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Asymmetric epoxidation of α,β-unsaturated ketones *via* an amine-thiourea dual activation catalysis

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ABSTRACT

A simple asymmetric epoxidation method is developed to effectively synthesize chiral α-carbonyl epoxides through an amine-thiourea dual activation catalysis. In this method, TBHP, as an oxidant, determined the reaction rate, and the chiral amine-thiourea catalyst effectively controlled the stereoselectivity of the reaction, and KOH promoted deprotonation. 22 examples of α,β-unsaturated ketones with various substituent groups are smoothly converted into α-carbonyl epoxides with moderate to excellent enantiomeric excess.

Chiral epoxides are very effective intermediates in organic synthesis [1]. Due to the special tension of the hetero-tricyclic ring, it is easy to achieve selective ring opening and functional group conversion reactions, so that many valuable optically active materials and drugs can be synthesized [2]. Since 1980s, Sharpless's group [3] has successfully achieved the asymmetric epoxidation reaction of allylic alcohol through Ti-tartaric acid catalysis, which made a major breakthrough in this field. Subsequently, various catalytic strategies [4] continued to emerge, among which organocatalysts have green economy and sustainability, and always received extensive attention [5].

Cinchona alkaloids have natural chiral environmental structure and strong ability to be modified later. Since 1853, *cinchona* alkaloids were first reported [6] to be used as chiral additives in asymmetric synthesis, and they have attracted much attention as organocatalysts or chiral ligands in asymmetric synthesis [7]. *Cinchona* alkaloids can also be used to catalyze epoxidation reactions, for example, Deng's group [8] initially realized the asymmetric epoxidation of chalcone with high enantiomeric excess (Fig. 1a). Saha-Möller's group [9] and Jurczak's group [10] developed an enantioselective epoxidation of α,β-unsaturated ketones with optically active phase-transfer catalysts derived from *cinchona* alkaloids (Fig. 1b-c). Very recently, a chiral amine-thiourea catalyzed enantioselective γ-elimination [11] process can also be applied to obtain epoxides (Fig. 1d). In addition, our group have used D-mannitol-derived novel chiral amine-thioureas [12] (Fig. 1e) to successfully achieve an asymmetric Henry reaction. In the amine-thiourea bifunctional catalysts [13] derived from *cinchona* alkaloids, the double hydrogen bond donor of the thiourea unit and the tertiary amine of quinine form a dual activation mode, thereby efficiently realizing asymmetric conversion.

Chiral α-carbonyl epoxides are important synthetic molecules for the synthesis of natural products and drugs [14], due to one or several stereogenic centers are either preserved or modified. Therefore, the development of asymmetric epoxidation reactions of α,β-unsaturated ketones are of great significance. Based on the application of amine-thiourea bifunctional catalysts of our previous works [12,13c–d], we envisaged the use of a large sterically hindered multi-chiral thiourea unit combined with quinine to form a bifunctional catalyst may realize the asymmetric epoxidation of chalcone compounds. Herein, we report an efficient method for asymmetric epoxidation of chalcone compounds, using cheap and easily available TBHP as an oxidant, and realizing chirality induction *via* a D-mannitol-derived chiral thioureas, and the enantiomeric excess was up to 96%.

In order to obtain chiral α-carbonyl epoxides with high enantioselectivities, we firstly screened the reaction conditions. With chalcone **2a** as the reaction template substrate and D-mannitol-derived chiral amine-thioureas **1e** as the catalyst, the reaction conditions including additives, solvents, oxidants and reaction temperatures were screened (Table 1). First, solvent had a great

