Combinatorial Approach to Enantiomeric Discrimination: Synthesis and ^{19}F NMR Screening of a Chiral Ionic Liquid-Modified Silane Library

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A parallel library of chiral ionic liquid (CIL)-modified silanes as potential chiral selectors was synthesized, and their enantiomeric discrimination abilities were screened by use of ^{19}F NMR spectroscopy. The screening method allows for rapid identification of the most enantioselective members of the library and simultaneous investigation of their chiral recognition mechanisms. The library compounds were synthesized using quaternization and anion-exchange reactions. Three major parameters (type of chiral cations, anions, and linker chain lengths) were included and investigated during the synthesis and screening. As expected, the structure of the chiral cation was found to play an important role in determining chiral recognition abilities. In addition, several types of intermolecular interactions including ion-pair, hydrogen bonding, $\pi-\pi$ stacking, dipole stacking, and steric interactions were found to impact chiral discrimination.

Introduction

Ionic liquids (ILs) are low melting organic salts composed solely of cations and anions, which makes them highly tunable for specific applications.[1] ILs are noted to have a number of unique properties, including negligible vapor pressures, good thermal stabilities, wide liquid temperature ranges, considerable ionic conductivities, wide electrochemical windows, and enhanced solvation interactions with both polar and nonpolar compounds.[2] These properties have been shown to be useful for a large number of applications. For example, ILs have been immobilized onto silica and used as HPLC stationary phases.[3]

Chiral ionic liquids (CILs) can be referred to as a subclass of ILs which are chiral. On the basis of the definition of CILs, either the cation or the anion, or both can be chiral and the chirality may be either central, axial, or planar. Recently, the synthesis of a variety of CILs and their applications have been reported.[4−10] CILs have been used in asymmetric catalysis and synthesis,[7,9] chiral recognition and discrimination,[11] determination of enantiomeric composition of pharmaceuticals,[12] as stationary phases in gas chromatography,[13] mobile phase additives in capillary electrophoresis (CE),[14] and pseudostationary phases in micellar electrokinetic chromatography (MEKC).[15]

As a category of functionalized or task-specific ILs (TSILs),[16] CILs possess a number of unique and advantageous properties. These properties include tunability of their structures and/or functionalities through judicious selection of their component ions. Indeed, these materials can be regarded as "tailor-made" or "designer"[17] chiral solvents. Thus, this approach affords novel molecular structures and materials, as well as new insights into chiral recognition and chiral induction. In this regard, hyphenation between combinatorial and high-throughput screening chemistry and the synthesis and screening of CILs for specific application would be a very desirable approach toward studying such interactions.

Combinatorial chemistry generally refers to methods for creating a collection of diverse compounds or materials using a relatively small set of precursors and/or methods. As currently practiced, combinatorial chemistry permits systematic exploration of the influence of structural variations in candidates by dramatically accelerating the rates at which they are created and evaluated.[18] Combinatorial chemistry has been effectively used in chiral technology to discover new asymmetric catalysts[19] and novel chiral stationary phases.[20] A large number of possible variations of molecular structures for CILs could be designed and prepared using a combinatorial approach by simply changing the structures of either the cation, anion, or both. These changes in molecular structures of CILs would significantly influence their chiral discrimination abilities. In addition, such structural changes may yield useful information regarding chiral interaction mechanisms through studies of structure–property relationships. However, surprisingly few examples can be cited where a combinatorial approach has been used in the design and synthesis of ILs or CILs.[21]

The large number of diverse compounds afforded by a combinatorial approach requires the use of simple and rapid methods to screen the compounds for desirable properties.

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Scheme 1. Combinatorial Approach for the Synthesis and Screening of CIL-Modified Silanes
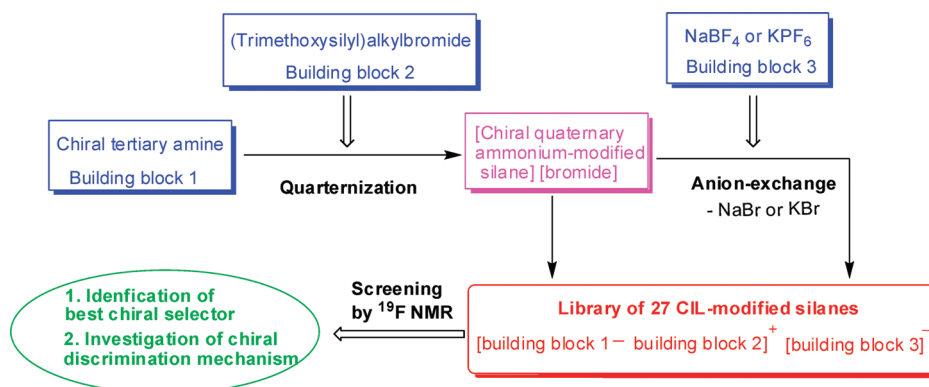
Recently, Wasserscheid et al. have described a method based on ^{19}F NMR spectroscopy to investigate the enantiomeric discrimination abilities of CILs.[22] In that study, the interactions between CILs and racemic Mosher's salt in deuterated solvent were determined using ^{19}F NMR. These interactions were quantified using the chemical shift difference or peak splitting of the two diastereomeric associates. The extent of peak splitting was assigned to the strength of the diastereomeric interactions. Therefore, under identical conditions, a larger splitting of the CF_3 chemical shift would suggest higher chiral discrimination of the CIL. It is also noteworthy that the chemical shift difference between the two diastereomeric CF_3 groups largely depends on the concentration of the CILs in the deuterated solvent.[22] This ^{19}F NMR method has been widely used to study chiral recognition abilities of various CILs.[23−27] In the study reported herein, ^{19}F NMR is used as a high-throughput screening tool to quickly and conveniently identify the best chiral selectors from a group of CIL-modified silanes which are synthesized using a combinatorial approach. This approach also provides a convenient means for investigating the mechanism of chiral recognition.

