Synthesis of Chiral Calixarene-Like Salen Ligand and Application in Catalytic Asymmetric Friedel–Crafts Reaction of Aromatic Amines with Glyoxylate

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Received 20 December 2005

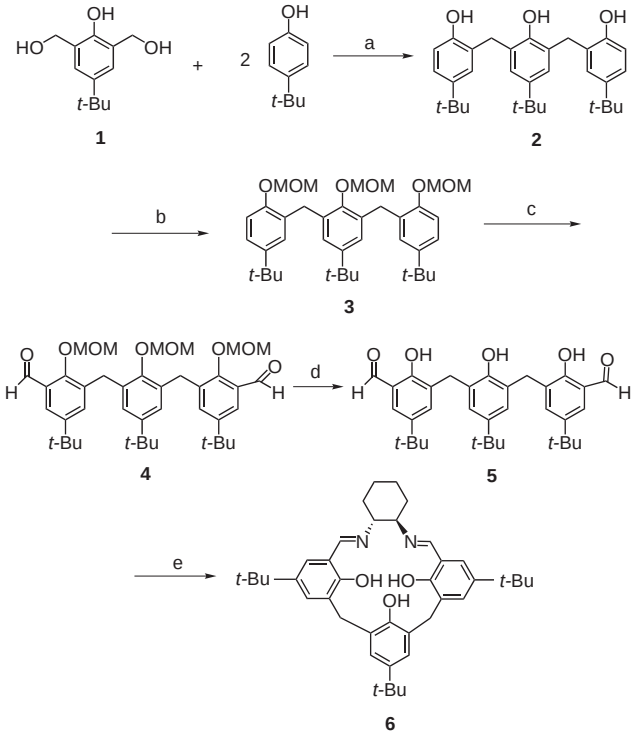
Abstract: A new calixarene-like salen ligand is efficiently prepared from 2,6-bishydroxymethyl-4-*tert*-butyl phenol as starting material by a five-step synthesis. The enantioselective Friedel–Crafts reactions of aromatic amine with glyoxylate are examined employing a titanium derivative of this new ligand as the chiral catalyst, and provide modest to excellent enantioselectivities up to 98% ee.

Key words: salen ligand, macrocycle, asymmetric catalysis, Friedel–Crafts reaction, titanium complex

The development of novel chiral ligands is crucial to the advancement of asymmetric catalysis.[1] Salen ligands are one of the most common types of chiral ligands which are becoming applicable for plenty of catalytic asymmetric synthesis.[2] Generally, the structural and electronic properties of salen ligands play important roles in the catalytic activities. Most of the chiral salen ligands reported to date are 'open' structure employed salicylaldehyde derivatives with different substituent groups.[3] Several chiral macrocycles bearing two salens with an enzyme-like chiral cavity were studied and exhibited good to excellent selectivity in asymmetric catalytic reactions.[4]

Calixarene scaffolds have attracted much attention with regard to complexing hosts for ions and molecules.[5] Several chiral salen and salan ligands have been developed in our group and successfully applied to different asymmetric catalytic reactions.[6] Herein, we wish to report the synthesis of a new calixarene-like salen ligand with well-defined and rigid chiral cavity, which might provide a better face or site discrimination in asymmetric reaction. The application of this ligand to Ti-catalyzed enantioselective Friedel–Crafts reaction of aromatic compounds with glyoxylate is also included.

As outlined in Scheme 1, treatment of 2,6-bishydroxymethyl-4-*tert*-butyl phenol (**1**) with excess 4-*tert*-butyl phenol in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene afforded the corresponding trimer **2** in 82% yield,[7] which was then treated with sodium hydride and chloromethyl methyl ether, and afforded the protected compound **3** in 90% yield. Following the directed orthometallation of **3** with *n*-butyllithium, formylation with *N*,*N*-dimethyl formamide provided **4** in 68% yield,[8] which was deprotected to give diformyl triphenol **5**. The chiral salen ligand **6** was prepared by the condensation of **5** and (1*R*,2*R*)-1,2-diaminocyclohexane in 65% yield.[9] The overall yield of the five-step synthesis is 34%. It could be expected that this new chiral motif could serve as ligand in miscellaneous asymmetric catalysis.



