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Trifluoromethylation and Pentafluoroethylation of Vinylic Halides with Low-Cost R_fH-Derived CuR_f (R_f = CF_3, C_2F_5)

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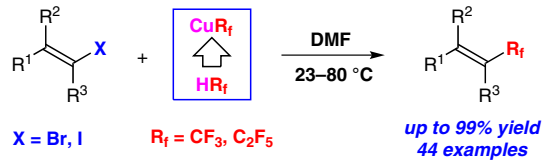

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Abstract A variety of vinylic bromides and iodides undergo smooth trifluoromethylation and pentafluoroethylation with R_fH-derived CuR_f (R_f = CF_3, C_2F_5) to give the corresponding fluoroalkylated olefins. These reactions employing the low-cost CuR_f reagents occur in high yield with excellent chemo- and stereoselectivity under mild conditions (23–80 °C). Crystal structures of one trifluoromethyl and one pentafluoroethyl derivative have been determined.

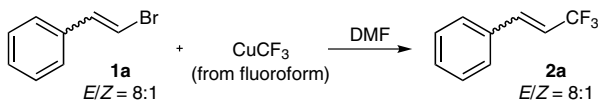
Key words trifluoromethylation, pentafluoroethylation, vinylic halides, copper, cross-coupling

Considerable progress has been made in the area of trifluoromethylation of aromatic halides for the synthesis of biologically active compounds and specialty materials.[1,2] Methodologically closely related perfluoroalkylation of vinylic halides, however, remains significantly less developed. Since the original 1960–1970 reports[3] on copper-mediated coupling of perfluoroalkyl iodides (R_fI) with haloalkenes, this method has been modified by employing such CF_3 and C_2F_5 sources as FO_2SCF_2I,[4] $FO_2SCF_2CO_2Me$,[5] $FSO_2(CF_2)_2OCF_2CO_2Me$,[6] $Hg(CF_3)_2$,[7] $ClCF_2CO_2Me$,[8] CF_3SiR_3/KF,[9] and C_2F_5COX (X = ONa,[10] Ph[11]).[12] In the vast majority of these reports, however, the scope is undefined, with styryl bromide[4,5a,6,10,11] or chloride[6] being the only vinylic halides explored. Single examples of trifluoromethylation of RCH=CHX (R = H, X = Br[8] and R = C_8H_{17}, X = I[9a]) have been mentioned briefly. One paper[5b] describes the trifluoromethylation of structurally alike 4-bromo-3-oxo-Δ^4-steroids and two more deal with a handful of rather specific 1,2-diiodo-[5c] and 1,1-dibromoolefin[5d] substrates. We are aware of only two reports detailing the scope of this type of transformations. Nowak and Robins[7] have demonstrated trifluoromethylation of 18 vinylic bromides and iodides in 75–95% yield. Regrettably, their method employs toxic $Hg(CF_3)_2$ as the CF_3 source. Hafner and Bräse[9b] have modified the Urata–Fuchikami protocol[9a] using CF_3TMS to perform the reaction on five vinylic bromides and six iodides in 23–99% yield. In order to avoid the side formation of C_2F_5-substituted products due to α-F elimination,[9] the reaction must be conducted in costly DMPU.[9b] Contamination of a desired triluoromethylated product with its C_2F_5 counterpart is a serious problem because separation of the two is difficult, if not impossible.

We have recently developed the synthesis of $CuCF_3$[13] and CuC_2F_5[14] directly from readily available and cheap CHF_3 (fluoroform)[15] and C_2F_5H, respectively. Governed by a unique mechanism,[16] the reaction of [K(DMF)][Cu(O*t*-Bu)$_2$] (prepared in situ from CuCl and 2 equiv of *t*-BuOK in DMF) with CHF_3 or C_2F_5H readily occurs at room temperature and atmospheric pressure to furnish the corresponding R_fCu in nearly quantitative yield.[13–15] The thus prepared reagents fluoroalkylate a broad variety of substrates in high yield and with excellent selectivities.[13–15,17] Notably, there is no need to use toxic CF_3 reagents[7] or expensive DMPU[9b] to eliminate the side formation of C_2F_5 derivatives in the reactions of CHF_3-derived $CuCF_3$. Furthermore, the low cost of our R_fCu reagents makes them potentially suitable for industrial applications.[15] In contrast, most other R_f sources, including popular CF_3TMS, are not only substantially less atom-economical, but also cost-prohibitive for large-scale operations. Considering all of the above, we set out to explore the possibility of fluoroalkylation of vinylic halides with the R_fH-derived $CuCF_3$ and CuC_2F_5 reagents.