Results and Discussion

Synthesis of a Library of 27 CIL-Modified Silanes. An important and favorable property of CILs is high tunability, which suggests that these molecules may be tailored for specific applications such as chiral discrimination, simply through a judicious choice of the cation and anion and/or combination of cation and anion. This property is especially advantageous for preparation and identification of optimum chiral selectors through combinatorial synthesis and screening.

Using a combinatorial approach (Scheme 1), a library of 27 ($C_3^1 \cdot C_3^1 \cdot C_3^1 = 3 \times 3 \times 3$) novel CIL-modified silanes was synthesized. Three chiral tertiary amines, Pro, Eph, and Peu (Figure 1) were used as building blocks to synthesize chiral cations by use of quaternization reactions (Table 1 and Scheme S2 in the Supporting Information). These three chiral tertiary amines consist of different functional groups including hydroxyl, phenyl, pyridyl, urea, and ester groups. These functional groups are conducive to multiple-site interactions with analytes, which are essential for chiral recognition.[28] Among these functional groups, the urea group with an amide bond is particularly beneficial to chiral recognition through hydrogen bonding.[29] Since these CIL-modified silanes are composed of both cations and anions, the anions may influence the chiral recognition abilities of the cations'. Moreover, different anions may lead to different hydrophobicities of the CILs. It has been established that the hydrophobicity of anions increases in the sequence of Br^- < BF_4^- < PF_6^-.[30] Therefore, in order to investigate the influence of various anions on chiral discrimination, three different anions, namely, Br^-, BF_4^-, and PF_6^-, were included in the combinatorial synthesis using anion exchange reactions (Table 2 and Scheme S3 in the Supporting Information). It is also known that the alkyl chain length of the linker may play an important role in chiral recognition.[31] For example, a longer linker may generate a hydrophobic region for interaction with the analyte. This property could be beneficial for chiral separation and enantiomeric recognition. For this reason, three linkers with alkyl chain lengths of 3, 7, and 11, respectively, were included in this study.

The three parameters investigated in this study were the type of cation, the type of anion, and the alkyl linker chain
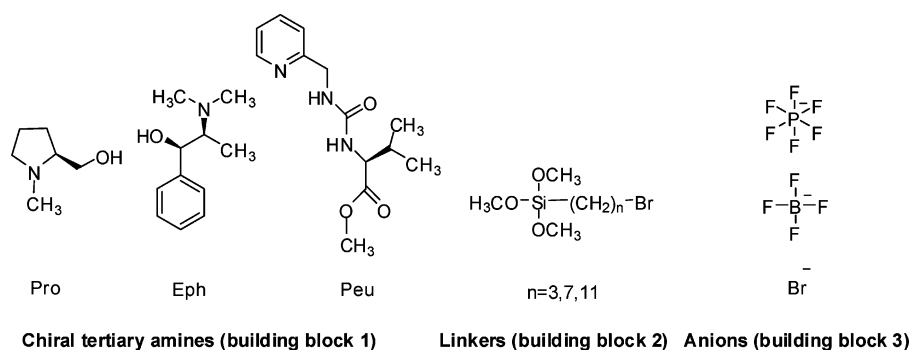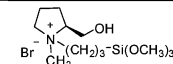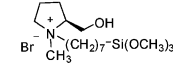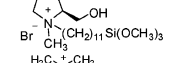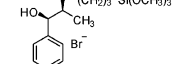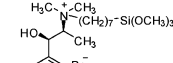

Figure 1. Building blocks used for the synthesis of CIL-modified silanes.

Table 1. Synthesis of Nine CIL-Modified Silanes with Br⁻ as Anions by Quaternization Reactions

Chiral tertiary amines + Bromoalkyltrimethoxysilanes → (Quaternization, EtOH, 80 °C, 48h, Ar) → CIL-modified silanes with Br⁻ as anions

Building block 1   Building block 2

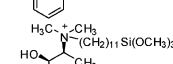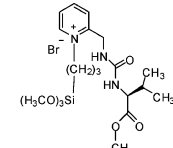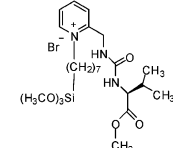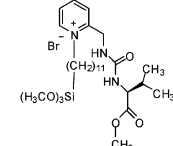| CIL-modified silanes	Chiral tertiary amines	Linker chain lengths	Anions	Structures	Yields (%)
1	Pro	3	Br⁻		87
2	Pro	7	Br⁻		92
3	Pro	11	Br⁻		84
4	Eph	3	Br⁻		84
5	Eph	7	Br⁻		81
6	Eph	11	Br⁻		85
7	Peu	3	Br⁻		92
8	Peu	7	Br⁻		90
9	Peu	11	Br⁻		95

length. Each parameter has three variations. In this work, a shorthand designation of A−B−C for the 27 CIL-modified silanes was used, where A represents the chiral cation (building block 1), B represents the linker length (building block 2), and C represents the anion (building block 3). The sequential numbering, molecular structures, and reaction yields of the 27 library compounds are shown in Tables 1 and 2.

It is worth noting that the nitrogen of Pro-containing CIL-modified silanes has four different alkyl groups after quaternization. Therefore, an additional nitrogen stereogenic center and epimeric compounds may form.[32,33] This phenomenon was not discussed in a previous study[15] which used the same (S)-(−)-1-methyl-2-pyrrolidinemethanol (Pro) as a chiral selector used in this work. However, it is apparent from the data presented in this study,[15] that this extra stereogenic center did not negatively impact the chiral separation ability of the CILs. Two acidic analytes were successfully separated using the CIL-modified surfactant polymer as a pseudostationary phase in MEKC separation. In another study, Kodama and co-workers used cationic chiral surfactants for the cathodic reduction of acetophenone
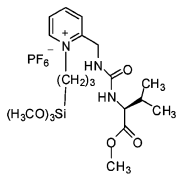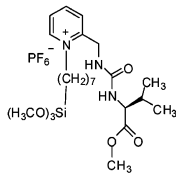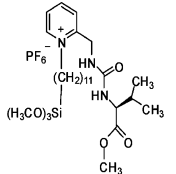
without separating the two epimeric surfactants.[34] An appreciable chiral induction was obtained using the chiral surfactants which were also synthesized from N-methylprolinol (Pro) by use of a quaternization reaction.[34] In our current study, the Pro-containing CIL-modified silanes were directly tested for chiral recognition abilities without separation of the two epimers. They exhibited moderate chiral recognition abilities toward racemic potassium Mosher's salt.

