# ENANTIOSELECTIVE HORNER-WADSWORTH-EMMONS REACTION USING CHIRAL LITHIUM 2-AMINOALKOXIDES

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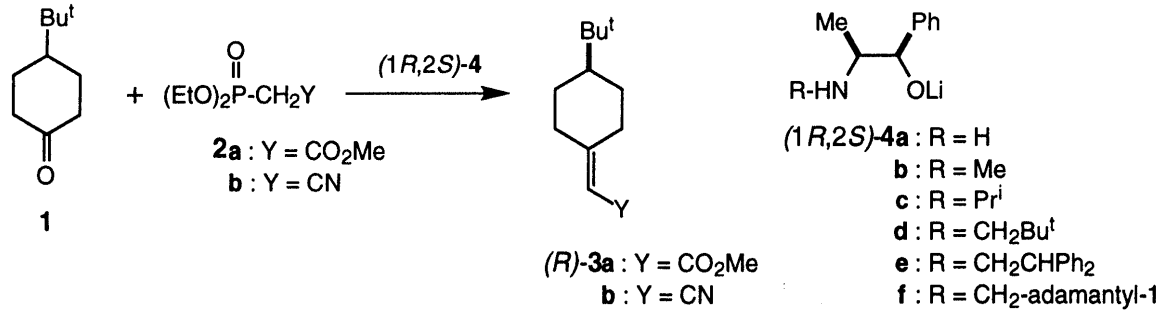
Chiral lithium 2-aminoalkoxides (*(1R,2S)*-**4**) were applied as chiral bases for the enantioselective Horner-Wadsworth-Emmons reaction between achiral phosphonates (**2**) and 4-*tert*-butylcyclohexanone (**1**). A chiral olefin (*(R)*-**3b**) was obtained in up to 52% enantiomeric excess (ee). It is shown that the formation of the lithium aldolate intermediate is reversible and is not responsible for the asymmetric induction.

**KEY WORDS** chiral base; chiral lithium 2-aminoalkoxide; Horner-Wadsworth-Emmons reaction; enantioselective asymmetric synthesis; chiral axis

The asymmetric Horner-Wadsworth-Emmons (HWE) reaction of prochiral ketones is one of the methods for the synthesis of compounds possessing a chiral axis.[1-3] Many examples of the asymmetric HWE reaction using chiral phosphonic acid derivatives have been reported.[4] However, little is known about the enantioselective HWE reaction of achiral phosphonates mediated by chiral external ligands. An example of the enantioselective Wittig reaction in the solid state is reported by forming inclusion complexes using optically active hosts.[5]

Metal alkoxides are bases that are used widely in organic synthesis. Previously, we reported on the enantioselective Michael reaction between methyl phenylacetate and methyl acrylate by employing chiral lithium 2-aminoalkoxides as chiral bases.[6] The result suggested that a well-defined chiral environment is formed for the reaction of achiral lithium enolate by coordination of chiral 2-aminoalcohols to the lithium. Based on this finding, we studied the possibility of using chiral lithium 2-aminoalkoxides (*(1R,2S)*-**4a~f**) as bases for the enantioselective HWE reaction between achiral phosphonates (**2**) and prochiral 4-*tert*-butylcyclohexanone (**1**).




The results are summarized in Table 1. Achiral phosphonates (**2**) were deprotonated by *(1R,2S)*-**4a~f** and then mixed with 4-*tert*-butylcyclohexanone (**1**) in toluene. The reaction of a phosphonate (**2a**) with a methoxycarbonyl group gave the product in low yield (run 1). When a phosphonate (**2b**) with a cyano group was used, the reaction proceeded smoothly (runs 2-10). The reaction of **2b** showed that the lithium alkoxides (*(1R,2S)*-**4d~f**) bearing a bulky *N*-substituent gave the product (*(R)*-**3b**)[7] in higher ee (runs 5, 9, 10). The solvent affects the degree of asymmetric induction (runs 5-8). Toluene gave the best result.

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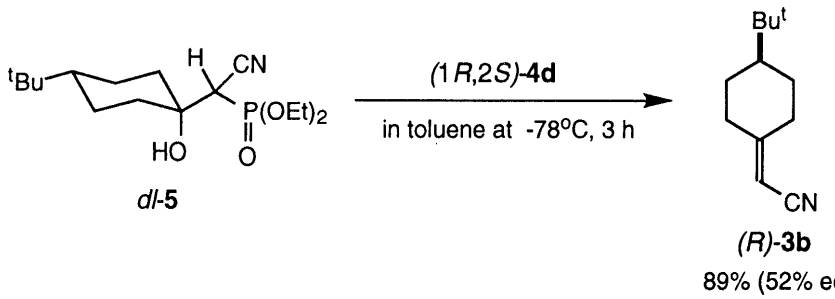
**Table 1. Enantioselective Horner-Wadsworth-Emmons Reaction between 1 and 2 to Give 3**

| Run | Phosphonate | Base | Solvent | Reaction conditions | Chemical y. (%) | ee (%) | Confign. |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | **4b** | Toluene | -45°C, 3 h | 18 | <1 | - |
| 2 | **2b** | **4a** | Toluene | -78°C, 3 h | 98 | 4 | *R* |
| 3 | **2b** | **4b** | Toluene | -78°C, 3 h | 88 | 17 | *R* |
| 4 | **2b** | **4c** | Toluene | -78°C, 3 h | 77 | 19 | *R* |
| 5 | **2b** | **4d** | Toluene | -78°C, 3 h | 92 | 52 | *R* |
| 6 | **2b** | **4d** | Ether | -78°C, 3 h | 94 | 34 | *R* |
| 7 | **2b** | **4d** | DME | -78°C, 3 h | 93 | <1 | - |
| 8 | **2b** | **4d** | THF | -78°C, 3 h | 87 | <1 | - |
| 9 | **2b** | **4e** | Toluene | -78°C, 3 h | 96 | 49 | *R* |
| 10 | **2b** | **4f** | Toluene | -78°C, 3 h | 86 | 51 | *R* |

