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Enantioselective Aza-Diels−Alder Reaction of Aldimines with "Danishefsky-Type Diene" Catalyzed by Chiral Scandium(III)-*N*,*N*′-Dioxide Complexes

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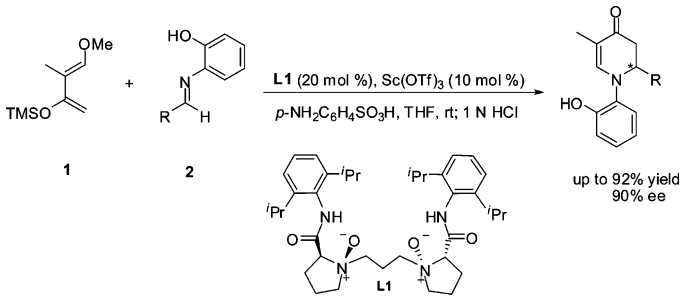
Received September 30, 2007



A new kind of complex prepared from scandium(III) triflate and L-proline-derived *N*,*N*′-dioxides has been developed to catalyze the enantioselective aza-Diels−Alder reaction between 1,3-butadiene (diene **1**) and aldimines **2**, affording the corresponding 2,5-disubstituted dihydropyridinones in moderate to high yields (up to 92%) with good enantioselectivities (up to 90% ee) at room temperature. A variety of aldimines including aromatic, heteroaromatic, conjugated, and aliphatic imines were found to be suitable substrates. Enantiopure samples (up to 99% ee) were obtained for some products by a single recrystallization. The absolute configuration of the products was determined by X-ray diffraction and CD analysis. On the basis of the investigation of ^{1}H NMR spectra and the positive nonlinear effect, the catalyst structure was carefully discussed.

Introduction

As a useful tool for the construction of six-membered heterocycles, the hetero-Diels−Alder reactions have been studied very intensively.[1] Interest has been focused on the construction of chiral pyrones and lactones, which are important intermediates for the synthesis of biologically active natural products.[2−5] Despite its importance for the preparation of six-

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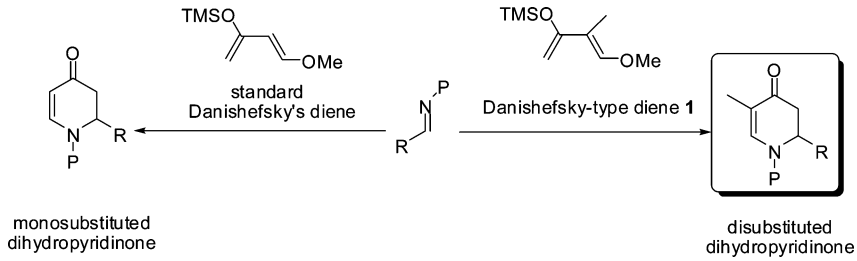
10.1021/jo7021263 CCC: $40.75
Published on Web 12/19/2007

SCHEME 1. Aza-Diels−Alder Reaction; TMS = Trimethylsilyl



membered optically active nitrogen-containing compounds, the hetero-Diels−Alder reaction of imines (aza-Diels−Alder reaction) has made progress only in recent years since the pioneering work of Danishefsky and co-workers.[6,7] Different kinds of chiral Lewis acids, such as boron, zirconium, silver, copper, and zinc complexes, have been employed to catalyze this type of reaction.[8−14] Although rare earth metals have shown excellent catalytic efficiency for the achiral aza-Diels−Alder reaction, chiral complexes especially for scandium have not been fully studied for this reaction.[15,16] Ishitani and Kobayashi developed a ytterbium−binaphthol complex to catalyze the enantioselective synthesis of tetrahydroquinoline derivatives using imine **2** as an azadiene in 1996.[17]

Furthermore, the products obtained in the previous works were mainly monosubstituted dihydropyridinones (Scheme 1). As for multisubstituted ones,[18] to the best of our knowledge, only three examples including zirconium−binaphthol,[9a] boron−binaphthol,[8a] and chiral copper ferrocene complexes[11c] were reported hitherto. As part of our ongoing program aimed at developing metal and amide *N*-oxide complexes as efficient catalysts,[19] we described here our efforts on the catalytic asymmetric aza-Diels−Alder reaction of Danishefsky-type diene **1** and aldimines **2**, using a novel scandium(III) complex of *N*,*N*′-dioxide as the catalyst. Various 2,5-disubstituted dihydropyridinones have been obtained with up to 92% yield and 90% ee.

