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A Facile Synthesis of Perfluoroalkyl Vinyl Iodides and Their Palladium-Mediated Cross-Coupling Reactions[1]

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Catalytic amounts of zinc, as low as 10 mol %, in the presence of trifluoroacetic acid (TFA) initiate the radical addition of perfluoroalkyl iodides to terminal alkynes with high regio- and stereoselectivities. Palladium-mediated cross-coupling of these (*E*)-perfluoroalkyl vinyl iodides allows for a facile synthesis of potentially useful fluoroorganic intermediates.

Considerable attention has been given to fluoroorganic compounds as agrochemical and pharmaceutical agents due to their unique properties arising from altered electron density, acidity, and hydrogen-bonding patterns.[2] Fluoroalkyl groups increase lipophilicity allowing for easier drug transportation, cellular absorption, blood−brain barrier penetration, and improve binding within hydrophobic pockets of receptors.[2] Accordingly, the development of newer methods for the syntheses of fluoroorganic compounds continues to be an important area of research in agricultural, medicinal, and organic chemistry.[3,4]

In continuation of our ongoing projects involving the hydroboration of fluorinated olefins for fluoroorganic syntheses,[5] we required a variety of perfluoroalkyl substituted olefins, dienes, and enynes. We envisaged the synthesis of such functionalized fluoroorganics via the cross-coupling of perfluoroalkyl vinyl iodides with a variety of nucleophiles.

Transition metal catalyzed cross-coupling is one of the very useful methods for carbon−carbon bond formation due to the considerable scope of functional group tolerance and simple reaction conditions.[6] However, the coupling of perfluoroalkyl vinyl iodides with organometallic reagents has not been fully investigated.[7] Herein, we wish to report a practical approach for the preparation of perfluoroalkyl vinyl iodides and their application for the facile synthesis of a wide array of fluorinated organic intermediates via palladium catalyzed cross-coupling.

Results and Discussion

Radical addition of a perfluoroalkyl iodide (R_FI) to terminal alkynes is one of the highly effective protocols for the synthesis of perfluoroalkyl vinyl iodides.[8−13] We sought a readily accessible and inexpensive, preferably catalytic, procedure for the synthesis of such compounds. A search of the literature revealed a report on the addition of R_FI to 2-methyl-3-butyn-2-ol, in the presence of a stoichiometric amount of zinc powder, en route to the synthesis of perfluorinated terminal acetylenes.[14]

We began our investigation by examining the addition of C_4F_9I (**2**) to 1-heptyne (**1a**) with 1 equiv of zinc in CH_2Cl_2 (1 M). Contrary to the previous report,[14] we observed no reaction after 6 h at room temperature (TLC). Even warming to reflux for 4 h was to no avail. It has been reported that a catalytic amount (10 mol %) of trifluoroacetic acid (TFA) facilitated the radical addition.[14] In our system, this was *critical* to initiate the reaction. Within 10 min at room temperature (rt), we obtained good yields of the corresponding product **3a** with high levels of regio- (> 99%) and stereoselectivities (91%) (Scheme 1).

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(1) (a) Contribution no. 6 from the Herbert C. Brown Center for Borane Research. (b) Dedicated to Professor Ei-ichi Negishi on the occasion of his 65th birthday and in recognition of his exemplary contributions to organometallic chemistry.

(2) (a) For several recent reviews, see: *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) *Biochemistry Invovlving Carbon−Fluorine Bonds*; Filler, R., Ed.; ACS Symposium Series 28; American Chemical Society: Washington, DC, 1976. (d) *Biomedical Aspects of Fluorine Chemistry;* Filler, R., Kobayashi, Y., Eds.; Elsevier Biomedical: Amsterdam, 1982. (e) Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proc. Int.* **1996**, *28*, 289. (f) Harper, D. B.; O'Hagan, D. *Nat. Prod. Rep.* **1994**, 123. (g) *Synthesis and Chemistry of Agrochemicals III*; Baker, D. R., Fenyes, J. G., Steffens, J. J., Eds.; ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992.

