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New chiral scandium(III)/bisimine and diol complexes catalyzed asymmetric Diels–Alder reaction

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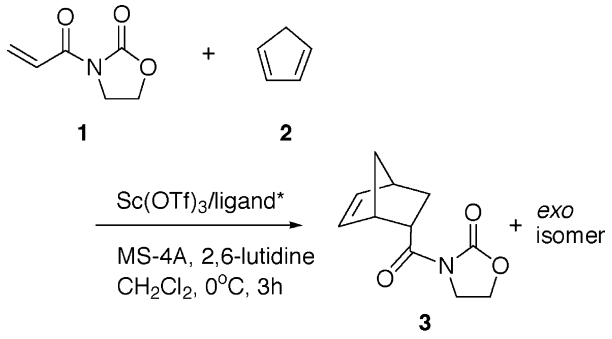
Abstract—Several bisimine and diol-based chiral ligands were examined as scandium(III) triflate complexes in the asymmetric Diels–Alder reaction of cyclopentadiene (**2**) with 3-acryloyloxazolidin-2-one (**1**) in the presence of 2,6-lutidine: the scandium/salen complex was revealed to be the most effective catalyst, which afforded the *endo* adduct in a good yield with 85% ee. Addition of a tertiary amine, such as 2,6-lutidine, was critical to achieve high enantioselectivity; enantioselectivity was remarkably decreased in the absence of the amine.

In recent years, rare earth (RE) complexes have been of interest, especially for asymmetric synthesis.[1] RE/BINOL[2] and pybox[3] complexes are efficient chiral Lewis acid catalysts for asymmetric reactions. We previously reported that the scandium/pybox complex was an effective catalyst for the enantioselective Diels–Alder reaction, where some commercial chiral ligands were screened as well as pybox.[4] We demonstrated there that salen (**4**) was not an effective ligand and that the Sc/salen complex gave the *endo* adduct with only 45% ee. We have now found that addition of 2,6-lutidine to the Sc/salen complex dramatically enhances the enantioselectivity of the reaction.[5] The enhancement of enantioselectivity was also observed with some bisimine and diol/scandium complexes. We would like to report a scandium catalyzed enantioselective Diels–Alder reaction using several bisimine and diol chiral ligands as well as salen in the presence of a tertiary amine.[6]

Representative bisimine chiral ligands **5**–**9** were readily prepared from 1,3-diformylarenes and chiral amines or amino alcohols.[7] We first evaluated the potential of these ligands with $Sc(OTf)_3$ as well as (*S*,*S*)-salen **4** in the benchmark Diels–Alder reaction of cyclopentadiene (**2**) with 3-acryloyloxazolidin-2-one (**1**) in the presence or absence of 2,6-lutidine (Scheme 1). The results of the reaction are summarized in Table 1.

The reaction was usually carried out by using 10 mol% of the scandium catalyst with 4 Å MS in dichloromethane (DCM) at 0°C for 3 h. The $Sc(OTf)_3$/**4** complex alone gave the *endo* adduct (*endo*/*exo* = 86/14) with only 45% ee (*S*-*endo*) (entry 1), while addition of one equivalent of 2,6-lutidine to scandium improved the enantioselectivity up to 85% ee (entry 3). The enhancement of enantioselectivity was hardly observed with the bisimine ligand (*S*,*S*)-**5** by addition of 2,6-lutidine, while significant improvement of the ee value (*R*-*endo*) was observed in the reaction with bisimine ligand (*S*,*S*)-**6a** (entries 4–7). Since the enhancement was remarkable with **4** and **6a**, the interaction between the hydroxy group and 2,6-lutidine may be involved in the formation of an efficient chiral complex; 2,6-lutidine assist in the coordination of the hydroxy groups to scandium. The use of bisimino diol ligands **7**, in which the pyridine unit of **6a** was replaced by benzene resulted



Scheme 1.

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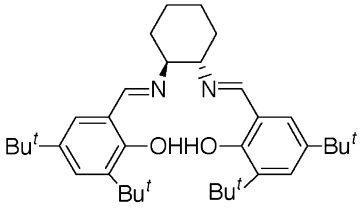
Table 1. Asymmetric Diels–Alder reaction of cyclopentadiene (**2**) with 3-acryloyloxazolidine-2-one (**1**) catalyzed by $Sc(OTf)_3$/chiral ligands[a]

Entry	Ligand	Additive	Yield	*endo*/*exo*	ee (%)[b] *endo*	Config.
1	**4**	–	84	79/21	45	*S*
2[c]	**4**	2,6-Lutidine	88	75/25	35	*S*
3	**4**	2,6-Lutidine	81	89/11	85	*S*
4	**5**	–	81	88/12	29	*S*
5	**5**	2,6-Lutidine	71	82/18	34	*S*
6	**6a**	–	81	89/11	23	*R*
7	**6a**	2,6-Lutidine	71	86/14	69	*R*
8	**6b**	2,6-Lutidine	82	81/18	9	–[d]
9	**7**	2,6-Lutidine	69	75/25	3	–[d]
10	**8**	2,6-Lutidine	87	80/20	9	–[d]
11	**9a**	2,6-Lutidine	80	90/10	68	*R*
12	**9b**	2,6-Lutidine	86	91/9	71	*R*
13	**10**	2,6-Lutidine	84	91/9	3	–
14	**11**	–	92	86/14	14	*R*
15	**11**	2,6-Lutidine	43	90/10	70	*R*
16[e]	**11**	2,6-Lutidine	65	86/14	83	*R*
17	**12**	2,6-Lutidine	84	80/20	29	*R*
18	**13**	2,6-Lutidine	74	85/16	5	–[d]

