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4-Substituted-α,α-diaryl-prolinols Improve the Enantioselective Catalytic Epoxidation of α,β-Enones

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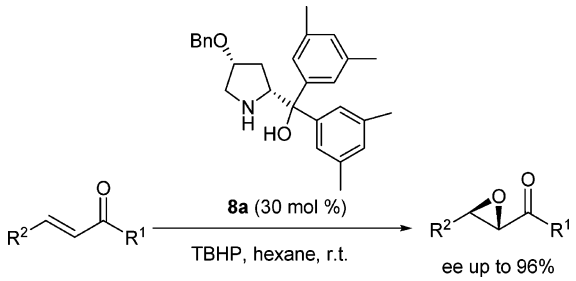

To seek novel metal-free organic catalysts for epoxidation with high stereoselectivity, a series of 4-substituted-α,α-diaryl-prolinols were synthesized in four steps from *trans*-4-hydroxyl-L-proline. These prolinol derivatives catalyzed the asymmetric epoxidation of α,β-enones to give the corresponding chiral epoxides in good yields and high enantioselectivities under mild reaction conditions. Studies of substituent effects on enantioselectivity revealed that steric bulk and electronic effect promoted higher enantioselectivity, and prolinol **8a** was found to be the best catalyst until now.

Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular of biologically active compounds.[1,2] The asymmetric epoxidation of functionalized and unfunctionalized olefins has emerged as a very versatile and important synthetic tool in organic synthesis.[3] Many asymmetric synthesis methods have been developed to meet this purpose in the past years. In the field of metal-catalyzed epoxidations, particularly, the Sharpless epoxidation for allylic alcohols and Jacobsen−Katsuki epoxidation for unfunctionalized olefins have opened a brand new field in organic chemistry.[4] At the same time, a spectacular advancement of metal-free enantioselective organocatalysis has appeared as a very potent chiral building blocks constructing method.[5] Up to now, many methods have been developed, and the epoxidation has been accomplished by homogeneous and heterogeneous catalysts.[6,7] Yet, improvement of the stereoselectivity and substrate scope is apparently a challenge. Organocatalysis is gaining more and more importance in asymmetric synthesis and has become a main focus of research in recent years.[8] Among various organocatalysts for enantioselective reactions, L-proline and its derivatives are most attractive.[9,10]

Recently, a new methodology for the catalytic asymmetric epoxidation of a wide variety of α,β-enones mediated by the bifunctional organocatalyst α,α-diphenyl-L-prolinol **3a** has been reported by Lattanzi (Scheme 1).[11a] The epoxides have been obtained in good yields and enantioselectivity (up to 80% ee) by employing 30 mol % catalyst loading at room temperature. Based on our experience in proline-type ligands design and synthesis,[10] in consideration of the proposed catalytic mechanism

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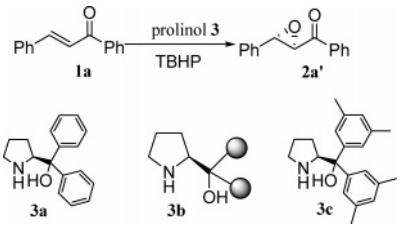
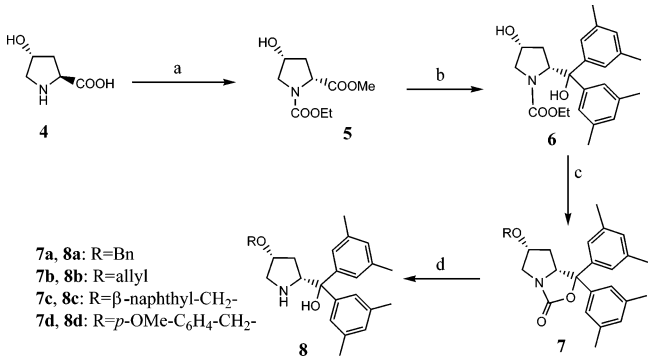
SCHEME 1. Enantioselective Epoxidation of α,*β*-Enones Catalyzed by Different Prolinol Derivatives



SCHEME 2. Synthesis of *cis*-4-Substituted-D-prolinol Catalysts 8a−d[a]



