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Asymmetric Diels–Alder reactions in supercritical carbon dioxide catalyzed by rare earth complexes

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Abstract—The rare earth(III) salt catalysed asymmetric Diels–Alder reaction of cyclopentadiene with a chiral dienophile in supercritical carbon dioxide ($scCO_2$) proceeded rapidly to give the adduct with a higher diastereoselectivity than that in dichloromethane; $Yb(ClO_4)_3$ gave the *endo* adduct with value up to 77% de at 40°C, 8 MPa. The chiral rare earth diketonate catalyzed hetero Diels–Alder reaction of the Danishefsky's diene with benzaldehyde gave a higher yield and an enantioselectivity in $scCO_2$ than that in dichloromethane. Scandium/pybox **8a** complex catalysed asymmetric Diels–Alder reaction of 3-crotonoyl-2-oxazolidinone with cyclopentadiene in the presence of MS4A proceeded smoothly in $scCO_2$ to give the *endo* adduct **10** in a good yield with up to 88% ee.

1. Introduction

In recent years, rare earth complexes have been of interest in stereo-controlled organic synthesis.[1] High stereoselectivity is due to effective chelation control by complexation of the rare earth metal to a functional group such as a carbonyl group. The remarkable feature of the complex is that it works well as a Lewis acid catalyst in aqueous media where most of the Lewis acids are inactivated and scarcely catalyze the reaction. This aqueous reaction is environmentally benign and is advantageous from the viewpoint of green chemistry.

An alternative choice for the green medium is supercritical carbon dioxide ($scCO_2$), which has recently received considerable attention in organic synthesis not only because it is a nontoxic and environmentally friendly medium but also because it often enhances the selectivity and/or rate of the organic reactions compared to conventional organic solvents.[2] Transition–metal-complex catalysed reactions in supercritical fluids are intensively studied and particularly successful in asymmetric synthesis.[3] On the other hand, the $scCO_2$ conditions (over 40°C at 8 MPa) does not seem to be suitable for a Lewis acid catalyzed asymmetric synthesis, because a reaction usually must be carried out at low temperature to control stereoselectivity. Indeed, the trial of titanium-catalyzed asymmetric Mukaiyama aldol reaction in $scCO_2$ has not been successful.[4]

Rare earth salt is often used for reactions in $scCO_2$ as a Lewis acid,[5] however, significantly advantageous reactions have rarely been reported comparing to those in organic solvent.[6] We have found a dramatic enhancement of selectivity in the diastereoselective Diels–Alder reaction of a chiral dienophile with cyclopentadiene using rare earth salts by tuning the pressure in $scCO_2$.[7] We report here on rare earth complex catalyzed asymmetric Diels–Alder reactions in $scCO_2$ which successfully yield a product with higher enantioselectivity than in an organic solvent.

2. Results and discussion

2.1. Diastereoselective Diels–Alder reaction of the chiral dienophile with cyclopentadiene

We chose Evans's 3-acryloyl-(4*S*)-isopropyloxazolidin-2-one **1** as a good chiral dienophile for the reaction with cyclopentadiene **2** after screening several chiral dienophiles.[8] We carried out the reaction using a catalytic amount (10 mol%) of rare earth salts (REX_3) in $scCO_2$ and organic solvents for comparison (Scheme 1). We employed rare earth triflate and perchlorate as a catalyst, and the representative results are shown in Table 1. Here, the reaction without REX_3 should be carried out to estimate the contribution from uncatalyzed reaction in $scCO_2$ at 8–10 MPa because an intermolecular cycloaddition reaction can proceed under high pressure (Table 1, entries 1–2): the uncatalyzed reaction scarcely occurred in CH_2Cl_2 (entry 3).[9] The catalyzed reaction in $scCO_2$ (40°C, 10 MPa) proceeded smoothly and more quickly than in CH_2Cl_2 to give the *endo*-(2*R*,4′*S*)-**3** mainly in high yield with moderate to good diastereoselectivities. It is noteworthy that each

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Keywords: Diels–Alder reactions; cyclopentadiene; asymmetric synthesis.

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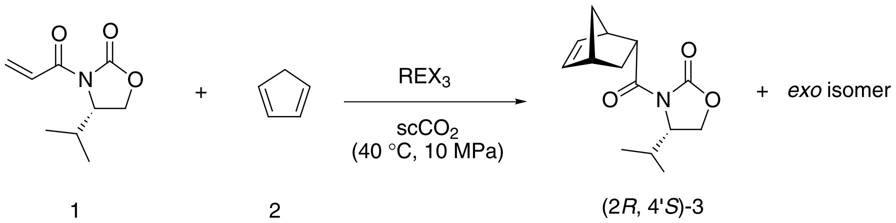


Scheme 1.

