Catalytic Asymmetric Benzylation of Achiral Lithium Enolates Using a Chiral Ligand for Lithium in the Presence of an Achiral Ligand

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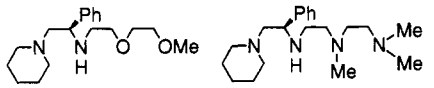
Asymmetric C–C bond formation at the α-position of carbonyl group has been the focus of great attention in synthetic organic chemistry.[1] In particular, enantioselective reactions of achiral lithium enolates with carbon electrophiles constitute the most desirable processes in the synthesis of optically active α-substituted carbonyl compounds.[2] We[3] and others[4–7] have reported enantioselective protonation,[3a,4] carboxylation,[5] alkylation,[3b,c,6] and aldol condensation[3d,7] of achiral lithium enolates using stoichiometric amounts of chiral ligands for Li as enantiocontrol elements. However, to date there has been no example of enantioselective lithium enolate reactions using a catalytic amount of chiral ligand for Li.[8,9] Recently, we reported an efficient enantioselective benzylation of lithium enolate **5** derived from 1-tetralone using a stoichiometric amount of chiral ligand **1** in the presence of lithium bromide (LiBr) in toluene to give (*R*)-2-benzyl-1-tetralone ((*R*)-**6**) in 92% enantiomeric excess (ee) with 89% isolated yield.[3c] In this reaction, the importance of the formation of a ternary complex, composed of lithium enolate **5**, chiral ligand **1**, and



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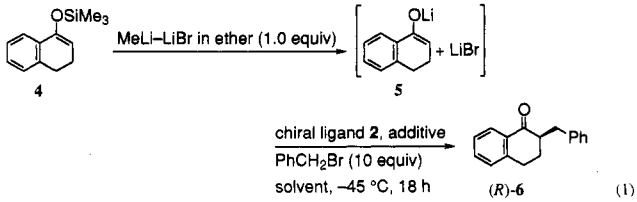
LiBr, for high asymmetric induction was indicated on the basis of the effect of added LiBr.[3c] In the course of developing this system, efforts were made to achieve a catalytic reaction. Here, we describe the first efficient enantioselective reaction of achiral lithium enolates using a *catalytic* amount of chiral ligand for Li. Highly enantioselective benzylation of lithium enolate **5** (in up to 96% ee with 76% yield) was achieved by using 5 mol % of chiral tetraamine ligand **2** together with a large excess of *N,N,N′,N′*-tetramethylpropanediamine (**3**) in the presence of LiBr.

Table 1. Enantioselective Benzylation of **5** with Chiral Ligand **2** in the Presence of TMEDA[a]

run	**2** (equiv)	TMEDA (equiv)	solvent	isolated yield (%)	ee (%)
1	1.0	0	toluene	56	97
2	0	0	toluene	<1	
3	0.2	0	toluene	<1	52
4	0.2	1.0	toluene	68	87
5	0.2	2.0	toluene	89	86
6	0.2	3.0	toluene	87	87
7	0.2	4.0	toluene	80	79
8	0.2	8.0	toluene	37	52
9	0	2.0	toluene	12	
10[b]	0.2	2.0	toluene	90	78
11	0.2	2.0	cyclopentane	38	50
12	0.2	2.0	ether	40	78
13	0.2	2.0	THF	42	77
14	0.2	2.0	DME	79	92

[a] The general experimental procedure is described in footnote 11. [b] The result from using a halide-free solution of MeLi in ether.[16]

Benzylation of lithium enolate **5** in the presence of LiBr, using a stoichiometric amount (1.0 equiv) of chiral tetraamine ligand **2**[10] in toluene by the procedure shown in eq 1,[11] afforded (*R*)-**6**[14] in 97% ee[15] with 56% isolated yield (Table 1, run 1). Without



(1)

a chiral ligand, the reaction proceeded little (<1% yield with 86% recovery of the desilylated starting material (1-tetralone); run 2). These results demonstrate that chiral tetradentate ligand **2**,

(1) For reviews, see: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983–1984; Vols. 2 and 3. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vols. 2 and 3.

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(9) (a) Gold-catalyzed aldol reaction, see: Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253. (b) For implications for catalysis in the aldol reaction, see: Pospisil, P. J.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1992**, *114*, 7585.

(10) For the synthesis of optically pure **2**, see: Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690.

