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Authors	Shengli Zuo, Shuxiang Zheng, Jianjun Liu and Ang Zuo
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ORCID® iDs	Ang Zuo - https://orcid.org/0000-0002-4075-8786

Mechanochemical Synthesis of Unsymmetrical Salens for the Preparation of Co-Salen Complexes and Their Catalytic Evaluation for the Synthesis of α-Aryloxy Alcohols via Asymmetric Phenolic Kinetic Resolution of Terminal Epoxide

Shengli Zuo,[a] Shuxiang Zheng,[a] Jianjun Liu,*[,a] and Ang Zuo*[,b]

[a] State Key Laboratory of Chemical Resource Engineering, Department of Applied Chemistry, College of Chemistry, Beijing University of Chemical Technology, Beijing 100124, China

[b] Department of Pharmaceutical Sciences, College of Pharmacy and UICentre, University of Illinois at Chicago, Chicago, Illinois 60612, United States

ABSTRACT

In this paper, we report the mechanochemical synthesis of unsymmetrical salens using grinding and ball milling technologies, respectively, both of which were afforded in good yield. The chelating effect of unsymmetrical salens with zinc, copper, and cobalt was studied and the chiral Co-salen complex (**2f**) yielded upto 98%. Hydrolytic kinetic resolution (HKR) of epichlorohydrin with water catalyzed by **2f** was explored and resulted in 98% in ee, suggesting **2f** could serve as an enantioselective catalyst for the asymmetric ring-opening of phenols to terminal epoxides. A library of α-aryloxy alcohols (**3**) was thereafter synthesized in good yield and great ee using **2f** via the phenolic KR of epichlorohydrin.

INTRODUCTION

In the past decade, more than twenty chiral small molecule drugs were approved by FDA, including ruxolitinib, afatinib, sonidegib, encorafenib, lorlatinib, darolutamide, alpelisib, artesunate, maribavir, ponesimod, daridorexant and others.[1] The enantioselective synthesis in modern chemistry turns out to be accumulatively essential for the preparation of chiral drugs, which has a huge growing market in the future. Indeed, asymmetric ring-opening of terminal epoxides is one of the important strategies for synthesizing drug-like building blocks and key organic intermediates in the drug discovery and process chemistry.[2] Chiral metal-salen complexes were designed for catalyzing reaction processes that result in good yield, high regioselective and enantioselective controls for the asymmetric ring-opening of terminal epoxides. Extensive transitional metals have been researched to explore and optimize the catalytic property of chiral metal-salens, such as Cr,[3] Co,[4] Fe,[5] Ti,[6] Al,[7] Y[8] and Mn[9] with numerous nucleophiles to afford chiral molecules. In addition to the development of transitional metals, salen ligands have also been studied in the aspect of conformational differences, for instance, oligosalen,[10] macrocyclic oligosalen[11] and polymeric salen.[12]

