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Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters with Chiral Yttrium–Biaryldiol Complexes

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Abstract: The full details of the asymmetric epoxidation of α,β-unsaturated esters catalyzed by yttrium complexes with biaryldiol ligands are described. An yttrium–biphenyldiol catalyst, generated from $Y(OiPr)_3$–biphenyldiol ligand–triphenylarsine oxide (1:1:1), is suitable for the epoxidation of various α,β-unsaturated esters. With this catalyst, β-aryl α,β-unsaturated esters gave high enantioselectivities and good yields (≤99% *ee*). The reactivity of this catalyst is good, and the catalyst loading could be decreased to as little as 0.5–2 mol% (the turnover number was up to 116), while high enantiomeric excesses were maintained. For β-alkyl α,β-unsaturated esters, an yttrium–binol catalyst, generated from $Y(OiPr)_3$–binol ligand–triphenylphosphine oxide (1:1:2), gave the best enantioselectivities (≤97% *ee*). The utility of the epoxidation reaction was demonstrated in an efficient synthesis of (−)-ragaglitazar, a potential antidiabetes agent.

Keywords: asymmetric catalysis · asymmetric synthesis · epoxidation · rare-earth metals · yttrium

Introduction

Chiral epoxides are synthetically versatile building blocks, and, therefore, asymmetric epoxidations are interesting to synthetic organic chemists.[1] Among asymmetric epoxidations, catalytic asymmetric epoxidation of electron-deficient olefins is one of the most important classes of reactions.[2] Since the early reports by Wynberg and co-workers,[3a] Julia et al.,[3b] and others,[2] catalytic asymmetric epoxidation of α,β-unsaturated ketones has been intensively studied by many groups,[2,4] including ours.[5] High enantioselectivity and broad substrate generality are realized with α,β-unsaturated ketones. There are only a few reports, however, in which α,β-unsaturated esters have been used as substrates, and this is probably because the reactivity of α,β-unsaturated esters is much lower than that of α,β-unsaturated ketones. A salen–manganese complex[6] (salen = *N*,*N*′-ethylenebis(salicylideneiminato) and chiral ketones[7] have been utilized for catalytic asymmetric epoxidation of α,β-unsaturated esters. These catalysts, however, are not applicable to substrates that have functional groups such as carbon–carbon double bonds and ketones, owing to chemoselectivity issues. Thus, there remains room for improvement, particularly in terms of substrate generality.

As part of our continuing research program on the asymmetric epoxidation of electron-deficient olefins,[5] we have investigated a series of rare-earth metal–binol complexes for epoxidations of α,β-unsaturated *N*-acylimidazoles,[8] amides,[9] and *N*-acylpyrroles[10] as carboxylic acid derivatives. Our strategy relies on Wietz–Scheffer-type epoxidation,[11] for which 1,4-addition of a rare-earth metal peroxide generated in situ from a rare-earth metal–binol complex and *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CMHP) is used. Thus, chemoselective epoxidation of an electron-deficient carbon–carbon double bond in the presence of other functional groups can be realized. We previously communicated a catalytic asymmetric epoxidation of α,β-unsaturated esters, for which a new yttrium–biphenyldiol complex **1a** (Figure 1) was used.[12] Although **1a** gave excellent enantiomeric excesses for β-aryl α,β-unsaturated esters (mostly >95% *ee*), the enantioselectivity of β-alkyl α,β-unsaturated esters was less satisfactory (mostly <95% *ee*). In this article, we report the full details of the asymmetric epoxidation of α,β-unsaturated esters catalyzed by the yttrium–biaryldiol ligand complex. Trials to improve the enan-

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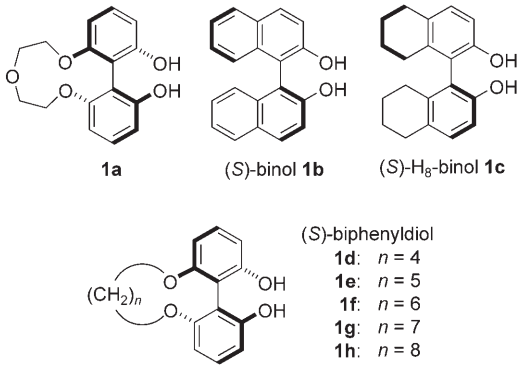
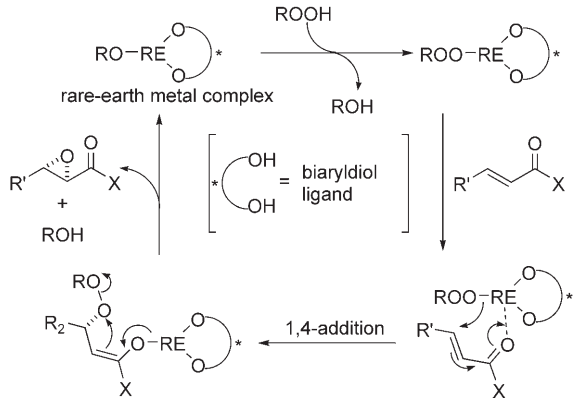


Figure 1. Structures of (*S*)-biaryldiol ligands **1a**–**h**.

tioselectivity for β-alkyl α,β-unsaturated esters as well as synthetic applications are also described.

