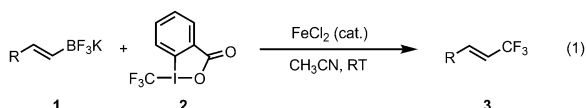


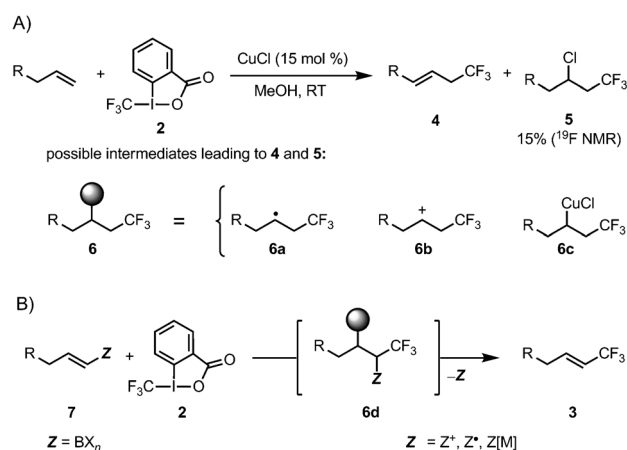
Iron(II)-Catalyzed Trifluoromethylation of Potassium Vinyltrifluoroborates**

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 (CF₃) substituent has gained considerable attention in recent years. Several new methods for the direct formation of C–CF₃ 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–CF₃ 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, which provides rapid access to allyl–CF₃ 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–CF₃ bond formation (Scheme 1A). 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–CF₃ containing molecules) might be accessed through a similar type of reactive intermediate. Toward this end, we sought to evaluate the presumed product-forming step



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

through the use of a functionalized vinyl substrate such as a vinylboron reagent (Scheme 1B). 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–CF₃ 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 FeCl₂ (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–CF₃ 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 BF₃-based leaving group might be slow to eliminate, resulting in the high *E/Z* product ratio observed.

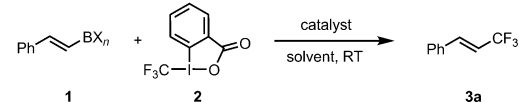
Since the potassium trifluoroborate salt provided an excellent *E/Z* ratio of > 95:5, optimization was continued by using styryl–BF₃K as a model substrate. Additional increases in yield were achieved through a lowering of catalyst loading and the use of acetonitrile as the solvent. Furthermore, employing **2** as the limiting reagent prevented the formation

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



Entry	Cat. (mol %)	BF ₃ K	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) ₃	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

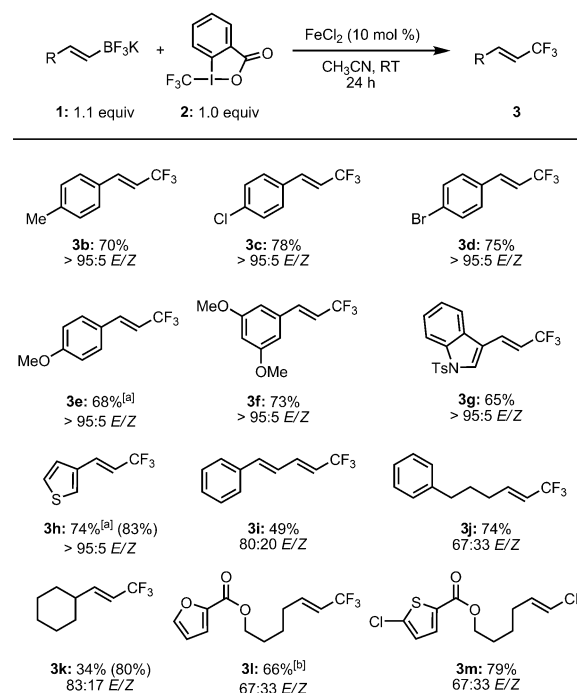
[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 or 0.18 mmol), and catalyst in 0.50 mL solvent at room temperature for 24 hours. [b] Yield and E/Z ratio were determined by ¹⁹F NMR spectroscopy. [c] Ultrapure FeCl₂ (99.998% based on trace metals, Sigma-Aldrich) was used. [d] n.d. = not determined. pin = pinacolato.

of side products. Use of ultrapure FeCl₂ (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-BF₃K and 2-heteroarylvinyl-BF₃K 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-CF₃ 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.

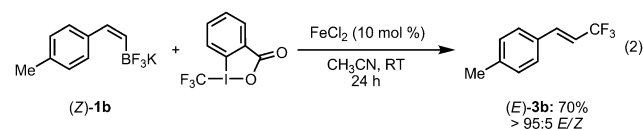
During the course of this study, we found that this reaction has some limitations. For example, electron-deficient substrates give trifluoromethylated products in poor yields. Trisubstituted vinyl-BF₃K salts were also poor substrates and furnished only trace amounts of trifluoromethylated product.^[12] 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.

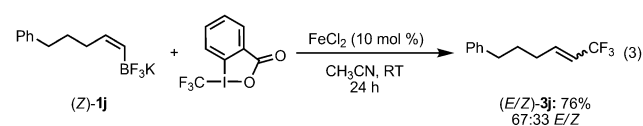


Scheme 2. Scope of the iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates using **2**. Reaction conditions: **1** (1.1–0.55 mmol, 1.1 equiv), **2** (1.0–0.50 mmol, 1.0 equiv), FeCl₂ (10 mol %), [2]_{total} = 0.40 M. The reaction time was not optimized, and the yields of isolated products are given as average of two independent trials. Yields in parentheses were determined by ¹⁹F NMR spectroscopy. E/Z ratios were determined by ¹⁹F and ¹H NMR spectroscopy. [a] Contains 10–15 mol % of a protodeboronated side product. [b] 15 mol % FeCl₂ 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

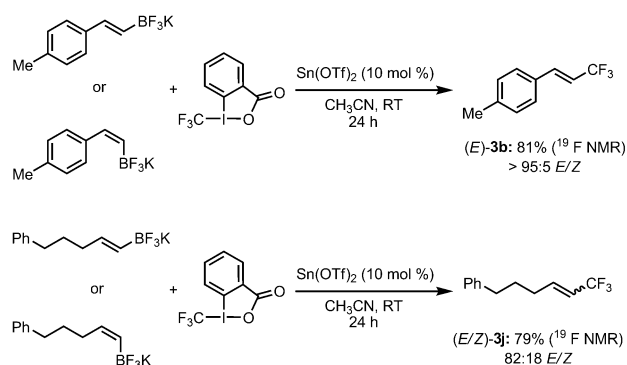


compared to (*E*)-**1j** [Eq. (3)]. The stereoconvergence of the *E* and *Z* substrate isomers causes us to disfavor a mechanism that proceeds through a transmetalation/reductive elimination



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-CF₃ 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-CF₃ 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 ¹⁹F NMR spectroscopy) are satisfactory when Sn(OTf)₂ is used, the formation of numerous trifluoromethylated side products causes us to prefer FeCl₂ 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 FeCl₂-catalyzed trifluoromethylation of vinyl-BF₃K 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 NaHCO₃ (≈ 10 mL) by using CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, and adsorbed onto silica gel. The products were purified by flash chromatography using the solvent system indicated in the Supporting Information.

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