Chiral Amplification in the Synthesis of (*R*)-Muscone by Conjugate Addition of Chiral Alkoxydimethylcuprate to (*E*)-Cyclopentadec-2-enone

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Chiral amplification is observed in the synthesis of (*R*)-muscone by enantioselective conjugate addition of chiral alkoxydimethylcuprate to (*E*)-cyclopentadec-2-enone.

There is considerable interest in the nonlinear correlation between enantiomeric excess (e.e.) of a chiral auxiliary and e.e. of a product in asymmetric synthesis because this phenomenon provides useful information on the reaction mechanism.[1,2] In particular, the convex deviation from linearity or chiral amplification is very attractive from a synthetic viewpoint since a product with high e.e. is available from a chiral auxiliary of low e.e. Until now this phenomenon has been observed in only four types of asymmetric syntheses: the epoxidation of geraniol by the Sharpless reagent,[1] the

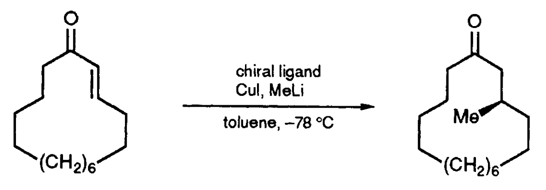
Table 1 Nonlinear effect in the synthesis of (*R*)-muscone by conjugate addition of chiral alkoxydimethylcuprate to (*E*)-cyclopentadec-2-enone

% E.e. of chiral ligand	(*R*)-Muscone Yield (%)	E.e. (%)
100	89	100
80	75	93
60	82	76
50	77	33
40	96	26
20	93	6

glyoxylate–ene reaction,[3] the Diels–Alder reaction catalysed by chiral titanium complexes[4] and the addition of diethylzinc to benzaldehyde catalysed by tertiary β-aminoalcohols.[5] We wish to report the first chiral amplification in enantioselective conjugate addition of an organocopper reagent to a macrocyclic enone.[6]

Recently we have reported the highly enantioselective synthesis of (*R*)-muscone from (*E*)-cyclopentadec-2-enone **1** in the conjugate addition reaction of chiral alkoxydimethylcuprate 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 (MPATH-**3**), MeLi, CuI and MeLi in the stoichiometric ratios 2 : 2 : 1 : 2.[7]

We have found that the reaction of **1** with the organocopper reagent (60% e.e.) prepared from 80% of MPATH-**3** and 20% of its enantiomer MPATH-**8** in toluene containing a small amount of tetrahydrofuran (THF) as additive produced (*R*)-muscone in 76% e.e. and 82% chemical yield. The convex deviation from a linear correlation is clearly seen at higher e.e. of the chiral ligand as shown in Table 1.† The deviation is sensitive to the concentration of MPATH-**3** and the concavity is observed at lower e.e.



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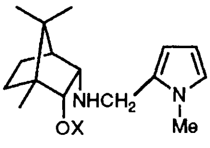
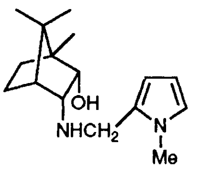
2; (*R*)-Muscone



3; X = H
4; X = Li
5; X = Cu
6; X = CuMe$_2$Li$_2$



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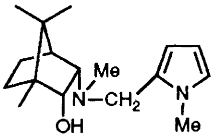

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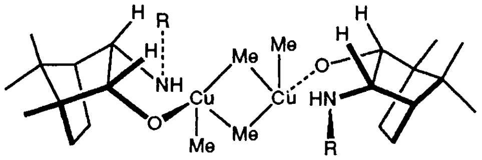

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Fig. 1

This phenomenon can be explained by considering the difference in chemical properties of the diastereoisomeric dinuclear complexes, or the homochiral dimer and the heterochiral dimer.[1,5] This is consistent with the fact that organocuprates such as lithium dimethylcuprate and lithium diarylcuprate were shown to exist as dimers in solution from vapour-pressure depression measurements and from ebullioscopic measurements.[8] Fig. 1 shows the proposed homochiral dimeric structure **9** of the alkoxydimethylcuprate which possesses chiral C_2 symmetry [R = (1-methylpyrrol-2-yl)methyl].‡

In order to elucidate the structure of the chiral copper reagent, the conjugate addition was carried out with the enone **1** using a solution containing MPATH-**3** : MeLi : CuI : MeLi in a 2 : 2 : 1 : 1 ratio. Under these conditions, the chemical yield of (*R*)-muscone with e.e. of 97% decreased to 17% yield. The use of 2 equiv. of MeLi is essential for the preparation of the chiral cuprate species **6**. When the stoichiometric ratio was increased to 2 : 3 : 1 : 1, the yield of (*R*)-muscone (100% e.e.) was improved to 47% but this is still low compared to the reaction in the ratio of 2 : 2 : 1 : 2. The addition of excess MeLi to the solution of **3** is detrimental for the conjugate addition, probably because MeLi is consumed to interact with the NH group of **4**. The presence of the NH moiety of **9** is crucial to both the enantioselectivity and the chemical yield. Thus, the reaction of a cuprate reagent, prepared from the *N*-methyl derivative **7** of MPATH-**3**, with (*E*)-cyclopentadec-2-enone afforded (*R*)-muscone in 40% yield with an e.e. of 8%. Although further studies will be necessary in order to characterize this alkoxydimethylcuprate reagent, the present chemical evidence provides a great insight into the mechanism of the organocopper conjugate addition reactions.

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† The following experimental procedure was used for the preparation of (*R*)-(–)-muscone of 76% e.e. from MPATH of 60% e.e. To a solution of (1*R*, 2*R*, 3*S*, 4*S*)-3-[(1-methylpyrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (MPATH-**3**) (2.890 g, 11.0 mmol) and its (1*S*, 2*S*, 3*R*, 4*R*)-isomer (MPATH-**8**) (0.722 g, 2.75 mmol) in dry toluene (112.5 ml) at 0°C under argon was added methyllithium (1.00 mol dm^{-3} diethyl ether solution containing lithium bromide, 13.75 mmol). The solution was stirred at 0 °C for 30 min and then cooled to –20 °C. Copper(I) iodide (1.309 g, 6.88 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 (13.75 mmol) was added dropwise. After this the suspension was stirred for 30 min at –78 °C, warmed to –5 °C during 2h, and again cooled to –78 °C. Dry THF (2.2 ml) was added and the solution was stirred at –78 °C for 15 min. A solution of **1** (0.834 g, 3.75 mmol) in dry toluene (10 ml) was added dropwise at –78 °C and the mixture was stirred overnight at this temperature. After quenching by addition of 15 ml of a 1 : 1 mixture of saturated aqueous ammonium chloride–30% aqueous ammonia and extraction with diethyl ether, the organic extracts were washed with brine, dried (MgSO$_4$) and concentrated. Chromatography on silica gel (hexane : ethyl acetate 45 : 1) afforded 0.73 g of (*R*)-muscone (82%) as a colourless oil as a single peak by GLPC, and this was distilled to give 0.62 g (70%) of the pure muscone (76% e.e.), $[\alpha]_D^{23}$ –8.92° (*c* 2.05, MeOH) (lit.[7] $[\alpha]_D$ –11.7° (*c* 0.80, MeOH). A satisfactory C and H analysis was obtained.

‡ Enantioselectivities in conjugate additions are explained on the hypothesis that chiral cuprate reagents exist as dimers in solution.[9]

We thank the Bio Research Center, Nippon Mining Co., Ltd., for financial support.

Received, 4th September 1991; Com. 1/04590C

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