$Na_2S_2O_4$-Promoted Radical Addition Reaction of Perfluoroalkyl Iodides with Allenes and the Pd(0)-Catalyzed Stereoselective Sonogashira Coupling Reaction of Addition Products with Propargyl Alcohol

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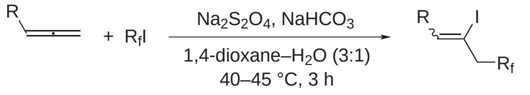
Abstract: A $Na_2S_2O_4$-promoted radical addition reaction of perfluoroalkyl iodides with allenes affording 1-perfluoroalkyl-2-alken-2-yl iodides **3** in 52–69% yields has been developed. Kinetic resolution of the *Z*/*E* mixture via the Pd(0)-catalyzed Sonogashira coupling reaction was applied to prepare pure vinylic iodides (*Z*)-**3** and the related coupling products (*E*)-**4** up to 98:2 *E*/*Z* ratio.

Key words: perfluoroalkyl iodides, allenes, radical addition, propargyl alcohol, Sonogashira coupling

For a long period of time, allenes have been considered as highly unstable, which has seriously retarded the development of their chemistry.[1] The situation has changed dramatically during the last ten years, now allenes have become an important class of compounds with unique reactivity and selectivity in organic synthesis.[2,3] In particular, the transition metal-catalyzed or -promoted reactions of allenes have become very powerful tools for organic transformations.[4] However, the radical chemistry of allenes has not been well-established.[5,6] In this paper, we wish to disclose our recent observations on the $Na_2S_2O_4$-promoted radical addition of perfluoroalkyl iodides with allenes, which afforded a *Z*/*E* mixture of 1-perfluoroalkyl-2-alken-2-yl iodides. These products may be efficiently resolved by the Pd(0)-catalyzed Sonogashira coupling reactions with propargylic alcohols.

It is well-known that $Na_2S_2O_4$ can be used to promote the radical addition of perfluoroalkyl iodides with alkenes[7] or alkynes.[8] However, when we treated 4-phenyl-1,2-butadiene with $I(CF_2)_4Cl$ in CH_2Cl_2–H_2O (3:1) or benzene–H_2O (3:1), no expected product **3a** was formed; when the reaction was carried out in aqueous DMF, DMA, DMSO, or THF, **3a** was formed in 15–25% yields. Best results were obtained when 1,4-dioxane was used as the solvent. Thus, we chose 1,4-dioxane as the solvent to study the scope of this radical addition reaction. Some of the most typical results are shown in Table 1;[11] it can be concluded that either benzyl-, *n*-alkyl-, or cyclohexyl-substituted allenes can undergo the radical addition reaction with perfluoroalkyl iodides affording the radical addition products vinylic iodides **3** in 52–69% yields.

Table 1 $Na_2S_2O_4$-Initiated Radical Addition of Perfluoroalkyl Iodides with Different Allenes[a]



1 **2** **3**

Entry	R	R^f	Yield of **3** (%)[b]	*E*/*Z*[c]
1	Bn (**1a**)	$Cl(CF_2)_4$ (**2a**)	63 (**3a**)	1:1.80
2	Bn (**1a**)	*n*-C_4F_9 (**2b**)	65 (**3b**)	1:1.78
3	*n*-C_5H_{11} (**1b**)	$Cl(CF_2)_4$ (**2a**)	55 (**3c**)	1:2.41
4	*n*-C_5H_{11} (**1b**)	*n*-C_4F_9 (**2b**)	52 (**3d**)	1:2.33
5	*n*-C_7H_{15} (**1c**)	$Cl(CF_2)_4$ (**2a**)	63 (**3e**)	1:2.75
6	*n*-C_7H_{15} (**1c**)	*n*-C_4F_9 (**2b**)	69 (**3f**)	1:2.34
7	*c*-C_6H_{11} (**1d**)	$Cl(CF_2)_4$ (**2a**)	59 (**3g**)	1:2.22
8	*c*-C_6H_{11} (**1d**)	*n*-C_4F_9 (**2b**)	62 (**3h**)	1:2.21

[a] Ratio of **1**:**2**:$Na_2S_2O_4$:$NaHCO_3$ = 1:1.5:1.5:1.5.
[b] Isolated yield. The *E* and *Z* isomers cannot be separated by flash chromatography.
[c] Determined by NMR spectra.

Although the reactions afforded the products **3** as an *E*/*Z* mixture with the ratio ranging from 1:1.78 to 1:2.75, it was observed that the *Z* and *E* isomers of **3b** reacted very differently with propargyl alcohol, i.e., the *E* isomer reacted very fast producing **4b** with a *Z*/*E* ratio as high as 4:96 while (*Z*)-**3b** remained unreacted (Table 2).[9,10]

In this way (*Z*)-**3** may be prepared highly stereoselectively. After some optimization, a standard procedure was established for applying the Pd(0)-catalyzed Sonogashira coupling reaction[12] to the highly stereoselective synthesis of (*Z*)-**3** and (*E*)-**4** (Table 3).[11] From the results shown in Table 3 it can be concluded that (*Z*)-**3** can be prepared in the pure form in very high yields, while the *E*/*Z* ratio for

