where the BPin and B(OH)$_2$ appear to eliminate rapidly to provide a nearly equimolar ratio of isomers. The BF$_3$-based leaving group might be slow to eliminate, resulting in the high E/Z product ratio observed.

Since the potassium trifluoroborate salt provided an excellent E/Z ratio of > 95:5, optimization was continued using styryl– BF$_3$K as a model substrate. Additional increases in yield were achieved through a lowering of catalyst loading and the use of acetonitrile as the solvent. Furthermore, employing **2** as the limiting reagent prevented side product formation. Use of ultra pure (99.998% metals basis) FeCl$_2$ resulted in an equally efficient trifluoromethylation of **1**, suggesting that the catalyst system is iron-based (entry 8). No detectable amounts of β-trifluoromethylstyrene product **3a** were formed in the absence of a metal catalyst (entry 10).

With an optimized protocol in hand, we examined the range of potassium vinyltrifluoroborates capable of undergoing iron(II)-catalyzed trifluoromethylation using **2** (Table 2). 2-Aryl and heteroarylvinyl–BF$_3$K salts were excellent substrates for this method, providing good yields and high E/Z product ratios. Linear aliphatic substrates furnish high yields of the vinyl–CF$_3$ products, but with poor E/Z selectivity. Isomeric ratios were improved when branched aliphatic substrates were used, but remained modest at 83:17 E/Z for a cyclohexyl-substituted substrate (product **3k**). The mild reaction conditions allow for the trifluoromethylation of substrates not suitable for many Cu or Pd-based systems. Notably, all reactions could be set up on the bench top (run under an inert atmosphere) and carried out at room temperature.

During the course of this study, we found that this reaction has some limitations. For example, electron-deficient substrates give a poor yield of trifluoromethylated product. Trisubstituted vinyl–BF$_3$K salts were also poor substrates, furnishing only trace amounts of trifluoromethylated product.[12] We are currently working to address these issues in order to expand the generality of this transformation.

We originally felt that the vinyl trifluoromethylation of **1** might proceed through the cleavage of the π-bond of the olefin in a homo- or heterolytic manner. After our synthetic studies, however, the mechanistic details of this transformation were unclear. We could not rule out the possibility that a transmetallation/reductive elimination-type mechanism is

occurring. We sought to gain insight into the details of this transformation through the examination of selected substrates as mechanistic probes.

Since potassium (*E*)-2-arylvinyltrifluoroborates, such as **1b**, provide high selectivity for the *E* isomer, we sought to determine whether this was a stereospecific trifluoromethylation. Thus, we prepared potassium 4-methylphenylvinyltrifluoroborate **1b** in > 95:5 *Z* isomeric purity. Subjecting (*Z*)-**1b** to the standard reaction conditions furnished β-trifluoromethylstyrene derivative **3b** exclusively as the *E* isomer (eq 2). We conducted an analogous experiment using (Z)-**1j** and obtained identical results when compared to (*E*)-**1j** (eq 3). The stereoconvergence of the *E* and *Z* substrate isomers causes us to disfavor a mechanism that proceeds through a transmetallation/reductive elimination sequence. We believe these experiments suggest a mechanism involving generation of a radical or carbocationic intermediate, similar to **6a** or **6b** (Figure 1).
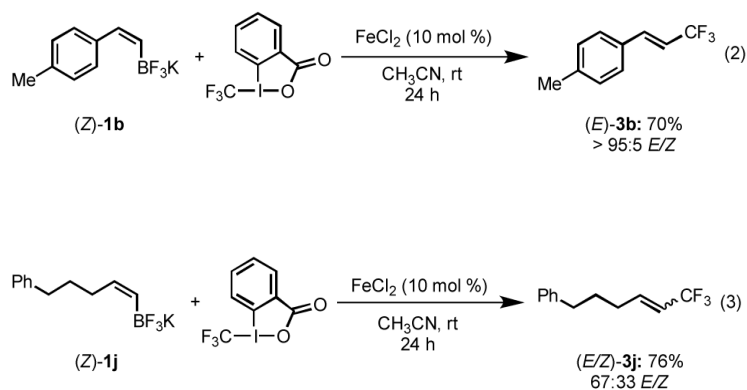
The results obtained in eqs 2-3 led us to investigate whether product formation may be achieved using Lewis acid catalysis (via direct formation of a cationic intermediate, c.f. Figure 1). Thus, we conducted the trifluoromethylation of (*E*)-**1b** in the presence of various Lewis acids. We found that a range of other catalysts provided an appreciable amount of vinyl–CF_3 product. $Sn(OTf)_2$ was the most efficient Lewis acid of those examined, affording (*E*)-**3b** in 80% yield and high *E/Z* ratio. To further examine the transformation catalyzed by $Sn(OTf)_2$, we also conducted trifluoromethylations of (*Z*)-**1b** and (*E/Z*)-**1j** (Scheme 1). Trifluoromethylation of these substrates provided identical *E/Z* ratios and yield regardless of the geometry of the potassium vinyltrifluoroborate starting material. These results further suggest that the trifluoromethylation is not proceeding through a transmetallation/reductive elimination pathway. It should be noted that while the ^{19}F NMR yields of **3b** and **3j** are satisfactory when $Sn(OTf)_2$ is used, the formation of numerous trifluoromethylated side products causes us to prefer $FeCl_2$ as the catalyst for this transformation.

