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The room temperature preparation of the 1-chloro-2,2-difluorovinylzinc reagent from HCFC-133a (CF_3CH_2Cl). The first ambient, high yield, one-flask preparation of α-chloro-β,β-difluorostyrenes

R. Anilkumar and Donald J. Burton*

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

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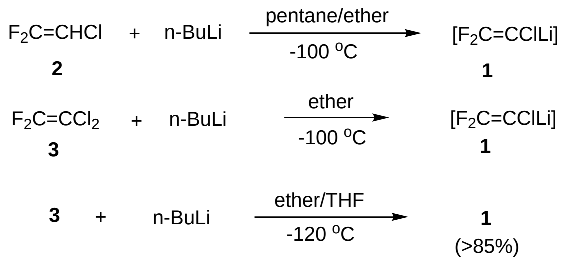
Abstract—The reaction of LDA (2.0 equiv.) with a THF solution of $ZnCl_2$ (1.0 equiv.) and HCFC-133a (CF_3CH_2Cl) (1.0 equiv.) at 15–20°C gives a 91% yield of [F_2C=CClZnCl]. Addition of ArI and $Pd(PPh_3)_4$ at rt to 65°C gives 65–85% isolated yields of ArCCl=CF_2. This one-flask procedure provides the first room temperature generation of the 1-chloro-2,2-difluorovinylzinc reagent and the first high yield preparation of α-chloro-β,β-difluorostyrenes from a cheap, readily available industrial precursor. © 2002 Elsevier Science Ltd. All rights reserved.

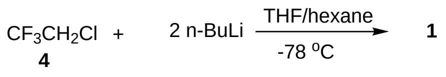
Tarrant and co-workers reported the first preparation of 1-chloro-2,2-difluorovinyllithium **1** via metallation of 1-chloro-2,2-difluoroethylene **2** with *n*-BuLi at low temperatures.[1] Two decades later, Normant et al. utilized halogen–metal exchange with 1,1-dichloro-2,2-difluoroethylene **3** and *n*-BuLi to prepare **1**.[2] Subsequently, Normant reported an improved yield of **1** from **3** via addition of a molar equivalent of tetrahydrofuran (THF) as a co-solvent.[3] Similar results were obtained by Okuhara.[4] Scheme 1 summarizes these initial preparations.

Recently, based on the work of Coe with CF_3CFH_2,[5–8] Percy and co-workers developed an excellent, high yield preparation of **1** from 1-chloro-2,2,2-trifluoroethane (HCFC-133a) **4** at low temperatures (Scheme 2).[9] This dehydrofluorination–metallation approach was successfully utilized by Percy for the synthesis of fluorinated allylic alcohols[9] and fluorinated succinic acid derivatives.[10]

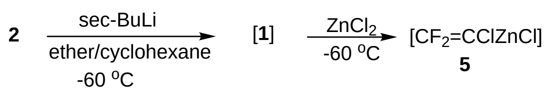
The most recent preparation of **1** was reported by Kumadaki and co-workers.[11,12] These workers reacted **2** with *sec*-BuLi in the presence of zinc chloride at −60°C in ether. The intermediate lithium reagent **1** is presumably trapped in situ by the zinc chloride to form the 1-chloro-2,2-difluorovinylzinc reagent **5** (Scheme 3). The in situ formed **5** was subsequently reacted with 3,8-diiododeuteroporphyrin derivatives with Pd(0) catalysis to give a 99% yield of 3,8-bis(1-chloro-2,2-difluorovinyl)deuteroporphyrin derivatives. The yield of



Scheme 1.



Scheme 2.



Scheme 3.

Keywords: HCFC-133a; chlorodifluorovinylzinc; Pd(0) coupling; chlorodifluorovinyllithium; α-chloro-β,β-difluorostyrene.

* Corresponding author. Fax: 319-335-1270; e-mail: donald-burton@uiowa.edu

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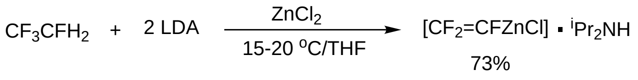
5 is not reported in this work; however, calculation of the yield from data reported in the experimental section of this paper[11] indicates that the yield of **5** is ~28–29%. Consequently, the in situ preparation of **5** is achieved at −60°C; however, the efficiency of the in situ preparation is modest, at best. In the Pd(0) coupling reaction, 13 equivalents of **5** (per vinyl iodide) is utilized to achieve the cross-coupled product, and the yield of the coupled product was reportedly based on the vinyl iodide.