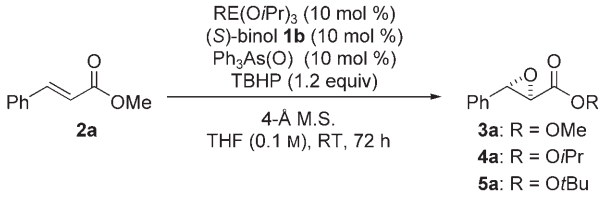
Results and Discussion

In rare-earth-metal-catalyzed epoxidation reactions, the rare-earth metal (RE) has two functions.[13] As shown in the proposed catalytic cycle in Scheme 1,[14] an RE alkoxide moiety functions as a Brønsted base to generate an RE peroxide in situ, while at the same time functioning as a Lewis acid to activate an electrophile. 1,4-Addition of the RE peroxide to an α,β-unsaturated compound affords an enolate intermediate; this is followed by epoxide formation to regenerate the RE alkoxide. For this reaction to be promoted efficiently, it is important that the Lewis acidity of the RE and the nucleophilicity of the RE peroxide are in balance. A suitable RE–ligand complex should be selected on the basis of the properties of the substrate. Guided by our related previous epoxidations,[8–10] we examined the RE effects with 10 mol% (*S*)-binol **1b** as ligand, 10 mol% triphenylarsine oxide as an additive (Table 1, entries 1–5), and methyl



Scheme 1. Postulated catalytic cycle of asymmetric epoxidation promoted by a chiral RE–biaryldiol complex.

Table 1. RE effects in catalytic asymmetric epoxidation of **2a** with RE(O*i*Pr)$_3$, (*S*)-binol **1b**, and $Ph_3As(O)$.



Entry	RE	Yield of **3a**[a] [%]	Yield of **4a**+**5a**[b] [%]	*ee* of **3a**[c] [%]
1	La	7	–	75
2	Pr	24	–	88
3	Sm	8	–	94
4	Gd	13	–	94
5	Dy	33	3	96
6	Y	36	5	95
7	Sc	0	–	–

[a] Yield of isolated analytically pure compound. [b] Isolated as a mixture of **4a** and **5a**. [c] Determined by chiral HPLC. M.S. = molecular sieves.

(*E*)-cinnamate (**2a**) as substrate. In our previous studies of α,β-unsaturated ketones,[5] *N*-acylimidazoles,[8] amides,[9] and *N*-acylpyrroles,[10] either La(O*i*Pr)$_3$ or Sm(O*i*Pr)$_3$ gave the best enantioselectivities and reactivities; however, neither La(O*i*Pr)$_3$ (Table 1, entry 1, 7% yield, 75% *ee*) nor Sm(O*i*Pr)$_3$ (Table 1, entry 3, 8% yield, 94% *ee*) gave satisfactory results. Among the REs and first-column transition metals examined (Table 1, entries 1–7), Y(O*i*Pr)$_3$ afforded the desired product **3a** in 95% *ee* and 36% yield (Table 1, entry 6), together with 5% of the epoxy isopropyl and *tert*-butyl esters **4a** and **5a**. In a control experiment in which the sterically hindered isopropyl (*E*)-cinnamate was used under the same reaction conditions, no reaction took place. Therefore, *trans* esterification occurred only from α,β-epoxy methyl ester **3a**. Isopropyl alcohol and *tert*-butyl alcohol were derived from Y(O*i*Pr)$_3$ and TBHP.

In our previous studies on asymmetric epoxidation of α,β-unsaturated *N*-acylpyrroles,[10] the dihedral angle as well as the electronic properties of the biaryl ligands affected reactivity and enantioselectivity. Therefore, we investigated ligand effects using H_8-binol **1c**[15] and 2,2′-biphenyldiol ligands **1d**–**h** (Figure 1 and Table 2). The ligand H_8-binol **1c** with a large dihedral angle gave trace amounts of product

Abstract in Japanese:

Y(O*i*Pr)$_3$、ビフェニルジオール配位子 **1a** 及び Ph_3As=O を 1:1:1 の比で調製した Y-**1a** 触媒は広汎なα，β-不飽和エステルの触媒的不斉エポキシ化反応に適した触媒系である。特に、β-アリール置換のα，β-不飽和エステルから高い収率及び不斉収率（最高 99% ee）で目的のエポキシドを得ることができた。Y-**1a** 触媒は高い反応性を示し、エナンチオ選択性を保ったまま触媒量を 0.5-2 mol % にまで減じることに成功した（最大触媒回転数 116 回）。また Y(O*i*Pr)$_3$, BINOL **1b** 及び Ph_3P=O を 1:1:2 の比で調製した Y-**1b** 触媒は、β-アルキル置換のα，β-不飽和エステルに対して良好なエナンチオ選択性で目的物を与えた（最大 97% ee）。また本エポキシ化反応の有用性を示すべく、糖尿病治療候補薬である(−)-ラガグリタザールの効率的合成を行った。

