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Unsymmetric Chiral Salen Schiff bases: A New Chiral Ligand Pool from Bis-Schiff Bases Containing Two Different Salicylaldehyde Units

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Abstract: An efficient and facile synthesis of a new class of novel chiral Salen Schiff base ligands has been developed via a stepwise approach. An important feature of these new Salen ligands is that they possess two different salicylaldehyde units, therefore, while steric factor or electronic factor can be fixed on one side, electronic or/and steric factors can be tuned from the other side with different substituents.

The development of chiral Schiff base ligands has received considerable interest since Jacobsen,[1] and subsequently Katsuki[2] reported significant success in asymmetric epoxidation of unfunctionalized olefins by the chiral manganese (III) Salen Schiff base catalysts. Salen ligands give complexes which also hold promises in enantioselective cyclopropanation of styrenes, asymmetric aziridination of olefins, asymmetric Diels-Alder cycloaddition, and enantioselective ring opening of epoxides.[3] Generally, the electronic and structural properties of the ligands play an important role in the catalytic properties.[4] In almost all of the Salen Schiff base complexes studied to date, the two identical salicylaldehyde moieties on both sides of the diamine in the ligands make the same electronic and steric contributions. While simple, often one-pot condensation of one diamine with two identical salicylaldehyde derivatives makes these symmetrical Salen Schiff base ligands easily accessible and available, we report here a facile and efficient synthesis of a new class of unsymmetrical chiral Salen Schiff base ligands which possess two different salicylaldehyde derivatives, each with different substituent groups (Fig.1). This unique combination allows tuning both the electronic properties from one side and the steric effects from the other side simultaneously and collectively to maximize the performance of the catalysts.

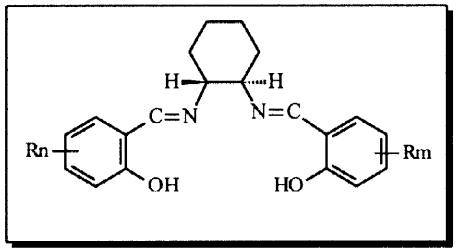

Fig. 1. Illustrated is the general structure of unsymmetrical chiral Salen Schiff base ligands where two different salicylaldehyde derivative uints are linked by a chiral diamine.

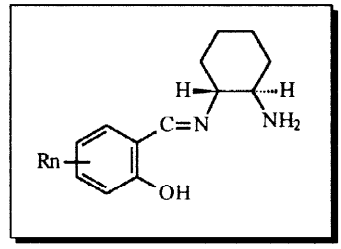

Fig. 2. Illustrated is the general structure of a "chiral half unit" which will lead to unsymmetrical chiral Salen Schiff base ligands.

The obvious difficulty in the synthesis of unsymmetrical Salen ligands is that the straight condensation methodology used for symmetrical Salen ligands is no longer applicable. Therefore, a stepwise protocol which requires a "chiral half unit" as shown in Fig. 2 is needed, and this intermediate would lead to the construction of the desirable target compounds by reacting the only one reactive free amine with other salicylaldehyde derivative.

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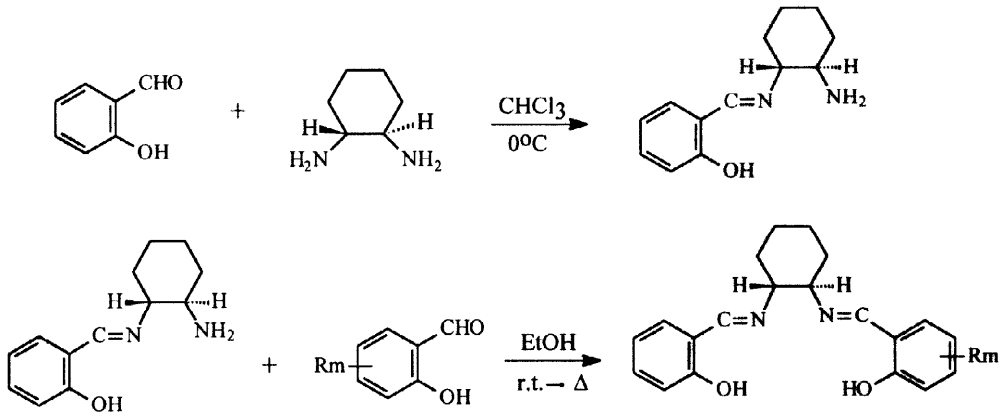
It turns out that this reactive chiral intermediate can be easily and reliably prepared by the treatment of salicylaldehyde with (1*R*,2*R*)-(-)-1,2-diaminocyclohexane in chloroform solution at 0 °C for five hours,[5] and then briefly at room temperature, leading to the formation of the "half unit" (Rn=H in Fig. 2) in 90~95% yield.[6] The practically pure half unit can be obtained without double condensation product when the molar ratio of amine to the aldehyde is maintained between 1:1 to 1.5:1. The solvent and unreacted starting materials are removed in situ under vacuum at 60 °C. Control of this temperature is critical in order for it to be sufficient for the removal of reactants, but still safe enough for the reactive chiral half unit. This isolated reactive half unit is remarkably stable at ambient temperature without decomposition for months as monitored by NMR. The excellent stability renders this half unit easy to manipulate in the next step for the preparation of new Salen ligands. The subsequent condensation of this half unit with another salicylaldehyde derivative in 1:1 molar ratio leads to desirable unsymmetrical chiral Schiff base ligands (Scheme 1) in good to excellent yields.[7]



