Simultaneous Chirality Sensing of Multiple Amines by ^{19}F NMR

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Supporting Information Placeholder

ABSTRACT: The rapid detection and differentiation of chiral compounds is important to synthetic, medicinal, and biological chemistry. Palladium complexes with chiral pincer ligands are demonstrated to have utility in determining the chirality of various amines. The binding of enantiomeric amines induced distinct ^{19}F NMR shifts of the fluorine atoms appended on the ligand that defines a chiral environment around palladium. It is further demonstrated that this method has the ability to evaluate the enantiomeric composition and discriminate between enantiomers with chiral centers several carbons away from the binding site. The wide detection window provided by optimized chiral chemosensors allows the simultaneous identification of as many as 12 chiral amines. The extraordinary discriminating ability of this method is demonstrated by the resolution of chiral aliphatic amines that are difficult to separate using chiral chromatography.

Rapid and facile methods to detect and discriminate chiral compounds are highly desirable to accelerate advances in synthetic and biological chemistry.[1] The challenges in analysis stem from the obvious fact that enantiomeric molecules have the same physical properties. Chemosensory systems designed for chirality determination have attracted increasing attention as a result of the low cost and simplicity as alternatives to traditionally employed X-ray crystallography and chiral chromatography.[2] For instance, on the basis of an intensity change of a fluorescence or circular dichroism (CD) signal, the enantiomeric excess (ee) value of a sample can be quickly evaluated.[3] In addition to the speed of detection, other desirable attributes of a chirality sensing system include simplicity in the measurement, broad substrate applicability, and the ability to analyze complex mixtures. A limitation of optical methods for routine applications is that they usually require pure sample with known enantiomeric excess to construct a calibration curve.[3] Herein, we introduce a ^{19}F NMR chemosensing system that doesn't suffer from these limitations in the differentiation of enantiomers. Specifically this method does not require enantiopure samples to determine the ee and is capable of predicting the absolute configuration. We also demonstrate for the first time that multiple chiral amines can be simultaneously identified in a single NMR experiment.

NMR is a useful tool to access chiral information by using chiral derivatizing or solvating agents to produce diastereomeric complexes that can be used to discriminate between enantiomers.[4,5] As these methods typically rely on the NMR signals of the substrate, the analysis often requires pure samples and is complicated if the

NMR signals overlap. One approach to address these limitations in NMR methods is to use a ^{19}F chiral derivatizing agent as a probe to simplify the NMR signal.[6] However, the discriminating ability of this approach is limited for aliphatic compounds. This is because aromatic rings are required to induce a pronounced shielding effect that facilitates the NMR signal splitting in a chiral environment (Scheme 1a). Furthermore, analytes with chirality centers remote to the derivatizing site are difficult to resolve through this approach. To achieve a chirality sensing method that addresses these limitations and eliminates the use of covalent derivatization, we targeted a ^{19}F NMR chemosensory system that utilizes a chiral ligand-metal complex that reversibly binds to the analytes (Scheme 1b).[7] The key elements that have led to the success of this chirality chemosensing platform are: (1) The dissociation of the chiral analyte and the metal is slow on the NMR time frame to generate "static complexes" with precise and characteristic ^{19}F NMR shifts. (2) The ligand is capable of creating a chiral environment to host the analyte wherein the subtle interactions between the ligand and the chiral analyte are transduced by the nearby appended ^{19}F probes (Scheme 1b).

**Scheme 1.** Comparison of Mosher Amide Based Approach and our Sensing Scheme for the Discrimination of Chiral Amines.
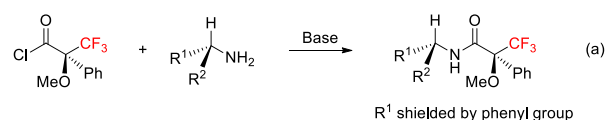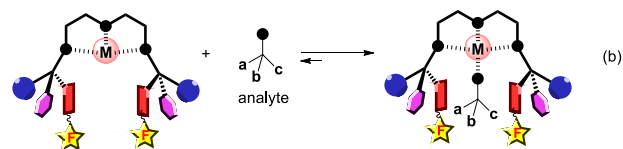
To examine the feasibility of our chemosensing scheme, we selected the amide-based palladium pincer complex **2** (Scheme 2) as a scaffold as a result of its easy preparation and well known coordination chemistry.[8] The coordination site that undergoes facile ligand exchange is flanked by pendant groups that are sensitive to through-bond and through-space interactions with analyte enantiomers. The chiral ligands were constructed by reacting 2,6-pyridinedicarbonyl dichloride (**1**) with various chiral amines. The

