Controlling Factors in Chiral Bisoxazoline-Catalyzed Asymmetric Lithium Ester Enolate–Imine Condensation Producing a β -Lactam

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A catalytic amount of external chiral bisoxazoline ligand **3a** bearing an isopropyl group as a stereocontrolling group catalyzed a reaction of a lithium ester enolate **4b**, generated from 3-pentyl 2-methylpropionate, with benzaldehyde anisidine-imine **5** to afford corresponding β -lactam **6** in higher 70% ee than that obtained by the reaction using a stoichiometric amount of the ligand. A bulkier ligand **3d** bearing a phenyl group gave 81% and 6% ees in stoichiometric and catalytic reactions, respectively. Examination of the varying factors suggested the involvement of mixed aggregates as a reactive species. A working model is presented for prediction of the sense of asymmetric induction.

Key words asymmetric reaction; catalysis; enolate; oxazoline

Condensation of a lithium ester enolate with an imine through an addition–elimination sequence is the established synthetic methodology of a β -lactam.¹⁾ Diastereoselective asymmetric reactions have been developed using chiral enolates or chiral imines.²⁾ Although asymmetric reactions of achiral silyl enol ethers with achiral imines have been reported using chiral promoters,³⁾ an asymmetric reaction of an achiral lithium ester enolate with a prochiral imine by an external chiral ligand methodology⁴⁾ has been the subject undeveloped.⁵⁾ We have already reported asymmetric condensation of a lithium ester enolate with an imine, which was mediated by binary as well as ternary complex reagents.⁶⁾ These reagents are constituted from two components of a lithium enolate and a chiral diether **1**⁷⁾ or an aminodiether ligand, and three components⁸⁾ of an enolate, a chiral ligand, and an achiral lithium amide, respectively. The external ligand methodology has been shown useful in synthesis of pharmaceutically active compounds.⁹⁾ During our efforts directed towards development of more efficient ligands, we found that a chiral bisoxazoline (Box) ligand **3** catalyzed asymmetric condensation of lithium ester enolate **4** with an imine **5** to afford β -lactam **6** in high enantiomeric excess (ee).¹⁰⁾ Unexpected behavior of the Box ligand was that the reaction, which uses a catalytic amount of Box, afforded the corresponding β -lactam **6** in higher ee than that obtained by the reaction using a stoichiometric amount of the ligand. The structural features of the Box ligand **3** crucially govern such efficiency of the reaction. As a continuing effort to determine critical controlling factors of the reaction, we studied the reaction systematically concerning equivalency, structure of the Box ligand, and involvement of co-products of the reaction.¹¹⁾ We describe herein the full detail of our study directed towards deeper understanding of chiral Box ligand behavior.¹²⁾

Catalytic Asymmetric Reaction of Lithium Ester Enolate **4** The lithium ester enolate **4b** ($R^2 = \text{CH}(\text{Et})_2$) was generated *in situ* by lithium diisopropylamide (LDA) treatment of 3-pentyl 2-methylpropionate in toluene. Reaction of 2 eq of **4b** with benzaldehyde anisidine-imine **5** was mediated by 2.6 eq of **1** in toluene at -20°C for 7 h to afford (+)-**6** in 95% yield (Table 1, entry 1). The ee was determined to be 60% by HPLC analysis using a chiral stationary phase col-

umn (DAICEL Chiralcel OD, iso-PrOH/hexane=1/100).^{8c)} The same reaction at 0°C for 5 h using 0.1 eq of **1** gave (+)-**6** in 99% yield and 45% ee (entry 2). Although it was surprising to find that the ether ligand **1** catalyzed the reaction and afforded **6** in 45% ee, the efficiency of the catalytic reaction is apparently inferior to that of the stoichiometric reaction. The Box ligand **2** was a poor stoichiometric ligand and afforded (–)-**6** in only 10% ee (entry 3). We were very pleased to find that two stoichiometric Box ligands **3b,c** bearing bulky phenyl and *tert*-butyl groups as R^1 gave (–)-**6** in 81% and 75% ees (entries 4, 6). However, it was again very disappointing to learn that the catalytic reactions using 0.1 eq of **3b,c** proceeded at higher temperature to give **6** in miserable 6% and 26% ees (entries 5, 7). The poor efficiency of **3b,c** in the catalytic asymmetric induction and rate acceleration is attributable to the bulkiness of R^1 , which prevents formation of a chelate with lithium enolate **4b** to allow the racemic reaction.