Scheme 1. For the preparation of the half unit from salicylaldehyde and (1*R*,2*R*)-(-)-1,2-diamino-cyclohexane and subsequent reaction with salicyladehyde derivative to prepare unsymmetrical chiral Salen Schiff base ligands.

Table 1 lists the required reaction times and isolated product yields for each substrate as well as solvents used in the reactions. The generality of this reaction is evident by successful application of different substituents ranging from strong electron-donating groups such as NEt_2 (entry 1) to strong electron-withdrawing groups such as NO_2 (entry 8). The reaction also utilizes two disubstituted salicylaldehydes (entries 7 and 9) without any difficulty. The reaction can be easily extended to bulky group-containing salicylaldehyde derivatives and, therefore, several ligands have been prepared with cyclic ring substituents ranging from cyclohexyl (entry 12) to admantyl (entry 13), with highly branched substituents such as *t*-butyl (entry 10) and *t*-pentyl (entry 11). When 5-(diphenylamino)salicylaldehyde[8] (entry 14) is used, chloroform has to be added as co-solvent to enhance solubility for homogeneous reaction (Table 2). The reaction usually takes 5 ~ 6 hours to complete with the yields between 77 and 99%.

Preliminary results indicate that these ligands can easily form chiral metal complexes upon reactions with metal ions. Cu (II), Ni (II), Mn (III) and Cr (III) complexes are being prepared and their asymmetric catalytic properties and scopes are being evaluated. The chiral half unit, a key intermediate to success, is also being extended to prepare other chiral ligands by reaction with non-salicylaldehyde derivatives.

In summary, a new class of novel unsymmetrical chiral Salen Schiff base ligands have been developed via a stepwise approach. The facile synthesis involves the preparation of an important chiral half unit, which is obtained from selective reaction of salicylaldehyde with one amine of chiral diaminocyclohexane, and then direct condensation of salicylaldehyde derivatives with the half unit. This methodology allows us to open new avenues of chiral Salen Schiff base ligands for asymmetric catalysts which may possess unique properties in the area where symmetrical chiral Salen Schiff base based catalysts are inferior.

Table 1. List for salicylaldehyde derivatives used for the preparation of the unsymmetrical chiral Salen Schiff base ligands and the reaction times as well as product yield

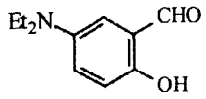
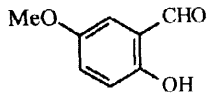
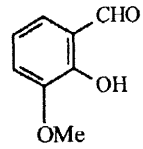
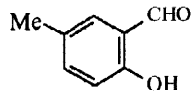
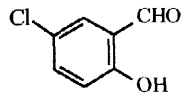
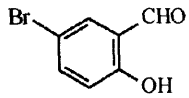
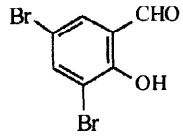
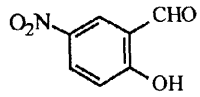
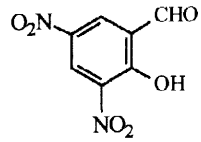
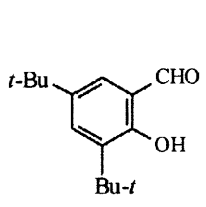
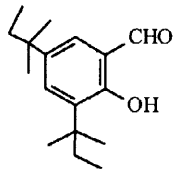
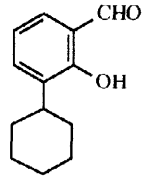
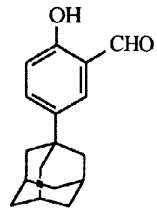
Entry		Reaction time(h)	Product yield(%)	Solvents
1		5	97	EtOH
2		5	95	EtOH
3		5	90	EtOH
4		5	87	EtOH
5		5	77	EtOH
6		5	93	EtOH
7		6	83	EtOH
8		5	97	EtOH
9		5	97	EtOH

