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Catalytic conversion of conjugated enones into optically active α-keto aziridines using chiral rare earth metal complexes

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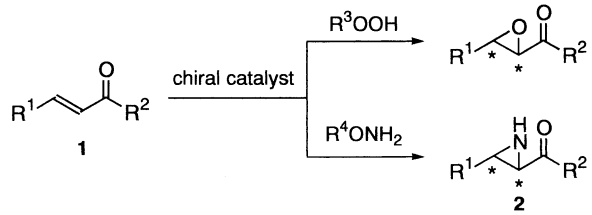
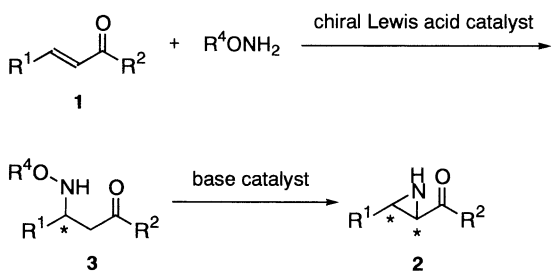
Abstract—Optically active *N*-unsubstituted α-keto aziridines **2** were synthesized from conjugated enones **1** via the Sc[(*R*)-BNP]$_3$-catalyzed enantioselective Michael addition of *O*-methylhydroxylamine followed by the La(O-*i*-Pr)$_3$-catalyzed ring closure of the corresponding β-methoxyamino ketones **3**. A remarkably high asymmetric amplification was observed during the Michael addition, and notable kinetic resolution was also realized during the ring closure reaction when a La(O-*i*-Pr)$_3$–(*R*)-BINOL catalyst system was employed.

Three-membered heterocycles such as epoxides and aziridines are versatile synthetic intermediates in organic syntheses because they can be converted into a variety of multifunctional compounds. Optically active α-keto aziridines are of special interest since they can potentially be useful precursors of various amino acid or β-lactam derivatives with medicinal or biological importance.[1] Although there have been a number of reports concerning the enantioselective synthesis of aziridines,[2] few methods are known for the catalytic asymmetric synthesis of α-keto aziridines.[3–5] Recently, we developed a practical and highly enantioselective epoxidation of conjugated enones using a La(O-*i*-Pr)$_3$–(*R*)-BINOL–Ph$_3$PO (1:1:3) precatalyst system (BINOL = 1,1′-bi-2-naphthol).[6,7] From the analogy with the epoxidation, we first applied the same precatalyst system to the aziridination of chalcone using *O*-methylhydroxylamine in place of an alkyl hydroperoxide (Scheme 1).

The chiral lanthanum complex in situ-prepared from La(O-*i*-Pr)$_3$,[8] (*R*)-BINOL and Ph$_3$PO (1:1:3) or La(O-*i*-Pr)$_3$, (*R*)-BINOL and Et$_3$N (1:1:3) promoted the desired reaction, however, the yields of the aziridine did not exceed the amount of the complexes used though notable enantioselectivities (38% and 72% ee, respectively) were observed.[9] Therefore, we turned our attention to a stepwise process, the Lewis acid-catalyzed enantioselective Michael addition,[10] followed by base-catalyzed aziridine ring formation (Scheme 2).[11] We report herein the two-step synthesis of the optically active α-keto aziridine **2** from the conjugated enone **1** using three kinds of rare earth metal complexes as effective catalysts.



Scheme 1.



Scheme 2.

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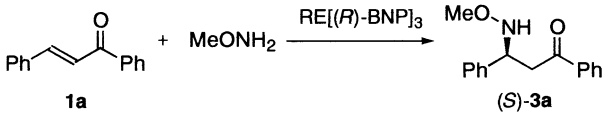
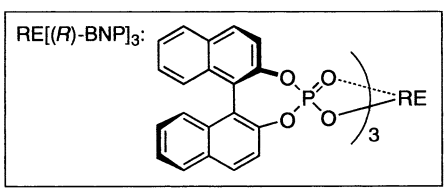
As a Lewis acid catalyst for the Michael addition, we adopted chiral rare earth complexes, RE[(*R*)-BNP]$_3$ (RE = rare earth, BNP = 1,1′-binaphthyl-2,2′-diyl phosphate), which have recently been developed as an efficient catalyst for the asymmetric hetero-Diels–Alder reaction.[12] Thus, several complexes were examined for the enantioselective Michael addition of *O*-methylhydroxylamine to chalcone **1a** under various conditions. Some selected results are summarized in Table 1. Among the complexes tested, Sc[(*R*)-BNP]$_3$ was found to be the most effective. Thus, the reaction catalyzed by the Sc[(*R*)-BNP]$_3$ complex in toluene afforded the corresponding β-methoxyamino ketone **3a** in good yield with modest enantioselectivity (57% ee) (entry 1). A higher enantioselectivity (69% ee) was obtained by lowering the reaction temperature to −20°C (entry 2), but the use of 2,6-lutidine[12b] or molecular sieves 4 Å[6a,7a,b] as an additive did not improve either the chemical or optical yields.

