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(*Z*)- or (*E*)-Selective Hydrogenation of Potassium (3,3,3-Trifluoroprop-1-yn-1-yl)trifluoroborate: Route to Either Isomer of *β*-Trifluoromethylstyrenes

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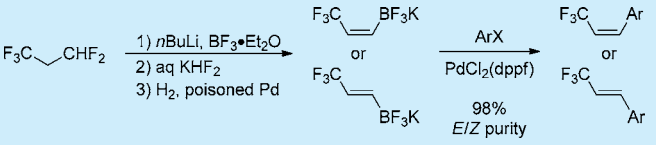
Supporting Information

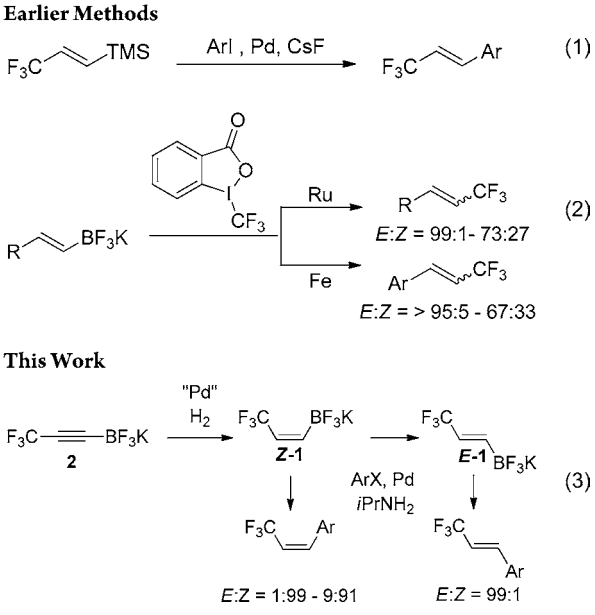
ABSTRACT: A Pd-catalyzed hydrogenation of potassium (3,3,3-trifluoroprop-1-yn-1-yl)trifluoroborate providing either the (*Z*)- or (*E*)-isomer of the vinylborate in >98% purity is described. The initially formed (*Z*)-isomer of the alkene is transformed to the (*E*)-isomer with time, irrespective of the catalyst used; coupling with bromo- and iodoarenes provides a variety of (*Z*)- or (*E*)-*β*-trifluoromethylstyrenes. Also, a safe synthesis of the alkynyltrifluoroborate from HFC-245fa and BF_3·OEt_2 has been described.



The unique effects of the trifluoromethyl moiety in the pharmacology of bioactive molecules attract medicinal chemists,[1] while the moiety's high thermal and oxidative stabilities appeal to materials chemists.[2] Direct insertion of a CF_3 group is preferred over the cumbersome regiospecific fluorination for their synthesis.[3] The reaction of CF_3-olefins has also been employed as a surrogate to introduce a CF_3 group. Accordingly, the stereospecific synthesis of CF_3-olefins has attained importance. Recent literature has witnessed an increase in nucleophilic, electrophilic, and radical trifluoromethylations,[3] but a corresponding vinylogous reaction to prepare CF_3-olefins has trailed.

Olefination of aldehydes via a Wittig-type reaction of CF_3-ylides results in either pure (*E*)-olefins or mixtures.[4] Photoredox-catalyzed hydrotrifluoromethylation of alkynes,[5] decarboxylative trifluoromethylation of cinnamic acids,[6] Heck-type coupling of in situ generated trifluoropropene,[7] and Suzuki coupling of (*E*)-CF_3-vinyldiphenylsulfonium salt[8] with arylboronic acids also provide (*E*)-olefins. Transition-metal-catalyzed coupling processes of (*E*)-CF_3-vinylmetal partners retained their stereochemistry and resulted in (*E*)-olefins. For example, Hiyama coupling of (*E*)-CF_3-vinylsilanes (eq 1)[9] and photo- or Fe(II)-catalyzed coupling of (*E*)-alkenylBF_3K with Togni's reagent (eq 2)[10] generated (*E*)-alkenes either selectively or predominantly. All of the aforementioned methodologies provided only the (*E*)-isomer.

