A Switch of Enantiofacial Selectivities Using Designed Similar Chiral Ligands in Zirconium-Catalyzed Asymmetric Aza Diels−Alder Reactions

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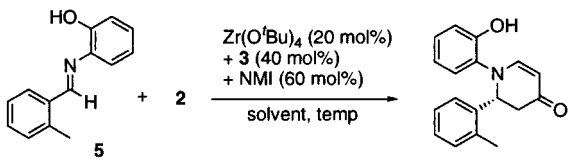
Synthesis of both enantiomers is a very important task not only in organic chemistry but also in medicinal and bioorganic chemistry.[1] In chemical transformations, syntheses of both enantiomers are generally carried out using both enantiomers of chiral sources. While there are many chiral sources in nature, it is sometimes difficult to obtain both enantiomers, for instance, those of amino acids, monosaccharides, alkaloids, etc. When such chiral sources are employed in asymmetric syntheses, preparation of both enantiomers is difficult. On the other hand, from a mechanistic point of view, both enantiomers can be produced by controlling the enantiofaces of prochiral compounds. Therefore, it would be possible to control them by designing ligands that even have the same chirality.[2,3] In this paper, we report an example of this; a switch of enantiofacial selectivities using similar types of ligands in chiral zirconium-catalyzed aza Diels−Alder reactions.

Recently, we reported the first enantioselective aza Diels−Alder reactions of imino dienophiles using a chiral zirconium catalyst (**1**) prepared from Zr(O-*t*-Bu)$_4$, (*R*)-6,6′-dibromo-1,1′-binaphthol ((*R*)-Br-BINOL), and *N*-methylimidazole (NMI).[4−6] According to these reactions, optically active piperidine derivatives having an *S*-configuration were prepared from achiral imines and 1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene,[7] **2**) in high enantioselectivities. In the course of our investigations to examine the catalyst−substrate interaction including the reaction course and to improve selectivities, it was indicated from both experiments and modeling studies that the substituents on the 3,3′-positions of the BINOL ligand influenced the enantioselectivities strongly.[8] We prepared 3,3′-substituted BINOL (**3** and **4**).[9] In the presence of Zr(O^{t}Bu)$_4$ (20 mol %), (*R*)-6,6′-dibromo-3,3′-diphenyl-1,1′-binaphthol (**3**, 40 mol %), and NMI (60 mol %), aldimine **5**, which was prepared from *o*-tolualdehyde and 2-aminophenol, reacted with **2** in toluene at −45 °C to afford the corresponding piperidine derivative in 84% ee (Table 1, entry 1). The absolute configuration was proved to be *R*, which was the reverse of that using (*R*)-Br-BINOL instead of **3** under the same reaction conditions (entry 2). Several reaction conditions were examined, and interesting effects of molecular sieves were found. When the reaction was carried out at 0 °C without molecular sieves, the enantioselectivity decreased to 57% ee. On the other

Table 1. Effect of Solvents, Temperature, and Molecular Sieves



entry	solvent	T/°C	MS	yield/%	ee/%
1	toluene	−45	none	66	84
2	toluene	−45	none	83	82 (*S*)[a]
3	toluene	0	none	45	57
4	toluene	0	MS 3A	80	90
5	toluene	0	MS 4A	76	89
6	toluene	0	MS 5A	77	89
7	toluene	−45	MS 3A	54	77
8	toluene	23	MS 3A	96	88
9	benzene	23	MS 3A	93	91

[a] Catalyst **1** was used.

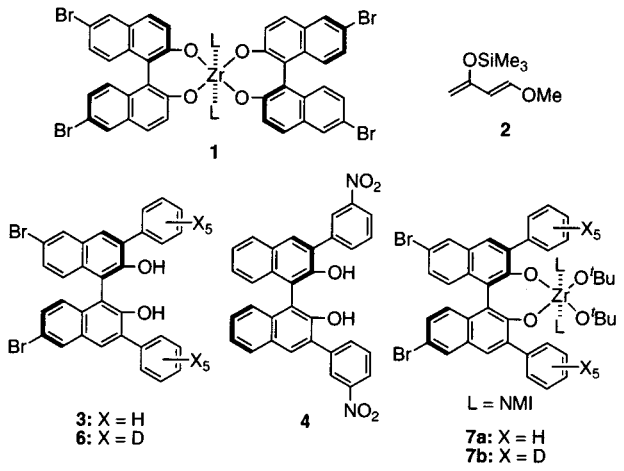


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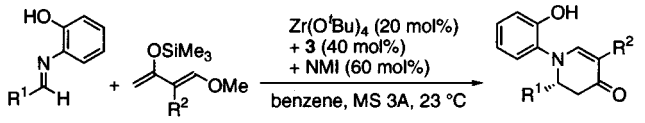
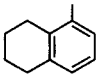
Table 2. Catalytic Asymmetric Aza Diels−Alder Reactions



R^1	R^2	yield/%	ee/%
Ph	H	94	82
Ph	Me	quant.	80
o-MePh	H	93	91
o-MePh	Me	98	89
α-Nap	H	88	84
α-Nap	Me	78	80
	H	67	85
	Me	78	87
	H	90	90
	Me	87	88
2-thiophene	H	74	86[a]
2-thiophene	Me	70	86[a]
c-C_6H_{11}	H	64	81[b]
c-C_6H_{11}	Me	67	80[b]

[a] **4** was used instead of **3**. [b] The imine was prepared from cyclohexanecarboxyaldehyde and 2-amino-3-methylphenol.

hand, 90% ee of the product was obtained when MS 3A was added to the reaction pot. While MS 4A and 5A were also effective, the enantioselectivity decreased when the reaction was carried out at −45 °C with MS 3A. Furthermore, the best result was obtained when the reaction was performed at 23 °C in benzene. It is noted that the chemical yield was also improved more than 25% and that 91% ee of the product was obtained even at 23 °C.[10]

Other examples were tested, and the results are summarized in Table 2.[11] In all cases, the reactions proceeded smoothly to afford the corresponding piperidine derivatives in high yields with high ee's. In addition, reverse enantioselectivities were observed in these reactions compared to those obtained using **1** as a catalyst. It is noteworthy that chemical yields and enantiomeric excesses were improved in most cases using the new catalyst system.

