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A Factor Affecting Enantioselective Reaction of A Ternary Complex of Lithium Ester Enolate with Imine

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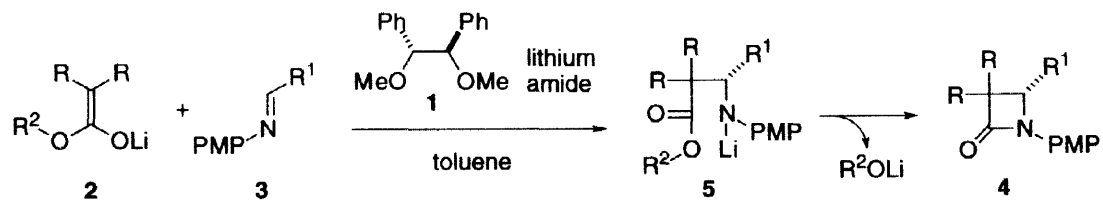
Abstract: Systematic investigation of the varying size of the alkoxy moiety of the lithium ester enolates in the chiral ligand mediated reaction with imines led to the improvement of the enantioselectivity of β-lactam products in up to 93%. The asymmetric induction step was indicated to be the addition step, not the cyclization step.

Lithium ester enolate is among the established, powerful carbonucleophiles in the formation of carbon-carbon bonds.[1] The promising application of the reagent into asymmetric reactions relies on a chiral external ligand, which opens a catalytic way to an asymmetric reaction.[2] We have been involved in the stoichiometric and catalytic asymmetric reactions of lithium ester enolates **2** with imines **3** based on a ternary complex reagent, which comprises three components; a chiral ether ligand **1**, an achiral lithium amide, and **2**, giving the corresponding β-lactams **4** in high enantiomeric excess (ee).[3,4]

The production of β-lactam **4** involves (1) an addition of enolate **2** to the azomethine carbon of **3** and (2) subsequent intramolecular nucleophilic attack of nitrogen to the carbonyl carbon of the ester **5** to eliminate lithium alkoxide. The alkoxy moiety of **2** is placed close to the reaction site in each step and its elimination from **5** put the equilibrium forcing the cyclization to **4**. Consequently, survey of the alkoxy moiety is expected to shed light on the asymmetric induction and also to improve the enantioselectivity. We describe herein the systematic examination of the alkoxy moiety of **2** and improvement of enantioselectivity of the reaction of the ternary complex.



Reactions of benzaldehyde imine **3** (R^1 = Ph, PMP = 4-methoxyphenyl) with eight variations of lithium ester enolate **2** (R = Me)[5] having the alkoxy moiety (R^2O) of varying size from methoxy to *tert*-butoxy were examined with use of lithium isopropylcyclohexylamide (LICA) and the chiral ligand **1** in toluene at –45 °C as summarized in Table 1.[6] The reactivity of the ternary complex is nearly independent on the size of the

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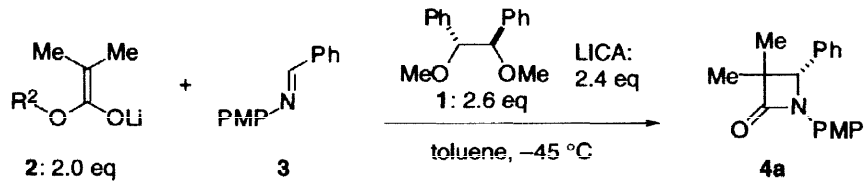
alkoxy moiety (entry 1-7), excepting *tert*-butoxy group which retards the reaction (entry 8). The enantioselectivity of **4a** (R = Me, R^1 = Ph) was determined by chiral stationary phase HPLC.[7] The enantioselectivity is apparently dependent on the size of the alkoxy moiety. The three primary alkoxy and isopropoxy groups exhibited the same level of enantioselectivity of 83-85% (entry 1-3, 5). Neopentoxy, 3-pentoxy, and 2,4-dimethyl-3-pentoxy groups exhibited the highest level of ee, 88-91% (entry 4, 6, 7). These alkoxy moiety effects are exhibited at the addition step, not at the cyclization step as shown below.

