

Chiral Amplification and the Catalytic Process in the Enantioselective Conjugate Addition of Chiral Alkoxydimethylcuprate to (*E*)-Cyclopentadec-2-en-1-one

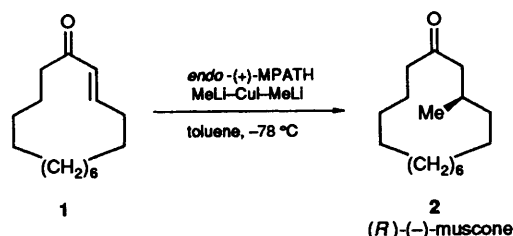
Kazuhiko Tanaka,* Junichi Matsui and Hitomi Suzuki

Department of Chemistry, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo, Kyoto 606, Japan

The stoichiometric conjugate addition with 60% enantiomeric excess (e.e.), of a chiral alkoxydimethylcuprate prepared from an 80:20 mixture 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 [*endo*-(+)-MPATH-3] and its enantiomer [*endo*-(-)-MPATH], to (*E*)-cyclopentadec-2-en-1-one **1** produced (*R*)-(-)-muscone **2** in 76% e.e. and 82% chemical yield. This chiral amplification can be explained by considering that the reaction proceeds *via* a homochiral dimeric cluster of the chiral alkoxydimethylcuprate. The catalytic conjugate addition was realized by adding methyl lithium and the enone alternately to a toluene solution of the chiral alkoxydimethylcuprate prepared from a catalytic amount of the chiral ligand and copper(I) salt. (*R*)-(-)-Muscone with 99% optical purity was obtained in 85% chemical yield by the use of 0.36 equiv. of *endo*-(+)-MPATH and 0.33 equiv. of copper(I) iodide. This methodology provides not only the highest enantioselectivity, but also useful information on the structure and mechanism of the conjugate addition of the organocuprate prepared from the copper(I) salt and alkyllithium.

The reactions of organocuprates with α,β -unsaturated carbonyl compounds, epoxides or terminal alkynes have been a topic of intense interest, since these reactions generally proceed with high regio- and stereo-selectivity.¹ In particular, the conjugate addition of organocuprates containing a chiral non-transferable ligand is one of the most efficient methods for producing chirality at the β -position of the carbonyl moiety,²⁻⁴ and this procedure leads directly to the selective formation of one enantiomer without removing a chiral auxiliary. The reactions of these organocuprates, however, are complex due to the fact that experimental variables such as solvent, temperature, order of additions, copper salt, concentration and stoichiometry of the reagents influence the reactivity and stability of organocupper reagents.³

We have studied the influence of various experimental parameters upon the enantioselectivity and chemical yields in the asymmetric conjugate addition.⁵ In these reactions, we employed bicyclic amino alcohols derived from D-camphor as chiral ligands, which have recently been developed in our laboratory.⁶ We now wish to describe chiral amplification and the catalytic process⁷ in the synthesis of (*R*)-(-)-muscone **2** by the alkoxydimethylcuprate conjugate addition to (*E*)-cyclopentadec-2-en-1-one **1** (Scheme 1).



Scheme 1

Results and Discussion

Chiral Amplification.—We have recently reported the first asymmetric synthesis of (*R*)-muscone, an odorous constituent isolated from musk, of essentially 100% optical purity in the reaction of (*E*)-cyclopentadec-2-en-1-one with the chiral