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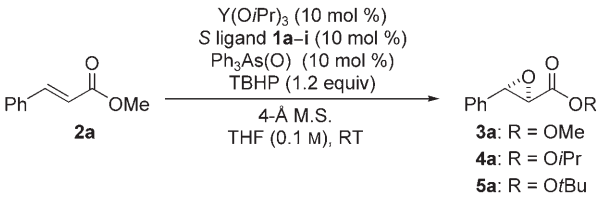
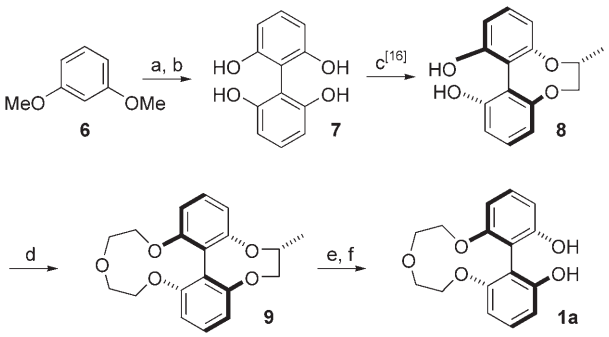
Table 2. Ligand effects in catalytic asymmetric epoxidation of **2a** with $Y(OiPr)_3$, (*S*)-biaryldiol ligands **1a**–**i**, and $Ph_3As(O)$.



Entry	Ligand	Dihedral angle[a]	*t* [h]	Yield of **3a**[b] [%]	Yield of **4a**+**5a**[c] [%]	*ee* of **3a**[d] [%]
1	**1b**	89.0	72	36	5	95
2	**1c**	101.9	72	trace	–	–
3	**1d**	62.7	144	4	14	92
4	**1e**	73.1	120	45	26	98
5	**1f**	73.5	120	49	33	99
6	**1g**	78.1	110	64	14	99
7	**1h**	76.5	110	28	30	98
8	**1a**	75.1	48	61	28	99

[a] Calculated by using the B3LYP method with 6-31G* as basis sets. For detailed calculation conditions, see Supporting Information. [b] Yield of isolated analytically pure compound. [c] Isolated as a mixture of **4a** and **5a**. [d] Determined by chiral HPLC.



Scheme 2. Synthesis of (*S*)-biphenyldiol ligand **1a**. Reagents and conditions: a) i) BuLi, TMEDA, THF, −78 to 0 °C, 4 h; ii) $FeCl_3$, 0 °C to room temperature, 2 h, 69 %; b) BBr_3, CH_2Cl_2 −78 °C to room temperature, 87 %; c) (*S*)-1,2-propanediol bismesylate, Cs_2CO_3, DMF, 80 °C, 16 h, 68 %; d) $(BrCH_2CH_2)_2O$, K_2CO_3, DMF, 80 °C, 9 h, 70 %; e) lithium 4,4′-di-*t*Bu-biphenyl, THF, 0 °C, 1 h, 74 %, 98 % *ee*; f) enantio-enrichment as quinine salt. DMF = *N*,*N*-dimethylformamide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyleneethylenediamine.

(Table 2, entry 2). Therefore, less-hindered 2,2′-biphenyldiols were examined in detail. To investigate the effects of the dihedral angle, we synthesized 2,2′-biphenyldiols **1d**–**h** with various linker lengths (Figure 1).[16,17] Ligand **1d** with a four-carbon linker (calculated dihedral angle: 62.7°) gave poor results (Table 2, entry 4), whereas ligands **1e**–**g** with five- to seven-carbon linkers (73.1°–78.1°) resulted in good conversion of ester **2a** (Table 2, entries 4–6, 71–82 % total yield of epoxides **3a**, **4a**, and **5a**), although there was a significant amount of *trans* esterification. Ligand **1h** with an eight-carbon linker also afforded better results than binol **1b** (Table 2, entry 7, 58 % total yield), although the yield was slightly worse than with ligands **1e**–**g**. Good conversion was achieved with ligands **1e**–**g** (Table 2, entries 4–6), but the long reaction time (5 days) was problematic.

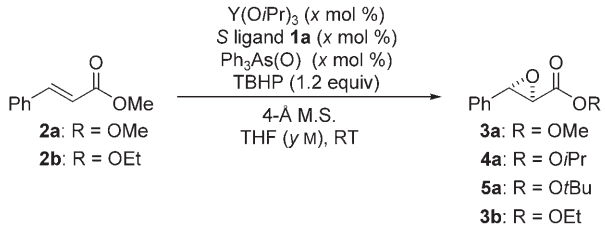
The effect of a heteroatom in the linker on the reaction rate was then examined, because heteroatoms in ligands often change the coordination nature of RE catalysts and drastically change reactivity and/or enantioselectivity.[18] When ligand **1a** linked by diethylene ether was used (Table 2, entry 8), the reaction rate increased and the epoxides were obtained in 89 % yield (61 % **3a** and 28 % **4a** and **5a**) after 48 h. The linker length as well as the dihedral angle of **1a** (75.1°) was similar to those of **1e** with its five-carbon linker. Although the precise reason for the positive effects of the diethylene ether linker is unknown, we speculate that an oxygen atom in the linker would increase the polarity of the ligand, thereby promoting the generation of a reactive monomeric yttrium species.