As part of our program on fluoro-organic synthesis via boranes,[11] we required both stereoisomers of CF_3-styrenes. The Suzuki coupling of (*Z*)-CF_3-vinylboron seemed an obvious choice to prepare the (*Z*)-olefins. However, the steric/electronic effects of the CF_3 group on the coupling were a concern because isomerization of (*Z*)-alkenyl-Pd with bulky groups such as *t*-butyl has been reported.[12] We report herein the preparation of either isomer of pure *β*-CF_3-styrenes involving a facile synthesis of $CF_3C{\equiv}CBF_3K$ (**2**) from



$CF_3CH_2CHF_2$ (**4**), a stereoselective hydrogenation, and Suzuki coupling (eq 3).

The preparation of the vinyl trifluoroborate ((*Z*)-**1**) was the initial step in our project. In the hydrocarbon series, hydroboration of 1-haloalkynes, followed by reductive rearrangement, is a routine process to prepare the corresponding (*Z*)-vinylboron.[13] However, the instability of $CF_3C{\equiv}CBr$[14] and the potential for Markovnikov hydroboration of CF_3-alkynes[11,15] dissuaded us from adopting this pathway.

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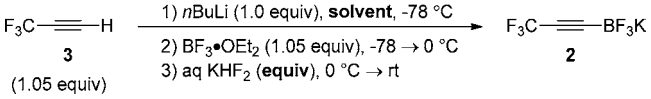
Fortunately, the preparation of **2** has been reported,[16] and we envisaged a stereoselective hydrogenation to achieve our goal.

Frohn's synthesis of **2** involved the alkynylation of $B(OMe)_3$, followed by treatment with aqueous KHF_2 in the critical presence of HF.[17] Due to safety concerns,[18] we opted to explore other protocols for the preparation of **2**. Utilization of $BF_3{\cdot}Et_2O$ as a source of boron to prepare R_FBF_3K has been reported in the literature. For example, Chambers et al. reported the formation of CF_3BF_3K by trapping the CF_3 anion from Me_3SnCF_3 with BF_3[19] and converting the ate complex formed to the desired salt using KF. Recently, Stefani et al. reported the formation of $KRBF_3$ from lithiated 2-substituted 1,3-dithianes using $B(OMe)_3$ and KHF_2.[20] When necessary, they used $BF_3{\cdot}OEt_2$ to improve yields. Adopting this for a possible safe synthesis of **2** from 3,3,3-trifluoropropyne (**3**), we performed a protocol standardization by varying the solvents, concentration, and equiv of KHF_2 (Table 1; entry 5 is the optimal condition).

Table 1. Optimization of the Formation of 2

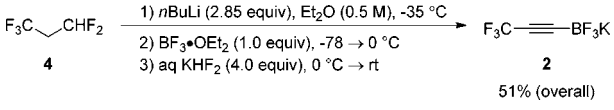


entry	solvent	concn[a] (M)	equiv of KHF_2	yield[b] (%)
1	THF	1.0	4.0	67
2	Et_2O	1.0	4.0	79
3	THF	0.5	4.0	83
4	THF	0.5	1.2	49
5	Et_2O	0.5	4.0	89

[a]Concentration of **3**. [b]Isolated yield.

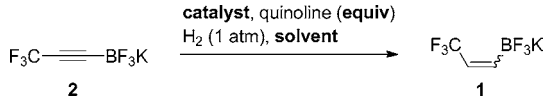
The cost of **3** became a concern for the scale up of **2**. The preparation of $CF_3C{\equiv}CLi$ from 2-bromo-3,3,3-trifluoropropene[21] and HFC-245fa ($CF_3CH_2CHF_2$, **4**)[16,22] has been reported. The latter commodity chemical was converted to **2** by adopting our optimized protocol in a moderate 51% yield for a 0.7 mol scale reaction (Scheme 1).

