## Scandium(III) Triflate/Isopropyl-Pybox Complex as an Efficient Catalyst for Asymmetric Diels-Alder Reaction

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**Abstract:** The chiral scandium (III) triflate/*i*-Pr-pybox complex efficiently catalyzes the asymmetric Diels-Alder reaction of 1,3-dienes with acyl-1,3-oxazolidin-2-ones (**1a-c**) afford the corresponding adducts in good yields with up to 90% ee. The reaction can be carried out in less toxic benzotrifluoride and supercritical carbon dioxide while remaining good selectivity (65-75% ee)

**Key words:** scandium, asymmetric catalysis, asymmetric synthesis, Diels-Alder reactions, cycloadditions, supercritical carbon dioxide

Nowadays, rare earth compounds have become one of the standard reagents in organic synthesis and they are effective especially in stereo-controlled reactions.<sup>1</sup> In recent years, rare earth complexes have been of the interest especially for asymmetric synthesis. Some of the complexes work as a Lewis acid catalyst and some work as a Lewis base. Well-designed complexes may provide an excellent selectivity for the asymmetric reactions such as the aldol reaction and Diels-Alder reaction. We have succeeded in the highly stereoselective asymmetric Diels-Alder reaction<sup>2</sup> using the Sc(OTf)<sub>3</sub>/*i*-Pr-pybox complex as a catalyst.<sup>3</sup> We wish to report the asymmetric reaction using not only conventional dichloromethane (DCM) but also the less toxic benzotrifluoride (BTF)<sup>4</sup> and supercritical carbon dioxide( $scCO_2$ )<sup>5</sup> as a solvent in terms of green chemistry.6

First, we carried out the reaction of cyclopentadiene (2)with 3-acryloyl-2-oxazolidinone (1a) in the presence of a catalytic amount (10 mol%) of Sc(OTf)<sub>3</sub> and a chiral additive(1equiv to Sc); *i*-Pr-pybox **4**,<sup>7</sup> bisoxazoline **5**,<sup>7</sup> sulfonamide  $6^{,8}$  salen derivative  $7^{,9}$  and sparteine  $8^{7}$  were screened as a chiral ligand (Scheme 1). The reaction was usually carried out as follows. A mixture of Sc(OTf)<sub>3</sub> (0.05 mmol) and a chiral ligand (0.05 mmol) was stirred at 0 °C in the presence of MS-4A (150 mg) in DCM (4 mL) for 30min. To the resulting solution was added 1a (0.5 mmol) and 2 (1.5 mmol) and then stirred at 0 °C for 2 h. After the usual workup, the product was isolated by PTLC and the isomer ratio (endo/exo) and enantiomeric excess (% ee) were determined by HPLC using a chiral column (Daicel Chiralcel OD). The results, which are shown in Table 1, suggest that *i*-Pr-pybox, **4** should be the most efficient and suitable ligand for the reaction; the use of 4 as a chiral ligand afforded a 63% yield of the adduct (endo/exo = 92/8) with 82% ee (S-endo).





Scheme 1

 Table 1
 Asymmetric Diels-Alder Reaction of Cyclopentadiene (2)

 with 3-Acryloyl-2-oxazolidinone (1a) Catalyzed by Sc(OTf)<sub>3</sub>/Chiral Ligand<sup>a</sup>

entry	ligand	yield(%)	endo/exo ʰ	ee (%)⁵ ( <i>endo</i> )	config.
1	4	63	92/8	82	S
2	5	60	81/19	1	-
3	6	71	85/15	4	R
4 <sup>c</sup>	7	87	70/30	45	S
5	8	78	87/13	4	S

<sup>a</sup>**1a** (0.5 mmol), **2** (1.5 mmol), REX<sub>3</sub> (0.05 mmol), ligand (0.05 mmol), MS-4A (150 mmg); the Sc(OTf)<sub>3</sub>/chiral ligand complex was prepared at 0 °C in DCM, then the reaction was carried out at 0 °C for 2 h. <sup>b</sup>Determined by HPLC. c the Sc(OTf)<sub>3</sub>/7 complex was prepared at rt.

We next examined the catalytic ability of some rare earth salts (REX<sub>3</sub>) using **1** with respect to the enantioselectivity of the *endo* product. These results are shown in Table 2.  $Sc(OTf)_3$  gave the highest enantiomeric excess value for

the (*S*)-adduct among examined the rare earth triflates (entry 1). The use of scandium(III) perfluorooctanesulfonate  $[Sc(OPf)_3]^{10}$  and scandium(III) trifluoromethansulfonimide  $[Sc(NTf_2)_3]^{11}$  resulted in a lower enantioselectivity although they were expected to act as more powerful Lewis acids than  $Sc(OTf)_3$ (entries 2-3). These results suggest that all the reactions should be carried out using  $Sc(OTf)_3/4$  as the chiral Lewis acid catalyst.