[a] **1** (0.5 mmol), **2** (1.5 mmol), $Sc(OTf)_3$ (0.05 mmol), ligand (0.05 mmol), 4 Å MS (150 mg); the $Sc(OTf)_3$/chiral ligand complex was prepared at 0°C in DCM, then the reaction was carried out at 0°C for 3 h.
[b] Determined by HPLC (Chiralcel OD-H).
[c] Witout 4 Å MS.
[d] Not determined.
[e] The reaction was carried out at −10°C.

in poor selectivity (entry 9). This result may suggest that coordination of the pyridine group to scandium is required for an efficient chiral scandium complex. The thiophene unit (**8**) was not suitable for the complex; both of the two imine groups would be too far away from scandium for tridentate coordination. The ligand with phenol unit (*S*,*S*)-**9a**-**b** instead of the pyridine unit **6a**–**b** gave a good ee value (71% ee); the chiral complex should contain the phenol group for coordination to scandium. For all these bisimine ligands, the addition of 2,6-lutidine was essential to achieve high enantioselectivity, ee values being reduced without it. The chiral ligand (*R*,*R*)-**10**, the samarium alkoxide of which has been employed in the asymmetric Meerwein–Pondrof–Verley reduction, resulted in low selectivity (entry 11).[8] In connection with the potent hydroxy group participation in **4** or **6a** for scandium complex formation, simple chiral diols **11**–**13** were also examined.[6] Here again 2,6-lutidine was added to all the ligands in the benchmark reaction. Even with the less sterically demanding diol, (2*R*,4*R*)-pentandiol **11**, 70% enantioselectivity was obtained; the ee value could be improved by carrying out the reaction at −10°C. However, the more sterically demanding chiral 1,3-diol **12** gave lower selectivity (entry 17). (1*R*,2*R*)-Cyclo-



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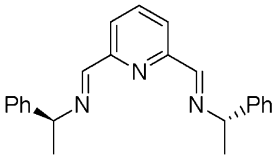

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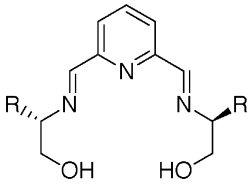
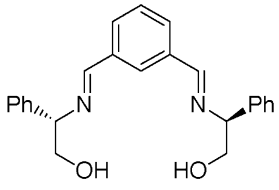


6a: R = Ph
6b: R = *i*-Pr



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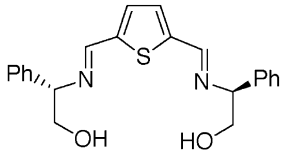

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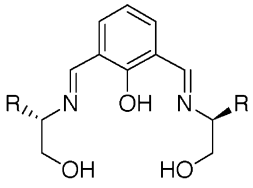
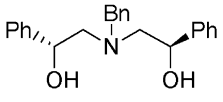


9a: R = Ph
9b: R = *i*-Pr



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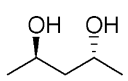

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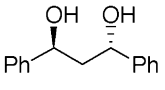

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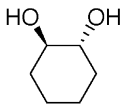

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Table 2. Asymmetric Diels–Alder reaction of **2** with **1** catalyzed by $Sc(OTf)_3$/**4** in the presence of various additives[a]

Entry	Additive	Yield (%)	*endo*/*exo*[b]	ee (%)[b] *endo*	Config.
1	–	92	86/14	45	*S*
2	Pyridine	81	95/5	80	*S*
3	2,6-Lutidine	92	95/5	85	*S*
4	2,4,6-Collidine	85	86/14	63	*S*
5	DMAP	84	95/5	80	*S*
6	DTBP	89	94/6	66	*S*
7	PMP	74	86/14	10	*S*
8	Et_3N	54	91/9	74	*S*
9	CH_3CN	92	80/20	33	*S*
10	Acetone	95	78/22	40	*S*

[a] **1** (0.5 mmol), **2** (1.5 mmol), $Sc(OTf)_3$ (0.05 mmol), **4** (0.05 mmol), 4 Å MS (150 mg), additive (0.10 mmol).
[b] Determined by HPLC (Chiralcel OD-H).

hexanediol **13** was an unsuitable chiral ligand for the scandium complex (entry 18) even in the presence of 2,6-lutidine.

Table 2 summarizes the additive effect of tertiary amines on the enantioselectivity of the reaction. Pyridine and its derivatives, 2,4,6-collidine and dimethylaminopyridine (DMAP) were as effective as 2,6-lutidine, but 2,6-di-*tert*-butylpyridine (DTBP) was not so effective. Addition of triethylamine improved the selectivity to some extent. 1,2,2,6,6-Pentamethylpiperidine (PMP) and acetonitrile rather spoiled the enantioselectivity (entries 7 and 9).

The formation of the scandium complex with **4** could be observed by ^1H NMR measurements.[9] Addition of one equivalent of $Sc(OTf)_3$ to **4** changed its NMR spectrum in CD_2Cl_2 at 0°C. The arene (two singlets, 7.16 and 7.45 ppm) and imine protons (8.41 ppm) were shifted downfield from the original signals (7.00, 7.27, and 8.31 ppm, respectively). The C*H*N protons of cyclohexane ring also shifted from 3.42 to 3.7–3.8 ppm as a broad peak. The addition of 2,6-lutidine, however, did not give new signals; signals are from the uncoordinated salen appearing instead. Signals of coordinated 2,6-lutidine to scandium appears; the methyl signal shifted from 2.48 to 2.81 ppm, and the pyridine ring protons also shifted from 6.92 and 7.41 ppm to 7.50 and 8.15 ppm, respectively. Although this NMR experiment could not show the formation of the scandium/salen/2,6-lutidine complex, 2,6-lutidine was significant for the formation of an active chiral scandium catalyst since the reaction without it resulted in low enantioselectivity.

Acknowledgements

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