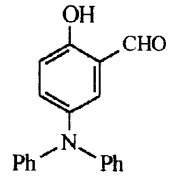
Table 2. List for bulky group-containing salicylaldehyde derivatives for the preparation of the unsymmetrical chirl ligands and the reaction times as well as product yield











Entry	10	11	12	13	14
Reaction time(h)	5	5	5	6	6
Reaction solvents	EtOH	EtOH	EtOH	EtOH	EtOH/$CHCl_3$
Product yield(%)	86	88	86	95	99

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4. Jacobsen, E. N.; Zhang, W.; Güler, M. *J. Am. Chem. Soc.* **1991**, *113*, 6703. Also see: Jacobsen, E. N. in *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; Hegedus, L. S., Eds.; Pregamon: New York, **1995**, vol. 12. and Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189. Also see: Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309; Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **1995**, *42*, 7739. Zhao, S.-H.; Ortiz, P. R.; Keys, B. A.; Davenprot, K. G. *Tetrahedron Lett.* **1996**, *37*, 2725.
5. A racemic compound with similar structure was proposed from a reaction which took a week, see: Matsumoto, N.; Nozaki, T.; Ushio, H.; Motoda, K.-i.; Ohba, M.; Mago, G.; Okawa, H. *J. Chem. Soc. Dalton Trans.* **1993**, 2157.
6. Procedure for the preparation of the chiral half unit: Salicylaldehyde (0.74 mL, 6.8 mmol) in chloroform (50 mL) was added dropwise to a vigorously stirred solution of (1*R*, 2*R*)-(-)-diaminocyclohexane (0.78 g, 6.8 mmol) in chloroform (150 mL) containing 4Å molecular sieves at 0 °C. The complete addition took approximately 5 hours, and then the mixture was warmed to room temperature for 15 minutes. Upon filtration, the filtrate was evaporated under vacuum at 60 °C to give a pale-yellow creamy solid, 1.43 g, 95 %. IR (CCl_4): 3404, 3093, 2935, 2858, 1631, 1581, 1502, 1466, 1423, 1297 cm^{-1}. ^1H NMR 400 MHz ($CDCl_3$/TMS): 1.11-1.50 (m, 4H), 1.51-1.77 (m, 3H), 1.77-1.93 (m, 2H), 2.71 (q, 1H), 3.20-3.29 (m, 1H), 6.72 (t, 1H), 7.07 (dd, 1H), 7.13-7.28 (m, 1H), 8.19 (s, 0.7H), 8.36 (s, 0.3H), 13.24 (s, 0.7H), 13.34 (s, 0.3H) ppm; ^{13}C NMR ($CDCl_3$/TMS): 165.1, 164.9, 161.5, 161.3, 132.6, 132.5, 131.8, 131.7, 119.0, 118.9, 117.4, 117.3, 117.1, 73.2, 55.0, 34.0, 33.8, 33.5, 25.2, 25.0, 24.5 ppm.
7. A typical procedure for the preparation of unsymmetric chiral Salen Schiff bases: To an ethanol solution (20 mL) of the chiral half unit (0.188g, 0.86 mmol) was added dropwise 5-adamantyl salicylaldehyde (entry 13) (0.211g, 0.86 mmol) in 20 mL of ethanol at ambient temperature. The mixture was gradually heated to 60 °C and then this temperature was maintained for 4 hours. Upon the removal of the solvent and cooling, a yellow precipitate was collected and recrystallized from ethanol to give 0.373 g of unsymmetric chiral ligand, yield: 95%, m.p.: 75-77 °C . Anal. for $C_{30}H_{36}N_2O_2$: C: 78.89, H: 8.33, Calc. C: 78.92, H: 7.94.
8. Liang, S.; Santos, J.; Bu, X. R. Mintz, E., manuscript in preparation.