catalyzed reaction in $scCO_2$ gave a higher diastereoselectivity than that of the corresponding catalyzed reaction in CH_2Cl_2 even though the reactions were compared at the same temperature (40°C); $La(OTf)_3$ gave 59–62% de of the adduct in $scCO_2$, while it was 38–42% de in CH_2Cl_2 (entries 4–6). Although the catalyzed reaction may be contaminated by the uncatalyzed reaction to some extent, high yield and selectivity were certainly achieved by the rare earth catalyst and $scCO_2$ reaction conditions. As for the rare earth triflates, the diastereoselectivity of the reaction increases in the order of La, Yb, and Sc, suggesting that this is the order of the ionic radius.[10] $La(ClO_4)_3$ and $Yb(ClO_4)_3$ also worked effectively in $scCO_2$ to give the adduct in good diastereoselectivities (entries 11 and 14). A significant enhancement of the diastereoselectivity in $scCO_2$ was also observed in the reaction with $Yb(ClO_4)_3$ at around 8.0 MPa. The chiral rare earth complex (+)-Eu$(hfc)_3$, which catalyzes asymmetric reactions, brought a good stereoselectivity to the reaction (entry 16). This high stereoselectivity may be due to the matching stereochemistry between (+)-Eu$(hfc)_3$ and the chiral auxiliary.

The reaction in $scCO_2$ was always accompanied by the possibility that the reaction might occur in a heterogeneous or phase-separated system, i.e. the catalyst or substrates might not be dissolved in $scCO_2$. The reaction in a non polar solvent such as hexane and toluene (10 ml) where the catalyst $La(OTf)_3$ was not dissolved sufficiently, i.e. the reaction system was apparently heterogeneous, gave the adduct in low selectivities; hexane: 46% de, toluene 40% de (Table 1 entries 7–8). It is reasonable to assume that a catalytic amount of $La(OTf)_3$ could be dissolved in $scCO_2$ sufficiently and work effectively as a catalyst. When the reaction was carried out without a solvent (Table 1, entry 10), the diastereoselectivity was lower (42% de) than that in $scCO_2$ demonstrating that the $scCO_2$ reaction system certainly improved the diastereoselectivity. The apparent heterogeneous reaction using the stoichiometric amount of $La(OTf)_3$ (0.50 mmol), which was not dissolved completely in $scCO_2$ (40°C, 10 MPa), gave almost the same selectivity as the catalytic reaction. From these results, only dissolved $La(OTf)_3$ could work as a catalyst and undissolved one could not. The question on the solubility of substrates may be clarified by carrying out the reaction using larger amounts of substrates. Even if the reaction was carried out using five times the amount of substrates (2.5 mmol) as the usual (0.5 mmol), yield and selectivity were almost the same as the usual case. It would be appropriate to consider that the substrates were dissolved within this range of concentration.

Table 1. Rare earth salt catalyzed diastereoselective Diels–Alder reaction with chiral dienophile **1** in $scCO_2$ and CH_2Cl_2[a]

Entry	REX_3	Solvent	Yield (%)	*endo*/*exo*	de(*endo*) (%)
1	None	$scCO_2$	47	83/17	46
2[b]	None	$scCO_2$	48	89/11	49
3	None	CH_2Cl_2	0	–	–
4	$La(OTf)_3$	$scCO_2$	84	70/30	59
5	$La(OTf)_3$	CH_2Cl_2	92	74/26	38
6[c]	$La(OTf)_3$	CH_2Cl_2	86	77/23	42
7[c]	$La(OTf)_3$	Hexane	34	80/20	46
8[c]	$La(OTf)_3$	Toluene	48	83/17	40
9	$La(OTf)_3$	$C_6H_5CF_3$	92	70/30	38
10[c]	$La(OTf)_3$	None	95	85/15	42
11[d]	$La(ClO_4)_3{\cdot}9H_2O$	$scCO_2$	67	90/10	49
12	$Yb(OTf)_3$	$scCO_2$	91	76/24	50
13	$Yb(OTf)_3$	CH_2Cl_2	96	76/24	32
14[b]	$Yb(ClO_4)_3{\cdot}8H_2O$	$scCO_2$	49	83/17	77
15	$Sc(OTf)_3$	$scCO_2$	95	75/25	49
16	(+)-Eu$(hfc)_3$	$scCO_2$	60	92/8	69

[a] **1** (0.5 mmol), **2** (1.0 mmol), REX_3 (0.05 mmol): in $scCO_2$, 40°C, 10 MPa, 0.5 h; in CH_2Cl_2, 0°C, 0.1 MPa, 2 h.
[b] 40°C, 8 MPa, 0.5 h.
[c] 40°C, 2 h.
[d] MS 4A was added.

