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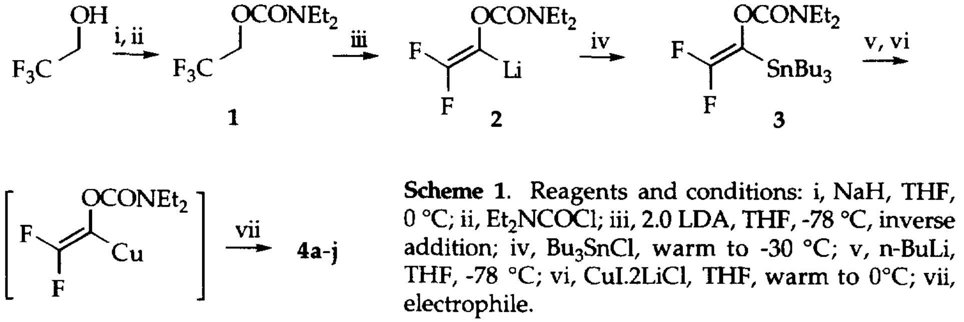
A Practical, Versatile Difluorovinylcopper Reagent

P.J. Crowley,[‡] J.A. Howarth,[a] W.M. Owton,[†] J.M. Percy* and K. Stansfield

School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
[‡]Zeneca Agrochemicals, Jeallots Hill Research Station, Bracknell, Berkshire RG12 6EY, UK.
[†]Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK.
[a]Current Address, Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK.

Abstract: *Transmetallation of an α–lithio-β,β–difluoroenol carbamate with a* CuX_3Li_2 *(2LiCl.CuI) produced a vinylcopper reagent that was thermally stable and reacted with activated haloalkanes and acid chlorides in moderate to high yield, extending considerably the scope of building block chemistry available from trifluoroethanol.* Copyright © 1996 Elsevier Science Ltd

Recently, we reported, in full, details of the chemistry of a metallated difluoroenol carbamate derived from trifluoroethanol.[1] Conversion of the readily-available and easy-to-handle fluoroalcohol to the sodium salt in THF, followed by acylation with *N,N*-diethylcarbamyl chloride afforded carbamate **1** which could be purified rigorously and isolated in high yield. Careful inverse addition (**Scheme 1**) to freshly-prepared LDA in THF at -78 °C afforded metallated enol carbamate **2** which reacted smoothly with aldehydes and ketones, carbon dioxide, epoxides and Group(IV) halides. Indeed stannane **3** can be prepared on a multigramme-scale and stored (in the freezer) for extended periods.

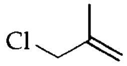
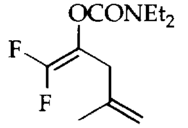
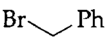
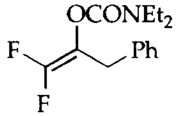
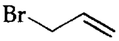
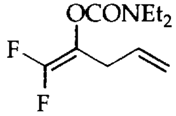
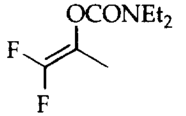
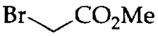
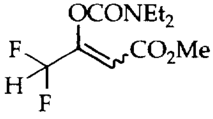
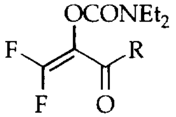


Scheme 1. Reagents and conditions: i, NaH, THF, 0 °C; ii, Et_2NCOCl; iii, 2.0 LDA, THF, -78 °C, inverse addition; iv, Bu_3SnCl, warm to -30 °C; v, n-BuLi, THF, -78 °C; vi, CuI.2LiCl, THF, warm to 0°C; vii, electrophile.

However, all our attempts to intercept the reactive intermediate **2** with alkyl halide electrophiles, including activated species, failed to result in carbon-carbon bond formation. For example, with iodomethane, no reaction occurred at low temperature, and **2** decomposed outside a narrow temperature window, bounded at the upper limit at -65 °C. With allyl bromide, bromination occurred and the addition of acyl halides yielded non-fluorinated products. Transmetallation appeared to present an obvious solution to the problem, but we were discouraged in the first instance by the absence of convenient preparations of fluorovinyl copper and fluorovinylcuprate reagents.[2,3]

