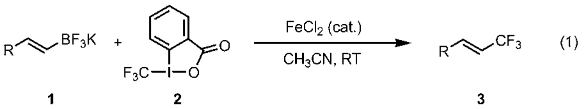
Angewandte
Chemie

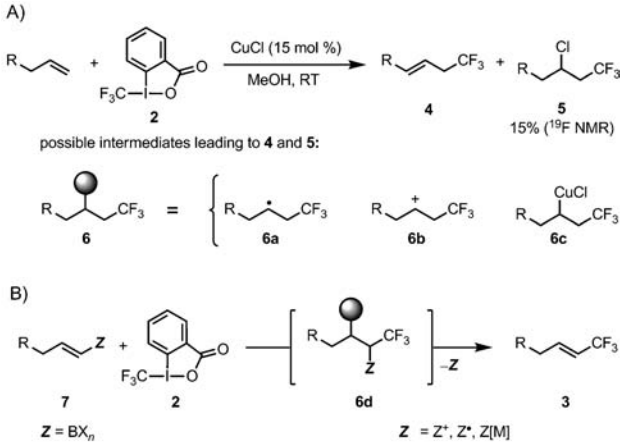
DOI: 10.1002/ange.201108267

Iron(II)-Catalyzed Trifluoromethylation of Potassium Vinyltrifluoroborates**

*Andrew T. Parsons, Todd D. Senecal, and Stephen L. Buchwald**

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] Because of its metabolic stability, lipophilicity, and electron-withdrawing character,[3] use of the trifluoromethyl (CF_3) substituent has gained considerable attention in recent years. Several new methods for the direct formation of C$-$CF$_3$ bonds have been reported recently, thus highlighting the importance of this transformation.[4,5] Efforts of our research group 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)].





Scheme 1. A) Observed chlorotrifluoromethylation of terminal olefins when CuCl and **2** are used, and B) the proposed vinyl trifluoromethylation of vinylboron reagents.

Recently, we reported an oxidative trifluoromethylation of terminal olefins, which provides rapid access to allyl$-$CF$_3$ containing products of type **4**.[9,10] During the course of our studies, we observed the formation of **5**, which is a side product that results from the transfer of the chloride counterion from CuCl to the olefin substrate subsequent to C$-$CF$_3$ bond formation (Scheme 1 A). We hypothesized several possible intermediates (summarized as **6**) that lead to the formation of both **4** and **5**. 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 evaluate the presumed product-forming step through the use of a functionalized vinyl substrate such as a vinylboron reagent (Scheme 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** by 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). Because of the low cost and cleaner reaction profile, we continued our studies by examining various vinylboron reagents using catalytic FeCl$_2$ (Table 1, entries 2–4). Interestingly, the E/Z product ratio varied significantly, depending on the identity of the styryl$-$BX$_n$ reagent employed. 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; the Bpin and B(OH)$_2$ moieties 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 by 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 the formation

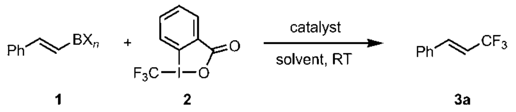
---

[*] Dr. A. T. Parsons, T. D. Senecal, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu

[**] We thank the National Institutes of Health (GM46059) for financial support of this project and for a postdoctoral fellowship to A.T.P. (F32M093532). The Varian 300 MHz and Bruker 400 MHz NMR spectrometers used in this work were supported by grants from the National Science Foundation (CHE-9808061 and DBI-9729592) and National Institutes of Health (1S10RR13886-01), respectively.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201108267.

