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Structure effect of TsDPEN derivatives on enantioselectivity of asymmetric transfer hydrogenation

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ABSTRACT

TsDPEN derivative (3,3′,5,5′-TMTsDPEN) was synthesized and applied in asymmetric transfer hydrogenation of ketones. The influence of chiral ligands' NCCN dihedral angles to the enantioselectivities of the reaction was discussed.

1. Introduction

Asymmetric transfer hydrogenation has emerged as a powerful method to build chiral secondary alcohols, which are one of the most valuable intermediates in pharmaceutical synthesis [1]. Noyori et al. first introduced the chiral ligand *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene diamine [2] (TsDPEN, **1**) to Ru(II)-catalyzed transfer hydrogenation of ketones with excellent enantiomeric excess in 1995. After this pioneering work, some modified TsDPEN analogs were also developed in recent years. Deng et al. prepared an *ortho*-sulfonated TsDPEN ligand [3] (**2**) which achieved high reactivity and enantioselectivity in Ru-catalyzed asymmetric transfer hydrogenation for most of prochiral aromatic ketones in water. Dominguez et al. synthesized *p*-methyl (or methoxyl) substituted TsDPEN ligands [4] (**3** and **4**) and used them for asymmetric transfer hydrogenation of ketones. Xiao et al. reported the poly-(ethylene glycol) supported ligand [5] (PTsDPEN **5**) and the related ruthenium catalyst. We recently designed a new ligand with a PEG chain on the aryl sulfate group (**6**), and the asymmetric transfer hydrogenation of ketones proceeded smoothly in water with high yields and good enantioselectivities. Herein, for studying the relationship between the structures of the ligands and their related catalytic activities, we report a new type of modified TsDPEN ligand (TMTsDPEN **7**) bearing four methyl groups on *meta*-position of phenyl backbone (see Scheme 1).

2. Results and discussion

The synthetic route of TMTsDPEN **7** was described as follows [6]: Reaction of benzil **8** and cyclohexanone (1 equiv. of each) with ammonium acetate–acetic acid at 120 °C for 1 h gave cyclic bis-imine **9**. Compound **9** was reduced stereospecifically with 4 equiv. of lithium in a mixture of tetrahydrofuran-liquid ammonia at −78 °C for 2 h to afford *trans*-imidazolidine **10**. Treatment of a solution of **10** in methylene chloride and successively with 1 M hydrochloric acid provided 3,3′,5,5′-TMDPEDA. After resolution by *L*-(+)-tartaric acid in methanol, *S*,*S*-form of **11** (>99% optical purity, determined by HPLC analysis of its toluenesulfonamide derivative) was obtained. By reaction with toluenesulfonate chloride in presence of triethylamine, diamine **11** was converted to toluenesulfonamide bis(3,5-dimethylphenyl) ethaneamine **7** (TMTsDPEN) (see Scheme 2).

Various aromatic ketones were used in the study of the asymmetric transfer hydrogenation, which was carried out in water with TMTsDPEN **7** as chiral ligand and HCOONa as the hydrogen donor. The results were listed in Table 1. Excellent conversions with good enantiomeric excesses were obtained in most cases. However, in contrast to the results employing Ru-TsDPEN catalyst, the Ru–TMTsDPEN catalyst afforded similar reaction rates but with a slightly decreased enantioselectivity. For example, when aceto-

