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Synthesis of new chiral imidazolium salts derived from amino acids: their evaluation in chiral molecular recognition

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ABSTRACT

A family of new imidazolium salts derived from natural amino acids has been synthesized and tested for NMR enantiodiscrimination, as chiral shift reagents, of carboxylic acids. These imidazolium receptors contain different structural modifications and the splitting of the signals of the acids, after addition of the corresponding CSRs, depends on these structural variables. Compound **8b** exhibited the strongest chiral solvating properties for racemic Mosher acid and was recognized as a suitable CSR for the determination of its enantiomeric composition.

1. Introduction

Due to the importance of chirality in pharmaceutical and biological chemistry,[1] the development of a fast and simple methodology for the measurement of enantiomeric purity is an important target.[2] Chiral shift reagents (CSRs) have a good potential for this purpose, because NMR spectroscopy has the advantages of good performance and accessibility and because enantiomeric excesses can be easily determined by adding the reagent to a chiral compound in a small amount of a deuterated solvent.[2,3] Moreover, the use of non-covalent chiral shift reagents provides the possibility of carrying out the experiment 'in situ', and the potential for recovering the chiral compound after measurement. Various types of chiral shift reagents have been reported for carboxylic acids; however, few of them are commercially available and useful for the application to pharmacologically active propionic acids. Although many enantioselective carboxylate receptors have shown their application in chiral resolution,[4] few such receptors can be used as chiral shift reagents to determine enantiomeric purities of chiral carboxylic acids by ^{1}H NMR accurately. This is often associated with their structural complexity or to the fact that the ^{1}H chemical shift nonequivalences are too small to achieve baseline resolution.[3e,5]

2. Results and discussion

Taking this into account, we decided to search for a family of versatile and powerful non-covalent chiral shift reagents that could be easily synthesized from the chiral pool. In this regard, we used natural amino acids as the starting chiral materials and ionic and hydrogen bonding as the driving forces for the interaction and approached imidazolium salts with the general structure shown in Figure 1 as effective chiral shift reagents. The main structural variables considered for the synthesis of these imidazolium salts were the amino acid side chain residue, the aromatic moiety attached to the nitrogen atom, and the counter anion.

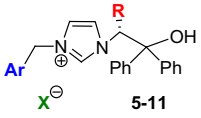

Figure 1. Structural variables in imidazolium salts.

Several chiral imidazolium salts with ionic liquid properties (CILs) have been described in the literature as good shift reagents for the potassium salt of the Mosher acid.[6] To date, however, there are only a few examples of chiral imidazolium compounds, prepared from amino acids, as artificial receptors for chiral molecular recognition.[7] Herein, we wish to report on the preparation of new chiral imidazolium salts and their investigation as CSRs using the Mosher salt as the standard guest. In addition some of the imidazolium salts that presented **5–11** can be qualified as CILs.[8]

The first step of the synthesis was the preparation of the enantiopure imidazole rings derived from L-amino acids, which were used as the precursors of the desired final chiral imidazolium salts. For this purpose we followed the procedure described by Bao et al.[8c] The general synthetic route is outlined in Scheme 1. Sodium L-2-(1-imidazolyl) alkanoic acids **1** were obtained from L-amino acids having different side chains. In our case, L-valine, L-isoleucine, and L-phenylalanine were used as the starting materials (R = $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, and CH_2Ph). The respective ethyl esters **3b** and **3c** were prepared from Phe and Val using anhydrous EtOH and HCl.[9] On the other hand, the methyl esters derived from