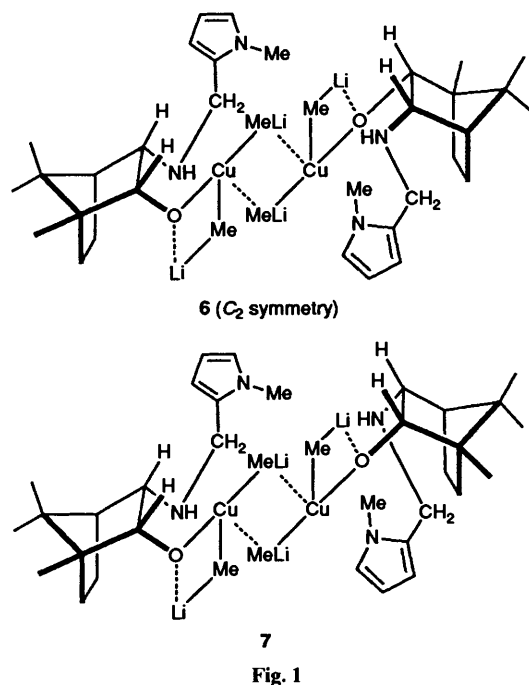
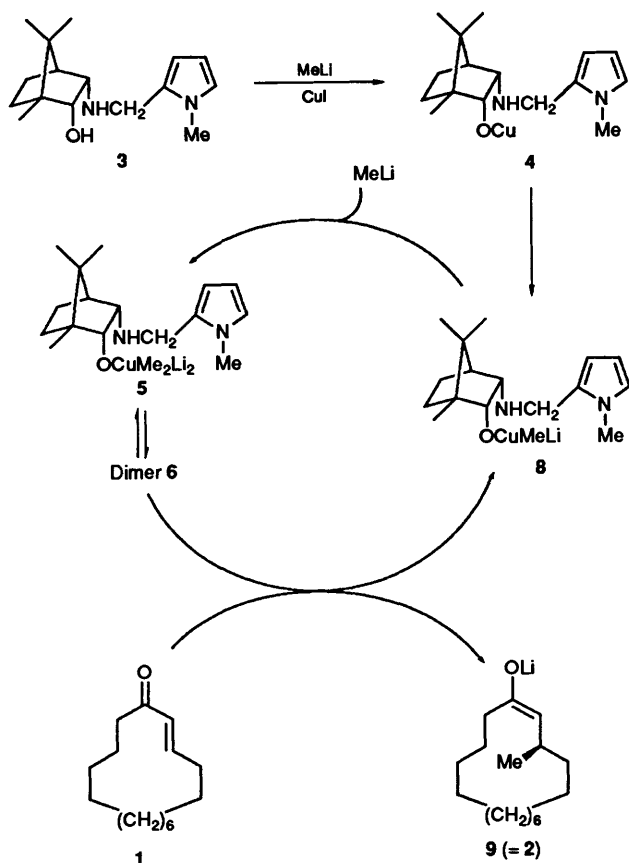
alkoxydimethylcuprate **5**, prepared from *endo*-(+)-MPATH-3, methyl lithium, copper(I) iodide and methyl lithium in the stoichiometric ratios 2:2:1:2 in the presence of small amounts of THF in toluene.^{5b,†}

By the use of 3.67 equiv. of chiral ligand with 60% e.e., prepared from a mixture of 80% of *endo*-(+)-MPATH and 20% of its enantiomer *endo*-(-)-MPATH, the alkoxydimethylcuprate **4** was prepared by sequential addition of methyl lithium (3.67 equiv.), copper(I) iodide (1.83 equiv.) and methyl lithium (3.67 equiv.).

The conjugate addition with the enone (1.00 equiv.) in the presence of small amounts of THF produced **2** in 76% e.e. and 82% chemical yield. This is the first chiral amplification in the enantioselective conjugate addition of organocuprates.^{5d,8} Chiral amplification has been observed in six types of asymmetric synthesis: the epoxydation of geraniol by the Sharpless reagent,⁹ the glyoxylate-ene reaction,¹⁰ the Diels-Alder reaction catalysed by chiral titanium complexes¹¹ and the addition of diethylzinc to benzaldehyde catalysed by chiral amines,^{12,13} the conjugate addition of diethylzinc to chalcone catalysed by chiral nickel complexes¹⁴ and trimethylsilylcyanation of aldehydes by chiral titanium Schiff's base complexes.¹⁵

If the conjugate addition proceeds on monomeric organocuprate, the chiral amplification is not observed since there is no difference in the chemical reactivity between two enantiomers. When these enantiomeric reagents interact in the solution, three possible dimers, one heterochiral complex and two homochiral complexes, would be generated in a thermodynamically controlled ratio. The relative concentrations and the relative reactivities of these complexes will regulate the enantioselectivity of the conjugate addition, thus causing the nonlinear correlation between the enantiomeric excess of a chiral reagent and the optical yield of a product.^{9,12b} The present chiral amplification indicates that the chiral homochiral dimer generated by interaction of alkoxydimethylcuprate **5** is more reactive than the heterochiral dimer. This is consistent

† When *exo*-(-)-MPATH-3, prepared from D-camphor, was employed as a chiral ligand in this reaction, (*S*)-(+)-muscone was obtained in 57% e.e., although the reaction conditions were not optimized.