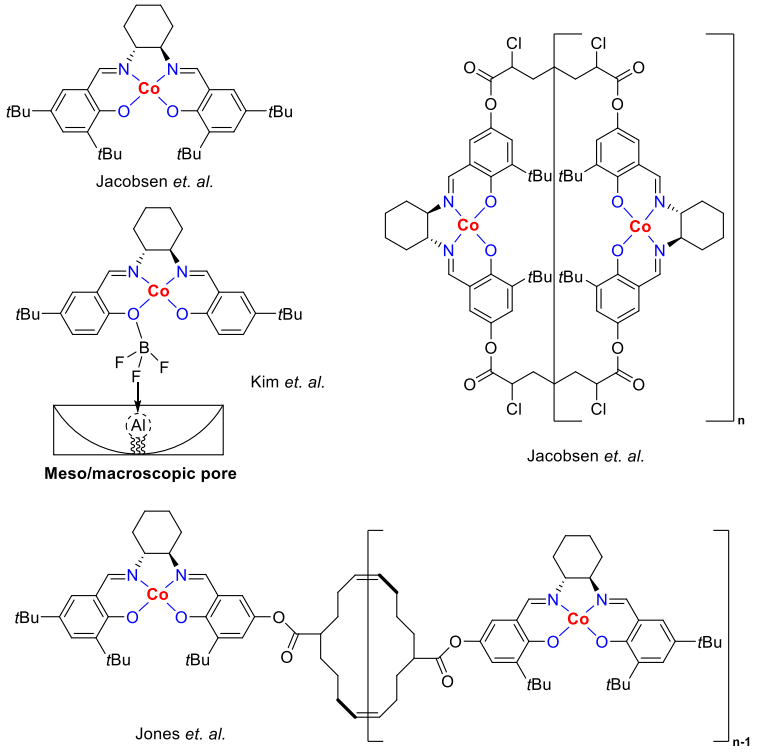
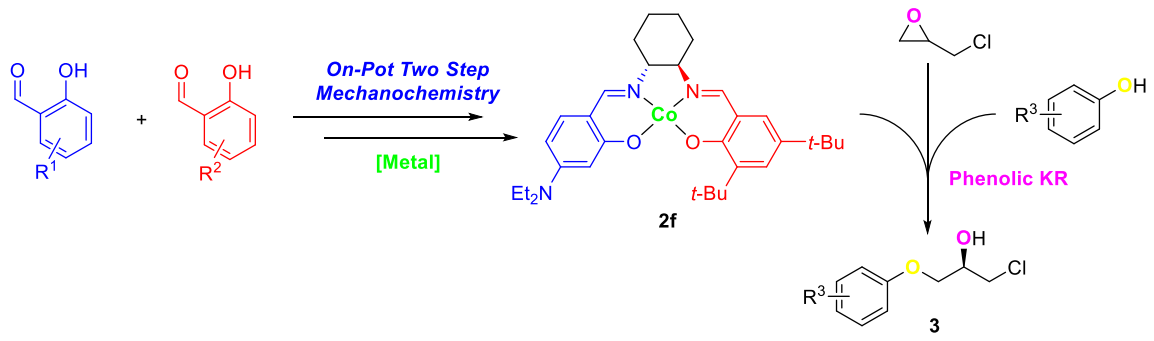


Figure 1. Representative asymmetric Co-salen catalysts

Jacobsen and coworkers reported the first synthesis of α-aryloxy alcohols through the phenolic kinetic resolution (KR) of terminal epoxides using Co-salen catalyst.[13] Since their discovery, researchers have investigated several Co-salen complexes for the KR of epoxides with phenols as nucleophiles (Figure 1).[14] Kim *et. al.* described a catalytic system of chiral Co-salen immobilized on meso/macro porous silica monoliths for the ring-opening of epoxides.[15] Jones *et. al.* designed a cyclooctene-based Co-salen macrocycle catalyst for the phenolic KR of ring-openings of epichlorohydrin and 1,2-epoxyhexane.[16] However, these Co-salen systems are limited to several reasons such as tedious preparation of salen scaffolds, excess use of epoxides, high catalyst loadings, narrower scopes and needs of Lewis acidic or basic co-catalysts.[17] A more efficient preparation of Co-salen catalyst is therefore of a great need for the asymmetric ring-opening of epoxides, and thus becomes extremely attractive to us.



Scheme 1. Synthetic approaches of our Co-unsymmetrical salen catlalyst (**2f**) for the asymmetric synthesis of α-aryloxy alcohols

