

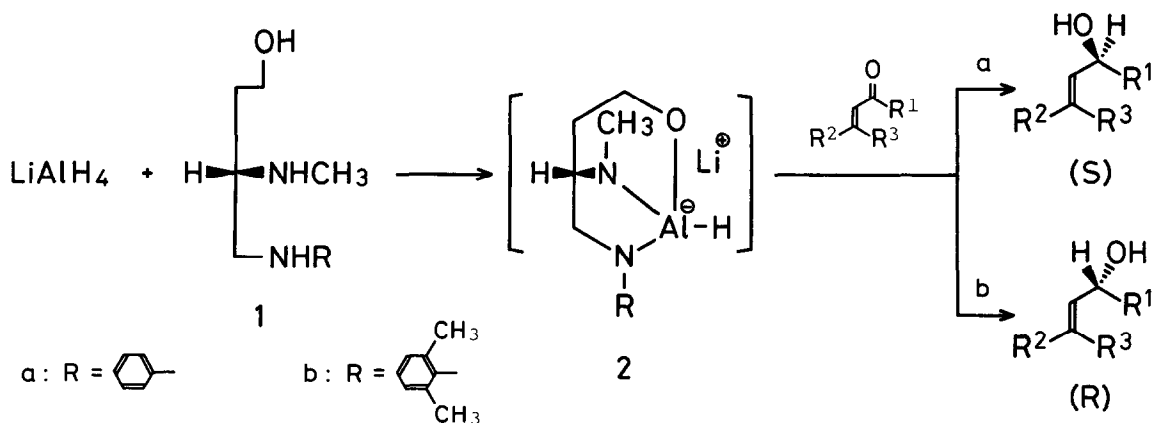
ASYMMETRIC REDUCTION OF  $\alpha,\beta$ -UNSATURATED KETONES WITH CHIRAL HYDRIDE REAGENTS  
 PREPARED FROM LITHIUM ALUMINUM HYDRIDE AND (S)-4-ANILINO- AND  
 (S)-4-(2,6-XYLIDINO)-3-METHYLAMINO-1-BUTANOL

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**Summary:** *The asymmetric reduction of prochiral  $\alpha,\beta$ -unsaturated ketones with chiral hydride reagents derived from lithium aluminum hydride and (S)-4-anilino- and (S)-4-(2,6-xylylidino)-3-methylamino-1-butanol gives (S)- and (R)-allylic alcohols in high chemical and optical yields, respectively.*

Asymmetric reduction of prochiral ketones with chiral hydride reagents has provided an efficient tool for the synthesis of optically active secondary alcohols.<sup>1</sup> High enantioselectivity in the reduction of aryl alkyl ketones<sup>2</sup> and  $\alpha,\beta$ -acetylenic ketones<sup>3</sup> has been achieved by various chiral reagents. However, there have been a few examples<sup>2a,3a,4</sup> of asymmetric reduction of  $\alpha,\beta$ -unsaturated ketones which gives optically active allylic alcohols, useful intermediates in natural product synthesis.<sup>5</sup> We disclose here an effective asymmetric reduction of  $\alpha,\beta$ -unsaturated ketones with lithium aluminum hydride modified by (S)-4-anilino- and (S)-4-(2,6-xylylidino)-3-methylamino-1-butanol (1a and 1b), prepared easily from (S)-aspartic acid, to afford the corresponding (S)- and (R)-allylic alcohols, respectively.

Chiral aluminum hydride reagent 2a (empirical formula), prepared by mixing



lithium aluminum hydride with the tridentate ligand, diamino alcohol 1Q has been shown to be effective in the reduction of aryl alkyl ketones to the corresponding secondary (*S*)-alcohols.<sup>6</sup> When an  $\alpha,\beta$ -unsaturated ketone was treated with 3 equiv of reagent 2Q in THF at  $-100\text{ }^{\circ}\text{C}$  for  $3 \sim 4\text{ h}$ , the corresponding optically active alcohol was isolated after ordinary aqueous workup and purification by TLC on silica gel and/or by bulb-to-bulb distillation.