Table 1: Optimization studies for the trifluoromethylation of styryl-based vinylboron reagents.[a,b]



Entry	Cat. (mol%)	BX$_n$	**2** [equiv]	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	n.d.[d]	9
10	none	BF$_3$K	0.9	CH$_3$CN	–	0

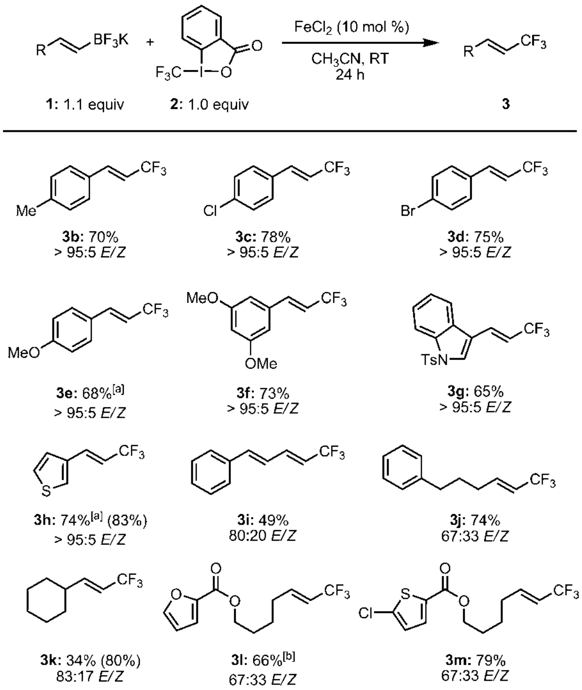
[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 or 0.18 mmol), and catalyst in 0.50 mL solvent at room temperature for 24 hours. [b] Yield and *E*/*Z* ratio were determined by ^{19}F NMR spectroscopy. [c] Ultrapure FeCl$_2$ (99.998% based on trace metals, Sigma–Aldrich) was used. [d] n.d. = not determined. pin = pinacolato.

of side products. Use of ultrapure FeCl$_2$ (99.998% based on trace metals) resulted in an equally efficient trifluoromethylation of **1**, thus suggesting that the catalyst system is iron-based (Table 1, entry 8). No detectable amounts of β-trifluoromethylstyrene product **3a** were formed in the absence of a metal catalyst (Table 1, entry 10).

With an optimized protocol in hand, we examined the range of potassium vinyltrifluoroborates that are capable of undergoing iron(II)-catalyzed trifluoromethylation with **2** (Scheme 2). 2-Arylvinyl–BF$_3$K and 2-heteroarylvinyl–BF$_3$K salts were excellent substrates for this method and provided the products in good yields and high *E*/*Z* product ratios. Linear aliphatic substrates furnished vinyl–CF$_3$ products in high yields, 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 that are not suitable for many copper- or palladium-based systems. Notably, all reactions could be set up on the bench top (run under an inert atmosphere) and carried out at room temperature.

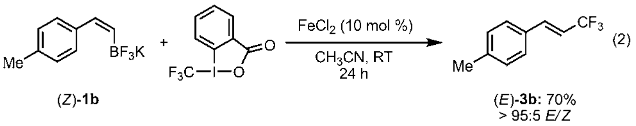
During the course of this study, we found that this reaction has some limitations. For example, electron-deficient substrates give trifluoromethylated products in poor yields. Trisubstituted vinyl–BF$_3$K salts were also poor substrates and furnished only trace amounts of trifluoromethylated product.[12] 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 mechanism including transmetalation and reductive elimination is occurring. We sought to gain insight into the details of this transformation through the examination of selected substrates as mechanistic probes.

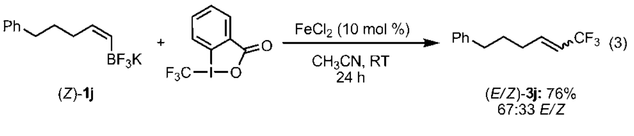


Scheme 2. Scope of the iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates using **2**. Reaction conditions: **1** (1.1–0.55 mmol, 1.1 equiv), **2** (1.0–0.50 mmol, 1.0 equiv), FeCl$_2$ (10 mol%), $[\mathbf{2}]_{t=0} = 0.40$ M. The reaction time was not optimized, and the yields of isolated products are given as average of two independent trials. Yields in parentheses were determined by ^{19}F NMR spectroscopy. *E*/*Z* ratios were determined by ^{19}F and ^{1}H NMR spectroscopy. [a] Contains 10–15 mol% of a protodeboronated side product. [b] 15 mol% FeCl$_2$ was used.