 Table 2
 Asymmetric Diels-Alder Reaction of Cyclopentadiene (2)

 with 1a Catalyzed by Rare Earth Salts/*i*-Pr-pybox<sup>a</sup>

entry	REX <sub>3</sub>	yield(%)	endo/exo <sup>b</sup>	ee (%) <sup>b</sup> ( <i>endo</i> ) <sup>c</sup>
1	Sc(OTf) <sub>3</sub>	63	92/8	82
2	Sc(OPf) <sub>3</sub>	60	81/19	65
3	Sc(NTf <sub>2</sub> ) <sub>3</sub>	78	87/13	68
4 <sup>d</sup>	ScCl <sub>3</sub>	74	89/11	0
5 <sup>d</sup>	La(OTf) <sub>3</sub>	65	91/9	1
6 <sup>e</sup>	Sm(OTf) <sub>3</sub>	59	86/14	7
7	Yb(OTf) <sub>3</sub>	63	65/35	34

<sup>a</sup>**1a** (0.5 mmol), **2** (1.5 mmol), REX<sub>3</sub> (0.05 mmol), **4** (0.05 mmol), MS-4A (150 mg); the Sc(OTf)<sub>3</sub>/4 was prepared at 0 °C in DCM, then the reaction was carried out at 0 °C for 2h. <sup>b</sup>Determined by HPLC. <sup>c</sup>The absolute configuration was *S*. <sup>d</sup>Reaction was carried out for 24 h. <sup>e</sup>Reaction was carried out for 22 h.

Table 3 summarizes the reaction of **1a**, 3-crotonoyl- (**1b**) and 3-cinnamoyl-2-oxazolidinone (**1c**) with **2** in DCM, BTF or scCO<sub>2</sub>. The reaction with each dienophile proceeded smoothly in each solvent to give a product in moderate to good yields with high enantioselectivity for the *endo* product (*endo/exo* = 80/20–98/2). The preparation of the Sc(OTf)<sub>3</sub>/**4** complex at a lower temperature (-78 °C) improved the enantioselectivity somewhat decreased in BTF and scCO<sub>2</sub> compared to DCM in the reaction with **1a**, but it still remained a satisfactory value even though the reaction in scCO<sub>2</sub> was carried out at high temperature (40 °C) (entries 3-4). For the reaction with **1b**, the enantioselectivity was almost the same as in DCM and

in BTF (76-78% ee) (entries 5-8). It is noteworthy that the reaction proceeded more rapidly in scCO<sub>2</sub>; the adduct can be obtained in a good yield in a short time.<sup>5</sup> To our best knowledge, this Sc(OTf)<sub>3</sub>/4 catalyzed reaction in scCO<sub>2</sub> is the first example of Lewis acid catalyzed asymmetric reaction in scCO<sub>2</sub>.<sup>13</sup>

The reaction of **1a** with isoprene (**9**) and *trans*-1,3-pentadiene (**11**) required an extended reaction time (48 h) and/ or higher temperature (25 °C) to obtain a satisfactory yield. The use of BTF as a solvent remarkably decreased the yields of the adducts with these 1,3-dienes although the enantioselectivity value remained moderate (Scheme 2).



Scheme 2

Since the  $Sc(OTf)_3/i$ -Pr-pybox complex effectively worked as a catalyst in the asymmetric Diels-Alder reaction in an environmentally friendly solvent such as BTF and  $scCO_2$  as well as conventional DCM, it would be a promising Lewis acid complex in green asymmetric synthesis.<sup>14</sup>

 Table 3
 Asymmetric Diels-Alder Reaction of 3-Acyl-2-oxazolidinones (1a-c) with 2 Catalyzed by Sc(OTf)<sub>3</sub>/

 *i*-Pr-pybox<sup>a</sup>

entry	dienophile	solvent	time (h)	yield(%)	endo/exo <sup>b</sup>	ee (%) <sup>b</sup> ( <i>endo</i> )	config.°
1	1a	DCM	2	63	92/8	82	S
2 <sup>d</sup>	1a	DCM	2	60	98/2	90	S
3	1a	BTF	2	61	96/4	70	S
4 <sup>e</sup>	1a	scCO <sub>2</sub>	0.25	67	91/9	65	S
5	1b	DCM	18	99	89/11	78	(2 <i>S</i> , 3 <i>R</i> )
6 <sup>d</sup>	1b	DCM	18	94	91/9	83	(2 <i>S</i> , 3 <i>R</i> )
7	1b	BTF	18	89	88/12	76	(2 <i>S</i> , 3 <i>R</i> )
8 <sup>e</sup>	1b	scCO <sub>2</sub>	0.5	68	88/12	63	(2 <i>S</i> , 3 <i>R</i> )
9 <sup>r</sup>	1c	DCM	48	27	78/22	75	(2 <i>R</i> , 3 <i>R</i> )

<sup>a</sup>**1** (0.5 mmol), **2** (1.5 mmol), Sc(OTf)<sub>3</sub> (0.05 mmol), **4** (0.05 mmol), MS-4A (150 mg); the Sc(OTf)<sub>3</sub>/**4** complex was prepared at 0 °C, then the reaction was carried out at 0 °C. <sup>b</sup>Determined by HPLC (Chiralcel OD or Chiral-pak AD) and/or <sup>1</sup>H NMR. <sup>c</sup>Determined according to the literature. See ref 1a and references are cited therein. <sup>d</sup>The complex was prepared at -78 °C. <sup>e</sup>40 °C, 100 atm, without MS-4A. <sup>f</sup>The reaction temperature was 25 °C.

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