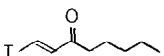
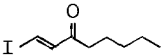
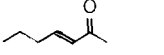
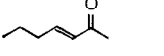
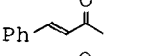
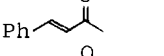
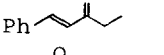
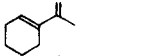
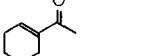
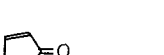


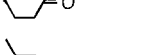
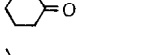
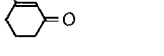
Several examples of asymmetric reduction of  $\alpha,\beta$ -unsaturated ketones using reagent 2Q are listed in Table. All of the ketones are consistently reduced to the allylic alcohols with the same absolute configuration of *S*. A linear  $\alpha,\beta$ -unsaturated methyl ketone, 3-hepten-2-one gave (*S*)-3-hepten-2-ol in a high optical yield of 88% (entry 3). Reagent 2Q is effective in the asymmetric reduction of not only linear ketones but also cyclic ones to give the corresponding cyclic (*S*)-allylic alcohols. Especially in the case of 2-cyclohexen-1-one, complete enantioselection can be realized (entry 11). Introduction of methyl substituent on the 3-position of 2-cyclohexen-1-one, however, decreased remarkably the optical yield (entry 13).

When a chiral auxiliary ligand for asymmetric reduction is derived from natural products such as amino acids, terpenes, sugars, alkaloids, and so on, the chiral source is often limited to only one configuration, therefore it is generally difficult to obtain highly optically active alcohols of both (*R*)- and (*S*)-configurations. After exploring several types of tridentate ligands derived from (*S*)-aspartic acid, (*S*)-4-(2,6-xylylidino)-3-methylamino-1-butanol<sup>7</sup> (1b) was found to be an efficient one to afford (*R*)-allylic alcohols in contrast to ligand 1Q which gives (*S*)-alcohols as mentioned above. Several results of asymmetric reduction using chiral hydride reagent 2b are summarized in Table. While (*R*)-3-hepten-2-ol of 84% ee was obtained by the reduction of a linear ketone, 5-hepten-2-one with reagent 2b, 2-cyclohexen-1-one gave (*R*)-2-cyclohexen-1-ol in only 13% optical yield (entries 4 and 12). Reagent 2b is superior to 2Q in the reduction of 1-acetyl-1-cyclohexene to give the corresponding (*R*)-alcohol of 61% ee (entries 8 and 9).

A typical procedure is exemplified by the reduction of 2-cyclohexen-1-one with 2Q. Ligand 1Q (3.50 g, 18 mmol) in THF (50 ml) was added to 1.12 M THF solution of lithium aluminum hydride (18 mmol) at  $0\text{ }^{\circ}\text{C}$ . After stirring the mixture at room temperature for 1 h, the solution of 2Q was cooled to  $-100\text{ }^{\circ}\text{C}$  and 2-cyclohexen-1-one (0.577 g, 6 mmol) in THF (6 ml) was added dropwise. After stirring the mixture for 4 h, methanol (3 ml) and then water (3 ml) were added. precipitated white solid was filtered off and washed with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with 10% sulfuric acid and brine successively and dried over  $\text{Na}_2\text{SO}_4$ . Bulb-to-bulb distillation ( $100 \sim 105\text{ }^{\circ}\text{C}/100\text{ mmHg}$ ) gave pure (*S*)-2-cyclohexen-1-ol (0.558 g) in 95% yield. Ligand 1Q was recovered in over 80% yield from the acidic solution without racemization.

Further applications of these novel reducing reagents with chiral tridentate

Table. The Asymmetric Reduction of  $\alpha,\beta$ -Unsaturated Ketones with Chiral Hydride Reagent 2

