Optically Active Lithium-Alkoxide Catalyzed Asymmetric Reduction of Imines with Trimethoxyhydrosilane

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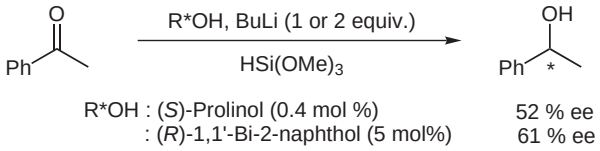
Abstract: Optically active lithium alkoxide catalyzed asymmetric reduction of imines with trimethoxhydroysilane in moderate enantioselectivity (up to 72% ee).

Key words: asymmetric reduction, lithium alkoxide, imine, solvent effect

Hydrosilanes have come into wide use in transition metal-catalyzed asymmetric hydrosilylation of carbon-carbon or carbon-heteroatom double bonds.[1] In 1986 we first found that in situ generated lithium alkoxide catalyzed reduction of carbonyl compounds with trialkoxysilanes.[2,3] We also found the reaction proceeded in diastereoselective and enantioselective manner[4] (Scheme 1). For example, reduction of acetophenone with dilithiosalt of (*S*)-prolinol (0.4 mol%) showed moderate enantioselectivity (52% ee) at room temperature. After that, some groups reported improvement of the system. Kagan et al. demonstrated that mono lithiosalt of (*R*)-1,1′-bi-2-naphthol (5 mol%) catalyzed the reduction of acetophenone at 0 °C with 61% ee.[5]

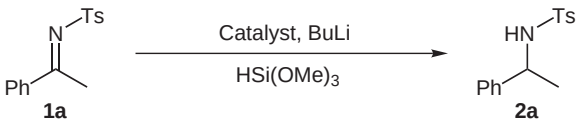


Scheme 1 Enantioselective reduction of acetophenone

We also found that lithium methoxide catalyzed reduction of imines with trimethoxyhydrosilane.[6] Thus, we expected that the method is able to apply for enantioselective reduction of imines.[7] In this paper, we describe the enantioselective reduction of imines with trimethoxyhydrosilane by using mono or dilithiosalts of optically active alcohols as catalyst.

At first, we examined the reaction of **1a** with catalysts using various dilithio salts in tetrahydrofuran (Table 1). Amino alcohols showed only poor enantioselectivity (entry 1–4). (*R*,*R*)-2,3-Butanediol and (*R*,*R*)-hydrobenzoin showed modest enantioselectivity of 28% ee and 32% ee, respectively (entry 5,6). Using tartrate-derived chiral 1,4-diol **3** (TADDOL, Figure 1), very poor enantioselectivity was shown (entry 7). In contrast, enantioselectivity was enhanced up to 57% ee by using (*R*)-1,1′-bi-2-naphthol **4** (entry 8). Then we carried out modification of **4** and examined the reaction. However, enantioselectivities were decreased to only low level (entry 9, 10). We also examined the reaction with monolithio salt of **4**. Contrary to the reduction of ketones,[5b] lower enantioselectivity of 36% ee than that of dilithiosalt of **4** was shown (entry 12).

Table 1 Asymmetric Reduction of Imine **1a** with Various Catalysts[a]



Entry	Catalyst	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	(*S*)-Isoleucinol	56	13	*S*
2	(*S*)-Valinol	28	13	*S*
3	(*S*)-Phenylalaninol	45	4	*S*
4	(*S*)-Prolinol	48	1	*S*
5	(*R*,*R*)-2,3-Butanediol	60	28	*R*
6	(*R*,*R*)-Hydrobenzoin	37	32	*R*
7	**3**	68	2	*R*
8	**4**	53	57	*R*
9	**5**	37	21	*R*
10	**6**	27	2	*R*
11[e]	(*R*)-Phenylethylalcohol	49	0	–
12[e]	**4**	70	36	*R*

[a] All reactions were carried out with 20 mol% of catalyst, 40 mol% of BuLi and 2 equiv of $(MeO)_3SiH$ at r.t. for 48 h in THF.
[b] Isolated yields.
[c] Determined by HPLC analysis using optically active column (DAICEL CHIRALPAK AD-H, hexane–2-propanol, 9:1).
[d] Configuration was determined by the comparison of the elution order with the authentic sample.
[e] The reaction was carried out in the presence of 20 mol% of BuLi.

