Communication

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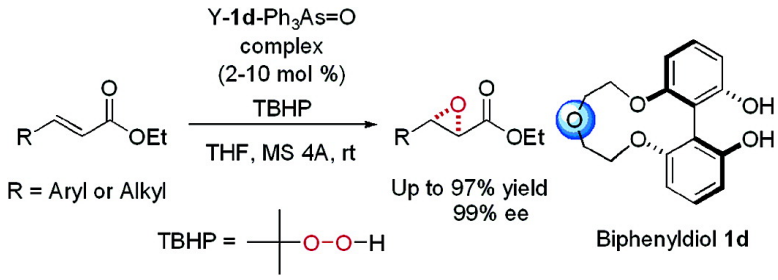

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Catalytic Asymmetric Epoxidation of α,β-Unsaturated Esters Using an Yttrium-Biphenyldiol Complex

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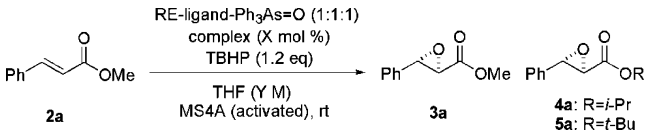
Catalytic asymmetric epoxidation of α,β-unsaturated esters is a synthetically useful reaction in organic synthesis.[1] The resulting enantiomerically enriched epoxy esters can be easily converted to many types of useful chiral compounds. There are only a few reports of general and efficient catalytic asymmetric epoxidations of α,β-unsaturated esters using chiral ketones[2,3] or (salen)Mn catalysts.[4] These catalysts, however, cannot be applied to substrates that have functional groups such as a C−C double bond and a ketone, due to the poor chemoselectivity. Thus, there is room for improvement, particularly in terms of substrate generality. In this communication, we report a catalytic asymmetric epoxidation of α,β-unsaturated esters via conjugate addition of an oxidant using chiral yttrium catalysts.

We previously reported that alkali-metal free lanthanide−BINOL-Ph_3As═O complexes, generated from Ln(O-*i*-Pr)$_3$, BINOL, and Ph_3As═O in a ratio of 1:1:1 were useful catalysts for asymmetric epoxidation of enones,[5] α,β-unsaturated amides,[6] and ester surrogates.[6b,7] Thus, we initiated our studies of a catalytic asymmetric epoxidation using methyl (*E*)-cinnamate (**2a**) as a substrate and Ln−BINOL-Ph_3As═O complexes as a catalyst. The use of Ln such as Pr was very unsatisfactory in terms of yield (Table 1, entry 1). On the other hand, we were pleased to find that Y gave a better yield with high enantiomeric excess (entry 2).[8] Next, to overcome the problem of low reactivity, we hypothesized that 6,6′-disubstituted 2,2′-biphenyldiols **1**[9] would give higher reactivity than BINOL due to less steric hindrance. As expected, 6,6′-disubstituted 2,2′-biphenyldiol **1b** gave higher yield than BINOL without decreasing the enantiomeric excess (entry 4). On the basis of this finding, the effects of the dihedral angles of ligands were carefully investigated by changing the linker length.[10] Ligands with a shorter linker **1a** or longer linker **1c** (see Figure 1) did not dramatically increase the reactivity (entries 3,5). These results led us to examine the effects of heteroatoms on the linker, because heteroatoms on ligands often change the coordinating natures of rare earth catalysts and dramatically increase the reactivity.[11] Intensive investigation of ligands indicated that ligand **1d** linked by diethylene ether had dramatically greater reactivity (entries 6−10). Transesterification from α,β-epoxy methyl ester to *iso*-propyl ester **4a** or *tert*-butyl ester **5a**, which were derived from Y(O-*i*-Pr)$_3$ and TBHP, remained a significant problem, however, due to the high reactivity of the catalyst derived from ligand **1d**. To prevent the formation of byproducts, we very carefully examined the reaction conditions. First, by reducing catalyst loading, the formation of byproducts was suppressed (entries 7−9). Moreover, under highly concentrated conditions (1.0 M), the reaction proceeded very well with as little as 2 mol % catalyst loading, affording the product in 81% yield and 99% ee (entry 9). Having optimized the reaction conditions,[8] substrate generality was investigated (Table 2). The Y-ligand **1d**−Ph_3As═O catalyst system had a broad generality for epoxidation of various β-aromatic α,β-unsaturated esters (Table 2). It was also applicable to ethyl (*E*)-cinnamate (**2b**),

Table 1. Optimization of the Reaction Conditions



entry	RE[a]	ligand	catalyst (X mol %)	concn.[b] (Y M)	time (h)	yield (%) 3a[c]	yield (%) 4a+5a[c]	ee (%) 3a[d]
1	Pr	BINOL	10	0.1	72	24	-	88
2	Y	BINOL	10	0.1	72	36	5	95
3	Y	**1a**	10	0.1	144	4	14	92
4	Y	**1b**	10	0.1	120	45	26	98
5	Y	**1c**	10	0.1	120	49	33	99
6	Y	**1d**	10	0.1	48	61	25	99
7	Y	**1d**	5	0.2	48	65	21	99
8	Y	**1d**	3	0.33	50	79	11	99
9	Y	**1d**	2	0.5	50	77	12	99
10	Y	**1d**	2	1.0	65	81	8	99

[a] RE = rare earth metals. [b] Concentration of **2a**. [c] Isolated yield. [d] Determined by chiral HPLC.

