Unexpected Catalytic Behavior of Chiral Bisoxazoline in Asymmetric Reaction of Lithium Ester Enolate with Imine

Takeshi KAMBARA and Kiyoshi TOMIOKA*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606–8501, Japan.

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Reaction of a lithium ester enolate with benzaldehyde anisidine-imine was catalyzed by a catalytic amount of bisoxazoline ligand to afford the corresponding β-lactam in higher ee than that obtained by the reaction using a stoichiometric amount of the ligand. Investigation of the varying factors suggested the involvement of steric factors.

Key words asymmetric reactions; catalysis; enolates; oxazolines

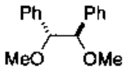
A catalytic asymmetric reaction of a lithium ester enolate[1] relies on a chiral external ligand.[2,3] We have been involved in the stoichiometric and catalytic asymmetric reactions with imine based on a complex formation with a chiral diether ligand **1**.[4,5] As part of our studies along this line,[6] we describe herein how the chiral bisoxazoline (Box) ligand **2** catalyzed the condensation reaction of a lithium ester enolate with imine to afford the corresponding β-lactam **5** in up to 81% ee.[7] Furthermore, the efficiency of the reaction using a catalytic amount of **2** was highly dependent on the steric features to give **5** in up to 70% ee.

The lithium ester enolate **3b** was generated *in situ* by LDA treatment of 3-pentyl 2-methylpropionate in toluene. Reaction of 2 equivalents of **3b** with benzaldehyde anisidine-imine **4** was mediated by 2.6 equivalents of *i*-Pr-Box **2a**[8] in toluene at −20 °C for 1.5 h to afford **5** in 99% yield and 56% ee (Table 1, entry 3).[9] The box **2a** was recovered quantitatively for reuse without loss of optical purity. Since the same reaction mediated by **1** took 7 h for completion to afford *ent*-**5** in 60% ee,[6] **2a** apparently activated **3b** much more efficiently than **1** did. However, a stoichiometric amount of more bulky *t*-Bu-**2b** and Ph-**2c** mediated the same reaction at a higher temperature or for a longer reaction time to afford **5** quantitatively in 75% and 81% ees (entries 5, 7). The higher selectivity and weaker activation observed using **2b** and **2c** rather than **2a** indicate that formation of a reacting complex between **2** and **3b** is sterically affected, and needs a higher reaction temperature and longer reaction time.

We examined the same reaction of **3b** with **4** using a catalytic amount of **2a**. It was surprising to find that 0.1 equivalent of **2a** catalyzed the reaction at −20 °C for 4 h, producing **5** in 69% ee higher than that obtained using 2.6 equivalents of **2a** (entries 3, 4). The results obtained using various catalytic amounts of **2a** are summarized in Fig. 1. The ee of **5** increased to 70% from 56% along with a decrease in the amount of **2a** from 2.6 to 0.2 equivalents. It was maintained at 70—65% with 1 to 0.1 equivalents of **2a**, and then with 0.06 equivalents dropped to 58%, which was still higher than that obtained using 2.6 equivalents of **2a**. Interestingly, such a catalytic effect on enantioselectivity was not observed using 0.1 equivalent of the more bulky **2b** and **2c** giving **5** in 26% and 6% ees (entries 6, 8).

Variation of the alkoxy group of **3** was also an influencing factor. The reaction of **3a** bearing the less bulky isopropoxy group was catalyzed by 0.2 equivalent of **2a** to afford **5** in 65% ee, which was higher than 45% ee of the reaction using 2.6 equivalents of **2a** (entries 1, 2). On the other hand, the reaction of **3c** bearing the most bulky alkoxy group gave **5** in a significantly lower 12% ee than the 58% ee obtained by the stoichiometric reaction (entries 9, 10).

The unexpected behavior of Box ligand **2** was apparently governed by the steric factor of **2** and **3**. The catalytic amount of **2a** less than the amount of **3b** gave **5** in the higher ee than equal equivalents of **2a** and **3b** did. Therefore it is probable that the reactive enolate species involve **2**, **3**, and several other components such as the resulting lithium amide intermediate, **5**, and lithium alkoxide generated *in situ* through the reaction.[10] However, the previously developed ternary



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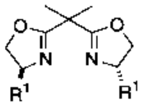
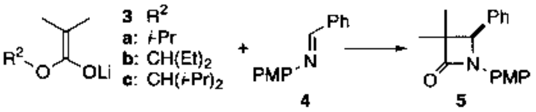


BOX
2 R^1
a: *i*-Pr
b: *t*-Bu
c: Ph



3 R^2
a: *i*-Pr
b: CH(Et)$_2$
c: CH(*i*-Pr)$_2$

4 **5**

Table 1. Asymmetric Reaction of **3** with **4** Catalyzed by **2** Giving **5**

Entry	2	R^1	2/equiv	3	R^2	Temp/°C	Time/h	Yield/%	ee/%
1	**a**	*i*-Pr	2.6	**a**	*i*-Pr	0	1	91	45
2	**a**		0.2			0	2	94	65
3	**a**		2.6	**b**	CH(Et)$_2$	−20	2	99	56
4	**a**		0.1			−20	4	92	69
5	**b**	*t*-Bu	2.6			0	1	97	75
6	**b**		0.1			20	4	95	26
7	**c**	Ph	2.6			−20	5	99	81
8	**c**		0.1			20	4	99	6
9	**a**	*i*-Pr	2.6	**c**	CH(*i*-Pr)$_2$	−20	2	98	58
10	**a**		0.1			−20	4	95	12

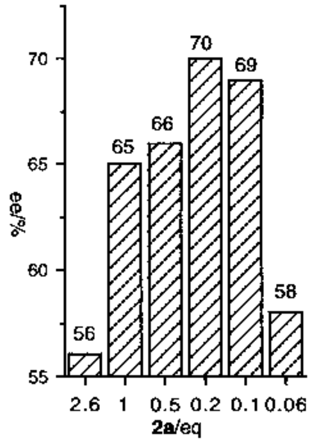


Fig. 1. The %ee of **5** and Equivalent of **2a** in the Reaction of **3b** with **4**

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* To whom correspondence should be addressed.

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complex reagent,[6] for example, **3**-**2**-LDA, was ruled out. The reaction using 2 equivalents of **3b**, 2.6 equivalents of **2a**, and 2.4 equivalents of LDA afforded **5** in 43% ee lower than those obtained in the absence of excess of LDA (Fig. 1).

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.

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10) Involvement of the Box ligand **2a** and the lithium enolate **3b** in a ratio of 1: over 2 may not be ruled out at the present time.