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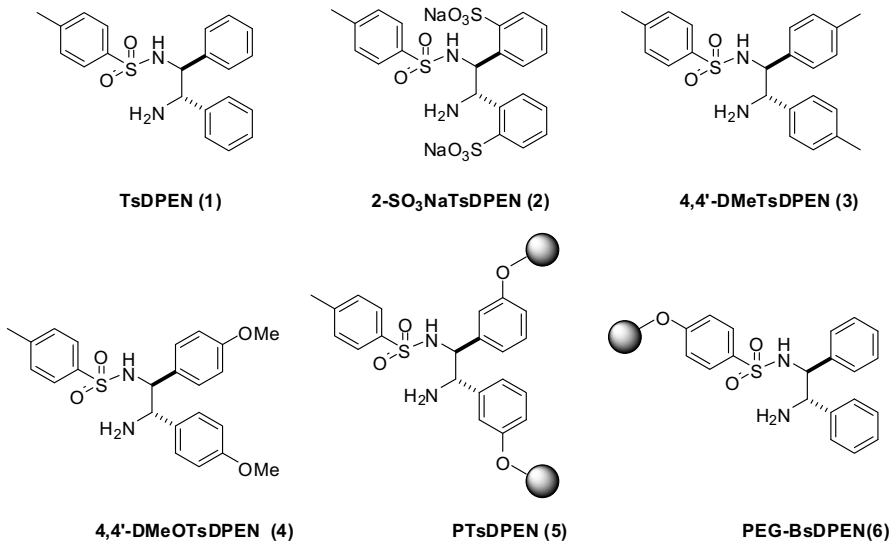
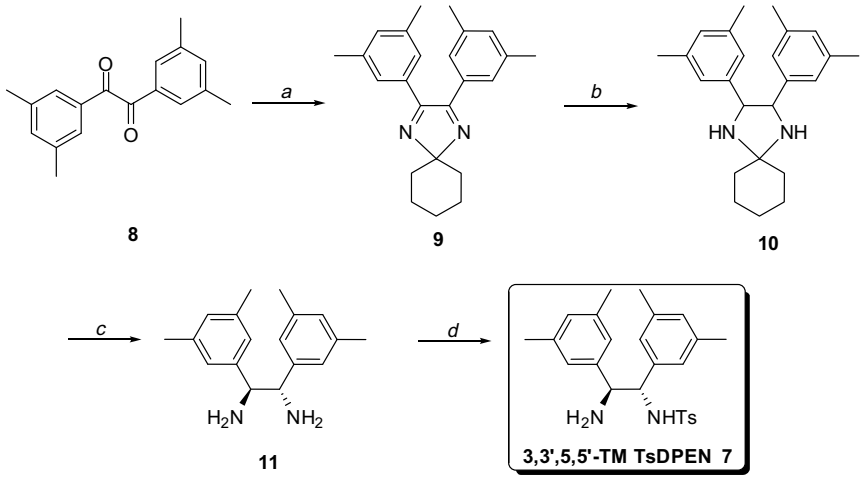
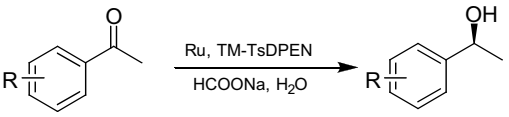


Scheme 1. TsDPEN and its derivatives.



Scheme 2. Synthetic route of TMTsDPEN **7**. Reagents and conditions: (a) Cyclohexanone, NH_4OAc, HOAc; (b) Li/NH_3(liq.), THF; (c) 1 M HCl, then resolution by *L*-(+)-tartaric acid in methanol; and (d) TsCl, Et_3N, CH_2Cl_2.

Table 1
Asymmetric transfer hydrogenation of various ketones in water[a]



Entry	Substrates	Conversion[b] (%)	ee[c]
1	Acetophenone	99	89
2	4′-Fluoroacetophenone	99	93
3	4′-Chloroacetophenone	99	90
4	4′-Bromoacetophenone	95	90
5	4′-Methoxyacetophone	99	90
6	4′-Methylacetophenone	99	86
7	4′-Nitroacetophone	95	91
8	Propiophenone	99	83
9	1-Tetralone	99	94
10	1-Indanone	99	92
11	2-Acetylnaphthalene	99	85
12	2-Acetylfuran	95	86

[a] The reactions were carried out with Ru–TM TsDPEN catalyst at 40 °C in water.
[b] The Conversion was determined by GC with an HP-5 capillary column.
[c] The ee value was determined by chiral HPLC with a chiralcel OD-H or OB-H column.

phenone was used as the substrate, 89% ee was obtained using TMTsDPEN as chiral ligand and 94% ee with TsDPEN under the same reaction conditions [7].