Results and Discussion

Initially, *N*,*N*′-dioxide **L1** (Figure 1) was complexed with various metal salts to catalyze the aza-Diels−Alder reaction of diene **1** and aldimine **2a** (Table 1). Racemic products were obtained with $Zn(OTf)_2$, $Cu(OTf)_2$, and $In(OTf)_3$ as Lewis acids (Table 1, entries 4−6). $Zr(O^iPr)_4$, which had proved to be effective for this kind of reaction, gave only poor results (Table 1, entry 7).[9a] However, $Yb(OTf)_3$, $Sc(OTf)_3$, and $Sm(OTf)_3$ showed good inductive potential in this reaction (Table 1, entries 1−3). Especially for $Sc(OTf)_3$, 91% yield and 25% ee could be afforded (Table 1, entry 2).

The molar ratio of central metal to ligand significantly affected the enantioselectivity. Because of the strong background reaction of $Sc(OTf)_3$, excess amount of metal in the catalytic system increased the yield dramatically, while the enantioselectivity decreased (Table 2, entries 1−3). In contrast, lowering the amount of metal turned out to be favorable for the reaction

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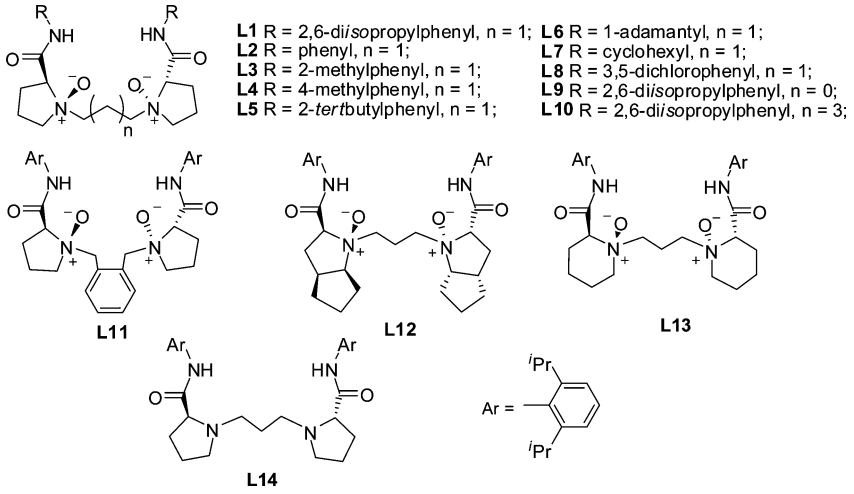
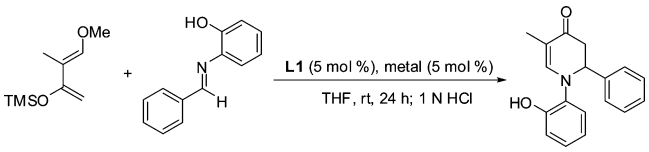


FIGURE 1. Ligands employed for the aza-Diels−Alder reaction.

TABLE 1. Survey of Central Metals on Aza-Diels−Alder Reaction of Aldimine 2a with Diene 1[a]

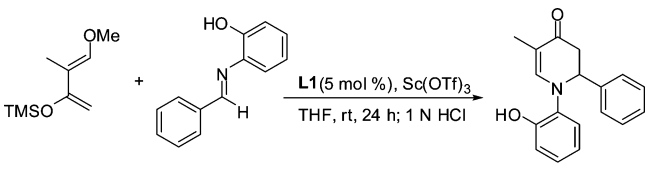


1 2a 3a

entry	metal	yield (%)[b]	ee (%)[c]
1	$Yb(OTf)_3$	>99	17
2	$Sc(OTf)_3$	91	25
3	$Sm(OTf)_3$	41	23
4	$Zn(OTf)_2$	25	0
5	$Cu(OTf)_2$	45	0
6	$In(OTf)_3$	63	0
7	$Zr(OiPr)_4$	trace	N.D.[d]

[a] All reactions were carried out on a 0.2 mmol scale in 2.0 mL of THF with 5 mol % catalyst loading (metal−ligand = 1:1) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Not determined.

TABLE 2. Effect of Molar Ratio between Metal and Ligand on Aza-Diels−Alder Reaction[a]



1 2a 3a

entry	metal loading (mol %)	ratio (**L1**−metal)	yield (%)[b]	ee (%)[c]
1	5.0	0:1	>99	
2	7.5	1:1.5	>99	7
3	6.0	1:1.2	>99	25
4	5.0	1:1	91	25
5	3.3	1.5:1	88	37
6	2.5	2:1	59	57
7	2.0	2.5:1	53	54

[a] All reactions were carried out on a 0.2 mmol scale in 2.0 mL of THF at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column.

enantioselectivity (Table 2, entries 4−7). The best result was obtained when 1:2 molar ratio of $Sc(OTf)_3$−**L1** was used (Table 2, entry 6).