We examined the density dependence of diastereoselectivity of the Diels–Alder reaction of **1** with **2** using $La(OTf)_3$ at 40°C. Figure 1 shows a plot of the CO_2 density versus de values (*endo* adduct) for the reaction.[11] The diastereoselectivity seemed to be almost independent on the CO_2 density, but the de value may be somewhat increased in the near critical region (40°C, 7.8 MPa).[12] Selectivity was the lowest in a liquid CO_2, where the CO_2 density is almost 0.9 g/ml. A catalytic amount of the rare earth salt is sufficient for good selectivity, while the reaction with this dienophile always needs a stoichiometric amount of a Lewis acid catalyst to obtain a high stereoselectivity.[8]

2.2. Enantioselective hetero Diels–Alder reaction with Danishefsky's diene 4

Danishefsky et al. first reported the enantioselective hetero Diels–Alder reaction of 1-methoxy-3-trimethylsiloxy-1,3-butadiene **4** (Danishefsky's diene) with benzaldehyde **5** using (+)-Eu$(hfc)_3$ as a catalyst in $CDCl_3$ to give the adduct *R*-**6** after treatment with trifluoroacetic acid in a low enantiomeric excess (18% ee).[13] When we re-examined the reaction in CH_2Cl_2 at room temperature, *R*-**6** was obtained in low yield with low ee% (12% ee) after a long reaction time (24 h) (Table 2, entry 3). As previously stated, the stereoselectivity of the reaction can be improved in $scCO_2$ comparing to the reaction in the organic solvent. We then applied the reaction in $scCO_2$ (50°C, 10 MPa) expecting the enhancement effect of stereoselectivity (Scheme 2). Table 2 summarizes the results of the chiral rare earth complex catalyzed hetero Diels–Alder reaction in $scCO_2$. A yield of the product was significantly improved, but the enantio-

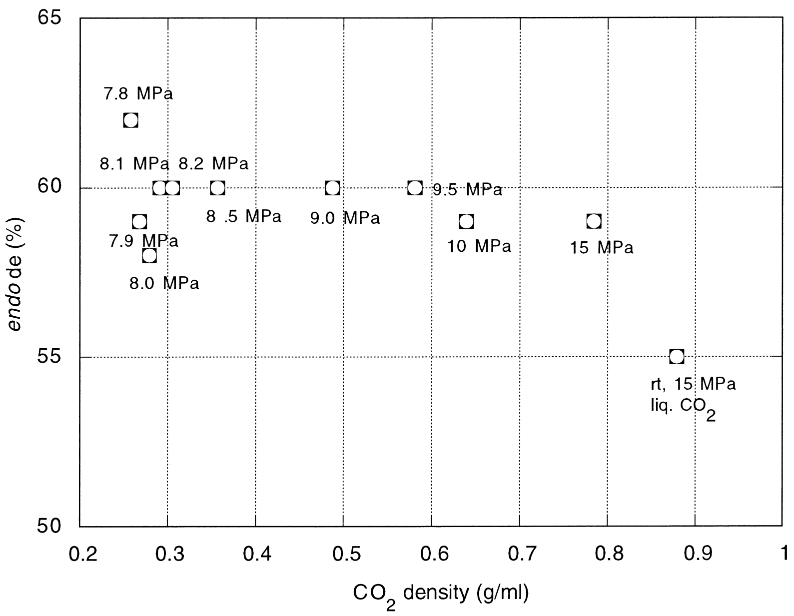


Figure 1. Co_2 density vs. *endo* de% in the Diels–Alder reaction with the chiral dienophile **1**.

Table 2. Chiral rare earth complex catalyzed enantioselective hetero Diels–Alder reaction with Danishefsky's diene **4** in $scCO_2$ and CH_2Cl_2[a]

Entry	REL^*_3	Slovent	Yield (%)	ee(config) (%)
1	None	CH_2Cl_2	0	–
2	None	$scCO_2$	0	–
3[b]	(+)-Eu(hfc)$_3$	CH_2Cl_2	22	12 (*R*)
4	(+)-Eu(hfc)$_3$	$scCO_2$	67	22 (*R*)
5	(+)-Yb(hfc)$_3$	CH_2Cl_2	18	23 (*R*)
6	(+)-Yb(hfc)$_3$	$scCO_2$	78	35 (*R*)
7	(+)-Sc(hfc)$_3$	CH_2Cl_2	14	31 (*R*)
8	(+)-Sc(hfc)$_3$	$scCO_2$	66	38 (*R*)
9[c]	**7**: Yb(BNP)$_3$	CH_2Cl_2	50	73 (*R*)
10	**7**: Yb(BNP)$_3$	$scCO_2$	20	13 (*R*)
11	Sc(OTf)$_3$/**8a**	CH_2Cl_2	93	0
12	Sc(OTf)$_3$/**8a**	$scCO_2$	39	3
13	Yb(OTf)$_3$/**8a**	CH_2Cl_2	71	0
14	Yb(OTf)$_3$/**8a**	$scCO_2$	30	5

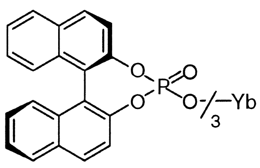
[a] **4** (0.7 mmol), **5** (0.5 mmol), REL^*_3 (0.05 mmol): in $scCO_2$, 50°C, 10 MPa, 0.5 h; in CH_2Cl_2, 25°C, 0.1 MPa, 24 h.