It is well known that chiral chelating ligand's dihedral angle have significant influence on enantioselectivities. Changes in the dihedral angle of diphosphine ligands in ruthenium-mediated asymmetric hydrogenation led to variations in the enantioselectivities of products. The narrower dihedral angle gave the better enantioselectivity [8]. As the dihedral angle of biaryl backbone is geometrically related to the bite angle and is known to determine the proximity of the pseudoequatorial aryl groups and the chelating substrate around the metal center [9], we believed that the decreased enantioselectivity with TMTsDPEN **7** as chiral ligand in the asymmetric transfer hydrogenation of aromatic ketones was related to the gentle changes of chiral backbone's dihedral angle (NCCN).

To obtain information on the dihedral angle between the NCCN, geometry optimization was performed at the *ab initio* level by using the B3LYP DFT hybrid method and the 6-31G(d) basis set. The results indicated that TsDPEN had a narrower angle (46.19°) than 3,3′,5,5′-TMTsDPEN (47.03°). The dihedral angle of 2-SO_3Na

Table 2
NCCN dihedral angles, enantioselectivity in asymmetric transfer hydrogenation of TsDPEN and its derivatives in HCOONa–water system

Entry	Ligand	NCCN dihedral angle of ligand[a]	NCCN dihedral angle of complex[b]	ee (%)
1	2-SO_3H TsDPEN (**2**)	45.86°	31.65°	95
2	TsDPEN (**1**)	46.19°	41.78°	94
3	3,3′,5,5′-TM TsDPEN (**7**)	47.03°	53.34°	89

[a] Geometry optimization was performed by using the B3LYP DFT hybrid method with the 6-31G(d) basis set.
[b] Structure optimization of Ru-complexes was carried out with MM2 calculation.

Table 3
NCCN dihedral angles, enantioselectivity in asymmetric transfer hydrogenation of TsDPEN and its derivatives in HCOOH–Et_3N azeotropic system

Entry	Ligand	NCCN dihedral angle of ligand[a] (°)	NCCN dihedral angle of complex[b] (°)	ee (%)
1	TsDPEN (**1**)	46.19	41.78	97
2	4,4′-DM TsDPEN (**3**)	46.36	52.30	92
3	4,4′-DMeO TsDPEN (**4**)	46.77	52.91	91
4	3,3′,5,5′-TM TsDPEN (**7**)	47.03	53.34	85

[a] Geometry optimization was performed by using the B3LYP DFT hybrid method with the 6-31G(d) basis set.
[b] Structure optimization of Ru-complexes was carried out with MM2 calculation.

TsDPEN (45.86°), a ligand which gave better enantioselectivity (95% ee) was also obtained with the same calculated method. The relationship between NCCN dihedral angle and enantioselectivity of TsDPEN and its derivatives in HCOONa–H_2O system was listed in Table 2. The results indicated the narrower dihedral angle gave the better enantioselectivity in the asymmetric transfer hydrogenation. We also carried out the MM2 calculation of corresponding Ru-Complex according to the literature's methods [8,9] and the results were consistent with the results of ligands.

The NCCN dihedral angles (both ligands and Ru-complexes), enantioselectivity in asymmetric transfer hydrogenation of TsDPEN and its derivatives **3**, **4** and **7** in HCOOH–Et_3N azeotropic system were listed in Table 3. The result was consistent with the HCOONa–H_2O system, the narrowest dihedral angle (TsDPEN, 46.19°) gave the best enantioselectivity (97% ee) and the largest dihedral angle (3,3′,5,5′-TM TsDPEN, 47.03°) gave the worst enantioselectivity (85% ee). 4,4′-DM TsDPEN (**3**) and 4,4′-DMeO TsDPEN (**4**) with 46.36° and 46.77° NCCN dihedral angle afforded 92% and 91% ee, respectively.

3. Conclusion

In conclusion, we have developed a new chiral lignad-TM TsDPEN and applied it in asymmetric transfer hydrogenation of aromatic ketones. The study between the structure of the ligands and their related catalytic activities indicated the narrower NCCN dihedral angle was favorable for the enantioselectivity in asymmetric transfer hydrogenation. Development of other new ligands derived from DPEN and further investigation between the structures and enantioselectivites of these ligands are underway.