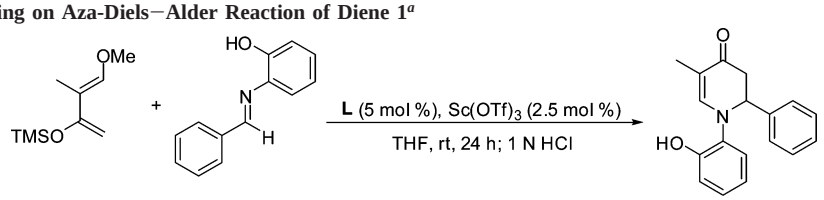
To clarify the influence of each unit of the ligand on the reaction, L-proline-derived *N*,*N*′-dioxides with different amide groups and with varying chain length of the spacer as well as other amino acid derivatives were examined. The steric effect of *R* groups of amide moiety played an important role on the enantioselectivity, and bulkier groups provided better results (Table 3, entries 1−6). Ligand bearing electron-withdrawing groups gave only racemic product (Table 3, entry 8). When *R* was aliphatic cyclic group, low yield and ee value were obtained (Table 3, entry 7). L-Proline-derived *N*,*N*′-dioxide **L1** exhibited its superiority toward this reaction compared with other amino acid derivatives (Table 3, entry 1 vs 12 and 13). Further decreasing or increasing the length of the carbon chain did not give better results (Table 3, entry 1 vs 9, 10, and 11). On the other hand, when the complex of amide ligand **L14** and scandium(III) triflate was applied to this reaction, only racemic product was obtained, which confirmed the importance of *N*-oxide moiety (Table 3, entry 14). Accordingly, **L1** was chosen as the ligand for the next investigation.[20]

Further solvent examination exhibited their important effect in terms of both enantioselectivity and yield. The reaction carried out in toluene, CH_2Cl_2, or Et_2O only delivered the product with up to 29% ee (Table 4, entries 2−4). Although 1,4-dioxane provided similar enantioselectivity, the yield was somewhat low (Table 4, entry 5). Use of MeOH as solvent improved the yield of corresponding 2,5-disubstituted dihydropyridinone **3a** to 99%, but the enantioselectivity was deteriorated (Table 4, entry 6). Therefore, THF was still the best solvent for this reaction (Table 4, entry 1).

We next turned our attention to investigate the influence of other protecting groups of imine on this reaction (Table 5). When electron-withdrawing tosyl group was used instead, no ee value was obtained, although the yield was satisfying (Table 5, entry 4).[11c] The aza-Diels−Alder reaction of phenyl and 4-methoxyphenyl imines also proceeded without stereoselectivity (Table 5, entries 2 and 5). It should be noticed that when the hydroxy group of imine was methylated, no reaction occurred, which established the importance of the phenolic group (Table 5, entry 6 vs 1). Accordingly, it was speculated that both the hydroxy group and nitrogen atom on imine coordinated with the central metal. The steric hindrance of the bulky 2-methox-

(20) Although **L9** provided similar results as **L1**, **L1** was still chosen as the standard ligand because of its easier preparation compared with **L9**.

TABLE 3. Ligand Screening on Aza-Diels−Alder Reaction of Diene 1[a]

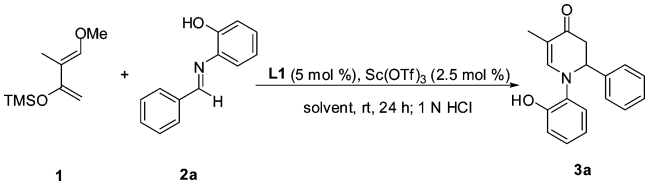


1 2a 3a

entry	ligand	yield (%)[b]	ee (%)[c]
1	**L1**	59	57
2	**L2**	30	7[d]
3	**L3**	61	30
4	**L4**	57	17
5	**L5**	50	43
6	**L6**	70	25
7	**L7**	38	14
8	**L8**	36	0
9	**L9**	58	57
10	**L10**	35	40
11	**L11**	44	33
12	**L12**	47	50
13	**L13**	52	40
14	**L14**	52	0

[a] All reactions were carried out on a 0.2 mmol scale in 2.0 mL of THF with 2.5 mol % catalyst loading (metal−ligand = 1:2) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] The product was obtained with *R* configuration, and the others were *S*.