corresponding palladium complexes **2** were prepared with a weakly bound acetonitrile that is rapidly replaced by Lewis basic analytes. In addition to the C2-symmetric complex (**2a**), we also prepared a nonsymmetric complex (**2b**) that is derived from (S)-α-methylbenzylamine and 3,5-bis(trifluoromethyl)aniline with the aim to evaluate the influence of a remote chirality on the ^{19}F NMR shifts in our sensing system. The nonsymmetric ligand of **2b** was readily prepared by a sequential addition of the corresponding aniline and amine to a solution of **1** in toluene.

Scheme 2. The Preparation and Structures of Palladium Complexes with Chiral Pincer Ligands.
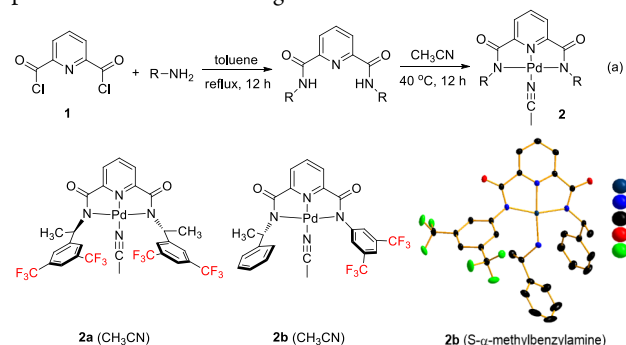
We began by exploring the ^{19}F NMR chirality sensing potential of complex **2a**. Initial studies revealed that the Lewis basic oxygens of amide groups act as ligands to produce insoluble oligomeric species.[9] This oligomerization is prevented by the addition of 15 equivalent of CH3CN to produce clear stable monomeric solutions of **2a**. We then selected a series of readily available chiral amines and amino alcohols as the analytes to test the differentiation of enantiomers. The observation of discrete signals at precise chemical shifts that are not concentration dependent indicated the formation of "static" complexes on the NMR time scale (Figure S1 in SI). As a result, for a given solvent, each enantiomer can be correlated to a NMR signal with precise chemical shift. With amine binding, a new high field signal was observed that is indicative of an increased shielding effect caused by the analyte relative to the displaced acetonitrile ligand (Figure 1a). The shielding effect imposed by a pair of enantiomers to the chiral ligand is different and generates discrete NMR signals for identification. It is noteworthy that the association of **2a** and amines is fast and the equilibrium is reached before the NMR analysis. Figure 1A illustrates the ability of **2a** to resolve most of the enantiomers. One noteworthy feature of sensor **2a** is the high sensitivity provided by 12 equivalent fluorine atoms, which allowed analysis to be performed at low concentrations (50 μg of analyte was adequate for the experiments in Figure 1 using a 400 MHz NMR spectrometer).

