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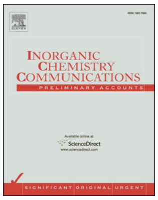

Short communication

A chiral multidentate salan-supported heterobimetallic catalyst for asymmetric Friedel-Crafts reaction

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ABSTRACT

A new hydroxymethyl-pendant salan (**3**) containing a chiral backbone and an extra O_4 cavity has been prepared through a facile one-pot procedure. The ligand has been characterized by ESI-MS, elemental analysis and 2D NMR techniques. To continue our previous work on the catalytically asymmetric F-C reactions using multimetallic complexes involving salan-type ligands, we investigated the applicability of **3** for both asymmetric Henry and F-C reactions, in comparison with previously reported results using salans **1** and **2**. It was revealed that although **3** was not a suitable ligand for homometallic copper-catalyzed Henry reaction, it was effective for the hetereobimetallic Cu/Zn-catalyzed asymmetric F-C reaction, affording desired alkylated product with good yield and moderate enantiomeric excess (ee), after screening of various catalyst combinations.

Salen and its derivatives as a class of well-known *bis*-Schiff base type N_2O_2 ligands are constantly attracting great attention in many aspects of fundamental and applied research as they provide useful building blocks for the construction of a large variety of metal complexes [1–7]. The strong chelating ability and large structural variation of salens allow them to bind almost all kinds of metal ions to form not only simple mononuclear complexes, but also binuclear, trinuclear and polynuclear complexes or coordination polymers [8]. The capability of salen in constructing high-nuclearity complexes or extended coordination networks is owing to the existence of oxygen donors that are able to connect two metal centers through μ_2-O-bridging modes [9]. In addition, the nearly square-planar metal-N_2O_2 motif tends to form extended structures through additional coordination of metal center in its axial directions [10–14].

The easiness of ligand modification on the salen backbone allows for not only facile tuning of electronic properties of specific metal complexes, but also the introduction of additional functional groups containing extra donating sites for metal complexation. The latter has led to new synthesis and applications of salen ligands bearing functional groups such as hydroxyl or alkoxyl groups [8,15–18], pyridyl groups [19], polyether macrocycles [20–23] and carboxylates [24–26]. We have been recently interested in fabricating carboxylato functionalized metal-salen networks as well as alkoxy pendant salen ligands for multimetallic complexes or networks [7]. Indeed, salen-type Schiff base ligands with a pendant O_4 cavity have been extensively explored for bimetallic catalysts for a range of asymmetric organic transformations such as aldol, nitroaldol or mannich-type reactions mainly by the Shibasaki group [27–32]. In addition, salan, the reduced salen (Scheme 1) proved to improve the catalytic performance of its bimetallic complexes in asymmetric Henry (nitroaldol) reaction and Friedel-Crafts (F-C) alkylation [33–36].

Metal-catalyzed F-C alkylation offers an efficient and atom-economical route to the C—C bond formation between two substrates, and therefore, is one of the most attractive research topics in synthetic chemistry [37–39]. The asymmetric version of F-C reactions requires a chiral catalyst and has been achieved by a variety of chiral metal- or organo-catalysts previously [40,41]. While monometallic complexes have been popular choices for this conversion, bimetallic or multimetallic complexes developed for highly enantioselective F-C reactions remained scarce [42–44]. We have recently demonstrated that ethoxyl-pendant salan (**1**) was an excellent ligand for hetereotrimetallic (Cu_2Eu or Pd_2Sm) complexes that catalyzed highly enantioselective F-C reactions of indoles or pyrroles with nitroalkenes [35,36], in addition to bimetallic copper-catalyzed asymmetric Henry reaction [33]. To continue our exploration on the asymmetric F-C reactions catalyzed by multimetallic complexes involving salan-type ligands, we were interested to investigate the synthesis of a new hydroxymethyl-pendant salan (**3**) incorporating a chiral backbone, and its applications in catalytically asymmetric reactions. Herein, we report the results of **3**-supported Cu/Zn bimetallic complex-catalyzed enantioselective F-C alkylation of indole with nitrostyrene.

Previously, salan **1** has been found to readily react with both a transition metal (Cu or Pd) and lanthanide (Eu, Sm, etc.) to form trimetallic complexes, which exhibited excellent activity and selectivity for the F-C reactions of indoles or pyrroles with nitroalkenes. In contrast, altering

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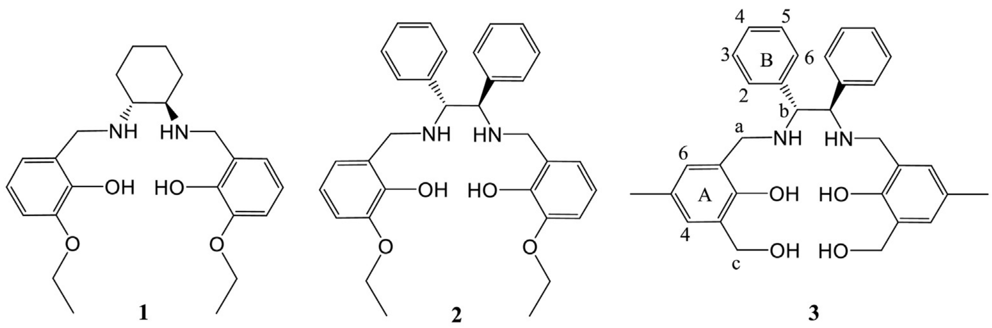
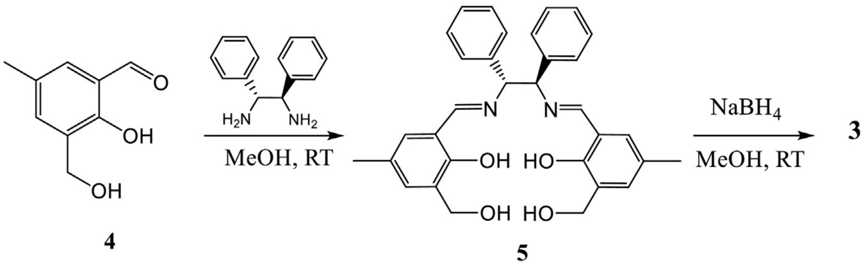


