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Dispiroketals in Synthesis (Part 14)[1]: Functionalised Dispiroketals as New Chiral Auxiliaries; Highly Stereoselective Michael Additions to a Bifunctional, C_2-Symmetrical Chiral Auxiliary.

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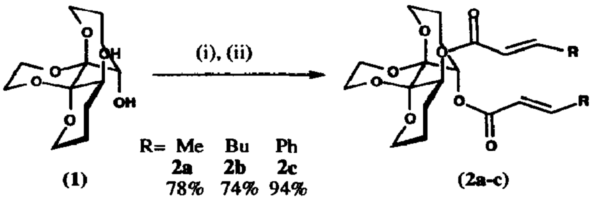
Abstract: A bifunctional, C_2-symmetrical chiral auxiliary derived from dihydroxylated dispiroketals has been used to induce a high degree of asymmetry in Michael additions of cuprates to a variety of di-α,β-unsaturated ester systems.

In the previous papers we reported the preparation and application of a C_2-symmetrical dispiroketal diol (**1**) as a readily obtained chiral auxiliary for asymmetric Diels-Alder reactions. During this study a diacrylate derivative underwent highly stereoselective Lewis acid-catalysed Diels-Alder reactions with a variety of dienes.

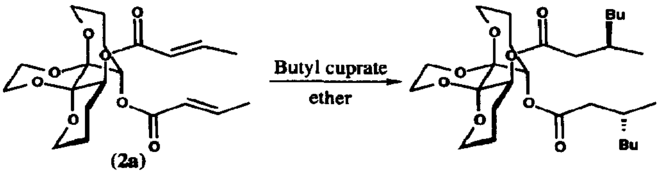
In this paper we would like to report the application of (**1**) to the synthesis of a variety of bifunctional Michael acceptors (**2a-c**)[2] and to describe a variety of highly stereoselective additions of cuprate reagents to these systems.[3] The Michael acceptors were synthesised by quenching of the dialkoxide anion of (**1**) with the appropriate acid chloride (Scheme 1).



(i) KO^tBu, THF, 0°C-rt; (ii) Acid chloride, -78°C.

Scheme 1

Initial investigations centred on the dicrotonate (**2a**) and the addition a variety of butyl organocopper reagents to this system (Scheme 2). These included organocopper reagents, homo- and heterocuprate reagents and copper-catalysed Grignard reagents[4] (Table 1).



Scheme 2

Entry	Butyl Cuprate	Temp, Time	Yield	Config.	e.e.
1	BuCu.BF$_3$.PBu$_3$	-60°C, 16 hrs	88%	R	96%
2	BuCu.BF$_3$.PBu$_3$	-45°C, 16 hrs	63%	R	89%
3	Bu$_2$CuCNLi$_2$, ZnCl$_2$	-60°C, 16 hrs	80%	R	63%
4	BuMgCl, CuBr.DMS, ZnCl$_2$	-60°C, 16 hrs	40%	R	28%
5	Bu$_2$CuCNLi$_2$	-60°C, 16 hrs	82%	S	35%

Table 1

It was of interest to note that in all cases where a species which may act as a bidentate Lewis acid is present in the reaction medium, the stereochemistry of the product was *R*. In the case where no such Lewis acidic species existed, the net stereofacial selectivity was reversed. This result was consistent with our model for the prediction of the stereochemical outcome of asymmetric Diels-Alder reactions proposed in the previous communication.

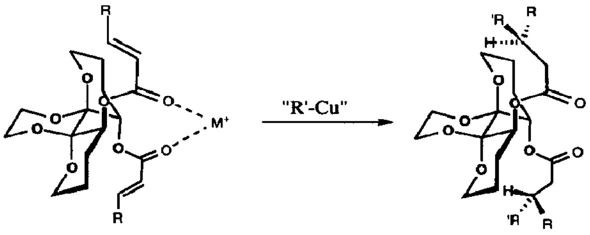
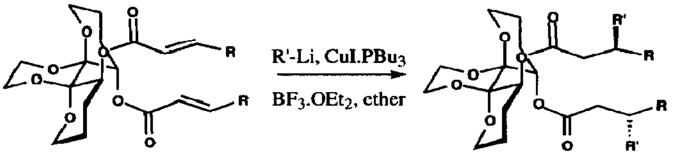


Figure 1

In our model, a bidentate Lewis acid is envisaged to chelate the two carbonyls in the system (Figure 1). The enoate adopts a conformation where the carbonyl bond in antiplanar with the olefinic bond. The *Si*-face of the enoate is thus shielded by the pyran rings of the dispiroketal forcing the cuprate to approach from the *Re*-face of the enoate to give the *R* product.

