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Dynamic covalent binding and chirality sensing of mono secondary amines with a metal-templated assembly

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ABSTRACT

The recognition and analysis of mono-functionalized organics is an intensive area of research in organic chemistry. Toward this end, an in situ-generated metal-templated dynamic multi-component covalent assembly for the reversible binding and chirality sensing of mono secondary amines is presented. The reaction of pyridine-2-carboxyaldhyde, di(2-picolyl)amine, zinc triflate, tetrabutylammonium chloride, and a series of secondary amines, affords tripodal aminal zinc complexes. The dynamic nature of the system was demonstrated by component exchange of both amines and aldehydes. The equilibrium can be modulated by changing counteranions, concentrations, as well as structural feature of the amines. The competition between two iminium pathways resulted in a unique distribution of components. Due to the enantiotopicity of iminiums, decent diastereoselectivity was observed for chiral secondary amines. The resulting diastereomeric helical complexes were employed for the determination of enantiomeric excess with high accuracy.

1. Introduction

Asymmetric catalysis is one of the cutting edge research areas in modern organic chemistry. A variety of reactions, based on organometallic catalysts,[1] organocatalysts,[2] or a combination of both,[3] have been and are being developed for a broad range of functionalities. As a result, there is a demand for quick analysis of the optical purity of the chiral products to accelerate the overall screening and optimization process. Compared to the chromatographic techniques of GC and HPLC,[4] optical chirality sensing is fast, cost-effective, and adaptable to high-throughput screening (HTS) of enantiomeric excess (*ee*), and thereby, has generated significant interest within the supramolecular chemistry community.[5] Absorbance, fluorescence, as well as circular dichroism (CD), have all been utilized as signal outputs for optical *ee* sensing.[5a,5c,6] Moreover, both the approach of receptor-spacer-reporter and competition based indicator displacement assay were employed for signal transduction.[7]

Amines are one of the most common functional groups in chemistry, and they are widespread in nature and synthetic materials, such as amino acids, alkaloids, and many commercial pharmaceuticals. Substantial efforts are being devoted to prepare chiral amines, and many transformations have been developed, such as the Mannich reaction,[8] hydrogenation of iminiums,[9] and direct C–H amination,[10] to name a few. Due to their high nucleophilicity, a number of elegant supramolecular or dynamic covalent systems have been reported recently for the *ee* sensing of chiral primary amines, especially with circular dichroism (CD) as the signal output.[11] For example, zinc-porphyrin tweezers bearing three electron withdrawing pentafluorophenyl motifs were employed for direct binding and determination of the absolute configuration of bifunctional substrates, such as diamines[12] and amino alcohols.[6b] A biphenol with two bulky porphyrins can bind chiral mono-amines to create *P* or *M* helical complexes.[13] Simple Cu^{+}, Pd^{2+}, or Zn^{2+} complexes with either chiral or racemic ligands have been utilized for differentiation of enantiomeric amines.[11b,14] Based on dynamic imine formation, a series of stereodynamic probes with rigid scaffolds, such as 1,8-diarylnaphthalenes,[15] arylacetylenes,[16] 2,2′-

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dihydroxybenzil,[17] and 2,2′-dihydroxybenzophenone,[18] were developed for *ee* sensing of mono-amines. We developed several in situ multi-component dynamic imine assemblies for *ee* measurement with commercially available reagents.[19]

However, no general system has been reported for the chirality sensing of mono secondary amines, to the best of our knowledge. Compared to primary amines, secondary amines are more bulky and less reactive toward nucleophilic additions, and hence their molecular recognition is much more challenging. Recently, we discovered a dynamic multi-component covalent assembly of pyridine-2-carboxaldehyde (**2-PA**), di(2-picolyl)amine (**DPA**), zinc triflate, and mono-alcohols to create tripodal complexes with high efficiency.[20] The reaction is reversible and proceeds via an activated iminium intermediate. The sign and magnitude of the exciton coupled circular dichroism (ECCD) spectra of the diastereomeric complexes are alcohol dependent and was employed for the discrimination and determination of the enantiopurity of the chiral secondary alcohols.[21] In the current report, the multi-component assembly reaction was exploited for the reversible binding of mono secondary amines (Scheme 1). The equilibrium, as well as the reaction pathway, was modulated through multiple variables. The scope was then expanded by identifying the structural features of a series of secondary amines. Finally, the created metal complexes were utilized for chirality differentiation and *ee* measurement in conjunction with CD spectroscopy.