[b] 18% ee in $CDCl_3$ (Ref. 11).

[c] Ref. 14a.

selectivity was still low (22% ee) though it was increased (entry 4). The use of (+)-Yb(hfc)$_3$ and (+)-Sc(hfc)$_3$ improved enantioselectivity to 35–38% ee. These values were higher than those in CH_2Cl_2 (entries 5–8). The reaction must not be contaminated by an uncatalyzed reaction because it scarcely proceeded in the absence of a catalyst even under the high-pressure $scCO_2$ conditions (entry 2).

Because the enantioselectivity with (+)-Sc(hfc)$_3$ was still unsatisfactory, we employed tris[(*R*)-1,1′-binaphtyl-2,2′-phosphonate] ytterbium [Yb(BNP)$_3$] **7** which is known to bring good enantioselectivity to the hetero Diels–Alder reaction.[14] However, it did not work effectively and resulted in a low yield and selectivity probably due to its low solubility in $scCO_2$. A combination of rare earth triflate and pybox (pyridine bisoxazoline) **8a** gave poor results either in CH_2Cl_2 or $scCO_2$.[15] These results are also shown in Table 2.



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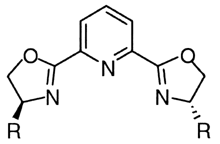
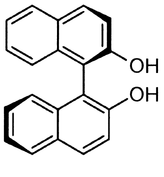


8a: R = *i*Pr
8b: R = Ph
8c: R = Bn
8d: R = *t*Bu



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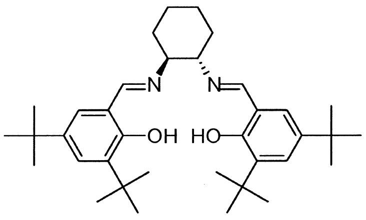

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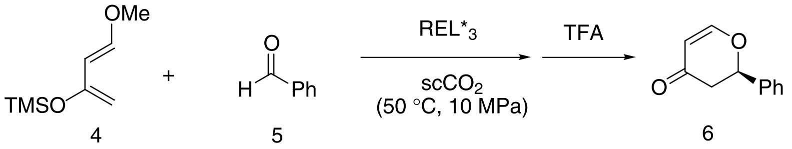
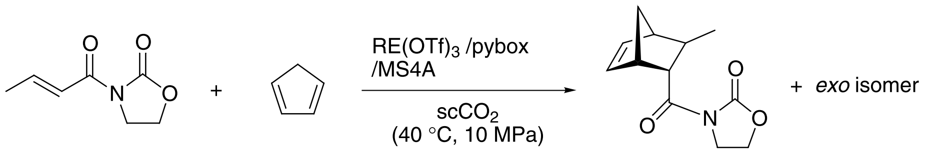


Scheme 2.



9: R = Me **2** (2*S*, 3*R*)-**10**

Scheme 3.

Table 3. Rare earth triflate/pybox catalyzed enantioselective Diels–Alder reaction with 3-crotonoyloxazolidine-2-one **9b** in $scCO_2$[a]

Entry	$RE(OTf)_3$	Pybox	Yield (%)	*endo*/*exo*	ee(*endo*) (%)
1	None	–	0	–	–
2[b]	None	–	0	–	–
3	$Sc(OTf)_3$	**8a**	71	93/7	83 (2*S*,3*R*)
4[c]	$Sc(OTf)_3$	**8a**	68	85/15	63 (2*S*,3*R*)
5[b]	$Sc(OTf)_3$	**8a**	94	90/10	83 (2*S*,3*R*)
6	$Sc(OTf)_3$	**8b**	75	95/5	41 (2*S*,3*R*)
7	$Sc(OTf)_3$	**8c**	33	88/12	54 (2*S*,3*R*)
8	$Sc(OTf)_3$	**8d**	41	92/8	70 (2*S*,3*R*)
9	$Sc(OPf)_3$	**8a**	65	89/11	61 (2*S*,3*R*)
10	$Y(OTf)_3$	**8a**	9	96/4	24 (2*S*,3*R*)
11	$La(OTf)_3$	**8a**	Trace	–	–
12	$Sm(OTf)_3$	**8a**	Trace	–	–
13	$Yb(OTf)_3$	**8a**	21	89/11	25 (2*S*,3*R*)

[a] **9** (0.25 mmol), **2** (0.75 mmol), $RE(OTf)_3$ (0.025 mmol), pybox **8** (0.025 mmol): in $scCO_2$, 40°C, 10 MPa, 0.5 h.