(11) The general experimental procedure is as follows. Under argon atmosphere, trimethylsilyl enol ether **4** or **7** (1.0 mmol) was treated with a solution of methyllithium (MeLi) (1.0 equiv) in diethyl ether (ether) containing LiBr[12] at room temperature. The whole was stirred for 1.5 h to generate lithium enolate **5** or **9**. After addition of a solvent (7 mL), the whole was cooled to –20 °C. A solution of **2** (0.01–1.0 equiv) in a solvent (5 mL) and an achiral ligand were added successively, and the whole was stirred at –20 °C for 30 min and then cooled to –78 °C. A solution of benzyl bromide (10 equiv)[13] in a solvent (2 mL) was added at –78 °C. The reaction mixture was warmed to –45 °C and allowed to stand for 18 h at this temperature. After addition of 10% aqueous citric acid (10 mL), the product was isolated by the usual workup and purification [column chromatography (silica gel, hexane/ether)] to give pure (*R*)-**6** or (*R*)-**8** as a colorless oil.

(12) Purchased from Kanto Chemical Co., Inc.

(13) A 10-fold excess of benzyl bromide was used in order to obtain better yields.

(14) For the absolute configuration of (*R*)-**6**, see ref 3c.

(15) The ee values of (*R*)-**6** and (*R*)-**8** were determined by HPLC analysis using a chiral column (Waters Opti-Pak TA).

(16) Purchased from Aldrich Chemical Co., Inc.

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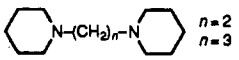
Table 2. Effect of Additives on Enantioselective Benzylation of **5** with a Substoichiometric Amount (0.2 equiv) of **2** in Toluene[a]

run	additive	isolated yield (%)	ee (%)
1	$Me_2NCH_2NMe_2$	<3	83
2[b]	$Me_2N(CH_2)_2NMe_2$ (TMEDA)	89	86
3	$Me_2N(CH_2)_3NMe_2$ (**3**)	83	92
4	$Me_2N(CH_2)_4NMe_2$	42	93
5		63	86
6		38	96
7	Me_2NEt	9	95
		9[c]	95[c]
8	$Me_2N(CH_2)_2N(Me)(CH_2)_2NMe_2$	87	47
9	$MeO(CH_2)_2OMe$ (DME)	15	86

[a] Experimental conditions: MeLi–LiBr in ether (1.0 equiv), **2** (0.2 equiv), additive (2.0 equiv), $PhCH_2Br$ (10 equiv), toluene, –45 °C, 18 h. The product was of the *R* configuration in all cases. [b] Table 1, run 5. [c] The result with 4.0 equiv of Me_2NEt.

as well as **1**, accelerates the reaction of lithium enolate **5**. Surprisingly, reducing chiral ligand **2** to a substoichiometric amount (0.2 equiv) gave a yield of only <1% with 87% recovery of 1-tetralone (run 3). The chiral ligand **2** was recovered almost quantitatively (94%) without any loss of optical purity after the reaction. For this unexpected suppression of the reaction, we have considered the following explanation. Chiral ligand **2** is inactivated by complexation with LiBr (presumably in 1:2 stoichiometry) because of the presence of LiBr in large excess relative to **2** at the beginning of benzylation. Therefore, *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was added with the intention of trapping LiBr. Both the yield and ee were then increased greatly (runs 4–8). The best results were obtained by using 2.0 or 3.0 equiv of TMEDA. TMEDA alone gave a poor yield (run 9). The ee decreased substantially when LiBr was absent at the beginning of benzylation (run 5 vs 10). The yield and ee were found to be dependent on the solvent used (runs 5 and 11–14). Toluene and 1,2-dimethoxyethane (DME) were most effective.

The effect of various achiral additives (2.0 equiv) on benzylation of **5** with 0.2 equiv of **2** in toluene was examined. The results are shown in Table 2. Of linear terminal diamines (runs 1–4), TMEDA and **3** were found to be excellent additives with respect to both yield and ee, probably because they trap LiBr effectively by the formation of a five- or six-membered chelated structure with the Li^+ ion. Changing the two dimethylamino groups to the more hindered piperidino groups gave poorer yields, while the ee values remained high (run 2 vs 5 and run 3 vs 6). The results using monodentate or tridentate ligands as isostructural analogues of TMEDA (run 7 and 8, respectively) suggest that the bidentate ligands function more effectively. DME, which is an isostructural oxygen ligand of TMEDA, decreased the yield substantially (run 9).

