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An Approach to Catalytic Enantioselective Protonation of Prochiral Lithium Enolates[1]

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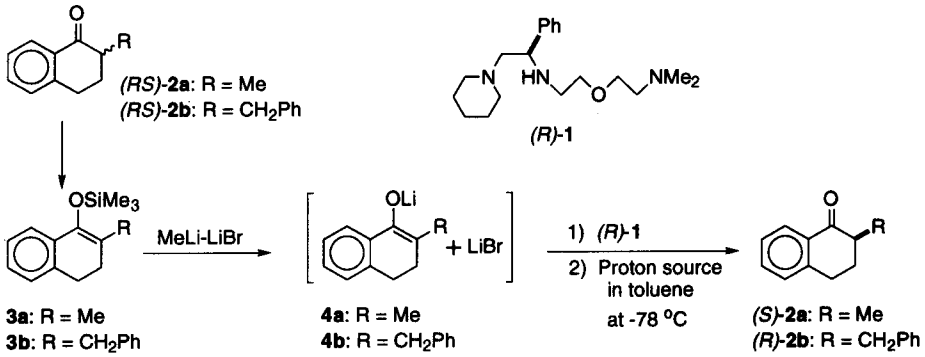
Abstract: Protonation of prochiral lithium enolates (**4**), prepared from racemic 2-substituted-1-tetralones (**2**) *via* their silyl enol ethers (**3**), with excess succinimide in the presence of lithium bromide and 0.2 equivalent of a chiral tetradentate amine (*(R)*-**1**) in toluene at -78 °C gave optically active **2** in up to 83% ee.

Enantioselective protonation of prochiral enolates is a promising method for the preparation of optically active carbonyl compounds having a chiral tertiary carbon at the α-position of the carbonyl group, because this method makes it possible to convert the racemic carbonyl compounds into the corresponding optically active ones. Since the pioneering work by Duhamel,[3] many examples have been reported to date,[4] including catalytic versions of this process.[5]

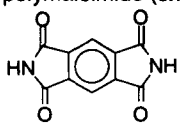


Scheme 1. Enantioselective Protonation

We have previously reported enantioselective protonation of prochiral lithium enolates (**4**) by acetic acid using a stoichiometric amount of a chiral tetradentate amine (*(R)*-**1**) as a chiral source as shown in Scheme 1.[6] Thus, racemic 2-substituted-1-tetralones (**2**) were converted to their corresponding silyl enol ethers (**3**), which were treated with methyllithium-lithium bromide (LiBr) in ether to give the lithium enolates (**4**) containing LiBr. After addition of *(R)*-**1** (1 equivalent), protonation by acetic acid was carried out in toluene at -78 °C to give optically active **2** in up to 91% ee (Table 1, run 1). By a similar strategy, enantioselective alkylation of the

lithium enolate of 1-tetralone was realized using alkyl halides as electrophiles instead of acetic acid.[7] It is postulated that the reactive intermediate in these enantioselective reactions should be a ternary complex formed from a lithium enolate, a chiral tetradentate amine, and LiBr.[6-8] Catalytic enantioselective alkylation was also realized by this strategy using less than a stoichiometric amount of a chiral tetradentate amine as a chiral source in the presence of an achiral bidentate amine. This means that the lithium enolate that is complexed with a chiral tetradentate amine reacts with alkyl halides faster than the lithium enolate that is not complexed or is complexed with a bidentate amine, and that ligand exchange *in situ* occurs faster than alkylation.[7b,8] Although protonation is obviously faster than alkylation, the above data suggest the possibility that catalytic enantioselective protonation by using less than a stoichiometric amount of *(R)*-**1** may be possible, if some device could be designed whereby the protonation of the lithium enolates that are complexed with *(R)*-**1** could be made to take place slower than the ligand exchange.

Table 1. Enantioselective Protonation of **4** to Give **2**[a]

Run	Substrate	*(R)*-**1** (eq.)	Proton source (eq.)	Reaction mixture	Product **2**	Product E.e. (%)[g]
1[b]	**3a**	1.03	AcOH (1.02)	homogeneous	*(S)*-**2a**	91
2[c]	**3a**	0.1	AcOH (1.2)	homogeneous	*(S)*-**2a**	28
3[d]	**3a**	0.1	di-^{t}Bu malonate (1.2)	homogeneous	*(S)*-**2a**	15
4[e]	**3a**	0.1	2,4,6-tri-^{t}Bu-phenol (1.2)	homogeneous	*(S)*-**2a**	51
5[f]	**3a**	0.1	2-piperidinone (1.2)	homogeneous	*(S)*-**2a**	59
6[f]	**3a**	0.1	phthalimide (1.2)	heterogeneous	*(S)*-**2a**	55
7[f]	**3a**	0.1	Me_2NEt HCl (1.2)	heterogeneous	*(S)*-**2a**	67
8[f]	**3a**	0.1	succinimide (1.2)	heterogeneous	*(S)*-**2a**	69
9[f]	**3a**	0.1	polymaleimide (excess)	heterogeneous	*(S)*-**2a**	72
10[f]	**3a**	0.1	 (1.2)	heterogeneous	*(S)*-**2a**	74
11[f]	**3a**	0.1	succinimide (10)	heterogeneous	*(S)*-**2a**	73
12[f]	**3a**	0.2	succinimide (10)	heterogeneous	*(S)*-**2a**	83
13[f]	**3b**	0.1	succinimide (1.2)	heterogeneous	*(R)*-**2b**	68
14[f]	**3a**	0.011	succinimide (3.8)	heterogeneous	*(S)*-**2a**	54