[b] In CH_2Cl_2, 0°C, 18 h.

[c] Without MS4A.

2.3. Enantioselective Diels–Alder reaction of 3-acyloxazolidin-2-one 9 with cyclopentadiene

Because the combination of rare earth triflate and pybox **8a** was effective for the enantioselective Diels–Alder reaction with 3-acyloxazolidin-2-one in CH_2Cl_2, the complex was applied in the $scCO_2$ reaction (Scheme 3).[16] Table 3 summarizes the reaction of 3-crotonoyl-2-oxazolidinone **9** with cyclopentadiene **2** in $scCO_2$ (40°C, 10 MPa) where additional pybox derivatives (**8a–d**) and representative rare earth triflates were examined. The combination of $Sc(OTf)_3$ and **8a** afforded the *endo*-(2*S*,3*R*)-**10** product (*endo*/*exo*=80:20–98:2) in a good yield with high enantioselectivity (83% ee). The value of ee% was as high in $scCO_2$ as in CH_2Cl_2 even though the reaction was carried out at a higher temperature (40°C) than in CH_2Cl_2 (0°C) (entries 3 and 5). A contribution of the uncatalyzed reaction need not be considered because no reaction proceeded without the catalyst under the conditions (Table 3, entry 1). The addition of MS4A was essential to achieve high enantioselectivity, the %ee value decreasing to 63% without it (entry 4). As for the pybox derivative, the isopropyl derivative **8a** was most effective, the phenyl, benzyl, and *t*-butyl ones **8b**–**8d** affording lower ee% (entries 6–8). Rare earth triflates other than scandium were not suitable for this reaction, they work poorly as a catalyst (entries 10–13). It is worth noting that the reaction proceeded more rapidly in $scCO_2$; the adduct can be obtained in a good yield in a short time (0.5 h), while the reaction in CH_2Cl_2 requires 18 h for completion. Since Mikami et al. reported that an asymmetric Mukaiyama aldol reaction $scCO_2$ by a chiral titanium complex resulted in a low yield with a moderate ee%,[3] it has been thought that the Lewis acid catalyzed asymmetric reaction in $scCO_2$ may have been difficult. However, this first success of the $Sc(OTf)_3$/**8a** catalyzed reaction in $scCO_2$ may be a landmark of Lewis acid catalyzed asymmetric synthesis in $scCO_2$ with an advantage over the reaction in a harmful organic solvent.

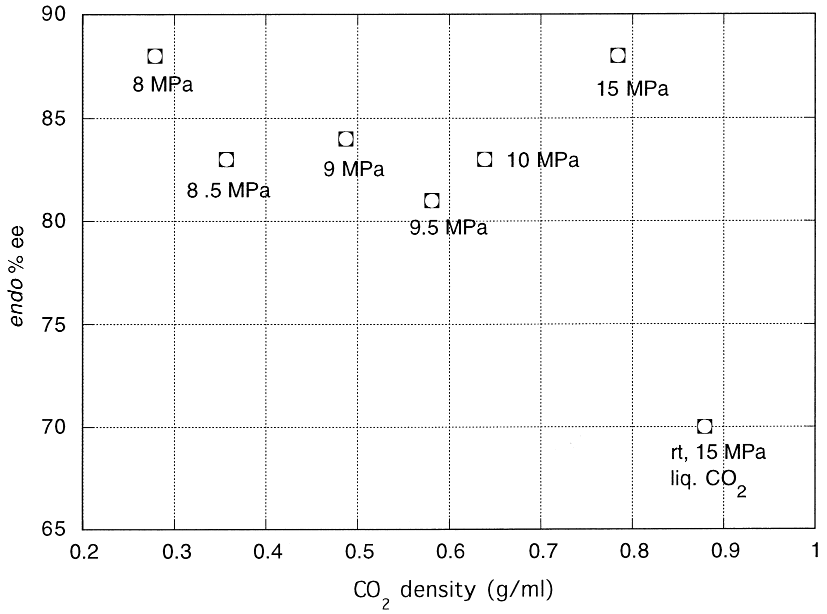
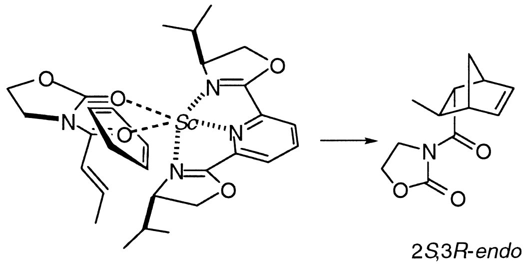


Figure 2. Co_2 density vs. *endo* ee% in the enantioselective Diels–Alder reaction.