[a] Reagents and conditions: (a) (i) $(CH_3CO)_2O$, 90 °C; (ii) 2 N HCl, refluxing; (iii) ClCOOEt, MeOH, rt, 24 h; 25% overall yield; (b) ArMgBr, THF, rt, 5 h, 60%; (c) 1.2 equiv of NaH, 1.2 equiv of RBr, THF, rt, 20 h, 88%; (d) KOH, MeOH/H_2O, 100 °C, 24 h, 80%.

of this reaction, the electronic and steric effects of the catalysts and the position of the hydroxy moiety could be important in affecting the enantioselectivity. In our and Lattanzi's continuous works, dendritic catalyst (**3b**) and 3,5-dimethylphenyl catalyst (**3c**) were independently used in epoxidation of enones, and an obvious improvement in reactivity and enantioselectivity was observed.[11b,12] Inspired by these promising results, we hypothesized that the substituents on the other positions, such as C(4) of the prolinol backbone, could also have a visible effect on the reactivity and enantioselectivity of the reaction. In this context, we have been interested in designing organocatalysts

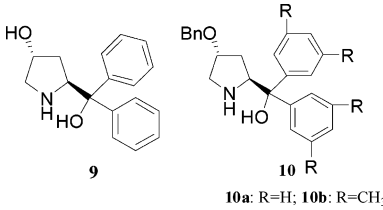


FIGURE 1. The structures of *trans*-4-substituted-α,α-diaryl-L-prolinols **9** and **10a**−**d**.

that bear sterically and electronically tunable substituents on both the C(4) position of the prolinol backbone and the hydroxy moiety; these catalysts may simultaneously have a steric hindrance effect on both sides to increase the enantioselectivity. Herein, we wish to report our investigation on the synthesis of different 4-substituted-diaryl-2-pyrrolidinemethanols, which led to the development of a highly effective system for the asymmetric epoxidation of a wide variety of α,*β*-enones under mild and simple reaction conditions.

First, a series of 4-substituted-diaryl-2-pyrrolidinemethanols **8a**−**d** were synthesized from commercially available *trans*-4-hydroxyl-L-proline **4** (Scheme 2). *trans*-4-Hydroxyproline **4** reacted with acetic anhydride and then hydrolyzed in 2 N HCl.[13] The mixture was reacted with ethyl chloroformate without further purification to give carbamate ester **5**. Treatment of compound **5** with 3,5-dimethylphenyl magnesium bromide furnished a tertiary alcohol **6**. Compounds **7** were prepared from **6** through etherification of C(4)−OH with a variety of alkyl bromides. Hydrolysis of compounds **7** gave the desired *cis*-4-substituted-D-prolinol **8**. Under similar reaction conditions, *trans*-4-substituted-L-prolinols (**9**, **10a**,**b**) were also prepared successfully in good yields from the corresponding *trans*-4-hydroxyl-L-proline (Figure 1, and Supporting Information, p S2).

A preliminary exploration was performed on the catalytic property of these catalysts in the asymmetric organocatalytic epoxidation of α,*β*-enones with TBHP in different solvents. 1,3-Diphenyl-propenone (**1a**) was selected as a model substrate to carry out this reaction using 30 mol % of catalysts at room temperature. As shown in Table 1, bis-(3,5-dimethylphenyl)-L-prolinol **3c**, which was used by Lattanzi,[11b] afforded **2a′** in 82% yield and 88% ee in our reaction system (Table 1, entry 1). When *trans*-4-hydroxyl-α,α-diphenyl-L-prolinol **9** was used as catalyst in hexane, unfortunately, diastereoisomerically pure *trans*-(2*R*,3*S*)-**2a′** was isolated in only 32% yield and 66% ee possibly due to the C(4)−OH of compound **9**, which may undergo a competition with the tertiary hydroxyl in reaction progress (Table 1, entry 2). This result prompted us to design new prolinol catalysts **10a**,**b** and **8a**−**d**, which have hydroxyl groups at the C(4)-position being protected to improve both reactivity and enantioselectivity. When compound **10a** having benzyloxy groups at the 4-position was used as a catalyst, both reactivity and enantioselectivity were significantly improved (Table 1, entry 3 vs entry 2). *trans*-4-Benzyloxy-α,α-bis-(3,5-dimethylphenyl)-L-prolinol **10b** gave a much improved result, as expected (Table 1, entry 4). To demonstrate that the configurations of C(2) and C(4) positions have a great influence