TABLE 4. Solvent Effect on the Aza-Diels−Alder Reaction of Imine 2a[a]



1 2a 3a

entry	solvent	yield (%)[b]	ee (%)[c]
1	THF	59	57
2	toluene	46	29
3	CH_2Cl_2	70	29
4	Et_2O	87	16
5	1,4-dioxane	43	55
6	CH_3OH	99	5

[a] All reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent with 2.5 mol % catalyst loading (metal−ligand = 1:2) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column.

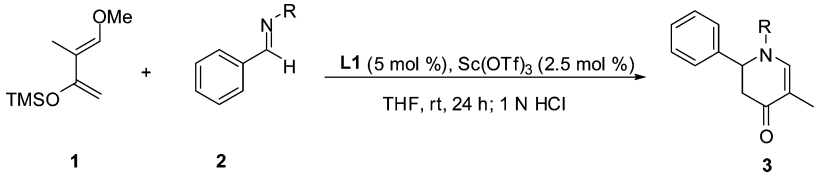
yphenyl and benzhydryl groups could shield the coordination of central metal with imines and hence prevent the reaction (Table 5, entries 3 and 6).

To further improve the reactivity and enantioselectivity of the reaction, some acids acting as additives were employed.[21] In the presence of toluenesulfonic acid or sulfanilic acid, product **3a** was obtained with 75% ee (Table 6, entries 2 and 7). Comparably, sulfanilic acid showed higher reactivity, which might attribute to the buffer action of the amino group on the sulfanilic acid. In contrast, use of weaker or stronger acids deteriorated the enantioselectivity deeply (Table 6, entries 4−6). The reaction carried out with 5 mol % toluenesulfonic acid and 5 mol % aniline together as additives provided results similar to that with sulfanilic acid, which further established the significance of the suitable acidity of the additives for the reaction (Table 6, entry 8 vs 7). The addition of sodium toluenesulfonate gave almost the same results as that in the absence of additive (Table 6, entry 3 vs 1). Therefore, the possibility that toluenesulfonic anion functioned as a ligand to coordinate with the central metal was excluded. Further attempts to decrease the substrate concentration and increase the catalyst loading (10 mol %) improved the ee value to 81% (Table 6, entries 9−13).

When the substrate scope of this reaction was probed, 15 mol % of sulfanilic acid seemed to be more suitable for other substrates to obtain better results (Table 7, entries 3−5). Accordingly, the optimized catalytic system was 10 mol % scandium(III)−*N*,*N*′-dioxide **L1** (1:2), 0.2 mmol aldimine, and 2.0 equiv of diene in 3.0 mL of THF in the presence of 15 mol % *p*-sulfanilic acid at room temperature. Under these conditions, aromatic, heteroaromatic, conjugated, and aliphatic aldimines were converted into the corresponding 2,5-disubstituted dihydropyridinones with moderate to good yield and up to 90% ee. For aromatic imines bearing electron-donating substituents, up to 77% yield and 86% ee could be obtained (Table 7, entries 6, 10, 13, 16, 17, and 23). Notably, this method was rather efficient for imines bearing electron-withdrawing groups at the para position, a class of substrates that, to our knowledge, had never been mentioned previously (Table 7, entries 5, 11, 15, 20, and 21). For example, the aza-Diels−Alder reaction of *p*-cyanobenzaldehyde-derived imine **2b** proceeded well to give 1-(2-hydroxyphenyl)-2-(4-cyanophenyl)-5-methyl-2,3-dihydropyridin-4-one in 84% yield with 90% ee (Table 7, entry 5). Even α,*β*-unsaturated imine **2i** and heteroaromatic imine **2u** were tolerated in the catalytic reaction (Table 7, entries 12 and 24). For aliphatic imines, which were hard to prepare, a new in situ imine generation strategy was employed. Fortunately, 74% ee could also be obtained for substrate **2v** (Table 7, entries 25 and 26). Additionally, for products **3f**, **3j**−**3l**, and **3q**, enantiopure samples (up to 99% ee) were obtained upon a single recrystal-

(21) Review: Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577. For a representative example using acid as additive, see ref 14b.

TABLE 5. Investigation of the Protecting Group of Imine 2 on the Aza-Diels−Alder Reaction[a]

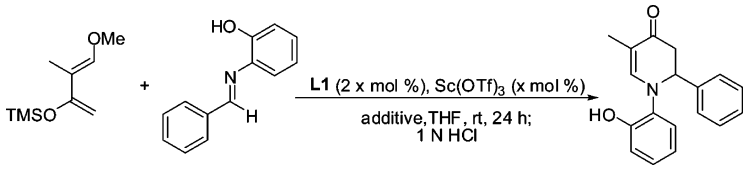


1 2 3

entry	R	yield (%)[b]	ee (%)[c]
1	2-hydroxyphenyl	59	57
2	phenyl	50	0
3	benzhydryl	N.R.[d]	
4	tosyl	75	0
5	4-methoxyphenyl	39	0
6	2-methoxyphenyl	N.R.[d]	

[a] All reactions were carried out on a 0.2 mmol scale in 2.0 mL of THF with 2.5 mol % catalyst loading (metal−ligand = 1:2) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] No reaction.