The combination of Sc(OTf)$_3$ with (*R*)-BINOL **11**[17] and (*S*,*S*)-salen **12**,[18] which are effective for the reaction in CH$_2$Cl$_2$, did not give reasonable results: **11**, 38% yield, 8% ee; **12** 18% yield, 18% ee.

The pressure dependence of the enantioselectivity was examined even in here, as it was examined in the former diastereoselective reaction. Figure 2 shows a plot of the CO$_2$ density versus ee% values (*endo*-**10**) for the reaction at 40°C. The ee% value was almost independent from the CO$_2$ density (pressure): The ee% values 82–88% may involve the experimental error except for the reaction in liquid CO$_2$.

The stereochemical course of the cycloaddition can be explained by the chelation model as illustrated in Scheme 4.[19] In this model two carbonyl groups in the dienophile **9b** coordinate to scandium as the alkene group directed toward the less hindered site where the isopropyl group does not shield the space. MS4A may promote coordination of the oxazolidinone group to the scandium metal center. The attack of cyclopentadiene from the *si* face is favored, and the (*S*,*R*)-*endo* adduct would be a major product.



Scheme 4.

3. Conclusions

Stereoselectivities in the rare earth catalyzed Diels–Alder reaction were significantly increased in scCO$_2$ compared to the reactions in CH$_2$Cl$_2$ by optimizing the CO$_2$ pressure. Though the actual reason for the enhanced stereoselectivity in scCO$_2$ is not yet clarified, there is a potential for the REX$_3$ catalyzed asymmetric reaction in scCO$_2$ in the area of stereoselective synthesis.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR (300 MHz) or JEOL A-400 NMR (400 MHz) spectrometer as solutions in CDCl$_3$. The chemical shifts are reported in δ units downfield from the internal reference, Me$_4$Si. The infrared spectra were obtained using a JASCO Herschel FT/IR-230A spectrometer. The HPLC analyses were carried out on a Hitachi L-7100 apparatus equipped with a UV detector using chiral columns. The GC/MS analyses were carried out on a Hewlett–Packard 5980/5972 instrument equipped with a capillary column (HP-5ms) (0.25 mm, 30 m) (helium as carrier gas). The optical rotations were determined by a JASCO DIP-370 apparatus. The elemental analyses were carried out using a Yanaco CHN CORDER MT-5. Preparative TLC was conducted using a 20×20 cm glass sheet coated with a 2-mm-thick layer of Merck Kieselgel 60 PF$_{254}$

4.2. Materials

Chiral and achiral 3-acyloxazolidin-2-ones were prepared from the reaction of acyl chlorides with the corresponding chiral and achiral oxazolidin-2-ones by the reported method.[8] (+)-Eu(hfc)$_3$ and (+)-Yb(hfc)$_3$ were purchased from Aldrich, and (+)-Sc(hfc)$_3$ was prepared from ScCl$_3$ and heptafluorocamphor according to the literature method.[20] Lanthanum(III) and ytterbium(III) perchlorates were purchased from Soekawa Chemicals Co., Ltd. All rare earth (Sc, Y, La, Yb) triflates were prepared by the literature method.[21] All pybox derivatives **8a–d** were commercially available (TCI Co., Ltd) except *tert*-Bu derivative **8d**, which was prepared by the reported method.[22] Danishefsky's diene (1-methoxy-3-(trimethylsiloxy)-1,3-butadiene) was purchased from Aldrich Co., Ltd and used without further purification. Cyclopentadiene was obtained by pyrolytic distillation of dicyclopentadiene at 180°C just prior to use. All other commercial organic compounds were used without further purification.

4.3. Reactor

As with all reactions under high pressure, adequate safety precautions must be taken. For carrying out reactions in scCO$_2$, a stainless steel cylindrical vessel with a volume of 10 ml and see-through windows (sapphire glass) (JASCO VCI) was used. Stirring is accomplished with a remote magnetic stirrer. A Swagelok pressure relief valve with a release pressure of 40 MPa is employed as a safety precaution. Reagents can be injected into the system using a Rheodyne injector valve. The system is pressurized using a JASCO PU-1580 HPLC pump equipped with a cooling unit, which draws from a CO$_2$ cylinder. Temperature control is accomplished by covering the vessel with a hot-water jacket. The flow diagram of the scCO$_2$ reactor is illustrated in Figure 3.