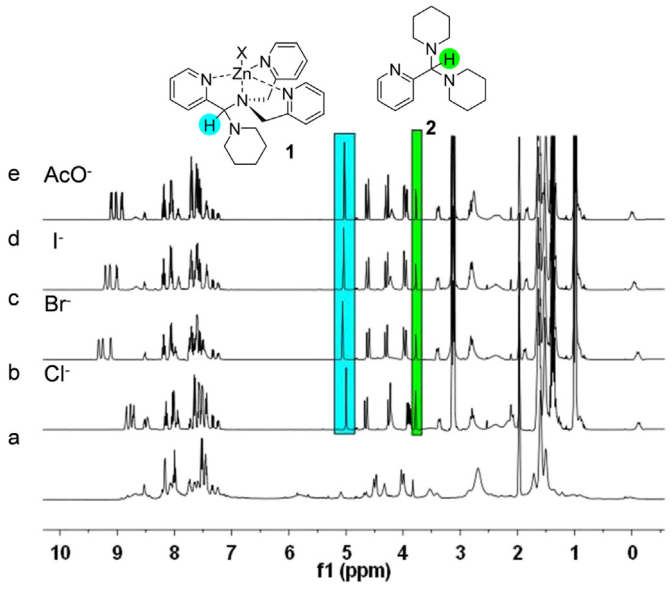
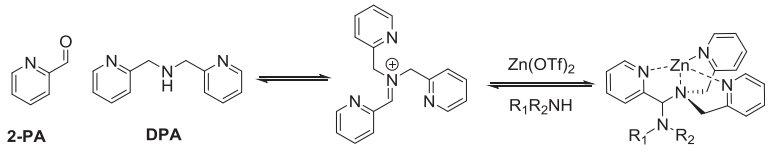


Fig. 1. ^{1}H NMR of multi-component assembly from piperidine with (b∼e) or without (a) various tetrabutylammonium salts Bu_4NX in CD_3CN (X=counteranion).



Scheme 1. Proposed dynamic covalent binding of mono secondary amines with Zn^{2+}.

2. Results and discussion

2.1. Design

We postulated that due to the high reactivity of the tris(pyridine) iminium intermediate shown in Scheme 1, the addition of secondary amines may occur. However, key differences between secondary amines and alcohols exist. First, amines are more nucleophilic than their oxygen counterpart, and hence, direct addition of amines to **2-PA** is possible, complicating the system. Second, secondary amines are also more sterically hindered. Such opposite effects of reactivity and sterics may offset each other. Third, Brønsted acid was required to catalyze the assembly reaction with secondary alcohols. In contrast, the use of acid can be a drawback because of high basicity of amines.

2.2. Screen and optimization

With the strategy in place, the multi-component assembly was conducted with piperidine as a model The reaction was performed with **2-PA** (1 equiv), **DPA** (1.2 equiv), $Zn(OTf)_2$ (1 equiv), and piperidine (2 equiv) in acetonitrile in the presence of 3 Å molecular sieves (MS). ^{1}H NMR revealed that all **2-PA** was consumed, but a complex mixture was obtained (Fig. 1a). To shift the equilibrium toward the desired complex, a series of tetrabutylammonium salts with different anions (Bu_4NX, X=Cl^-, Br^-, I^-, and OAc^-) were added to the reaction mixture to supply a good apical ligand. A singlet peak emerged at 5.03 ppm. Moreover, four doublets with geminal coupling (J=16.8 Hz) between 3.90 and 4.70 ppm were observed, indicating that all four benzylic protons are diastereotopic. These results are in agreement with the formation of the tripodal aminal complex with **DPA** (**1**), in which a new stereocenter (from the aldehyde CHO) was created. The four anions afforded varied amount of the assembly, with halogens (80%) better than acetate (70%). This counteranion effect is rationalized by the creation of more stable five coordinate zinc complex adopting a trigonal bipyramidal geometry. The anion binding was further validated by the chemical shift changes of the pyridine hydrogens. Tetrabutylammonium chloride was used in the following studies.

It is noteworthy that a resonance at 3.77 ppm was found after a detailed examination of the spectrum. This peak is from the aminal **2** due to the relatively high reactivity of piperidine. To confirm and minimize this side product, we set out to further optimize the multi-component reaction. One facile approach is to simply change the concentration of the reactants as a means of modulating the equilibrium. With 3 equiv of piperidine, the amount of the complex **1** decreased (58%), while there was an increase in the percentage of aminal **2** (42%, Table 1). When 1 equiv of piperidine was used, the desired product was afforded in 90% yield, with no detectable aminal. However, there was a residual amount of **2-PA** as well as hemiaminal complex **3** present (Scheme 2). More accurate amount of piperidine, such as 1.2 and 1.5 equiv, didn't afforded larger percentage of **1**. The formation of aminals **1** and **2** was also supported by their corresponding m/z peaks in ESI mass spectrum: 472.4 for the tripodal