[a] Two reaction procedures (for runs 2~13, and for run 14) are described in the text. The products (**2**) were isolated in over 88% yields. [b] Data taken from ref. 6. [c] Proton source was added slowly during 45 min. [d] Proton source was added within 1 min. [e] Proton souce was added slowly during 150 min. [f] Proton source was added in one portion. [g] Determined by HPLC using a chiral column.[14]

Protonation experiments were carried out as shown in Scheme 1 using less than a stoichometric amount of *(R)*-**1** in toluene at -78 °C. In all cases, the products were isolated in over 88% yield. The results are summarized in Table 1 (runs 2~13). By slow addition of acetic acid (*pKa* 4.76 in water[9]) in toluene during 45 min in the presence of 0.1 equivalent of *(R)*-**1**, *(S)*-**2a** was obtained in 28% ee (run 2), indicating that *(R)*-**1** is actually recycled *in situ*.. Quick addition of the less acidic di-*tert*-butyl malonate (*pKa* 13.5[10]) gave *(S)*-**2a** in lower ee (run 3), but still shows the recycling of *(R)*-**1**. On the other hand, very slow addition of 2,4,6-tri-*tert*-

butylphenol (*pKa* 12.2 in water[11]) in toluene during 150 min gave *(S)*-**2a** in 51% ee (run 4). Interestingly, quick addition of 2-piperidinone was found to be effective (run 5).

Based on the assumption that slow addition of the proton source may be realized by using acids that are solid and are not practically soluble in toluene, phthalimide (*pKa* 8.3 in water[12]), *N,N*-dimethylethylamine hydrochloride (*pKa* 9.99 in water[13]) and succinimide (*pKa* 9.6 in water[10]) were powdered and added in one portion (runs 6~8). A heterogeneous mixture was obtained, which was stirred at -78 °C for 1 hr. Acids having an imide moiety, such as polymaleimide and pyromellitic diimide, were also examined in a similar way (runs 9, 10). It is shown that ee's of *(S)*-**2a** were found to be increased. By using a large excess of succinimide and 0.2 equivalent of *(R)*-**1**, ee of *(S)*-**2a** was further increased to 83% (run 12). In a similar way, by using 0.1 equivalent of *(R)*-**1**, **4b** was enantioselectively protonated to give *(R)*-**2b** in 68% ee (run 13).

A typical experimental procedure (Table 1, run 12) is as follows. A solution of MeLi-LiBr in ether (1.03 *M* in MeLi, 0.75 mL, 0.77 mmol) was added to **3a** (171.6 mg, 0.72 mmol) at room temperature, and the whole was stirred at this temperature for 90 min. Toluene (7 mL) was added, and the resulting mixture was cooled to -20 °C. A solution of *(R)*-**1** (46.0 mg, 0.144 mmol) in toluene (1.5 mL) was added, and the resulting clear solution was stirred at -20 °C for 40 min, and then at -78 °C for 20 min. Powdered succinimide (712 mg, 7.2 mmol) was added in one portion, and the resulting suspension was stirred at -78 °C for 1 hr. 10% aqueous citric acid (10 mL) was added to the reaction mixture, and the whole was extracted with ether (20 mL x 3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent to dryness under reduced pressure gave *(S)*-**2a** (103 mg, 90%) as a colorless liquid of 83% ee.[14]

Protonation can be carried out in a different way as follows (run 14). A solution of **4a** and LiBr was prepared from **3a** (612.3 mg, 2.63 mmol) and MeLi-LiBr in ether (1.03 *M* in MeLi, 2.76 mL, 2.84 mmol) followed by dilution with toluene (20 mL) as described above, and was added very slowly to a suspension of *(R)*-**1** (10.0 mg, 0.03 mmol) and powdered succinimide (995 mg, 10 mmol) in toluene (18 mL) at -78 °C during 5 hr using a microfeeder. Work-up as described above gave *(S)*-**2a** (383 mg, 91%) as a colorless oil of 54% ee.[14] The reason for the lower ee of *(S)*-**2a** in this case may be due to the amount of *(R)*-**1** (0.011 equiv. to **4a**), or to the partial racemization of *(S)*-**2a** because of the longer reaction time. However, this result may mean the necessity of forming the intermediate complex prior to the protonation. Details are under investigation.

In conclusion, it is shown that, in the presence of LiBr, catalytic enantioselective protonation of achiral lithium enolates (**4**), prepared from racemic 2-substituted-1-tetralones (*(RS)*-**2**), was achieved by using less than a stoichiometric amount of *(R)*-**1** and excess amount of proton sources that are solid and are not practically soluble in toluene.

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REFERENCES AND NOTES

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