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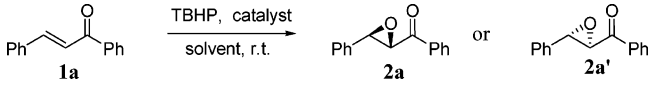
TABLE 1. Optimizing the Catalysts and Reaction Conditions for Asymmetric Epoxidation of α,β-Enones[a]

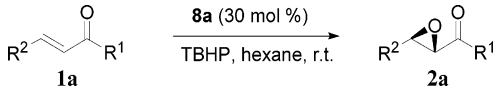


1a **2a** **2a'**

entry	catalyst	solvent	oxidant	product[d]	*t* (h)	yield (%)[b]	ee (%)[c]
1	**3c**	hexane	TBHP	**2a′**	144	82	88
2	**9**	hexane	TBHP	**2a′**	144	32	66
3	**10a**	hexane	TBHP	**2a′**	144	56	72
4	**10b**	hexane	TBHP	**2a′**	144	76	85
5	**8a**	hexane	TBHP	**2a**	144	75	94
6	**8b**	hexane	TBHP	**2a**	144	76	93
7	**8c**	hexane	TBHP	**2a**	144	60	93
8	**8d**	hexane	TBHP	**2a**	144	32	80
9	**8a**	CCl_4	TBHP	**2a**	144	76	94
10	**8a**	toluene	TBHP	**2a**	144	61	92
11	**8a**	THF	TBHP	**2a**	144	trace	nd[e]
12[f]	**8a**	hexane	TBHP	**2a**	144	42	92
13[g]	**8a**	hexane	TBHP	**2a**	144	61	90
14[h]	**8a**	hexane	H_2O_2	**2a**	144	trace	nd[e]

[a] Unless otherwise specified, the reaction was carried out with 1.3 equiv of TBHP in the presence of 30 mol % of catalyst at room temperature. [b] Isolated yield by flash column chromatography. [c] Enantiomeric excess was determined by the HPLC analysis by using the chiral column Daicel Chiralcel OD. [d] Absolute configurations of **2a** and **2a′** were determined to be (2*S*,3*R*) and (2*R*,3*S*), respectively, by comparison of the HPLC retention times with known data. [e] Not determined. [f] 0.1 equiv of **8a** was loaded. [g] 4 Å molecular sieves were added. [h] 0.1 equiv of tetrabutylammonium bromide was added.

TABLE 2. Asymmetric Epoxidation of α,β-Enones Catalyzed by 8a[a]



1a **2a**

entry	R^1	R^2	*t* (h)	yield (%)[b]	ee (%)[c] (config.)[d]
1	Ph	Ph	144	**2a**, 75	94 (2*S*,3*R*)
2[e]	*p*-$CH_3O-C_6H_4$	Ph	144	**2b**, 70	96 (2*S*,3*R*)
3	*p*-$Cl-C_6H_4$	Ph	96	**2c**, 80	90 (2*S*,3*R*)
4	*p*-$F-C_6H_4$	Ph	100	**2d**, 82	89 (2*S*,3*R*)
5[e]	*p*-$NO_2-C_6H_4$	Ph	120	**2e**, 86	91 (2*S*,3*R*)
6	Ph	*p*-$CH_3-C_6H_4$	122	**2f**, 72	94 (2*S*,3*R*)
7	Ph	*p*-$Cl-C_6H_4$	105	**2g**, 76	96 (2*S*,3*R*)
8[e]	Ph	*p*-$NO_2-C_6H_4$	96	**2h**, 90	94 (2*S*,3*R*)
9[e]	*p*-$CH_3O-C_6H_4$	*p*-$Cl-C_6H_4$	144	**2i**, 66	94 (2*S*,3*R*)
10	*p*-$Cl-C_6H_4$	*p*-$CH_3-C_6H_4$	144	**2j**, 70	92 (2*S*,3*R*)
11	CH_3	Ph	144	**2k**, 49	94 (3*S*,4*R*)
12	*i*-Pr	Ph	120	**2l**, trace	nd[f]
13	furan-2-yl	Ph	120	**2m**, 78	95 (2*S*,3*R*)
14	CH_3	$CH_3(CH_2)_4$	120	**2n**, 61	72 (3*S*,4*R*)

