Enantioselective [2,3] sigmatropic rearrangement mediated by a butyllithium–chiral ligand complex

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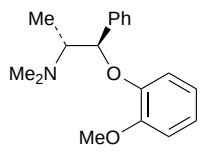
The first enantioselective [2,3] sigmatropic rearrangement of acyclic diprop-2-ynyl ethers and alkenyl benzyl ethers is achieved by a BuLi–chiral ligand complex.

The [2,3] sigmatropic rearrangement has been studied with regard to its stereochemical course in view of its synthetic application to the preparation of highly functionalized derivatives.[1] Asymmetric [2,3] sigmatropic rearrangement involving chiral auxiliaries has been investigated by Nakai and co-workers and Enders and co-workers in order to achieve high diasteroselectivity.[2] However, the enantioselective version of this reaction has remained one of the unsolved problems in the field of synthetic organic chemistry. Marshall and Lebreton reported the first example of this reaction, in which a 13-membered cyclic ether afforded the prop-2-ynylic alcohol in 70% ee by the use of a chiral lithium amide.[3] But it has also been reported that the same lithium amide was not effective for acyclic substrates.[3,4] Fujimoto and Nakai demonstrated an enantioselective reaction for acyclic substrates *via* a boron ester enolate.[5] Gladysz and co-workers reported the enantioselective [2,3] sigmatropic rearrangement of sulfur ylides using a chiral rhenium complex.[6] However, no examples of an enantioselective reaction of acyclic substrates involving an sp^3 carbanion, which are the most typical substrates in this rearrangement, have been demonstrated so far. We report herein the first example of an enantioselective [2,3] sigmatropic rearrangement of acyclic ethers involving an sp^3 carbanion.[7]

Recently, this reaction was reported to proceed with complete inversion of configuration at the carbanion carbon centre to give the newly generated chiral centre.[8] On the other hand, Hoppe *et al.* and Beak and co-workers have shown that asymmetric deprotonations can be effected with Bu^sLi–(−)-sparteine complex to give a chiral dipole-stabilized carbanion which reacts with electrofiles to give enantiomerically enriched products.[9] So it is expected that an enantioselective [2,3] sigmatropic rearrangement could be possible if a chiral carbanion can be generated by use of a BuLi–chiral ligand complex. We have found that a complex of butyllithium with a chiral ligand **1**[10]‡§ exerts a pronounced effect on this rearrangement.

Initially acyclic diprop-2-ynyl ethers **2** were studied as they have simple and symmetrical structures. The first attempt at enantioselective [2,3] sigmatropic rearrangement of **2a** mediated by a complex of BuLi–(−)-sparteine was unsuccessful. Although (−)-sparteine is known as a good chiral ligand in many reactions, **3a** was obtained in only 23% yield and 9% ee. As a result the chiral amino ether **1** was designed, and was found to work as a good chiral ligand for BuLi in this reaction.¶ Some representative results are summarized in Table 1.‖



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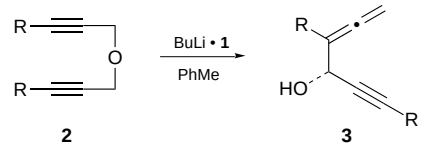
This chiral amino ether **1**–BuLi complex is effective not only for diprop-2-ynyl ether **2** but also for *cis*-but-2-enyl benzyl ether **4** (Scheme 1). The reaction gives *syn* alcohol **5** and *anti* alcohol **6** in a ratio of 9 : 1 in 50% yield.[11] The ee of *syn* alcohol **5** was 64% and the ee of *anti* alcohol **6** was 80%. Relative stereochemistries were determined by ^1H NMR coupling constants,[12] and the ee and absolute configuration of the *syn* alcohol were determined by ^1H NMR after conversion to the corresponding (*R*)-MTPA ester.[13]** The ee of *anti* alcohol **6** was determined directly by chiral HPLC [DAICEL CHIRALCEL OJ, hexanes–Pr^iOH (50 : 1), 0.75 cm^3 min^{-1}, λ = 254 nm].

