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

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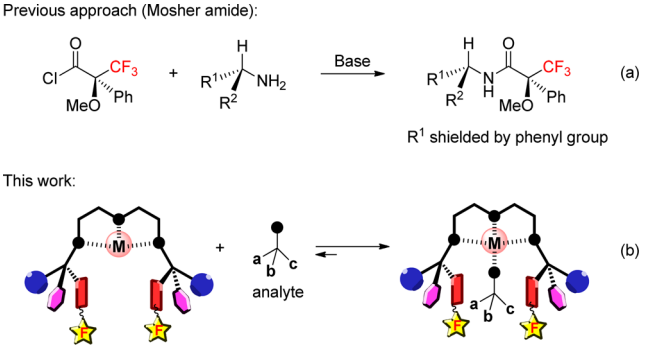
Supporting Information

**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 induces 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 their 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 samples with known enantiomeric excess values to construct a calibration curve.[3] Herein we introduce an $^{19}$F NMR chemosensing system that does not 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 spectroscopy is a useful tool to access chiral information by the use of 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 an $^{19}$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 because aromatic rings are needed to induce a pronounced shielding effect that facilitates the NMR signal splitting in a chiral environment (Scheme 1a).

**Scheme 1. Comparison of the Mosher Amide-Based Approach and Our Sensing Scheme for the Discrimination of Chiral Amines**




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 an $^{19}$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 the following: (1) The dissociation of the chiral analyte and the metal is slow on the NMR time scale, generating "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 subtle interactions between the ligand and the chiral analyte are transduced by the nearby appended $^{19}$F probes (Scheme 1b).

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

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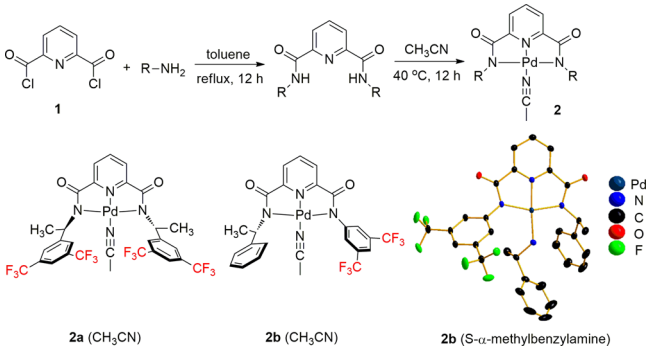
**Scheme 2. Preparation and Structures of Palladium Complexes with Chiral Pincer Ligands**




prepared with a weakly bound acetonitrile that is rapidly replaced by Lewis basic analytes. In addition to the $C_2$-symmetric complex **2a**, we also prepared the nonsymmetric complex **2b** derived from (*S*)-α-methylbenzylamine and 3,5-bis(trifluoromethyl)aniline with the aim to evaluate the influence of remote chirality on the $^{19}$F NMR shifts in our sensing system. The nonsymmetric ligand of **2b** was readily prepared by sequential addition of the corresponding aniline and amine to a solution of **1** in toluene.

We began by exploring the $^{19}$F NMR chirality sensing potential of complex **2a**. Initial studies revealed that the Lewis basic oxygens of the amide groups act as ligands to produce insoluble oligomeric species.[9] This oligomerization was prevented by the addition of 15 equiv of $CH_3CN$ 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 the Supporting Information). As a result, for a given solvent, each enantiomer can be correlated to an NMR signal with a 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 effects on the chiral ligand imposed by a pair of enantiomers are different and generate discrete NMR signals for identification. It is noteworthy that the association of **2a** and amines is fast, reaching equilibrium 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 chemically equivalent fluorine atoms, which allowed analyses 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 confirm our designs, and the chemical shift range induced by the bound analyte is larger for **2b** than for **2a.** Specifically, in the case of (*R*)-α-methylbenzylamine, we observed NMR shifts of 0.39 and 0.15 ppm relative to the signals of **2b** ($CH_3CN$) and **2a** ($CH_3CN$), respectively. Furthermore, **2b** produced a satisfactory resolution of (*R*)- and

