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A New Pinane-Type Tridentate Modifier for Asymmetric Reduction of Ketones with Lithium Aluminum Hydride

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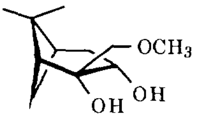
Abstract: The reduction of aryl and alkenyl methyl ketones using lithium aluminum hydride modified with (1*R*,2*S*,3*S*,5*R*)-(+)-10-anilino-3-ethoxy-2-hydroxypinane (**3**), afforded chiral secondary alcohols in 83–96% yields and 53–97% optical yields. The modifier **3** was prepared from (1*R*)-(–)-myrtenol and was readily recovered (>96%) after reduction. The reduction of acetophenone in the presence of lithium iodide gave the alcohol product with higher optical yield.

Enantiomerically pure chiral secondary alcohols are important starting materials for the total synthesis of natural products.[1] High degrees of asymmetric induction have been realized in the reduction of prochiral ketones using chirally modified lithium aluminum hydride (LAH) reagents to give optically active secondary alcohols.[2] We have recently demonstrated that secondary alcohols can be obtained in moderate optical yields in the reduction of prochiral ketones by LAH using pinane-based modifiers **1** and **2**.[3]



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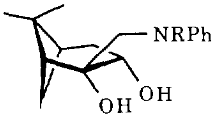


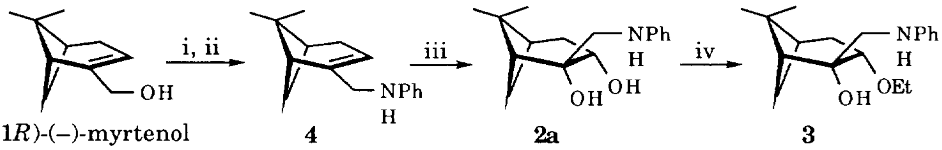
2a, R = H; **2b**, R = CH_3

After molecular modelling analysis of the putative transition structures[3] in an attempt to develop more effective modifiers, we envisaged that a C-3 alkoxy group is sterically more demanding than a hydroxyl group and therefore can better differentiate the two reaction faces of the reactant. Thus a new, rationally designed, pinane-based modifier **3**, possessing a rigid bicyclic pinane skeleton and an ethoxy substituent at C-3, has been prepared. Compound **3** proved to be very efficient in the sense of product yields, optical yields and reuse of the modifier. We herein describe the preparation of (1*R*,2*S*,3*S*,5*R*)-(+)-10-anilino-3-ethoxy-

2-hydroxypinane (**3**) from (1*R*)-(−)-myrtenol and its application as an improved chiral modifier for lithium aluminum hydride in the reduction of prochiral ketones.

As delineated in Scheme I, (1*R*)-(−)-myrtenol was reacted with PBr_3 to give (1*R*)-(−)-myrtenyl bromide in 85% yield[4] which was converted to the desired diol **2a** by the known procedure.[3] Selective alkylation of the secondary hydroxyl group with sodium hydride and bromoethane furnished the desired modifier **3** in 83% yield.[5]

Scheme I



(1*R*)-(−)-myrtenol **4** **2a** **3**

i. PBr_3/pyridine/benzene, rt, 85% ii. KH/aniline/THF, rt, 85%
iii. $OsO_4/(CH_3)_3N\rightarrow O$, reflux, 50% iv. NaH/EtBr, 83%

The chiral reducing agent was prepared *in situ* by mixing a standardized stock solution of LAH in ether with modifier **3** at room temperature for 1 h.[3,6] THF solutions of prochiral ketones were then added at −78 °C and stirred for 60 min to furnish the corresponding secondary alcohols in 83–96% chemical yields (Table 1). The chiral modifier **3** was recovered nearly quantitatively (> 96%) from the reaction mixture by silica-gel chromatography. It was noted in the reduction of acetophenone and 4-phenyl-3-buten-2-one that the enantioselectivities varied remarkably in different solvent systems.[7] A 1:10 mixture of Et_2O/THF appeared to be the solvent of choice for the asymmetric LAH reduction. In such a solvent system, several mono- and disubstituted acetophenones were reduced by LAH/modifier **3** to afford the corresponding phenethanols in favor of the (*R*)-configuration (66–97% optical yields). The reduction of methyl 2-nitrophenyl ketone (entry 7) was not prevented by the nitro group and gave 85% of the desired alcohol. 2-Acetylfuran, 1-acetylnaphthalene, 2-acetylnaphthalene, 2-acetylphenanthrene and 2-acetylfluorene were similarly reduced to give 55, 85, 53, 93 and 86% optical yields respectively. As the addition of HMPA or lithium iodide is known to affect the enantioselectivities in certain reactions (such as alkylation reactions of enolates or allylmetals),[8] we also examined their effects in the LAH reductions. The preliminary results indicated that the optical yield of the alcohol products were increased in some instances by addition of LiI (entries 2, 12, and 18). On the other hand, the enantioselectivity decreased in the reduction of 1-acetylnaphthalene in the presence of the cosolvent HMPA (entry 13).