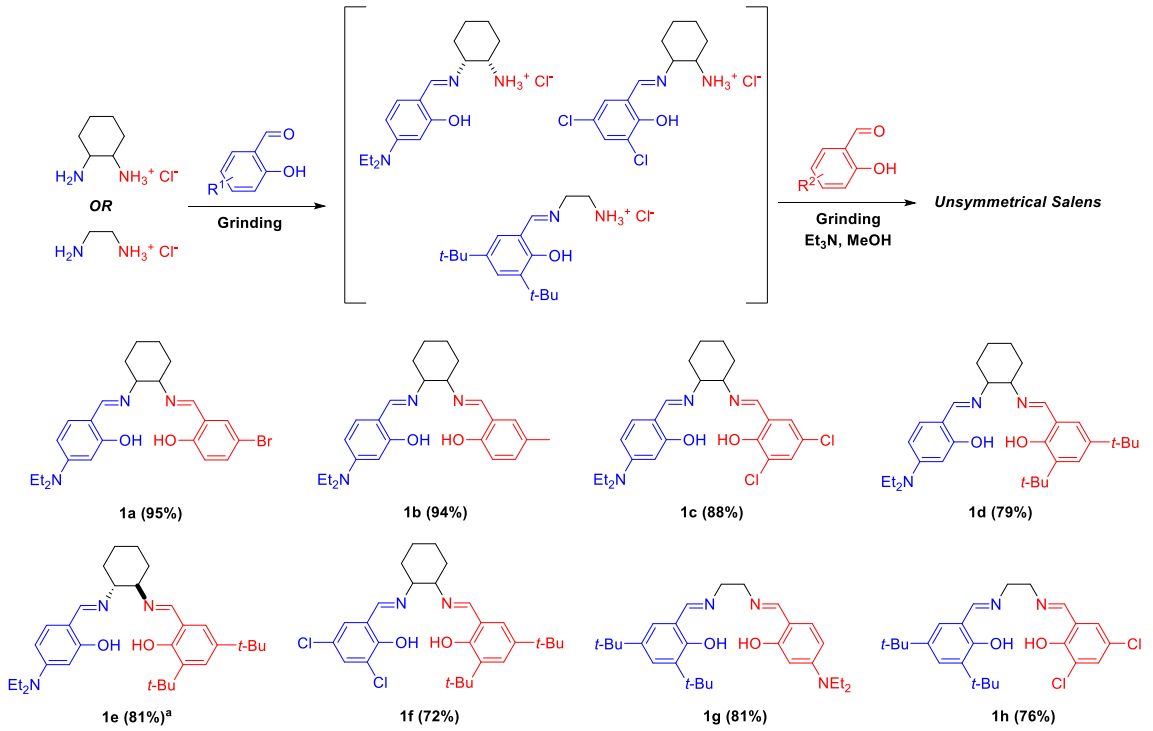
In order to synthesize a novel Co-salen catalyst, the design and preparation of salen compounds or sometimes described as bis-imine Schiff bases should be proceeded at the beginning. Imines were originally synthesized by Schiff from the condensation of carbonyls with amines.[18] Thereafter, syntheses of salens were extensively reported using timely technologies.[19] Inspired by the mechanochemical chemistry technology to simplify chemical processes and eliminate the use of organic solvents, salen compounds have been synthesized by the "green" grinding strategy previously.[20] Herein, we report an one-pot two step mechanochemical synthesis of unsymmetrical salens for the preparation of Co-salen complexes and their catalytic evaluation to synthesize α-aryloxy alcohols through the phenolic KR of terminal epoxides (Scheme 1). Advantages to break the C_2-symmetry in Co-salen complexes were reported before.[17b,21] Lewis basic NEt_2 (–$N(CH_2CH_3)_2$) group was introduced to the salen scaffold to facilitate purification, enhance catalytic efficiency, and improve the thermal stability.[22] Chelating effect of salen compounds (**1**) with different metals were explored as well. Furthermore, we presented the hydrolytic kinetic resolution (HKR) of epichlorohydrin with water using Co-salen complexes (**2**), and α-aryloxy alcohols were

synthesized by **2f** catalytic system through the asymmetric ring-opening of epichlorohydrin and phenols.