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.¹⁶ The overall sequence is illustrated in Scheme 2.

Fig. 1 shows the proposed homochiral dimeric structure **6** of the chiral alkoxydimethylcuprate, which possesses chiral C_2 symmetry, and the heterochiral (meso) dimeric structure **7**.

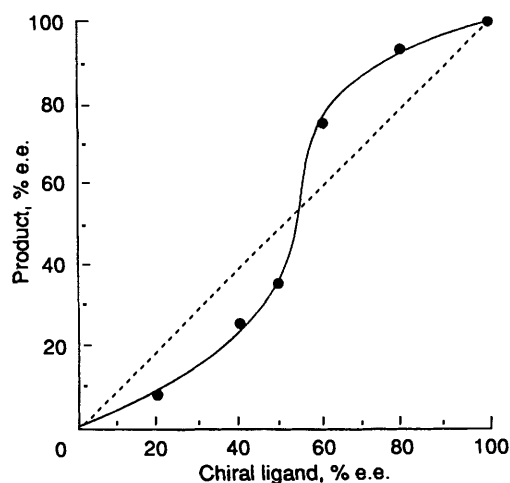


Fig. 2 Nonlinear correlation between %e.e. of the chiral ligand and %e.e. of the product in enantioselective conjugate addition of the chiral alkoxydimethylcuprate

In this conjugate addition reaction, the convex deviation from a linear correlation is clearly seen at higher %e.e. of the chiral ligand as shown in Fig. 2, although it is sensitive to the concentration of the chiral alkoxydimethylcuprate **5** and the concavity is observed at lower %e.e. of the chiral ligand.*† The results indicate that the reactive dinuclear complex, homochiral dimer **6**, which produces (*R*)-muscone selectively, is more reactive at higher concentration than at lower concentration. It should be emphasized that concentrations of organocuprate significantly affects the stereoselectivity of the conjugate addition.

Catalytic Conjugate Addition.—In enantioselective conjugate addition, the use of at least 1 equiv. of a chiral ligand to 1 equiv. of a substrate is essential for high selectivity. Since the chiral ligands are not always readily available as commercially produced reagents, conjugate addition using a catalytic amount of a chiral ligand is highly desirable. However, the realization of the catalytic conjugate addition of organocuprates prepared from organolithium reagents is very difficult since lithium reagents, which exist in excess in the reaction mixture compared to catalytic amount of copper salt,¹⁷ react with enones exclusively, affording 1,2-adducts. Recently, Lippard reported the first catalytic conjugate addition to cyclohex-2-enone using less nucleophilic Grignard reagents in the presence of a chiral copper(I) catalyst derived from *N,N'*-dialkylsubstituted aminotroponimines as ligands.¹⁸ A similar catalytic conjugate addition of methylmagnesium iodide to benzylideneacetone was reported by van Koten and co-workers, who utilized 2-[1-(*R*)-(dimethylamino)ethyl]phenylthiol copper(I) as a chiral catalyst to prepare the 1,4-product in 57 %e.e. With methyl-lithium, however, the enantioselectivity was 0 %e.e.⁷

We have now obtained (*R*)-muscone in 73% optical yield and 78% chemical yield using 0.50 equiv. of *endo*-(+)-MPATH and 0.50 equiv. of copper(I) iodide by adding the enone and methyl-lithium alternately in order to suppress the direct reaction of methyl-lithium with the enone leading to 1,2-adduct (Table 1, entry 4).

* Since we used the same volume of toluene (16.4 cm³ to 1 mmol of the cuprate) in each case, the concentration of a reactive dimer in the solution at higher %e.e. of the chiral ligand is different from that at lower %e.e. of the chiral ligand.

† The chiral ligand used in the reaction was easily recovered by silica gel chromatography without loss of optical purity.