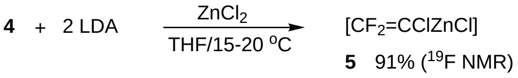
Recently, we reported the in situ preparation of [F_2C=CFZnCl] at room temperature via the reaction of CF_3CFH_2 with LDA and zinc chloride (Scheme 4).[13] Subsequent Pd(0) cross-coupling of this zinc reagent with an aryl iodide is a cost-effective route to α,β,β-trifluorostyrenes.[13]

The success of this previous work prompted us to determine: (a) if this in situ preparative route could be utilized to prepare **5** in good yield (at room temperature), in contrast to the poor yield attained by the previous procedure;[11,12] (b) if the *cisoid* and *transoid* structures of **5** proposed by these workers[12] had any validity, and (c) if the in situ generation of **5** (by our methodology) could be utilized in Pd(0) cross-coupling reactions without the necessity of a large excess of **5**.[11]

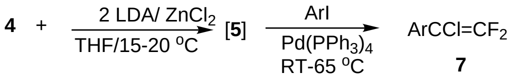
We now wish to report that when a THF solution of **4** and anhydrous zinc chloride is treated with LDA at 15–20°C, a 91% yield of **5** is formed (as detected by ^{19}F NMR analysis of the reaction mixture) (Scheme 5).[†] Zinc iodide reacted similarly in this reaction. When the reaction mixture was quenched with iodine, F_2C=CClI,[14] **6** was isolated, consistent with the formation of **5**. When **6** was reacted with activated zinc powder in THF, a 86.5% yield of [F_2C=CClZnI] was produced.[15]



Scheme 4.



Scheme 5.



Scheme 6.

In order to test the viability of **5** in Pd(0)-catalyzed cross-coupling processes, addition of an aryl iodide and $Pd(PPh_3)_4$ to the solution of **5** and warming (rt to 65°C) provided the α-chloro-β,β-difluorostyrenes **7** in excellent isolated yields (Scheme 6).[‡] In this Stille type cross-coupling reactions a ratio of 1:0.85 (**5**/aryl iodide) was employed to ensure that **all** the aryl iodide was consumed (to facilitate the isolation of **7**); no large excess of **5** was necessary. Table 1 summarizes the preparation of several derivatives of **7** prepared by this methodology. As noted in Table 1, the reaction is tolerant of a wide variety of functional groups and gives good yields of **7** even with a hindered *ortho* substituent (entry 4). It should also be noted that the reaction is readily scaled up, and a stock solution of **5** can be prepared and subsequently employed in functionalization reactions.

When **4** is reacted in situ with LDA and zinc chloride (as described above), a clear, pale yellow solution of **5** is produced in 91% ^{19}F NMR yield. The ^{19}F NMR spectrum of the zinc reagent **5** in THF/$^iPr_2NH$ shows two major doublets at −78.9 and −92.9 ppm, respectively, with J_{FF} = 59.0 Hz, assigned to the mono zinc reagent complexed to THF and/or diisopropylamine.[16] This data is similar to the data reported by Kumadaki for **5** generated from **2** and *sec*-BuLi/Et_2O/cyclohexane (Normant's procedure).[11]

[†] General procedure for the preparation of stock solution of **5**: a two-neck 500 mL round bottom flask fitted with a nitrogen tee and a septum was charged with diisopropylamine (42.0 mL, 300.0 mmol) and dry THF (120.0 mL). The solution was cooled to 0°C and 2.5 M *n*-BuLi (120.0 mL, 300.0 mmol) was slowly added to the amine/THF solution over 40 min; then the solution was stirred for an additional 10 min. A 1 L three-neck round bottom flask fitted with a dry ice/isopropanol condenser, septum, and a low temperature thermometer was assembled while hot and flushed with N_2 as it cooled. The flask was charged with $ZnCl_2$ (20.4 g, 150.0 mmol) and THF (110.0 mL). This saturated solution was cooled to 15°C with a cold water bath, then CF_3CH_2Cl (14.0 mL, 165.0 mmol) was condensed into the THF/$ZnCl_2$ solution. Then, the pre-generated LDA was slowly added to the THF/$ZnCl_2$/CF_3CH_2Cl solution (1.5 h) through a cannula, maintaining the temperature between 15 and 20°C (the tip of the cannula was dipped into the THF to avoid decomposition of the vinyllithium **1** at the tip of the cannula). After the addition of the LDA solution was completed, the reaction mixture was stirred at 20°C for 2 h, then allowed to settle. The ^{19}F NMR spectrum of the zinc reagent was recorded (using $C_6H_5CF_3$ as an internal standard), and the ^{19}F NMR yield of **5** was determined to be 91%.

