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Highly Enantioselective Epoxidation of α,β-Unsaturated Ketones Catalyzed by Rare-Earth Amides $[(Me_3Si)_2N]_3RE(\mu\text{-}Cl)Li(THF)_3$ with Phenoxy-Functionalized Chiral Prolinols

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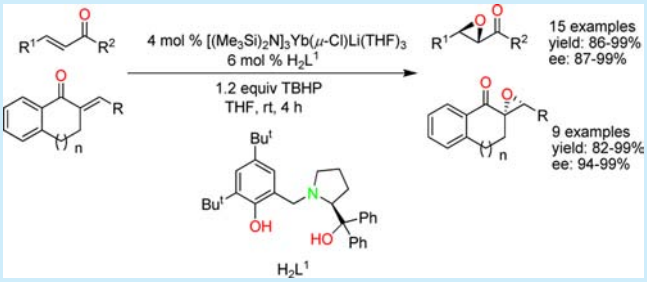
Supporting Information

ABSTRACT: A simple and efficient catalytic enantioselective epoxidation of α,β-unsaturated ketones has been successfully developed, which was catalyzed by rare-earth metal amides $[(Me_3Si)_2N]_3RE(\mu\text{-}Cl)Li(THF)_3$ (RE = Yb (**1**), La (**2**), Sm (**3**), Y (**4**), Lu (**5**)) in the presence of phenoxy-functionalized chiral prolinols at room temperature using *tert*-butylhydroperoxide (TBHP) as the oxidant. The combination of an Yb-based amide **1** and a chiral proligand (*S*)-2,4-di-*tert*-butyl-6-((2-(hydroxydiphenylmethyl)pyrrolidin-1-yl)methyl)phenol) performed very well, and both the yields and the enantiomeric excess of the chiral epoxides reached up to 99% and 99% ee.



Enantioselective epoxidations of olefins have been extensively studied due to the importance of the chiral epoxide products, which are significant building blocks for further preparations of natural products.[1] During the past decades, numerous studies on developing highly efficient synthetic strategies for enantioselective epoxidation of olefins have been published.[2−8] Sharpless' asymmetric epoxidation of allylic alcohols, which was regarded as a milestone discovery in the 1980s, opened a brand new area of research.[9] Subsequently, many chemists have significant progress in the asymmetric epoxidation of the C−C double bond, including simple alkenes,[10] electron-rich olefins,[11,12] and electron-poor olefins.[13,14] Despite the wealth of catalytic enantioselective epoxidations of α,β-unsaturated ketones,[15] the lack of substrate diversity, the requirement for additives, the relatively low reactivity and selectivity, or the relatively high catalyst loading were somewhat below expectation. Investigation of high performance methods for a simple transformation is still needed. Very recently, our group developed a strategy for the enantioselective epoxidation of α,β-unsaturated ketones employing a heterobimetallic rare-earth-lithium complex bearing a phenoxy-functionalized diphenylprolinolate ligand.[16] Although the high enantioselectivity and good yields of the desired epoxides were achieved, the details of the mechanism remain unclear. The relationship between the structures and the efficiency of catalysts is worthy of exploration. Moreover, in consideration of the importance of trisubstituted cyclic α,β-epoxyketones,[17] a simple, efficient, and additive-free catalyst system is also required. Here we address a further issue of enantioselective epoxidations of α,β-unsaturated ketones catalyzed by rare-earth amides $[(Me_3Si)_2N]_3RE(\mu\text{-}Cl)Li(THF)_3$ with a series of phenoxy-functionalized chiral prolinols, which gives us both excellent yields and satisfactory enantioselectivities.

To optimize the reactivity and selectivity of our catalytic systems, a series of phenoxy-functionalized chiral prolinols with various different substituents were prepared according to the reported method.[18] They were subsequently screened in the asymmetric epoxidation reaction of chalcone catalyzed by ytterbium amide **1** $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$ in the presence of oxidant TBHP at rt. The results shown in Table 1 illustrate that the structure of the ligand strongly affects the reactivity and enantioselectivity. The low yields and poor ee values were observed when there are H-atoms or methyl substitutes on the hydroxymethyl carbon in the prolinol fragment (Table 1, entries 2−3). With regards to the dramatic drop of ee values and yields of epoxides, the ligands bearing too small or too bulky groups on the adjacent carbon to the phenolic hydroxyl group were not ideal (Table 1, entries 4−6). The substituent on the *para* position of the phenolic hydroxyl group has a slight effect on the reactivity and enantioselectivity with a decreased yield and a lower ee value (Table 1, entry 7). To our delight, proligand H_2L^1 ((*S*)-2,4-di-*tert*-butyl-6-[[2-(hydroxydiphenylmethyl)pyrrolidin-1-yl]methyl]-phenol) was the best partner, delivering an excellent yield and excellent optically pure epoxide (Table 1, entry 1).