Chiral Discrimination Tests of Chiral Tertiary Amines (Building Block 1 Compounds). To evaluate the influence of a positive charge on chiral discrimination, the three chiral tertiary amines (building block 1, noncharged and without linker) were investigated as controls. Pro and Eph showed no chiral discrimination toward Mosher's salt since only a singlet peak was observed in the ¹⁹F NMR spectra. However, Peu exhibited good chiral recognition with a chemical shift difference of 8.32 Hz, suggesting that Peu is a good chiral selector even without a positive charge. This behavior was probably due to the multiple functional groups of Peu such as pyridyl, urea, and an ester. After introduction of a positive charge through the quaternization reaction, the chiral Peu-modified silanes showed significantly enhanced chiral dis-

Table 2. Synthesis of 18 CIL-Modified Silanes with BF_4^- or PF_6^- as Anions by Anion-Exchange Reactions

CIL-modified silanes with Br⁻ as anions + KPF₆ or NaBF₄ →[Anion-exchange / Acetonitrile, r.t.] CIL-modified silanes with BF_4^- or PF_6^- as anions

CIL-modified silanes	Chiral tertiary amines	Linker chain lengths	Anions	Structures	Yields (%)
10	Pro	3	BF_4^-		73
11	Pro	7	BF_4^-		64
12	Pro	11	BF_4^-		67
13	Pro	3	PF_6^-		56
14	Pro	7	PF_6^-		59
15	Pro	11	PF_6^-		63
16	Eph	3	BF_4^-		70
17	Eph	7	BF_4^-		71
18	Eph	11	BF_4^-		75
19	Eph	3	PF_6^-		65
20	Eph	7	PF_6^-		68
21	Eph	11	PF_6^-		71
22	Peu	3	BF_4^-		75
23	Peu	7	BF_4^-		78
24	Peu	11	BF_4^-		69

Table 2 Continued

CIL-modified silanes	Chiral tertiary amines	Linker chain lengths	Anions	Structures	Yields (%)
25	Peu	3	PF_6^-		64
26	Peu	7	PF_6^-		68
27	Peu	11	PF_6^-		59

crimination abilities. For example, the respective splittings were 13.47, 11.23, and 10.95 Hz using Peu-3-PF_6 (compound **25**), Peu-7-PF_6 (compound **26**), and Peu-11-PF_6 (compound **27**). After introduction of a positive charge, the Pro and Eph compounds also displayed significant chiral discrimination abilities. For example, the Pro-11-BF_4 (compound **12**) and Eph-11-BF_4 (compound **18**) showed respective splittings of 3.53 and 10.76 Hz (Figure 2). This confirms that the presence of a positive charge is an important factor for chiral discrimination of anionic Mosher's salt involving an ion-pair interaction. This is consistent with the observation of Shamsi and co-workers that electrostatic interactions between the acidic analytes (($\pm$)-α-bromophenylacetic acid and ($\pm$)-2-(2-chlorophenoxy)propanoic acid) and cationic ionic liquid micelle played a profound role in enantioseparation.[15] In another study, Wasserscheid et al. reported an asymmetric synthesis that solely used the strength of ion pairing in a CIL to induce high enantioselectivity in asymmetric hydrogenation reaction.[35] This work is an elegant example of the importance of the ion-pair interaction in chiral induction or chirality transfer.

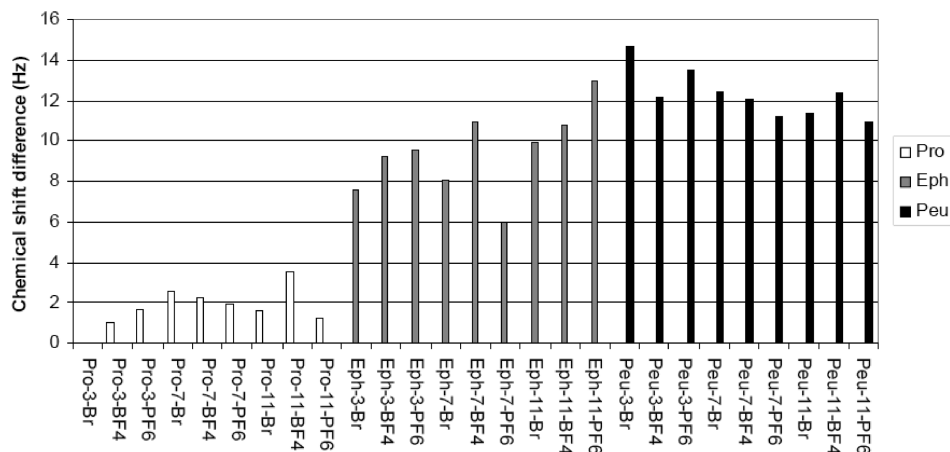**Screening Chiral Discrimination Abilities of the 27**

CIL-Modified Silanes by Use of ¹⁹F NMR. In examining the influence of the cations' structures on chiral recognition for a given alkyl linker chain length and anion combinations, we found that most of the CIL-modified silanes exhibited a trend of Peu > Eph > Pro (Figure 2). For example, the chemical shift difference was 2.21 Hz when Pro-7-BF_4 (compound **11**) was used as the chiral selector (Figure 2). The splitting increased to 10.90 Hz with Eph-7-BF_4 (compound **17**) as the chiral selector, while it further increased to 12.01 Hz using Peu-7-BF_4 (compound **23**) as the chiral selector. The ¹⁹F NMR spectra of these representative tests are shown in Figure 3. It is worth noting that the chemical shifts in the four cases were not identical. Therefore, they were normalized to provide easier comparison and the chemical shift scale was removed from the NMR spectra. Only the values of chemical shift differences were considered in this study.