Interestingly, the ee was sensitive to the substitution pattern of the alkene. For instance, when *trans*-but-2-enyl benzyl ether is used, the reaction gives **5** and **6** in the ratio 65 : 35 in 48% yield. The ee of the *syn* alcohol **5** decreased to 16%, and the ee of the *anti* alcohol **6** also decreased to 12%. In the case of 3-methylbut-2-enyl benzyl ether **7** (Scheme 2), the desired product **8** was obtained in 68% yield and in 40% ee.††

In summary, the chiral ligand **1**–BuLi complex is effective for the enantioselective [2,3] sigmatropic rearrangement of acyclic ethers involving an sp^3 carbanion.

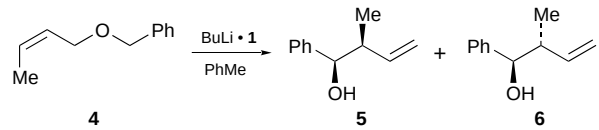
The author would like to thank Professor Kenji Koga for helpful discussions.

Table 1 Rearrangement of **2** to give **3**



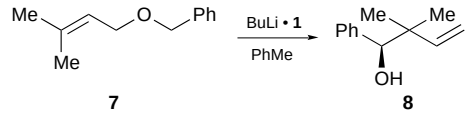
2 **3**

	R	Yield (%) of **3**	Ee (%)
2a	C_7H_{15}	50	61
2b	c-Hex	51	62
2c	Bu^t	29	59
2d	Ph	57	48
2e	Me_3Si	37	46



4 **5** **6**

Scheme 1



7 **8**

Scheme 2

Footnotes

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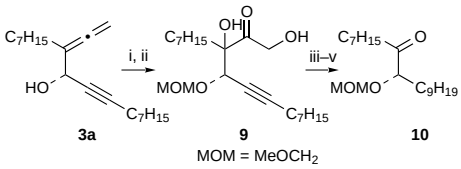
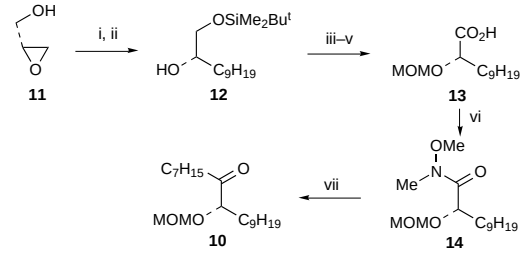
‡ All new compounds gave satisfactory spectroscopic data.
§ Compound **1** was prepared from (1*R*, 2*R*)-(−)-norpseudoephedrine in two steps: (i) HCHO, HCO_2H (100%); (ii) guaiacol, DEAD, PPh_3, THF (25%). ^{1}H NMR (270 MHz, [$^2H_6$]benzene): δ 7.4–6.6 (9 H, m), 5.15 (1 H, d, *J* = 6.6 Hz), 3.43 (3 H, s), 3.13 (1 H, dd, *J* = 6.6, 6.9 Hz), 2.40 (6 H, s); mp 57 °C; $[\alpha]_D^{24}$ −79 (*c* 2.3, $CHCl_3$). Mitsunobu reaction proceeded, with net retention of configuration, *via* the azirizinium ion. The relative configuration was determined by X-ray analysis. The kind assistance of Dr Makoto Nakajima (Pharmaceutical Sciences, Hokkaido University) with the X-ray analysis is gratefully acknowledged.
¶ Typical procedure: To a solution of chiral ligand **1** (315 mg, 1.10 mmol) in toluene (16 cm^3), BuLi (0.63 cm^3, 1.67 m hexane solution, 1.05 mmol) was added dropwise at −78 °C under Ar atmosphere. After 5 min diprop-2-ynyl ether **2a** (290 mg, 1.0 mmol) in toluene (1 cm^3) was added dropwise to the resulting pale yellow solution *via* a cannula. The flask was rinsed with toluene (1 cm^3). The whole mixture was stirred at −78 °C for 5 h. The reaction was quenched with 1 m HCl (20 cm^3), and the aqueous layer was extracted with ethyl acetate (30 cm^3 × 3). The organic layer was washed with 1 m HCl (20 cm^3), saturated aqueous $NaHCO_3$ (20 cm^3) and brine (20 cm^{-3}). After drying the mixture over Na_2SO_4, the mixture was concentrated. The residue was then purified by silica gel column chromatography, and hydroxy allene **3a** (145 mg, 50%) was obtained as a colourless oil.
‖ *Spectroscopic data* for **3a**: ^{1}H NMR: δ 4.95 (1 H, d, *J* = 3.0 Hz), 4.93 (1 H, d, *J* = 3.0 Hz), 4.82 (1 H, dd, *J* = 1.9, 1.9 Hz), 2.23 (1 H, dt, *J* = 1.9, 7.0 Hz), 2.22 (1 H, dt, *J* = 1.9, 7.0 Hz), 2.1–2.0 (2 H, m), 1.68 (1 H, brs), 1.6–1.1 (20 H, m), 0.89 (6 H, t, *J* = 6.3 Hz); ^{13}C NMR: δ 204.37, 106.33, 86.38, 79.43, 79.03, 63.25, 31.81, 31.72, 29.27, 29.11, 28.77, 28.54, 27.68, 27.53, 22.59, 18.71, 14.04; ν_{max}/cm^{-1} 3400, 3000–2850, 2210, 1950, 850; *m/z* 290 (M^+), 289 ($M^+ - 1$); $[\alpha]_D^{24}$ + 18 (*c* 0.95, $CHCl_3$). For **3a**, **3b** and **3c**, ees were determined by HPLC analysis [DAICEL CHIRALCEL OD-H, hexanes–Pr^{i}OH (300 : 1), λ = 254 nm] of the corresponding *p*-nitrobenzoates. For **3c**, the ee was determined by chiral HPLC analysis [DAICEL CHIRALCEL OD-H, hexanes–Pr^{i}OH (300 : 1), λ = 254 nm] of the corresponding 3,5-dinitrobenzoates. For **3d**, the ee was determined by HPLC analysis [DAICEL CHIRALCEL OD-H, hexanes–Pr^{i}OH (300 : 1), λ = 254 nm]. Compound **3a** could be converted to ketone **10** in four steps, as shown in Scheme 3.