We next examined a Box ligand **3a**¹³⁾ bearing a smaller iso-Pr group as R^1 . Enantioselectivity was moderate, 56% ee. However, it was very surprising to find that the reactions using 0.2 and 0.1 eq of **3a** proceeded at -20°C , the same temperature as the stoichiometric reaction, and gave (–)-**6** in 70% and 69% ees apparently higher than that obtained in the stoichiometric reaction (entries 8–10). The size of a base affected the enantioselectivity to afford **6** in 45% ee when lithium cyclohexyl-isopropylamide (LICA) was used as a lithiation reagent (entry 11). A catalytic amount of **3a** gave **6** in higher 55% ee than that of stoichiometric reaction (entry 12).

Fig. 1. Lithium Enolate–Imine Condensation Using a Chiral Ligand

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Dedicated to the memory of Dr. Kyosuke Tsuda.

Table 1. Asymmetric Reaction of **4** with **5** Catalyzed by **1**–**3** Giving (–)-**6**

Entry	1 – 3	R ¹	Eq	4	R ²	Base	Temp/°C	Time/h	Yield/%	Ee/%
1	1		2.6	b	CH(Et) ₂	LDA	–20	7	95	60 ^{a)}
2			0.1			LDA	0	5	99	45 ^{a)}
3	2		2.6			LDA	0	1	99	10
4	3c	Ph	2.6			LDA	–20	5	99	81
5			0.1			LDA	20	4	99	6
6	3b	<i>tert</i> -Bu	2.6			LDA	0	1	97	75
7			0.1			LDA	20	4	95	26
8	3a	iso-Pr	2.6			LDA	–20	2	99	56
9			0.2			LDA	–20	4	96	70
10			0.1			LDA	–20	4	92	69
11			2.6			LICA	–20	2	90	45
12			0.2			LICA	–20	4	96	55
13			2.6	a	iso-Pr	LDA	0	1	91	45
14			0.2			LDA	0	2	94	65
15			2.6	c	CH(iso-Pr) ₂	LDA	–20	2	98	58
16			0.1			LDA	–20	4	95	12

a) The enantiomer (+)-**6** was obtained.

Table 2. Influence of the Equivalency of **3a** on Asymmetric Reaction of **4b** at –20 °C Giving (–)-**6**^{a)}

Entry	3a /eq	Time/h	Yield/%	Ee/%
1	4.0	2	70	37
2	2.6	2	99	56
3	1.0	2	99	66
4	0.5	3	96	65
5	0.2	4	95	70
6	0.1	4	92	69
7	0.05	5	81	58
8	0.01	5	62	50

a) Two eq of **4b** were used.

The size of the alkoxy group of **4** was also one of the influencing factors. The reaction of **4a** bearing the less bulky isopropoxy group was catalyzed by 0.2 eq of **3a** to afford (–)-**6** in 65% ee, which was higher than 45% ee of the reaction using 2.6 eq of **3a** (entries 13, 14). On the other hand, the reaction of **4c** bearing the bulkiest alkoxy group gave **6** in a significantly lower 12% ee than the 58% ee obtained by the stoichiometric reaction (entries 15, 16). These clearly indicate that a complex formation of lithium enolate **4** with **3** and other species is dependent on the bulkiness of components and is likely when bulkiness is moderate as shown by **4a**, **b** and **3a**.

Unexpected Dependency of Enantioselectivity on the Amount of **3a** We then examined the same reaction of **4b** with **5** using varying amounts of **3a** from 4 eq to 0.01 eq. It was surprising to find that 0.01 eq of **3a** catalyzed the reaction at –20 °C for 5 h, producing **6** in 50% ee higher than that obtained using 4 eq of **3a** (Table 2, entries 1, 8). The ee of **6** increased up to 70% from 37% along with a decrease of **3a** from 4.0 to 0.2 eq. It was maintained at 70–65% with 1 to 0.1 eq of **3a**, and then with 0.05 eq dropped to 58%, which was still higher than that obtained using 2.6 eq of **3a**. It is also important to note that prolonged reaction time was required for the completion of the reaction with a catalytic amount of **3a**.