We initially found that fluoroform-derived $CuCF_3$ readily trifluoromethylates β-bromostyrene (**1a**, *E*/*Z* = 8:1), the substrate of choice for our initial studies, with full retention of stereochemistry. A summary of the optimization work is presented in Table 1 showing that the trifluoromethylation of **1a** occurs at as low as ambient temperature. Our goal was to drive the reaction to nearly full conversion in order to eliminate the need to separate the product PhCH=CHCF_3 from the unreacted starting material. To achieve >90% yield at ≥99% conversion, the reaction was performed at 40–50 °C with 2.5 equivalents of $CuCF_3$ in the presence of $Et_3N{\cdot}3HF$ as a promoter.[17c]

Table 1 Optimization of Reaction Conditions for Trifluoromethylation of β-Bromostyrene with Fluoroform-Derived $CuCF_3$



Entry[a]	$CuCF_3$ (equiv)	$Et_3N{\cdot}3HF$ (equiv)[b]	Temp (°C)	Time (h)	Conv. (%)[c]	Yield (%)[d]
1	1.5	0.33	50	23	84	76
2	2	0.33	23	120	95	86
3	2	0.33	50	25	97	84
4	2	0.43	50	24	96	92
5	2	0.53	50	20	94	87
6	2	0.63	50	20	92	85
7	2.5	0.43	50	24	99	93
8	2.5	0.53	50	26	98	91
9	2.5	0.63	50	26	96	90
10	2.5	0.43	40	62	99	90
11	2.5	0.53	40	62	98	90
12	2	0.53	80	4 + 1[e]	89	86

[a] Reaction conditions: **1a** (0.125–0.25 mmol), $CuCF_3$ in DMF (0.35–0.38 M) in the presence of 1,3-bis(trifluoromethyl)benzene or 4,4′-difluoro-1,1′-biphenyl as internal standards (see Supporting Information for details).
[b] Equiv per 1 equiv of $CuCF_3$.
[c] Determined by GC–MS.
[d] Determined by ^{19}F NMR spectroscopy (accuracy ±5%).
[e] $CuCF_3$ in DMF was added during 4 h via a syringe pump, followed by heating for one additional h.

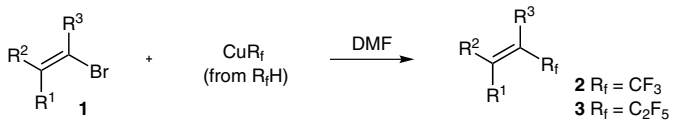
After the optimization work, we proceeded to explore the substrate scope, using various vinylic bromides. The trifluoromethylation and pentafluoroethylation were performed in parallel (Table 2). The enhanced thermal stability of the CuC_2F_5 reagent[14] allowed us to use it in only 10% excess to achieve full conversion for most of the substrates, while running the reactions at 70–80 °C. The data collected in Table 2 show that styryl bromides bearing such substituents as Me (**1b**–**d**), MeO (**1e**), F (**1f**), Cl (**1g**,**h**), and Br (**1i**,**j**) in various positions of the aromatic ring undergo clean perfluoroalkylation to give the desired products in ≥90% yield (Table 2, entries 1–20). The stereochemistry of the starting material is retained in the product. While F and Cl on the ring remain intact during the reaction, the aromatic C–Br bond in **1i** and **1j** (Table 2, entries 17–20) undergoes fluoroalkylation, albeit only to a minor extent (5–8%). Therefore, unactivated bromoarenes are estimated to be approximately an order of magnitude less reactive toward CuR_f than β-bromostyrene. This difference in reactivity provides an opportunity for further functionalization of the R_f-substituted styrene products bearing a halogen atom on the ring, for example, via a variety of coupling reactions. The fluoroalkylation of β-bromostyrenes with geminal CHO (**1k**) or CO_2Me (**1l**) also proceeded smoothly to furnish the corresponding products in 68–80% yield (Table 2, entries 21–24). Although the stereochemistry is not fully preserved in the reactions of these substrates, the *E*/*Z* ratio ranges from good (85:15, Table 2, entries 21 and 23) to excellent (99:1, Table 2, entry 24). In accord with the literature data,[9b] α-bromostyrene (**1n**) was less reactive, likely for steric reasons, furnishing the desired product in only 26% and 64% yield at 50% and 100% conversion in the reactions with $CuCF_3$ and CuC_2F_5, respectively (Table 2, entries 27 and 28). In contrast, α-methyl-β-bromostyrene (**1m**) underwent perfluoroalkylation in >90% yield with full retention of stereochemistry (Table 2, entries 25 and 26). Bromoethylene (**1o**), isopropenyl bromide (**1p**), and 2-bromo-2-butene (**1q**) were perfluoroalkylated in 35–78% yield (Table 2, entries 29–33).