In summary, we have developed an iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates. 2-Arylvinyl substrates in particular provide good yields and excellent *E/Z* ratios. The reactions are amenable to a bench top set up and proceed under exceedingly mild reaction conditions. Preliminary mechanistic analyses suggest the reaction proceeds through a carbocationic intermediate via Lewis acid catalysis, but we are currently unable to rule out a radical-type mechanism. Future efforts in our lab will aim to further elucidate the mechanistic details and expand the scope of this transformation.

Experimental Section

General Procedure for the FeCl$_2$-catalyzed trifluoromethylation of vinyl–BF$_3$K reagents

An oven-dried reaction tube was charged with the potassium vinyltrifluoroborate (1.1 equiv), Togni reagent **2** (1.0 equiv), and iron(II) chloride (0.10 equiv). The tube was sealed with a PTFE-lined screw cap and evacuated and backfilled with argon (repeated for a total of three times). The vial was then charged with acetonitrile (2.5 mL/mmol **2**) and the reaction mixture was stirred at room temperature for 24 h. The contents of the vial were then transferred to a separatory funnel containing saturated NaHCO$_3$ (approx. 10 mL) using CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na$_2$SO$_4$, and concentrated onto silica gel. The products were purified by flash chromatography using the indicated solvent system.

Supplementary Material

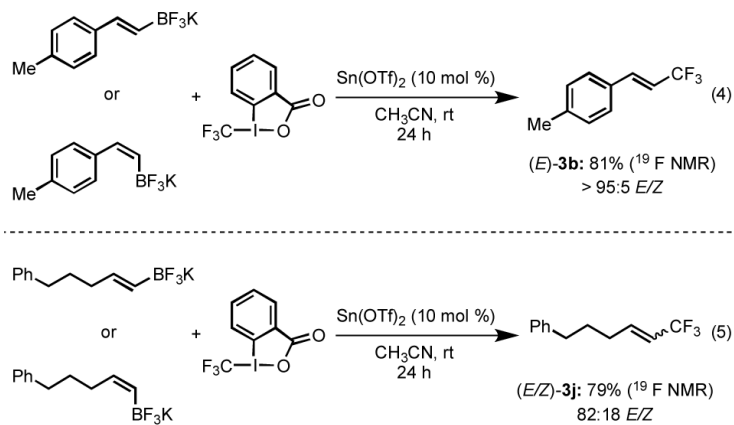Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

[1]. Hiyama, T. Fluorine Compounds: Chemistry and Applications. Springer; Berlin: 2000.

[2]. Muller K, Faeh C, Diederich F. Science. 2007; 317:1881. [PubMed: 17901324]

[3]. Yamazaki, T.; Taguchi, T.; Ojima, I. Fluorine in Medicinal Chemistry and Chemical Biology. Ojima, I., editor. Wiley-Blackwell; Chichester: 2009. p. 3

[4]a). Prakash GKS, Yudin AK. Chem. Rev. 1997; 97:757. [PubMed: 11848888] b) Ma J-A, Cahard D. Chem. Rev. 2008; 108:R1.c) Tomashenko OA, Grushin VV. Chem. Rev. 2011; 111:4475. [PubMed: 21456523]