To obtain the α-keto aziridine **2a**, the β-methoxyamino ketone **3a** was first treated with 10 mol% of sodium methoxide in THF at room temperature for 24 h. Unfortunately, the aziridine ring formation did not cleanly proceed thus affording **3a** in 62% isolated yield.[11] We anticipated that the high coordination number and strong Lewis acidity of the lanthanoid ions would be effective for the activation of the N–OMe bond through double coordination of the oxygen and nitrogen atoms as shown in Fig. 1. As expected, when 10 mol% of La(O-*i*-Pr)$_3$ or Yb(O-*i*-Pr)$_3$ was employed as a catalyst, the desired ring formation was completed within 4 h at room temperature to give the α-keto aziridine **2a** in 99% isolated yield. Any loss in the optical purity of **3a** or the retro-Michael reaction leading back to chalcone was not detected.

Table 1. RE[(*R*)-BNP]$_3$-catalyzed Michael addition of methylhydroxylamine to **1a**[a,b]





Entry	RE	Solvent	Yield (%)[c]	Ee (%)[d]
1	Sc	Toluene	81	57
2[e]	Sc	Toluene	80	69
3	Sc	PhCl	42	39
4	Sc	PhOMe	44	60
5	Sc	CH_2Cl_2	33	50
6	La	Toluene	33	6
7	Yb	Toluene	57	31

[a] The reaction was carried out at room temperature for 18 h under argon in the presence of 10 mol% of the catalyst unless otherwise noted.
[b] 1.0–1.2 Equiv. of *O*-methylhydroxylamine was used.
[c] Isolated yield.
[d] Determined by HPLC using Daicel CHIRALCEL OD.
[e] The reaction was carried out at −20°C for 72 h.

At this stage, we thought that if the two OR groups on the metal ion in Fig. 1 are chiral, there must be a difference in the cyclization speed of the two enantiomers, (*R*)-**3a** and (*S*)-**3a**. We then investigated the kinetic resolution of **3a** using a chiral lanthanum alkoxide catalyst prepared in situ from 10 mol% each of La(O-*i*-Pr)$_3$ and (*R*)-BINOL in the presence of molecular sieves 4 Å.[7] The results are shown in Table 2; 16% yield (maximum 50% in theory) of (*R*)-**3a** with 93% ee was recovered starting from *rac*-**3a** after the 48 h reaction.

On the basis of the above results, (*S*)-enriched **3a** (69% ee, cf. entry 2 in Table 1) was treated with the La(O-*i*-Pr)$_3$–(*S*)-BINOL catalyst and after a 28% conversion, the ee of the recovered (*S*)-**3a** reached 86% (Scheme 3).

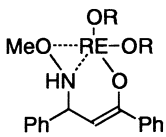
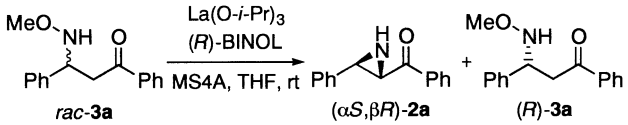


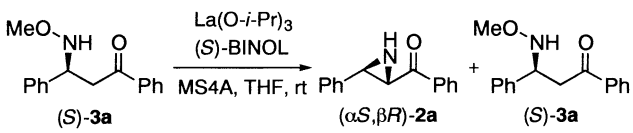
Figure 1.

Table 2. La(O-*i*-Pr)$_3$–(*R*)-BINOL complex-catalyzed kinetic resolution of racemic **3a**[a]



Entry	Time (h)	Conv. (%)	Ee of **2a** (%)[b]	Ee of **3a** (%)[b]
1	3	25	48	18
2	20	78	22	74
3	48	84	10	93

[a] 10 mol% each of La(O-*i*-Pr)$_3$ and (*R*)-BINOL was used. No side reaction was detected.
[b] Determined by HPLC using Daicel CHIRALCEL OD.