Table 1. Alkoxy Moiety Effect on Asymmetric Reaction of Ternary Complex with Imine **3** (R^1 = Ph)

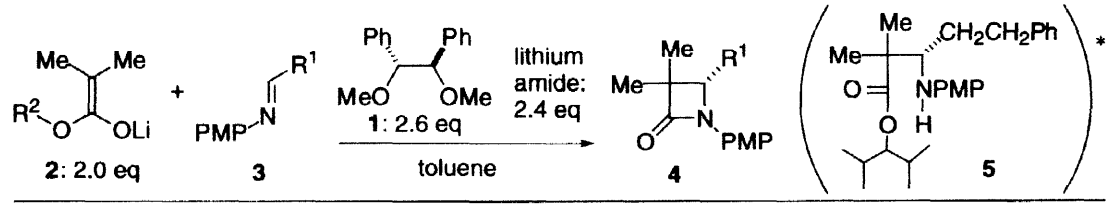


entry	R^2	time/h	ee%	yield%	entry	R^2	time/h	ee%	yield%
1	Me	3	83	77	5	*i*-Pr	2	85	80
2	Et	3	85	90	6	Et_2CH	3	88	85
3	Hex	4	84	96	7	*i*-Pr_2CH	2	91	79
4	*t*-$BuCH_2$	2	89	90	8	*t*-Bu	3	85	31

It is important to note that the reaction of a binary complex, lithium ester enolate **2** (R = Me, R^2 = 2,4-dimethyl-3-pentyl) and **1** in the absence of additional LICA at the higher temperature gave **4a** in lower ee.

We then examined effects of the alkoxy moiety on the reactions of the ternary complex with imines **3** bearing R^1 = phenyl, 4-methoxyphenyl, 2-naphthyl, and phenylethyl substituents as shown in Table 2.

Table 2. Asymmetric Reaction of Ternary Complex with Imine **3**



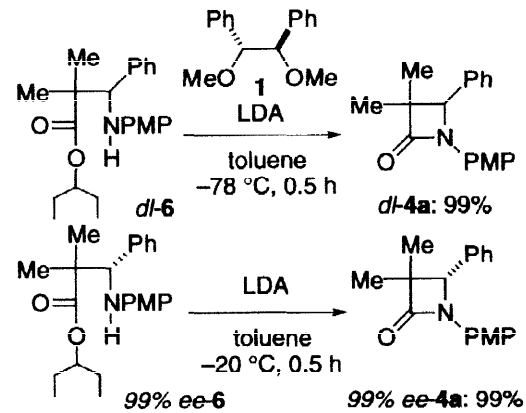
entry	R^2	R^1	lithium amide	temp/°C, (time/h)	ee%	yield%
1	*i*-Pr_2CH	Ph	LICA	–78 (9), –25 (0.5)	92	74
2	Et_2CH			–60 (5)	88	85
3	*i*-Pr_2CH	PMP	LICA	–45 (24)	91	70
4	Et_2CH			–50 (20)	79	70
5	*i*-Pr_2CH	2-Naph	LICA	–60 (24), –45 (15)	93	82
6	Et_2CH			–50 (15)	90	85
7	*i*-Pr_2CH	$Ph(CH_2)_2$	LDA	–78 (1)	86, 90*	18, 41*
8	Et_2CH			–78 (1)	90	80

Generally, 2,4-dimethyl-3-pentyl ester afforded **4** in ee of over 90% (entry 1, 3, 5, 7) higher than 3-pentyl ester (entry 2, 4, 6, 8).[8]

It is interesting that the adduct **5** was not observed by tlc in the reaction of 3-pentyl ester, however, **5** was observed in the reaction of 2,4-dimethyl-3-pentyl ester. Therefore, the reaction of 2,4-dimethyl-3-pentyl ester enolate was conducted at the lower temperature until consumption of **3** by monitoring tlc and was then allowed to warm up to complete cyclization to **4** (entry 1, 5).

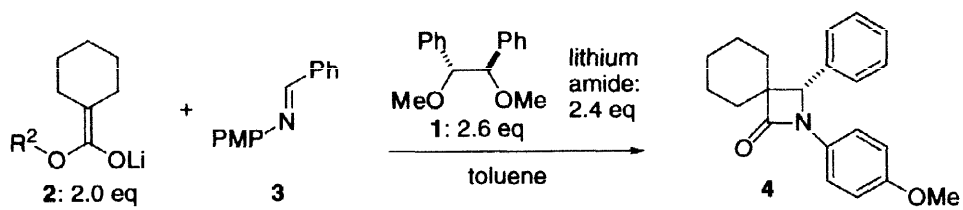
It is worthy to note that the addition product **5** (R^1 = $Ph(CH_2)_2$) was isolated at –78 °C for 1 h as the major product in 90% ee (entry 7), which was then treated with LDA at –25 °C to afford the cyclized β-lactam **4** (R^1 = $Ph(CH_2)_2$) in 90% ee without loss of optical purity of **5**. This indicates that the asymmetric induction step is the addition of the enolate **2** to the imine **3**, not the cyclization step of **5** to **4**. This was confirmed unambiguously as follows.