Although more costly and often less accessible than their bromo counterparts, vinylic iodides are considerably more reactive coupling partners. We therefore explored fluoroalkylation of a series of iodoalkenes with $CuCF_3$ and CuC_2F_5 (Table 3).

The mono β-substituted iodoethylenes appeared reactive enough to undergo the fluoroalkylation at room temperature (Table 3, entries 1–8). Importantly, full conversion of these substrates was reached with only 1.1 equivalents of the CuR_f reagent not only for $R_f = C_2F_5$, but also for $R_f = CF_3$. The fluoroalkylations of more sterically hindered and therefore less reactive iodoalkenes were performed at 50–70 °C (Table 3, entries 9–12). The formation of the desired products in excellent yields of up to 97% was observed in all cases.

After the substrate scope studies (Tables 2 and 3), a number of vinylic halides were selected for the synthesis and isolation of the corresponding CF_3[18] and C_2F_5[19] derivatives on a 1–10 mmol scale (Scheme 1). As can be seen from Scheme 1, the new protocol is suitable for the preparation and isolation in pure form of trifluoromethylated and pentafluoroethylated olefins in up to 93% yield. Note that the diminished yields of 74–86% are mainly due to losses during the isolation of these rather volatile compounds and hence likely can be improved in the synthesis on a larger scale. Single-crystal X-ray diffraction studies of two of the isolated products, (*E*)-1-(trifluoromethyl)-2-(4-methoxyphenyl)ethylene (**2e**, Figure 1) and (*E*)-1-(pentafluoroethyl)-2-(2-naphthyl)ethylene (**3s**, Figure 2) confirmed the structures and stereochemistry in the solid state.[20]

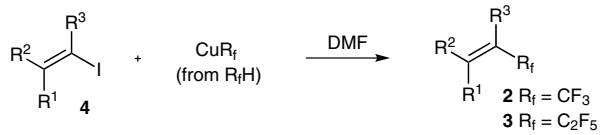
Table 2 Trifluoromethylation and Pentafluoroethylation of Bromoalkenes with CuR_f in DMF



Entry[a]	R^1	R^2	R^3	Product	Temp (°C)	Time (h)	Conv. (%)[b]	Yield (%)[c]	*E*/*Z* ratio	
									Substrate[d]	Product[c]
1	H	Ph	H	**2a**	50	24	99	93	89:11	89:11
2				**3a**	70	14	100	97		
3	H	2-MeC_6H_4	H	**2b**	50	23	100	93	99:1	99:1
4				**3b**	70	20	100	92		
5	H	3-MeC_6H_4	H	**2c**	50	23	100	92	99:1	99:1
6				**3c**	70	20	100	99		
7	H	4-MeC_6H_4	H	**2d**	50	23	99	96	100:0	100:0
8				**3d**	70	14	100	99		
9	H	4-$MeOC_6H_4$	H	**2e**	50	24	100	90	99:1	99:1
10				**3e**	70	18	100	91		
11	H	4-FC_6H_4	H	**2f**	50	23	100	97	98:2	98:2
12				**3f**	70	20	100	98		
13	H	4-ClC_6H_4	H	**2g**	50	23	100	94	100:0	100:0
14				**3g**	70	14	100	97		
15	H	2-ClC_6H_4	H	**2h**	50	24	100	90	99:1	99:1
16				**3h**	70	18	100	94		
17[e]	H	4-BrC_6H_4	H	**2i**	50	21	99	87 + 5[f]	100:0	100:0
18[e]				**3i**	70	16	100	89 + 5[f]		
19[e]	H	2-BrC_6H_4	H	**2j**	50	21	100	89 + 7[f]	99:1	99:1
20[e]				**3j**	70	16	100	89 + 8[f]		
21	H	Ph	CHO	**2k**	50	24	100	71	0:100	15:85
22				**3k**	50	16	100	80		6:94
23	H	Ph	CO_2Me	**2l**	50	25	86	74	28:72	16:84
24				**3l**	70	16	98	68		1:99
25	Me	Ph	H	**2m**	50	25	96	94	97:3	97:3
26				**3m**	80	14	100	92		
27	H	H	Ph	**2n**	50	28	50	26	–	–
28				**3n**	70	30	100	64		
29	H	H	H	**2o**	50	30	60	35	–	–
30	H	H	Me	**2p**	50	28	55	58	–	–
31				**3p**	80	21	92	70		
32	Me	H	Me	**2q**	50	28	65	60	50:50	63:37
33				**3q**	80	21	91	78		56:44