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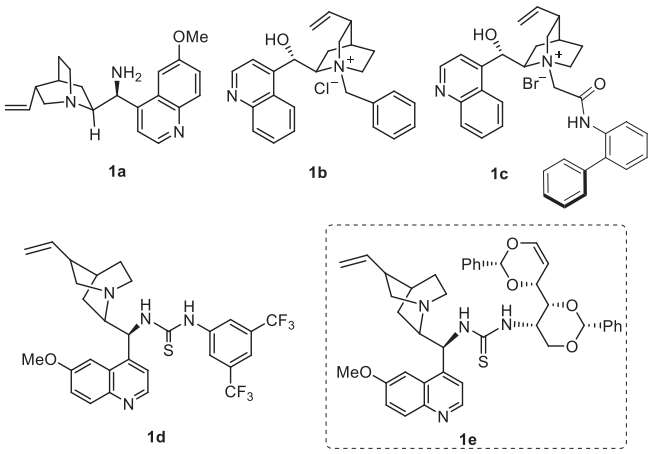


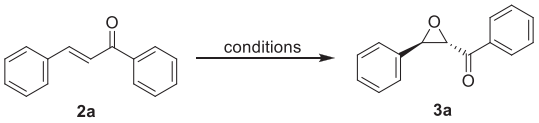
Fig. 1. Quinine and its derivatives are used to synthesize α,β-epoxy ketones.

influence on the asymmetric epoxidation reaction (Table 1, entries 1–7). When the reaction was proceeded in DMF, ether, ethanol, and THF, **2a** was transformed to **3a** with the opposite configuration (Table 1, entries 1–4). In comparison, xylene and acetone showed high conversion activities but low enantioselectivities (Table 1, entries 5–6). Toluene can be used as the best solvent to gain **3a** with high yield and moderate enantiomeric excess (Table 1, entry 7). Later, we adjusted the amount of KOH with toluene as the solvent (Table 1, entries 8–10). Surprisingly, we chose 0.2 equivalents of KOH as the matching additive, and found that the enantioselectivity of **3a** was slightly improved, while the reaction yield had a bit reduction (Table 1, entry 9). However, when less than 0.2 equivalents of KOH was used, the reaction yield and enantioselectivity were reduced (Table 1, entry 10).

In this transformation, the amount of oxidant [4a,5a,8–10,15] and the method of addition were very critical. Initially, we made detailed adjustments to the amount of oxidant. When 1.7, 1.2, 0.6, and 0.2 equivalents of TBHP were used, the yields of **2a** were greatly reduced as the amount of TBHP decreased, but the enantiomeric excess of **2a** gradually increased (Table 1, entries 11–14). **3a** with an enantiomeric excess of 65% was obtained when 0.2 equivalent of TBHP was used (Table 1, entry 14). Therefore, we adopted the method of adding oxidant in batches to reduce the reaction rate to obtain high conversion and enantioselectivity (Table 2, entry 15). Temperature was also very important for the chiral induction process (Table 1, entries 16–18). By reducing the reaction temperature to −20 °C, **3a** can be obtained with a yield of 75% and an enantioselectivity of 94% (Table 1, entry 17).

With the optimal reaction conditions in hand, we investigated the range of α,β-unsaturated ketones. When the 4-position substituents of phenyl were electron-withdrawing groups of F, Cl, Br, I, NO_2, **3b-3f** were obtained in moderated yields (58–90%) and high enantiomeric excesses (84–96%). Specifically, when the substituent was CF_3, **2g** was transformed to **3g** with a 40% yield and a 44% enantiomeric excess. Substrates with electron-donating substituents at the 4-position of phenyl, including Me and *t*Bu to achieve good performance asymmetric epoxidation with 83–89% enantiomeric excesses (**3h**-**3i**). **3j** was synthesized with high conversion rate, but the enantiomeric excess was only 42%. The above results demonstrated that the 4-position substituted substrates with electron donating or withdrawing group both can efficiently realize the asymmetric epoxidation reaction, except individual groups, such as CF_3 and OMe. Subsequently, we considered the 3-position substitution chalcones. Unexpectedly, the 3-OMe substituted substrate **2n** got the product **3n** with an 81% enantiomeric excess, while the 3-Cl substituted substrate **2k** only got 66% enantiomeric excess, and these results were inconsistent with the products of 4-position substituent. **2l** and **2m** could give the products with 83% and 80% enantiomeric excesses. Above this, substrates with substituted groups at the 3-position have a certain weakening effect on the asymmetric epoxidation transformation. In contrast, modification of the 2-position on the phenyl group greatly affected the asymmetric transformation. When Cl and Br were used to modify the 2-position of the phenyl group, the products **3o** and **3p** with (*αR, βS)* configuration were obtained. However, the products **3q** and **3r** were generated with electron-donating Me and OMe have