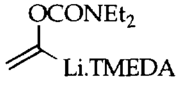
The CuX_3Li_2 reagents[4] are easy to prepare[5] and handle, and we decided to explore the consequences of the transmetallation of **2**. The addition of a THF solution of the CuX_3Li_2 reagent (one equivalent) to a cold (-78 °C) solution of **2** (generated by tin-lithium exchange from stannane **3**) afforded an new intermediate that could be warmed to room temperature without apparent decomposition.[6] The addition of alkyl halides allowed the isolation of adducts **4a-j** in moderate to good yields (**Table 1**).[7]

Table 1

Electrophile	Product		% Yield
		**4a**	76
		**4b**	53
		**4c**	66
CH_3I		**4d**	40
		**4e**	42[a]
RCOCl			
R = Et;		**4f**	76
R = *i*Pr;		**4g**	67
R = *i*Bu;		**4h**	72
R = *t*Bu;		**4i**	78
R = Ph.		**4j**	77

[a] A single stereoisomer was isolated.

The reactivity profile resembles that described by Sengupta and Snieckus,[8] for desfluoroenol carbamate **5**, indicating that the deactivating effect of the two β-fluorine atoms is not deleterious in the case of the organocopper reagent. The reaction with ethyl bromoacetate is particularly interesting; double-bond migration (into conjugation) occurred, even after careful work-up, suggesting that the basicity of the diisopropylamine is sufficiently high for deprotonation of the immediate (β,γ-unsaturated) product to occur, triggering isomerisation.



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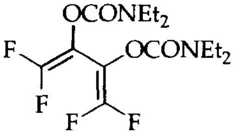

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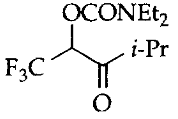

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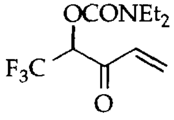

8

With acyl halides, a limiting case in the reactivity of the intermediate was approached. The addition of ethyl chloroformate resulted in the isolation of diene **6** as the sole fluorine-containing product. The diene arises from the well-known oxidative dimerisation of vinylcopper reagents.[9] With the more reactive acid chlorides, smooth trapping occurred and adducts **4f**-**4j** were isolated in good to excellent yields following ammoniacal work-up, though the stabilities of the adducts were variable. For example, **4j** survived flash column chromatography and could be stored in the freezer, but analogue **4g** started to decompose on a silica column to afford hydrofluorination product **7**. When we attempted the reaction with acryloyl chloride, **8** was the only product we were able to isolate (in 36% yield).[10] These results are particularly interesting set against the wide range of apparently stable related compounds (α-alkyl-β,β-difluoroenones) reported by Ichikawa *via* metallate rearrangements from boron.[11] Here, the CuX_3Li_2 reagent is the transmetallating species of choice; treatment of solutions of **2** with freshly recrystallised[12] copper bromide.dimethyl sulfide complex afforded lower yields of products and was considerably less convenient.[13]

The availability of a reactive difluorovinylcopper reagent extends considerably the range of building block chemistry[14] accessible from trifluoroethanol.[15] In a subsequent paper, we will report cycloaddition reactions of the difluoroenones.

Acknowledgements

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2. Burton, D.J.; Yang, Z.Y.; Morken, P.A.; *Tetrahedron*, **1994**, 50, 2993-3063.
3. Methods based on the corresponding zinc reagents failed in our hands; see Gillet, J.P.; Sauvêtre, R.; Normant, J.F.; *Synthesis*, **1986**, 538-543.
4. Alexakis, A.; Mutti, S.; Normant, J.F.; *J. Am. Chem. Soc.*, **1991**, *113*, 6322-6324.

