

## The Asymmetric Reduction of Prochiral Ketones Using (*S*)-2,2'-Dihydroxy-4,5,6,4',5',6'-hexamethoxybiphenyl

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
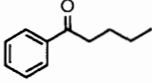

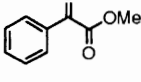


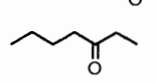
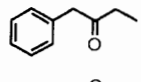
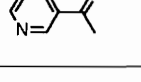

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Excellent enantioselection is observed in the reduction of a wide variety of prochiral ketones using LiAlH<sub>4</sub> modified with biphenol **4**.

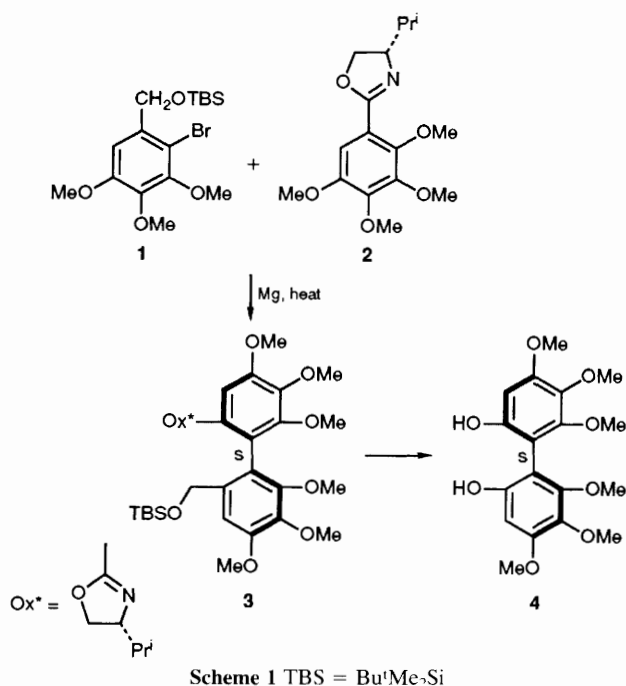
Over the last two decades there has been much interest in the asymmetric reduction of prochiral ketones using aluminium and boron hydrides modified by optically active protic substances, such as diols, amino alcohols and diamines.<sup>1</sup> Using the aryl oxazoline **2**, we recently observed a highly

stereoselective biaryl coupling to **1** which gave a 98 : 2 mixture of atropisomers (separable by column chromatography). The major diastereoisomer of **3** was converted into the axially chiral biphenol **4** [ $>98\%$  enantiomeric excess (e.e.)] in a high yielding five-step procedure (Scheme 1).<sup>2</sup> The biphenol is

**Table 1** Reduction using 4-LiAlH<sub>4</sub>-EtOH

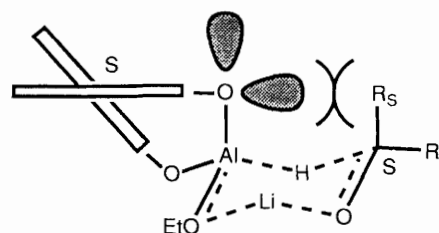
|   | Yield of carbinol (%) | % E.e. <sup>a</sup> | (% E.e. from BINAL-H) <sup>3</sup> |
|---|-----------------------|---------------------|------------------------------------|
|    | 93                    | 97                  | (95)                               |
|    | 84                    | 94                  | (100)                              |
|    | 79                    | 86                  | (95 for bromide)                   |
|    | 86                    | 81                  | (24)                               |
|    | 54 <sup>b</sup>       | 78                  | (78 for 3-methylbutan-2-one)       |
|    | 68                    | 83                  |                                    |
|    | 76                    | 76                  | (24) <sup>c</sup>                  |
|   | 83                    | 36                  |                                    |
|  | 72                    | 93                  | (24 for 1-phenylpropan-2-one)      |
|  | 53                    | 62                  |                                    |

<sup>a</sup> Enantiomeric excess determined from the <sup>1</sup>H and <sup>19</sup>F NMR spectra of the Mosher's esters. <sup>b</sup> No reaction at -78 °C but complete reaction after 10 h at -40 °C. <sup>c</sup> (*R*)-BINAL-H gave the *S*-alcohol as the major product.



readily recognized as a configurationally stable analogue of the widely used 2,2'-binaphthol (BINAL-H), developed by Noyori as a chiral modifier of LiAlH<sub>4</sub> to access chiral carbinols in high enantiomeric excess.<sup>3</sup>

The highest levels of enantioselective reduction, using the binaphthol, were reached from the addition of prochiral

**Fig. 1**

ketone to a threefold excess of the reagent at low temperature.<sup>3</sup> The same conditions and reagent ratios using biphenol **4** as the chiral modifier, were used<sup>†</sup> to reduce a large number of prochiral ketones to the corresponding carbinols (Table 1).

BINAL-H is one of the most efficient asymmetric reducing agents for unsaturated ketones (aryl, alkenyl and alkynyl) but gives much lower enantioselectivities for other classes of ketones. Asymmetric reducing agents, such as Masamune's (*R,R*)- and (*S,S*)-2,5-dimethylborolane,<sup>5</sup> were reported to

<sup>†</sup> In a typical experimental procedure, EtOH (1.37 mmol) and **4** (1.37 mmol) were added to a stirred solution of LiAlH<sub>4</sub> (1.37 mmol) in tetrahydrofuran (THF) (5 ml) at room temperature under an argon atmosphere. After 2 h this solution was cooled to -100 °C and the prochiral ketone (0.46 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred (2 h) and warmed to -78 °C overnight (10–12 h). The mixture was quenched with methanol and warmed to room temperature. Both the optically enriched carbinol and **4** were recovered in good yield by flash column chromatography (eluting firstly with 30% EtOAc-hexane and then with EtOAc) using Grace 951 silica gel (58 micrometer, Aldrich).

result in good enantioselectivity in the reduction of fully saturated prochiral ketones but have not been used in the reduction of other unsaturated ketones. As can be seen from Table 1, the reducing agent derived from **4** gave satisfactory levels of enantioselection for all classes of prochiral ketones studied, except those with similar steric characteristics (*e.g.* heptan-3-one).

In every case in Table 1 the absolute configuration of the major carbinol enantiomer (obtained by the sign of the optical rotation) was identical to that of the biphenol **4**. It should be noted that the axial chirality in **4** is determined solely by the amino alcohol used to prepare the oxazoline, and therefore it is possible to access (*R*) secondary alcohols starting from *D*-valinol. A chair-like transition state is presently postulated to explain these results (Fig. 1), with steric effects seemingly playing the major role in determining the absolute configuration and optical purity of the product.‡ The most favourable transition state conformation is that in which steric repulsions appear to be minimized when the smaller (*R<sub>s</sub>*) group occupies the axial position.

The overall smaller size of the biphenol **4** compared with binaphthol (BINAL-H) would be expected to produce a more compact transition state and could account for the subtle

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‡ Noyori<sup>3</sup> was able to rationalize the results of BINAL-H reduction by assuming that electronic differences in the substituents on the carbonyl were the main factor governing the enantiofacial differentiation, with steric effects playing only a minor role.

differences in reduction efficiency between the two reducing agents.

The levels and predictability of enantioselectivities obtained from the reduction of a wide range of prochiral ketones makes this one of the more versatile asymmetric reducing agents thus far reported. At present, studies are underway to assess the biphenol **4** as both a catalyst and mediator for other asymmetric reactions.

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