The procedure used to prepare ligand **1a** is summarized in Scheme 2. For the protection of tetraol **7** with (*S*)-propane-1,2-diol bismesylate, a reported procedure was followed.[16a] Linkage with a diethylene ether followed by selective cleavage of the chiral auxiliary afforded **1a** in 98 % *ee*. Partial racemization occurred during deprotection. Ligand **1a** was obtained in enantiomerically pure form (>99 % *ee*) after enantio-enrichment as a **1a**–quinine salt.

The attempts to decrease catalyst loading are summarized in Table 3. As shown in Table 3, entries 1–4, catalyst loading was successfully lowered to 5, 3, and 2 mol % without any problems. The concentration of catalyst was kept constant to obtain good reactivity and selectivity.[19] Therefore, when the catalyst loading was decreased, the substrate concentration was increased accordingly. In Table 3, entry 5, the reaction was performed in 1.0 M of **2a**. The volumetric productivity of the present system is noteworthy. On the other hand, it was difficult to suppress *trans* esterification with methyl ester **2a**. Therefore, we changed the substrate from methyl cinnamate (**2a**) to ethyl cinnamate (**2b**) to simplify the analysis by suppressing *trans* esterification. The epoxidation of **2b** was smoothly promoted by 2 mol % of $Y(OiPr)_3$, (*S*)-biphenyldiol **1a**, and $Ph_3As(O)$ (1:1:1), giving **3b** in 89 % yield and 99 % *ee* (Table 3, entry 6). With ethyl ester **2b**, only trace *trans* esterification was observed. With 1 mol % catalyst, the reaction stopped at 62 % conversion under standard reaction procedures, in which 1.2 equivalents of TBHP was added in one portion (Table 3, entry 7). We speculate that TBHP in great excess in the reaction mixture would decompose the yttrium catalyst. Therefore, a part of the TBHP was added slowly over 12 h, and this resulted in a better yield of **3b** (Table 3, entry 8, 86 % yield, turnover number (TON) = 86, 99 % *ee*). With 0.5 mol % catalyst, the reaction stopped at 58 % conversion, even though TBHP was added slowly over 24 h (Table 3, entry 9, TON = 116).

With a suitable ligand **1a** in hand, we re-examined the effect of the RE to confirm the superiority of $Y(OiPr)_3$ over other metals (Table 4). The reactivities matched the reported values of the Lewis acidities of the REs well.[20] The relationship between the yield and *ee* of epoxide **3b** and the Lewis acidity of the REs is summarized in Figure 2. The yield was lowest with the less Lewis acidic metals lanthanum

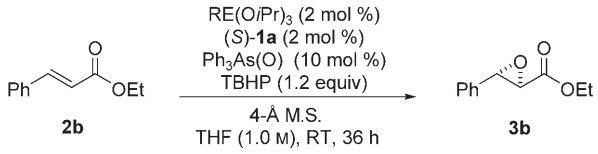
Table 3. Trials to reduce catalyst loading.[a]



Entry	Ester	x [mol %]	y[b] [M]	t [h]	Yield of **3**[c] [%]	Yield of **4a**+**5a**[d] [%]	TON	*ee* of **3**[e] [%]
1	**2a**	10	0.1	48	61	28	8.9	99
2	**2a**	5	0.2	48	65	21	17.2	99
3	**2a**	3	0.33	48	79	11	30	99
4	**2a**	2	0.5	48	77	12	44.5	99
5	**2a**	2	1.0	60	81	8	44.5	99
6	**2b**	2	1.0	36	89	trace	44.5	99
7	**2b**	1	2.0	48	62	trace	62	99
8[f]	**2b**	1	2.0	48	86	trace	86	99
9[g]	**2b**	0.5	4.0	72	58	trace	116	98

[a] TBHP (1.2 equiv) was added in one portion unless otherwise noted. [b] Concentration of substrates. [c] Yield of isolated analytically pure compound. [d] Isolated as a mixture of **4a** and **5a**. [e] Determined by chiral HPLC. [f] TBHP (0.6 equiv) was added in one portion, and then additional TBHP (0.6 equiv) was slowly added over 12 h. [g] TBHP (1.05 equiv) was used: TBHP (0.2 equiv) was added in one portion, and then additional TBHP (0.85 equiv) was slowly added over 24 h.

Table 4. RE effect in catalytic asymmetric epoxidation of methyl (*E*)-cinnamate (**2b**) with $RE(OiPr)_3$, (*S*)-biphenyldiol **1a**, and $Ph_3As(O)$.



Entry	RE	Yield[a] [%]	*ee*[b] [%]
1	La	2	75
2	Pr	7	91
3	Sm	22	94
4	Gd	39	98
5	Dy	63	98
6	Y	89	99
7	Sc	0	–

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC.

and praseodymium (Table 4, entries 1–2), and gradually increased with more Lewis acidic metals. Yttrium gave the best yield and *ee* (Table 4, entry 6). The results suggest that Lewis acidity is important for the activation of α,β-unsaturated esters, which are much less electrophilic than α,β-unsaturated ketones. Although scandium has the highest Lewis acidity, epoxide **3b** was not obtained (Table 4, entry 7), probably because the nucleophilicity of scandium peroxide is poor. We assume that the balance between the Lewis acidity of the RE and the nucleophilicity of the RE peroxide is important.