Scheme 1. Synthesis of 2 from HFC-245fa



Attention was now turned to a selective hydrogenation to prepare (*Z*)-**1**. Brown et al. standardized the hydrogenation of alkynyl-$B(OiPr)_2$ in dioxane to yield >95% (*Z*)-isomer using Lindlar catalyst in the presence of quinoline.[23] Soderquist et al. reported a hydroboration−protodeboronation approach for similar (*Z*)-alkenylboron species.[24] Due to stability concerns for **2** in the presence of acids, Brown's protocol was adopted. Monitored by ^{19}F NMR spectroscopy, **2** was semihydrogenated in the presence of Lindlar catalyst with added quinoline in 1,2-dimethoxyethane (DME) (Table 2, entry 1).[25] To our surprise, we observed that the peak at δ −61 ppm, corresponding to the initial product, shifted with time to δ −66 ppm, along with the formation of an additional triplet at δ −70 ppm, corresponding to the over-reduced product **5**. The (*Z*)-isomer gradually converted almost entirely (2:80) to the thermodynamically stable (*E*)-isomer (along with 18% of **5**), as confirmed by coupling[26] with 1-bromonaphthalene (**6a**) in the presence of

Table 2. Optimization of Semihydrogenation



					product ratio[c]			
entry	time (h)	solvent (M)	Pd[a]	Q[b]	**2**	(*Z*)-**1**	(*E*)-**1**	**5**
1	1.5	DME (0.3)	L (5)	10	0	2	80	18
2	1.5	MeOH (0.3)	L (1)	5	0	3	73	24
3	1.5	DME (1.0)	L (0.5)	5	0	44	42	14
4	1.0	DME (1.0)	L (0.5)	5	9	79	9	3
5	1.0	DME (0.3)	B (5)	10	34	57	5	4
6	1.5	DME (0.3)	B (5)	10	0	0	56	44
7	1.0	DME (0.3)	R (5)	10	1	79	14	6
8	3.0	DME (0.3)	R (5)	10	0	6	60	34
9	1.0	THF (0.5)	R (5)	10	0	89[d]	8	3
10	3.0	THF (0.5)	R (5)	10	0	6	63	31
11	3.9	DME (0.3)	L (5)	10	0	1	80[e]	19
12	2.5	THF (0.5)	R (5)	10	0	92[f]	5	3

[a]Pd catalyst (mol %): L = Pd/$CaCO_3$/Pb, B = Pd/$BaCO_3$, R = Pd/$BaSO_4$. [b]Quinoline (mol %). [c]Determined by ^1H and ^{19}F NMR. [d]Yield 43% (*Z*:*E*:alkane = 96:3:1) by recrystallization from EtOAc/$CHCl_3$. [e]Yield 56%. [f]Yield 59% (*Z*:*E*:alkane = 98:1.5:0.5) by recrystallization from *i*PrOH.

Et_3N to yield pure (*E*)-**7a** (Table 3). To the best of our knowledge, this may be the first example of the formation of essentially pure (*E*)-alkene via Lindlar catalyst-mediated hydrogenation.[27−29]

Returning to our original goal, we probed the necessary conditions for the isolation of the initially formed (*Z*)-**1**. The influence of solvent was examined, and the reaction was carried out in MeOH when we noticed a similar ratio (Table 2, entry 2). The catalyst loading was then examined when we obtained ∼1:1 *Z*/*E* mixture (entry 3). When hydrogenation was terminated within 1 h, the ratio was improved in favor of (*Z*)-**1** (entry 4).

We also noticed that replacing hydrogen with a nitrogen atmosphere after the initial reaction (1.5 h) and continued stirring for an additional 30 min did not change the product ratio any further (Table 2, entry 3). It appears that the hydrogen atmosphere plays an important role in the isomerization from (*Z*)- to (*E*)-**1**. We believe that the isomerization should proceed via a palladated intermediate that can proceed to yield (*E*)-**1** via β-hydride elimination or **5** via a reductive elimination. The fact that >18% of **5** is produced always with (*E*)-**1** supports this assumption.