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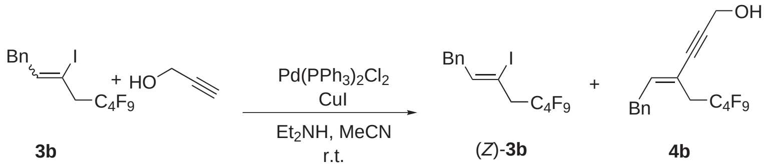
Table 2 Optimization of Reaction Conditions for the Pd(0)-Catalyzed Kinetic Resolution Reaction of **3b** with Propargyl Alcohol



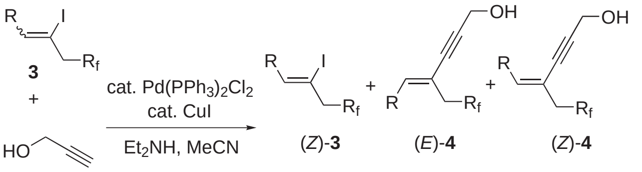
Entry	Alcohol–Et$_2$NH, 1:1 (equiv)	Catalyst (mol%)	Time (min)	Yield of (*Z*)-**3b** (%)	Yield of **4b** (%)	*E*/*Z* ratio of **4b**[a]
1	0.6	3.0	50	54[b]	26	95:5
2	0.7	3.5	25	48	29	93:7
3	0.9	4.5	12	61	33	96:4
4	0.6	4.5	30	54	30	96:4
5	**0.6**	**3.5**	**30**	**57**	**32**	**95:5**
6	0.7	3.0	12	53	34	91:9
7	0.9	3.0	12	50	35	88:12

[a] The *Z*/*E* ratio of **4b** was determined by GC analysis.
[b] 16% of (*E*)-**3b** remained unreacted.

the Sonogashira coupling products **4** ranging from 9:1 to 22:1. These two isomers may also be easily separated via chromatography on silica gel, enabling the synthesis of both (*Z*)-**4** and (*E*)-**4**.

In conclusion, we have developed a $Na_2S_2O_4$-promoted radical addition of perfluoroalkyl iodides with allenes. Although the stereoselectivity is not good and the *Z*/*E* isomers are inseparable, the subsequent Pd(0)-catalyzed Sonogashira coupling reaction enables the highly stereoselective synthesis of the Sonogashira coupling products (*E*)-4-perfluoroalkylmethyl-4-alken-2-ynol [(*E*)-**4**] and the *Z* isomer of the radical addition products (*Z*)-**3**. Further studies in this area are being carried out in our laboratory.

Table 3 Kinetic Resolution of Different 1-Perfluoroalkyl-2-iodo-2-alkenes by the Pd(0)-Catalyzed Sonogashira Coupling Reaction with Propargyl Alcohol[a,b]



R	R$_f$	Temp (°C)/Time (min)	Yield of (*Z*)-**3** (%)[a]	Yield of (*E*)-**4** (%)[a]	Yield of (*Z*)-**4** (%)[a]
Bn	$Cl(CF_2)_4$ (**3a**)	11/30	55	28	3
n-C_5H_{11}	C_4F_8Cl (**3c**)	0/60	45	22	2
n-C_7H_{15}	*n*-C_4F_9 (**3f**)	0/60	58	22	1
c-C_6H_{11}	$Cl(CF_2)_4$ (**3g**)	13/30	47	25	2

[a] Isolated yield.
[b] Reaction conditions: **3**:propargyl alcohol:$Pd(PPh_3)_2Cl_2$:CuI = 1:0.6:0.035:0.035 (molar ratio).

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(11) **Typical Procedure.**
The reaction of **1a** (258.8 mg, 1.99 mmol), IC_4F_9 (**2b**, 1.0482 g, 3.03 mmol), $Na_2S_2O_4$ (523.6 mg, 3.01 mmol), and $NaHCO_3$ (253.4 mg, 3.02 mmol) in 16 mL of mixed solvent of 1,4-dioxane and H_2O (3:1) afforded 612.7 mg (65%) of **3b**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 2 H), 7.28–7.20 (m, 2 H), 7.20–7.14 (m, 1 H), 6.84 (*E* isomer, t, *J* = 7.6 Hz, 0.36 H), 6.04 (*Z* isomer, t, *J* = 6.6 Hz, 0.64 H), 3.61–3.37 (m, 4 H). The *E*/*Z* mixture was subjected to the next step without further characterization.
Then the reaction of **3b** (118.7 mg, 0.25 mmol, *E*/*Z* = 1:1.78), propargyl alcohol (8.5 mg, 0.15 mmol), $Pd(PPh_3)_2Cl_2$ (6.2 mg, 8.84×10^{-3} mmol, 3.5 mol%), CuI (1.8 mg, 9.47×10^{-3} mmol, 3.8 mol%), and Et_2NH (11.0 mg, 0.15 mmol) in 0.5 mL of MeCN afforded 50.9 mg (43%) of (*Z*)-**3b**, 4.0 mg (4%) of (*Z*)-**4b**, and 33.9 mg (34%) of (*E*)-**4b**.

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