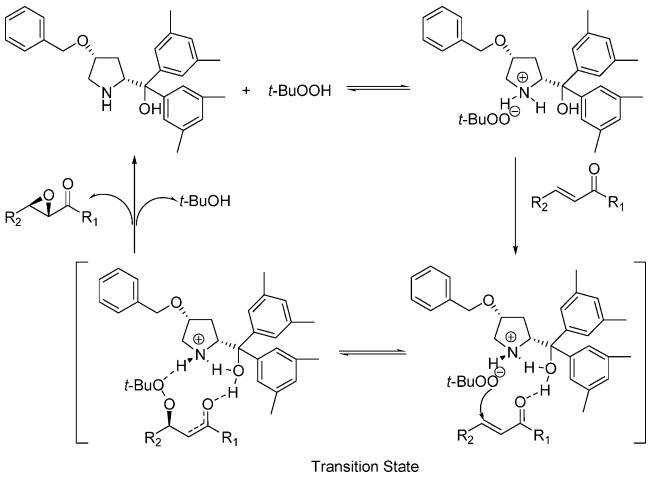
[a] Unless otherwise specified, the reaction was carried out with 1.3 equiv of TBHP in the presence of 30 mol % of catalyst **8a** at rt in hexane. [b] Isolated yields by column chromatography.s [c] Enantiomeric excess was determined by the HPLC analysis by using the chiral column (see Supporting Information). [d] Absolute configuration of **2** was determined to be (2*S*,3*R*) by comparison of the HPLC retention times with known data. [e] Reaction was performed in CCl_4. [f] Not determined.

on the reactivity and enantioselectivity of prolinol catalysts, we synthesized a series of *cis*-4-substituted-bis-(3,5-dimethylphenyl)-D-prolinols **8a**−**d** that could increase steric hindrance on both C(2) and C(4) sides. As we expected, the reaction using **8a**, which has a sterically congested benzyloxy moiety at the *cis*-4-position, preceded smoothly under similar conditions to give the desired epoxide **2a** with excellent enantioselectivity (94% ee) that was much improved as compared to **3c**'s result (Table 1, entry 5 vs entry 1). Catalyst with a less bulky group (allyloxy at the *cis*-4-position) gave a similar result albeit with a little decrease in enantioselectivity (Table 1, entry 6). Large substituents at *cis*-4-positions have a deleterious effect on the reaction. *cis*-4-Naphthalen-2-ylmethoxy-prolinol **8c** furnished an obviously slow reaction (Table 1, entry 7), while *p*-methoxylbenzyloxy-substituted catalyst **8d** afforded a poor result both in yield and in enantioselectivity (Table 1, entry 8).

Using the catalyst **8a**, the epoxidation carried out in tetrachloromethane that was used in our previous work[12] gave a result similar to that obtained in hexane (Table 1, entry 9). Reactions in toluene gave a satisfying ee but slow rate (Table 1, entry 10). Polar solvent, such as tetrahydrofuran (Table 1, entry 11), was totally inert to the epoxidation in our reaction system. It should be emphasized that reducing the catalytic loading (10 mol %) had a deleterious effect on reaction rate, but still an excellent ee value was observed (Table 1, entry 12). Surprisingly, 4 Å molecular sieves, which were used as an additive in our previous work,[12] showed a harmful effect on this reaction system (Table 1, entry 13). When aqueous hydroperoxide was used as an oxidant in the presence of phase-transfer catalyst, the reaction failed to give any product (Table 1, entry 14).

To demonstrate the substrate scope and potential for the asymmetric epoxidation organocatalyst **8a**, a series of different *trans*-α,β-unsaturated ketones were evaluated in the presence

