Pergamon

*Tetrahedron: Asymmetry* Vol. 5, No. 8, pp. 1431-1432, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00199-5

# Chiral Lithium 2-Aminoalkoxides as Reagents for Enantioselective Michael Reaction

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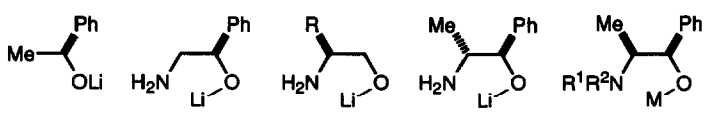
***Abstract:*** Chiral lithium alkoxides were designed and applied to enantioselective Michael reaction of methyl phenylacetate and methyl acrylate to give the corresponding adduct in enantiomeric excess up to 84 %. The catalytic enantioselective Michael reaction is also effected by this type of reagents.

Alkoxides are a class of the most versatile bases and widely used in synthetic organic chemistry. Despite their potentiality as bases, there are only a few examples to apply chiral alkoxides to enantioselective reactions.[1,2] We have previously reported efficient enantioselective reactions using chiral lithium amides having an internal ligation site for the lithium.[3] It is postulated that a well-defined chiral environment is created in these chiral lithium amides due to the formation of the five-membered chelated rings. Based on the same concept, we examined the possibility of using the chiral alkali-metal 2-aminoalkoxides **2-6** (1.1 eq.) for enantioselective Michael reaction[4] of methyl phenylacetate **7** (2.0 eq.) and methyl acrylate **8** (1.0 eq.)[5] (Scheme 1). The results are summarized in Table 1.

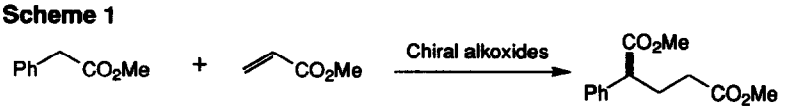
**Figure 1**




(*S*)-**1** (*R*)-**2** (*S*)-**3** R=Me (*1R, 2R*)-**5** (*1R, 2S*)
(*S*)-**4** R=Ph

**6a** $R^1$=$R^2$=H, M=Li
**6b** $R^1$=H, $R^2$=Me, M=Li
**6c** $R^1$=$R^2$=Me, M=Li
**6d** $R^1$=H, $R^2$=$^i$Pr, M=Li
**6e** $R^1$=$R^2$=H, M=Na
**6f** $R^1$=$R^2$=H, M=K

**Scheme 1**




**7** **8** (*S*)-**9**

Lithium alkoxide **1** having no internal ligation site for the lithium gave the low ee in THF (entry 1). The enantioselectivity was improved with **2** bearing an amino group at β-position (entry 2). Examinations of some lithium 2-aminoalkoxides have lead to find out that **6a** gives the best result in 84%ee (entry 2-6). The solvent effects were not observed in terms of the ee except with toluene (entry 6-9). The increase of the bulkiness of *N*-substituent(s) lead to the decrease in enantioselectivity (entry 6, 10-12). Dramatic reduction of the ee with employing the alkoxides with other alkali-metals ($Na^+$ for **6e**, $K^+$ for **6f**) shows that the lithium is crucial for the chiral induction (entry 13, 14).

A typical experimental procedure (entry 6) is as follows. Under argon atmosphere, a solution of *n*-BuLi (1.63 M solution in hexane; 1.65 mmol) was added to a solution of (*1R, 2S*)-norephedrine (250 mg, 1.65 mmol) in dry THF (5 mL) at 0°C and the whole was stirred at room temperature for 30 min. A solution of **7** (451 mg,

**Table 1** Enantioselective Michael Reaction Using Chiral 2-Aminoalkoxides[a]

| Entry | Alkoxide | Solvent | Reaction condition | | Yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | (*S*)-**1** | THF | -78°C | 3h | 11 | 2 |
| 2 | (*R*)-**2** | THF | -78°C | 3h | 59 | 20 |
| 3 | (*S*)-**3** | THF | -78°C | 3h | 80 | 7 |
| 4 | (*S*)-**4** | THF | -78°C | 3h | 83 | 47 |
| 5 | (*1R, 2R*)-**5** | THF | -78°C | 3h | 60 | 12 |
| 6 | (*1R, 2S*)-**6a** | THF | -78°C | 60h | 68 | 84 |
| 7 | (*1R, 2S*)-**6a** | DME[c] | -78°C | 60h | 15 | 86 |
| 8 | (*1R, 2S*)-**6a** | $Et_2O$ | -78°C | 60h | 22 | 85 |
| 9 | (*1R, 2S*)-**6a** | Toluene | -78°C | 60h | 4 | 69 |
| 10 | (*1R, 2S*)-**6b** | THF | -78°C | 3h | 54 | 58 |
| 11 | (*1R, 2S*)-**6c** | THF | -78°C | 3h | 2 | 38 |
| 12 | (*1R, 2S*)-**6d** | THF | -20°C | 3h | 17 | 3 |
| 13 | (*1R, 2S*)-**6e** | THF | -78°C | 3h | 95 | 1 |
| 14 | (*1R, 2S*)-**6f** | THF | -78°C | 3h | 60 | 3 |

[a] For procedure, see text. [b] The product having (*S*) configuration was obtained in all cases. [c] DME = dimethoxyethane.

3.00 mmol) in THF (5 mL) was added at -78°C and the whole was stirred at -78 °C for 1 h. A solution of **8** (129 mg, 1.50 mmol) in THF (5 mL) was added to the reaction mixture, and the whole was allowed to stand at -78 °C for 60 h. After the addition of saturated aqueous $NH_4Cl$ (10 mL), **9** (242 mg, 68% yield based on **8**) was isolated by the usual workup followed by silica gel column chromatography (hexanes/AcOEt = 20/1-10/1). The enantiomeric excess was determined to be 84% by HPLC analysis (DAICEL CHIRALCEL OD-H, hexanes/ isopropanol = 100/1, 1.0 mL/ min). The absolute configuration was determined to be (*S*)[6] by the optical rotation [$[\alpha]_D^{25}$+74.4 (*c* 3.1, EtOH)].

Catalytic amount of the chiral lithium alkoxides were applied to this reaction. 0.1 equivalent of **6b** gave (*S*)-**9** in 49% yield and 41% ee in THF at -45°C; the ee is close to that obtained with 1.1 equivalents of **6b** at -45°C (78% yield and 49% ee).

In conclusion, examples are shown in which the chiral lithium alkoxides bearing a 2-amino group as an internal ligation site can work as chiral bases for the enantioselective Michael reaction of methyl phenylacetate and methyl acrylate.

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(*Received in Japan* 13 *May* 1994)