With the exception of C-11-PF_6 (C = Peu, Eph, or Pro; compounds **27**, **21**, or **15**), when the linker chain lengths and anions were kept constant, the variation of cations from Pro to Eph to Peu produced increased splittings. This trend was expected and can be interpreted as follows. Pro-7-BF_4
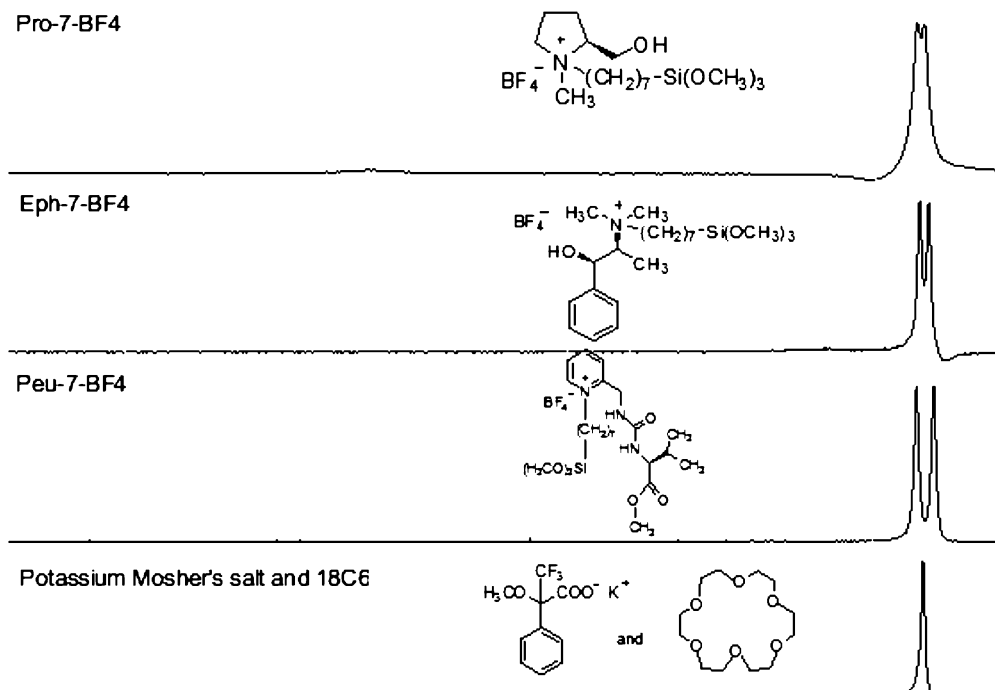

Figure 2. Splittings of ¹⁹F NMR chemical shift of potassium Mosher's salt using 27 CIL-modified silanes as chiral selectors.

Figure 3. ^{19}F NMR (CDCl$_3$, 0.5 mL) spectra of potassium Mosher's salt (0.015 mmol) with CIL-modified silane (Pro-7-BF$_4$, Eph-7-BF$_4$, or Peu-7-BF$_4$, 0.075 mmol) as chiral selectors in the presence of crown ether 18C6 (0.015 mmol). The chemical shifts are normalized for easier comparison.

(compound **11**) has only one hydroxyl functional group which could offer hydrogen bonding interaction with potassium Mosher's salt. However, Eph-7-BF$_4$ (compound **17**) contains both hydroxyl and aromatic functionalities which offer possible chiral recognition through respective hydrogen bonding and $\pi-\pi$ interactions. The important role of $\pi-\pi$ interaction in chiral recognition was also observed in enantiomeric discrimination tests using other CILs as chiral selectors. For example, Gaumont and co-workers investigated the chiral recognition ability of novel chiral *N*-benzylthiazolinium IL toward Mosher's salt.[24] The results of that study indicated the importance of an aromatic group for $\pi-\pi$ stacking interactions in chiral recognition since the corresponding *N*-ethylthiazolinium CIL only showed considerably weaker interactions.[24] Such $\pi-\pi$ interactions are inherently multipoint, and thus, a diastereomeric complex could provide the necessary three-point contact via $\pi-\pi$ interaction in combination with another interaction.[28] In regard to Peu-7-BF$_4$ (compound **23**), it contains an aromatic pyridyl, as well as an ester functional group. Moreover, the bulky alkyltrimethoxysilane in the 1-position and the 2-positioned alkyl urea and methyl butyrate group may lead to steric interactions. The urea structure of Peu-7-BF$_4$ (compound **23**) is highly beneficial for chiral recognition through hydrogen bonding interactions.[29] Therefore, Peu-7-BF$_4$ (compound **23**) showed the largest splitting among the three silanes.

The influence of the alkyl linker chain length on chiral discrimination was also investigated. No universal trend was observed in this component of our study. However, some trends were observed and are discussed below for various subsets. Some CIL-modified silanes exhibited a trend of C11 > C7 > C3 alkyl chain. For instance, chemical shift splittings increased from 1.06 to 2.21 Hz and then to 3.52 Hz, when the Pro-*x*-BF$_4$ (*x* = 3, 7, 11, and compounds **10**, **11**, and **12**)
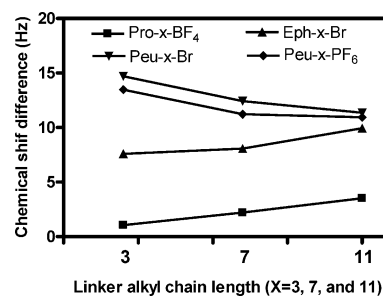

Figure 4. Influence of alkyl chain lengths on chiral discrimination.