Scheme 1 Synthesis of macrocyclic calixarene-like salen ligand. *Reagents and conditions*: (a) *p*-TSA (cat.), benzene, reflux, 24 h, 82%; (b) NaH, CH_3OCH_2Cl, THF, 90%; (c) (i) *n*-BuLi, Et_2O, –78 °C, 3 h; (ii) DMF, –78 °C to r.t. 12 h, 68%; (d) HCl (6 N), MeOH, reflux, 5 h, quant.; (e) (1*R*,2*R*)-1,2-diaminocyclohexane, CH_2Cl_2, anhyd Na_2SO_4, r.t., 24 h, 65%.

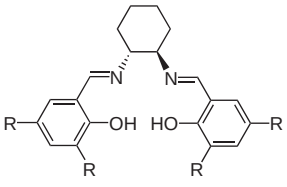
The Friedel–Crafts reaction is one of the most fundamental reactions in organic chemistry, and the catalytic enantioselective Friedel–Crafts reaction of aromatic compounds with carbonyl compounds has been an extensive interest in asymmetric catalysis.[10] The reaction of aromatic compounds with α-dicarbonyl compounds provided

SYNLETT 2006, No. 8, pp 1221–1224
Advanced online publication: 05.05.2006
DOI: 10.1055/s-2006-939684; Art ID: W33005ST

a simple procedure for the preparation of optically active mandelic acid derivatives with important biological properties.[11,12] Employing the new calixarene-like salen compound **6** as chiral ligand, we then studied the Friedel–Crafts reaction of amino-substituted aromatic compounds with glyoxylate catalyzed by titanium catalyst.

The reaction of *N*,*N*-dimethylaniline with ethyl glyoxylate was initially studied as a model reaction at room temperature in the presence of 10 mol% chiral titanium catalyst prepared in situ by mixing the ligand **6** and Ti(O*i*-Pr)$_4$ with 1:1 molar ratio in toluene.[11b] To our delight, the reaction gave 2-(4-dimethylaminophenyl)-2-hydroxyacetic acid ethyl ester in 75% ee and 91% chemical yield (entry 1, Table 1). The reaction conditions were then optimized as shown in Table 1 with Ti-**6** as the catalyst. The nature of the solvent was revealed to have a remarkable effect upon the enantioselectivity and chemical yield. Of the seven solvents we investigated, toluene, dichloromethane, and hexane gave higher enantioselectivities and good chemical yields (entries 1–3). When using THF and MeCN as solvents, moderate ee values were obtained (entries 4 and 5). DMF provided very poor chemical yield and enantioselectivity (entry 6). Diethyl ether was proven to be the best solvent in terms of selectivity (entry 7). With Et_2O as the solvent, a variation of the reaction temperature from room temperature to 0 °C caused a significant increase of the ee value to 98% (entry 8), but there was a little decrease when the reaction was carried out at –20 °C (entry 9). We were pleased to find that there was no significant change in enantioselectivity and chemical yield when the catalyst amount was decreased to 5 mol% (entry 10). The reaction still showed good result even with only 2 mol% catalyst used (entry 11). Those results demonstrated that the Ti-**6** catalyst was very efficient for the reaction.