[‡] Typical procedure for the cross-coupling reaction of **5** with aryl iodides: 25.0 mmol of the zinc reagent **5** was added (via syringe) to a three-neck 250 mL flask equipped with a condenser, stopper and septum under a nitrogen atmosphere. 4-Iodotoluene (21.3 mmol) and tetrakistriphenylphosphine palladium (~1.5 mol%) were added to the above zinc reagent **5** and the reaction mixture was stirred at rt for 12 h. The reaction progress was monitored by ^{19}F NMR by sampling small aliquots of the reaction mixture. After the reaction was completed, the reaction mixture was triturated several times with pentane or hexane (6×20 mL) and the combined extracts concentrated by rotary evaporation. The crude liquid obtained was distilled under reduced pressure (bp 51°C @ 9 mm) or purified by column chromatography (silica gel) to obtain *p*-methyl-α-chloro-β,β-styrene as a clear liquid in 83% (3.33 g, 17.7 mmol) yield. Spectral characteristics: ^{19}F NMR ($CDCl_3$): δ −84.6 (d, J = 35.2 Hz, 1F), −89.9 (d, J = 35.4 Hz, 1F); ^{1}H NMR ($CDCl_3$): δ 7.39 (dd, J = 1.2, 8.2 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.9 (dd, J = 287.3, 292.0 Hz), 138.9 (s), 129.3 (s), 127.8 (d, J = 5.5 Hz), 127.6 (dd, J = 2.9, 5.4 Hz), 93.4 (dd, J = 22.9, 37.5 Hz), 21.9 (s). GC–MS: 190 (M^++2, 32), 188 (M^+, 100), 153 (48), 133 (85). HRMS: calcd for $C_9H_7{}^{35}ClF_2$ 188.0204, obsd. 188.0204; calcd for $C_9H_7{}^{37}ClF_2$ 190.0175, obsd. 190.0180.

Thus, the chemical shift and coupling constants show minor variation due to complexation of **5** with different solvents, but are consistent with the formation of **5**. However, when **2** is reacted with *sec*-BuLi/Et_2O/cyclohexane in the presence of zinc chloride,[11] Kumadaki reports the formation of a 'new' zinc reagent with the following ^{19}F NMR data: −86.96 ppm (1F, d, $J=42$ Hz), −87.16 ppm (1F, d, $J=42$ Hz), and −91.47 ppm (2F, d, $J=42$ Hz).[11,12] He ascribes this data to a mixture of *cisoid* and *transoid*-bis (1-chloro-2,2-difluorovinyl)-zinc.[12] We question the assignment of this data to the *cisoid* and *transoid*-bis-zinc reagent. As noted by Kumadaki, "the chemical shifts of his zinc reagent are very similar to those of **2**, but coupling patterns of both spectra are different and a different distance between mid peaks at lower field is observed".[11,12] We have generated **5** from **4** as described above. When the solution of **5** is partially hydrolyzed with glacial acetic acid, the following ^{19}F NMR spectrum was observed (cf. Fig. 1). Note that **both** the zinc reagent **5** and **2** can be readily distinguished. Fig. 2 shows **only** **2** after complete hydrolysis with glacial acetic acid. **2** was subsequently removed from this reaction mixture under reduced pressure. The ^{19}F NMR spectrum and HRMS spectrum[17] of the volatile material confirmed it to be **2**. Thus, we propose that the spectrum observed for the zinc reagent by Kumadaki is the spectrum of **2**. Slight modification of the peak heights and coupling constants can occur due to complexation with different solvents or phasing of the instrument. It is **not** necessary to invoke isomeric zinc reagents to account for the spectral data.