We next turned our attention to the nonsymmetric complex **2b**, which positions the ^{19}F probes closer to the analyte to create more pronounced changes in chemical shifts. The topology of **2b** is interesting because the chiral moiety effecting the chirality discrimination is separated from the ^{19}F probe by the analyte. We envisioned that this transduction mechanism could provide an orthogonal discriminatory ability relative to that of **2a**. The data in Figure 1B confirms our designs and the chemical shift range induced by the bound analyte is larger for **2b** in comparison to **2a**. Specifically, in the case of (R)-α-methylbenzylamine, we observed NMR shifts of 0.39 and 0.15
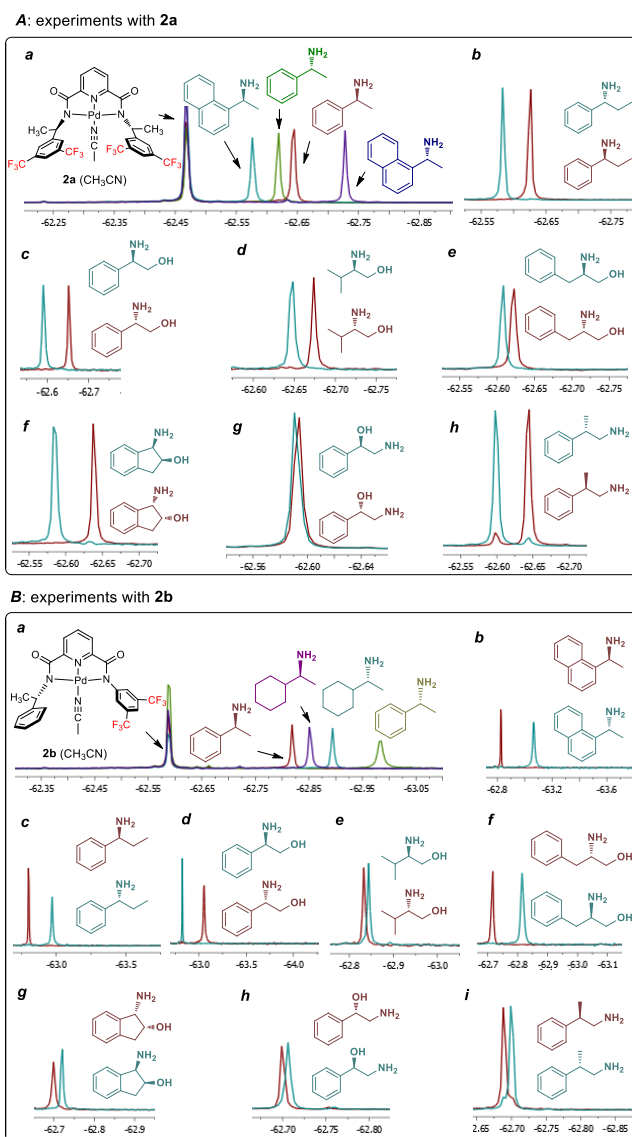
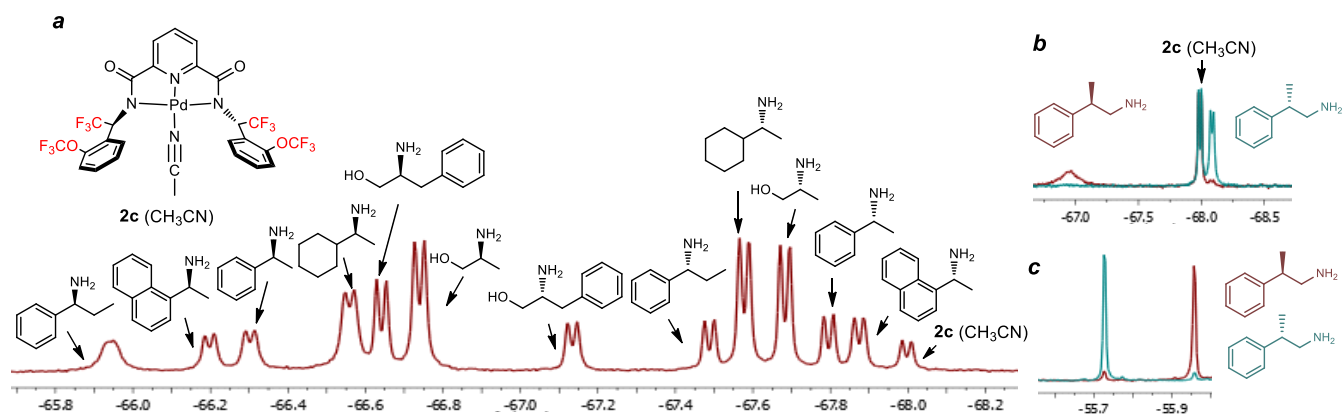**Figure 1.** ^{19}F NMR spectrum (64 scans each) of a mixture of complex **2a** or **2b** (1 mM in CDCl3), CH3CN (15 mM) and different chiral amines (1.0–2.0 mM). (a-i) superimposition of the spectra of complex **2a** or **2b** with each of the analyte collected independently.