The epoxidation of various β-aryl α,β-unsaturated esters were carried out with $Y(OiPr)_3$ and **1a** (Table 5).[21,22] The reaction proceeded smoothly with 2–5 mol% catalyst. For ester **2b**, 4 mol% of triphenylphosphine oxide worked as well as triphenylarsine oxide, although the enantioselectivity was slightly decreased (Table 5, entry 2, 97% *ee*).[23] The reactivity of ester **2d** with a sterically hindered 1-naphthyl group was lower than that of ester **2c** with a 2-naphthyl group (Table 5, entries 3 and 4); therefore, 5 mol% of catalyst was required for **2d**. The reactions of esters with electron-withdrawing groups **2e**–**g** proceeded smoothly with 2 mol% catalyst (Table 5, entries 5–7), whereas 5 mol% catalyst was required for esters with electron-donating groups **2h** and **2i** (Table 5, entries 8 and 9). The

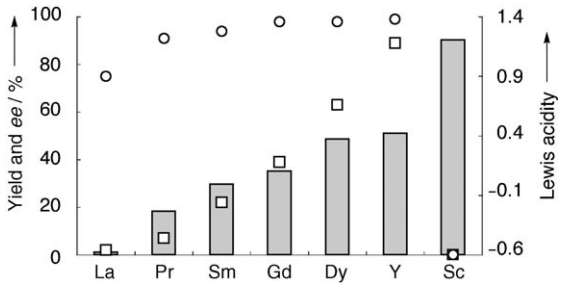
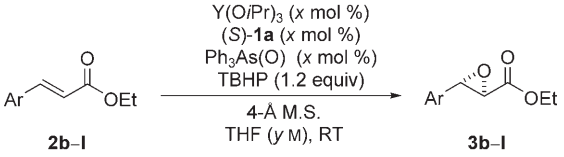


Figure 2. Relationship between yield and *ee* of **3b** and Lewis acidity of REs.[20] ■ = Relative Lewis acidity, □ = Yield, ○ = *ee*.

acetyl functionality remained intact under these reaction conditions, although the enantioselectivity was lower compared with other substrates (Table 5, entry 7, 89% *ee*). Heteroaromatic rings are often incompatible with oxidative conditions. Notably, the reactions of β-heteroaryl substrates proceeded chemoselectively at the electron-deficient carbon–carbon double bond, giving epoxides **3j**–**l** in good yield and *ee* (Table 5, entries 10–12, 78–97% yield, 92–98% *ee*). To the best of our knowledge, there are no previous reports of catalytic asymmetric epoxidation of β-heteroaryl α,β-unsaturated esters.

The $Y(OiPr)_3$–**1a** catalyst could also be applied to β-alkyl α,β-unsaturated esters **2m**–**p** (Table 6, entries 1–4). Notably, substrate **2n** with an additional carbon–carbon double bond and **2o** with a ketone moiety, which are not compatible with other asymmetric catalysts,[6,7] underwent epoxidation with this catalyst. However, as shown in Table 6, 10 mol% $Y(OiPr)_3$–**1a** was required for good conversion, and products were obtained with 91–96% *ee*. The enantioselectivities ob-

Table 5. Catalytic asymmetric epoxidation of β-aryl and β-heteroaryl α,β-unsaturated esters using $Y(OiPr)_3$, (*S*)-**1a**, and $Ph_3As(O)$.

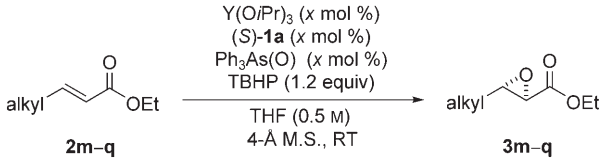


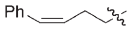
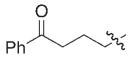
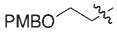
Entry	Ar	**2**	*x* [mol %]	*y*[a] [M]	*t* [h]	**3**	Yield[b] [%]	*ee*[c] [%]
1	Ph	**2b**	2	1.0	36	**3b**	89	99
2[d]	Ph	**2b**	2	1.0	45	**3b**	94	97
3	2-naphthyl	**2c**	2	1.0	24	**3c**	89	99
4	1-naphthyl	**2d**	5	0.4	40	**3d**	62	97
5	*m*-ClC_6H_4	**2e**	2	1.0	20	**3e**	92	99
6	*p*-ClC_6H_4	**2f**	2	1.0	24	**3f**	90	99
7	*p*-AcC_6H_4	**2g**	2	1.0	24	**3g**	89	89
8	*p*-MeC_6H_4	**2h**	5	0.4	24	**3h**	84	98
9	*p*-$MeOC_6H_4$	**2i**	5	0.4	45	**3i**	74	99
10		**2j**	5	0.4	27	**3j**	78	92
11		**2k**	3	0.67	24	**3k**	93	98
12		**2l**	3	0.67	24	**3l**	97	93