RESULTS AND DISCUSSION

The mechanochemical study examined the synthesis of several unsymmetrical salens using monoammonium salts and salicylaldehydes (Scheme 2). Agate mortar and pestle were used for the one-pot two step mechanochemical reactions (see in the Supporting Information). Initially, 1,2-diaminocyclohexane or ethylenediamine monohydrochlorides were grinded with a half equivalence of 4-diethylamino (Et_2N–), 3,5-dichloro (Cl–), or 3,5-di-*tert*-butyl (*t*-Bu–) salicylaldehydes (blue moieties in Scheme 2) in 10 minutes. The synthesis of diamine monohydrochlorides and characterization data of mono-imine ammonium salts were described before.[20] This process generates mono-imine ammonium salts as the stable intermediates in the mortar. Without implementing treatment such as filtration, evaporation of solvents, or further purification, mono-imine ammonium salts were subsequently treated with triethylamine (Et_3N), one equivalence of 5-bromo (Br–), 5-methyl, 4-diethylamino (Et_2N–), 3,5-dichloro (Cl–), or 3,5-di-*tert*-butyl (*t*-Bu–) salicylaldehydes (red moieties in Scheme 2), and trace methanol, followed by grinding in 20 minutes for the second step reaction completion, monitored by TLC. Trace amount of methanol was used to lubricate the molecular surface for an improved performance (known as liquid-assisted grinding, LAG). Unsymmetrical salens (**1a**–**1h**) were obtained in the yield of 72% to 95% after purified by column chromatography. Bromo-containing salen **1a** was yielded the best (95%), presumably due to the strong electron-withdrawing property of bromine. Because of the poor solubility in eluent, yield of dichloro-containing **1c** (88%) was lower than **1a** after isolating by column chromatography. This was also found between **1g** (81%) and **1h** (76%). Yields of **1d** (79%), **1e** (81%), and **1f** (72%) were less than **1a**–**c** caused by the steric hindrance of di-*tert*-butyl groups.

In the aspect of characterization of salens, two singlets were shown at around 8 ppm in the ^{1}H NMR spectrum, indicating two unsymmetrical imines. The broad peak at around 13 ppm suggests free hydrogen from phenol moieties. The signal at around 1615 cm^{-1} in the IR spectrum could also indicate the formation of imine (see in the Supporting Information).



Scheme 2. One-pot two-step synthesis of unsymmetrical salens mechanochemically

[a] Starting material is trans-1,2-diaminocyclohexane.

In addition to the use of grinding technology, a self-made ball milling was applied to the synthesis of unsymmetrical salens by us. The method and its principle were described previously.[23] Our ball milling was designed to mount a 40 mL glass reactor with zirconia and/or alumina composite balls (3.20 mm and 2.16 mm in diameter, respectively). Considering the safety in the synthesis of unsymmetrical salens, the working speed was set to be 700 rev/min. Similarly to the above reaction conditions, amounts of chemicals, and work-ups, the first step reaction between amino monohydrochlorides and salicylaldehydes (blue in Scheme 2) took 1 hour for reaction

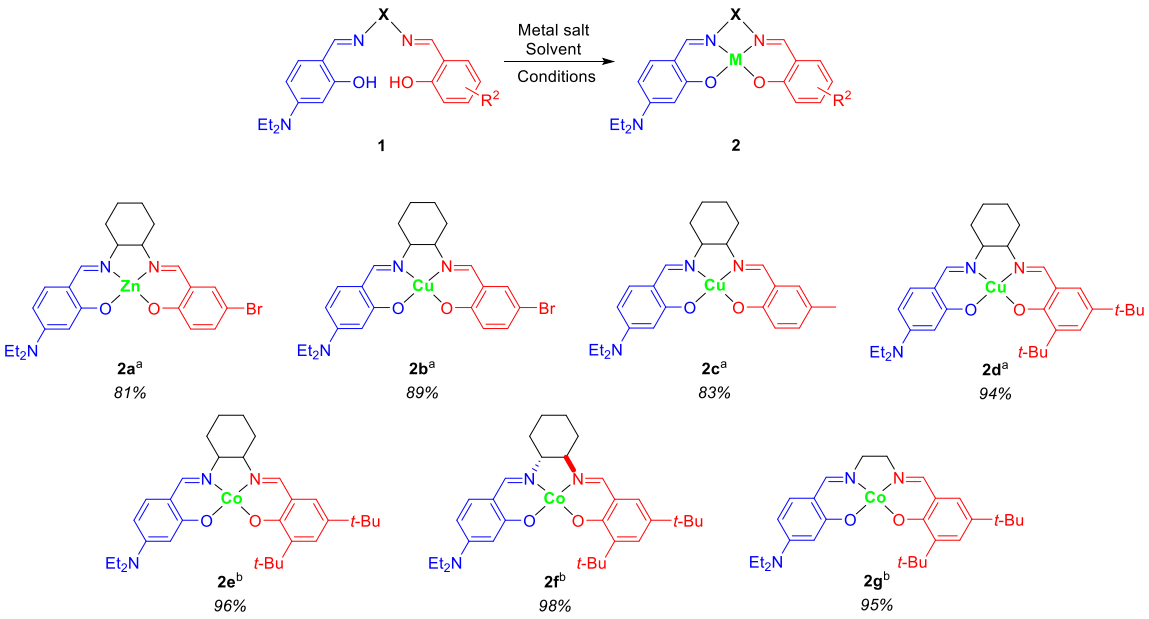
completion. After adding another salicylaldehydes (red in Scheme 2), Et_3N, and methanol, the second step reaction was completed in an additional hour, monitored by TLC. Yields of unsymmetrical salens using grinding and ball milling were summarized in Table 1. We were surprised that the overall yield from ball milling was lower than the overall yield from grinding, suggesting a higher revolution per minute (RPM) could be necessary to increase the reaction yield using ball milling.