Some Factors Affecting the Catalytic Asymmetric Reaction The unexpected behavior of Box ligand **3a** was apparently governed by the steric factors of **3** and **4**. A lesser

Fig. 2. Generation of Lithium Enolate from **7** and Condensation

Fig. 3. Controlling Factors of Asymmetric Reaction of Lithium Enolate

catalytic amount of **3a** than of **4b** gave **6** in the higher ee than did equal equivalents of **3a** and **4b**. Therefore, it is probable that the reactive enolate species involve **3**, **4**, and several other components such as a small amount of LDA, diisopropylamine (DIA), product **6**, the resulting lithium amide intermediate **9**, and lithium alkoxide **10** generated *in situ* through the reaction. Then, we compared %ees of **6** obtained in the stoichiometric reactions quenched after 2 h and 0.05 h, respectively, and found that there was no significant difference in them (Table 3, entries 1, 2). However, in the catalytic reactions, at the 27% conversion we observed the lower 65% ee than 70% ee at the full conversion (entries 3, 4). These results suggest involvement of some co-products as components of the reactive enolate species.

The previously developed ternary complex reagent, for example, **3a**–**4b**–LDA,⁸⁾ was ruled out. The reaction using 2 eq of **4b**, 2.6 eq of **3a**, and 2.4 eq of LDA afforded **6** in lower 43% ee than that obtained in the absence of such large excess of LDA (Table 3, entry 8). The effects of LDA and diisopropylamine on enantioselectivity were determined using a lithium enolate generated free from these species. Thus, the enolate **4b** was generated from a silyl enol ether **7** by treatment with butyllithium in diethyl ether. The stoichiometric and catalytic reactions of **4b** thus generated afforded **6** in

Table 3. Asymmetric Reaction of **4b** with **5** Catalyzed by Box **3a** Giving (–)-**6**^{a)}

Entry	Type	3a eq	LDA eq	DIA eq	10 eq	6 eq	Time h	Yield %	Ee %
1	Box–enolate	2.6	0.2	2.0	0	0	2	99	56
2		2.6	0.2	2.0	0	0	0.05 ^{b)}	47	54
3		0.2	0.2	2.0	0	0	4	96	70
4		0.2	0.2	2.0	0	0	0.1 ^{b)}	27	65
5		2.6	0	0	0	0	2	99	53 ^{c)}
6		0.2	0	0	0	0	4	86	48 ^{c)}
7		0.2	0.2	2.0	0	0	4	97	37 ^{d)}
8	Box–enolate–LDA	2.6	2.4	2.0	0	0	1	75	43
9	Box–enolate–alkoxide	2.6	0.2	2.0	2.4	0	2	86	42
10	Box–enolate–lactam	0.2	0.2	2.0	0	0.2	0.5 ^{b)}	80	62
11	Enolate–lactam	0	0.2	2.0	0	0.2	4	50	1

a) Initial equivalent was described. b) The reaction was quenched at the indicated reaction time. c) The lithium enolate **4b** was generated by treating a silyl enol ether **7** with butyllithium in ether. Therefore, the solvent for asymmetric reaction was a mixture of toluene and ether (8:3). d) Toluene–ether (8:3).

Fig. 4. Models for Probable Asymmetric Induction

53% and 48% ees, respectively (entries 5, 6). Since the reaction of **4b**, generated by LDA treatment of **8**, in the same toluene–ether (8:3) mixture as a solvent gave **6** in lower 37% ee than that obtained above, LDA and diisopropylamine unfavorably affect efficiency (entry 7). The effect of lithium alkoxide **10** was also unfavorable to afford **6** in 42% ee (entry 9). Co-existence of **6** significantly affected the efficiency. In the presence of 0.2 eq of optically pure (–)-**6**, the catalytic reaction proceeded rapidly to afford, after 0.5 h, 80% yield of **6** in 62% ee (entries 3, 10). In the absence of Box **3a**, the reaction was not rapid, and after 4 h gave 50% yield of **6** in marginal ee (entry 11). These reactions suggest that a ternary type complex reagent, constituted from **3a**, **4a**, and **6**, is involved in the asymmetric reaction as a reactive species.

Probable Models for Asymmetric Induction The asymmetric reaction mediated by chiral Box ligands **3** always gave (–)-**6**. Although the reactive enolate species are not simple, it is useful to present a fundamental mechanistic model for the sense of asymmetric induction. Models **11** and **12** are constructed based on a six-membered transition state hypothesis for an enolate–imine condensation. Two nitrogen atoms of Box **3a** coordinate to the lithium atom of the enolate to form a six-membered chelate. The stereocontrolling isopropyl group of a Box interferes with a phenyl group of **5** as shown in **12**. While, model **11** is free from such severe steric interference. Based on the above working hypothesis, model **11** predicts production of (–)-**6** that is really the preferential product of the asymmetric reaction.

