On the Diels–Alder reactivity of β,β-difluorinated dienophiles

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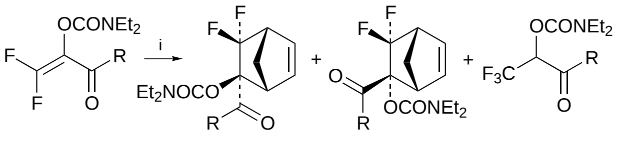
A range of substituted β,β-difluoroenones and a β,β-difluoroalkenoate underwent [4 + 2] cycloadditions with cyclopentadiene, and other dienes, under thermal and Lewis acid-catalysed conditions.

In the burgeoning area of the chemistry of fluorinated building blocks,[1] there are few concise ways of building ring systems that contain a fluorinated or difluorinated carbon atom. Diels–Alder cycloadditions of activated fluorinated dienophiles would therefore be extremely useful, but there are very few relevant reports. One tantalising example was provided by Leroy *et al.*[2] who described the [4 + 2] cycloaddition reaction between methyl 2,2-difluoropropenoate and furan in an approach to fluorinated analogues of shikimic acids. While the dienophile could be prepared *via* a reasonably short sequence, the cycloaddition and the manipulation of the cycloadducts were problematic and there do not appear to be any subsequent examples of applications of this chemistry.

Difluoroalkenyl compounds that contain electron-withdrawing groups undergo conjugate addition/elimination reactions which lead to loss of fluoride ion. Concomitant overall hydrofluorination follows, presenting a serious obstacle to the development of new chemistry. However, the presence of an *N*,*N*-diethylcarbamoyloxy group at the α-position in a β,β-difluoro dienophile offers some stabilisation against the side reaction.[3,4] Recently, we described some vinylcopper chemistry that allowed access to β,β-difluoroenones **1a**–**f**.[5] Heating the enones in sealed tubes in the presence of excess cyclopentadiene afforded inseparable mixtures of cycloadducts **2a**–**f** in moderate to good yields (Scheme 1, Table 1).‡ Stereoselectivities were low,[6] favouring the stereoisomer in which the π-acceptor group occupied the *exo* orientation. The *exo* : *endo* ratio increased as the ketonic alkyl group increased in size, while the yields of cycloadducts and hydrofluorination product **3** decreased and increased respectively. The stereoisomer ratios were determined by integrating ^{19}F NMR spectra. Structural correlation was achieved by dihydroxylation[7] of the crude *exo*–*endo* mixture followed by separation and crystallisation of the major diol product; the crystal structure data will be reported elsewhere.

Thermal reactions with all other dienes failed and **3** was isolated as the sole product. In an attempt to achieve cycloaddition at lower temperatures, we examined the effect of added trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) on the reaction and found that cycloaddition occurred between −78 °C and ambient temperature, and that the reaction became highly stereoselective (*exo* : *endo* = 8 : 1). Although the yield of isolated cycloadduct was lower, the reaction was more efficient in diene, requiring only 1 equiv. under the catalytic conditions. Nevertheless, other dienes still failed to react and the formation of **3** predominated. Other Lewis acids [such as $TiCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, ZnI_2] were ineffective promoters and **3** was formed instead.[8]

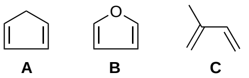
Palladium-catalysed coupling§ of our vinylcopper reagent with ethyl chloroformate[9] afforded **4**, a considerably more robust and (one order of magnitude) less reactive compound, which has undergone (to date) a limited number of Diels–Alder reactions affording cycloadducts with cyclopentadiene (**5a**, **5b**



1a–**f** **2a**–**f** *endo* **2a**–**f** *exo* **3**

Scheme 1 *Reagents and conditions*: i, cyclopentadiene, sealed tube, 100 °C, hydroquinone