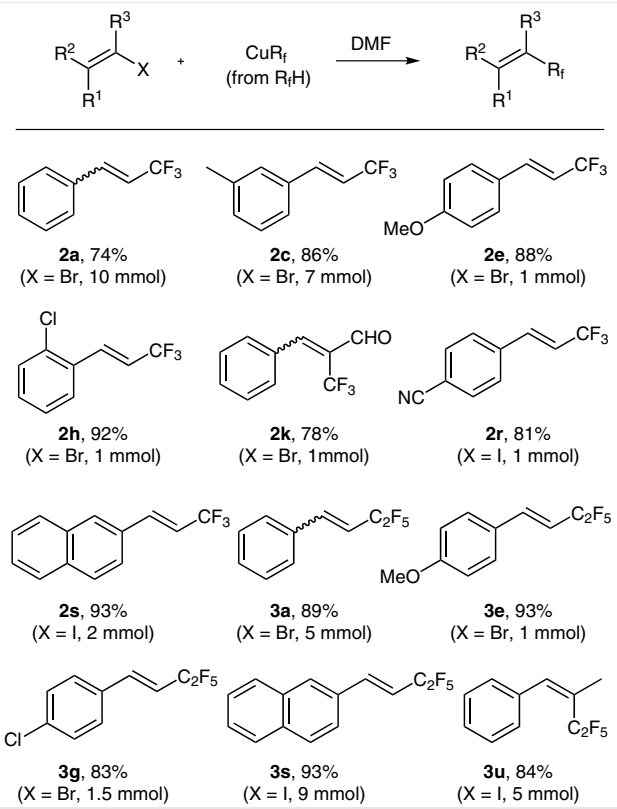
[a] Reaction conditions: bromoalkene **1** (0.125–0.25 mmol), $CuCF_3$ in DMF (0.35–0.38 M, 2.5 equiv) or CuC_2F_5 in DMF (0.67–0.70 M, 1.1 equiv), 1,3-bis(trifluoromethyl)benzene or 4,4′-difluoro-1,1′-biphenyl (internal standards). See Supporting Information for details.
[b] Determined by GC–MS.
[c] Determined by ^{19}F NMR spectroscopy (accuracy ±5%).
[d] Determined by ^1H NMR spectroscopy.
[e] 2.2 equiv of $CuCF_3$ or 1 equiv of CuC_2F_5.
[f] Bis-perfluoroalkylated side product was also formed.

Table 3 Trifluoromethylation and Pentafluoroethylation of Iodoalkenes



Entry[a]	R^1	R^2	R^3	Product	Temp (°C)	Time (h)	Yield (%)[b]
1	H	2-ClC_6H_4	H	**2h**	23	1.5	92
2				**3h**	23	10	90
3	H	4-NCC_6H_4	H	**2r**	23	1.5	92
4				**3r**	23	10	92
5	H	2-naphthyl	H	**2s**	23	2	91
6				**3s**	23	10	90
7	1-naphthyl	H	H	**2t**	23	6	89
8				**3t**	23	16	87
9	Ph	H	Me	**2u**	50	8	97
10				**3u**	50	24	95
11	H	$(CH_2)_4$		**2v**	50	13	93
12				**3v**	70	7	91

[a] Reaction conditions: iodoalkene **4** (0.125–0.25 mmol), $CuCF_3$ in DMF (0.36–0.38 M, 1.1 equiv) or CuC_2F_5 in DMF (0.68–0.70 M, 1.1 equiv), 1,3-bis(trifluoromethyl)benzene or 4,4′-difluoro-1,1′-biphenyl (internal standards). See Supporting Information for details.
[b] Determined by ^{19}F NMR spectroscopy (accuracy ±5%).