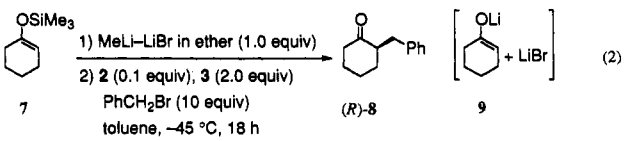
Since achiral ligand **3** was found to be most effective as an additive, the effect of decreasing the amount of **2** was examined to achieve a *catalytic* reaction. The results obtained with 2.0 equiv of **3** in toluene or in DME are summarized in Table 3. In both toluene (runs 1–4) and DME (runs 5–8), good yield and high ee were retained up to 0.05 equiv of **2**. The ee was maximal (96% ee) at 0.05 equiv of **2** in toluene (run 3). The higher yields obtained in DME compared to those obtained in toluene (runs 1–4 vs runs 5–8; compare also Table 1, runs 1–3 and Table 3, runs 9–11) may be due to a lower aggregation state of lithium enolate **5** attained by a stronger solvent–Li interaction. The enhancement of the reactivity of **5** by chiral ligand **2** (run 1 vs 2 in Table 1; run 9 vs 10 in Table 3) could be ascribed to the same factor.

Table 3. Enantioselective Benzylation of **5** with a Catalytic Amount (~0.01 equiv) of **2** in the Presence of **3** in Toluene or in DME[a]

run	**2** (equiv)	**3** (equiv)	solvent	isolated yield (%)	ee (%)
1[b]	0.2	2.0	toluene	83	92
2	0.1	2.0	toluene	78	95
3	0.05	2.0	toluene	76	96
4	0.01	2.0	toluene	29	89
5	0.2	2.0	DME	86	92
6	0.1	2.0	DME	91	93
7	0.05	2.0	DME	91	90
8	0.01	2.0	DME	55	48
9	1.0	0	DME	92	94
10	0	0	DME	28	
11	0.2	0	DME	82	82

[a] Experimental conditions: MeLi–LiBr in ether (1.0 equiv), **2** and/or **3**, $PhCH_2Br$ (10 equiv), solvent, –45 °C, 18 h. The product was of the *R* configuration in all cases. [b] Table 2, run 3.

We tried to extend this catalytic reaction to lithium enolate **9** derived from cyclohexanone. The experiment with trimethylsilyl enol ether of cyclohexanone (**7**) as a substrate and 0.1 equiv of **2** in toluene under conditions similar to those described for reactions of **4**[11] afforded (*R*)-2-benzylcyclohexanone[17] ((*R*)-**8**) in 52% yield and 90% ee[15] (eq 2). This result demonstrates that chiral ligand **2** also functions as a catalyst in benzylation of **9**.



7 (*R*)-**8** **9** (2)

The results described above evidently indicate that chiral ligand **2** turns over efficiently by addition of achiral ligand **3** to achieve highly enantioselective benzylation with a *catalytic* amount (~0.05 equiv) of **2**. We speculate that the role of **3** is to prevent inactivation of **2** by trapping LiBr, which exists in large excess relative to **2** at the beginning of benzylation and is generated as benzylation proceeds. Since chiral ligand **2** is a tetradentate ligand and the presence of LiBr from the beginning gave a higher enantioselectivity (*vide supra*), the reactive intermediate that is most effective for asymmetric induction is assumed to be a chiral ternary complex formed between a lithium enolate (**5** or **9**), chiral ligand **2**, and LiBr. Realization of good yields and high enantioselectivities despite the presence of 20–40 times as much quantity of **3** (2.0 equiv) as **2** (0.1–0.05 equiv) demonstrates that the enhancement of the reactivity of **5** or **9** by tetradentate chiral ligand **2** is much greater than that by bidentate achiral ligand **3** and supports that the chiral ternary complex mentioned above should be reactive.

In conclusion, we have found a novel catalytic system for enantioselective benzylation of lithium enolates, mediated by the chiral tetraamine ligand for Li. This finding is remarkable in the following sense. (1) This is the first efficient, catalytic asymmetric reaction of achiral lithium enolates using a chiral ligand for Li. (2) The good yields and high enantioselectivities of the present reaction are based on a marked acceleration of the reaction by the chiral auxiliary. (3) A highly enantioselective catalytic system has been developed for an alkylation reaction, which is one of the most versatile types of reactions. The strategy mentioned here should provide a superior and useful method for the preparation of optically active α-alkyl cyclohexanone and related compounds.

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