4.3.1. Diels–Alder reaction of 3-acryloyl-(4*S*)-isopropyl-oxazolidin-2-one 1 with cyclopentadiene 2 in scCO$_2$. The following provides the typical experimental procedure for the rare earth salt catalyzed Diels–Alder reaction of **1** with **2** in scCO$_2$. La(OTf)$_3$ (30.0 mg, 0.05 mmol, 10 mol%) and **1** (91.6 mg, 0.5 mmol) were placed in the pressure vessel with a magnetic stirring bar. The vessel was then sealed and charged to 7.0 MPa pressure with cooled CO$_2$ at 40°C. Stirring at 40°C was started, and a period of 15–20 min was allowed for equilibration. Freshly distilled **2** (82 ml, 1.0 mmol) was injected into the system, and the pressure increased to the desired level (8–10 MPa). After 0.5 h, the stirring and heating was stopped and the vessel was immersed in a dry ice–methanol bath. The pressure was then released through a trap of ethyl acetate (20 ml), and the vessel was washed with more ethyl acetate (30 ml) and water (30 ml). The combined organic layer was washed with brine and dried over MgSO$_4$. GC/MS analysis (J and W, HP-5ms, 30 m, He as carrier gas) of the solution revealed the presence of the stereoisomeric mixture of adducts **3**

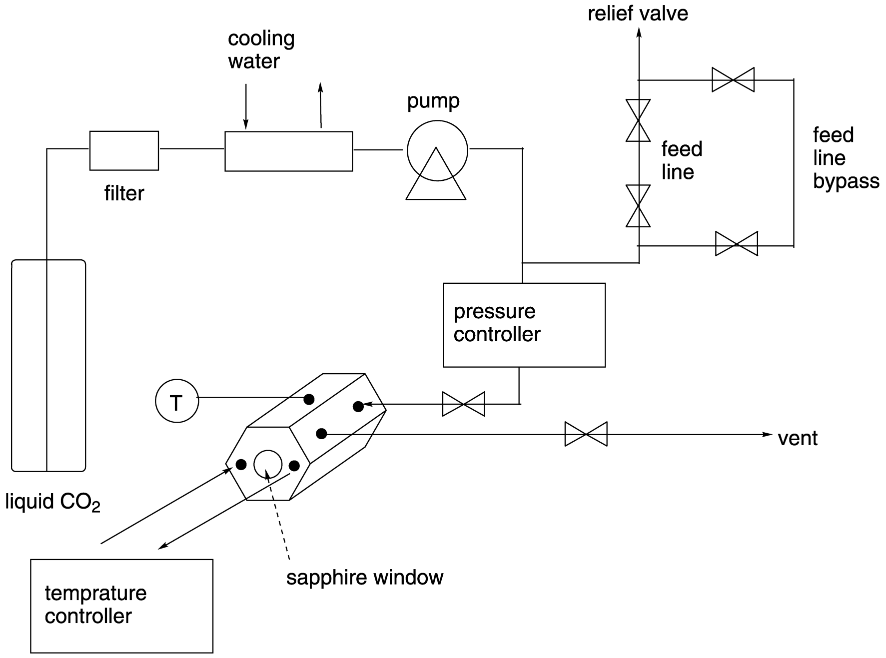


Figure 3. Reactor of scCo$_2$ and flow diagram.

(conversion 84%). The diastereomeric excess of the *endo* adduct was determined by GC/MS: temperature program; 180°C, 5 min, 4°C/min, 200°C, 20 min, 110 kPa, retention time; 8.8 min (*endo* minor), 9.0 min (*exo*), and 9.3 min (*endo* major). Evaporation of the solvent left a pale orange residue that was subjected to preparative TLC (hexane/ethyl acetate=4:1) to give *endo*-(2*R*,4′*S*)-**3** mainly.[8] Colorless oil. $[\alpha]_D^{25}$=+208.4 (*c*=0.23, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.85 (d, 6H, *J*=7.30 Hz), 1.4–2.6 (m, 5H), 2.89 (s, 1H), 3.32 (s, 1H), 3.8–4.4 (m, 4H), 5.73 (dd, 1H, *J*=2.7, 5.6 Hz), 6.20 (dd, 1H, *J*=3.2, 5.6 Hz); ^{13}C NMR: δ 14.4, 17.8, 28.1, 28.5, 42.9, 43.2, 46.8, 50.2, 58.2, 63.0, 130.8 130.8, 153.8, 174.1. Anal calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.35; H, 7.71; N, 5.56.