Due to the difficulty in separating the product, we examined other poisoned Pd catalysts, such as Pd/$BaCO_3$ or Pd/$BaSO_4$ (Rosenmund catalyst). Again, both of these catalysts revealed atypical stereoselection in that the initial (*Z*)-product transformed (entries 5 and 7, respectively) to the (*E*)-product with time (entries 6 and 8, respectively), along with the formation of **5**. Arresting the isomerization was targeted and the amounts of catalyst, additives, solvent, concentration, temperature, and time (see Supporting Information for details) were fine-tuned to achieve the optimal condition for the (*Z*)-isomer (entry 9). Prolonging the reaction provides the (*E*)-isomer predominantly (entry 10). The selectivity improved slightly during the gram-scale preparation of both (*E*)- (>98%, entry 11) and (*Z*)-isomers (93%, entry 12). Crystallization from *i*PrOH yielded

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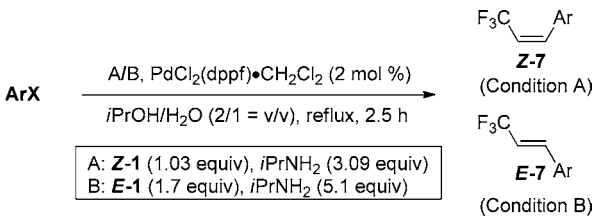
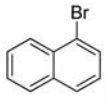
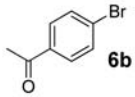
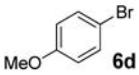
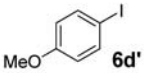
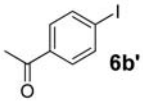
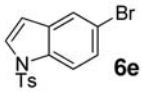
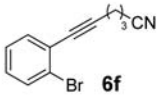
Table 3. Suzuki Coupling of (*E*)-1 and (*Z*)-1 with Aryl Halides



no.	ArX	condn	product no.	product yield (%)[a]	*E*:*Z*[b]
1	 **6a**	A	**Z-7a**	85	1:99
2	 **6b**	A	**Z-7b**	94	1:99
3	 **6c**	A	**Z-7c**	86	1:99
4	 **6d**	A	**Z-7d**	–[c]	2:98
5	 **6d'**	A	**Z-7d**	69[d]	9:91
6	 **6b'**	A	**Z-7b**	91	1:99
7	 **6e**	A	**Z-7e**	92	2:98
8	 **6f**	A	**Z-7f**	58 (67)[e]	1:99
9	**6a**	B	***E*-7a**	73	99:1
10	**6b**	B	***E*-7b**	91	99:1
11	**6c**	B	***E*-7c**	89	99:1
12	**6d'**	B	***E*-7d**	36	99:1
13	**6b'**	B	***E*-7b**	85	99:1

[a]Isolated yield. [b]Determined by ^{1}H and ^{19}F NMR. [c]Yield ~50% (mixture with unidentified *p*-methoxyphenyl byproduct). [d]Calculated for the mixture of the (*Z*)- and (*E*)-product (76% combined). [e]With 1.5 equiv of (*Z*)-**1**; the reaction time was 6 h.

>98% isomeric purity for (*Z*)-**1**. Thus, we achieved a stereoselective synthesis of (*Z*)- and (*E*)-**1** via a time-dependent hydrogenation.

The Suzuki coupling of the (*Z*)-isomer was examined first under conditions similar to those of the (*E*)-isomer (vide supra). Unfortunately, the product was isolated in only 17:3 diastereoselectivity. Replacing the base with $iPrNH_2$ suppressed the isomerization, and (*Z*)-**7a** was isolated in 99% isomeric purity. The standardized condition (A) yielded 85% of (*Z*)-**7a**. The generality of this procedure was demonstrated by preparing a series of (*Z*)-*β*-CF_3-styrenes (Table 3).

An electron-withdrawing group (EWG) at the *p*-position (entry 2) or sterically encumbered *o*-position (entry 3) did not affect the yield or selectivity. *p*-Bromoanisole (**6d**) was converted to the desired styrene ((*Z*)-**7d**) along with a byproduct that was difficult to separate (entry 4). This was avoided by replacing Br with I,[26] although some isomerization occurred during the coupling (entry 5). Unlike entry 5, iodide with a *p*-acetyl EWG did not affect the *E*/*Z* ratio (entry 6). A heteroaromatic, *p*-tosyl-5-bromoindole (**6e**) gave good yield and isomeric selectivity (entry 7). We also examined the CF_3-alkene synthesis to prepare an enyne by coupling with an aryl bromide bearing an internal alkyne (**6f**), which resulted in moderate yield and good selectivity (entry 8). A slight excess of (*Z*)-**1** and longer reaction time were necessary to achieve good yield of the product.

