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Enantioselective Protonation of Achiral Lithium Enolates Using a Chiral Amine in the Presence of Lithium Bromide†

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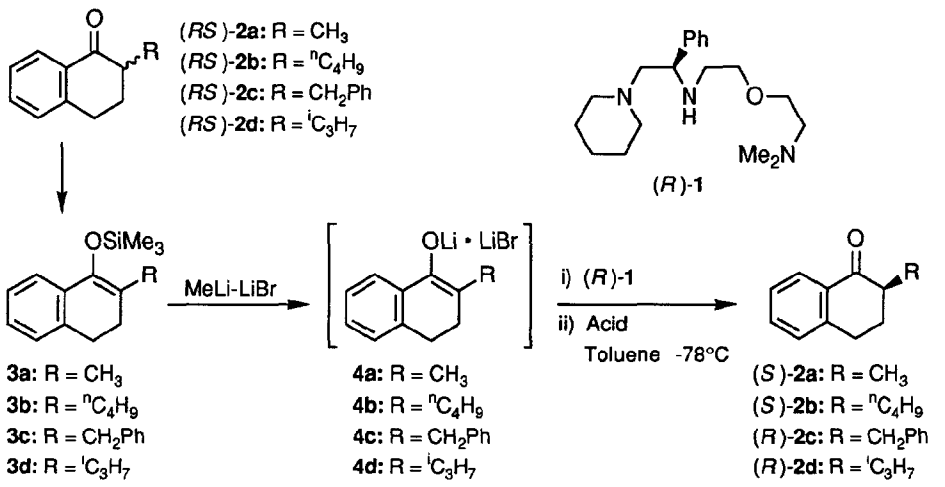
Abstract: Asymmetric synthesis of 2-alkyl-1-tetralones (**2**) was achieved in up to 91% e.e. by enantioselective protonation of their corresponding achiral lithium enolates (**4**) using a chiral amine ((*R*)-**1**) as a chiral source in the presence of lithium bromide. Enantioselective alkylation using (*R*)-**1** was also carried out, and it is found that the alkyl halide prefers the *si*-face of the lithium enolate **6** as oppose to the *re*-face preference of **4a** in case of protonation.

Enantioselective protonation of achiral enolates derived from racemic α-substituted carbonyl compounds is one of the efficient methods for obtaining optically active α-substituted carbonyl compounds,[1] since this method makes it possible to convert racemic carbonyl compounds into the corresponding optically active ones, and racemates are usually available readily. Some examples using chiral proton sources for enantioselective protonation are already reported,[2] and only one example[3a] is known in which high enantioselectivity is observed by using a chiral amine as a chiral source.



Scheme 1 Enantioselective Protonation of Achiral Lithium Enolates

† This paper is dedicated to Professor Albert I. Meyers on the occasion of his 60th birthday.

We have previously reported the enantioselective alkylation of ketones using a chiral lithium amide base in the presence of lithium bromide (LiBr).[4] It is considered that high enantiofacial differentiation of achiral lithium enolates would be realized by forming a chiral complex consisting of an achiral lithium enolate, a chiral amine, and LiBr, as is suggested in the above mentioned enantioselective alkylation of ketones. We made examinations on applying this strategy to enantioselective protonations in which proton is employed as an electrophile.

We describe herein an efficient method of enantioselective protonation of achiral lithium enolates (**4**) prepared from racemic 2-alkyl-1-tetralones ((*RS*)-**2**) to give optically active **2** by the use of a chiral amine ((*R*)-**1**) in the presence of LiBr. The results are summarized in Table 1.

Table 1 Enantioselective Protonation of Achiral Lithium Enolates Using (*R*)-**1**[a]

Entry	Substrate	Solvent	Acid[b]	Product	c.y. (%)[c]	e.e.(%)[d]	Confign.
1	**3a**	THF[e]	AcOH	**2a**	66	6	*S*
2	**3a**	DME[f]	AcOH	**2a**	87	2	*S*
3	**3a**	Et_2O	AcOH	**2a**	84	76	*S*
4	**3a**	CH_2Cl_2	AcOH	**2a**	78	77	*S*
5	**3a**	Toluene	AcOH	**2a**	88	91	*S*
6	**3a**	Toluene+HMPA[g]	AcOH	**2a**	82	79	*S*
7	**3a**	Toluene	$^tBuCO_2H$	**2a**	80	88	*S*
8	**3a**	Toluene	CF_3CO_2H	**2a**	84	84	*S*
9	**3a**	Toluene	2,4,6-Tri-^{t}Bu-phenol	**2a**	82	83	*S*
10	**3a**	Toluene	10%-Citric acid aq.[h]	**2a**	91	81	*S*
11	**3a**	Toluene	(*R,R*)-DPTA[i]	**2a**	80	82	*S*
12	**3a**	Toluene	(*S,S*)-DPTA[i]	**2a**	84	83	*S*
13[j]	**3a**	Toluene	AcOH	**2a**	87	0	-
14	**3b**	Toluene	AcOH	**2b**[k]	83	90	*S*
15	**3c**	Toluene	AcOH	**2c**	86	83	*R*
16	**3d**	Toluene	AcOH	**2d**[l]	89	67	*R*