were used, respectively (Figure 4). In another series of CIL-modified silanes, the splitting was 7.59 Hz with Eph-3-Br (compound **4**) as a chiral selector. The splitting increased to 8.08 Hz using Eph-7-Br (compound **5**) as the chiral selector. The chemical shift difference was further increased to 9.95 Hz upon an increase in the alkyl chain length to 11 in Eph-11-Br (compound **6**) (Figure 4). In these latter two cases, the longer alkyl chain may offer a more hydrophobic interactions with the Mosher's salt and could be instrumental in chiral recognition. However, the splitting showed the opposite trend when Peu-*x*-Br silanes (*x* = 3, 7, 11, and compounds **7**, **8**, and **9**) were used as chiral selectors. The splitting gradually decreased from 14.71 to 12.43 Hz and then, finally, to 7.90 Hz when the alkyl chain length increased from 3 to 7 and then to 11 (Figure 4). Similarly, the differences in chemical shift also gradually decreased with Peu-*x*-PF$_6$ (*x* = 3, 7, 11, and compounds **25**, **26**, and **27**) series silanes when the linker chain length increased (Figure 4). However, for Peu-*x*-BF$_4$ series compounds, Peu-3-BF$_4$ (compound **22**) showed a splitting of 12.20 Hz. The splitting decreased to 12.01 Hz with Peu-7-BF$_4$ (compound **23**) as the chiral selector. With a further increase of the link chain

length to 11, Peu-11-BF$_4$ (compound **24**) showed a slight increase of splitting of 12.41 Hz.

In the two cases (Peu-*x*-Br and Peu-*x*-PF$_6$, *x* = 3, 7, and 11), all six silanes have the same Peu cation. As seen in Table 2, the long and bulky 2-positioned side chain of Peu containing urea, alkyl, and ester groups may have a significant steric interaction with the 1-positioned alkyl linker containing a bulky trimethoxysilane group. Guillemin et al. demonstrated that a polar group on the lateral side chain and a bulky ortho substituent on the aromatic ring were complementary and necessary to obtain increased diastereomeric interactions between the chiral cation and the anionic analyte.[23] A bulky 2-*tert*-butyl group on the ortho position of the aromatic ring is thought to be responsible for enhanced chiral discrimination, which could be ascribed to greater steric interactions. Indeed, replacement of the initial bulky 2-*tert*-butyl group with a 2-methyl group considerably decreased splitting of the NMR signals.[23] In contrast, the interaction between the alkyl linker and the side chain is minimal for both the Pro- and Eph-containing silanes. Therefore, for compounds Peu-3-Br (compound **7**) or Peu-3-PF$_6$ (compound **25**) possessing a short alkyl chain length of three methylenes, the higher steric interaction may play a more important role in chiral recognition than a concomitant hydrophobic interaction. In some cases, steric interactions may provide a positive influence on chiral recognition as one point of the three-point interaction needed to obtain chiral recognition.

Finally, the influences of the various anions on enantiomeric recognition were also examined. The type of anion exhibited very different effects for different series of compounds (Figure 2). For example, in the Peu-11-X (X = Br, BF$_4$, and PF$_6$) series compounds, the anion-exchanged products, Peu-11-BF$_4$ (compound **24**) and Peu-11-PF$_6$ (compound **27**), showed respective splittings of 12.41 and 10.95 Hz, which are higher than that of compound **9**, Peu-11-Br (7.70 Hz). In contrast, regarding another Peu-3-X (X = Br, BF$_4$, and PF$_6$) series of compounds, the anion-exchanged products, Peu-3-BF$_4$ (compound **22**), and Peu-3-PF$_6$ (compound **25**) showed respective splittings of 12.20 and 13.47 Hz, which are lower than those of Peu-3-Br (14.71 Hz, compound **7**). These results suggest that the anion plays a different role in different CIL-modified silanes. For instance, the anion's hydrophobicity may play a profound role in certain cases, whereas its steric size might be a major influence in other cases. Wilhelm et al. also observed that the same anion may play significantly different roles in different CILs.[36] For example, a change in anion from BF$_4^-$ to NTf$_2^-$ [bis(trifluoromethylsulfonyl)imide] provided a significant increase in the splitting with the same chiral cation. However, with a different chiral cation, the change in anion from BF$_4^-$ to NTf$_2^-$ did not show any improved splitting.[36] There was no clear trend in other series of silanes investigated, which again suggests that the anion could have distinctly different influences on chiral recognition due either to its hydrophobicity or steric size.

Chiral Discrimination of Aromatic Alcohols. To date, many studies have used the ionic analyte potassium Mosher's salt to investigate the chiral discrimination ability of CILs.
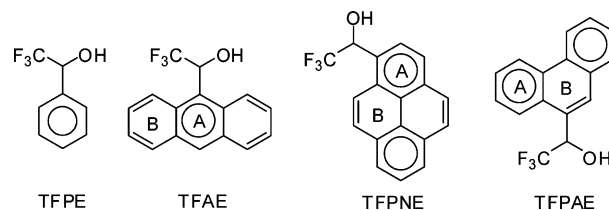

Figure 5. Chiral aromatic alcohols showing the Clar's structures. Clar's aromatic π-sextets are indicated with circles, and ring A has higher local aromaticity than ring B.

Herein, we also investigate the chiral discrimination of representative CIL-modified silanes toward neutral analytes. Four aromatic alcohols (Figure 5) containing CF$_3$ groups were tested under identical conditions as those used in the discrimination tests of potassium Mosher's salt. Three CIL-modified silanes, Pro-7-BF$_4$ (compound **11**), Eph-7-BF$_4$ (compound **17**), and Peu-7-BF$_4$ (compound **23**), were used as representative chiral selectors. The two chiral selectors Pro-7-BF$_4$ (compound **11**) and Eph-7-BF$_4$ (compound **17**) did not show chiral discrimination toward any of the four alcohols, while Peu-7-BF$_4$ (compound **23**) showed chiral discrimination toward two of the four alcohols. This is in agreement with our previous finding that the chiral silanes with Peu cations have higher enantiomeric recognition ability than those with either Pro or Eph cations. Interestingly, Peu-7-BF$_4$ (compound **23**) showed no enantiomeric discrimination of TFPE which has only one aromatic ring (phenyl). It was hypothesized that an increase in the number of aromatic rings may provide increased enantiomeric discrimination. Peu-7-BF$_4$ (compound **23**) showed discrimination toward TFAE and TFPNE, containing 3 and 4 aromatic rings, respectively. However, it should be noted that the number of aromatic rings was not an absolute predictor of chiral discrimination. When comparing TFAE and TFPAE, both having three aromatic rings (anthryl and phenanthryl, respectively), Peu-7-BF$_4$ (compound **23**) showed a discrimination of TFAE (7.8 Hz), but no discrimination of TFPAE. TFPNE, possessing four aromatic rings (pyrenyl), showed a smaller splitting (3.2 Hz) as compared to the three ringed TFAE (¹⁹F NMR spectra are provided in the Supporting Information).