In conclusion, we have described a general, high yield preparation of the 1-chloro-2,2-difluorovinylzinc reagent via the in situ reaction of CF_2CH_2Cl(HCFC-133a) with LDA/$ZnCl_2$ at room temperature. The HCFC-133a is a readily available industrial material and the reaction can be easily scaled up to provide a stable stock solution of the zinc reagent for functionalization reactions. The zinc reagent readily couples with aryl iodides with Pd(0) catalysis to provide the first, general high yield synthesis of α-chloro-β,β-difluorostyrenes.[18–20] Thus, the styrenes can be readily prepared from the cheap industrial precursor, CF_3CH_2Cl, via a one-flask procedure. Work is in progress with other CF_3CH_2X ($X=Br$, I, CF_3) derivatives, with additional functionalization reactions, as well as

Table 1. Preparation of α-chloro-β,β-difluorostyrenes (**7**) from HCFC-133a

$$CF_3CH_2Cl \quad + \quad ZnCl_2 \quad + \quad 2\,LDA \quad \xrightarrow[\text{2) ArI, Pd(PPh}_3)_4,\ \Delta]{\text{1) 15-20 °C, THF}} \quad \underset{\textbf{(7a-h)}}{ArCCl{=}CF_2}$$

Entry	Ar	Temp/Time	Styrene	NMR Yield (%)	Yield[a,b]
1	$C_6H_5^-$	65°C/1 h	**7a**	94	77
2	*p*-$MeC_6H_4^-$	rt/12 h	**7b**	99	83
3	*m*-$NO_2C_6H_4^-$	rt/15 h	**7c**	90	77
4	*o*-$^iPrC_6H_4^-$	65°C/12 h	**7d**	95	75
5	*p*-$EtO_2CC_6H_4^-$	65°C/3 h	**7e**	91	70
6	*m*-BrC_6H_4-[c]	rt/18 h	**7f**	96	85
7	*m*-$MeOC_6H_4^-$	60°C/3 h	**7g**	94	79
8	2-Thienyl	rt/4 h; 60°C/3 h	**7h**	87	65

[a] Isolated yields of pure products were obtained either by column chromatography or distillation under reduced pressure.

[b] All products give satisfactory ^{19}F, ^1H, ^{13}C NMR and HRMS data consistent with the assigned structure.

[c] 1% of the bis styrene was formed.

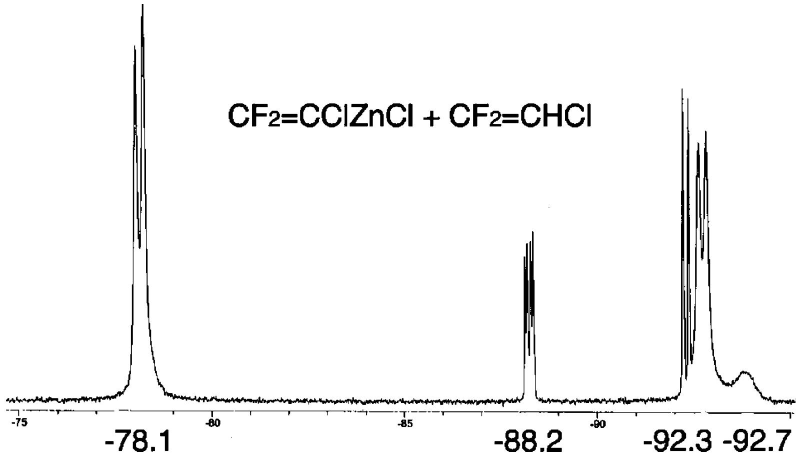


Figure 1. Partial hydrolysis of [CF_2=CClZnCl] with acetic acid.

