

## Catalytic Asymmetric Aza Diels-Alder Reactions Using a Chiral Lanthanide Lewis Acid. Enantioselective Synthesis of Tetrahydroquinoline Derivatives Using a Catalytic Amount of a Chiral Source

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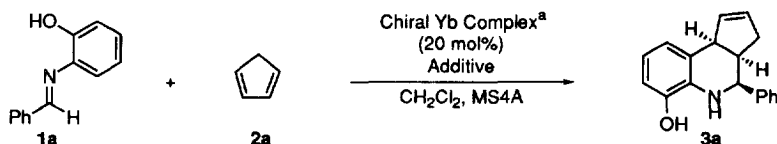
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**Abstract:** *In the presence of a catalytic amount of the chiral ytterbium Lewis acid, which was prepared from Yb(OTf)<sub>3</sub>, (R)-(+)-BINOL, diazabicyclo[5.4.0]undec-7-ene (DBU), and an additive, achiral imines reacted with achiral dienophiles to afford the corresponding tetrahydroquinoline derivatives in high yields with high diastereo- and enantioselectivities. This is the first example of aza Diels-Alder reactions using a catalytic amount of a chiral source.* Copyright © 1996 Elsevier Science Ltd

Recently asymmetric reactions using chiral Lewis acids have been demonstrated to achieve several highly enantioselective carbon-carbon bond-forming processes using catalytic amounts of chiral sources.<sup>1</sup> However, chiral Lewis acid-catalyzed asymmetric reactions of nitrogen-containing substrates are rare, probably because most chiral Lewis acids would be trapped by the basic nitrogen atoms to block the catalytic cycle. For example, aza Diels-Alder reactions are one of the most basic and versatile reactions for the synthesis of nitrogen-containing heterocyclic compounds.<sup>2</sup> Although asymmetric versions using chiral auxiliaries or a stoichiometric amount of a chiral Lewis acid have been reported,<sup>3</sup> examples using a catalytic amount of a chiral source are unprecedented as far as we know. In this paper, we describe the first example of catalytic asymmetric aza Diels-Alder reactions using a chiral lanthanide Lewis acid.

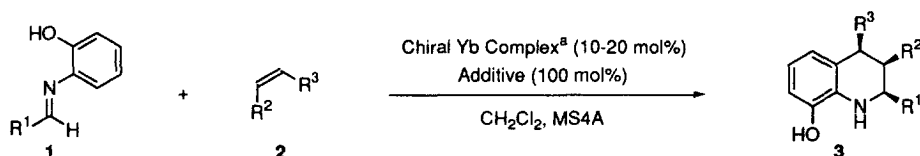
In the previous papers, we have shown that lanthanide triflates are excellent catalysts for achiral aza Diels-Alder reactions.<sup>4</sup> While stoichiometric amounts of Lewis acids are required in many cases, a small amount of the triflate effectively catalyzes the reactions. On the other hand, chiral lanthanide Lewis acids have been developed to realize highly enantioselective Diels-Alder reactions of 2-oxazolidin-1-one with dienes.<sup>5</sup> Bearing these hopeful results in mind, we started to investigate catalytic asymmetric aza Diels-Alder reactions.

First, the reaction of N-benzylideneaniline with cyclopentadiene was performed under the influence of 20 mol% of a chiral ytterbium Lewis acid prepared from ytterbium triflate (Yb(OTf)<sub>3</sub>),<sup>6</sup> (R)-(+)-1,1'-bi-2-naphthol (BINOL), and 1,3,5-trimethylpiperidine (TMP). The reaction proceeded smoothly at room temperature to afford the desired tetrahydroquinoline derivative in a 53% yield, however, no chiral induction was observed. At this stage, it was indicated that bidentate coordination between a substrate and a chiral Lewis acid would be necessary for reasonable chiral induction. We prepared N-benzylidene-2-hydroxyaniline (**1a**), and the reaction with cyclopentadiene (**2a**) was examined. It was found that the reaction proceeded smoothly to afford the corresponding 8-hydroxyquinoline derivative (**3a**)<sup>7</sup> in a high yield. The enantiomeric excess of the cis-adduct in the first trial was only 6%, however, the selectivity increased when diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of TMP (Table 1). It was indicated that the phenolic hydrogen of **1a** would interact with DBU, which should interact with the hydrogen of (R)-(+)-BINOL,<sup>8</sup> to decrease the selectivity. We then examined additives which interact with the phenolic hydrogen of **1a**. When 20 mol% of N-methylimidazole (MID) was used, 91% ee of the cis adduct was obtained, however, the chemical yield was