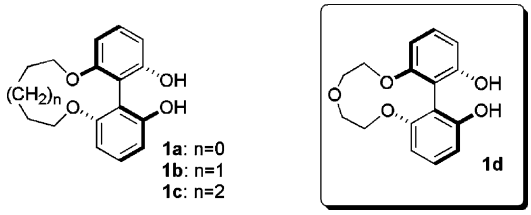


Figure 1. Structure of ligands **1a**−**d**.

and product **3b** was obtained with high yield and high enantiomeric excess (entry 1). The reaction of substrates with both electron-donating and electron-withdrawing substituents **2c**−**f** proceeded smoothly to afford **3c**−**f** in good yield and good enantioselectivity in the presence of 2−5 mol % of the catalyst (entries 3−6). Substrate with an acetyl substituent **2g** was smoothly epoxidized. Acetyl functionality remained intact under this epoxidation condition (entry 7). The reactions of substrates with bulkier β-naphthyl moieties proceeded well (entries 8,9). The catalyst was also applicable to β-heteroaromatic substrates **2j**−**l**. Heteroaromatic rings are easily decomposed under general oxidative conditions. In this epoxidation system, however, the reactions of these substrates proceeded to afford the corresponding epoxides **3j**−**l** without decomposition of heteroaromatic rings (entries 10−12). To the best of our knowledge, there are no reports of a catalytic asymmetric epoxidation of β-heteroaromatic substituted α,β-unsaturated esters. In addition, Y-ligand **1d**−Ph_3P═O complex was also effective, yielding products with slightly lower enantioselectivity (entry 2).[12] To apply the developed catalyst system to β-alkyl-substituted substrates, we further examined the reaction conditions. We determined that 0.5 M was a suitable condition for these substrates. Various substrates were smoothly epoxidized in good yield and

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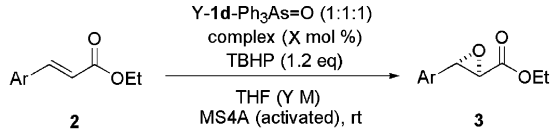
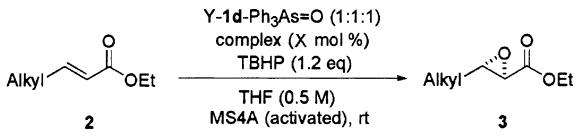
Table 2. Catalytic Asymmetric Epoxidation of β-Aromatic α,β-Unsaturated Esters Using Y-**1d**−Ph_3As=O Complex

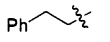
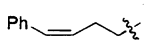
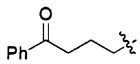
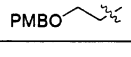


entry	Ar		catalyst (X mol %)	conc.[a] (Y M)	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	**2b**	2	1.0	36	89	99
2[d]			2	1.0	45	94	97
3	*p*-Me-C_6H_4	**2c**	5	0.4	24	84	98
4	*p*-MeO-C_6H_4	**2d**	5	0.4	45	74	99
5	*m*-Cl-C_6H_4	**2e**	2	1.0	20	92	99
6	*p*-Cl-C_6H_4	**2f**	2	1.0	24	90	99
7	*p*-Ac-C_6H_4	**2g**	2	1.0	24	89	89
8	1-naphthyl	**2h**	5	0.4	40	62	97
9	2-naphthyl	**2i**	2	1.0	24	89	99
10		**2j**	5	0.4	27	78	92
11		**2k**	3	0.67	24	93	98
12		**2l**	3	0.67	24	97	93

[a] Concentration of substrates. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 4 mol % of Ph_3P=O was used instead of Ph_3As=O as an additive.

Table 3. Catalytic Asymmetric Epoxidation of β-Aliphatic α,β-Unsaturated Esters Using Y-**1d**−Ph_3As=O Complex



entry	Alkyl		catalyst (X mol %)	time (h)	yield (%)[a]	ee (%)[b]
1		**2m**	10	47	86	91
2[c]			5	48	80	86
3		**2n**	10	71	81	93
4		**2o**	10	42	78	92
5		**2p**	10	66	81	96

[a] Isolated yield. [b] Determined by chiral HPLC. [c] 10 mol % of Ph_3P=O was used instead of Ph_3As=O as an additive.

good enantioselectivity (Table 3, entries 1−5). Also in this case, Ph_3P=O can be utilized as shown in entry 2. Particularly noteworthy is that this reaction was applicable to substrates that were functionalized with a C−C double bond or ketone, without overoxidation (entries 3,4).[13,14]

In conclusion, we developed a catalytic asymmetric epoxidation reaction of α,β-unsaturated esters via conjugate addition of an oxidant using a Y-chiral biphenyldiol complex. The success of the reaction depends on the properties of the newly developed diethylene ether-linked biphenyldiol ligand **1d**. Detailed mechanistic studies of the present reaction, especially to clarify the properties of the ligand, are currently in progress.

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Supporting Information Available: Experimental procedures and characterization of the products; other detailed results and discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Preliminary studies showed cis- and trisubstituted α,β-unsaturated esters were not suitable for the newly developed catalyst.

(14) Absolute configurations of **3a**, **3b**, **3d**, and **3m** were determined to be 2*R*, 3*S*. For the detailed data, see the Supporting Information.

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