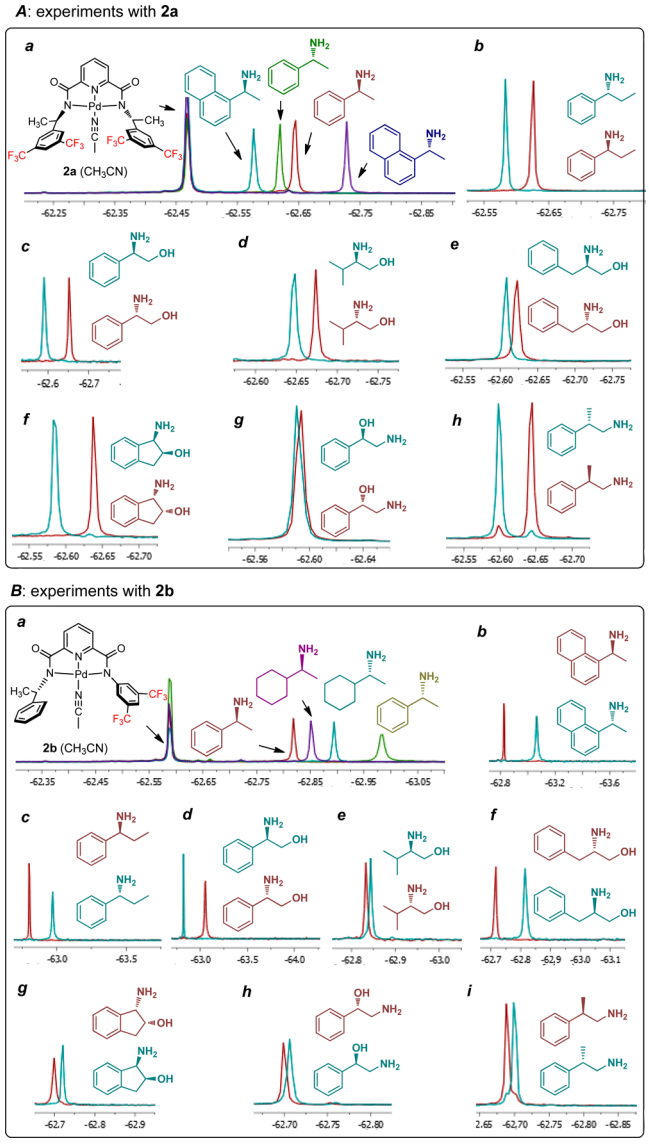



**Figure 1.** $^{19}$F NMR spectra (64 scans each) of mixtures of (A) **2a** or (B) **2b** (1 mM in $CDCl_3$), $CH_3CN$ (15 mM), and different chiral amines (1.0−2.0 mM). Panels (a−i) show superimpositions of the spectra of **2a** or **2b** with each analyte collected independently.

(*S*)-2-amino-3-phenyl-1-propanol, in contrast to the overlapped signals observed in the experiment with **2a** (Figure 1B(f) vs Figure 1A(e), respectively). Despite the larger chemical shift range, the resolution of certain enantiomers is still not satisfactory (Figure 1B(e,g−i)). This observation revealed that in addition to the spatial proximity of the fluorine probe to the analyte, the chiral environment plays a crucial role in our chirality chemosensing. This is illustrated by the crystal structure of **2b** bound to (*S*)-α-methylbenzylamine, wherein both the methyl group and the phenyl group on the 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 the desired resolution (Figure 1B(h,i)).[10]

We evaluated the potential of **2b** to determine ee values. Initial experiments showed that complexing **2b** with racemic α-methylbenzylamines produced two new diastereomeric palladium species with the same $^{19}$F NMR resonance intensity.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Therefore, we can determine the enantiomeric excess from $^{19}F$ NMR integration under our experimental conditions. We applied this method for the analysis of a series of nonracemic samples, and the calculated values are in excellent agreement with the actual enantiopurities (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), while secondary and tertiary amines generally do not coordinate to the palladium as a result of their steric hindrance.

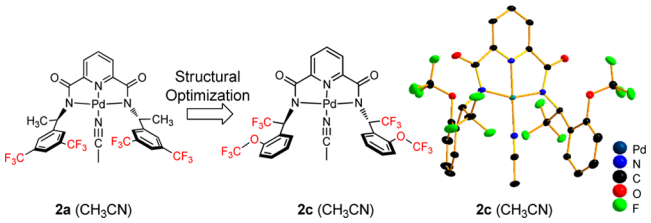
**Table 1. Quantitative Sensing Results**[a]

| (S)-α-methylbenzylamine | | | (R)-2-phenylglycinol | | |
|---|---|---|---|---|---|
| actual ee (%) | calcd ee (%) | absolute error (%) | actual ee (%) | calcd 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 | 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 $CDCl_3$/pentane (2:3) using **2b** (5 mM) and analyte (ca. 2 mM)

To achieve 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 those of **2a** and **2b**, promoting intimate interactions between the ligand and the analyte.[12] A trifluoromethoxy ($OCF_3$) 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 that the bulky ligand in **2c** inhibits the self-aggregation observed previously. Figure 2a illustrates that the wide detection window of **2c** allows the simultaneous identification of as many as 12 chiral analytes (the performance of a structurally similar sensor without the $OCF_3$ group is shown in Figure S7). Interestingly, a broader peak was observed in the experiment with β-methylphenethylamine using the $CF_3$ probe, while the $OCF_3$ probe produced sharp signals and good resolution (Figure 2b,c). Similar to the chirality sensing methods based on CD, empirical predictions of the absolute configuration can be made. For instance, we found that α-chiral amines with the *S* configuration always appear at a lower field compared with those having the *R* configuration (Figure 2a).