Time, h	Conversion, %	Ee of **2a**,[a] %	Ee of **3a**,[a] %
24	25	40	80
36	28	42	86

[a]Determined by HPLC using Daicel CHIRALCEL OD.

Scheme 3. La(O-*i*-Pr)$_3$–(*S*)-BINOL complex-catalyzed kinetic resolution of (*S*)-enriched **3a**.

By using the three lanthanoid complex-catalyzed reaction described above, i.e. (1) the Sc[(*R*)-BNP]$_3$-catalyzed Michael addition of *O*-methylhydroxylamine, (2) the La(O-*i*-Pr)$_3$–chiral BINOL complex-catalyzed kinetic resolution of the Michael adduct, and (3) the La(O-*i*-Pr)$_3$-catalyzed aziridine ring formation, we succeeded in the synthesis of the α-keto aziridine (α*S*,β*R*)-**2a** with as high as 86% ee in a 58% overall yield (Scheme 4). The absolute configuration of (α*S*,β*R*)-**2a** was determined by comparing its optical rotation and also its retention time on the HPLC using a chiral column with those of the authentic sample [(α*R*,β*S*)-**2a**, 99% ee] prepared from the corresponding epoxy ketone [(α*S*,β*R*)-**4**, 99% ee], which was obtained by the enantioselective epoxidation of chalcone using an efficient catalyst system recently developed in this laboratory,[6] according to the literature methods (Scheme 5).[13] The structure of the (α*S*,β*S*)-α-hydroxy-β-azido ketone **5** was unambiguously determined by the X-ray crystallographic analysis (Fig. 2).

In Table 3 the results of the Sc[(*R*)-BNP]$_3$-catalyzed Michael addition of *O*-methylhydroxylamine to a variety of conjugated enones are summarized. Modest to high enantioselectivities were obtained for the reaction of the aryl ketones (entries 1 and 4–7). However, in the case of the alkyl ketones (entries 2 and 3), the desired

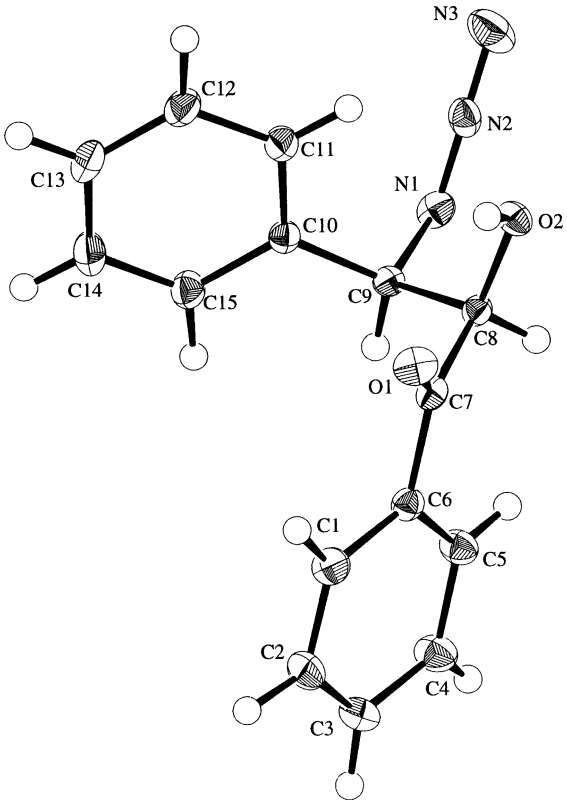
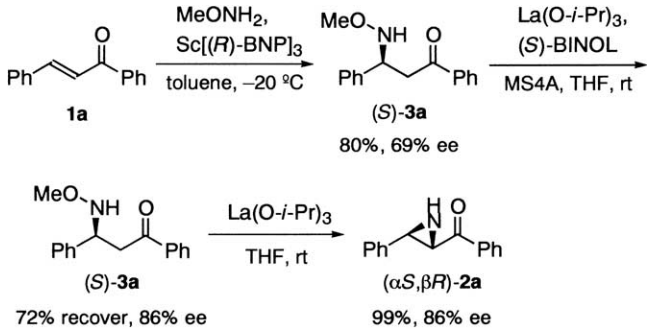
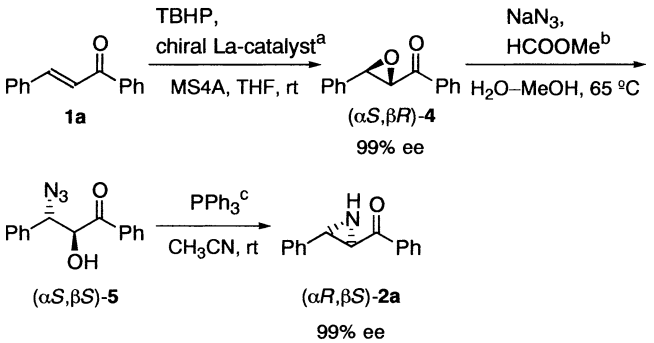


Figure 2. The ORTEP drawing of **5**.