With different ratios of catalyst to ligand, the model reactions proceeded almost quantitatively, while the enantiomeric excess values varied from 93% to 98% (Table 1, entries 1, 8, and 9). It is proved that the molar ratio of 1:1.5 was the best choice. The effects of rare earth metals in the amides **1**−**5** were investigated,

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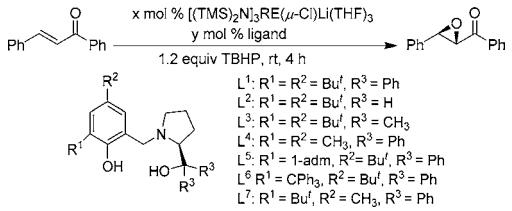
Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	x	ligand	y	yield (%)[b]	ee (%)[c]
1	Yb-1	5	H_2L^1	7.5	99	98
2	Yb-1	5	H_2L^2	7.5	30	15
3	Yb-1	5	H_2L^3	7.5	36	35
4	Yb-1	5	H_2L^4	7.5	80	75
5	Yb-1	5	H_2L^5	7.5	45	10
6	Yb-1	5	H_2L^6	7.5	46	21
7	Yb-1	5	H_2L^7	7.5	85	91
8	Yb-1	5	H_2L^1	5	99	93
9	Yb-1	5	H_2L^1	10	99	96
10	La-2	5	H_2L^1	7.5	90	9
11	Sm-3	5	H_2L^1	7.5	87	33
12	Y-4	5	H_2L^1	7.5	89	87
13	Lu-5	5	H_2L^1	7.5	74	75
14	Yb-1	4	H_2L^1	6	99	98
15	Yb-1	3	H_2L^1	4.5	81	98

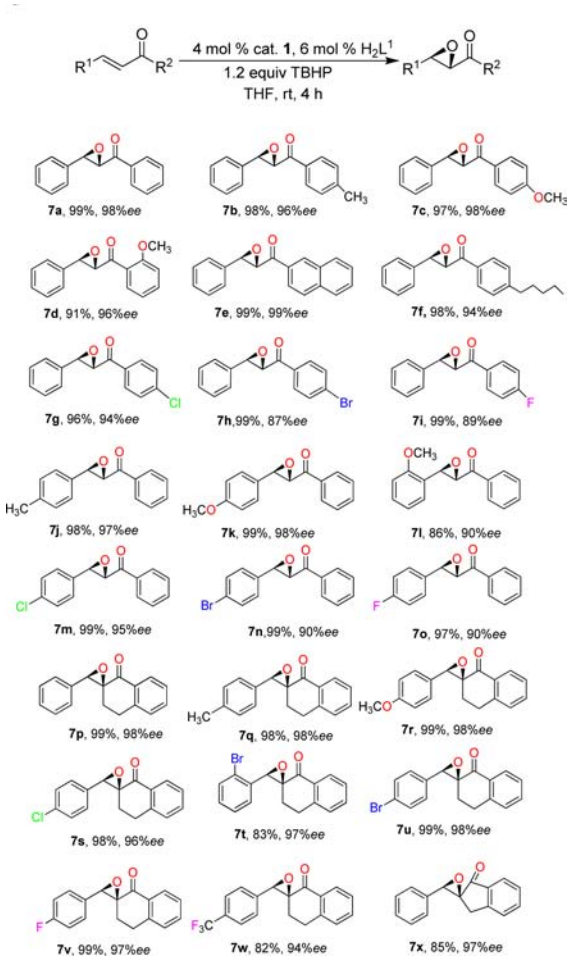
[a]Reactions were performed with chalcone (0.3 mmol), TBHP (0.36 mmol) in 1 mL of THF at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

and the results indicated that the central metals significantly influenced the enantiometric excess of epoxides with the decreasing tendency of Yb > Y > Lu > Sm > La (Table 1, entries 1 and 10−13). This may be attributed to the appropriate ionic radius of ytterbium matching the size of proligand H_2L^1, which is considered important in controlling the enantioselectivity in asymmetric synthesis. In an attempt to reduce the loading of catalyst, the amount of 4 mol % ytterbium amide was ideal for this transformation (Table 1, entries 1 and 14−15).

In the presence of 6 mol % of proligand H_2L^1, the investigation of the substrate scope was conducted using 4 mol % of complex **1** as the catalyst in THF at rt, and the results are summarized in Scheme 1. It can be seen that many substrates bearing various substituents proceeded smoothly to produce the corresponding epoxides in excellent yields and enantioselectivities. The electron-donating groups on phenyl rings had no significant effect on the results and gave rise to corresponding products with excellent ee values (94−98%) and 95−99% yields (Scheme 1, **7b**−**7f** and **7j**−**7l**), while the electron-withdrawing substituents on benzyl rings had the tendency to decrease the enantioselectivity since the ee value dropped to 87−90% (Scheme 1, **7g**−**7i** and **7m**−**7o**). The electron effect of the substituents on the phenyl ring in the current catalytic system is consistent with the previous published result.[19] Encouraged by these findings, additional chalcone derivatives with an exocyclic double bond were tested to obtain trisubstituted chiral *α,β*-epoxyketones, which are vital intermediates in organic synthesis.[20] The reaction outcomes of all the substrates are excellent, in terms of both the yields and ee values, which are better than the published results[15e,20] (Scheme 1, **7p**−**7x**).