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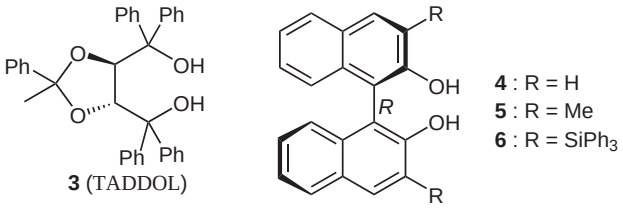


3 (TADDOL)

Figure 1

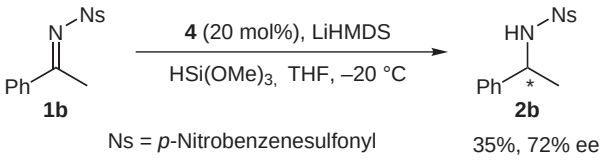
Next, we carried out optimization of the reaction condition by using dilithiosalt of **4** (base, solvent, additive and temperature, Table 2). Using lithium bistrimethylsilylamide (LiHMDS) in place of butyllithium, or adding *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in tetrahydrofuran, little influence was observed on enantioselectivity (entry 2, 5). We also carried out examination of counter cation effect. Using NaHMDS or KHMDS as base, only trace amounts of amine were observed (entry 3, 4). Contrary to tetrahydrofuran, noticeable solvent effect, reverse of the absolute configuration of the product, appeared by using diethyl ether that is less polar solvent (entry 9). Lithium bistrimethylsilylamide enhanced the enantioselectivity to 31% ee (entry 10). Moreover, addition of 2 equivalents of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine gave the product of opposite absolute configuration with moderate enantioselectivity of 59% ee (entry 11). We carried out further examination of other solvents, but more effective one was not found (entry, 8, 14, 15). We paid attention to the two solvent systems, which were tetrahydrofuran and diethyl ether–TMEDA, and examined temperature effect for each ones. In case of tetrahydrofuran, the reaction at lower temperature (0 °C) improved enantioselectivity up to 65% ee (entry 6). But the reaction at further lower temperature –20 °C), enantioselectivity was decreased (entry 7). The diethyl ether–TMEDA system at lower temperature, on the other hand, only modest enantioselectivities were shown (entry 12, 13). From these noticeable solvent and TMEDA effects, it is suggested that lithium cation deeply concern in the reaction, although the detailed reaction mechanism is not clear at present.[8]

Reduction of some other imines was also examined under optimized conditions, and the reduction of imine **1b** showed moderate enantioselectivity of 72% ee (Scheme 2).

Table 2 Asymmetric Reduction of Imine **1a**:[a] Effect of Base, Solvent, Additive, and Temperature

Entry	Base	Solvent	Additive	Temp (°C)	Yield (%)[b]	Ee[c] (%)	Config.[d]
1	BuLi	THF	–	r.t.	53	57	*R*
2	LiHMDS[e]	THF	–	r.t.	38	54	*R*
3	NaHMDS[f]	THF	–	r.t.	trace	–	–
4	KHMDS[g]	THF	–	r.t.	trace	–	–
5	BuLi	THF	TMEDA[h]	r.t.	52	51	*R*
6	BuLi	THF	–	0	43	65	*R*
7	BuLi	THF	–	–20	47	55	*R*
8	BuLi	DME	–	r.t.	44	25	*R*
9	BuLi	Et_2O	–	r.t.	30	12	*S*
10	LiHMDS[e]	Et_2O	–	r.t.	65	31	*S*
11	BuLi	Et_2O	TMEDA[h]	r.t.	63	59	*R*
12	BuLi	Et_2O	TMEDA[h]	0	75	19	*R*
13	BuLi	Et_2O	TMEDA[h]	–20	67	1	*R*
14	BuLi	*i*-Pr_2O	–	r.t.	28	6	*S*
15	BuLi	Toluene	–	r.t.	4	11	*S*

[a] All reactions were carried out with 20 mol% of **4**, 40 mol% of base and 2 equiv of $(MeO)_3SiH$ for 48 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using optically active column (DAICEL CHIRALPAK AD-H, hexane–2-propanol, 9:1).
[d] Configuration was determined by the comparison of the elution order with the authentic sample.
[e] LiHMDS = Lithium bistrimethylsilylamide.
[f] NaHMDS = Sodium bistrimethylsilylamide.
[g] KHMDS = Potasium bistrimethylsilylamide.
[h] Reaction was carried out in the presence of 2 equiv of TMEDA.



Scheme 2 Enantioselective reduction of Imine **1b**

Typical experimental procedure is exemplified with the reduction of imine **1a** with dilithio salt of **4** as chiral catalyst: To a solution of (*R*)-1,1′-bi-2-naphthol **4** (11.5 mg, 0.04 mmol) in dry THF (1.0 mL) was added BuLi (1.57 N in hexane solution, 51.0 μL, 0.08 mmol) under nitrogen, and stirred for 15 minutes. After stirred, this solution was cooled to 0 °C. To this solution were added trimethoxyhydrosilane (0.40 mmol, 55 μL) and imine **1a** (0.20 mmol, 54.7 mg), and the mixture was stirred for 72 hours at 0 °C. The reaction mixture was quenched with aqueous $NaHCO_3$ (0.1 N, 1.3 mL), extracted with diethyl ether, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give amine **2a** of 65% ee in 43% yield.

In conclusion, we were able to demonstrate that the lithium alkoxide-catalyzed enantioselective reduction system could be applied to imines in moderate enantioselectivity, and absolute configuration of product was switched by selection of solvents. Further investigation is in progress in our laboratory.

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(8) We have already found that diastereoselectivity was switched by selection of solvent in the reduction of α,β-epoxyketones. See ref.[4b]