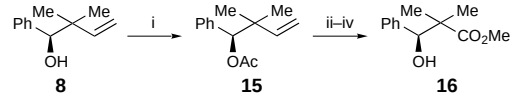
Scheme 3 *Reagents and conditions*: i, $MeOCH_2Cl$, Pr$^i_2$NEt, CH_2Cl_2, 70%; ii, OsO_4, pyridine, PhH, 50%; iii, H_2, $Pd(OH)_2$–C, MeOH; iv, $NaBH_4$, MeOH; v, $NaIO_4$, acetone, water, 30% (3 steps)

The absolute configuration of **3a** was determined by comparison of the optical rotation of **10**, which was derived from commercially available (*R*)-glycidol **11**, as shown in Scheme 4.

For **3b**–**d**, the absolute stereochemistries were assumed to be of the same orientation as for **3a** according to the ^{1}H NMR spectra of the corresponding (*R*)-*O*-methylmandelates. See J. A. Marshall and X. Xang, *J. Org. Chem.*, 1990, **55**, 2995.
** The absolute stereochemistry of the minor compound **12** was not determined.
†† Compound **8** was converted to **16** in four steps as shown in Scheme 5. The ee and the absolute configuration of compound **8** [$[\alpha]_D^{24}$ +22 (c = 0.84, $CHCl_3$)] were determined by optical rotation of compound **16**. The ee and absolute configuration of **16** are known: M. Gette, J. Capillon and J. P. Gette, *Tetrahedron*, 1973, **29**, 3659.



Scheme 4 *Reagents and conditions*: i, Bu^{t}Me$_2$SiCl, Et$_3$N, DMAP, CH_2Cl_2, quant.; ii, octylmagnesium bromide, CuI, THF, 66%; iii, $MeOCH_2Cl$, Pr$^i_2$NEt, CH_2Cl_2, quant.; iv, Bu_4NF, THF, 82%; v, Jones' reagent, acetone; vi, MeNH(OMe)·HCl, Diethyl cyanophosphonate, Et$_3$N, DMF, 76% (2 steps); vii, heptylmagnesium bromide, THF, 97%



Scheme 5 *Reagents and conditions*: i, Ac_2O, Et$_3$N, DMAP, CH_2Cl_2, 91%, ii, O_3, MeOH; iii, H_2O_2, aq. NaOH; iv, CH_2N_2, Et$_2$O, 30% (3 steps)

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Received in Cambridge, UK, 10th February 1997; Com. 7/00906B