**Scheme 3. Structural Optimization for Enhanced Chirality Sensing**




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 shown in Figure 3, where one fluorine probe produced a better resolution than the other. In this way, all of 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, further improving the resolution (Figure 3c).[13] In contrast to conventional chiral derivatization methods, the current method is also capable of resolving the amines with chiral centers several carbons away from the amino group (Figure 3d).

In summary, we have developed a new chirality chemosensory platform based on $^{19}F$ NMR spectroscopy and chiral palladium pincer complexes. The bonding of enantiomers produces diastereomeric complexes with distinct and precise $^{19}F$ NMR shifts. This approach provides 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 optimally positioned fluorine probes. We expect the combination

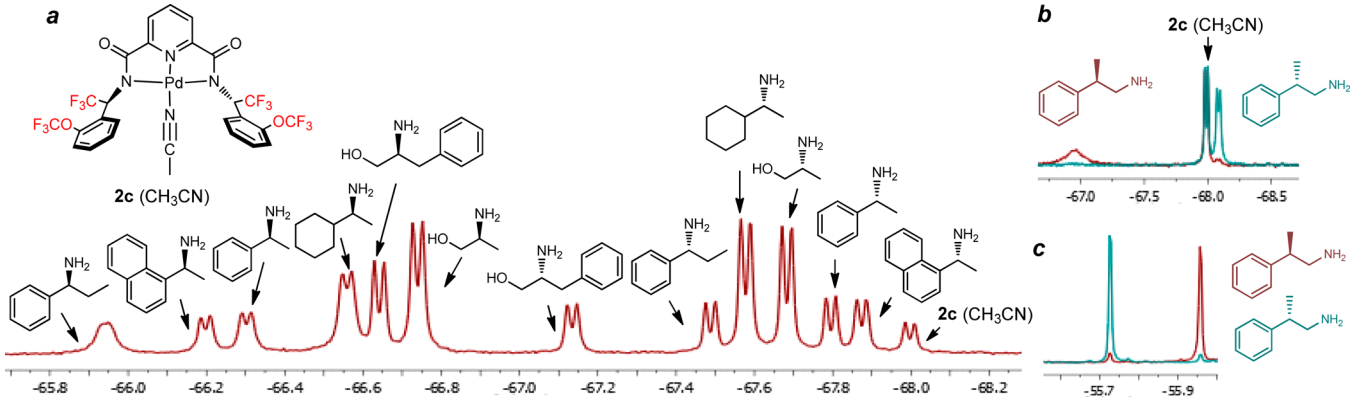



**Figure 2.** (a) $^{19}F$ NMR spectrum of the benzylic $CF_3$ region (128 scans) of a mixture of complex **2c** (5 mM in $CDCl_3$) and 12 different chiral amines (each 0.7–1.2 mM). (b, c) Superimpositions of the spectra showing the benzylic $CF_3$ (b) and $OCF_3$ (c) regions of complex **2c** (1.0 mM)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



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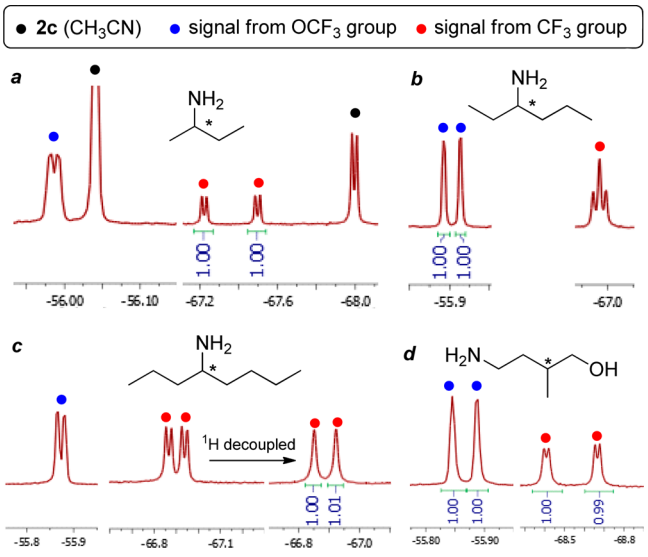


**Figure 3.** $^{19}$F NMR spectra (64 scans each) of mixtures of complex **2c** (1 mM in $CDCl_3$) and different chiral amines.

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.

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### Notes

The authors declare the following competing financial interest(s): The authors have filed a patent on this technology.

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