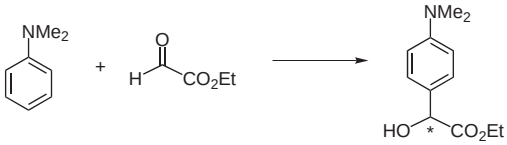
For comparison, the salen ligands **7** and **8** (Figure 1) were also examined in the Friedel–Crafts reaction of *N*,*N*-dimethylaniline with ethyl glyoxylate. They gave good reactivity but poor selectivity. Those results preliminarily demonstrate that ligand **6** is more efficient on the enantioselectivity in the reaction than that of 'open' analogues. Although the structure of Ti-**6** is not clear at this stage, the results shown above indicate that the cavity in **6** maybe provides a better site discrimination around the center metal than that of **7** and **8**, and the additional phenoxy group may play a beneficial role for the formation of a rigid structure of the catalyst.



7 R = H
8 R = *t*-Bu

Figure 1

Table 1 Enantioselective Friedel–Crafts Reaction of *N*,*N*-Dimethylaniline with Ethyl Glyoxylate Catalyzed by Different Salen–Ti Complexes under Various Conditions[a]



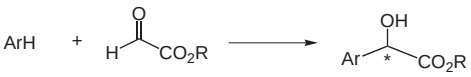
Entry	Ligand	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**6**	Toluene	r.t.	91	75
2	**6**	CH_2Cl_2	r.t.	92	73
3	**6**	*n*-Hexane	r.t.	89	75
4	**6**	THF	r.t.	90	60
5	**6**	CH_3CN	r.t.	83	55
6	**6**	DMF	r.t.	40	15
7	**6**	Et_2O	r.t.	90	80
8	**6**	Et_2O	0	85	98
9	**6**	Et_2O	–20	79	94
10[d]	**6**	Et_2O	0	83	98
11[e]	**6**	Et_2O	0	70	95
12	**7**	Et_2O	0	92	30
13	**8**	Et_2O	0	95	45

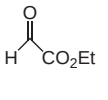
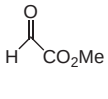
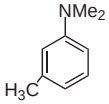
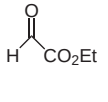
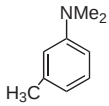
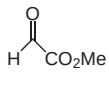
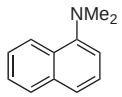
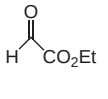
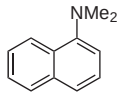
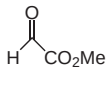
[a] Unless otherwise noted, all reactions were carried out for 20–24 h with the molar ratio: *N*,*N*-dimethylaniline–ethyl glyoxylate–Ti(O*i*-Pr)$_4$–**6** = 1:2:0.1:0.1.
[b] Isolated yield by prepared TLC.
[c] Determined by HPLC analysis on a Chiralcel OD-H chiral column.
[d] Reaction performed with catalyst loading of 5 mol%.
[e] Reaction performed with catalyst loading of 2 mol%.

We thus used Ti-**6** as the catalyst for the enantioselective Friedel–Crafts reactions[13] of *N*,*N*-dimethylaniline and *N*,*N*-dimethylaminonaphthalene with ethyl and methyl glyoxylate under optimized reaction conditions as in Table 1, entry 10. The results are shown in Table 2. All the reactions proceeded smoothly to afford corresponding mandelic acid ester derivatives in high yields. In terms of enantioselectivity, the reaction between *N*,*N*-dimethylaminonaphthalene with methyl glyoxylate afforded very high ee value, while entries 2 and 3 provided only moderate selectivity. No regular trends of steric effect displayed on the enantioselectivity.

In summary, the synthesis of a new chiral calixarene-like salen ligand **6** is accomplished from 2,6-bishydroxymethyl-4-*tert*-butylphenol as starting material by a five-step synthesis in 34% total yield. The enantioselective Friedel–Crafts reactions of amino aromatic compounds with glyoxylate are examined using Ti-**6** as the chiral

Table 2 Enantioselective Friedel–Crafts Reaction of Aromatic Amines with Glyoxylate Catalyzed by Ti-**6** Complex[a]



Entry	Amine	Glyoxylate	Yield (%)[b]	OR/ee (%)[c]
1			85	(*S*)[d]-(+) 98
2			90	(+) 57
3			78	(+) 84
4			80	(+) 76
5			81	(+) 50
6			84	(+) 93