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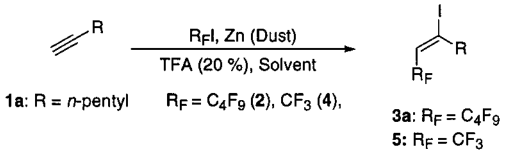
Scheme 1



Scheme 2

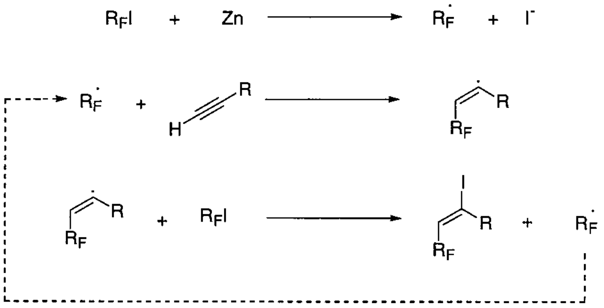
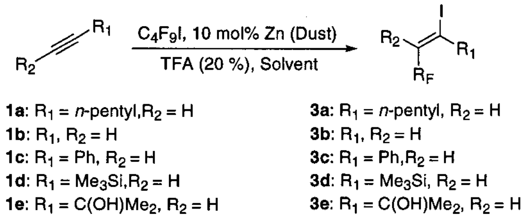


Table 1. Zinc-Mediated Addition of C_4F_9I to 1-Heptyne for 1 h

entry	Zn/**2**	solvent	concn (M)	yield (M)	*E*/*Z* ratio[a]
1	1:1	hexane	1	77	94:6
2	1:1	CH_2Cl_2	1	79	91:9
3	1:1	$CHCl_3$	1	77	91:9
4	1:1	none	1	78	90:10
5	1:1	hexane	0.5	52	95:5
6[b]	1:1	hexane	1	61	93:7
7	0.5:1	hexane	1	87	95:5
8	0.3:1	CH_2Cl_2	5	93	91:9
9	0.1:1	CH_2Cl_2	5	81	91:9
10[c]	1:1	CH_2Cl_2	1	81	86:14[d]

[a] Determined by ^{19}F NMR of the crude product. [b] At 0 °C. [c] $R_FI = CF_3I$. [d] Distillation improved the *E*/*Z* ratio to 92:8.

Scheme 3



Scheme 4

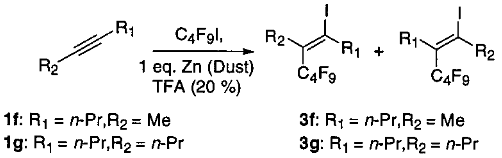


Table 2. Catalytic (10 mol %) Zinc-Mediated Radical Addition of C_4F_9I to Various Acetylenes in CH_2Cl_2 (5 M) for 1 h at Room Temperature

entry	acetylene	product	yield	*E*/*Z* ratio[a]
1	**1b**	**3b**	68	92/8
2[b,c]	**1c**	**3c**	30	
3	**1c**	**3c**	62	94/6
4	**1d**	**3d**	73	67/33
5	**1e**	**3e**	85	92/8
6[c,d]	**1f**	**3f**	72	91/9
7[c]	**1g**	**3g**	88	94/6

[a] Determined by ^{19}F NMR of the crude product. [b] Reaction in hexane. [c] 1 equiv of zinc was used. [d] 1:1 crude regioisomeric ratio.

Replacing the solvent with $CHCl_3$, or carrying out the reaction under neat conditions provided similar yields and selectivities in 1 h at room temperature. By employing hexane as the medium, enhanced selectivities were observed (*E*/*Z* 94:6) with a comparable yield. On changing the R_FI to CF_3I (**4**), the reaction was complete within 1 h at room temperature and provided **5** with a slightly lower stereoselectivity, (*E*/*Z* 86:14). Upon distillation, the isomeric ratio increased to 92:8. The results of radical mediated addition of **2** to **1a** are summarized in Table 1.