Since potassium (*E*)-2-arylvinyltrifluoroborates, such as **1b**, provide high selectivity for the *E* isomer, we were interested in determining 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 by 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 transmetalation/reductive elimina-



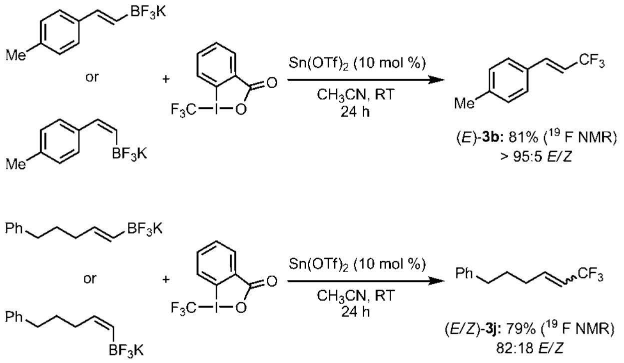
(2)



(3)

tion sequence. We believe these experiments suggest a mechanism involving generation of a radical or carbocationic intermediate, similar to **6a** or **6b** (Scheme 1).

The results shown in Equations (2) and (3) led us to investigate whether product formation may be achieved by using Lewis acid catalysis (through the direct formation of a cationic intermediate, see Scheme 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 and afforded (*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 3).



Scheme 3. Evidence that Lewis acid activation resulting in direct formation of a cationic intermediate is a viable pathway that leads to vinyl–CF_3 product formation.

Trifluoromethylation of these substrates provided identical *E*/*Z* ratios and yields regardless of the geometry of the potassium vinyltrifluoroborate starting material. These results further suggest that the trifluoromethylation is not proceeding through a transmetalation/reductive elimination pathway. It should be noted that while the yields of **3b** and **3j** (determined by ^{19}F NMR spectroscopy) 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 products in 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 by Lewis acid catalysis, but we are currently unable to rule out a radical-type mechanism. Future efforts of our research group 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_3K reagents. An oven-dried reaction tube was charged with 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, evacuated, and backfilled with argon (repeated three times). The vial was then charged with acetonitrile (2.5 mL mmol^{-1} **2**) and the reaction mixture was stirred at room temperature for 24 hours. The contents of the vial were then transferred to a separatory funnel that contained saturated $NaHCO_3$ (≈10 mL) by using CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and adsorbed onto silica gel. The products were purified by flash chromatography using the solvent system indicated in the Supporting Information.

Received: November 23, 2011

Keywords: fluorine · homogeneous catalysis · iron · trifluoromethylation

---

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

[2] K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.

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

[4] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1; c) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475.

[5] a) S. Noritake, N. Shibata, S. Nakamura, T. Toru, M. Shiro, *Eur. J. Org. Chem.* **2008**, 3465; b) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; d) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; e) A. Matsnev, S. Noritake, Y. Nomura, E. Tokunaga, S. Nakamura, N. Shibata, *Angew. Chem.* **2010**, *122*, 582; *Angew. Chem. Int. Ed.* **2010**, *49*, 572; f) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2010**, *132*, 7262; g) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060; h) Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464; i) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411; j) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632; k) C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 9516; l) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga, N. Shibata, *Org. Lett.* **2011**, *13*, 3596; m) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro, N. Shibata, *Org. Lett.* **2011**, *13*, 3972; n) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; o) E.-J. Cho, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 6552; p) X. Jiang, L. Chu, F.-L. Qing, *J. Org. Chem.* **2012**, DOI: 10.1021/jo202566h.

[6] a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661; b) T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 18106.

[7] a) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; b) T. D. Senecal, A. T. Parsons, S. L. Buchwald, *J. Org. Chem.* **2011**, *76*, 1174.

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

[9] A. T. Parsons, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9286; *Angew. Chem. Int. Ed.* **2011**, *50*, 9120.

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

[11] For examples of Cu^{I}-catalyzed trifluoromethylation of aryl and vinylboronic acids, see: a) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342; b) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu, L. Liu, *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$-$CF$_3$ product when subjected to the reaction conditions described in Scheme 2.