Table 1 Conjugate addition of methylolithium to (*E*)-cyclopentadec-2-en-1-one **1** using **6** as a catalyst

Entry	<i>endo</i> -(+)-MPATH (equiv.)	CuI (equiv.)	Additive	Concentration of cuprate (mol dm ⁻³)	<i>(R)</i> -(-)-Muscone	
					Yield (%) ^a	%e.e. ^b
1	2.20	1.10	THF (10 equiv.)	0.061	93	100
2	1.10	1.10	THF (10 equiv.)	0.061	80	91
3	0.50	0.50 ^c	none	0.056	83	42 ^d
4	0.50	0.50 ^c	none	0.056	78	73
5	0.55	0.50 ^c	none	0.056	79	76
6	0.33	0.33 ^e	none	0.056	76	54
7	0.28	0.25 ^f	none	0.056	70	41
8	0.22	0.20 ^g	none	0.056	68	47

^a Isolated yields after column chromatography and vacuum distillation. ^b Optical yields were determined from measurements of the optical rotation of the product. ^c MeLi (0.50 equiv.) and **1** (0.50 equiv.) were added in twice. ^d Ageing of the catalyst was omitted. ^e MeLi (0.33 equiv.) and **1** (0.33 equiv.) were added in three times. ^f MeLi (0.25 equiv.) and **1** (0.25 equiv.) were added in four times. ^g MeLi (0.20 equiv.) and **1** (0.20 equiv.) were added in five times.

Table 2 Catalytic conjugate addition using 0.33 equiv. of the chiral alkoxydimethylcuprate^a

Entry	Concentration of cuprate ^b (mol dm ⁻³)	Additive	Method ^c	<i>(R)</i> -(-)-Muscone	
				Yield (%)	%e.e.
1	0.056 ^d	none	A	76	54
2	0.056	THF (10 equiv.)	A	79	80
3	0.112	none	A	83	68
4	0.112	THF (10 equiv.)	A	78	82
5	0.112	THF (5 equiv.)	A	76	97
6	0.112	THF (1 equiv.)	B	85	99
7	0.112	TMSCl (5 equiv.)	A	72	79

^a MeLi (0.33 equiv.) and **1** (0.33 equiv.) were added in three times. ^b 0.36 Equiv. of *endo*-(+)-MPATH and 0.33 equiv. of copper(I) iodide were used. ^c The order of THF addition in Method B is different from that in Method A. ^d 0.33 Equiv. of *endo*-(+)-MPATH and 0.33 equiv. of copper(I) iodide were used.

The high chemical yields indicate that the conjugate adduct exists in solution as the lithium enolate **9**,¹⁹ not as the copper enolate (Scheme 2). For this reason, methylolithium added in the toluene solution does not react with the product, but exclusively with alkoxydimethylcuprate **8** to reproduce the reactive alkoxydimethylcuprate catalyst **5**, which is in equilibrium with the homochiral dimer **6** as described above.

As shown in Table 1, ageing of the dimethylcuprate (warming the toluene solution of the alkoxydimethylcuprate to -20 °C from -78 °C over 1 hour before the addition of the enone)* is crucial to high enantioselectivity (entry 3). As the turnover number increased, the optical yields gradually decreased due to a change in the organocuprate concentration caused by adding the toluene solution (10 cm³) of the enone (entries 6, 7, 8). This result is also clearly shown in Table 2, in which the effects of concentration of the dimethylcuprate, additives and order of additions are listed. Thus, higher concentration of the organocuprate markedly increased the enantioselectivity (compare entries 1 and 3). This behaviour is consistent with the results of the present chiral amplification, and the enantioselective ethylation of benzaldehyde catalysed by (-)-3-*exo*-(dimethylamino)isoborneol which indicates the presence of the homochiral dinuclear complex in higher concentration.¹³

It is interesting to note that the addition of small amounts of THF as additive increases the optical purity of (*R*)-muscone up to 99 %e.e. This indicates that THF may act as an external ligand in the dimeric cuprate cluster to form a rigid transition

state for enantioselective addition of methyl group.²⁰ The enantioselectivity, however, is sensitive to the amounts of THF, and the best result was obtained when 1 equiv. of THF was employed (entry 6). Probably, the use of an excess of THF alters the coordination or the composition of the dimeric cluster.^{5c} The addition of trimethylsilyl chloride²¹ did not show marked improvement in the enantioselectivity (entry 7).

By employing the optimized conditions (entries 5, 6 in Table 2), we investigated the catalytic activity in detail. The results are summarized in Table 3. The procedure using 0.33 equiv. of *endo*-MPATH is illustrated in Scheme 3. The use of 0.22 equiv. of *endo*-MPATH and 0.20 equiv. of copper(I) iodide in this procedure provides a higher level of enantioselection (90%).