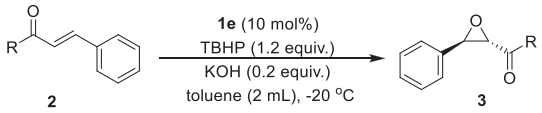
Table 1
Reaction Optimization.



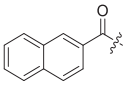
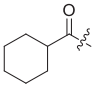
Entry[a]	Additive (*X* eq.)	Oxidant (*Y* eq.)	Solvent	Tem.(°C)	Yield(%)[b]	ee. (%)[c]
1	KOH (5)	TBHP (1.2)	DMF	r.t.	30	−51
2	KOH (5)	TBHP (1.2)	Et_2O	r.t.	40	−32
3	KOH (5)	TBHP (1.2)	EtOH	r.t.	35	−7
4	KOH (5)	TBHP (1.2)	THF	r.t.	65	−20
5	KOH (5)	TBHP (1.2)	xylene	r.t.	70	24
6	KOH (5)	TBHP (1.2)	acetone	r.t.	60	34
7	KOH (5)	TBHP (1.2)	toluene	r.t.	85	49
8	KOH (1)	TBHP (1.2)	toluene	r.t.	80	49
9	KOH (0.2)	TBHP (1.2)	toluene	r.t.	80	52
10	KOH (0.1)	TBHP (1.2)	toluene	r.t.	67	43
11	KOH (0.2)	TBHP (1.7)	toluene	r.t.	86	39
12	KOH (0.2)	TBHP (1.2)	toluene	r.t.	80	52
13	KOH (0.2)	TBHP (0.6)	toluene	r.t.	50	56
14	KOH (0.2)	TBHP (0.2)	toluene	r.t	20	65
15	KOH (0.2)	TBHP (1.2)[d]	toluene	r.t.	80	69
16	KOH (0.2)	TBHP (1.2)	toluene	0	78	75
17	KOH (0.2)	TBHP (1.2)	toluene	−20	75	94
18	KOH (0.2)	TBHP (1.2)	toluene	−45	50	92

[a] General conditions: **2** (0.1- mmol), **1e** (10-mol%), KOH (0.2 equiv.), TBHP (1.2 equiv.), toluene (2 mL), −20- °C), 5–72 h. [b]Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis using Chiralpak OD-H column, and absolute configuration was established by comparing with the literature data [4a]
[d] Adding TBHP in portions, 0.02 mmol each time.

Table 2
Substartes scope of α,β-unsaturated ketones in the asymmetric epoxidation.



2 3

Entry[a,b]	Substrate	Yield (%)[c]	ee (%)[d]	Product
1	R = Ph	75	94	3a
2	R = 4-F-Ph	61	86	3b
3	R = 4-Cl-Ph	62	88	3c
4	R = 4-Br-Ph	81	96	3d
5	R = 4-I-Ph	63	89	3e
6	R = 4-NO_2-Ph	90	84	3f
7	R = 4-CF_3-Ph	40	44	3g
8	R = 4-Me-Ph	71	89	3h
9	R = 4-*t*Bu-Ph	52	83	3i
10	R = 4-OMe-Ph	80	42	3j
11	R = 3-Cl-Ph	60	66	3k
12	R = 3-Br-Ph	61	83	3l
13	R = 3-NO_2-Ph	76	80	3m
14	R = 3-OMe-Ph	81	81	3n
15	R = 2-Cl-Ph	40	−51	3o
16	R = 2-Br-Ph	51	−67	3p
17	R = 2-Me-Ph	48	45	3q
18	R = 2-OMe-Ph	67	81	3r
19	R = 3,4-di-Me-Ph	78	91	3s
20		60	55	3t
21		25	79	3u
22		19	−31	3v