Scheme 1 Isolated trifluoromethylated and pentafluoroethylated products (1–10 mmol)

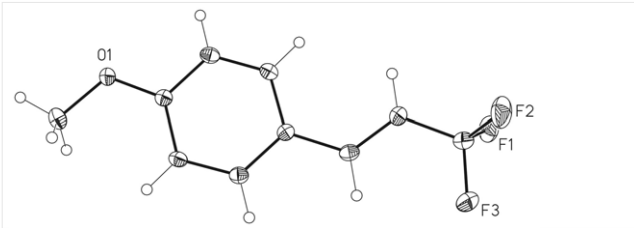


Figure 1 ORTEP drawing of **2e** with thermal ellipsoids drawn at the 50% probability level[20]

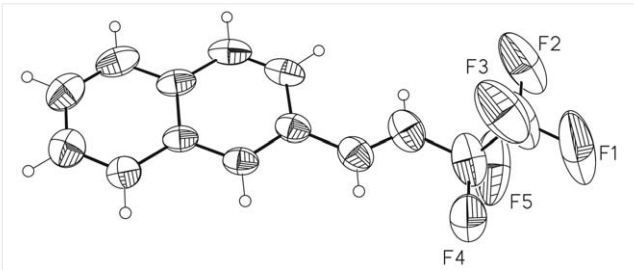


Figure 2 ORTEP drawing of **3s** with thermal ellipsoids drawn at the 50% probability level[20]

The high chemo- and stereoselectivity of the fluoroalkylation reactions described above suggests that radical processes are unlikely involved in the olefinic C–R_f bond formation. The fluoroalkylation reactions of vinylic halides are in many respects similar to those of aryl halides.[13,14,17c] As has been recently established,[21] the trifluoromethylation of haloarenes with fluoroform-derived $CuCF_3$ is a nonradi-

cal process that involves ArX oxidative addition (OA) to Cu(I), followed by ArR_f reductive elimination (RE) from the copper(III) intermediate. The fluoroalkylation reactions developed in the current work are likely governed by a similar OA–RE mechanism.

The new method compares favorably with the previously reported ones[4–12] for perfluoroalkylation of haloalkenes. Apart from the vastly lower cost of the R_f sources used, our procedures obviate the need for toxic mercury compounds[7] or expensive DMPU[9b] employed in the only two reported methods with a defined substrate scope.[22]

In summary, a general new protocol has been developed for the trifluoromethylation and pentafluoroethylation of vinylic bromides and iodides with R_fH-derived $CuCF_3$ and CuC_2F_5. The reactions occur at 23–80 °C with high chemo- and stereoselectivity to furnish the desired fluoroalkylated olefin products in high, often >90% yield. Various functional groups are well tolerated. The method employs the most economical CuR_f reagents known to date and neither costly nor toxic materials. Scalability and isolation of pure products have been demonstrated on selected examples. The new protocol may find use in both academic and industrial research.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379497.

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(18) **(*E*)-1-chloro-2-(3,3,3-trifluoroprop-1-enyl)benzene (2h); Typical Procedure**
To 1-chloro-2-(2-bromovinyl)benzene (**1h**; 218 mg; 1 mmol), was added under argon at room temperature $CuCF_3$ in DMF (0.38 M; 6.6 mL; 2.5 equiv) containing an extra 0.1 equiv of TREAT HF, and the mixture was stirred for 24 h at 50 °C. Pentane (50 mL), water (50 mL), and aqueous NH_3 (33%; 1 mL) were added in air. The organic layer was separated and the aqueous layer was washed with pentane (2 × 20 mL). The combined pentane solutions were washed with brine (2 × 25 mL), dried over $MgSO_4$, filtered, and evaporated (23 °C, 10 mbar). After column chromatography of the residue in pentane and subsequent trap-to-trap distillation, **2h** was obtained as a colorless oil (192 mg; 92%). The product contained 1% of the corresponding *Z*-isomer (GC-MS; ^{19}F NMR). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (dq, $^3J_{H-H}$ = 16.2 Hz, $^4J_{F-H}$ = 2.1 Hz, 1H), 7.56–7.51 (m, 1H), 7.45–7.40 (m, 1H), 7.36–7.27 (m, 2H), 6.22 (dq, $^3J_{H-H}$= 16.1 Hz, $^3J_{F-H}$= 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 134.6, 134.2 (q, $^3J_{C-F}$= 6.9 Hz), 131.9, 131.1, 130.3, 127.5, 127.3, 123.4 (q, $^1J_{C-F}$= 269.2 Hz), 118.5 (q, $^2J_{C-F}$= 34.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.7 (dd, $^3J_{H-F}$= 6.4 Hz, $^4J_{H-F}$ = 2.1 Hz, 3F).