[a] Concentration of substrates. [b] Yield of isolated analytically pure compound. [c] Determined by chiral HPLC. [d] 4 mol % of $Ph_3P(O)$ as an additive was used instead of $Ph_3As(O)$.

ents, and that the best chiral ligand and/or metal source for β-alkyl substrates should be different from that for β-aryl substrates. Therefore, we used methyl ester **2r** to re-examine ligand and metal effects (Table 7). RE effects were examined with binol **1b** (Table 7, entries 1–6). In contrast to the yields obtained with β-aryl esters (compare Table 1), the reactions shown in Table 7 proceeded in similar yields with all REs, but the enantioselectivity differed depending on the metal. $Y(OiPr)_3$ with triphenylarsine oxide gave the best enantioselectivity (Table 7, entry 6, 99% *ee*), albeit in modest yield (50%). When triphenylphosphine oxide was used as an additive, the yield increased and the high *ee* was maintained (Table 7, entries 7–9). For the optimum conditions in terms of

Table 6. Catalytic asymmetric epoxidation of β-alkyl α,β-unsaturated esters using $Y(OiPr)_3$, (*S*)-**1a**, and $Ph_3As(O)$.



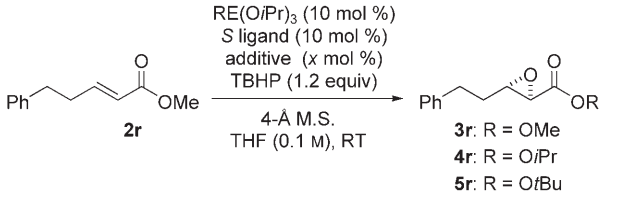
Entry	Alkyl	**2**	*x* [mol %]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1		**2m**	10	47	86	91
2		**2n**	10	71	81	93
3		**2o**	10	42	78	92
4		**2p**	10	66	81	96
5		**2q**	10	40	20	76

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC.

tained with β-alkyl esters **2m–p** (Table 6, entries 1–4) was slightly lower than those obtained with β-aryl substrates (compare Table 5). Substrate **2q** with a branched β-alkyl substituent resulted in a much less satisfactory result (Table 6, entry 5, 20% yield, 76% *ee*). Therefore, further improvement of conditions was required for β-alkyl α,β-unsaturated esters.

We hypothesized that the difference in enantioselectivity was due to the steric and electronic factors of the β substitu-

Table 7. Optimization of reaction conditions for β-alkyl α,β-unsaturated ester **2r**.

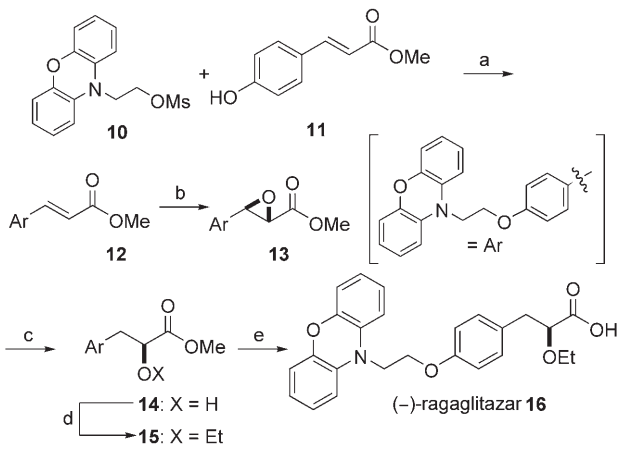


Entry	RE	Ligand	Additive	*x* [mol %]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1	La	**1b**	$Ph_3As(O)$	10	24	41	89
2	Pr	**1b**	$Ph_3As(O)$	10	24	58	88
3	Sm	**1b**	$Ph_3As(O)$	10	24	47	81
4	Gd	**1b**	$Ph_3As(O)$	10	24	66	78
5	Dy	**1b**	$Ph_3As(O)$	10	24	69	85
6	Y	**1b**	$Ph_3As(O)$	10	42	50	99
7	Y	**1b**	$Ph_3P(O)$	10	24	53	98
8	Y	**1b**	$Ph_3P(O)$	20	24	87	97
9	Y	**1b**	$Ph_3P(O)$	30	24	88	96
10[c]	Y	**1a**	$Ph_3As(O)$	10	24	59	90
11[c]	Y	**1a**	$Ph_3P(O)$	20	24	60	89

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC. [c] Reaction was performed at 0.5 M. At 0.1 M, the product was obtained in much less satisfactory yield.

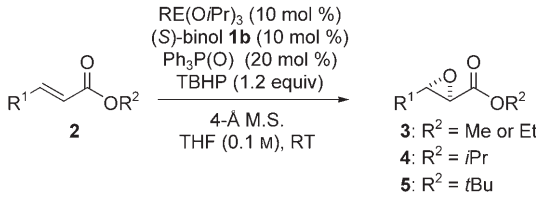
yield and *ee* (Table 7, entry 8, 87% yield, 97% *ee*), 20 mol % of triphenylphosphine oxide was used. With ligand **1a**, less-satisfactory enantioselectivities were obtained with both triphenylarsine oxide (Table 7, entry 10, 90% *ee*) and triphenylphosphine oxide (entry 11, 89% *ee*).