4.3.2. Hetero Diels–Alder reaction of Danishefsky's diene 4 with benzaldehydes 5 in scCO$_2$. The following provides the typical experimental procedure for the rare earth salt catalyzed hetero Diels–Alder reaction of Danishefsky's diene **4** with benzaldehyde **5** in scCO$_2$. (+)-Yb(hfc)$_3$ (6.1 mg, 0.005 mmol, 1.0 mol%) and **5** (53 mg, 0.5 mmol) were placed in the pressure vessel with a magnetic stirring bar. The vessel was then sealed and charged to 7.0 MPa pressure with cooled CO$_2$ at 50°C. Stirring at 50°C was started, and a period of 15–20 min was allowed for equilibration. **4** (120 ml, 0.7 mmol) was injected into the system, and the pressure increased to the desired level (10 MPa). After 0.5 h, stirring and heating was stopped and the vessel was immersed in a dry ice–methanol bath. The pressure was then released through a trap of ethyl acetate (20 ml), and the vessel was washed with more ethyl acetate (30 ml) and water (30 ml). The combined organic layer was washed with brine and dried over MgSO$_4$. Evaporation of the solvent left yellow oil that was treated with three drops of trifluoroacetic acid and four drops of pyridine. The resulting mixture was directly subjected to PTLC to give *R*-**6** (68.0 mg, 0.39 mmol, 78%), whose enantiomeric purity was determined to be 35% ee by HPLC using DAICEL CHIRALCEL OD-H (2-propanol/hexane=10:90, flow rate 0.5 ml/min, retention time; 23.4 min (*S*-enantiomer) and 27.2 min (*R*-**6**). Pale yellow liquid: $[\alpha]_D^{25}$=−56.5 (*c*=0.35, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.67 (dd, 1H, *J*=16.8, 3.2 Hz, one of CH$_2$C=O), 2.91 (dd, 1H, *J*=14.4, 16.8 Hz, one of CH$_2$C=O), 5.43 (dd, 1H, *J*=14.4, 3.2 Hz, CHPh), 5.53 (d, 1H, *J*=6.4 Hz, =CHC=O), 7.40 (s, 5H, Ph), 7.47 (d, 1H, *J*=6.4 Hz, =CO); ^{13}C NMR (CDCl$_3$): δ 43.0 (CH$_2$), 80.8 (CHPh), 107.1 (=*C*HC=O), 125.9, 128.6, 128.7, 137.6, 163.1 (=CO), 192.0 (C=O); IR (neat): 1675 ($\nu_{C=O}$), 1594 ($\nu_{C=C}$) cm^{-1}. Anal calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.78; H, 5.43.

4.3.3. Enantioselective Diels–Alder reaction of 3-acyloxazolidin-2-one 9 with 2 in scCO$_2$. The following provides the typical experimental procedure for the rare earth salt catalyzed Diels–Alder reaction of **9** with cyclopentadiene in scCO$_2$. Sc(OTf)$_3$ (12.3 mg, 0.025 , 10 mol%), **8a** (7.5 mg, 0.025 mmol), MS4A (75 mg), and **9** (38.8 mg, 0.25 mmol) were placed in the pressure vessel with a magnetic stirring bar. The vessel was then sealed and charged to 7.0 MPa pressure with cooled CO$_2$ at 40°C. Stirring at 40°C was started, and a period of 15–20 min was allowed for equilibration. Freshly distilled **2** (62 ml, 0.75 mmol) was injected into the system, and the pressure increased to the desired level (10 MPa). After 0.5 h, stirring and heating was stopped and the vessel was immersed in a dry ice–methanol bath. The pressure was then released through a trap of ethyl acetate (20 ml), and the vessel was washed with more ethyl acetate (30 ml) and water (30 ml). The combined organic layer was washed with brine and dried over MgSO$_4$. Evaporation of the solvent left a yellow residue which was subjected to PTLC (hexane/ethyl acetate=5:1 as an eluent) to give a mixture of *endo* and *exo* adduct (*endo*/*exo*=93:7) (39.0 mg, 71% yield). The enantiomeric purity of the *endo*-**10** was determined to be 83% ee by HPLC using DAICEL CHIRALPAK AD

(2-propanol/hexane=2.5:97.5, flow rate 1.0 ml/min, retention time; 19.2 min (*exo*), 20.0 min [(2*S*,3*R*)-*endo* **10**] 21.6 min (*exo* enantiomer), and 23.6 min (*endo* enantiomer).[15] Colorless solid, mp 88–89°C; $[\alpha]_{D}^{25}=-167.5$ (c=0.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, 3H, J=7.1 Hz), 1.48 (d, 1H, J=8.5 Hz), 1.70 (d, 1H, J=8.5 Hz), 2.05–2.10 (m, 1H), 2.52 (br s, 1H), 3.28 (br s, 1H), 3.55 (dd, 1H, J=4.39, 3.90), 3.9–4.1 (m, 2H), 4.41 (t, 2H, J=8.1 Hz), 5.79 (dd, 1H, J=2.7, 5.7 Hz), 6.37 (dd, 1H, J=3.2, 5.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.6, 36.6, 43.2, 47.3, 47.7, 49.7, 51.5, 62.1, 131.2, 139.9, 153.7, 174.6; IR (KBr) 1768, 1685 ($\nu_{C=O}$) cm^{-1}. Anal calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.44; H, 6.81; N, 6.28.

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