Table 1. Yields of unsymmetrical salens (**1**) using grinding and ball milling

Entry	ID	Grinding/Yield (%)	Ball milling/Yield (%)
1	**1a**	95	82
2	**1b**	94	71
3	**1c**	88	77
4	**1d**	79	66
5	**1e**	81	68
6	**1f**	72	57
7	**1g**	81	72
8	**1h**	76	61

We next examined the chelating effect of the above salens (**1**) with different transitional metals. A library of metal-salen complexes was synthesized as outlined in Table 2. Reaction conditions were described previously.[13,24] The yield of Zn complex (**2a**, 81%) is slightly lower than the Cu complex (**2b**, 89%). **1b** and **1d** reacted with Cu to afford **2c** and **2d** in the yields of 83% and 94%, respectively. The reaction affinity between Co and selected salens was high than Zn and Cu complexes, for instance, **2e** (96%), **2f** (98%), and **2g** (95%). *Tert*-butyl group played an important role as an electron-donating moiety for increasing the yield (**2d**-**g**). The slightly higher yield of **2f** over **2e** suggested a relatively more effective preparation for chiral salen complexes.

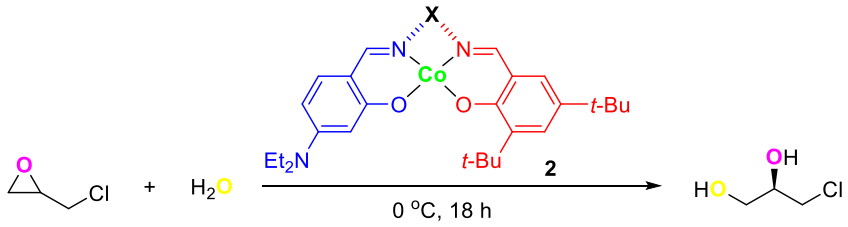
Table 2. Synthesis of unsymmetrical metal-salen catalysts (**2**)



[a] Reaction conditions: **1** (1 mmol), EtOH (7 mL), metal acetate hydrate (1 mmol), and MeOH (12 mL) were added gradually to a round bottom flask, and refluxed for 4 hours under nitrogen gas. Products were afforded by filtration and washed with cold methanol (20 mL X 2); [b] Reaction conditions: **1** (1 mmol), Cobalt(II) acetate tetrahydrate (1.2 mmol), and MeOH (10 mL) were added gradually to a round bottom flask, and stirred at 0 °C for 40 min under nitrogen gas. Products were afforded by filtration and washed with cold methanol (20 mL X 2).