4. Experimental

4.1. General

The NMR spectra were recorded with TMS as internal standard on a Varian 300 spectrometer. Coupling constants were given in Hertz. Enantiomeric excess was determined by chiral HPLC on chiralcel OB-H or OD-H columns. Optical rotation was determined on a Perkin–Elmer 341 polarmeter. MS spectra were recorded on an Agilent LC-MS 1200/6120 with ESI. The reactions were monitored by thin layer chromatography coated with silica gel-GF254.

4.2. Preparation of 1,2-bis(3,5-dimethylphenyl)-2-hydroxyethanone

To a 250-ml round bottomed flask charged with 50 ml of 95% ethanol and 53.7 g (400 mmol) of 3,5-dimethylbenzaldehyde (purified by vacuum distillation before use), a solution of 4.0 g (60 mmol) of potassium cyanide in 30 ml of distilled water was added. The mixture was stirred and heated under reflux for 3 h. The unreacted aldehyde was removed by steam distillation. The orange oily liquid dissolved in 30 ml of ethanol, and the solution was left to stand for crystallization. The yellow crude product was washed with 20 ml of 50% ethanol in water. White crystal was obtained after recrystallization from 95% ethanol. Yield: 59.6%. M.p.: 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (s, 2H), 7.14 (s, 1H), 6.92 (s, 2H), 6.88 (s, 1H), 5.85 (d, 1H, J = 4.8 Hz), 4.49 (d, 1H, J = 4.8 Hz), 2.30 (s, 6H), 2.25 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 199.0, 138.8, 138.4, 138.0, 135.3, 133.5, 21.2, 130.0, 126.8, 125.3, 76.0. ESI-MS: m/z 268.2 (M^+).

4.3. Preparation of 1,2-bis(3,5-dimethylphenyl)ethane-1,2-dione

A 250-ml round bottomed flask was charged with 30 g (112 mmol) of 1,2-bis(3,5-dimethylphenyl)-2-hydroxyethanone, 0.9 g (4.5 mmol) of cupric acetate, 30 g (375 mmol) of ammonium nitrate, and 100 ml of 80% acetic acid. The mixture was stirred and heated under reflux for 2 h. After the residue was cooled to room temperature, the precipitate was collected and washed with 30 ml of water. Pale yellow prism was obtained by recrystallization of the crude products from 95% ethanol. Yield: 80%. M.p.: 138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (s, 4H), 7.28 (s, 2H), 2.35 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 194.9, 138.5, 136.5, 132.8, 127.4, 21.1; ESI-MS: m/z 266.2 (M^+).

4.4. Preparation of bis(3,5-dimethylphenyl)-spiro-imidazole

Acetic acid (70 ml) was added to a flask containing 11.9 g (50 mmol) of 1,2-bis(3,5-dimethylphenyl) ethane-1,2-dione and 27 g (350 mmol) of ammonium acetate. 5.3 ml (51.5 mmol) of cyclohexanone was added and the mixture was heated under reflux for 4 h. After cooling to room temperature, the mixture was poured into 100 ml of water and placed overnight for crystallization. The crystals were collected and dried *in vacuo*. Recrystallization from ethyl acetate/hexane gave desired product. Yield: 75%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.10 (s, 4H), 7.03 (s, 2H), 2.26 (s, 12H), 1.66–1.95 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.0, 137.3, 132.7, 131.2, 126.5, 103.4, 34.7, 25.7, 24.1, 21.1; ESI-MS: m/z 345.3 (M^++H).