Table 1 Reduction of methyl ketones $RCOCH_3$ with $LiAlH_4$ and chiral modifier **3**.[a]

entry	Ar	additive (equiv)[b]	product yield (%)[c]	ee (%)[d]	optical yield (%)[e]	config.
1	Ph		85	62	66	*R*
2	Ph	LiI (1)	91	83	88	*R*
3	*o*-tolyl		86	79	84	*R*
4	2-bromophenyl		86	78	83	*R*
5	2-chlorophenyl		86	78	83	*R*
6	2-methoxyphenyl		86	91	97	*R*
7	2-nitrophenyl		85	72	77	*R*
8	2,4-dimethylphenyl		87	74	79	*R*
9	2,5-dimethoxyphenyl		91	91	97	*R*
10	2-furyl		88	52	55	*R*
11	1-naphthyl		93	80	85	*R*
12	1-naphthyl	LiI (1)	92	84	90	*R*
13	1-naphthyl	HMPA (6)	85	66	70	*R*
14	2-naphthyl		96	50	53	*R*
15	2-phenanthyl		94	87	93	
16	2-fluorenyl		95	81	86	
17	PhCH=CH		93	50	53	*R*
18	PhCH=CH	LiI(1)	91	52	55	*R*
19	1-cyclohexenyl		89	74	79	*R*

[a] The reactions were carried out in ether/THF (1:10) solution with the following stoichiometry: LAH/modifier 3/ketone = 2/2.2/1. [b] Based on ketone. [c] Isolated yields. [d] The optical yield is determined by HPLC analysis;[9] the major enantiomer has the (*R*)-configuration. [e] Calculated based on the maximum optical purity (93.8%) of the modifier 3.

A wide range of aromatic and alkenyl methyl ketones can be reduced by LAH in the presence of modifier **3** to give chiral secondary alcohols in synthetically useful yields and enantioselectivities. The facial selectivities realized in the LAH reduction of aromatic methyl ketones using modifier **3** are superior to those utilizing simple terpenic diol modifiers.[10] The reduction of alkenyl methyl ketones (entries 17–19) gave exclusively the allylic alcohols, no 1,4-reduction products were observed. Our results demonstrate the importance of the amino substituent at C-10 in modifier **3** for the chiral induction in the asymmetric reduction of ketones using chiral LAH reagents. The asymmetric induction was further improved by the ethoxy group at C-3 of modifier **3** compared with the hydroxyl group in modifiers **1** or **2**.

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4. (a) For converting an alcohol to a bromide, see: Noller, C. R.; Dinsmore, R. *Org. Synth. Coll. Vol. 2*, **1943**, 358. (b) For the preparation of myrtenyl bromide from β-pinene, see: Zweifel, G.; Whitney, C. C. *J. Org. Chem.* **1966**, *31*, 4178.
5. Modifier **3** gave satisfactory elemental analysis and was converted to (1*R*,2*S*,3*S*,5*R*)-(+)-10-(3,5-dinitrobenzanilido)-3-ethoxy-2-hydroxypinane (**5**) by reacting it with 3,5-dinitro benzoyl chloride in the presence of triethylamine in THF. The optical purity of the corresponding 3,5-dinitrobenzamide **5** was determined to be 93.8% ee by HPLC analysis using a CHIRALCEL OD (Daicel Chemical Ind. Ltd.) column (25 cm x 4.6 mm), eluted with 2-propanol/hexane (1/20, flow rate: 0.42 mL/min). The retention times for the major isomer [(+)-**5**] is 31.94 min and the minor is 42.78 min.
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