**Table 1.** Effect of Additive

Additive <sup>b</sup> /mol%	Temp/°C	Yield/%	cis/trans	ee/% (cis)
—	0	71	98 / 2	62
—	-15 to 0	48	99 / 1	68
MID (20)	-15 to 0	21	98 / 2	91
DTBP (20)	0	49	95 / 5	31
DTBP (100)	0	67	99 / 1	61
DMP (100)	0	14	98 / 2	56
DTBMP (100)	-15	82	>99 / 1	70
DTBP (100)	-15	92	>99 / 1	71

<sup>a</sup> Prepared from Yb(OTf)<sub>3</sub>, (*F*)-(+)-BINOL, and DBU. <sup>b</sup> MID: *N*-Methylimidazole. DTBP: 2,6-Di-*t*-butylpyridine. DMP: 2,6-Dimethylpyridine. DTBMP: 2,6-Di-*t*-butyl-4-methylpyridine.

**Table 2.** Asymmetric Synthesis of Tetrahydroquinoline Derivatives

Entry	R <sup>1</sup>	Alkene	Additive <sup>a</sup>	Amount of Catalyst /mol%	Temp /°C	Product	Yield /%	cis/trans	Ee/% (cis)
1	Ph ( <b>1a</b> )	(2b)	DTBP	20	-45	<b>3b</b>	58	94 / 6	61
2	Ph ( <b>1a</b> )	(2b)	DTBP	10	-45	<b>3b</b>	52	94 / 6	77
3	$\alpha$ -Naph ( <b>1b</b> )	(2b)	DTBP	20	-15	<b>3c</b>	69	>99/ 1	86
4	$\alpha$ -Naph ( <b>1b</b> )	(2b)	DPP <sup>b</sup>	20	-15	<b>3c</b>	65	99/ 1	91
5	$\alpha$ -Naph ( <b>1b</b> )	(2b)	DTBMP	20	-15	<b>3c</b>	74	>99/ 1	91
6	$\alpha$ -Naph ( <b>1b</b> )	(2b)	DTBMP	10	-15	<b>3c</b>	62	98/ 2	82
7	$\alpha$ -Naph ( <b>1b</b> )	(2c)	DTBMP	20	-15	<b>3d</b>	80	66/34	70
8	$\alpha$ -Naph ( <b>1b</b> )	(2d)	DTBMP	20	-15	<b>3e</b>	90	91 / 9	78
9	$\alpha$ -Naph ( <b>1b</b> )	(2d)	DPP <sup>b</sup>	20	-15	<b>3e</b>	67	93 / 7	86
10	$\alpha$ -Naph ( <b>1b</b> )	(2a)	DTBMP	20	-15	<b>3f</b>	69	>99/ 1	68
11 <sup>c</sup>	<i>c</i> -C <sub>6</sub> H <sub>11</sub> ( <b>1c</b> )	(2a)	DTBMP	20	-15	<b>3g</b>	58	>99/ 1	73

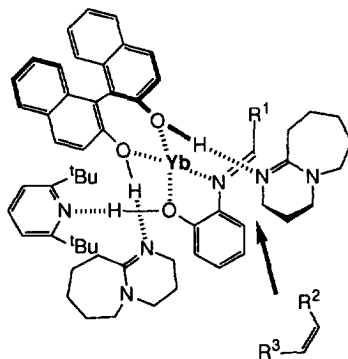
<sup>a</sup> See Table 1. <sup>b</sup> 2,6-Diphenylpyridine. <sup>c</sup> Sc(OTf)<sub>3</sub> was used. See text.

low. We screened other additives and found that the desired tetrahydroquinoline derivative was obtained in a 92% yield with high selectivities (*cis/trans* = >99/1, 71% ee), when 2,6-di-*t*-butylpyridine (DTBP) was used.