[a] General conditions: **2** (0.1 mmol), **1e** (10 mol%), KOH (0.2 equiv.), TBHP (1.2 equiv.), toluene (2 mL), −20 °C, 5–72 h.
[b] Adding TBHP in portions, 0.02 mmol each time.
[c] Isolated yield.
[d] Enantiomeric excess determined by chiral HPLC analysis, absolute configurations were established by comparing with the literature data [4a].

normally (α*S*, β*R*) configuration. In addition, **3s** had 3,4-dimethyl modification, which also achieved high conversion, with an 82% yield and a 91% enantiomeric excess.

In addition, we also expanded the substrates of other skeleton structures, but the results were not particularly desired. Substrate **2t** with naphthyl skeleton, in this catalytic system, a moderated yield and an enantiomeric excess were obtained. In addition, different aliphatic substrates have also been investigated. For example, when R was cyclohexyl, the yield of **3u** was only 25%, but the enantioselectivity was 79%. However, the product **3v** with a *tert*-butyl substitution, which had only a poor yield and a low enantiomeric excess. Besides, we also investigated that when the R group was methyl or cyclopropyl, the asymmetric epoxidation reaction could not proceed.

Based on the current results, plausible transition state (TS) models for this base-promoted epoxidation reaction of α,β-unsaturated ketones **2a** with TBHP catalyzed by chiral thioureas **1e** are proposed (Fig. 2). In transition state **A**, the carbonyl group of α,β-unsaturated ketones **2a** is activated by the double hydrogen bonds donor of the thiourea unit **1e** and TBHP is deprotonated by the tertiary amine of quinine in *cinchona* alkaloid moiety, which formed a dual activation mode. Under the advantageous chiral environment and the large steric hindrance of D-mannitol, [*t*BuOO$^-$] can attack the activated chalcone from *Si*-face, thereby providing a (α*S*, β*R*) configuration product **3a**, which is consistent with experiments [4a]. On the contrary, in the transition state B, it is preferable to perform a *Re*-face attack to obtain a product of (α*R*, β*S*) configuration.

In conclusion, an asymmetric epoxidation reaction of α,β-unsaturated ketones based on a TBHP-promoted amine-thiourea dual activation model was developed. A series of α-carbonyl epoxides with high optical activities were synthesized, and enantiomeric excess was up to 96%. In addition, a reasonable analysis of the reaction mechanism is carried out, and two possible reaction transition states are proposed. Here, we exhibited a successful asymmetric epoxidation reaction of α,β-unsaturated ketones, which was a good example to expand the synthetic application range of the novel amine-thiourea catalyst. Further research on the application of the *cinchona* based amine-thiourea catalysts is still going on.

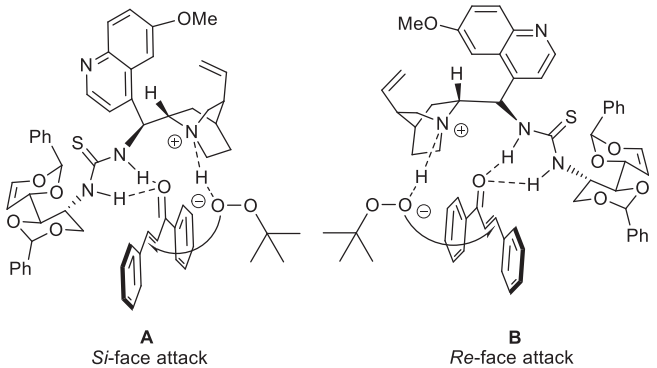


Fig. 2. Proposed reaction transition state models.

Declaration of Competing Interest

We declare that no conflict of interest exits in the submission of this manuscript and manuscript is approved by all authors for publication. The work described was original research that has not been published previously and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152941.

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