On the basis of the proposed single electron transfer (SET) mechanism,[14] a catalytic amount of zinc should be sufficient to promote the addition of **2** to **1a** (Scheme 2). Indeed, using 50 mol % of zinc in the presence of 20 mol % TFA, the reaction (1 M in hexane) was complete in 1 h at room temperature providing high selectivities and yield. However, the reaction became very sluggish with 30 mol % of zinc. Reducing the amount of solvent had no effect on the rate. By replacing hexane with CH_2Cl_2 and increasing the concentration to 5 M, the addition was complete within 30 min. The reaction proceeded efficiently to provide high levels of selectivity and yield even in the presence of 10 mol % zinc. However, the attempted addition of R_FI with <10 mol % catalyst was futile.

The generality of the reaction was demonstrated by the addition of **2** to acetylene (**1b**) and a variety of other alkynes of different steric and electronic environments. Radical additions to terminal alkynes, such as phenylacetylene (**1c**), trimethylsilylacetylene (**1d**), and 2-methyl-3-butyn-2-ol (**1e**), were complete within 1 h at room temperature in CH_2Cl_2 (5 M) by utilizing 10 mol % of zinc in the presence of 20 mol % of TFA (Scheme 3). Regio- (99%) and stereoselectivities (> 92% *E*) were high for all terminal acetylenes, except for **1d** (*E*/*Z* 2:1). The isolated yields were good in all cases.

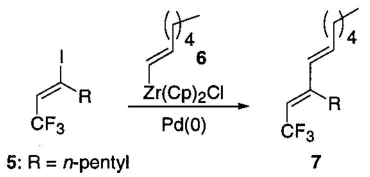
Unlike terminal acetylenes, internal alkynes, such as 2-octyne (**1f**) and 4-octyne (**1g**), reacted very slowly in the presence of catalytic amounts of zinc. However, upon the addition of 1 molar equiv of zinc and 20 mol % of TFA, the addition of **2** to **1f** provided **3f** with a respectable level of stereoselectivity, albeit with no regioselectivity. A symmetrical alkyne **1g** underwent radical addition with **2** and provided the perfluoroalkyl vinyl iodide **3g** with a satisfactory level of stereoselectivity within 2 h at room temperature (Scheme 4). The results are compiled in Table 2.

The preceding reactions are very economical and provide a practical method for the synthesis of perfluoroalkyl vinyl iodides in high regio- and stereoselectivites. We have now carried out this reaction repeatedly on a 0.25 mol scale without any difficulty. Most importantly, the catalyst can be recovered and used up to five times without loss of activity.

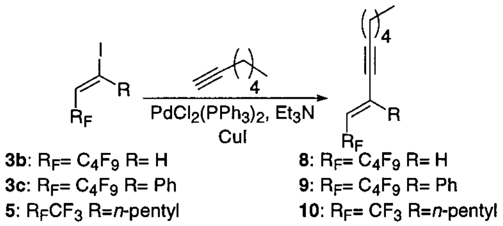
Having the fluorinated electrophiles in hand, our attention was turned to palladium-mediated cross-coupling with a variety of organometallic nucleophiles. For the sake of brevity, the survey was limited to Negishi,[6a] Sonogashira,[6b] and Suzuki[6c] coupling reactions.

We examined the Negishi coupling of an in-situ generated alkenylzirconium species with **5**. Hydrozirconation of **1a** with Schwartz reagent readily afforded the (*E*)-heptenylzirconium intermediate **6** within 1 h. Subsequent cross-coupling of **5** and **6** proceeded, in the presence of Pd(0) in THF at room temperature, to provide the

Scheme 5



Scheme 6



Scheme 7

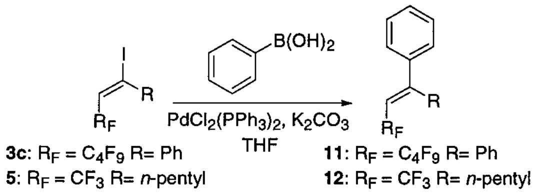


Table 3. Palladium-Mediated Cross-Coupling of Perfluoroalkyl Vinyl Iodides (3b, 3c, 5) with Organometallic Reagents

vinyl iodide		nucleophile		product	
R_F	R	R′	X[a]	yield (%)	E/Z ratio[b]
C_4F_9	Ph	n-heptynyl	H	84	98:2
C_4F_9	Ph	Ph	B	89	
C_4F_9	H	n-heptynyl	H	78	>98
CF_3	n-pentyl	n-heptynyl	H	88	92:8
CF_3	n-pentyl	Ph	B	89	93:7
CF_3	n-pentyl	(E)-heptenyl	Zr	91	>98