Treatment of the racemic adduct *dl*-**6**[9] having 3-pentoxy moiety with LDA in toluene at –78 °C for 0.5 h in the presence of **1** afforded racemic **4a** quantitatively. In turn, treatment of the adduct **6** of 99% ee[10] in the absence or presence of **1** gave **4a** of 99% ee quantitatively. These results strongly indicate that the addition step of **2** to **3**, not the cyclization step of **5** to **4**, is the asymmetric induction step.



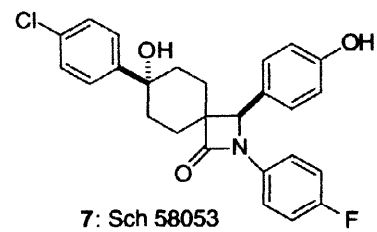
Ester enolate **2** bearing R other than methyl group is applicable as shown in Table 3. In this case, 2,4-dimethyl-3-pentyl ester was also shown to be superior to 3-pentyl ester. Asymmetric synthetic approach toward spirofused azetidinones, for example **7** endowed with potent cholesterol absorption inhibitory activity,[11] is becoming available utilizing present asymmetric reaction of the ternary complex.

Table 3. Asymmetric Reaction of Ternary Complex with Imine **3** (R^1 = Ph)



entry	R^2	lithium amide	temp/°C (time/h)	ee%	yield%
1	*i*-Pr_2CH	LICA	–78 (24), –45 (1)	86	73
2	Et_2CH		–50 (15)	75	83

Further studies directed toward structure tuning of the chiral ligand based on **1** for the improvement of the reaction efficiency are in progress in our laboratories.



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2. Tomioka, K. *Synthesis* **1990**, 541-549; Noyori, R. *Asymmetric Catalysis in Organic Synthesis* John Wiley and Sons, Inc. New York, 1994; Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis* 1995, John Wiley and Sons, Inc., New York.
3. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060-2061.
4. For the recently reported catalytic addition reaction of ester enolate equivalents with imines, see: Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**; *119*, 7153-7154; Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474-2475.
5. Lithium ester enolate was generated by treatment with 2.2 equiv of the lithium amide.
6. All new compounds described herein gave satisfactory analytical and spectroscopic data.
7. Daicel Chiralcel OD-H, *i*-PrOH/hexane = 1/50.
8. Typical procedure (Table 2, entry 1): A solution of 2,4-dimethyl-3-pentyl isobutylate (372 mg, 2.0 mmol) and **1** (630 mg, 2.6 mmol) in toluene (4 mL) was added to a preformed solution of LICA (4.4 mmol) in toluene (8 mL) at –78 °C. The mixture was stirred for 1 h and to this solution was then added a solution of **3** (211 mg, 1.0 mmol) in toluene (2 mL). After stirring at –78 °C for 9 h, and then at –20 °C for 0.5 h, aqueous 10% HCl was added at –78 °C and the mixture was extracted with EtOAc. The organic layer was washed with water, aq. $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration followed by purification through silica gel column chromatography (ether/hexane = 1/5) gave (*S*)-**4a** (R = Me, R^1 = Ph) (240 mg, 74%) as a pale yellow solid of mp 92-97 °C. $[\alpha]^{25}_D$ +122.8 (c 1.01, $CHCl_3$). Ee was determined by HPLC analysis to be 92% (Daicel Chiralcel OD-H, hexane-iPrOH (50:1), 0.5 mL/min, 250 nm, 22 min (*R*) : 27 min (*S*)). The chiral ligand **1** was recovered through column chromatography for reuse quantitatively.
9. Prepared by the reaction of the corresponding trimethylsilyl enol ether with benzaldehyde imine in the presence of zinc iodide.
10. Prepared by the reaction of methanolysis of **4a** of 99% ee, enantioenriched by recrystallization of **4a** of 88% ee, and following HCl catalyzed transesterification with 3-pentanol.
11. Chen, L.-Y.; Zaks, A.; Chackalamannil, S.; Dugar, S. *J. Org. Chem.* **1996**, 61, 8341-8343; McKittrick, B. A.; Ma, K.; Dugar, S. Clader, J. W.; Davis, Jr., H.; Czarniecki, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1947-1950; Wu, G.; Tormos, W. *J. Org. Chem.* **1997**, 62, 6412-6414.