It is noted that π−π stacking interactions may play an important role in chiral discrimination of the aromatic alcohols. Peu-7-BF$_4$ showed no discrimination of TFPE which has a phenyl group, yet provided discrimination of TFAE having an anthryl group. However, Peu-7-BF$_4$ showed chiral discrimination of only one of the two isomeric aromatic alcohols containing three aromatic rings (selectivity toward TFAE, but not TFPAE). This could possibly be explained by the different local aromaticity in various phenyl rings.[37]

Clar introduced the aromatic π-sextets, i.e. benzenelike moieties to characterize polycyclic aromatic hydrocarbons (PAHs).[38] The Clar structure of a given PAH is the resonance structure having the maximum number of isolated and localized aromatic π-sextets, with a minimum number of localized double bonds. Aromatic π-sextet rings are considered to be the most aromatic centers in PAHs.[39] The Clar-formula-like distribution of current patterns has been previously observed using scanning tunneling microscopy (STM).[39] Interestingly, the stereogenic center of TFPAE, the

isomer showing no discrimination, is located in the ring (B) which has less local aromaticity (Figure 5). However, the stereogenic centers of TFAE (splitting of 7.8 Hz) and TFPNE (splitting of 3.2 Hz) are located in rings (A) which have higher local aromaticity (Figure 5). It appears that polycyclic aromatic alcohols with a stereogenic center located in the π-sextet ring may be more readily resolved due to possible stronger $\pi-\pi$ stacking interactions.

Experimental Section

Materials and Chemicals. Racemic potassium Mosher's salts was obtained by neutralizing racemic Mosher's acid (($\pm$)-α-methoxy-α-(trifluoromethyl)phenylacetic acid) (Sigma-Aldrich) with potassium hydroxide and evaporation of water on a lyophilizer. (S)-(−)-1-Methyl-2-pyrrolidinemethanol, (1R,2S)-(−)-N-methyl-ephedrine, methyl (S)-(−)-2-isocyanato-3-methylbutyrate, 2-(aminomethyl)pyridine, potassium hexafluoro-phosphate, sodium tetrafluoroborate, and racemic Mosher's acid were obtained from Sigma-Aldrich (Milwaukee, WI). The linkers, (trimethoxysilyl)propylbromide, (trimethoxysilyl)heptylbromide, and (trimethoxysilyl)undecylbromide, were purchased from Gelest (Morrisville, PA). Chiral aromatic alcohols, 2,2,2-trifluoro-1-phenylethanol (TFPE), 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE), 2,2,2-trifluoro-1-(9-phenanthryl)-ethanol (TFPAE), 2,2,2-trifluoro-1-(1-pyrenyl)ethanol (TFPNE), and crown ether, 1,4,7,10,13,16-hexaoxacyclooctadecane (18C6), were obtained from Sigma-Aldrich. Ethanol, dichloromethane (DCM), and diethyl ether were of anhydrous grade (Sigma-Aldrich, Milwaukee, WI), and all other organic solvents such as acetonitrile, acetone, hexane, and water are of HPLC grade (J. T. Baker, Phillipsburg, NJ). Deuterated solvents including chloroform-d_1, dichloromethane-d_2, acetonitrile-d_3, acetone-d_6, toluene-d_8, benzene-d_6, D_2O, and dimethyl sulfoxide-d_6 were also obtained from Sigma-Aldrich. All reagents were used as received without further purification. Chiral tertiary amine, Peu, (S)-methyl 3-methyl-2-(3-(pyridin-2-ylmethyl)ureido)butanoate was synthesized employing a previously described procedure with minor modifications.[40] Detailed information on the synthesis characterization of Peu is provided in the Supporting Information.

Instrumentation. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired by use of a Bruker DPX 400 NMR spectrometer. The ^{1}H and ^{13}C chemical shifts are given in parts per million (δ) with TMS as an internal standard. ^{19}F NMR (236 MHz) spectra were acquired by use of a Bruker DPX 250 NMR spectrometer with trichlorofluoromethane (CFCl$_3$) as a reference standard. FT-IR was measured using a Bruker Tensor 27 FT-IR spectrometer. Samples were analyzed in pure form by use of a DuraSamp IR apparatus. All spectra were obtained using 8 scans for both sample and background, with a resolution of 4 cm^{-1}. A Thermo Scientific IEC Centra GP8 centrifuge was used to separate suspensions from solvents. Elemental analyses were contracted to Atlantic Microlab (Atlanta, GA).

Synthesis and Characterization of CIL-Modified Silanes Library Compounds. In general, building block 1 compounds (three chiral tertiary amines, Pro, Eph, and Peu) were reacted with building block 2 compounds (three

(trimethoxysilyl)alkylbromide) with an alkyl chain length of 3, 7, and 11 to make nine (3 × 3) CIL-modified silanes, all of which contained Br$^-$ as the anion (Table 1 and Scheme S2 in the Supporting Information). Subsequently, each of the nine silanes was divided into three equal portions. The first portion of each silane was used as CILs with Br$^-$ as anion. The second and third portion of the same CIL-modified silane underwent anion-exchange with building block 3 compounds (NaBF$_4$ or KPF$_6$, Table 2 and Scheme S2 in the Supporting Information). The detailed combinatorial synthesis procedure and characterization of the 27 CIL-modified silane library compounds by ^{1}H, ^{13}C, and ^{19}F NMR, FI-TR and C, H, N elemental analysis are provided in the Supporting Information.