[a] Reaction conditions: aromatic amine (1.0 mmol), glyoxylate (2.0 mmol), catalyst (5 mol%), Et_2O (2 mL), 0 °C, 20–24 h.
[b] Isolated yield by prepared TLC.
[c] Determined by HPLC analysis on a Chiralcel OD-H chiral column.
[d] The absolute configuration was determined by comparing the optical rotation with the literature value.[14]

catalyst, and provide modest to excellent enantioselectivities. Further studies on the structure of the catalyst and the application of this new ligand on other asymmetric reactions are now in progress in our laboratory.

Acknowledgment

We gratefully acknowledge the National Natural Science Foundation of China (20472028, 20332050) and Education Ministry for their financial support.

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(9) **Procedure for the Synthesis of Compound 6.**
To a solution of 1.5 g (2.80 mmol) diformyl triphenol (**5**) in 100 mL of dry CH_2Cl_2 was added 0.34 g (3 mmol) (1*R*,2*R*)-1,2-diaminocyclohexane and 2 g anhyd Na_2SO_4. The mixture was stirred for 24 h at r.t. After the solids were filtered, the solution was reduced to about 10 mL in vacuo. Addition of 30 mL of MeOH gave a yellow solid, which was then recrystallized with CH_2Cl_2–MeOH (1:1) to give 1.1 g of compound **6** (yield: 65%), yellow solid, mp 130–132 °C, $[\alpha]_D^{25}$ –25.8 (*c* 0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 14.05 (s, 3 H), 8.22 (s, 2 H), 7.07 (s, 2 H), 7.04 (s, 2 H), 6.97 (s, 2 H), 4.09 (d, *J* = 14.2 Hz, 2 H), 3.84 (d, *J* = 14.2 Hz, 2 H), 3.32 (s, 4 H), 1.91–1.40 (m, 8 H), 1.21 (s, 18 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 165.7, 158.5, 141.0, 131.7, 129.1, 127.4, 126.4, 125.9, 117.2, 72.0, 34.2, 33.6, 31.9, 31.7, 31.2, 24.5 ppm. IR (KBr): ν = 3421, 3252, 2935, 2890, 1628, 1532, 1485, 1410, 1360 cm^{-1}. MS (ES): *m/z* (%) = 609.5 (100). Anal. Calcd (%) for $C_{40}H_{52}N_2O_3$: C, 78.95; H, 8.55; N, 4.62. Found: C, 78.92; H, 8.60; N, 4.50.
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(13) **Typical Procedure for the Asymmetric Friedel–Crafts Reaction of Aromatic Amine with Glyoxylate.**
In a 15-mL Schlenk tube, salen compound **6** (32 mg, 0.05 mmol) was dissolved in 2 mL of Et_2O under argon atmosphere, followed by the addition of titanium tetraisopropoxide (0.5 M in Et_2O, 100 μL, 0.05 mmol) and the mixture was stirred for 2 h at r.t. The resulting solution

was cooled to 0 °C, and then *N*,*N*-dimethylaniline (125 μL, 1 mmol) and freshly distilled ethyl glyoxylate (160 μL, 2 mmol) were introduced into the reaction system, and stirred at 0 °C for about 24 h. The reaction process was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, the product was separated by preparative TLC (PE–EtOAc, 4:1) to give 180 mg (85% yield) 2-(4-dimethylaminophenyl)-2-hydroxyacetic acid ethyl ester. $[\alpha]_D^{25}$ +103.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 6.73–6.65 (m, 2 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 4.27–4.15 (m, 2 H), 3.33 (d, *J* = 6.0 Hz, 1 H), 2.96 (s, 6 H), 1.23 (t, 3 H). The ee was determined by HPLC on a Chiralcel OD-H column, hexane–2-PrOH = 95:5, flow rate = 1.0 mL/min; t_R = 18.64 (minor), t_R = 24.94 (major).

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