Table 1. Quantitative Sensing Results[a]

(S)-α-methylbenzylamine			(R)-2-phenylglycinol		
actual ee (%)	calculated ee (%)	absolute error (%)	actual ee (%)	calculated ee (%)	absolute error (%)
85.0	84.7	0.3	73.3	74.5	1.2
54.7	55.7	1.0	38.7	39.3	0.6
0	0.1	0	0	−0.8	0.8
−41.4	−42.2	0.8	−46.8	−45.7	1.1
−84.2	−84.2	0	−89.8	−88.0	1.8

[a]NMR measurements were performed in CDCl3/pentane (2:3) using **2b** (5 mM) and analyte (ca. 2 mM)

Figure 2. (a) ^{19}F NMR spectrum of the benzylic CF_3 region (128 scans) of a mixture of complex **2c** (5 mM in $CDCl_3$), and 12 different chiral amines (each 0.7–1.2 mM). (b,c) The superimposition of the spectra showing the benzylic CF_3 (b) and OCF_3 (c) regions of complex **2c** (1.0 mM) with each of the analyte (0.7 mM) collected independently.

**Scheme 3.** Structural Optimization for Enhanced Chirality Sensing.
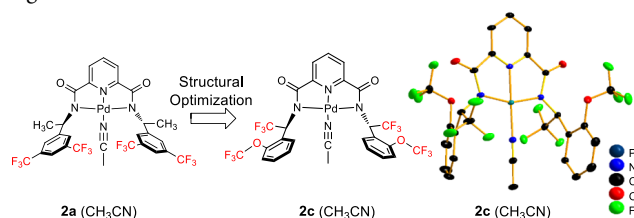
ppm relative to the signals of **2b** (CH_3CN) and **2a** (CH_3CN), respectively. Furthermore, **2b** produced a satisfactory resolution of (R)- and (S)-2-amino-3-phenyl-1-propanol in contrast to the overlapped signals observed in the experiment with **2a** (Figure 1e and Figure 2f). Despite of the larger chemical shift range, the resolution of certain enantiomers is still not satisfactory (Figure 1B, e, and g-i). This observation revealed that in addition to the spatial proximity of the fluorine probe to the analyte, the chiral environment has a crucial role in our chirality chemosensing. This is illustrated by the crystal structure of **2b** bound to (S)-α-methylbenzylamine, wherein both of the methyl and phenyl group on pincer ligand point toward the bound analyte to define a chiral cavity with the planar CF_3-substituted phenyl group on the other side (Scheme 2). The methyl and phenyl groups are relatively small, and as a result, the conformational changes of **2b** induced by certain analytes are not sufficient to provide a desired resolution (Figure 1B, h and i).[10]

We have evaluated the potential of **2b** to determine the enantiomeric excess values. Initial experiments showed that complexing **2b** with racemic α-methylbenzylamines produced two new diasteriomeric palladium species with the same ^{19}F NMR resonance intensity. Therefore, we can determine the enantiomeric excess from ^{19}F NMR integration under our experimental conditions. We have applied this method for the analysis of a series of nonracemic samples and Table 1 shows the calculated values are in excellent agreement with the actual enantiopurity (Table 1, left). In a similar way, the ee of nonracemic 2-phenylglycinol can be also accurately determined (Table 1, right). No calibration curve or derivatization is required, and this method has the potential to be adapted in routine asymmetric synthesis. Notably, nitriles and N-heterocycles are also potential analytes for this method (Figure S8 in SI), while sec-