(19) **(*E*)-2-(3,3,4,4,4-pentafluorobut-1-enyl)naphthalene (3s); Typical Procedure**
To (*E*)-2-(2-iodovinyl)naphthalene (2.52 g; 9 mmol), was added under argon at room temperature CuC_2F_5 in DMF (0.7 M; 14.1 mL; 1.1 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 10 h at 23 °C. Pentane (50 mL), water (100 mL), and aqueous NH_3 (33%; 10 mL) were added in air. The organic layer was separated and the aqueous layer was washed with pentane (2 × 25 mL). The combined pentane solutions were washed with brine (2 × 25 mL), dried over $MgSO_4$, filtered, and evaporated. Column chromatography of the residue in pentane produced **3s** as a white solid (2.27 g; 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.91–7.82 (m, 4H), 7.62 (dd, $^3J_{H-H}$= 8.6 Hz, $^4J_{H-H}$ = 1.7 Hz, 1H), 7.56–7.50 (m, 2H), 7.35 (dq, $^3J_{H-H}$= 16.2 Hz, $^4J_{H-F}$= 2.3 Hz, 1H), 6.29 (dtq, $^3J_{H-H}$ = 16.1 Hz, $^3J_{F-H}$ = 11.7 Hz, $^4J_{F-H}$ = 0.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 139.9 (t, $^3J_{C-F}$= 9.2 Hz), 134.2, 133.4, 131.1 (t, $^4J_{C-F}$= 1.2 Hz), 129.4 (t, $^4J_{C-F}$= 1.2 Hz), 128.9, 128.6, 127.9, 127.4, 127.0, 123.2, 119.3 (qt, $^1J_{C-F}$= 285.6 Hz, $^2J_{C-F}$= 38.6 Hz), 114.3 (t, $^2J_{C-F}$= 23.1 Hz), 113.1 (tq, $^1J_{C-F}$= 250.3 Hz, $^2J_{C-F}$= 38.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.2 (t, $^3J_{F-F}$ = 2.3 Hz, 3F), –113.6 (ddq, $^3J_{F-H}$ = 12.1 Hz, $^4J_{F-H}$ = $^3J_{F-F}$ = 2.3 Hz, 2F). Anal. Calcd. for $C_{14}H_9F_5$: C, 61.8; H, 3.3. Found: C, 61.7; H, 3.3.

(20) CCDC-1026478 (**2e**) and CCDC-1026964 (**3s**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(22) There are also certain advantages of perfluoroalkylation of vinylic halides over other synthetic means to build R_f-substituted olefin molecules.[23–32] The Julia–Kocienski,[23] Wittig,[24] Horner,[25a] and Horner–Wadsworth–Emmons reactions[25b,c] are stereochemically nonselective, usually furnishing a mixture of *Z* and *E* isomers. The trifluoromethylation of alkenyl boron compounds[26] requires an additional step as it employs substrates that are made from the corresponding halo olefins. Various X–CF_3 addition reactions to alkynes[27] are either limited in scope (X = H),[27b,f] leading to a mixture of stereoisomers, or introduce into the product molecule another substituent X that must be removed if not needed. A rather exotic enzyme-assisted perfluoroalkylation of alkynes with R_fI led directly to the desired products, however, only in low yield.[27h] Direct C–H olefinic trifluoromethylation methods[28] employ costly CF_3 reagents, require directing groups, and have a limited substrate scope. Palladium-catalyzed cross-coupling reactions are limited to only aromatic substrates.[29] The decarboxylative vinylic trifluoromethylation of α,β-unsaturated carboxylic acids leads to *trans* products which are often contaminated with the corresponding *cis*-isomer.[30] Perfluoroalkylated alkenes have been obtained by Reformatsky- or Grignard-type reactions of fluoroalkyl aldehydes with an organometallic compound and subsequent dehydratation of the formed alcohols.[31] This approach leads to the mixtures of isomers and is not particularly high yielding. Perfluoroalkyl aldehyde hemiaminals have been used to prepare perfluoroalkylated olefins,[32] but this method is limited to only enolizable carbonyl substrates.

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