The conditions offering the highest degree of stereocontrol were found to be modified Yamamoto conditions[5] (Entry 1, BuCu.BF$_3$.PBu$_3$) and these were applied to a variety of different systems (Scheme 3 and Table 2).



(2a-c)

Scheme 3

Entry	R	R'	Temp, Time	Yield	Config.	e.e.
1	Me	Bu	-60°C, 16 hrs	88%	*R*	94%
2	Me	Ph	-40°C, 36 hrs	68%*	*R*	81%
3	Me	$SiMe_2Ph$	-70°C, 12 hrs	92%#	*R*	76%
4	Ph	Me	-60°C, 16 hrs	83%	*S*	92%
5	Ph	$SiMe_2Ph$	-60°C, 16 hrs	91%#	*R*	71%
6	Ph	Bu	-60°C, 16 hrs	87%	*R*	92%
7	Bu	Me	-60°C, 16 hrs	79%	*S*	93%

Notes: * Yield based on recovered starting material. # Reaction carried out in 50:50 ether:THF.

Table 2

Michael additions involving methyl[6] and butyl[7] organocopper reagents (Entries 1,4,6 and 7) all proceeded in both high yield and stereoselectivity. In an example of the addition of phenyl organocopper reagent (Entry 2) both the yield and selectivity were reduced. This is probably due to the low reactivity of this cuprate which necessitated an elevated reaction temperature. The additions of Fleming's phenyldimethylsilyl cuprate[8] (Entries 3 and 5) to our dienoate system proceeded in high yield but with reduced stereofacial selectivity. The reason for this may be that the reactions were carried out in a 1:1 mixture of ether and THF and any bidentate chelate complexes involved in the control of the stereochemical outcome of these reactions may be partially destroyed by the presence of the THF.

The Michael adducts could be cleaved hydrolytically (NaOH, MeOH, H_2O, reflux) or reductively ($LiAlH_4$, ether, -30°C) and isolated in high yield from the recovered auxiliary as previously reported. The isolated carboxylic acids had data identical to that in the literature.[9]

In this communication we have shown that, as well as being an effective bifunctional chiral auxiliary for Diels-Alder reactions, (**1**) is able to induce a high degree of stereoselectivity in double conjugate additions to this system. The bifunctional nature of the auxiliary means that it has a very low effective molecular weight and is therefore a highly efficient auxiliary.

The exploitation of (**1**) for other asymmetric reactions is currently under way, as are investigations into other applications of dihydroxylated dispiroketals in asymmetric synthesis either as auxiliaries or ligands and modifiers for catalytic asymmetric processes.

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References and Footnotes

1. B.C.B.B. Bezuidenhaudt, G.H. Castle, J.V. Geden, S.V. Ley, Previous Communication.
2. (**2a**): m.p. 202 °C (from IPA/hexane); $[\alpha]_D^{27} = -197$ (c= 0.23, chloroform); ν_{max} (film)/cm^{-1} 3015, 2991, 1714 (C=O), 1659 (C=C), 1319, 1229, 1194, 1181, 1162, 1095, 1064, 1044, 928, 753; δ_H (200 MHz; $CDCl_3$) 1.4-2.1 (8H, m, 2 x H-3, 2 x H-4, 2 x H-10, 2xH-11), 1.87 (6H, dd, J 6.82, 1.81, 3 x H-4' and 3 x H-4"), 3.3-3.55 (4H, m, 2 x H-2 and 2 x H-9), 3.60 (2H, m, H_{eq}-14 and H_{eq}-15), 4.10 (2H, m, H_{ax}-14 and H_{ax}-15), 5.55 (2H, dd, J 11.1, 5.1, H-5 and H-12), 5.94 (2H, dq, J 15.3, 1.6, H-2' and H-2"), 6.95, 2H, dq, J 15.4, 6.9, H-3' and H-3"); δ_C (50 MHz; $CDCl_3$)

17.8 (C-4' and C-4"), 24.2 (C-3 and C-10), 25.3 (C-4 and C-11), 58.5 (C-2 and C-9), 59.7 (C-14 and C-15), 66.7 (C-5 and C-12), 96.1 (C-6 and C-7), 123.4 (C-2' and C-2"), 143.8 (C-3' and C-3"), 165.8 (C-1' and C-1"); *m/z* (EI) 369 $(M)^+$, 325, 311, 256, 212, 142, 113, 99, 69; Found: $(M)^+$, 396.1760. $C_{20}H_{28}O_8$.requires *M*, 396.1784. Analysis; Found: C, 60.41%; H, 7.12%. $C_{20}H_{28}O_8$ requires C, 60.59%; H, 7.12%.