| Entry | Ketone  | Hydride Reagent | Chemical Yield(%) <sup>a</sup> | Obsd. $[\alpha]_D^{23}$ (C, Solvent) | Optical Yield(%) <sup>e</sup> | Config.               |
|-------|---|-----------------|--------------------------------|--------------------------------------|-------------------------------|-----------------------|
| 1     |    | 2a              | 94                             | +5.00° (1.58, CH <sub>3</sub> OH)    | 51 <sup>b</sup>               | <i>S</i> <sup>b</sup> |
| 2     |    | 2b              | 51                             | -2.1° (1.44, CH <sub>3</sub> OH)     | 21 <sup>b</sup>               | <i>R</i> <sup>b</sup> |
| 3     |    | 2a              | 73                             | -8.20° (3.33, CHCl <sub>3</sub> )    | 88 <sup>c</sup>               | <i>S</i> <sup>c</sup> |
| 4     |    | 2b              | 80                             | +7.7° (1.72, CHCl <sub>3</sub> )     | 84 <sup>c</sup>               | <i>R</i> <sup>c</sup> |
| 5     |    | 2a              | 91                             | -29.7° (5.01, CHCl <sub>3</sub> )    | 72 <sup>d</sup>               | <i>S</i> <sup>e</sup> |
| 6     |    | 2b              | 88                             | +17.3° (5.43, CHCl <sub>3</sub> )    | 42 <sup>d</sup>               | <i>R</i> <sup>e</sup> |
| 7     |    | 2a              | 95                             | -6.6° (3.18, CHCl <sub>3</sub> )     | 75 <sup>f</sup>               | <i>S</i> <sup>f</sup> |
| 8     |    | 2a              | 88                             | -0.65° (4.60, CHCl <sub>3</sub> )    | 5 <sup>g</sup>                | <i>S</i> <sup>g</sup> |
| 9     |    | 2b              | 71                             | +7.60° (1.54, CHCl <sub>3</sub> )    | 61 <sup>g</sup>               | <i>R</i> <sup>g</sup> |
| 10    |    | 2a              | 77                             | -105.8° (1.14, CHCl <sub>3</sub> )   | 82 <sup>h</sup>               | <i>S</i> <sup>h</sup> |
| 11    |   | 2a              | 95                             | -112.5° (1.06, CHCl <sub>3</sub> )   | 100 <sup>i</sup>              | <i>S</i> <sup>j</sup> |
| 12    |  | 2b              | 35                             | +14.5° (1.55, CHCl <sub>3</sub> )    | 13 <sup>i</sup>               | <i>R</i> <sup>j</sup> |
| 13    |  | 2a              | 57                             | -26.7° (0.539, CHCl <sub>3</sub> )   | 28 <sup>k</sup>               | <i>S</i> <sup>k</sup> |
| 14    |  | 2b              | 87                             | +2.0° (0.52, CHCl <sub>3</sub> )     | 2 <sup>k</sup>                | <i>R</i> <sup>k</sup> |
| 15    |  | 2a              | 84                             | -17.4° (1.07, CHCl <sub>3</sub> )    | 50 <sup>d</sup>               | <i>S</i> <sup>l</sup> |

<sup>a</sup> All products were identified by <sup>1</sup>H NMR and IR spectroscopy and/or comparison with authentic materials. Isolated yields by distillation. <sup>b</sup> Optically pure (*S*)-alcohol gives  $[\alpha]_D^{24} +9.87^\circ$  (C 1.57, CH<sub>3</sub>OH), see ref. 4a. <sup>c</sup> Optical rotation of (*S*)-alcohol is  $[\alpha]_D^{20} -8.2^\circ$  (C 3.58, CHCl<sub>3</sub>, 88% ee), see ref. 4b. <sup>d</sup> Determined by <sup>1</sup>H NMR analysis of the diastereomeric (*R*)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid (MTPA) esters.<sup>8,9</sup> <sup>e</sup> See ref. 10. <sup>f</sup> The optical yield and absolute configuration were determined by optical rotation of (*S*)-1-phenyl-3-pentanol  $[\alpha]_D^{23} +20.2^\circ$  (C 5.00, EtOH), obtained by the catalytic hydrogenation of this alcohol, and pure one  $[\alpha]_D +26.8^\circ$  (C 5.0, EtOH).<sup>10,11</sup> <sup>g</sup> Optical rotation of (*S*)-alcohol is  $[\alpha]_D^{20} -9.8^\circ$  (C 4.25, CHCl<sub>3</sub>, 78% ee), see ref. 4b. <sup>h</sup> Determined by optical rotation of the (*S*)-(2-cyclopentenyl)acetic acid obtained from orthoethyl acetate-Claisen rearrangement<sup>12</sup> of 2-cyclopenten-1-ol,  $[\alpha]_D^{23} +89.3^\circ$  (C 5.89, CHCl<sub>3</sub>). Optically pure (*S*)-(2-cyclopentenyl)acetic acid has been reported to give  $[\alpha]_D^{30} +109.2^\circ$  (C 5.9, CHCl<sub>3</sub>).<sup>13</sup> <sup>i</sup> Based on  $[\alpha]_D^{20} -112.0^\circ$  (C 0.60, CHCl<sub>3</sub>)<sup>14</sup> and <sup>1</sup>H NMR analysis of the MTPA esters. <sup>j</sup> See ref. 15. <sup>k</sup> Optically pure (*S*)-alcohol gives  $[\alpha]_D^{20} -96.3^\circ$  (C 0.458, CHCl<sub>3</sub>).<sup>16</sup> <sup>l</sup> Tentatively assigned by considering <sup>1</sup>H NMR analysis of the MTPA ester.<sup>8</sup>

ligands to natural product synthesis are under progress.

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