4.5. Preparation of 1,2-bis(3,5-dimethylphenyl)ethane-1,2-diamine

Ammonia gas was slowly condensed into a solution of the 6.95 g (22 mmol) of spiro-imisazole in 50 ml of anhydrous tetrahydrofuran at −78 °C under argon atmosphere. The gas flow was stopped when the volume of the reaction mixture has approximately doubled. Lithium wire (0.62 g, 88 mmol) was added slowly ensuring that the temperature did not exceed −60 °C. After stirring for 60 min, 2.6 ml of ethanol was added. Ammonium chloride (6.2 g) was added after another one hour. The mixture was warmed to room temperature, then water and ether (100 ml, respectively) were added. The two layers were separated and the aqueous layer was extracted twice with 100 ml of ether. The combined organic phase was washed with brine and evaporated *in vacuo*. The resulting oil was dissolved in ether and then 2 equiv. of 10% HCl was

added. After the biphasic mixture was stirred for 90 min, the mixture was diluted with water. The aqueous layer was separated and the organic layer was extracted with water. The combined aqueous layers were washed with dichloromethane and the neutralized with aqueous potassium hydroxide until pH > 10. Dichloromethane (3 × 50 ml) was added to extract the crude product. The combined organic extracts were dried with sodium sulfate. The solvent was removed by rotary evaporator to give the product as yellowish oil. Yield: 94%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.94 (s, 4H), 6.86 (s, 2H), 4.07 (s, 2H), 2.30 (s, 2H), 1.61 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.0, 137.4, 128.3, 124.4, 61.0, 21.3; ESI-MS: m/z 269.1 (M^++H).

4.6. Resolution of (±)-1,2-bis(3,5-dimethylphenyl)ethane-1,2-diamine

Formation of a salt with *L*-(+)-tartaric acid in methanol/water and crystallization from methanol gave (S,S)-1,2-bis(3,5-dimethylphenyl)ethane-1,2-diamine in 95% ee. The optical purity can be increased to >99% with second crystallization. The optical purity was determined on OD-H column after converting the diamine to its tosylamide by reaction with 2 equiv. of toluene-4-sulfonyl chloride in presence of triethylamine. (Hex/IPA = 90/10; 254 nm; t_{minor} = 8.35 min, t_{major} = 18.24 min).

4.7. Synthesis of (1S,2S)-N-tosyl-1,2-bis(3,5-dimethyl phenyl)ethylamine

A solution of the 380 mg (2 mmol) of *p*-toluenesulphonyl chloride in 5 ml of dichloromethane was added dropwise to a solution of 836 mg (2 mmol) of (1 S,2S)-1,2-bis(3,5-dimethylphenyl) ethane-1,2-diamine and 0.28 ml (2 mmol) of triethylamine in 10 ml of anhydrous dichloromethane at 0 °C. The mixture was stirred at 0 °C for 2 h and allowed to room temperature overnight. Water was added and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine and water subsequently, dried over sodium sulfate. The crude *N*-tosyl-1,2-bis(3,5-dimethylphenyl)ethylamine was obtained by removing the solvent under reduced pressure which could be purified by column chromatography to give a white solid. Yield: 83%. $[\alpha]_D^{20}$ = +12.8° (c = 1.06). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.30–7.27 (d, J = 8.1 Hz, 2H), 6.88–6.85 (d, J = 8.1 Hz, 2H), 6.80 (s, 2H), 6.71 (s, 1H), 6.63 (s, 2H), 6.61 (s, 1H), 4.59–4.56 (d, J = 6.9 Hz, 1H), 4.44–4.42 (d, J = 6.9 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 6H), 2.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 141.82, 137.57, 137.32, 137.18, 129.38, 128.94, 128.63, 128.42, 128.06, 126.69, 125.16, 125.02, 62.51, 59.53, 21.36, 21.20, 21.077; HR-MS Calc. for $C_{25}H_{30}N_2O_2S$ (M^+ + H): 423.2101. Found: 423.2111.

4.8. General procedure for asymmetric transfer hydrogenation of ketones in water

A suspension of 3.1 mg (0.005 mmol) of $[RuCl_2(p\text{-cymene})]_2$ and 16 mg (0.012 mmol) of (1S,2S)-3,3′,5,5′-TMTsDPEN in 2 ml of H_2O was purged with argon and stirred at 40 °C for 1 h. After that 340 mg (5.0 mmol) of HCOONa and a ketone (1 mmol) were introduced. The mixture was purged with argon and stirred at room temperature. After the reaction completed, the organic compounds were extracted with 5 ml of *n*-hexane. The conversion and the enantioselectivity were determined by GC and chiral HPLC, respectively.

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