[5]a). Noritake S, Shibata N, Nakamura S, Toru T, Shiro M. Eur. J. Org. Chem. 2008:3465.b) Oishi M, Kondo H, Amii H. Chem. Commun. 2009:1909.c) Nagib DA, Scott ME, MacMillan DWC. J. Am. Chem. Soc. 2009; 131:10875. [PubMed: 19722670] d) Allen AE, MacMillan DWC. J. Am. Chem. Soc. 2010; 132:4986. [PubMed: 20297822] e) Matsnev A, Noritake S, Nomura Y, Tokunaga E, Nakamura S, Shibata N. Angew. Chem. 2010; 122:582.Angew. Chem. Int. Ed. 2010; 49:572.f) Chu L, Qing F-L. J. Am. Chem. Soc. 2010; 132:7262. [PubMed: 20450157] g) Chu L, Qing F-L. Org. Lett. 2010; 12:5060. [PubMed: 20923196] h) Ye Y, Lee SH, Sanford MS. Org. Lett. 2011; 13:5464. [PubMed: 21932827] i) Ji Y, Brueckl T, Baxter RD, Fujiwara Y, Seiple IB, Su S, Blackmond DG, Baran PS. Proc. Nat. Acad. Sci. 2011; 108:14411. [PubMed: 21844378] j) Zhang C-P, Wang Z-L, Chen Q-Y, Zhang C-T, Gu Y-C, Xiao J-C. Chem. Commun. 2011; 47:6632.k) Zhang C-P, Cai J, Zhou C-B, Wang X-P, Zheng X, Gu Y-C, Xiao J-C. Chem. Commun. 2011; 47:9516.l) Kawai H, Furukawa T, Nomura Y, Tokunaga E, Shibata N. Org. Lett. 2011; 13:3596. [PubMed: 21667988] m) Furukawa T, Nishimine T, Tokunaga E, Hasegawa K, Shiro M, Shibata N. Org. Lett. 2011; 13:3972. [PubMed: 21699265] n) Nagib DA, MacMillan DWC. Nature. 2011; 480:224. [PubMed: 22158245] o) Cho E-J, Buchwald SL. Org. Lett. 2011; 13:6552. [PubMed: 22111687]

[6]a). Watson DA, Su M, Teverovskiy G, Zhang Y, García-Fortanet J, Kinzel T, Buchwald SL. Science. 2009; 325:1661. [PubMed: 19679769] b) Maimone TJ, Milner PJ, Kinzel T, Zhang Y, Takase MK, Buchwald SL. J. Am. Chem. Soc. 2011; 133:18106. [PubMed: 21999801]

[7]a). Cho EJ, Senecal TD, Kinzel T, Zhang Y, Watson DA, Buchwald SL. Science. 2010; 328:1679. [PubMed: 20576888] b) Senecal TD, Parsons AT, Buchwald SL. J. Org. Chem. 2011; 76:1174. [PubMed: 21235259]

[8]a). Eisenberger P, Gischig S, Togni A. Chem. – Eur. J. 2006; 12:2579. [PubMed: 16402401] b) Stanek K, Koller R, Togni A. J. Org. Chem. 2008; 73:7678. [PubMed: 18771328] c) Koller R, Stanek K, Stolz D, Aardoom R, Niedermann K, Togni A. Angew. Chem. 2009; 121:4396.Angew. Chem. Int. Ed. 2009; 48:4332.d) Koller R, Huchet Q, Battaglia P, Welch JM, Togni A. Chem. Commun. 2009:5993.e) Fantasia S, Welch JM, Togni A. J. Org. Chem. 2010; 75:1779. [PubMed: 20121229] f) Eisenberger P, Kieltsch I, Armanino N, Togni A. Chem. Commun. 2008:1575.

[9]. Parsons AT, Buchwald SL. Angew. Chem. 2011; 123:9286.Angew. Chem. Int. Ed. 2011; 50:9120.

[10]a). Related methods were subsequently reported. See: Xu J, Fu Y, Luo D-F, Jiang Y-Y, Xiao B, Liu Z-J, Gong T-J, Liu L. J. Am. Chem. Soc. 2011; 133:15300. [PubMed: 21913663] Wang X, Ye Y, Zhang S, Feng J, Xu Y, Zhang Y, Wang J. J. Am. Chem. Soc. 2011; 133:16410. [PubMed: 21936560]

[11]a). For examples of Cu(I)-catalyzed trifluoromethylation of aryl and vinylboronic acids, see Liu T, Shen Q. Org. Lett. 2011; 13:2342. [PubMed: 21473568] Xu J, Luo D-F, Xiao B, Liu Z-J, Gong T-J, Fu Y, Liu L. Chem. Commun. 2011; 47:4300.

[12]. For example potassium (*E*)-(4-(trifluoromethyl)styryl)trifluoroborate and potassium (1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)trifluoroborate provided < 5% yield of the desired vinyl–CF3 product when subjected to the reaction conditions described in Table 2.