SCHEME 3. Proposed Mechanism of 8a-Catalyzed Epoxidation Reaction



of catalyst **8a** (30 mol %). The results are summarized in Table 2. It should be emphasized that the level of enantiocontrol for all substrates was impressive. In most of the examples, diastereoisomerically pure *trans*-(2*S*,3*R*)-epoxides were obtained in 89−96% ee. α,*β*-Enones with substituted groups of different electronic characters on the phenyl ring of the carbonyl side (α-phenyl) afforded satisfying results (Table 2, entries 1−5). Electron-donating groups decreased the reaction activity but increased the enantioselectivity, while the electron-withdrawing ones had the opposite effects. For example, *p*-OMe-substituted substrate (Table 2, entry 2) gave a high ee and a relatively low yield, but *p*-NO_2-substituted (Table 2, entry 5) gave the opposite. Substitution on the *β*-phenyl ring of the enones by *p*-Me, *p*-Cl, *p*-NO_2 groups (Table 2, entries 6−8) did not change the enantioselectivity; the ee values were within the experimental error. Yet, a definite trend to higher yields was displayed by these para substituents in the order *p*-NO_2 > *p*-Cl > *p*-Me; specifically, when the enone bearing a strong electron-withdrawing nitro-group in *β*-phenyl ring was used as the substrate, it was found that epoxide was obtained in an excellent yield (90%). The superiority of **8a** can be successfully extended to *β*-methyl-substituted enone (Table 2, entry 11), which led to a satisfying result as compared to Lattanzi's procedure.[11b] However, the reaction failed when R^1 was isopropyl, which may be ascribed to its bulkiness (Table 2, entry 12). Enones with aromatic heterocycle substituted on the carbonyl side, such as 1-furan-2-yl-3-phenyl-propenone, afforded an excellent enantioselectivity with high yield (Table 2, entry 13). To our great delight, the aliphatic enone, which was considered as a more challenging substrate, was selectively epoxidized with moderate enantioselectivity (Table 2, entry 14).

Although the reaction mechanism is not exactly clear, a possible mechanism for this epoxidation of enones was proposed according to the catalytic cycle by Lattanzi (Scheme 3).[11] First, the catalyst **8a** activated TBHP by deprotonation to produce ammonium salt and *tert*-butyl hydroperoxide anion. Next, the tertiary hydroxyl activated the enone by forming a hydrogen bond with the carbonyl group. A hypothetic transition state was proposed, which was the same as Lattanzi's conjecture. Furthermore, catalyst **8a** had a benzyloxy at the *cis*-4-position of the prolinol backbone, which was also at the same side of the reaction area. The stereo hindrance between benzyloxy and the methyl of the *tert*-butyl hydroperoxide anion induced a front-side nucleophilic attack to the double bond, which could give a visible increase in enantioselectivity as compared to Lattanzi's catalyst **3c**. By the steric effects of both 3,5-dimethyl-phenyl and benzyloxy, a dominant configuration was formed, and, as a result, a high enantioselectivity was observed. As compared to **8a**, catalyst **8d** gave quite a poor result, which indicated that there might be an electronic effect along with the steric effect on the reaction progress. Our continuous work on the prolinol derivatives may give an approach to the key of this question on the mechanism.

In summary, we reported a highly enantioselective asymmetric epoxidation for α,*β*-enones using easily obtained prolinol organocatalyst **8a** as a catalyst and TBHP as an oxidant. High yields and excellent enatioselectivity have been obtained for a number of substrates with different steric and electronic properties. The asymmetric epoxidation reactions were performed with a simple and mild protocol without any protection and additional treatment, so an impressive breakthrough was achieved for steroselective epoxidation of α,*β*-enones.

Experimental Section

General Procedure for the Asymmetric Epoxidation of Enones 1 Catalyzed by 8a. To a solution of enone **1** (0.2 mmol) and catalyst **8a** (19.53 mg, 0.06 mmol) in hexane (1 mL) was added TBHP (0.26 mmol, 36 μL) at room temperature, and the resulting mixture was stirred for the specified time (Table 2). The crude reaction mixture was concentrated on the rotary evaporator. The residue was directly purified by flash chromatography on silica gel (petroleum ether/diethyl ether 40:1) to obtain the pure epoxides **2**, which were confirmed by the comparison of the ^{1}H NMR data with that reported in the literature. The ee's were identified by HPLC analysis.

Compound **2a**: white solid (33.6 mg, 75%); mp 88−90 °C; $[\alpha]^{24.3}_D$ = 152.1 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 1H), 4.23 (s, 1H), 7.32−7.45 (m, 7H), 7.54 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H). HPLC-separation conditions: Chiralcel OD, 20 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.00 mL/min; t_{major} = 15.8 min, t_{minor} = 16.9 min.[7d]

Compound **2b**: white solid (35.6 mg, 70%); mp 79−80 °C; $[\alpha]^{24.0}_D$ = 220.6 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.07 (s, 1H), 4.26 (s, 1H), 6.96 (d, J = 7.8 Hz, 2H), 7.39 (s, 5H), 8.02 (d, J = 8.1 Hz, 2H). HPLC-separation conditions: Chiralcel AD, 20 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.00 mL/min; t_{major} = 30.6 min, t_{minor} = 32.2 min.[7d]

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Supporting Information Available: Scheme S1, experimental procedure, and characterization data, including ^{1}H NMR spectral data and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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