[a] Zr = $Zr(Cp)_2Cl$, B = $B(OH)_2$. [b] Determined by ^{19}F NMR of the crude product.

trifluoromethyl substituted diene **7** in good yield with an excellent level of stereoselectivity (Scheme 5).[6a]

The Sonogashira cross-coupling of (*E*)-1-iodo-3,3,4,4,5,5,6,6,6-nonafluorohexene (**3b**), (*E*)-1-iodo-1-phenyl-3,3,4,4,5,5,6,6,6-nonafluorohexene (**3c**), and (*E*)-3-iodo-1,1,1-trifluoro-2-octene (**5**) with **2** in the presence of 3 mol % of $PdCl_2(PPh_3)_2$ and CuI in Et_3N as solvent proceeded smoothly to provide the corresponding di- and trisubstituted enynes **8**, **9**, and **10**, respectively, within 4 h at 40 °C in very high yields and stereoselectivities (≥92%) (Scheme 6).

By utilizing the same Pd(II) catalyst and K_2CO_3 in refluxing THF, Suzuki cross-coupling of phenylboronic acid with vinyl iodides **3c** and **5** provided the aromatic trisubstituted olefins **11** and **12**, respectively, within 3 h in very high yields (89%) and stereoselectivities (≥93%) (Scheme 7). The results of palladium-catalyzed cross-coupling of **3b**, **3c**, and **5** with various nucleophiles are summarized in Table 3.

Conclusions

This study has developed a practical method for the radical addition of perfluoroalkyl iodides (R_FI) to terminal alkynes. By utilizing a catalytic amount of zinc (10 mol %) in the presence of 20 mol % TFA, we have obtained perfluoroalkyl vinyl iodides in high regio- and stereochemical purity. The catalyst can be recovered and used up to five times without loss of activity, rendering this methodology very attractive from an ecological and economical perspective. We have also developed a facile method for the construction of fluoroalkyl dienes, enynes, and trisubsituted olefins via palladium-catalyzed cross-coupling of organometallic nucleophiles with the corresponding perfluoralkyl iodovinyl electrophiles.

Experimental Section

All of the reactions were performed under an inert atmosphere of either Ar or N_2 in oven-dried glassware (150 °C for 4 h). Perfluoroalkyl iodides were obtained from Synquest and used without purification. Phenylboronic acid, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, and Schwartz's reagent were purchased from Aldrich and used as received. Methylene chloride was distilled over CaH_2 and tetrahydrofuran (THF) over sodium/benzophenone ketal under a N_2 atmosphere.

All of the NMR spectra were recorded on a 300 MHz Varian spectrometer. ^1H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: 0 ppm) or chloroform ($CHCl_3$: 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ or trifluoroacetic acid (TFA) as the internal standard.

Typical Experimental Procedure for the Zinc-Catalyzed Addition. Zinc (powder, 10 mol %, 1.63 g, 25 mmol) was placed into a 250 mL round-bottom flask followed by 50 mL of CH_2Cl_2 and **1a** (24.0 g, 250 mmol). To this mixture were added **2** (86.5 g, 250 mmol) and 20 mol % of TFA (slowly). The mixture was allowed to stir for 1 h at room temperature, diluted with 100 mL of CH_2Cl_2, and filtered to remove zinc. The solvent was removed in vacuo to provide 90 g of **3a** (81%, *E*/*Z* 91:9). The perfluoroalkyl vinyl iodide is sufficiently pure for subsequent reactions.

The synthesis of perfluoroalkyl vinyl iodide **3g** is as follows. Zinc (powder, 1.63 g, 25 mmol) was placed into a 100 mL round-bottom flask followed by 25 mL of CH_2Cl_2 and 4-octyne (2.75 g, 25 mmol). To this mixture were added 1-iodo-2,2,3,3,4,4,5,5,5-nonafluorobutane (8.65 g, 25 mmol) and 20 mol % of TFA (slowly). The mixture was allowed to stir for 2 h at room temperature, diluted with 20 mL of CH_2Cl_2, and filtered to remove zinc. The solvent was removed in vacuo to provide 10.03 g (88%, *E*/*Z* 94:6) of the symmetrical vinyl iodide: ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (m, 6H), 1.5−1.7 (m, 4H), 2.35 (t, 2H), 2.68 (t, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −18.7 (3F), −40.6 (2F), −60.1 (2F), −63.9 (2F).