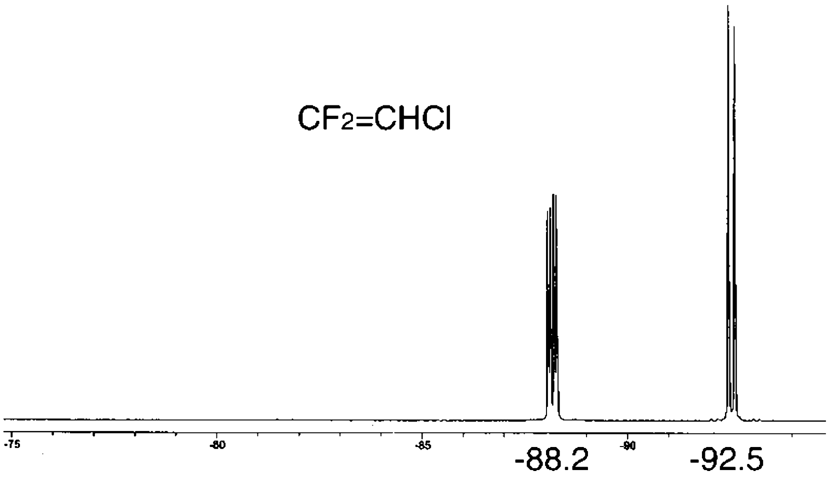


Figure 2. Complete hydrolysis of [CF_2=CClZnCl] with acetic acid.

other metal halides trapping agents, to elucidate the generality of this new, in situ approach.

Acknowledgements

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References

1. Drakesmith, F. G.; Richardson, R. D.; Stewart, O. J.; Tarrant, P. *J. Org. Chem.* **1968**, *33*, 286–291.
2. Masure, D.; Sauvetre, R.; Normant, J. F.; Villieras, J. *Synthesis* **1976**, 761–764.
3. Masure, D.; Chuit, C.; Sauvetre, R.; Normant, J. F. *Synthesis* **1978**, 458–460.
4. Okuhara, K. *J. Org. Chem.* **1976**, *41*, 1487–1494.
5. Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *Chem. Commun.* **1996**, 49–50.
6. Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluorine Chem.* **1999**, *99*, 127–131.
7. Coe, P. L. *J. Fluorine Chem.* **1999**, *100*, 45–52.
8. Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluorine Chem.* **1997**, *85*, 151–153.
9. Bainbridge, J. M.; Brown, S. J.; Ewing, P. N.; Gibson, R. R.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2541–2545.
10. Brown, S. J.; Corr, S.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 5269–5273.
11. Shigeoka, T.; Kuwahara, Y.; Watanabe, K.; Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2000**, *103*, 99–103.
12. Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **1999**, *100*, 135–146.
13. Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2731–2733.
14. F_2C=CClI: ^{19}F NMR: (THF/$^iPr_2NH$): −77.3 ppm (d, $J_{FF}=28.1$ Hz) and −81.4 ppm (d, $J_{FF}=29.2$ Hz). HRMS: calcd for $C_2F_2{}^{35}ClI$ 223.8701, obsd. 223.8701; calcd for $C_2F_2{}^{37}ClI$ 225.8672, obsd. 225.8665.
15. ^{19}F NMR data for [F_2C=CClZnI] (THF): −76.4 ppm (d, $J_{FF}=51.3$ Hz) and −91.1 ppm (d, $J_{FF}=51.5$ Hz); ^{19}F NMR data for [F_2C=CClZnI] (THF/TMEDA); ^{19}F NMR: −76.6 (d, $J=54.5$ Hz) and −90.9 (d, $J=55.0$ Hz).
16. The bis-zinc reagent (minor product) can show minor variations in chemical shifts, dependent on the solvent. With TMEDA, the ^{19}F NMR spectrum of the bis-reagent **5** exhibits a doublet at −76.4 ppm ($J=58.3$ Hz) and a doublet at −92.2 ppm ($J=59.0$ Hz).
17. HRMS: **2** calcd for $C_2HF_2{}^{35}Cl$: 97.9735, obsd. 97.9733; calcd for $C_2HF_2{}^{37}Cl$: 99.9705, obsd. 99.9709.
18. Cohen, S. G.; Wolosinski, H. T.; Scheuer, P. J. *J. Am. Chem. Soc.* **1949**, *71*, 3439–3440.
19. Wheaton, G. A.; Burton, D. J. *J. Org. Chem.* **1978**, *43*, 2643–2651.
20. Burton, D. J.; Anderson, A. L.; Takei, R.; Koch, H. F.; Shih, T. L. *J. Fluorine Chem.* **1980**, *16*, 229–235.