5. The procedure described recently by Reetz and Kindler was followed. Reetz, M.T.; Kindler, A.; *J. Chem. Soc., Chem. Commun.*, **1994**, 2509-2510.
6. Metallated fluoroalkenes darken dramatically when allowed to warm above a critical temperature. In the case of the transmetallated species, that temperature clearly lies above 15°C.
7. In a typical procedure, *n*-butyllithium (0.86 ml of a 1.6 M soution in hexane) was added dropwise over five minutes to a solution of stannane **3** (0.5 ml, 1.37 mmol) in dry THF (2.5 ml) at -78 °C. The resulting blue coloured solution was stirred at -78 °C for one hour. The pre-formed CuX_3Li_2 complex (1.4 ml of a 1 M solution in dry THF) was added in one portion. The solution was stirred for one hour further at -78 °C, before being warmed to 0 °C over fifteen minutes. Methallyl chloride (0.16 ml, 1.64 mmol) was added to the resulting green coloured mixture. The mixture was stirred at 0 °C for two hours, and then stirred overnight¶ at room temperature. The reaction was quenched with 10 % ammoniacal ammonium chloride solution (15 ml) and extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were removed *in vacuo*. Flash column chromatography afforded diene **4a** (0.24 g, 76 %) as a colourless oil, R_f 0.31 (10 % EtOAc/Hexane): δ_H(300 MHz; $CDCl_3$) 4.83 (1H, *s*, $=CH_aH_b$), 4.79 (1H, *s*, $=CH_aH_b$,) 3.40-3.22 (4H, *m*, $N(CH_2CH_3)_2$), 2.97 (2H, *br s*, $CH_2C(CH_3)$), 1.76 (3H, *s*, allylic CH_3), 1.15 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(75 MHz; $CDCl_3$) 154.8 (*dd*, $^1J_{C\text{-}F}$ 288.2, 279.9), 152.8, 140.2, 113.3, 110.0 (*dd*, $^2J_{C\text{-}F}$ 45.9, 14.7), 42.4 , 41.9 , 35.4 , 21.7 , 13.9, 13.2 ; δ_F(90 MHz; $CDCl_3$) -90.6 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -112.3 (1F, *d*, $^2J_{F\text{-}F}$ 61.0); (Found 234.1236. $C_{11}H_{17}NO_2F_2$ requires 234.1232); *m/z* (CI) 234 ($[M+H]^+$, 100 %), 100 ($[CONEt_2]^+$, 42).
¶In the case of acid chloride electrophiles, the reactions were run for 4 hours before work-up, rather than overnight.
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9. Ley, S.V.; Woods, M.; Zanittigerosa, A.; *Synthesis*, **1992**, 52-54.
10. From a 2.1 mmol scale experiment, ketone **8** (0.19g, 36%) was obtained as a clear oil following flash column chromatography, R_f 0.18 (10% EtOAc/Hexane): δ_H(300 MHz; $CDCl_3$) 6.61 (1H, *dd*, $^3J_{H\text{-}H}$ 17.0, $^3J_{H\text{-}H}$ 9.0, $COCH=CH_aH_b$), 6.47 (1H, *d*, $^3J_{H\text{-}H}$ 17.0, $COCH=CH_aH_b$), 5.93 (1H, *d*, $^3J_{H\text{-}H}$ 9.0, $COCH=CH_aH_b$), 5.62 (1H, *q*, $^3J_{H\text{-}F}$ 9.0, F_3CCH), 3.45-3.20 (4H, *m*, $N(CH_2CH_3)$), 1.25 (3H, *t* $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)$), 1.15 (3H, *t*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)$); δ_C(75 MHz; $CDCl_3$) 188.6, 153.2, 131.9, 131.4, 121.9 (*q*, $^1J_{C\text{-}F}$ 281.5), 74.2 (*q*, $^2J_{C\text{-}F}$ 32.7), 42.8, 42.0, 13.9, 13.3; δ_F(90 MHz; $CDCl_3$) -72.2 (*d*, $^2J_{H\text{-}F}$ 9.0); *m/z* (CI) 254 (100% $[M+H]^+$, 271 (20, $M+NH_4^+$), 100, (30, $[CONEt_2]^+$).
11. Ichikawa, J.; Kobayashi, M.; Yokota, N.; Minami, T.; *Tetrahedron*, **1994**, *50* 11637-11646.
12. Taylor, R.J.K.; Casy, G.; in "*Organocopper Reagents: A Practical Approach*", ed. by Taylor, R.J.K.; Oxford University Press, Oxford, 1994, Chapter 2, 38.
13. For example, the following yields were obtained with $CuBr.SMe_2$: **4a**, 42%; **4b**, 35%; **4c**, 40%; **4d**, 25%.
14. Percy, J.M.; *Contemp. Org. Synth.*; **1995**, *4*, 251-268.
15. Patel, S.T.; Percy, J.M.; Wilkes, R.D.; *J. Org. Chem.*, **1996**, *61*, 166-173 and references therein.

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