In conclusion, we have shown the first example of chiral amplification in enantioselective conjugate addition of the alkoxydimethylcuprate, that possesses a dimeric homochiral structure in solution.^{5b,8} The catalytic enantioselective conjugate addition by use of 0.36 equiv. of the chiral ligand and 0.33 equiv. of copper(I) iodide provides (*R*)-(-)-muscone with 99 %e.e. in high chemical yield. The catalytic process, where the homochiral dimer possessing C₂ symmetry exists in the dynamic equilibrium, is proposed. Efforts are currently under way to develop this potentially useful reaction.

Experimental

Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl immediately before use. Toluene was distilled from calcium hydride and stored over 4Å molecular sieves. The ether solution of methylolithium (containing lithium bromide) was titrated using diphenylacetic acid.^{5b}

IR spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. NMR spectra were obtained on a Varian Gemini-200 (200 MHz) or JEOL (JMN-GX400 (400 MHz) spectrometer in CDCl₃ with tetramethylsilane as an internal standard. *J* values are given in Hz. Optical rotations were measured in 1 dm path length cells of 2 cm³ on a JASCO Model DIP-181 polarimeter; [α]_D values are given in 10⁻¹ deg cm² g⁻¹. GLC was performed on a Shimadzu Model GC-8A gas chromatograph using a 0.15 cm × 120 cm glass column (20% Silicone DC-550 on Celite 545). Thin layer chromatography was performed by using Merk precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100–200 mesh was used for column chromatography. Mass spectra were determined on a JMS-DX-300. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.

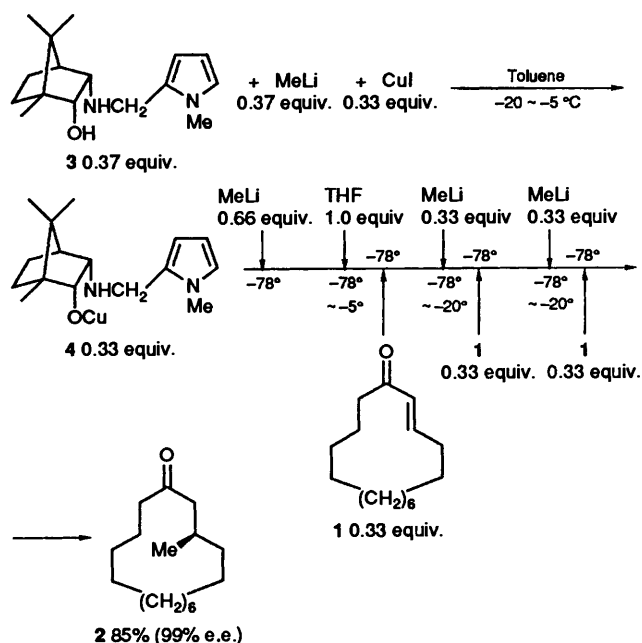
* White yellow suspension turned into colourless or pale yellow solution during the ageing of the cuprate.

General Procedure for Chiral Amplification [Conjugate Addition using 60 %e.e. of *endo*-(+)-MPATH-3].—To a

Table 3 Catalytic conjugate addition in the optimized condition^a

Entry	<i>endo</i> -MPATH (equiv.)	CuI (equiv.)	THF (equiv.)	<i>(R)</i> -(-)-Muscone	
				Yield (%)	%e.e.
1	1.1	1.0	5	77	100
2	0.55	0.50 ^b	5	79	100
3	0.36	0.33 ^c	1	85	99
4	0.28	0.25 ^d	5	78	80
5	0.28	0.25 ^d	1	82	92
6	0.22	0.20 ^e	5	84	70
7	0.22	0.20 ^e	1	80	90

^a The reaction carried out employing Method B. ^b MeLi (0.50 equiv.) and **1** (0.50 equiv.) were added in twice. ^c MeLi (0.33 equiv.) and **1** (0.33 equiv.) were added in three times. ^d MeLi (0.25 equiv.) and **1** (0.25 equiv.) were added in four times. ^e MeLi (0.20 equiv.) and **1** (0.20 equiv.) were added in five times.