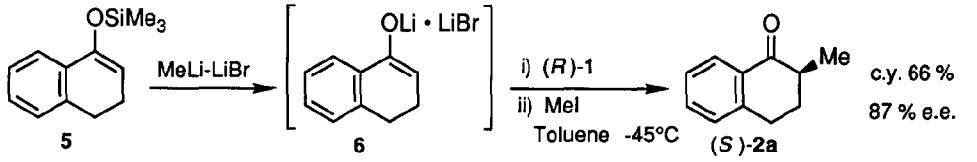
[a] Reaction procedure is described in the text. [b] Amount of acid used was 1.2-1.3 eq. [c] Isolated yield. [d] Determined by HPLC using a chiral column (Waters Opti-Pak XC for **2a**, **2b**, and **2d**, Opti-Pak TA for **2c**). [e] THF = tetrahydrofuran. [f] DME = 1,2-dimethoxyethane. [g] Before addition of AcOH, 1 eq. of HMPA (hexamethylphosphoric triamide) was added. [h] Added in large excess. [i] DPTA = *O,O*-dipivaloyltartaric acid, see ref 2a. [j] Methyllithium (1.4M solution in ether, halide content *ca.* 0.05M) was used to generate a lithium enolate. [k] **2b** ($[\alpha]^{25}_D$ -19.2 (c 3.52 MeOH), 90% e.e. by HPLC analysis) showed $[\theta]_{336}$ -3730 (c 0.02 EtOH), having *S*-configuration.[7] [l] **2d** ($[\alpha]^{25}_D$ -10.3 (c 3.56 dioxane), 67% e.e. by HPLC analysis) showed $[\theta]_{338}$ -4950 (c 0.02 EtOH), having *R*-configuration.[7]

A typical experimental procedure (entry 5 in Table 1) is as follows. Under argon atmosphere, a solution of MeLi-LiBr complex (0.86 mmol) in ether (1.54 M solution) was added to trimethylsilyl enol ether **3a** (0.86 mmol), and the whole was stirred at room temperature for 1.5 hr. Toluene (8 ml) was added to the reaction mixture, and the reacting solution was then cooled to -20 °C. A solution of (*R*)-**1**[5] (0.89 mmol) in toluene (5 ml) was added and the whole was stirred at -20 °C for 40 min and then at -78 °C for 20 min. Acetic acid (1.0 mmol) in toluene (2 ml) was added dropwise during 2 min. Stirring was continued at -78 °C for 20 min. After addition of 10%-citric acid aq. (10 ml), the product was isolated by usual work-up and purification (column chromatography (silica gel, ether : hexane = 1:30) followed by bulb-to-bulb distillation (160 °C at 0.6 mmHg)) to give the corresponding ketone ((*S*)-**2a**) of 91% e.e. ($[\alpha]^{22}_{D}$ -46.7 (c 3.26, dioxane)) in 88% chemical yield.

Absolute configurations of **2a**[6] and **2c**[4] are known, while those of **2b** and **2d** were determined by circular dichroism.[7] It is shown that the sense of asymmetric induction is the same as that shown in Scheme 1.

It is shown that the degree of asymmetric induction is highly dependent on the solvent used, and toluene gave the best result. Enantiomeric excess is found to decrease in polar solvents, especially in THF and DME. It is noteworthy that enantioselectivity is affected by the kind of acid employed. Among various acids as shown in Table 1, acetic acid gave the highest e.e. Acids with higher acidity (entry 8) and with lower acidity (entry 9) resulted in somewhat less enantioselectivity. It is also interesting to find that both antipodes of *O,O*-dipivaloyltartaric acid (DPTA) gave the ketone **2a** with the same absolute configuration and in almost the same e.e. (entry 11 and 12).

The effect of LiBr is remarkable. In the absence of LiBr, the ketone **2a** obtained was a racemate (entry 13). On the other hand, (*S*)-**2a** was obtained in 91% e.e. in the presence of LiBr (entry 5). Therefore, LiBr is found to be essential for asymmetric induction, and it is thus reasonable to assume that the formation of an achiral lithium enolate-a chiral secondary amine-LiBr complex is responsible for this highly enantioselective protonation.



Scheme 2 Enantioselective Alkylation Using (*R*)-**1**

Chiral amine (*R*)-**1** is also effective for enantioselective alkylation. As depicted in Scheme 2, (*S*)-**2a** was obtained from trimethylsilyl enol ether **5** in 87% e.e. by the same method previously reported.[4] Interestingly, the alkyl halide (MeI) prefers the *si*-face of the lithium enolate **6** (as shown in Scheme 2), whereas protonation proceeds preferentially from the other face (*re*-face) of the lithium enolate **4a**. Therefore, in both cases, by using **1** with the same absolute configuration, **2a** with the same absolute configuration is obtained.

The enantioselective protonation described here indicates an efficient approach of obtaining optically active α-substituted ketones from the corresponding racemic ones in high chemical and optical yields, and also provides a basis for further elucidation of interaction between lithium enolates and secondary amines. Mechanistic study of protonation process by means of deuteration experiments is currently under way.[8]

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8. Partially deuterated (*S*)-**2a** (the deuterium content at α-position of carbonyl group was *ca.* 20%) was obtained by the preliminary deuteration experiment using AcOD instead of AcOH.