Figure 1.
A) Observed chlorotrifluoromethylation of terminal olefins using CuCl and 2 and B) the proposed vinyl trifluoromethylation of vinylboron reagents.
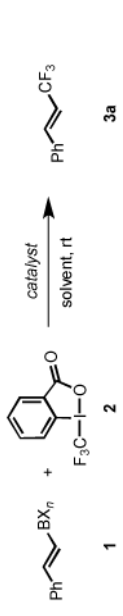
Scheme 1.
Evidence that Lewis acid activation resulting in direct formation of a cationic intermediate is a viable pathway leading to vinyl–CF_3 product formation

Table 1

Optimization studies for the trifluoromethylation of styryl-based vinylboron reagents.[a],[b]

entry	cat (mol %)	BX$_n$	equiv 2	solvent	E/Z	yield
1	CuCl (25)	BF$_3$K	1.2	MeOH	96:4	75%
2	FeCl$_2$ (25)	BF$_3$K	1.2	MeOH	94:6	80%
3	FeCl$_2$ (25)	B(OH)$_2$	1.2	MeOH	50:50	74%
4	FeCl$_2$ (25)	BPin	1.2	MeOH	55:45	73%
5	FeCl$_2$ (10)	BF$_3$K	1.2	MeOH	>95:5	77%
6	FeCl$_2$ (10)	BF$_3$K	1.2	CH$_3$CN	98:2	88%
7	FeCl$_2$ (10)	BF$_3$K	0.9	CH$_3$CN	99:1	86%
8[c]	FeCl$_2$ (10)	BF$_3$K	0.9	CH$_3$CN	99:1	89%
9	FeCl$_3$ (10)	BF$_3$K	0.9	CH$_3$CN	nd[d]	9%
10	none	BF$_3$K	0.9	CH$_3$CN	–	0%

[a]Reaction conditions: **1** (0.20 mmol), **2** (0.24 or 0.18 mmol), and catalyst in 0.50 mL solvent at room temperature for 24 h.
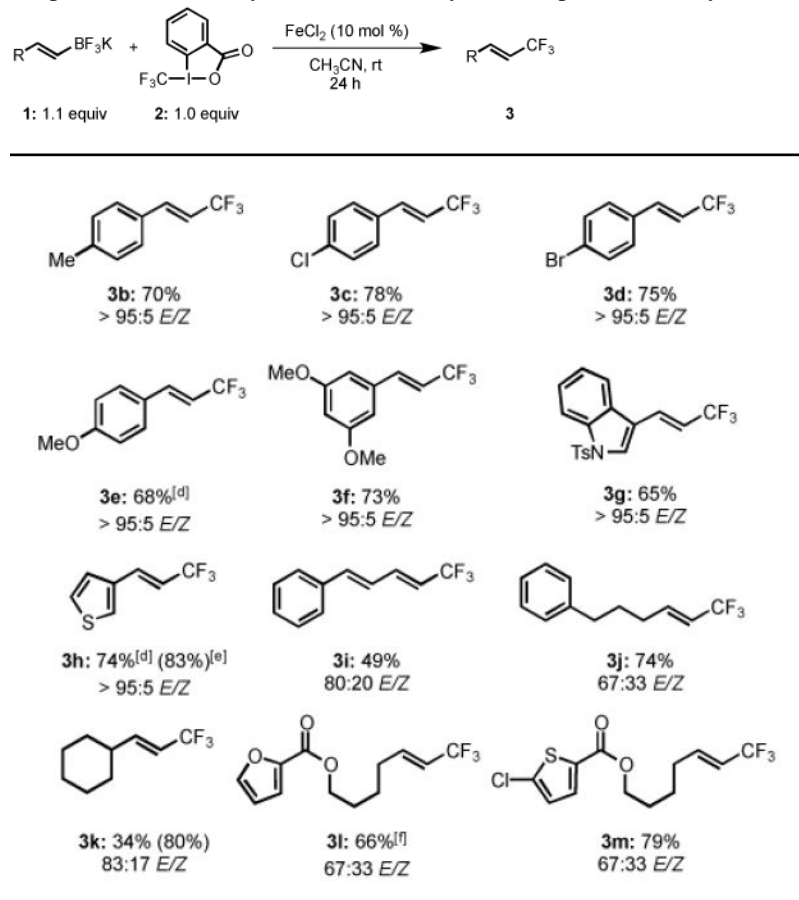
[b]Yield and E/Z ratio were determined by ^{19}F NMR spectroscopy.

[c]FeCl$_2$ (99.998% pure, Aldrich) was used.

[d]nd = not determined.

Table 2

Scope of the Fe^{II}-catalyzed trifluoromethylation of potassium vinyltrifluoroborates using 2.[[a],[b],[c]]

[a] Reaction conditions: **1** (1.1–0.55 mmol, 1.1 equiv), **2** (1.0–0.50 mmol, 1.0 equiv), FeCl$_2$ (10 mol %), [**2**]$_{t=0}$ = 0.40 M. Reaction time was not optimized.

[b] Isolated yield, average of two independent trials.

[c] Determined by ^{19}F and ^{1}H NMR spectroscopy.

[d] Contains 10-15 mol % of a protodeboronated side product.

[e] Yields in parentheses were determined by ^{19}F NMR spectroscopy.

[f] 15 mol % FeCl$_2$ was used.