

Catalytic Enantioselective Conjugate Addition of Chiral Alkoxydimethylcuprate to (*E*)-Cyclopentadec-2-enone

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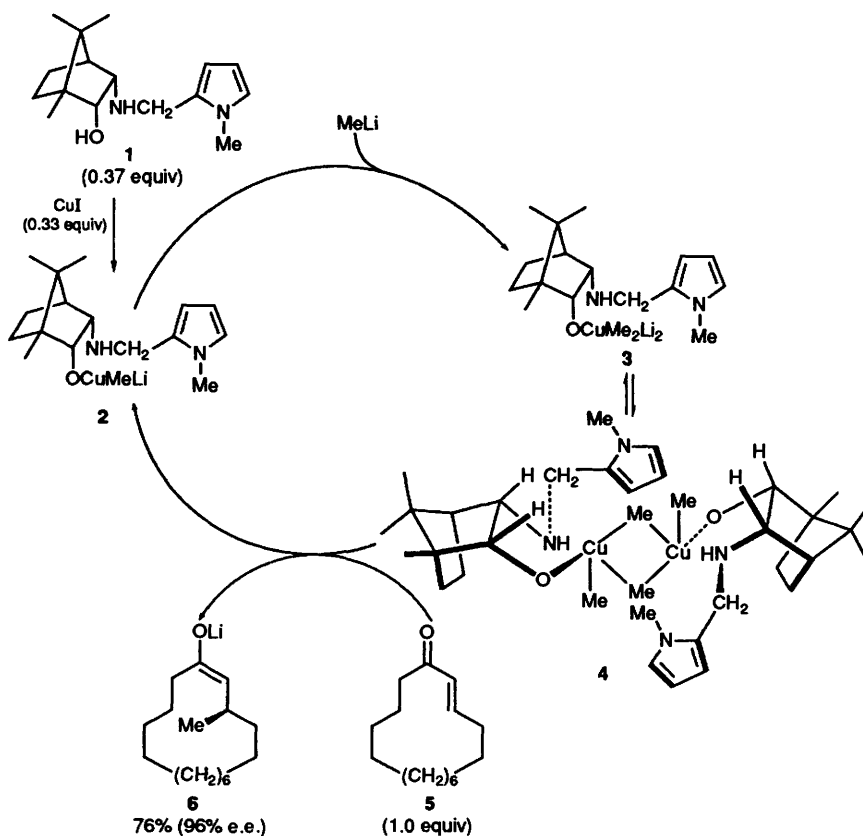
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Asymmetric 1,4-addition of methyllithium to (*E*)-cyclopentadec-2-enone was promoted by the chiral cuprate catalyst prepared from (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol and copper(I) iodide to give (*R*)-(-)-muscone in 76% chemical yield and 96% enantiomeric excess.

In enantioselective conjugate additions, a topic of considerable interest in recent years,^{1,2} stoichiometric amounts of chiral auxiliaries and copper(I) salts are necessary for the preparation of optically active lithium dialkylcuprates. Catalytic enantioselective 1,4-conjugate addition is, therefore, a challenging goal in asymmetric syntheses. The enantioselective conjugate additions of organolithium reagents catalysed by organocopper complexes is very difficult since lithium reagents are highly nucleophilic³ towards α,β -enones, affording 1,2-adducts exclusively. By using less nucleophilic Gignard reagents such as butyl- and phenyl-magnesium chloride, Lippard recently achieved the first enantioselective conjugate addition catalysed by a chiral copper complex prepared from 1-[(*R*)-1- α -methylbenzylamino]-7-[(*R*)- α -methylbenzylamino]cyclohepta-1,3,5-triene and CuBr·MeS₂.⁴ Similar catalytic 1,4-conjugate additions have been reported in the reaction of cyclohex-2-enone with isopropylmagnesium bromide in the presence of

chiral organozinc complexes prepared from (1*R*,2*S*)-3,6,6-trimethyl-1-phenyl-3,6-diazahexanol and zinc(II) chloride at -90 °C,⁵ and in the reaction of chalcone with less electrophilic metals⁶ such as diethylzinc and dibutylzinc in the presence of chiral organonickel complexes prepared from (1*S*,2*R*)-*N,N*-dibutylnorephedrine, 2,2'-bipyridyl and Ni(acac)₂.⁷

We now report the enantioselective conjugate addition of methyllithium to (*E*)-cyclopentadec-2-enone 5 catalysed by a chiral copper complex derived from (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (MPTAH-1), which has recently been developed in this laboratory.² The catalyst was prepared at -78 °C by adding methyllithium to the toluene solution of alkoxydimethylcuprate 2 prepared from 1 (0.37 equiv.) and CuI (0.33 equiv.) and the mixture was stirred at this temperature for 1 h. It was then allowed to warm to -20 °C over 1 h prior to the addition of (*E*)-cyclopentadec-2-enone 5. This 'ageing' is crucial to the