ondary and tertiary amines generally do not coordinate to the palladium as a result of their steric hindrance.
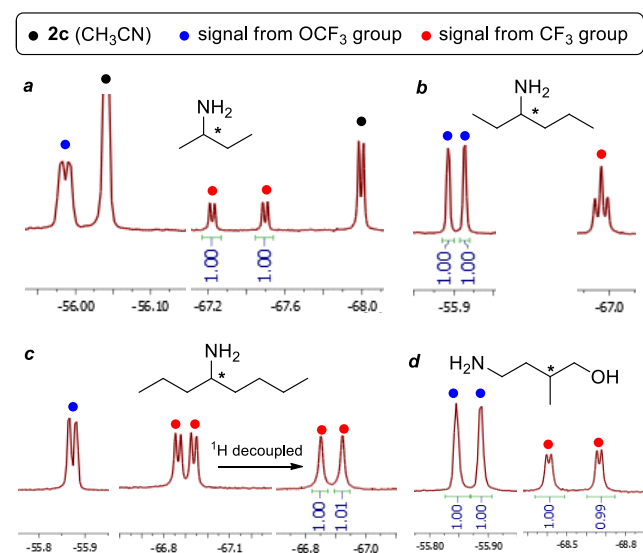
Figure 3. ^{19}F NMR spectrum (64 scans each) of a mixture of complex **2c** (1 mM in $CDCl_3$) and different chiral amines.

To achieve a simultaneous resolution of multiple chiral analytes, we prepared complex **2c** (Scheme 3). The replacement of the methyl group of **2a** by a trifluoromethyl (CF_3) group brings the fluorine probe closer to the analyte and extends the ^{19}F NMR detection window.[11] As a CF_3 group is significantly bigger than a methyl group, the internal cleft flanked by this ligand becomes more confined than that of **2a** and **2b**, to promote intimate interactions between the ligand and analytes.[12] A trifluoromethoxyl (OCF_3) group was further introduced to increase the bulkiness of the phenyl group and to add an additional fluorine probe to **2c**. Another benefit of this design is the self-aggregation that was observed previously is inhibited by **2c**'s bulky ligand. Figure 2a illustrates that the wide detection window of **2c** allows the simultaneous identification of as many as 12 chiral analytes (for the performance of a structurally similar sensor without OCF_3 group, see Figure S7 in SI). Interestingly, a broader peak was observed in the experiment

of the β-methylphenethylamine using the CF_3 probe, while the OCF_3 probe produced sharp signals and a good resolution (Figure 2b,c). Similar to the chirality sensing methods based on circular dichroism, empirical predictions of the absolute configuration can be made. For instance, we find that α-chiral amines of S configuration always appear at a lower field as compared to those of R configuration (Figure 2a). The extraordinary discriminating ability provided by **2c** is further demonstrated by the resolution of aliphatic amines. Racemic samples were mixed with the chloroform solution of **2c** and the ^{19}F NMR spectrum was recorded. The discrimination of these amines is difficult because the alkyl groups connected to the chiral center differ solely in a single methylene unit (Figure 3a-c). One appealing feature of **2c** is its orthogonal resolving ability provided by the CF_3 and OCF_3 probes which increases its success in resolving challenging analytes. This is revealed by inspection of the results illustrated in Figure 3, where one fluorine probe produced a better resolution than the other. In this way, all the aliphatic amines in Figure 3 can be differentiated. Proton-decoupled NMR experiments collapsed the doublet signal of the CF_3 group to a singlet, for further improved resolution (Figure 3c).[13] In contrast to conventional chiral derivatizing methods, the current method is also capable of resolving the amines with chiral center several carbons away from the amino group (Figure 3d).

In summary, we have developed a new chirality chemosensory platform based on ^{19}F NMR and chiral palladium pincer complexes. The bonding of enantiomers produced diastereomeric complexes with distinct and precise ^{19}F NMR shifts. This approach provided a simple and robust differentiation of chiral amines that are not easily resolved with chiral HPLC. The key to the success of this approach is to bind enantiomers with an environment that is flanked by chiral ligands with fluorine probes optimally positioned. We expect the combination of the current strategy and diversified supramolecular scaffolds will produce a powerful sensing platform that addresses chirality differentiations relevant to chiral synthesis and biological chemistry.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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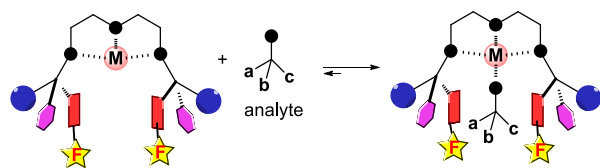
No derivatization
Detection and identification
Enantiomeric excess determination