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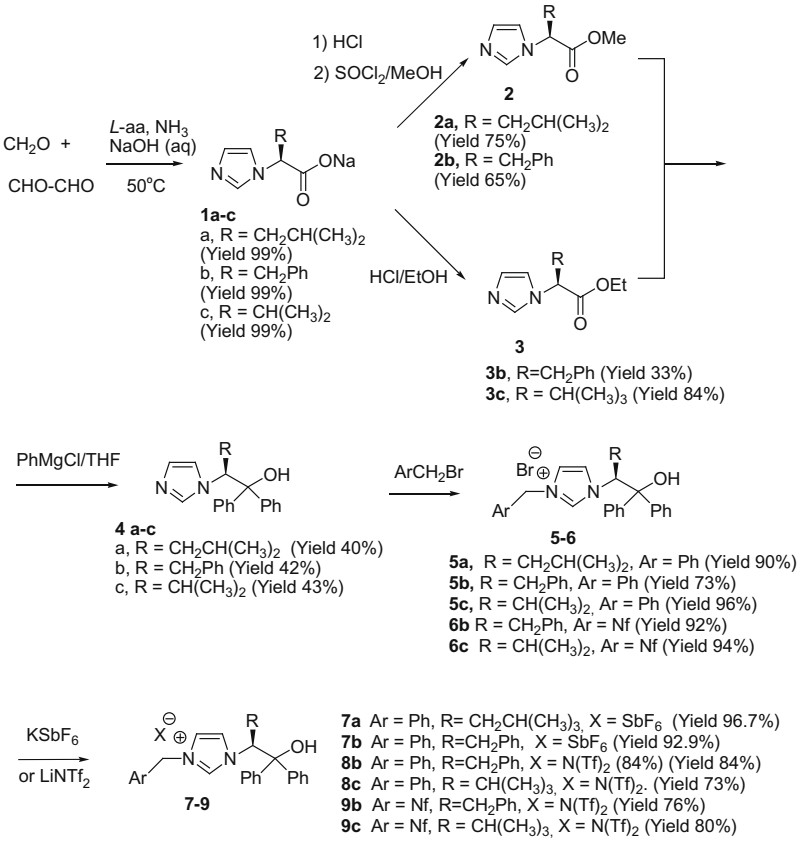

Scheme 1. Synthesis of imidazolium-based salts.

L-isoleucine **2a** and L-phenylalanine **2b** were prepared by refluxing **1a** and **1b**, respectively, in a mixture of anhydrous MeOH and $SOCl_2$ based on known procedures described for the preparation of esters of amino acids.[9] The corresponding alcohols **4** were prepared by addition of an excess of PhMgCl to compounds **2** and **3** in dry THF at reflux in good yields.[9] Imidazolium salts **5–6** were obtained by reaction of **4** with the corresponding bromides in THF. Yields for quaternization were good (80–90%). Finally the desired products **7–9** were prepared by anion metathesis of **5–6** with $KSbF_6$ or $LiNTf_2$. The chiral imidazolium salts **7–9** prepared were white solids with melting points ranging from 70 to 120 °C. The structures of the new chiral receptors were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.[10]

^1H NMR spectroscopy was used to investigate the chiral recognition ability of compounds **5b** and **7–9**, with racemic chiral carboxylic acids as the guests. For the initial studies, the racemate of the Mosher acid salt was chosen as the guest and 3:1 mixtures of **5b, 7–9,** and the potassium salt of the Mosher acid were examined.[11] The signal of the methoxy group of this guest is a sharp singlet at 3.56 ppm in CD_3CN and does not overlap with the peaks of the other proton signals in the ^1H NMR spectra either for the host or for the guest. Therefore, it is an ideal probe for chiral discrimination. As shown in Figure 2, upon addition of the imidazolium receptors, the signal of the methoxy protons of the Mosher acid was upfield shifted and splits into two peaks due to the formation of two diastereotopic complexes between the CSRs and the enantiomers of the guest, which confirms that chiral recognition has occurred. When binding **8b**, chemical shift values of the (*R*)- and (*S*)-Mosher acid salt exhibit 0.016 and 0.041 ppm upfield shifts, respectively. These results suggest a different chemical environment for the two enantiomers of the Mosher acid, and that host-guest instantaneous complexes had been formed.