TABLE 6. Investigation of Additive, Substrate Concentration, and Catalyst Loading on Aza-Diels−Alder Reaction of Aldimine 2a with Diene 1[a]



1 2a 3a

entry	*x* (mol %)	additive (mol %)	solvent (mL)	yield (%)[b]	ee (%)[c]
1	2.5		2.0	59	57
2	2.5	*p*-$CH_3C_6H_4SO_3H$ (5%)	2.0	55	75
3	2.5	*p*-$CH_3C_6H_4SO_3Na$ (5%)	2.0	54	61
4	2.5	CH_3CO_2H (5%)	2.0	30	28
5	2.5	$C_6H_5CO_2H$ (5%)	2.0	46	42
6	2.5	CF_3SO_3H (5%)	2.0	66	26
7	2.5	*p*-$NH_2C_6H_4SO_3H$ (5%)	2.0	73	75
8	2.5	*p*-$CH_3C_6H_4SO_3H$ (5%)[d]	2.0	57	76
9	2.5	*p*-$NH_2C_6H_4SO_3H$ (5%)	3.0	65	78
10	2.5	*p*-$NH_2C_6H_4SO_3H$ (5%)	4.0	49	77
11	5.0	*p*-$NH_2C_6H_4SO_3H$ (5%)	3.0	65	76
12	10.0	*p*-$NH_2C_6H_4SO_3H$ (5%)	3.0	74	81
13	15.0	*p*-$NH_2C_6H_4SO_3H$ (5%)	3.0	77	74

[a] All reactions were carried out on a 0.2 mmol scale in THF (metal−ligand = 1:2) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] 5 mol % aniline was used together as additive.

lization (Table 7, entries 9, 13, 14, 15, and 20).[22] Undoubtedly, this good substrate generality combined with the simplicity of the experimental procedure for this reaction made it very attractive from a synthetic point of view.

Through the Bijvoet method, the absolute configuration of product **3r** was determined unambiguously to be *S* with an absolute structure parameter of −0.002(15) on the basis of anomalous dispersion of bromine heavy atom. Compared with the Cotton effect in the CD spectra of **3r**, the products of **3a**−**3h**, **3j**−**3q**, **3s**, and **3t** possessed the same *S* configuration (for details, see the Supporting Information).

Catalyst Structure Consideration. For this reaction, the best result was obtained when the molar ratio of ligand to metal was 2:1 with acid as additive. Therefore, a series of ^{1}H NMR spectra of ligand−scandium (2:1) complex were examined to gain preliminary insight into the structure of the catalyst (Figure 2). In the ^{1}H NMR spectra of ligand **L14** (the precursor of *N*,*N*′-dioxide **L1**) and scandium(III) triflate (2:1) complex, the resonance of NH protons shifting from 9.16 to 9.61 ppm confirmed the coordination between **L14** and scandium (Figure 2a,b). Considering the four magnetically equivalent NH protons and the steric effect of the bulky 2,6-diisopropylphenyl groups, we assumed that the carbonyl oxygens, rather than the amide nitrogens, participated in the coordination with the scandium (complex **A**).

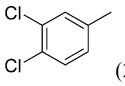
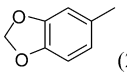
The NH proton of *N*,*N*′-dioxide **L1** showed a strong deshielding effect at 13.58 ppm due to the strong hydrogen bond between *N*-oxide and the NH proton (Figure 2c).[23] When the ^{1}H NMR spectra of scandium(III)−*N*,*N*′-dioxide **L1** (1:2) complex was studied, the signal at 13.58 ppm of **L1** completely disappeared and two new signals at 9.64 and 11.69 ppm were observed (Figure 2d). Compared with the chemical shift of NH proton at 9.61 ppm in complex **A**, the new peak at 9.64 ppm suggested the coordination of carbonyl oxygen with scandium. In addition, according to the appearance of the signal at 11.69 ppm, we speculated that, for all the amide hydrogens of complex **B** in

(22) The catalytic products were recrystallized in CH_2Cl_2−CH_3OH−*n*-hexane to provide the enantiomerically pure compounds with 50−70% yield.