To gain some insight into the mechanism of the asymmetric epoxidation, we attempted to separate the real active species in the process. Treatment of Yb-based amide **1** with 1.5 equiv of proligand H_2L^1 in THF for 1 h, after workup, produced colorless

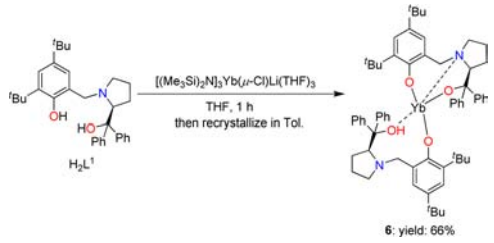
Scheme 1. Epoxidation of *α,β*-Unsaturated Ketones Catalyzed by Complex 1[a]



[a]Reactions were performed with the substrate (0.3 mmol), TBHP (0.36 mmol) in 1 mL of THF at rt. The ee values were determined by chiral HPLC.

crystals of complex **6** $[L^1Yb(L^1H)]$ in toluene. The solid structure of complex **6** was confirmed by X-ray diffraction analysis, which consists of one ytterbium atom and two chiral prolinolates as shown in Scheme 2. It is unexpected that the

Scheme 2. Synthesis of Complex 6



structure of complex **6** lacks both a lithium ion and chloride. It was subsequently proven that the chiral catalyst did not exhibit high performance in the asymmetric epoxidation of chalcone under the standard conditions mentioned before, evidenced by poor ee value of only 51% (Table 2, entry 1). Compared with the outcome of the epoxidation using catalyst **1** in the presence of H_2L^1 (Table 1 entry 1), the existence of LiCl in catalyst **1** is

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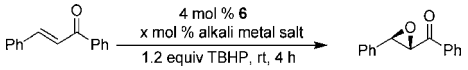
Table 2. Effect of Alkali Metals and Halides in the Asymmetric Epoxidation of Chalcone[a]



entry	alkali metal salt	loading (x mol %)	yield (%)[b]	ee (%)[c]
1	LiCl	0	95	51
2	LiCl	4	95	96
3	LiCl	8	95	88
4	LiCl	12	94	88
5	LiBr	4	81	43
6	LiI	4	74	21
7	NaCl	4	85	65
8	KCl	4	85	65

[a]Reactions were performed with chalcone (0.3 mmol), TBHP (0.36 mmol), alkali metal salt (x mol %), complex **6** (4 mol %) in 1 mL of THF at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

influential in enhancing the enatioselectivity of the asymmetric epoxidation of chalcone, which varied from 51% to 98% ee. An epoxidation of chalcone in the presence of complex **6** with lithium chloride in varying stoichiometry was carried out to verify the hypothesis. The values in Table 2 indicate that the addition of lithium chloride indeed affected the asymmetric catalytic process and the enantioselectivity of the desired epoxide was obviously improved with the increased ee value of 96%, meanwhile the yield of the product maintained 95% (Table 2, entry 2). Addition of a higher loading of LiCl did not improve reaction performance (Table 2, entries 3−4). Considering the obvious difference between the activities of the current catalytic system of catalyst **1** and complex **6** with external LiCl, a new question arose regarding if lithium chloride is the best partner of $[L^1Yb(L^1H)]$ in improving the activity. Thus, some commercially available alkali metal salts were screened under the standard reaction conditions. However, either changing halides or changing the alkali metal led to a dramatic decrease in yields and ee values (Table 2, entries 5−8). Therefore, the results indicated that Yb-based amide **1** is a precatalyst in the asymmetric epoxidation of chalcones, and the real active species is a more complicated complex, probably combining two parts of complex **6** and LiCl in 1:1 molar ratio. The synergistic action of heterobimetallic RE−lithium is also present in the current catalyst, which is often observed in other systems.[21] Unfortunately, the exact structure of the real active catalyst is still unknown after many laborious attempts. It may contribute to the poor solubility of LiCl in toluene, a necessary solvent in the process of recrystallization. A detailed study of the mechanism is underway in our laboratory.

In summary, five readily prepared rare-earth metal amides $[(Me_3Si)_2N]_3RE(\mu\text{-}Cl)Li(THF)_3$ were employed in the enantioselective epoxidation reaction of α,β-unsaturated ketones in the presence of phenoxy-functionalized chiral prolinols. The catalyst system of ytterbium amide **1** and proligand H_2L^1 in a 1:1.5 molar ratio was proven to be the best partner in the asymmetric reaction, which gives rise to excellent yield and high to excellent optically pure epoxides of chalcone and its derivatives at ambient temperature using TBHP as the oxidant. After many efforts, the real active catalyst was still unclear and the exploration of a new efficient catalyst is in process in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General procedures for preparations of complexes and substrates and catalysis, characterization data, ^1H and ^{13}C NMR spectra, HPLC chromatograms, crystallographic data for complex **6** (CCDC: 1053049), and figures depicting solid state structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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