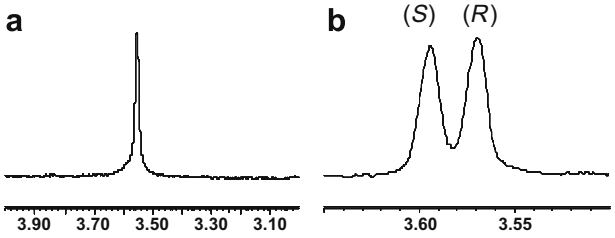

Figure 2. Partial ^1H NMR spectra (CD_3CN, 500 MHz) of (a) potassium salt of Mosher acid. (b) Potassium salt of Mosher acid after the addition of 3 equiv of **8b** showing the splitting of the signal corresponding to the OMe group attached to Cα. The signals for the enantiomers were assigned by adding a known amount of one enantiomer to the racemic solution.

The determination of the stoichiometry of the species formed is important to analyze the structure of the complexes. Therefore, the stoichiometric ratios of the host–guest complexes were investigated by the Job plot method.[12] The Job plot for the complexation of **8b** with the (*R*)- and (*S*)-potassium salts of the Mosher acid is illustrated in Figure 3, where X_H is the molar fraction of **8b** and X_G is the molar fraction of the potassium salt of the Mosher acid. The total concentration of the two compounds was kept constant (10 mM) and $\Delta\delta$ is the chemical shift change of the C2 imidazolium proton signal of **8b**. The plot exhibits a maximum at $X = 0.5$, indicating 1:1 complexation.

To evaluate the chiral discrimination abilities of the different chiral imidazolium salts **5b** and **7–9**, we measured the NMR spectra for the 3:1 mixtures of the corresponding imidazolium salt and the potassium salt of the Mosher acid in CD_3CN. Some results are summarized in Table 1 where shifts of the methyl H and F nuclei for the potassium salt of the Mosher acid are shown. Chemical shift

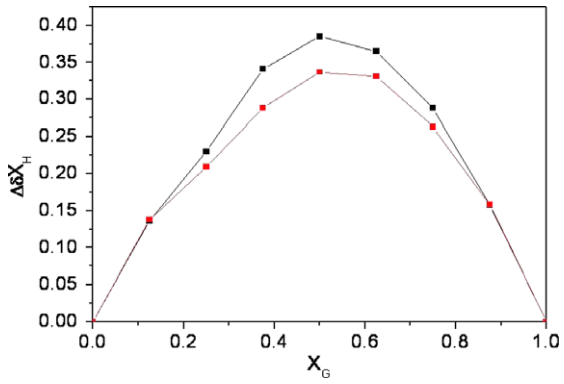

Figure 3. Job plot of **8b** with (*R*)- and (*S*)-potassium salt of the Mosher acid. Total concentration of 10×10^{-3} M.

Table 1
Selected ^{1}H and ^{19}F chemical shift nonequivalences of the racemic potassium salt of Mosher acid in the presence of imidazolium salts **5b** and **7–9** by NMR (500 MHz) in CD_3CN at 30 °C.

Entry	Host[a]	Ar	X	$\Delta\delta$[b]	$\Delta\Delta\delta$[c] (ppm)	$\Delta\Delta\delta$[d] (ppm)
1	**7a**	Phenyl	SbF_6	0.011	0.008	0
2	**7b**	Phenyl	SbF_6	0.028	0.017	0
3	**5b**	Phenyl	Br	0.012	0.019	0
4	**8b**	Phenyl	NTf_2	0.026	0.026	0.023
5	**9b**	Naphthyl	NTf_2	0.035	0.024	0.032
6	**8c**	Phenyl	NTf_2	0.015	0	0
7	**9c**	Naphthyl	NTf_2	−0.050	0	0

[a] All samples were prepared by mixing 1 equiv of racemic potassium Mosher salt (0.01 M in CD_3CN) and 3 equiv of chiral host (0.01 M in CD_3CN) in NMR tubes.
[b] Averaged between signals from both enantiomers.
[c] ^{1}H chemical shift nonequivalences of methyl protons of the potassium salt of Mosher acid.
[d] ^{19}F chemical shift nonequivalences of the potassium salt of Mosher acid.

nonequivalences were observed in many cases. Chiral imidazolium salts derived from L-phenylalanine **8b** and **9b** showed to be the best shift reagents, with ^{1}H chemical shift nonequivalences of 0.026 ppm for the methylic protons. However, only ^{1}H chemical shift nonequivalences of 0.008 pm were obtained when imidazolium salts derived from leucine **7a** were used as CSRs (entry 1) and no chiral recognition was observed for imidazolium salts derived from L-valine (entries 6 and 7).