The HKR of epichlorohydrin with water was selected as a classical model to evaluate the catalytic activity of Co-unsymmetrical salen complexes (**2e**, **2f**, and **2g**) for the asymmetric ring-opening of epoxides. Enantiomeric excess (ee) results of 3-chloro-1,2-propanediol from the HKR reactions were summarized in Table 3. The complex **2** (0.5 mmol) and trace amount of glacial acetic acid were added to dry dichloromethane. The mixture solution was evaporated after the reaction color changed from orange-red to dark brown in 30 min. Racemic epichlorohydrin and deionized water were subsequently added to the reaction and stirred for 18 hours at 0 °C. Upon the reaction completion, 3-chloro-1,2-propanediol in highly enantioenriched structure was afforded using chiral catalyst **2f**, while non-chiral catalysts **2e** and **2g** displayed nonenantioselective results (Table 3).

Table 3. HKR of epichlorohydrin with water catalyzed by **2**.

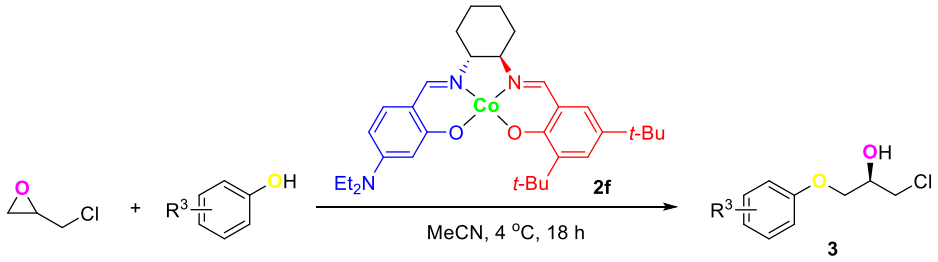


Entry	Catalyst	ee (%)[a]
1	**2e**	0
2	**2f**	98
3	**2g**	0

[a] Determined by chiral HPLC analysis.

To broaden the use of our chiral catalyst, α-aryloxy alcohols were thereafter synthesized through the phenolic KR of epichlorohydrin with different phenols using chiral Co-salen catalyst **2f** (Table 4). Meta-substituted methyl phenol showed less reactivity and selectivity (entry 2), while *tert*-butyl monosubstitution at the para-position on the phenol slightly increased in light of the yield and ee (entry 3). Bulky phenol afforded no product (**3e**), suggesting in good agreement with Co-salen catalytic mechanism.[2c] Phenols with both electron-donating and electron-withdrawing moieties participated in the asymmetric ring-opening of epichlorohydrin provided α-aryloxy alcohols in an overall high yield and a complete enantioselectivity.

Table 4. Synthesis of α-aryloxy alcohols (**3**) by phenolic KR of epichlorohydrin with phenols catalyzed by Co-salen complex (**2f**).



Entry	ID	R^3	Yield (%)[a]	ee (%)[b]
1	**3a**	H	60	98
2	**3b**	*m*-CH_3	67	93
3	**3c**	*p*-*t*-Bu	75	99
4	**3d**	*p*-CHO	56	96
5	**3e**	di-*o*-*t*-Bu; *p*-CH_3	0	-

[a] Isolated yields based on alcohol; [b] Determined by chiral HPLC analysis.

CONCLUSION

In summary, we mechanochemically synthesized unsymmetrical salens **1** for preparing metal-salen catalysts **2** at the first time. Use of grinding technology provided **1** in an overall higher yield in comparison to the self-made ball milling. Faster RPM (over 700 rev/min) might be necessary to increase the reaction efficiency through a ball milling technology. Chelating effort of **1** with different metals was explored and metal-salen complexes **2a**-**2g** were highly yielded, demonstrating an intimate affinity of unsymmetrical salens chelating with metals. The HKR of epichlorohydrin with water catalyzed by Co-salens **2** was studied and chiral **2f** showed an outstanding catalytic ability to afford the diol product in great ee (98%). A library of α-aryloxy alcohols was thereafter synthesized through the asymmetric ring-opening of epichlorohydrin with different phenols in the presence of **2f**, resulting in good yield and high ee. Further application of chiral Co-salen complexes and their reaction mechanism will be addressed in the due course.

ASSOCIATED CONTENT

The Supporting Information is available.

AUTHOR INFORMATION

Corresponding Author

*Email: azuo@uic.edu

ORCID

Ang Zuo: 0000-0002-4075-8786

Notes

The authors declare no competing financial interest.

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