The substrate scope of the Y(O*i*Pr)$_3$–binol **1b**–triphenylphosphine oxide (1:1:2) system is summarized in Table 8.[22] Epoxides were obtained with up to 96–97% *ee* (Table 8, entries 1–5). The enantioselectivity was higher than that shown in Table 6, in which Y(O*i*Pr)$_3$–**1a** was used as catalyst. The amount of *trans* esterification strongly depended on the substrate. With esters **2r**, **2u**, and **2v**, *trans* esterification was negligible, whereas isopropyl and *tert*-butyl epoxy esters were obtained in 22% and 16% yield with esters **2s** and **2t** (Table 8, entries 2 and 3). Notably, Y(O*i*Pr)$_3$–binol **1b** catalyst is applicable to **2v** with branched substituents, giving epoxide **3v** in 72% yield and with 93% *ee* (Table 8, entry 5). Both a control experiment in which Y(O*i*Pr)$_3$–**1a** was used as catalyst (Table 8, entry 6, 26% total yield, 84% *ee*) and the result in Table 6, entry 5 indicate that only binol **1b** is suitable for sterically crowded β-branched-alkyl esters. On the other hand, the substrate scope of the Y(O*i*Pr)$_3$–binol **1b** catalyst is limited to β-alkyl methyl esters (Table 8, entries 1–5). With β-alkyl ethyl ester **2m**, epoxide **3m** was obtained with only 71% *ee*, albeit in good yield (Table 8, entry 7, 89%). β-Aryl ester **2a** had poor reactivity (Table 8, entry 8, 41% total yield) with binol **1b**, as previously discussed (compare Table 2).



Scheme 3. Catalytic asymmetric synthesis of (−)-ragaglitazar. Reagents and conditions: a) **10** (1 equiv), **11** (1 equiv), K_2CO_3 (2 equiv), xylene, 130 °C, 23 h, 83%; b) Y(O*i*Pr)$_3$ (5 mol%), (*R*)-**1a** (5 mol%), $Ph_3As(O)$ (5 mol%), TBHP (1.2 equiv), THF, room temperature, 48 h; c) Pd/C (10 mol%), H_2, EtOAc, room temperature, 24 h, 64%, 98% *ee* (2 steps from **12**); d) $Et_3O^+ \cdot BF_4^-$, proton sponge, CH_2Cl_2, 0 °C, 82%; e) 3 M aq. NaOH, MeOH, room temperature, 4 h, 98%.

Table 8. Catalytic asymmetric epoxidation of β-alkyl α,β-unsaturated esters with Y(O*i*Pr)$_3$, (*S*)-binol **1b**, and $Ph_3As(O)$.



Entry	R^1	R^2	**2**	*x* [mol%]	*t* [h]	Yield[a] of **3** [%]	Yield[b] of **4**+**5** [%]	*ee*[c] of **3** [%]
1	Ph	Me	**2r**	10	24	87	1	97
2	Ph	Me	**2s**	10	40	66	22	96
3	Ph	Me	**2t**	10	48	70	16	96
4	Ph, O	Me	**2u**	15	48	72	trace	96
5		Me	**2v**	15	40	72	trace	93
6[d]			**2v**	15	40	23	3	84
7	Ph	Et	**2m**	10	42	89	trace	71
8	Ph	Me	**2a**	10	72	36	5	95

[a] Yield of isolated analytically pure compound. [b] Isolated as a mixture of **4** and **5**. [c] Determined by chiral HPLC. [d] Control experiment with 15 mol% Y(O*i*Pr)$_3$–**1a**–$Ph_3As(O)$ (1:1:1).

To demonstrate the utility of the present method, we applied the Y(O*i*Pr)$_3$–**1a** catalyst to the synthesis of (−)-ragaglitazar (**16**),[24,25] which is an antidiabetes agent (Scheme 3). α,β-Unsaturated ester **12** with a phenoxazine group was synthesized from **10** and **11**, and used for the epoxidation reaction. Notably, the epoxidation proceeded without problems with the phenoxazine group. With 5 mol% of Y(O*i*Pr)$_3$, (*R*)-**1a**, and triphenylarsine oxide, epoxide **13** was obtained with 98% *ee*.[26] Because the obtained epoxide was relatively unstable and partially decomposed during purification on silica gel, crude epoxide **13** was subjected to the next hydrogenation step without purification. Ring opening proceeded regioselectively with Pd/C–H_2, and α-hydroxy ester **14** was obtained in 64% yield (two steps from **12**). Ethylation (82%) afforded known compound **15**, and hydrolysis under reported conditions afforded **16** (98%).