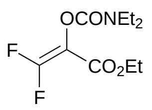
Table 1



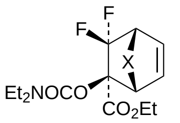
A **B** **C**

Diene	Dienophile	R	Conditions[a]	Cycloadduct	Yield (%)[b]	Ratio (*exo* : *endo*)[c]	**3** (%)[c]
A	**1a**	Ph	A	**2a**	64	1 : 1	10
A	**1b**	Et	A	**2b**	81	1.5 : 1	0
A	**1b**	Et	B	**2b**	54	8 : 1	0
A	**1c**	$\mathrm{Bu^n}$	A	**2c**	54	1.5 : 1	0
A	**1d**	$\mathrm{Bu^i}$	A	**2d**	67	1.5 : 1	5
A	**1e**	$\mathrm{Pr^i}$	A	**2e**	64	2.5 : 1	5
A	**1f**	$\mathrm{Bu^t}$	A	**2f**	17	3 : 1	34
A	**4**	—	C	**5**	74	1.5 : 1	—
B	**4**	—	D	**6**	5[d]	1.5 : 1	—
B	**4**	—	E	**6**	20	1.5 : 1	—
C	**4**	—	D	**7**	67[d,f]	—	—

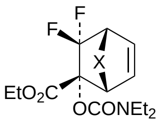
[a] Conditions: A, neat cyclopentadiene (20 equiv.), 100 °C, 4 h, sealed tube; B, cyclopentadiene (1.0 equiv.), Me_3SiOTf (0.1 equiv.), CH_2Cl_2, −78 °C to room temp.; C, neat cyclopentadiene (20 equiv.), 100 °C, 40 h, sealed tube; D, neat diene (20 equiv.), 100 °C, 72 h, sealed tube; E, neat furan (20 equiv.), ZnI_2 (0.5 equiv.), 80 °C, 48 h. [b] Isolated yields after chromatography are reported. [c] Determined by ^{19}F NMR spectroscopy. [d] Starting material 4 was also recovered. [e] Ratio based on isolated yields after chromatographic separation of stereoisomers. [f] A 1 : 1 mixture of regioisomeric products was isolated.



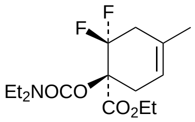
4



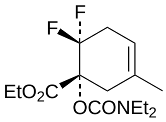
5a X = CH_2
6a X = O



5b
6b



7a



7b

74%), furan (**6a**, **6b** 20%, zinc iodide catalysis) and isoprene (**7**, 67%). Importantly, the alkenoate could be recovered from each reaction suggesting that considerable scope exists for the development of efficient catalytic conditions and thus, mild general syntheses of highly functionalised difluorinated cyclohexene derivatives. We should emphasise that the lower reactivity is acceptable because the problematic hydrofluorination reaction appears to be considerably slower in the case of **4**. We now wish to explore the effects exerted by the *N*,*N*-dialkylcarbamoyloxy group upon the stereoselectivity and reactivity of these transformations.

Footnotes and References

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‡ *Typical procedure* for **2b** *exo*/*endo*: Enone **1b** (0.24 g, 1 mmol) was dissolved in freshly-cracked cyclopentadiene (1.32 ml, 20 mmol) together with a crystal of hydroquinone. The mixture was degassed and sealed in a ACE pressure tube which was immersed in an oil bath (100 °C). After 4 h, the tube was removed from the bath, cooled and opened. Purification of the residue by flash column chromatography (10% ethyl acetate–hexane, R_f = 0.18) afforded adducts *exo* and *endo* **2b** as a clear oil (0.24 g, 81%).