On the other hand, when we studied the influence of the anion of the starting chiral imidazolium salt for the phenylalanine derivatives **5b**, **7b,** and **8b**, we observed better shift nonequivalences for soft anions such as NTf_2, in particular for ^{19}F signals (entry 4). Finally, the same chiral discrimination ability was found for compounds **8b** and **9b** (entries 4 and 5). This result suggests the absence of a π–π interaction in the diastereomeric complexes involving the benzylic or naphthylic moiety bound to the second nitrogen atom of the imidazolium ring.

Considering the results obtained, and to understand the origin of the discrimination, we performed a molecular modeling study for the complex **8b**/Mosher acid. Initially, a Monte Carlo conformational search using the conformer distribution option available in SPARTAN'04 was used.[13] With this option, an exhaustive Monte Carlo search without constraints was performed for every structure. The torsion angles were randomly varied and the structures obtained were fully optimized using the MMFF. Thus, 100 minima of energy within an energy gap of 10 kcal/mol were generated. When studying the different structures derived from the conformational study, we observed the absence of any π–π interaction in the diastereomeric structures, in accordance with the experimental evidence.

The global minima from this conformational search were optimized in a DFT study with both (*R*)- and (*S*)-Mosher acids and host **8b**.[14] The optimized structures are shown in Figure 4. As can be seen, both diastereomeric complexes show hydrogen bonding between hydroxy and carboxylate groups, but only one diastereomeric complex displays a hydrogen bond between the C2 proton of the imidazolium ring and the carboxylate group. This hydrogen bond seems to allow the formation of more stable complexes (ΔE = 1.2 kcal/mol). This is in accordance with the experimental results derived from the 1:1 diastereomeric complexes between **8b** and the enantiopure potassium salt of Mosher acid (see Table 2). This interaction model may explain why host **8b** can discriminate both enantiomers of Mosher acid as guest.

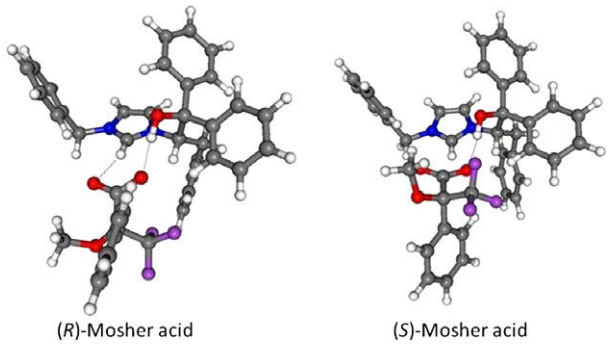

Figure 4. Optimized structure obtained by DFT search for the diastereomeric complexes between **5c** and potassium salt of Mosher acid.

Table 2
Association constants (K_a), Gibbs free energy changes ($-\Delta G_o$), enantioselectivity $K_a(S)/K_a(R)$), or $\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of **8b** with (*S*)- or (*R*)-Mosher salt in CD_3CN at 30 °C.

Entry	Guest[a]	K_a (mol/l)	$K_a(S)/K_a(R)$	$-\Delta G_o$ (kcal/mol)	$\Delta\Delta G_o$ (kcal/mol)
1	(*R*)	16.37 ± 2.04		1.68	
2	(*S*)	2.26 ± 1.65		0.49	
3			7.24		1.19

[a] Concentration of host 0.01 M.