Scheme 1. The structures of known ligands **1** and **2**, and new ligand **3** studied in this work, with atom-labeling for NMR assignment.

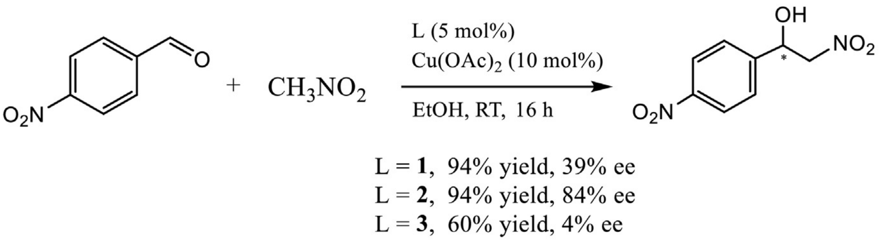


Scheme 2. The synthetic route to **3**.

the chiral backbone in **1** to give a similar salan **2** has drastic effect on the catalytic reactivity and selectivity, and in fact the combination of **2** with trimetallic Cu_2Eu system led to the F-C product in only moderate yield and no enantioselectivity [36]. However, in term of Henry reaction between benzaldehydes and nitromethane, **2** performed much better while combined with two copper(I) metal ions than **1** under the same conditions [33,34]. This indicates the chiral ligand backbone played an important role in tuning reactivity and selectivity towards various organic reactions. Now, we are curious whether changing the pendant functional groups on the salan would influence the catalytic activity of the corresponding metal complexes. Thus, the new ligand **3** containing hydroxymethyl groups on the phenoxy ring was synthesized in one-pot according to the method shown in Scheme 2.

Commercially available 2,6-*bis*(hydroxymethyl)-*p*-cresol was first selectively mono-oxidized with manganese(IV) dioxide in toluene at room temperature for 4 days, according to a literature method [45]. Pale-yellow crystalline mono-aldehyde **4** was isolated as a key precursor in 42% yield by SiO_2 column chromatography. Effective Schiff base condensation between two equiv. of **4** and the optically pure (1*S*, 2*S*)-(−)-1,2-diphenylethane-1,2-diamine in methanol at room temperature afforded an imine intermediate **5**, which was successively reduced by adding an excess amount of sodium borohydride in the same reaction solution. Accordingly, after standard workup procedure **3** was isolated by column chromatography in 87% overall yield as an off-white solid [46]. **3** was characterized by ^1H and ^{13}C NMR spectroscopy, ESI-MS and elemental analysis. ESI-MS spectrum shows the base peak envelop at m/z 513.3, assigned to $[M + H]^+$, and a peak with lower intensity at m/z 535.2 that arises from $[M + Na]^+$. The ^1H and ^{13}C NMR spectra of **3** in $CDCl_3$ were assigned by 2D techniques and were in complete agreement with the molecular structure shown in Scheme 1. The signal for proton H^{A4} and H^{A6} were assigned from NOESY cross peaks to the resonances for two different methylene (with H^a and H^c) groups, respectively, and that for $H^{B2/B6}$ from the NOESY cross peak to the signal for H^b. In addition, the diastereotopic protons H^a appear as two doublets ($J = 13.4$ Hz) at δ 4.35 and 3.12 ppm, respectively. Signal for H^{NH} is also observed at downfield region (δ 6.93 ppm) as a broad peak. Interestingly, the resonances for the methylene (with H^c) group give rise to two far separate doublet ($J = 14.7$ Hz) at δ 5.26 and 4.77 ppm, indicating that these long-distance methylene groups could sense the presence of the stereogenic centers.

With the new multidentate salan ligand in hand, we next examined its catalytic activity towards asymmetric C—C bond forming reactions upon coordinating with two metal centers, in order to compare with the results obtained from ligands **1** and **2**. Whereas **2** was found to be a good ligand compartment for two Cu^I centers in the asymmetric Henry reactions, the pendant O_4 cavity in **1** or **2** was better suited to larger metal ions (rare earth metals), as evidenced by X-ray structural analysis of isolated trimetallic complexes [35,36]. In contrast, the four hydroxyl groups of **3** generate a smaller cavity that apparently better fits with the size of a transition metal ion. Therefore, it is anticipated that the combination of two transition metals would impart higher catalytic activity and/or selectivity to relevant reactions, unlike the cases of



Scheme 3. Catalytic test for the asymmetric Henry reaction.