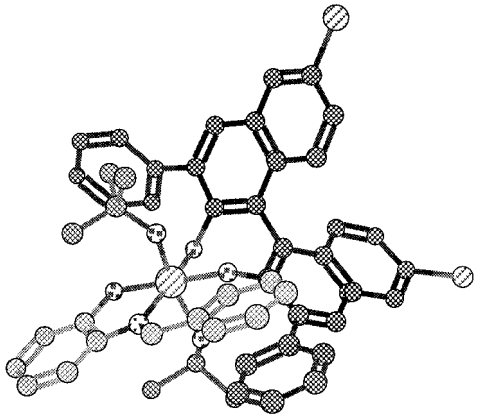
We then examined the precise structure of the zirconium catalyst by NMR analysis. When Zr(O-*t*-Bu)$_4$ (1 equiv), **6** (2 equiv),[12] and NMI (3 equiv) were combined in benzene-d_6 at 23 °C, two independent species that were assigned to a new zirconium catalyst and free **6** were observed. While the signals of free **6** were still observed when Zr(O-*t*-Bu)$_4$ (1 equiv), **6** (1 equiv), and NMI (3 equiv) were stirred at 23 °C, only the signals assigned to the new zirconium catalyst were detected when the mixture was stirred at 80 °C for 2.5 h. These results indicated the formation of **7b** as the new zirconium catalyst. The structure was also supported by the following experiment: Zr(O-*t*-Bu)$_4$ (0.2 equiv), **3** (0.2 equiv), NMI (0.6 equiv), and MS 3A were combined in benzene, and the mixture was stirred for 2.5 h at 80 °C (formation of **7a**). Imine **5** (1 equiv) and **2** (1.2 equiv) were then added to the catalyst solution, and the mixture was stirred for 48 h at 23 °C. After the same workup procedures described above, the desired piperidine derivative was obtained in a >98% yield with an 89% ee, values comparable to those obtained when the catalyst was prepared by combining Zr(O-*t*-Bu)$_4$ (1 equiv), **3** (2 equiv), and NMI (3 equiv) at 23 °C (Table 1, entry 9).[13]

(10) When 10 mol % of the catalyst was used, chemical yield and enantioselectivity decreased (81%, 77% ee).

(11) Experimental details are shown in the Supporting Information.

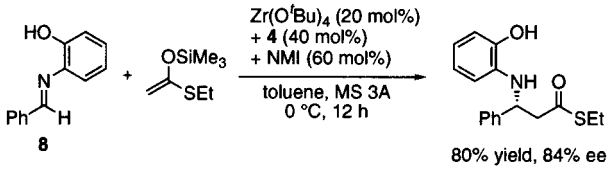
(12) Prepared from (*R*)-(+)-1,1′-bi-2-naphthol and bromobenzene-d_5. See the Supporting Information.

Scheme 1. Working Model



Our working model to obtain such interesting selectivities is shown in Scheme 1. The two bulky *tert*-butoxy groups are expected to locate at the two apical positions. One of the 3,3′-phenyl groups would effectively shield one face of an imine, and consequently, a diene attacks from the opposite side.[14] Judging from this model, similar selectivities were expected in the Mannich-type reactions of imines with silyl enolates. Actually, when ligand **4** was used in the reaction of imine **8** with *S*-ethylthio-1-trimethylsiloxyethene, the corresponding *β*-amino thioester was obtained in an 84% ee (Scheme 2). As expected, the sense of the chiral induction in this case was the reverse of that observed when using catalyst **1**.[6a,15]

Scheme 2. Mannich-Type Reaction



In summary, a switch of enantiofacial selectivities using a 3,3′-disubstituted BINOL (**3** or **4**) has been achieved in chiral zirconium-catalyzed asymmetric aza Diels−Alder reactions. While piperidine derivatives with *S* configurations were prepared using **1** (reported previously), the same piperidine derivatives having *R* configurations were produced using a similar ligand **3** or **4**. In addition to the synthetic utility preparing both enantiomers of the piperidine derivatives, this report has demonstrated the possibility of changing reaction courses (enantiofacial selectivities) by designing chiral sources even with the same chiralities.

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Supporting Information Available: Experimental procedures and physical data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) It was assumed that formation of **7** was slow and incomplete at 23 °C due to the bulky 3,3′-phenyl groups of **3**.

(14) One of the reviewers pointed out that the *tert*-butoxy group of the catalyst would play a major role in shielding one or the other side of the imino moiety. Actually, we performed the reaction using a catalyst having an *n*-propoxy group instead of a *tert*-butoxy group and found that the selectivity was slightly decreased. Further investigations are needed to clarify the precise transition states. We that the reviewer for the fruitful suggestions.

(15) For the assumed transition states of the reactions using **1**, see refs 4a and 6. See also: Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161.