The binding constants (K_a) for the association of **8b** for the (*R*)- and (*S*)-Mosher salt enantiomers were determined by NMR titrations, assuming a 1:1 complexation. The K_a values were calculated by means of a nonlinear least-squares method applied to the downfield shift of the C2 imidazolium proton signal observed upon addition of the guest, based on the Benesi–Hildebrand equation.[15] Association constants (K_a) and free energy changes ($-\Delta G_o$) are shown in Table 2. The (*R*)-Mosher salt enantiomer has an association constant seven times higher than the (*S*)-enantiomer. Thus, the (*R*)-Mosher salt/**8b** complex is 1.19 kcal/mol more stable than the (*S*)-Mosher salt/**8b** complex (entry 1).

Finally, we have also demonstrated the practical applicability of receptor **8b** for the measurement of the ee of carboxylate salts, using the Mosher acid salt as a model compound. Samples containing different proportions of both enantiomers of the Mosher acid salt were prepared and analyzed with **8b** as a CSR (Fig. 5), rendering an excellent linear response (R^2 = 0.9992).

3. Conclusion

In conclusion, we have designed and synthesized a new family of CSRs based on imidazolium salts derived from natural amino acids. They are efficient for discrimination of the potassium salt of the Mosher acid by ^{1}H NMR spectroscopy. The formation of diastereomeric complexes is fast and quantitative, making possible

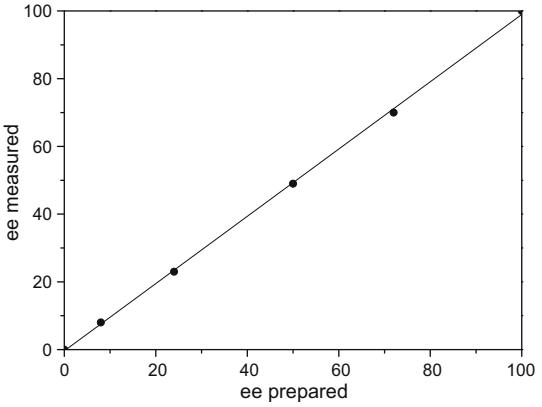

Figure 5. Correlation between theoretical and observed ee values obtained by 500 MHz ^{1}H NMR titrations of enantiomerically enriched mixtures of the Mosher acid salt using **8b** as CSR.

the analysis in situ in a 500 MHz NMR spectrometer. Moreover, interaction between receptor and substrate is non-covalent, and the receptor can be separated and recovered by a simple acid extraction procedure. Further studies to improve the receptor structure and for the application to guests of biological and medicinal relevance are in progress.