Choice of Deuterated Solvents for ^{19}F NMR Screening. Eight deuterated solvents including acetonitrile-d_3, acetone-d_6, D_2O, DMSO-d_6, toluene-d_8, benzene-d_6, dichloromethane-d_2, and chloroform-d_1 were tested. No chiral recognition was observed in strongly polar solvents such as deuterated DMSO, acetone, and acetonitrile. The strongly polar interactions between the solvents and CIL-modified silanes possibly mask or impair the chiral interactions between the CIL-modified silanes and potassium Mosher's salt. However, both the potassium Mosher's salt and the chiral silanes showed very low solubility in low polarity solvents such as deuterated toluene and benzene. Most of the CIL-modified silanes were also insoluble in D_2O and dichloromethane-d_2. Therefore, none of these solvents were suitable for ^{19}F NMR.

The largest chemical shift splitting between the two diastereomeric associates was obtained in chloroform-d_1. Tran and co-workers also reported that a larger splitting value was found in chloroform-d_1 than in acetonitrile-d_3 when investigating chiral recognition between a chiral borate anion and racemic imidazolium cations.[35] This suggests that ion pair interactions between the Mosher's acid anion and the chiral IL's cation is stronger in a solvent with lower dielectric constant. This creates stronger interactions between the anion and cation.[41] Therefore, chloroform-d_1 was used as the solvent of choice for all ^{19}F NMR tests. Moreover, the addition of crown ether such as 18C6 to the solution could increase the solubility of potassium Mosher's salt in chloroform-d_1 due to the complexation between potassium and crown ether.[23] Hence, in all the ^{19}F NMR screening tests, 18C6 was added to enhance the solubility of potassium Mosher's salt in chloroform-d_1

Preparation of NMR Stock Solutions. Racemic potassium Mosher's salt (121.3 mg, 0.45 mmol) and 18C6 (119.5 mg, 0.45 mmol) were dissolved in chloroform-d_1 (15 mL) as the feedstock solution for ^{19}F NMR tests. The NMR stock solutions containing aromatic alcohols (Figure 5) were prepared by dissolving individual alcohols 2,2,2-trifluoro-1-phenylethanol, TFPE; 2,2,2-trifluoro-1-(9-anthryl)ethanol, TFAE; 2,2,2-trifluoro-1-(9-phenanthryl)-ethanol, TFPAE; 2,2,2-trifluoro-1-(1-pyrenyl)ethanol, TFPNE) in chloroform-d_1. All alcohol solutions for NMR had the same concentrations (0.03 mmol/mL) as that used in potassium Mosher's acid solution. For each ^{19}F NMR screening test, 0.5 mL of the stock solution was used. CIL-modified silane (5 equiv with respect to potassium Mosher's

salt or aromatic alcohol) was dissolved in 0.5 mL of the feedstock solution. The sample solution was sonicated for 20 min before ^{19}F NMR analysis.

Conclusions

In summary, a library of 27 novel CIL-modified silanes was synthesized using a combinatorial approach and their chiral discrimination abilities toward racemic potassium Mosher's salt and aromatic alcohols were screened and evaluated using ^{19}F NMR spectroscopy. The optimum CIL-modified silanes were identified and could possibly be used as new chiral stationary phases after immobilization onto silica by a silanization reaction. Investigation of chiral recognition mechanisms (structure−property relationships) were possible using this combinatorial approach which identified several types of intermolecular interactions including ion-pairing, hydrogen bonding, $\pi-\pi$ stacking, dipole stacking, hydrophobic, and steric interactions affecting chiral discrimination. This work showcases the advantages of hyphenation between combinatorial chemistry and the preparation and application of CILs due to rapid, economical, and convenient operations. This combinatorial design and synthesis of chiral ionic liquids offers great potential for rapid and convenient development of novel chiral selectors, which could be used both in the development of new asymmetric catalysts or chiral resolving agents in chiral separation.

Supporting Information Available. Experimental procedures for the synthesis of 27 CIL-modified silans, ^{1}H, ^{13}C, ^{19}F NMR, FT-IR, elemental analysis characterization of the compounds, and the ^{19}F NMR spectra of chiral recognition of aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.

(2) Mallick, B.; Balke, B.; Felser, C.; Mudring, A. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7635–7638.

(3) (a) Wang, Q.; Baker, G. A.; Baker, S. N.; Colń, L. A. *Analyst* **2006**, *131*, 1000–1005. (b) Sun, Y.; Cabovska, B.; Evans, C. E.; Ridgway, T. H.; Stalcup, A. M. *Anal. Bioanal. Chem.* **2005**, *382*, 728–734. (c) Van Meter, D. S.; Oliver, N. J.; Carle, N. B.; Dehm, S.; Ridgway, T. H.; Stalcup, A. M. *Anal. Bioanal. Chem.* **2009**, *393*, 283–294.

(4) Chen, X.; Li, X; Hu, A.; Wang, F. *Tetrahedron: Asym.* **2008**, *19*, 1–14.

(5) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J. C.; Gaumont, A. C. *Tetrahedron: Asym.* **2005**, *16*, 3921–3945.

(6) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A. C.; Plaquevent, J. C. *Tetrahedron: Asym.* **2003**, *14*, 3081–3093.

(7) Patil, M. L.; Sasai, H. *Chem. Record* **2008**, *8*, 98–108.

(8) Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, *19*, 3235–3250.

(9) Winkel, A.; Reddy, P. V. G.; Wilhelm, R. *Synthesis* **2008**, *7*, 999–1016.

(10) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281–292.

(11) Bwambok, D. K.; Marwani, H. M.; Fernand, V. E.; Fakayode, S. O.; Lowry, M.; Negulescu, I.; Strongin, R. M.; Warner, I. M. *Chirality* **2008**, *20*, 151–158.