Conclusion

Although the enantioselectivity is not extremely high, we believe that the catalytic asymmetric reaction demonstrated here will a promising approach to the efficient catalytic carbon–carbon bond forming reaction. Further studies directed

toward structural elucidation of the active species and structural tuning of the chiral ligand for the improvement of efficiency are in progress in our laboratories.

Experimental¹⁴⁾

Catalytic Asymmetric Reaction Controlled by **3a (Table 1, Entry 9)** A solution of 3-pentyl 2-methylpropionate **8** (316 mg, 2.0 mmol) and **3a** (53 mg, 0.2 mmol) in toluene (3 ml) was added to a solution of LDA (2.2 mmol) in toluene (5 ml) at –78 °C. The mixture was stirred for 1 h and to this solution was then added a solution of imine **5** (211 mg, 1.0 mmol) in toluene (3 ml). After stirring at –20 °C for 4 h, brine (20 ml) was added and the mixture was extracted with EtOAc (30 ml×3). The organic layer was washed with brine and then dried over Na₂SO₄. Concentration followed by purification through silica gel column chromatography (ether/hexane=1/5, then ether) gave (–)-**6** (268 mg, 96%) as a colorless solid of mp 97–99 °C and $[\alpha]_D^{25}$ –95.3 (*c*=1.02, CHCl₃). Ee was determined by HPLC analysis to be 70% (Daicel Chiralcel OD-H, hexane–iso-PrOH (100:1), 1.0 ml/min, 250 nm, 12 min (85%, R); 15 min (15%, S)). Spectral data were identical with those reported previously.^{8c)}

[1-(1-Ethylpropoxy)-2-methylpropenyloxy]trimethylsilane (7**)** Chlorotrimethylsilane (8.28 ml, 65 mmol) was added to a cooled solution of LDA, prepared from 8.22 ml (59 mmol) of diisopropylamine and 34.1 ml of butyllithium solution in hexane (55 mmol), in 80 ml of THF at –78 °C. Then, 3-pentyl 2-methylpropionate (8.0 g, 51 mmol) in THF (5.5 ml) was added dropwise over 5 min, and the mixture was allowed to warm up to room temperature. The whole was stirred for 1 h and then diluted with 1.6 l of pentane. Concentration followed by distillation (69 °C, 9 mmHg) gave **7** as a pale yellow oil (8.74 g, 93%). ¹H-NMR (CDCl₃, 90 MHz) δ: 0.20 (9H, s, TMS), 0.90 (6H, t, *J*=7.5 Hz, Me), 1.30–1.73 (10H, m), 3.85 (1H, quint, *J*=6.3 Hz). ¹³C-NMR (CDCl₃, 67.8 MHz) δ: 0.16 (q, TMS), 9.31 (q, Me), 16.70 (q, Me), 17.20 (q, Me), 24.78 (t, CH₂), 74.24 (d, CH), 91.95 (s), 146.42 (CO). IR (neat): 1710 cm^{–1}. MS *m/z*: 230 (*M*⁺). HR-MS *m/z*: Calcd for C₁₂H₂₆O₂Si: 230.1703. Found. 230.1716.

Asymmetric Reaction Starting from Silyl Enol Ether **7 Controlled by **3a** (Table 3, entry 5)** To silyl enol ether **7** (506 mg, 2.2 mmol) in Et₂O (3 ml) was added butyllithium (1.24 ml, 1.61 N, 2.0 mmol) at –78 °C. The mixture was stirred for 1 h at room temperature. To this suspension was added a solution of **3a** (691 mg, 2.6 mmol) in toluene (5 ml) at –78 °C. After stirring for 1 h at –20 °C, a solution of **5** (211 mg, 1.0 mmol) in toluene (3 ml) was added at –78 °C. After stirring of pale yellow solution for 2 h at –20 °C, brine (20 ml) was added and the whole was extracted with EtOAc (20 ml×3). The organic layer was washed with brine (10 ml), and then dried over Na₂SO₄. Concentration followed by purification through silica gel column chromatography (ether/hexane=1/5, then ether) gave (–)-**6** (281 mg, 99%) as a colorless solid of mp 93–98 °C and $[\alpha]_D^{25}$ –72.7 (*c*=1.35, CHCl₃). Ee was determined to be 53%.

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