**Scheme 3** A procedure for catalytic conjugate addition

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 [*endo*-(+)-MPATH] (2.890 g, 11.0 mmol) and its (1*S*,2*S*,3*R*,4*R*)-isomer [*endo*-(-)-MPATH] (0.722 g, 2.75 mmol) in dry toluene (112.5 cm³) at 0 °C under argon was added methyllithium (1.00 mol dm⁻³; 13.75 mmol). The solution was stirred at 0 °C for 30 min and then cooled to -20 °C. Copper(I) iodide, purified by a literature procedure,²² (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 the suspension was stirred for 30 min at -78 °C, warmed to -5 °C during 2 h, and again re-cooled to -78 °C. Dry THF (2.2 cm³) was added and the solution was stirred at -78 °C for 15 min. A solution of (*E*)-cyclopentadec-2-en-1-one **1** (0.834 g, 3.75 mmol) in dry toluene (10 cm³) was added dropwise at -78 °C and the mixture was stirred overnight at this temperature. After quenching by addition of a 1:1 mixture of saturated aqueous ammonium chloride-30% aqueous ammonia (15 cm³) and extraction with diethyl ether, the organic extracts were washed with brine, dried (MgSO₄) and concentrated. Chromatography on silica gel (hexane-ethyl acetate 45:1) afforded 0.73 g (82%) of (*R*)-(-)-muscone as a colourless oil as a single peak by GLPC,

and this was distilled to give 0.62 g (70%) of pure muscone (76 %e.e.), [α]_D²³ -8.92 (*c* 2.05, MeOH) [lit.⁵ [α]_D -11.7 (*c* 0.80, MeOH)] (Found: C, 80.45; H, 12.8. C₁₆H₃₀O requires: C, 80.60; H, 12.68%).

General Procedure for Catalytic Conjugate Addition [Synthesis of (*R*)-(-)-Muscone **2 from 0.37 Equiv. of *endo*-(+)-MPATH-**3** and 0.33 Equiv. of Copper(I) Iodide] Method A.** To a solution of *endo*-(+)-MPATH (0.488 g, 1.83 mmol) in dry toluene (15 cm³) at 0 °C under argon was added methyllithium (1.83 mmol). The solution was stirred at 0 °C for 1 h and then cooled to -20 °C. Copper(I) iodide (0.319 g, 1.67 mmol) was added and the resulting white suspension was allowed to warm to -5 °C over 2.5 h. The brown suspension was cooled to -78 °C and methyllithium (3.33 mmol) was added dropwise. After the suspension had been stirred for 30 min at -78 °C, it was warmed to -5 °C during 2 h, and then re-cooled to -78 °C. To the resulting yellow solution was added dry THF (0.67 cm³, 8.33 mmol) and the solution was stirred for 15 min at -78 °C. A solution of **1** (0.371 g, 1.67 mmol) in dry toluene (3.0 cm³) was added dropwise at -78 °C and the mixture was stirred for 1 h at this temperature. Methyllithium (1.67 mmol) was then added at -78 °C. The resulting mixture was stirred for 1 h, allowed to warm to -20 °C over 1 h, and re-cooled to -78 °C. A solution of **1** (0.371 g, 1.67 mmol) in dry toluene (3.0 cm³) was added and the reaction mixture was stirred for 1 h at -78 °C. Methyllithium (1.67 mmol) and a solution of **1** (0.371 g, 1.67 mmol) in dry toluene (3.0 cm³) were added in the same way. After quenching, similar workup afforded (*R*)-(-)-muscone (1.01 g, 86%) as a colourless oil. Distillation of the oil gave 0.89 g (76%) of muscone; [α]_D²⁴ -11.3 (*c* 1.98, MeOH).

Method B. To a solution of *endo*-(+)-MPATH (0.388 g, 1.48 mmol) in dry toluene (12 cm³) at 0 °C under argon was added methyllithium (1.48 mmol). The solution was stirred for 1 h at 0 °C and then cooled to -20 °C. Copper(I) iodide (0.254 g, 1.33 mmol) was added and the resulting suspension was allowed to warm to -5 °C over 2.5 h. The brown suspension was cooled to -78 °C and dry THF (0.11 cm³, 1.33 mmol) and methyllithium (2.67 mmol) were added successively. After the suspension was stirred for 1 h at -78 °C, warmed to -5 °C during 1 h, and then re-cooled to -78 °C. To the resulting colourless solution were added a solution of **1** (0.296 g, 1.33 mol) in dry toluene (2.5 cm³) and methyllithium (1.33 mmol) in two and three times respectively in the same way described above. After quenching, similar workup afforded (*R*)-(-)-muscone (0.89 g, 93%). Distillation gave 0.81 g (85%) of muscone; [α]_D²⁴ -11.5 (*c* 1.96, MeOH).

Acknowledgements

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