Exo: δ_H(300 MHz; $CDCl_3$) 6.26–6.18 (2 H, m), 3.72–3.60 (1 H, m), 3.50–3.18 (4 H, m), 3.12–3.00 (1 H, m), 2.44 (2 H, q, $^2J_{H\text{-}H}$ 7.0), 2.20–2.10 (1 H, m), 1.95–1.85 (1 H, m), 1.30–1.10 (9 H, m); δ_F(284 MHz; $CDCl_3$) −101.7 (1 F, d, $^2J_{F\text{-}F}$ 226.8), −106.4 (1 F, d, $^2J_{F\text{-}F}$ 226.8); δ_C(75 MHz; $CDCl_3$) 204.5, 153.7, 138.1, 133.7 (d, $^3J_{C\text{-}F}$ 6.2), 127.9 (dd, $^1J_{C\text{-}F}$ 276.6, 277.1), 87.5 (dd, $^2J_{C\text{-}F}$ 30.2, 30.9), 49.4 (dd, $^2J_{C\text{-}F}$ 24.1, 20.7), 48.3, 44.3 (d, $^3J_{C\text{-}F}$ 5.3), 42.2, 42.0, 32.2, 14.2, 13.6, 7.7.

Endo: δ_H(300 MHz; $CDCl_3$) 6.68–6.62 (1 H, m), 5.96–5.90 (1 H, m), 3.72–3.60 (1 H, m), 3.50–3.18 (4 H, m), 3.10–3.00 (1 H, m), 2.44 (2 H, q, $^2J_{H\text{-}H}$ 7.0), 2.12–2.04 (1 H, m), 1.90–1.80 (1 H, m), 1.30–1.10 (9 H, m); δ_F(270 MHz; $CDCl_3$) −100.5 (1 F, d, $^2J_{F\text{-}F}$ 223.9), −104.7 (1 F, d, $^2J_{F\text{-}F}$ 223.9); δ_C(75 MHz; $CDCl_3$) 203.0, 153.9, 138.9, 129.2 (d, $^3J_{C\text{-}F}$ 6.2), 127.4 (dd, $^1J_{C\text{-}F}$ 276.6, 277.1), 89.6 (dd, $^2J_{C\text{-}F}$ 27.5, 27.5), 49.4 (dd, $^2J_{C\text{-}F}$ 24.1, 20.7), 48.6, 44.3 (d, $^3J_{C\text{-}F}$ 5.3), 42.8, 42.3, 32.1, 14.4, 13.4, 7.5; *m/z* (CI) 302, (100%, [M + H]$^+$), 100 (20, [CONEt$_2$]$^+$); HRMS calc. for $C_{15}H_{22}NO_3F_2$: 302.15687; found: 302.15563.

§ A solution of 1-(diethylcarbamoyloxy)-2,2-difluoroethenylcopper[5] (1.37 mmol) was cooled to −78 °C and $Pd_2(dba)_3$ (0.025 g, 0.03 mmol) was added followed by ethyl chloroformate (0.35 ml, 3.24 mmol). The reaction was warmed to room temperature over 30 min then stirred for 24 h. The reaction was quenched with 10% aqueous ammonium chloride and the products extracted with Et_2O, then the combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (10% ethyl acetate–hexane, R_f = 0.14) afforded **4** as a colourless oil. (0.42 g, 67%); δ_H(300 MHz; $CDCl_3$) 4.25 (2 H, q, $^3J_{H\text{-}H}$ 7.0), 3.30 (4 H, q, $^3J_{H\text{-}H}$ 7.0), 1.40–1.10 (9 H, m); δ_F(284 MHz; $CDCl_3$) −81.4. (d, $^2J_{F\text{-}F}$ 9.0), −84.6 (d $^2J_{F\text{-}F}$ 9.0); δ_C(75 MHz; $CDCl_3$); 163.6, 155.7 (t, $^1J_{C\text{-}F}$ 300.2), 151.6, 101.4 (t, $^2J_{C\text{-}F}$ 25.0), 61.7, 42.7, 42.2, 14.0, 13.0, 13.2; *m/z* (CI) 252 (100%, [M + H]$^+$, 100, (70 [CONEt$_2$]$^+$). HRMS calc. for $C_{10}H_{16}NO_4F_2N$: 252.10485; found: 252.10447.

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