Acknowledgments

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10. *Characterization of the imidazolium salt derivatives* **7–9**. Compound **7a**: White solid. Mp = 70 °C; $[\alpha]_D^{20} = +99.8$ *c* 0.009, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 0.85 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.6, 3H), 1.25–1.41 (m, 1H), 1.64–1.76 (ddd, *J* = 14.9, 10.1 and 1.7 Hz, 1H), 2.09–2.22 (m, 1H), 5.21(d, 1H, *J* = 14.8 Hz), 5.28 (d, 1H, *J* = 14.8 Hz), 5.44 (dd, *J* = 11.9 and 1.5 Hz, 1H), 7.01–7.07 (m, 3H), 7.11–7.15 (m, 2H), 7.23–7.44 (m, 9H), 7.50 (s, 1H), 7.60 (d, *J* = 8 Hz, 2H), 8.88 (s, 1H). ^{13}C NMR δ (ppm): 20.5, 22.6, 25.1, 38.4, 52.8, 67.3, 79.6, 121.3, 125.0, 126.0, 126.9, 127.5, 128.1, 128.1, 128.5, 129.0, 129.2, 134.1, 136.1, 143.8, 143.8. IR (KBr): 3547, 3158, 2961, 2873, 1552, 1496, 1449, 1154, 1063, 749, 703, 662 cm^{-1}. MS (ESI$^+$, *m*/*z*): 411.2 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 234.9 [SbF_6^-, 100%]. Anal. Calcd (%) for $C_{28}H_{31}F_6N_2OSb$: C, 51.95; H, 4.83; N, 4.33. Found: C, 52.39; H, 5.62; N, 4.27. Compound **7b**: White solid. Mp = 105–111 °C; $[\alpha]_{20}^{D} = +35$ (*c* 0.010, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 3.26–3.32 (m, 2H), 5.05 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 5.63–5.76 (m, 1H), 6.93–7.23 (m, 12H), 7.29–7.41 (m, 6H), 7.47 (dd, *J* = 7.7 and 7.4 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 8.76 (s, 1H). ^{13}C NMR δ (ppm): 36.0, 52.6, 70.5, 79.4, 121.2, 123.7, 125.0, 125.9, 127.1, 127.3, 127.9, 128.2, 128.7, 128.8, 128.9, 129.0, 129.2, 134.0, 136.0, 136.4, 143.6, 143.8. IR (KBr): 3547, 3155, 3064, 2958, 1551, 1496, 1450, 1149, 1064, 745, 703, 656 cm^{-1}. MS (ESI$^+$, *m*/*z*): 445.4 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 234.8 [SbF_6^-, 100%]. Anal. Calcd (%) for $C_{31}H_{29}F_6N_2OSb$: C, 54.65; H, 4.29; N, 4.11. Found: C, 55.03; H, 5.01; N, 4.10. Compound **8b**: White solid. Mp = 60–63 °C; $[\alpha]_D^{20} = +41.4$ (*c* 0.004, CH_3OH). ^{1}H NMR (500 MHz, CD_3CN) δ (ppm): 3.21–3.36 (m, 2H), 5.14 (s, 2H), 5.60 (dd, *J* = 11.7 and 3.0 Hz, 1H), 6.96–7.01 (m, 2H), 7.02 (s, 1H), 7.10–7.19 (m, 5H), 7.21 (s, 1H), 7.24–7.27 (m, 3H), 7.35 (d, *J* = 7.0 Hz, 2H), 7.73–7.78 (m, 2H), 7.39–7.43 (m, 4H), 7.54 (dd, *J* = 7.8 and 7.5 Hz, 2H), 7.75 (d, *J* = 7.7 Hz, 2H), 8.47 (s, 1H). ^{13}C NMR δ (ppm): 36.0, 53.2, 70.4, 79.9, 116.4, 118.9, 120.8, 121.5, 123.6, 124.0, 125.0, 125.5, 127.5, 127.7, 128.1, 128.3, 128.8, 129.2, 129.5, 129.5, 132.2, 135.7, 136.2, 142.6, 143.0. IR (KBr): 3504, 3146, 3069, 3033, 1551, 1497, 1450, 1351, 1199, 1135, 1058, 742, 701, 662, 615, 570, 512 cm^{-1}. MS (ESI$^+$, *m*/*z*): 445.4 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 280.2 [NTf_2^-, 100%]. Anal. Calcd (%) for $C_{33}H_{29}F_6N_3O_5S_2$: C, 54.62; H, 4.03; N, 5.79. Found: C, 54.32; H, 3.98; N, 5.72. Compound **8c**: White solid. Mp = 110 °C; $[\alpha]_D^{20} = +46.9$ (*c* 0.011, CH_3OH). ^{1}H NMR (500 MHz, CD_3Cl) δ (ppm): 0.90 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 2.44–2.56 (m, 1H), 3.26 (br, 1H, OH), 