(23) Qin, B.; Liu, X. H.; Shi, J.; Zheng, K.; Zhao, H. T.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 2374−2378.

TABLE 7. Scope of the Enantioselective Aza-Diels−Alder Reaction between Diene 1 and Aldimines 2[a]

1 **2a-2v** **3a-3v**

Entry	R	Additive (mol%)	Product	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	5	**3a**	74	81(*S*)
2	Ph (**2a**)	10	**3a**	63	71(*S*)
3	*p*-CNC_6H_4 (**2b**)	5	**3b**	66	84(*S*)
4	*p*-CNC_6H_4 (**2b**)	10	**3b**	80	88(*S*)
5	*p*-CNC_6H_4 (**2b**)	15	**3b**	84	90(*S*)
6	*p*-$CH_3OC_6H_4$ (**2c**)	15	**3c**	66	86(*S*)
7	*o*-$NO_2C_6H_4$ (**2d**)	15	**3d**	54	84(*S*)
8	α-Naphthyl (**2e**)	15	**3e**	80	87(*S*)
9	*β*-Naphthyl (**2f**)	15	**3f**	85	84(*S*)(99)[d]
10	*o*-$CH_3C_6H_4$ (**2g**)	15	**3g**	65	80(*S*)
11	*p*-FC_6H_4 (**2h**)	15	**3h**	66	85(*S*)
12	(*E*)-PhCH=CH (**2i**)	15	**3i**	92	84
13	*p*-$CH_3C_6H_4$ (**2j**)	15	**3j**	77	85(*S*)(>99)[d]
14	*m*-$NO_2C_6H_4$ (**2k**)	15	**3k**	69	80(*S*)(>99)[d]
15	*p*-$NO_2C_6H_4$ (**21**)	15	**31**	69	89(*S*)(>99)[d]
16	*p*-PhC_6H_4 (**2m**)	15	**3m**	72	84(*S*)
17	*m*-$PhOC_6H_4$ (**2n**)	15	**3n**	46	84(*S*)
18	*o*-ClC_6H_4 (**2o**)	15	**3o**	89	83(*S*)
19	*m*-ClC_6H_4 (**2p**)	15	**3p**	69	80(*S*)
20	*p*-CIC_6H_4 (**2q**)	15	**3q**	64	85(*S*)(>99)[d]
21	*p*-BrC_6H_4 (**2r**)	15	**3r**	73	87(*S*)[e]
22	 (**2s**)	15	**3s**	72	82(*S*)
23	 (**2t**)	15	**3t**	57	81(*S*)
24	2-thienyl (**2u**)	15	**3u**	46	82[f]
25	2-propyl (**2v**)	15	**3v**	67	71[g]
26	2-propyl (**2v**)	15	**3v**	41	74[h]

[a] Without otherwise noticing, all reactions were carried out on a 0.2 mmol scale in 3.0 mL of THF with 10 mol % scandium(III) triflate and 20 mol % **L1** at room temperature for 72 h, using sulfanilic acid as additive. [b] Isolated yield. [c] Determined by HPLC on chiral columns. The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **3r**. [d] After a single recrystallization. [e] The absolute configuration was determined by X-ray crystal structural analysis of **3r** on the basis of the anomalous dispersion of the heavy bromine atom. [f] Reaction time was 120 h. [g] Catalyst was added to the imine generated in situ. [h] Imine generated in situ was added to the catalyst.

the catalytic system, some of them ($\delta = 11.69$ ppm) were still affected by the intramolecular hydrogen bond interaction, while others ($\delta = 9.64$ ppm) were not. The molar ratio of these two kinds of hydrogens was determined to be 3:7 on the basis of the integral level of the ^{1}H NMR spectra (Supporting Information). After the addition of toluenesulfonic acid, the intramolecular hydrogen bond in complex **B** totally broke down. Therefore, the signal at 11.69 ppm disappeared (Figure 2, part e vs d). Moreover, only two NH hydrogens (totally four hydrogens) were observed in Figure 2 (parts d and e), which delivered two amide nitrogen anions complexed with scandium (as shown in Figure 2, complex **B**). On the basis of these observations and the discussion here, it was plausible that the *N*,*N*′-dioxide **L1** coordinated with scandium in a 2:1 manner, and **L1** provided a carbonyl oxygen and an amide nitrogen for coordination (as shown in Figure 2). In the presence of *p*-toluenesulfonic acid, a C_2 symmetric scandium−*N*,*N*′-dioxide **L1** (1:2) complex with good chiral environment might be generated.