The generality for the (*E*)-styrenes was then probed, standardizing the preparation of (*E*)-**7a** described earlier (vide supra). The stoichiometry of (*E*)-**1** and the amine were adjusted to account for the presence of **5** in the reaction medium, and the coupling was conducted with a selected series of aryl halides (**6a**, **6c**, **6d′**). Although the diastereomeric ratio remained excellent, the yield (42−66%) was slightly lower compared to the (*Z*)-isomers. Increasing the equivalent of (*E*)-**1** (condition B) helped improve the yield and achieved the synthesis of (*E*)-CF_3-styrenes in yields matching that of the (*Z*)-isomer.

In conclusion, we have accomplished the preparation of (*Z*)- and (*E*)-*β*-CF_3-styrenes in excellent yields.[30] The corresponding Suzuki coupling partners, (*Z*)- or (*E*)-CF_3-vinylBF_3K, were prepared via a stereoselective semihydrogenation using poisoned Pd catalysts. The precursor, $CF_3C{\equiv}CBF_3K$, was successfully prepared in quantity avoiding the use of HF. We are further examining the details of the stereoselectivity control during the Pd-catalyzed hydrogenation, which will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization, and ^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(30) **Preparation of potassium (3,3,3-trifluroprop-1-yn-1-yl) trifluoroborate (2).** *n*BuLi (800 mL, 2.5 M in hexane) was added to a solution of **4** (67.2 mL, 0.702 mol) in Et_2O (1.4 L) in a 5 L RB flask at −35 °C. After being stirred for 1 h, $BF_3{\cdot}OEt_2$ (86.6 mL, 0.702 mol) was added at −78 °C, and the mixture was stirred for 10 min, followed by stirring at 0 °C for an additional 0.5 h. Aqueous KHF_2 (219 g, 2.81 mol, in 600 mL of H_2O) was added to the mixture and stirred for 20 min at 0 °C, 1 h at rt, and opened to air. The residue, after removal of solvents, was extracted with acetone, filtered, concentrated, and precipitated with CH_2Cl_2. The solid was filtered and washed with CH_2Cl_2 to yield 68.3 g (51%) of **2**. **Preparation of potassium [(*Z*)-3,3,3-trifluoroprop-1-en-1-yl]trifuoroborate ((*Z*)-1).** THF was added to **2** (10.0 g, 50.0 mmol), $Pd/BaSO_4$ (5.32 g, 2.5 mmol, 5 wt %), and quinoline (0.59 mL, 5.0 mmol). The reaction mixture was stirred under H_2 at rt and monitored by ^{19}F NMR. The reaction was completed after being stirred for 2.5 h; the reaction mixture was filtered through Celite, which was washed with EtOAc. The product was precipitated with minimal amount of CH_2Cl_2, after removing the solvents, and recrystallized from *i*PrOH (250 mL) to obtain (*Z*)-**1** (6.07 g, 59%, *Z*/*E*/alkane = 98:1.5:0.5). **Preparation of potassium [(*E*)-3,3,3-trifluoroprop-1-en-1-yl]trifuoroborate ((*E*)-1).** A similar reaction as above for 4 h in DME using $Pd/CaCO_3$/Pb (5.32 g, 2.5 mmol, 5 wt %) as the catalyst to **2** (10.0 g, 50.0 mmol) yielded (*E*)-**1** (7.06 g, 56%, *Z*/*E*/alkane = 1:80:19). **General procedure for Suzuki coupling (Conditions A/B).** To a solution of (*Z*)-**1**/(*E*)-**1** (A: 208.0 mg, 1.03 mmol/B: 343.3 mg, 1.70 mmol), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (16.3 mg, 0.02 mmol), aryl halide (1.00 mmol) in degassed (freeze−pump−thaw) *i*PrOH/H_2O (2/1 = v/v, 10 mL) was added $iPrNH_2$ (A: 0.27 mL, 3.09 mmol/B: 0.44 mL, 5.1 mmol) under N_2. The reaction mixture was stirred at reflux for 2.5 h, diluted with H_2O (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), filtered through Na_2SO_4, concentrated, and purified by column chromatography to obtain (*Z*)/(*E*)-*β*-trifluoromethylstyrenes.

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