Negishi Cross-Coupling of Perfluoroalkyl Vinyl Iodides with an in Situ Generated Alkenylzirconium Species. In a 50 mL round-bottom flask fitted with a septum was placed $ZrHClCp_2$ (1.56 g, 6 mmol) and 12 mL of benzene. To this was added 1-heptyne (0.597 g, 6.1 mmol), and the mixture was stirred at room temperature until complete dissolution had occurred (generally 1−1.5 h). In a 100 mL round-bottom flask fitted with a septum were added $PdCl_2(PPh_3)_3$ (5 mol %, 0.146 g, 0.15 mmol) and 10 mL of THF. To this was added DIBAL-H (5 mol %, 0.15 mL, 1 M in hexanes, 0.15 mmol), and the resulting brown solution was allowed to stir at room temperature. After 30 min, the trifluoromethyl vinyl iodide (0.876 g, 3 mmol) was added in 5 mL of THF. To this was added the in situ hexenylzirconium species via cannula, and the reaction was allowed to stir at room temperature for 24 h. Et_2O was then added, and the solid byproduct was removed by gravity filtration. The product was then extracted with Et_2O (3 × 10 mL) and washed with deionized H_2O followed by brine. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude diene was analyzed by ^1H and ^{19}F NMR to determine diastereoselectivity. Column chromotagraphy (1% ethyl acetate in hexane) provided 0.602 g (81%) of the pure diene (>98% diastereomeric purity): ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.2−1.5 (m, 12H), 2.15 (q, 2H), 2.27 (t, 2H), 5.42 (q, 1H), 5.88−6.05 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ 6.11 (d, 3F).

Sonogashira Cross-Coupling of Perfluoroalkyl Vinyl Iodides with Terminal Acteylenes. In a 50 mL round-bottom flask fitted with a reflux condenser and a septum fitted sidearm were placed $PdCl_2(PPh_3)_2$ (3 mol %, 87.0 mg, 0.09 mmol) and CuI (3 mol %, 17.1 mg, 0.09 mmol) followed by 8 mL of Et_3N. To this were added the fluorinated vinyl iodide (3 mmol) and 1-heptyne (3.1 mmol), and the solution was stirred at 40 °C for 4 h. Et_2O was added, and the solid byproduct was removed by gravity filtration. The product was then extracted with Et_2O (3 × 10 mL) and washed with deionized H_2O followed by brine. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude enyne was analyzed by ^1H and ^{19}F NMR to determine diastereoselectivity. Column chromotagraphy (1% ethyl acetate in hexane) provided the pure enynes **8**−**10**.

Suzuki Cross-Coupling of Perfluoroalkyl Vinyl Iodides with Phenylboronic Acid. In a 50 mL round-bottom flask fitted with a reflux condenser and a septum fitted sidearm were placed $PdCl_2(PPh_3)_2$ (3 mol %, 87.0 mg, 0.09 mmol) and K_2CO_3 (6 mol %, 24.8 mg, 0.18 mmol) followed by 10 mL of THF and 2 mL of H_2O. To this were added the fluorinated vinyl iodide (3 mmol) and phenylboronic acid (6.0 mmol), and the solution was stirred at 80 °C for 6 h. Et_2O was added, and the solid byproduct was removed by gravity filtration. The product was then extracted with Et_2O (3 × 10 mL) and washed with deionized H_2O followed by brine. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude olefin was analyzed by ^1H and ^{19}F NMR to determine diastereoselectivity. Column chromatography (1% ethyl acetate in hexane) provided the pure alkenes **11** and **12**.

Acknowledgment. We thank the Herbert C. Brown Center for Borane Research for financial assistance.

Supporting Information Available: Spectroscopic data for compounds **3b**, **3c**, **5**, and **7**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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