Meanwhile, the relationship between the enantiomeric excess of the product **3a** and the chiral ligand **L1** was studied (Figure 3). In both cases, strong positive nonlinear effect was observed, which further validated the existence of **L1**−$Sc(OTf)_3$ (2:1) complex such as complex **B** (Figure 2). It was logical to suggest that homochiral and heterochiral complexes such as (−)(−)-complex **B** and (+)(−)-complex **B** coexisted in the reaction system. As could be found in Girard and Kagan's excellent review of nonlinear effects, the homochiral one seemed to be more active than the heterochiral one, which resulted in the positive nonlinear effect.[24]

Conclusion

The asymmetric aza-Diels−Alder reaction of a variety of aldimines with Danishefsky-type diene **1** has been achieved by

(24) Reviews: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017. For an example, see: (c) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479−4491.

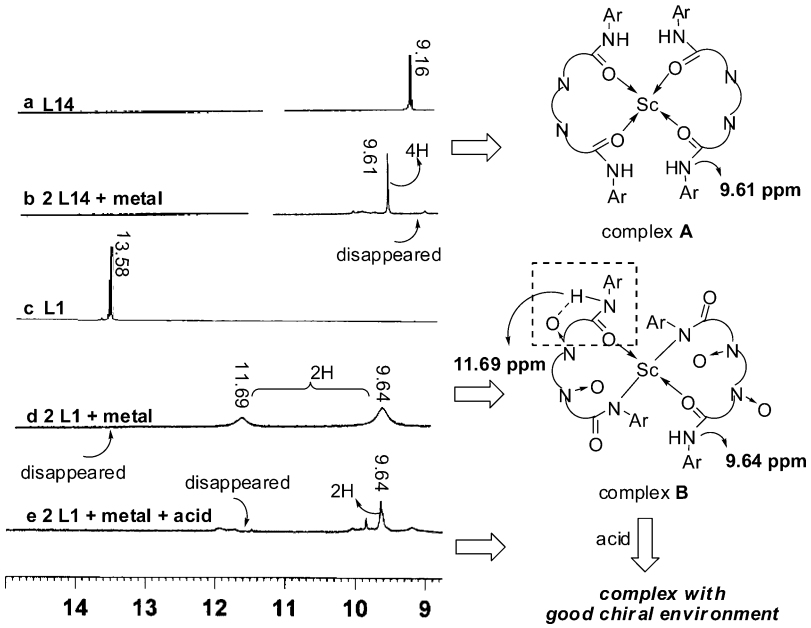


FIGURE 2. ^{1}H NMR spectra investigation of amide protons: (a) **L14**; (b) ligand **L14**−scandium(III) triflate complex (ratio 2:1); (c) **L1**; (d) ligand **L1**−scandium(III) triflate complex (ratio 2:1); (e) ligand **L1**−scandium(III) triflate complex with toluenesulfonic acid as additive (ratio 2:1:2).

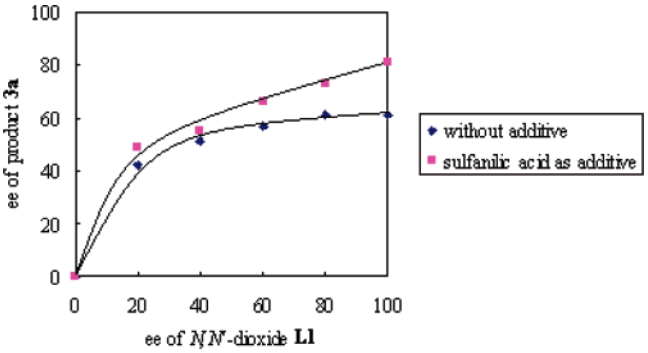


FIGURE 3. Amplification observed in the aza-Diels−Alder reaction of **1** and **2a** using scandium(III) triflate complex of *N*,*N*′-dioxide **L1** as the catalyst.

the catalysis of chiral scandium complex of *N*,*N*′-dioxides, which has added a new catalyst for this class of reactions. Various 2,5-disubstituted dihydropyridinones have been produced in high enantioselectivities (up to 90% ee; single recrystallization, up to 99% ee) and moderate to high yields (up to 92%). On the basis of ^{1}H NMR spectra investigation and the positive nonlinear effect, the catalyst structure is carefully discussed. Further efforts will be devoted to the investigation of the details of the reaction mechanism, the aza-Diels−Alder reaction with other kinds of dienes, and synthetic application of the products.