5.12 (d, *J* = 14.8 Hz, 1H), 5.25 (d, *J* = 14.8 Hz, 1H), 5.48 (d, *J* = 5.8 Hz, 1H), 6.81 (s, 1H), 6.96 (d, *J* = 7.4 Hz 2H), 7.05 (m, 1H), 7.13 (dd, *J* = 7.7 and 7.7 Hz, 2H), 7.27–7.43 (m, 8H), 7.50 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 9.11 (s, 1H). ^{13}C NMR δ (ppm): 19.2, 22.2, 29.8, 53.4, 72.4, 81.4, 118.9, 120.5, 121.4, 123.6, 124.7, 124.9, 127.5, 128.2, 128.3, 128.8, 129.4, 129.6, 129.6, 132.8, 137.7, 143.4, 143.6. IR (KBr): 3506, 3138, 3074, 2975, 1555, 1450, 1346, 1184, 1128, 1056, 741, 704, 640, 593, 569 cm^{-1}. MS (ESI$^+$, *m*/*z*): 397.4 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 280.2 [NTf_2^-, 100%]. Anal. Calcd (%) for $C_{29}H_{29}F_6N_3O_5S_2$: C, 51.40; H, 4.31; N, 6.20. Found: C, 52.17; H, 5.10; N, 6.24. Compound **9b**: White solid. Mp = 120 °C; $[\alpha]_D^{20} = +27.4$ *c* 0.005, CH_3OH). ^{1}H NMR (500 MHz, CD_3Cl) δ ppm: 3.24 (dd, *J* = 14.8 and 12.2 Hz, 1H) 3.38 (dd, *J* = 14.9 and 1.9 Hz, 1H), 3.68 (br, 1H, OH), 5.23 (s, 2H), 5.71 (dd, *J* = 11.8 and 2.4 Hz, 1H), 6.73 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 7.02 (dd, *J* = 7.4 and 7.3 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 2H), 7.10–7.20 (m, 6H), 7.34–7.40 (m, 3H), 7.48 (dd, *J* = 7.8 and 7.5 Hz, 2H), 6.54–7.58 (m, 2H), 7.59 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.79–7.87 (m, 3H), 8.97 (s, 1H). δ (ppm): ^{13}C NMR δ (ppm): 36.1, 53.6, 70.5, 79.9, 118.9, 120.7, 121.4, 123.3, 124.9, 125.0, 125.4, 127.2, 127.4, 127.5, 127.7, 128.0, 128.2, 128.3, 128.4, 128.7, 128.8, 129.2, 129.5, 129.7, 130.1, 133.3, 133.6, 135.6, 136.5, 142.5, 142.8. IR (KBr): 3512, 3149, 3066, 3025, 1352, 1187, 1128, 1051, 746, 699, 617, 599, 569 cm^{-1}. MS (ESI$^+$, *m*/*z*): 495.2 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 280.1 [NTf_2^-, 100%]. Anal. Calcd (%) for $C_{37}H_{31}F_6N_3O_5S_2$: C, 57.28; H, 4.03; N, 5.42. Found: 57.98; H, 4.85; N, 5.58. Compound **9c**: White solid. Mp = 65–69 °C; $[\alpha]_{20}^{D} = +74.7$ *c* 0.011, CH_3OH). ^{1}H NMR (500 MHz, CD_3Cl) δ (ppm): 0.91 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 2.45–2.54 (m, 1H), 3.19 (br, 1H, OH), 5.26 (d, *J* = 14.6 Hz, 1H), 5.42 (d, *J* = 14.7 Hz, 1H), 5.50 (d, *J* = 5.8 Hz, 1H), 6.84 (s, 1H), 6.93 (dd, *J* = 7.4 and 7.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 7.8 and 7.4 Hz, 2H), 7.27–7.33 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.41 (dd, *J* = 7.2 and 7.5 Hz, 2H), 7.5 (s, 1H), 7.54–7.58 (m, 2H), 7.61 (s, 1H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.80–7.88 (m, 3H), 9.20 (s, 1H). ^{13}C NMR δ (ppm): 20.0, 22.2, 29.8, 72.7, 81.2, 118.9, 120.7, 121.5, 124.2, 124.6, 125.0, 125.0, 127.2, 127.3, 127.4, 128.1, 128.3, 128.7, 129.2, 130.2, 133.4, 133.6, 136.9, 143.4, 143.7. IR (KBr): 3512, 3149, 3066, 2972, 1551, 1446, 1346, 1187, 1128, 1051, 740, 704, 611, 599, 569 cm^{-1}. MS (ESI$^+$, *m*/*z*): 447.4 [M$^+$, 100%], (ESI$^-$, *m*/*z*): 280.2 [NTf_2^-, 100%]. Anal. Calcd (%) for $C_{33}H_{31}F_6N_3O_5S_2$ C, 54.46; H, 4.29; N, 5.77. Found: C, 54.95, H, 4.56; N, 5.75.

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