The typical experimental procedure is as follows (run 5 in Table 1). A solution of butyllithium in hexane (1.58 M, 0.37 ml, 1.15 mmol) was added to a solution of *(1R,2S)*-2-(2,2,-dimethylpropylamino)-1-phenyl-1-propanol (254 mg, 1.15 mmol) in toluene (4 ml) under an argon atmosphere at 0°C. The mixture was stirred for 30 min at room temperature, and was then cooled to -78°C. A solution of **2b** (203 mg, 1.15 mmol) in toluene (3 ml) was added. After stirring for 30 min, a solution of **1** (161 mg, 1.04 mmol) in toluene (3 ml) was added. The reaction mixture was stirred at -78°C for 3 h. Saturated aqueous ammonium chloride (10 ml) was added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate (10 ml). The organic layers were combined, washed successively with 10% aqueous citric acid (10 ml) twice, saturated aqueous sodium bicarbonate (10 ml) and brine (10 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a colorless oil, which was purified by column chromatography (silica gel, hexane-ethyl acetate [30:1]) to give *(R)*-**3b** (170 mg, 92% based on **1**) as colorless prisms of mp 31-33°C, $[\alpha]_D^{25}$ -49.1° (*c* 1.43, $CHCl_3$), corresponding to be 52% ee by chiral GC[8] and HPLC[9] analyses.

The HWE reaction is known to proceed in a stepwise manner, i.e., the phosphonate carbanion attacks the carbonyl to give the corresponding aldolate, which then decomposes to give an olefin and a phosphate.[2c] To investigate at which stage asymmetric induction occurs in the present asymmetric HWE reaction, a racemic aldol-type compound (*dl*-**5**)[10] was synthesized by the reported procedure,[11] and was treated with 1.1 equivalents of *(1R,2S)*-**4d** in toluene at -78°C. The product (*(R)*-**3b**) was isolated in 89% yield and in 52% ee, which means that the *(R)*-isomer and *(S)*-isomer are obtained in 67.6% yield and 21.4% yield, respectively. Since the yield of the *(R)*-isomer is more than 50%, it is clear that asymmetric induction in the present reaction is not due to the kinetic resolution of *dl*-**5**. In the presence of 1.0 equivalent of benzaldehyde, *dl*-**5** gave cinnamonitrile (32% yield, E/Z = 97:3) and *(R)*-**3b** (40% yield, 18% ee).




*dl*-**5** *(R)*-**3b**

89% (52% ee)

These data show that the initially formed lithium aldolate is not responsible for the asymmetric induction, because the reversible dissociation of aldolate to **1** and the anion of **2b** occurs during the present asymmetric HWE reaction. It is conceivable, therefore, that the rates of decomposition of the diastereomeric complexes between the lithium aldolate and 2-aminoalcohol differ under the reversible formation and dissociation of the lithium aldolate. This possibility is a matter for future study.

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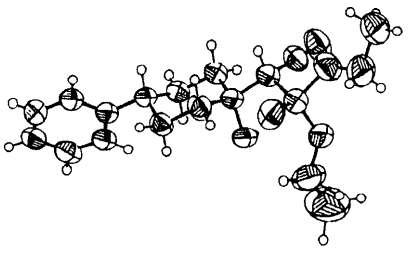
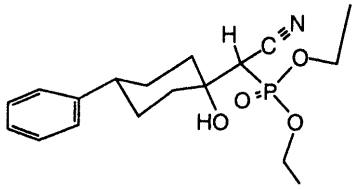
7) (-)-**3b** ($[\alpha]_D^{25}$ -50.0° (*c* 1.30, $CHCl_3$), corresponding to 51% ee[8,9]) was treated with diisobutylaluminum hydride (1.1 equivalents) in toluene at -78°C for 15 min gave the corresponding *(R)*-aldehyde (72% yield, $[\alpha]_{546}^{25}$ -23.5° [*c* 1.40, $CHCl_3$]), whose absolute configuration is known. Duraisamy M., Walborsky H. M., *J. Am. Chem. Soc.*, **105**, 3252-3264 (1983).
8) Chiral column for GC analysis: CHROMPAK CP-Cyclodextrin-β-236-μ, 50 m.
9) Chiral column for HPLC analysis: DAICEL CHIRALCEL OD-H; solvent: hexane-2-propanol (1000:1).
10) *dl*-**5** (mp 77-78°C) was obtained as a single diastereomer from **1** and **2b** using methylmagnesium bromide as a base[11] in THF. The corresponding phenyl analogue (*dl*-**6**) (mp 99-100°C) was obtained as a single diastereomer from 4-phenylcyclohexanone and **2b** under the same procedure. From the X-ray crystal structure of *dl*-**6** (shown below), we assume that the relationship between the *tert*-butyl group and the hydroxyl group on the cyclohexane ring of *dl*-**5** is *cis*. The chemical shifts (δ, in $CDCl_3$) of the methine protons adjacent to the phosphonate group are observed at 3.03 ppm (d, *J*=23.0 Hz) for *dl*-**5**, at 3.44 ppm (d, *J*=24.1 Hz) for the other diastereomer of *dl*-**5**, and at 3.09 ppm (d, *J*=22.4 Hz) for *dl*-**6**.



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