Experimental Section

General Procedure for the Enantioselective Aza-Diels−Alder Reaction. Ligand **L1** (24.8 mg, 0.04 mmol), $Sc(OTf)_3$ (10.0 mg, 0.02 mmol), sulfanilic acid (1.7 mg, 0.01 mmol), and imine **2a** (39.4 mg, 0.2 mmol) were dissolved in 3.0 mL of THF and stirred in a test tube under Ar atmosphere. After 15 min, diene (100 μL, 0.4 mmol) was added to the mixture and stirred at room temperature for 24 h. Then, the mixture was cooled to 0 °C, 1 N HCl (1 mL) was added, and this solution was stirred for another 1 h. Saturated $NaHCO_3$ (5 mL) was added, and the solution was stirred for an additional 5 min. It was diluted with 5 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether−ethyl acetate, 3:2) to afford a yellow solid (42 mg, 74% yield, 81% ee). The ee was determined by HPLC analysis using a chiral OD-H column (hexane−2-propanol, 90:10, 1.0 mL/min, t_r (major) = 9.787 min, t_r (minor) = 11.572 min). Mp 148−149 °C; $[\alpha]^{25}_D$ +101.4° (*c* 0.214, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−6.74 (m, 11H), 5.10 (dd, J = 9.0, 6.2 Hz, 1H), 3.07 (dd, J = 16.5, 6.2 Hz, 1H), 2.92 (dd, J = 16.6, 9.2 Hz, 1H), 1.78 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 154.1, 151.8, 138.8, 131.9, 128.5, 128.0, 127.9, 127.1, 126.4, 119.8, 117.1, 106.3, 62.7, 43.1, 12.8 ppm; ES-HRMS calcd for $C_{18}H_{16}NO_2$ [M$^-$], 278.1187; found, 278.1181.

Experimental Procedure for the Enantioselective Aza-Diels−Alder Reaction in a New in Situ Imine Generation Strategy. 2-Aminophenol (21.8 mg, 0.2 mmol), isobutyraldehyde (36 μL, 0.4 mmol), and Na_2SO_4 (85.2 mg, 0.6 mmol) were dissolved in 2.0 mL of THF and stirred in a test tube at room temperature under Ar atmosphere. After 2 h, the solution was added to another test tube containing ligand **L1** (24.8 mg, 0.04 mmol) and $Sc(OTf)_3$ (10.0 mg, 0.02 mmol) in 0.5 mL of THF under Ar atmosphere. After the addition of sulfanilic acid (5.2 mg, 0.03 mmol), this test tube was washed with another 0.5 mL of THF. The mixture was stirred at room temperature for 15 min, and diene (100 μL, 0.4 mmol) was added and stirred at room temperature for 96 h. Then, the mixture was cooled to 0 °C, 1 N HCl (1 mL) was added, and this solution was stirred for another 1 h. Saturated $NaHCO_3$ (5 mL) was added, and the solution was stirred for an additional 5 min. It was diluted with 5 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether−ethyl acetate, 2:1) to afford a yellow oil (20 mg, 41% yield). The product was treated with 3 mL of 20% MeI-acetone and 100 mg of K_2CO_3.[9c] The mixture was stirred at room temperature for 6 h, and saturated aqueous NH_4Cl was added to quench the reaction. After extraction of the aqueous layer with CH_2Cl_2, the crude product was chromatographed on silica gel (petroleum ether−ethyl acetate, 2:1) to afford the corresponding methylated product with 74% ee as a yellow oil. The ee was determined by HPLC analysis using a chiral OD-H column (hexane−2-propanol, 99:1, 1.0 mL/min, t_r

(major) = 20.508 min, t_r (minor) = 23.758 min). $[\alpha]^{25}_D$ +60.7° (*c* 0.270, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−6.96 (m, 5H), 3.96 (dd, J = 12.0, 6.8 Hz, 1H), 3.88 (s, 3H), 2.79 (dd, J = 16.4, 6.4 Hz, 1H), 2.58 (dd, J = 16.4, 7.6 Hz, 1H), 1.96 (m, 1H), 1.72 (s, 3H), 0.85 (dd, J = 8.4, 7.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 154.6, 152.0, 133.9, 127.9, 127.7, 121.0, 112.0, 105.4, 63.6, 55.7, 55.6, 36.3, 29.3, 19.6, 17.2, 12.6 ppm; ES-HRMS Calcd for $C_{16}H_{22}NO_2$ [M + H^+], 260.1645; found, 260.1649.

Acknowledgment. This work was financially supported by the National Nature Science Foundation of China (Nos. 20732003 and 20472056). We also thank Sichuan University Analytical & Testing Center for NMR spectra, X-ray diffraction, and CD spectrum analysis.

Supporting Information Available: Experimental procedures, structural proofs for catalysts, spectral and analytical data for the products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO7021263