Conclusions

In summary, we have developed a method for the catalytic asymmetric epoxidation of α,β-unsaturated esters by using Y(O*i*Pr)$_3$–biaryldiol complexes. Selection of both a suitable rare-earth metal and a chiral ligand was crucial for good reactivity and enantioselectivity to be obtained. An yttrium–biphenyldiol **1a** catalyst, generated from Y(O*i*Pr)$_3$–biphenyldiol **1a**–$Ph_3As(O)$ (1:1:1), was suitable for various α,β-unsaturated esters. High enantioselectivities (89–99% *ee*) and good yields were realized for β-aryl and β-heteroaryl α,β-unsaturated esters when 0.5–5 mol% catalyst was used (TON up to 116). For β-alkyl α,β-unsaturated esters, an yttrium–

binol **1b** catalyst, generated from Y(O*i*Pr)$_3$–binol **1b**–$Ph_3P(O)$ (1:1:2), gave better enantioselectivities (93–97% *ee*) than **1a**.

Experimental Section

General

Spectral data and ^{13}C NMR spectra of all new compounds, detailed procedures for the epoxidations and the synthesis of **1a**, **2**, and **16**, conditions for the calculation of the dihedral angles, and determination of the absolute configurations are available in the Supporting Information. RE(O*i*Pr)$_3$ complexes were purchased from Kojundo Chemical Laboratory Co., LTD., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: (+81) 492-84-1351, e-mail: sales@kojundo.co.jp). Same-grade Y(O*i*Pr)$_3$ is commercially available from Aldrich. 4-Å molecular sieves (MS) were purchased from Fluka (Molecular Sieve UOP 4 Å, powder).

Syntheses

Representative procedure for catalytic asymmetric epoxidation: 4-Å molecular sieves were dried for 3 h at 180 °C under reduced pressure (0.7 kPa) (activation of the molecular sieves is important if good reactivity is to be achieved). A solution (0.2 M) of Y(O*i*Pr)$_3$ in THF (0.125 mL, 0.025 mmol) was added to a mixture of the 4-Å molecular sieves (250 mg), **1a** (7.2 mg, 0.025 mmol), and triphenylarsine oxide (8.1 mg, 0.025 mmol) in THF (1.125 mL) at room temperature. After the mixture was stirred for 45 min at room temperature, a solution (4.0 M) of TBHP in toluene (0.375 mL, 1.5 mmol) was added. After the mixture was stirred for 10 min, **2b** (220.3 mg, 1.25 mmol) was added, and the mixture was stirred at room temperature. After complete consumption of the starting material (36 h), the reaction mixture was diluted with ethyl acetate (10 mL) and quenched with citric acid (2%, 2.5 mL). The aqueous layer was extracted with ethyl acetate (2×10 mL), and the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 100:1–50:1); this gave **3b** (212.7 mg, 89%) as a clear oil. The enantiomeric excess of **3b** was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALPAK AD-H, *i*PrOH/hexane = 2:98, flow rate = 0.4 mL min^{-1}, t_R = 31.5 min (2*S*,3*R*) and 38.0 min (2*R*,3*S*), detection at 254 nm, $[\alpha]_D^{24} = -158.8$ (c = 1.06, $CHCl_3$). Absolute configuration of **3b** was determined to be (2*R*,3*S*) by comparison of the sign of optical rotation with reported data.[7b] $[\alpha]_D^{25} = +160.1$ (c = 1.15, $CHCl_3$, (2*S*,3*R*)).

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[19] Previous mechanistic studies suggested that the concentration of the catalyst is important to maximize the formation of the active species in equilibrium; see reference [5b]. Similar effects were observed in asymmetric epoxidations in which a samarium complex was used; see reference [10].

[20] The values for the relative Lewis acidity in Figure 2 are reported data of the ion-peak ratio $\ln\{[MF(OTf)(hmpa)_2]^+/[M(OTf)_2(hmpa)]^+\}$ observed by use of tandem mass spectrometry (M = rare-earth metal, hmpa = hexamethylphosphoramide); see: a) H. Tsuruta, K. Yamaguchi, T. Imamoto, *Chem. Commun.* **1999**, 1703; b) H. Tsuruta, K. Yamaguchi, T. Imamoto, *Tetrahedron* **2003**, *59*, 10419.

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[22] Among the molecular sieves, the use of 4-Å molecular sieves gave the best results in terms of enantioselectivity and yield of epoxides. For example, the epoxidation of **2b** with 2 mol% $Y(OiPr)_3$, (*S*)-**1a**, and $Ph_3As(O)$ gave **3b** in 89% yield (36 h), 99% *ee* with 4-Å molecular sieves (Table 5, entry 1), whereas **3b** was obtained in 62% yield (48 h) and 96% *ee* with 3 -Å molecular sieves, 81% yield (48 h) and 98% *ee* with 5-Å molecular sieves, 28% yield (48 h) and 93% *ee* with MS 13X, and 7% yield (48 h) and 94% *ee* without molecular sieves. A similar trend was observed with the $Y(OiPr)_3$, (*S*)-**1b**, and $Ph_3P(O)$ system. The reaction of **2r** gave **3r** in 87% yield (24 h) and 97% *ee* with 4-Å molecular sieves (Table 8, entry 1, 10 mol% catalyst), 52% yield (30 h) and 90% *ee* with 3-Å molecular sieves, 76% yield (30 h) and 93% *ee* with 5-Å molecular sieves, 8% yield (30 h) and 97% *ee* with MS 13X, and 14% yield (30 h) and 85% *ee* without molecular sieves.

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