(2b): m.p. 52 °C (from petrol); $[a]^{26}_{D}$ = -159 (c= 0.62, chloroform); ν_{max} (film)/cm^{-1} 2956, 2930, 2873, 1654 (C=O), 1316, 1276, 1212, 1080, 1065, 1046, 972, 925, 668; δ_H (200 MHz; $CDCl_3$) 0.80 (6H, t, J 7.1, CH3-7' and CH3-7"), 1.0-1.9 (16H, m, 2 × H-3, 2 × H-4, 2 × H-10, 2 × H-11, 2 × H-5', 2 × H-6', 2 × H-5", 2 × H-6"), 2.09 (4H, m, 2 × H-4', 2 × H-4"), 3.20-3.60 (4H, m, 2 × H-2, 2 × H-9), 3.51, 2H, m, H_{eq}-14 and H_{eq}-15), 4.01 (2H, m, H_{ax}-14 and H_{ax}-15), 5.46 (2H, dd, J 11.0, 4.8, H-5 and H-12), 5.81 (2H, d, J 15.6, H-2' and H-2"), 6.88 (2H, dt, J 15.4, 6.9, H-3' and H-3"); δ_C (50 MHz; $CDCl_3$) 13.6 (C-7' and C-7"), 21.9, 24.0 (C-5', C-6', C-5", C-6"), 25.0 (C-3 and C-10), 29.9 (C-4 and C-11), 31.5 (C-4' and C-4"), 58.3 (C-2 and C-9), 59.5 (C-14 and C-15), 66.5 ; *m/z* (EI) 480 $(M)^+$, 352, 299, 265, 197, 155, 111, 99, 71, 55; Found: $(M)^+$, 480.2688. $C_{26}H_{40}O_8$ requires *M*, 480.2723; Analysis; Found: C, 64.97%; H, 8.47%. $C_{26}H_{40}O_8$ requires C, 64.98%; H, 8.39%.

(2c): m.p. 189 °C (from IPA/hexane); $[\alpha]^{27}_{D}$ = -67° (c= 0.26, chloroform); ν_{max} (film)/cm^{-1} 2956, 2930, 2873, 1654 (C=O), 1316, 1276, 1212, 1080, 1065, 1046, 972, 925, 668; d_H (200 MHz; $CDCl_3$) 1.60-2.10 (8H, m, 2 × H-3, 2 × H-4, 2 × H-10, 2 × H-11), 3.35-3.65 (4H, m, 2 × H-2, 2 × H-9), 3.65 (2H, m, H_{eq}-14 and H_{eq}-15), 4.15 (2H, m, H_{ax}-14 and H_{ax}-15), 5.70 (2H, dd, J 10.8, 5.1, H-5 and H-12), 6.59 (2H, d, J 15.9, H-2' and H-2"), 7.38 (6H, m, H_{meta}-Ar), 7.54 (4H, m, H_{ortho}-Ar and H_{para} -Ar), 7.72 (2H, d, J=16.0, H-3' and H-3"); d_C (50 MHz; $CDCl_3$) 24.2 (C-3 and C-10), 25.2 (C-4 and C-11), 58.6 (C-2 and C-9), (59.8 (C-14 and C-15), 67.2 (C-5 and C-12), 96.2 (C-6 and C-7), 118.9 (C-2' and C-2"), 128.1 (C_{meta}-Ar), 128.8 (C_{ortho}-Ar), 130.0 (C_{para}-Ar), 134.7 (C_{ipso}-Ar), 144.3 (C-3' and C-3"), 166.4 (C-1' and C-1"); *m/z* (EI) 520 $(M)^+$, 372, 319, 285, 257, 246, 202, 175, 131, 103, 71, 51; Found: $(M)^+$, 520.2112. $C_{30}H_{32}O_8$ requires: *M*, 520.2097; Analysis; Found: C, 69.06%; H, 6.14%. $C_{30}H_{32}O_8$ requires C, 69.22%; H, 6.20%.

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9. For data on the carboxylic acids corresponding to entries **1**, **2**, **4**, **6** and **7** see: *The Dictionary of Organic Compounds*, J. Buckingham, Ed., Chapmen and Hall, New York, **1982**. For data on the carboxylic acids corresponding to entries **3** and **5** see: I. Fleming, N.D. Kinden, *J. Chem. Soc., Chem. Commun.*, **1987**, 1177 and references therein.

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