Scheme 1

Table 1 Conjugate addition of methyllithium to (*E*)-cyclopentadec-2-enone **5** using **3** as a catalyst

Entry	MPATH-1		CuI (equiv.)	Additive (equiv.)	Yield of (<i>R</i>)-muscone ^a (%)	E.e. (%)
	(equiv.)	concentration (mol dm ⁻³)				
1	1.10	0.061	1.10	THF (10.0 equiv.)	80	91
2	0.50	0.056	0.50 ^b	None	83	42 ^c
3	0.50	0.056	0.50 ^b	None	78	73
4	0.55	0.061	0.50 ^b	None	79	76
5	0.55	0.061	0.50 ^b	Me ₃ SiCl (5.0 equiv.)	70	56
6	0.33	0.056	0.33 ^d	None	76	54
7	0.37	0.122	0.33 ^d	None	83	68
8	0.28	0.061	0.25 ^e	None	70	41
9	0.22	0.061	0.20 ^f	None	68	47

^a Isolated yields after column chromatography and vacuum distillation. ^b MeLi (0.50 equiv.) and **5** (0.50 equiv.) were added ($\times 2$). ^c Ageing of the catalyst was omitted. ^d MeLi (0.33 equiv.) and **5** (0.33 equiv.) were added ($\times 3$). ^e MeLi (0.25 equiv.) and **5** (0.25 equiv.) were added ($\times 4$). ^f MeLi (0.20 equiv.) and **5** (0.20 equiv.) were added ($\times 5$).

high enantioselectivity in this conjugate addition reaction. In order to suppress 1,2-adduct formation in the reaction of methyllithium with the enone **5**, the reagents were added alternately to the toluene solution of the chiral alkoxyethylcuprate **2** (see Table 1 and experimental procedure). This methodology provides not only the highest enantioselectivity (96% e.e.) so far in the introduction of a methyl group into an enone,⁴ but also provides useful information on the mechanism of the organocopper conjugate addition. Thus, the high chemical yield (76%) indicate that the conjugate adduct exists in solution as a lithium enolate **6**⁹ -78°C , not as a copper(I) enolate, and methyllithium reacts exclusively with the copper complex **2** to produce the cuprate catalyst **3**. A reaction pathway which appears to be consistent with the present result and the chiral amplification reported in the previous communication^{2d} is illustrated in Scheme 1. The use of methylmagnesium chloride, however, was ineffective in this reaction, a 1,2-adduct being obtained in 55% yield. When copper(I) iodide was replaced by zinc(II) chloride, no conjugate addition took place.

Experimental

The following experimental procedure was used for the preparation of (*R*)-(-)-muscone from MPATH-1 (0.5 equiv.) and CuI (0.5 equiv.). To a solution of (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (MPATH-1) (0.525 g, 2.00 mmol) in dry toluene (36.0 cm³) at 0°C under argon was added methyllithium [1.00 mol dm⁻³ ether solution containing lithium bromide (2.00 mmol)]. The solution was stirred at 0°C for 1 h and then cooled to -20°C . Cuprous iodide (purified by a literature procedure;¹¹ 0.381 g, 2.00 mmol) was added and the resulting suspension was allowed to warm to -5°C over 2.5 h. The dark grey suspension was cooled to -78°C and methyllithium (4.00 mmol) was added dropwise. The suspension was then stirred at -78°C for 30 min, after which it was warmed to -5°C during 2 h, and then recooled to -78°C . A solution of **5** (0.445 g, 2.00 mmol) in dry toluene (5.0 cm³) was added dropwise at -78°C and the mixture was stirred for 3 h at this temperature. Further methyllithium (2.00 mmol) was then added at -78°C and the resulting mixture was stirred for 1 h; it was then allowed to

warm to -20°C over 1 h, and recooled to -78°C . A solution of **5** (0.445 g, 2.00 mmol) in dry toluene (5.0 cm³) was added and the reaction mixture was stirred overnight at 78°C . It was then quenched with a 1:1 mixture of saturated aqueous ammonium chloride–30% aqueous ammonium hydroxide (10 cm³) and extracted with ether. The organic extract was washed with brine, dried (MgSO₄), and concentrated. Chromatography on silica gel (hexane–ethyl acetate 45:1) afforded (*R*)-muscone (0.84 g, 91%) as a colourless oil as a single peak by GLPC; this was distilled to give the pure muscone (0.725 g, 78%) (73% e.e.), $[\alpha]_D^{25} -8.57$ (*c* 2.16, MeOH) (Found: C, 80.45; H, 12.8. Calc. for C₁₆H₃₀O: C, 80.60; H, 12.68%).

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