(12) Tran, C. D.; Oliveira, D. *Anal. Biochem.* **2006**, *356*, 51–58.

(13) Ding, J.; Welton, T.; Armstrong, D. W. *Anal. Chem.* **2004**, *76*, 6819–6822.

(14) Tran, C. D.; Mejac, I. *J. Chromatogr. A* **2008**, *1204*, 204–209.

(15) Rizvi, S. A. A.; Shamsi, S. A. *Anal. Chem.* **2006**, *78*, 7061–7069.

(16) (a) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Davis, J. H., Jr.; Rogers, R. D.; Mayton, R.; Sheff, S.; Wierzbicki, A. *Chem. Commun.* **2001**, 135–136. (b) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, Se; Wierzbicki, A.; Davis, J. H., Jr.; Rogers, R. D. *Environ. Sci. Technol.* **2002**, *36*, 2523–2529.

(17) Freemantle, M. *Chem. Eng. News* **1998**, *76*, 32.

(18) Vince, M.; Alfred, H.; Damodaram, P. WO0032572 (A2), 2000.

(19) (a) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem.−Eur. J.* **2004**, *10*, 2872–2884. (b) Pamies, O.; Dieguez, M. *Chem.−Eur. J.* **2008**, *14*, 944–960. (c) Jagt, R. B. C.; Toullec, P. Y.; Schudde, E. P.; De Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *J. Comb. Chem.* **2007**, *9*, 407–414. (d) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188–4189.

(20) (a) Brahmachary, E.; Ling, F. H.; Svec, F.; Frechet, J. M. J. *J. Comb. Chem.* **2003**, *5*, 441–450. (b) Lewandowski, K.; Murer, P.; Svec, F.; Fréchet, J. M. J. *J. Comb. Chem.* **1999**, *1*, 105–112. (c) Welch, C. J.; Bhat, G.; Protopopova, M. N. *J. Comb. Chem.* **1999**, *1*, 364–367. (d) Welch, C. J.; Pollard, S. D.; Mathre, D. J.; Reider, P. J. *Org. Lett.* **2001**, *3*, 95–98. (e) Murer, P.; Lewandowski, K.; Svec, F.; Fréchet, J. M. J. *Chem. Commun.* **1998**, 2559–2560. (f) Weingarten, M. D.; Sekanina, K.; Still, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 9112–9113. (g) Wang, Y.; Bluhm, L. H.; Li, T. *Anal. Chem.* **2000**, *72*, 5459–5465.

(21) (a) Wasserscheid, P.; Drieβen-Hölscher, B.; val Hall, R.; Steffens, H. C.; Zimmermann, J. *Chem. Commun.* **2003**, 2038–2039. (b) Zhang, L.; Luo, S.; Mi, X.; Liu, S.; Qiao, Y.; Xu, H.; Cheng, J. *Org. Biomole. Chem.* **2008**, *6*, 567–576. (c) Soutullo, M. D.; Odom, C. I.; Salter, E. A.; Stenson, A. C.; Sykora, R. E.; Wierzbicki, A.; Davis, J. H. *J. Chem. Commun.* **2007**, *9*, 571–573.

(22) Wasserscheid, P.; Boesmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200–201.

(23) Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J. C. *Chem. Commun.* **2004**, 1224–1225.

(24) Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A. C. *Chem. Commun.* **2003**, 2914–2915.

(25) Kumar, V.; Pei, C.; Olsen, C. E.; Schaeffer, S. J. C.; Parmar, V. S.; Malhotra, S. V. *Tetrahedron: Asym.* **2008**, *19*, 664–671.

(26) HervéLoïse, C.; Boulanger, N. A.; Loïc, T.; Marc, M.; Jean-Claude, G. *Chem. Commun.* **2004**, 1224–1225.

(27) Tran, C. D.; Oliveira, D.; Yu, S. *Anal. Chem.* **2006**, *78*, 1349–1356.

(28) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347–362.

(29) Feibush, B. *Chirality* **1998**, *10*, 382–395.

(30) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275–297.

(31) Huang, J.; Li, T. *J. Chromatogr. A* **2005**, *1062*, 87–93.

(32) Dehmlow, E. V.; Klauck, R.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Tetrahedron: Asym.* **1998**, *9*, 2235–2244.

(33) Ceccacci, F.; Diociaiuta, M. L.; Galantini, G.; Mancini, P.; Mencarelli, A.; Scipioni, C. V *Org. Lett.* **2004**, *6*, 1565–1568.

(34) Kodama, Y.; Fujiwara, A.; Kawamoto, H.; Ohta, N.; Kitani, A.; Ito, S. *Chem. Lett.* **2001**, 240–241.

(35) Schulz, P. S.; Müller, N.; Bösmann, A.; Wasserscheid, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 1293–1295.

(36) Jurčřk, V.; Gilani, M.; Wilhelm, R. *Eur. J. Org. Chem.* **2006**, 5103–5109.

(37) Huertas, O.; Poater, J.; Fuentes-Cabrera, M.; Oroaco, M.; Solá, M.; Luque, F. J. *J. Phys. Chem. A* **2006**, *110*, 12249–12258.

(38) (a) Clar, E. *The Aromatic Sextet*; Wiley: New York, 1972. (b) Randić, M. *Chem. Rev.* **2003**, *103*, 3449–3605. (c) Portella, G.; Poater, J.; Solá, M. *J. Phys. Org. Chem.* **2005**, *18*, 785–791.

(39) Gutman, I.; Tomović, Ž.; Müllen, K.; Rabe, J. P. *Chem. Phys. Lett.* **2004**, *397*, 412–416.

(40) Ni, B.; Zhang, Q.; Headley, A. D. *J. Org. Chem.* **2006**, *71*, 9857–9860.

(41) Yu, S.; Lindeman, S.; Tran, C. D. *J. Org. Chem.* **2008**, *73*, 2576–2591.