Other substrates were tested, and the results are summarized in Table 2. Vinyl ethers (**2b-2d**) also worked well to afford the corresponding tetrahydroquinoline derivatives (**3b-3e**) in good to high yields with good to excellent diastereo- and enantioselectivities (entries 1-9). Use of 10 mol% of the chiral catalyst also gave the adduct in high yields and selectivities (entries 2 and 6). As for additives, 2,6-di-*t*-butylpyridine (DTBP) gave the best result in the reaction of imine **1a** with ethyl vinyl ether (**2b**), while higher selectivities were obtained when DTBMP or 2,6-diphenylpyridine (DPP) was used in the reaction of imine **1b** with **2b**. This could be explained by the slight difference in the asymmetric environment created by Yb(OTf)<sub>3</sub>, (*R*)-(+)-BINOL, DBU, and the additive (see below). While use of butyl vinyl ether (**2c**) decreased the selectivities (entry 7), dihydrofuran (**2d**) reacted smoothly to achieve high levels of selectivity (entries 8, 9). It was found that the imine (**1c**) prepared from cyclohexanecarboxaldehyde and 2-hydroxyaniline was unstable and difficult to purify. The asymmetric aza Diels-Alder reaction was successfully carried out using the three component coupling procedure (successively adding the aldehyde, the amine, and cyclopentadiene) in the presence of Sc(OTf)<sub>3</sub><sup>6a,9</sup> (instead of Yb(OTf)<sub>3</sub>), (*R*)-(+)-BINOL, DBU, and DTBMP.

A typical experimental procedure is described for the reaction of **1b** with **2b**: To a suspension of Yb(OTf)<sub>3</sub> (62.0 mg, 0.10 mmol), MS4A (125.0 mg), and (*R*)-(+)-BINOL (32.3 mg) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) was added DBU (36.5 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) at 0 °C. The mixture turned yellow immediately and was stirred for 0.5 h at the same temperature. The resulting suspension was cooled to -15 °C, and then **1b** (123.7 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub>(0.25 ml), DTBP (102.3 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub>(0.25 ml), and ethyl vinyl ether (**2b**, 108.2 mg, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub>(0.25 ml) were successively added. After the mixture was stirred for 20 h, water was added. The insoluble materials were filtrated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. After a usual work up, the crude product was chromatographed on silica gel to afford the corresponding tetrahydroquinoline (**3c**, 118.2 mg, 74%, *cis/trans* = >99/1). The optical purity of the adduct (91% ee) was determined by HPLC analysis<sup>10</sup> (using Daicel Chiralpak AD).

We assume a transition state of this reaction as shown in Scheme 1. Yb(OTf)<sub>3</sub>, (*R*)-(+)-BINOL, and DBU form a complex with two hydrogen bonds, and the axial chirality of (*R*)-(+)-BINOL is transferred via the hydrogen bonds to the amine parts. The additive would interact with the phenolic hydrogen of the imine, which is fixed by bidentate coordination to Yb(III). Since the top face of the imine is shielded by the amine, the dienophiles approach from the bottom face to achieve high levels of selectivity.



**Scheme 1.** Assumed Transition State<sup>a</sup>

<sup>a</sup>Triflate anions are omitted for clarification.

In summary, we have developed catalytic asymmetric aza Diels-Alder reactions of imines with alkenes using a chiral lanthanide Lewis acid, to afford 8-hydroxyquinoline derivatives in high yields with high diastereo- and enantioselectivities. Characteristic points of this reaction are as follows: (i) Asymmetric aza Diels-Alder reactions between achiral azadienes and dienophiles have been achieved using a catalytic amount of a chiral source. (ii) The unique reaction pathway in which the chiral Lewis acid activates not dienophiles but dienes, is revealed. In most asymmetric Diels-Alder reactions reported using chiral Lewis acids, the Lewis acids activate dienophiles.<sup>1,11</sup> (iii) A unique lanthanide complex including an azadiene and an additive, which is quite different from the conventional chiral Lewis acids, has been developed.

Further investigations to exploit new asymmetric reactions using the chiral lanthanide Lewis acids are now in progress.

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