Catalytic asymmetric reaction of lithium ester enolates with imines

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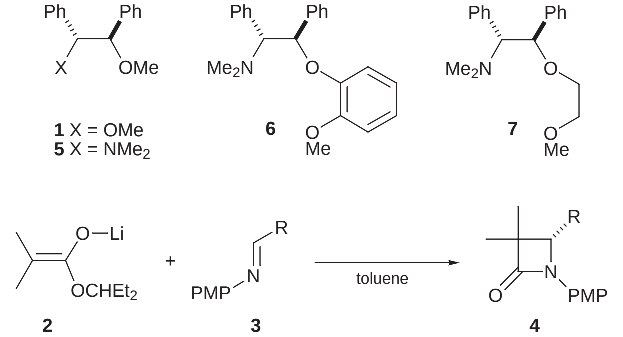
An external chiral tridentate amino diether ligand 7 catalyzed the condensation reaction of a lithium ester enolate 2 with an imine 3 to give the enantiomerically enriched β-lactam 4 in high yield.

Condensation of a lithium ester enolate with an imine is the established synthetic methodology for β-lactams.[1] Although the asymmetric reaction has been developed using chiral enolates or chiral imines,[2] the asymmetric reaction of achiral lithium ester enolates with prochiral imines in the presence of an external chiral controller is undeveloped.[3,4] We have reported that a ternary complex reagent, constituted from a lithium enolate, chiral diether **1** and an achiral lithium amide, enables the asymmetric condensation of the lithium ester enolate with the imine.[5] However, this methodology lacks generality because strong lithium amides cause undesirable side reactions such as deprotonation and nucleophilic attack. During continuing efforts directed towards the development of simple catalytic reactions which use lithium enolates and catalytic amounts of chiral ligands as a nucleophile and a catalyst, we found that 5–20 mol% of a tridentate amino diether ligand catalyzed asymmetric condensation of lithium ester enolates with imines to afford β-lactams in high ee. The efficiency of the reaction is crucially governed by the structural features of the ligand.

At the beginning of studies, we examined the catalytic activity of chiral diether **1** and found that condensation of 2.2 equiv. of lithium ester enolate **2**, generated from pentan-3-yl 2-methylpropanoate and LDA, with imine **3a** (R = Ph, PMP = $4\text{-MeOC}_6\text{H}_4$) in the presence of 5 mol% of **1** in toluene at 0 °C for 7 h gave (*S*)-**4a** (R = Ph) quantitatively in 40% ee (Scheme 1).[6] It was a logical extension to examine the catalytic activity of amino ether ligand **5** because the dimethylamino group of **5** would coordinate to lithium and enhance the reactivity of the lithium enolate more efficiently than the methoxy group of **1** does.[7] As expected, the reaction was catalyzed by 5 mol% of **5** more efficiently at −20 °C for 3 h to afford **4a** quantitatively in 49% ee. Encouraged by these results, we examined the reaction in the presence of a tridentate amino diether ligand **6** which had been found to be a good ligand for the asymmetric Michael reaction of lithium thiophenoxide.[8] Although the reaction was completed within 1 h at −20 °C, the selectivity was not satisfactory, affording **4a** in only 47% ee even if 2.6 equiv. of **6** were used. However, we were pleased to find that a stoichiometric amount of amino diether **7**,[8] bearing a methoxyethoxy group in place of the methoxyphenoxy group of **6**, gave **4a** quantitatively in 91% ee after 1 h at −20 °C. Catalytic reactions using 10 and 5 mol% of **7** at −20 °C for 1.5 h gave **4a** quantitatively in 88 and 84% ees, respectively. Recrystallization of **4a** of 84% ee from Pr$^{\rm i}_2$O gave optically pure **4a** in 75% overall yield. The chiral ligand **1** was recovered quantitatively for reuse.



Scheme 1

The efficiency of the catalytic reaction was examined in the presence of 20 mol% of **7** using imines **3a-f** having aryl, vinyl and alkyl groups as shown in Table 1. The arylimines were converted to **4a-d** in 90–84% ee. The imine **3e** bearing a vinyl group also gave **4e** in 82% ee, whereas alkylimine **3f** was converted to **4f** in a lower 65% ee.

Table 1 The asymmetric condensation of **2** with **3** giving **4** catalyzed by **7**[a]

Entry	3	R	*t*/h	Yield (%)	Ee (%)[b]
1	**a**	Ph	1.5	99	89
2	**b**	PMP	3.5	99	90
3	**c**	1-Naphthyl	1.5	99	84
4	**d**	2-Naphthyl	2.5	99	88
5	**e**	CMe=CHPh	5	90	82
6	**f**	CH_2CH_2Ph	0.5	99	65

[a] Reaction was carried out using 20 mol% of **1** in toluene at −20 °C. [b] The ee was determined *via* chiral stationary phase HPLC using Daicel Chiralcel OD or OD-H, Pr$^{\rm i}$OH–hexane (1 : 100). The absolute configuration was determined according to the reported procedure (ref. 5).

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

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