Scheme 4. Enantioselective catalytic conversion of **1a** into the optically active **2a**.



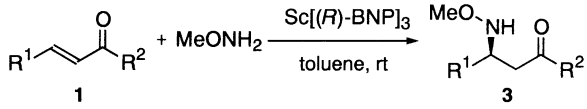
Scheme 5. The synthesis of (α*R*,β*S*)-**2a**. (a) La(O-*i*-Pr)$_3$–(*R*)-BINOL (1:1, 5 mol%), $Ph_3P{=}O$ (15 mol%), 0.5 h, 99%. (b) 5 h, 39%. (c) 4 h, 66%.

Michael adducts were hardly obtained under these conditions and the reaction of methyl ketone **1b** mainly afforded the corresponding oxime. The Michael adducts **3d–g** could be converted into α-keto aziridines **2** by using a catalytic amount of La(O-*i*-Pr)$_3$ (Table 4).

Finally, the possibility of a nonlinear effect[12c,14] was briefly examined for the Michael reaction of **1f**. When the Sc[(*R*)-BNP]$_3$ catalyst with 50% ee, which was prepared by mixing enantiopure Sc[(*R*)-BNP]$_3$ and Sc[(*S*)-BNP]$_3$ in a ratio of 75:25, was used, a notable asymmetric amplification (80% ee) was observed. The results suggest that the active catalyst may not be monomeric but rather dimeric or oligomeric as previously discussed for the Yb(BNP)$_3$-catalyzed hetero-Diels–Alder reaction.[12c]

In conclusion, it was demonstrated that the optically active α-keto aziridines could be catalytically synthesized from the corresponding conjugated enones using two or three types of rare earth metal complexes. A notable asymmetric amplification observed in the Lewis acid-catalyzed Michael reaction and the kinetic resolution realized in the base-catalyzed ring closure reaction seem to be responsible for the high coordination number and strong Lewis acidity of the lanthanoid ions. Further study is under way in this laboratory exploring the efficient asymmetric catalysis with chiral lanthanoid complexes.

Table 3. Sc[(*R*)-BNP]$_3$-catalyzed Michael addition of methylhydroxylamine into various conjugated enones[a,b]

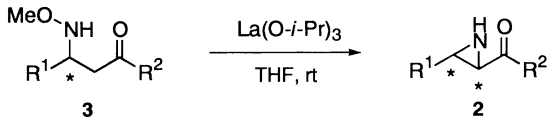


1 3

Entry	Enone	R^1	R^2	Adduct	Yield (%)[c]	Ee (%)[d]
1	**1a**	Ph	Ph	**3a**	90	54
2	**1b**	Ph	Me	**3b**	–[e]	
3	**1c**	Ph	*t*-Bu	**3c**	–[f]	
4	**1d**	4-ClPh	Ph	**3d**	68	40
5	**1e**	4-NCPh	Ph	**3e**	39	72
6	**1f**	4-O_2NPh	Ph	**3f**	97	84
7	**1g**	*i*-Pr	Ph	**3g**	94	81

[a] The reaction was carried out at room temperature under argon in the presence of 10 mol% of the catalyst.
[b] 1.6 Equiv. of *O*-methylhydroxylamine was used.
[c] Isolated yield.
[d] Determined by HPLC using Daicel CHIRALCEL OD. Absolute configuration of the predominantly formed enantiomer is not determined except for **3a** (entry 1).
[e] No desired reaction occurred and the oxime was yielded.
[f] No reaction.

Table 4. La(O-*i*-Pr)$_3$-catalyzed ring closure reaction of various β-methoxyaminoketones[a]



3 2

Entry	Ketone	R^1	R^2	Aziridine	Yield (%)[b]
1	**3d**	4-ClPh	Ph	**2d**	93
2	**3e**	4-NCPh	Ph	**2e**	61
3	**3f**	4-O_2NPh	Ph	**2f**	59
4	**3g**	*i*-Pr	Ph	**2g**	99

[a] The reaction was carried out for 2–6 h under argon in the presence of 10 mol% of the catalyst.
[b] Isolated yield.

Acknowledgements

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