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A remarkable chiral recognition of racemic mosher's acid salt by naturally derived chiral ionic liquids using ¹⁹F NMR

Received 00th January 20xx, Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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A new class of D-xylose derived imidazolium-based chiral ionic liquids were designed and synthesized by simple tuning approaches. The developed chiral ionic liquids were tested for their chiral recognition property using racemic Mosher's acid salt by ¹⁹F NMR.For the first time, we demonstrate the excellent enantioselective discrimination of racemic salt using very less equivalents of cabohydrate derived chiral ionic liquids. Determined the enantiomeric excess values of non-racemic mixtures of Mosher's acid salt by ¹⁹F NMR.

In modern organic chemistry, ionic liquids (ILs) showed significant applications due to their outstanding physical, chemical properties and they also displayed considerable effect on reaction kinetics, specificity, recyclability and catalyst recovery.¹ Among the variety of ILs reported, chiral ionic liquids(CILs) are of special interest, because of their ability to influence the stereo chemical outcome of the reaction by acting as either chiral solvent or chiral catalyst.² CILs have showed good applications in asymmetric synthesis,³ chromatography⁴ and stereoselective polymerization.⁵ Based on the available literature, majority of the CILs were derived from natural amino acids, because they provide the essential source for chirality.⁶ Some of the CILs known for their chiral recognition ability and they were used as NMR chiral shift reagents for the discrimination of racemates.⁷ Malhotra and co-workers were synthesized bis(ammonium) based CILs derived from isomannide that showed good chiral recognition of racemic Mosher's acid salt.⁸

The major class of naturally occurring organic molecules in nature are carbohydrates and are produced from various biorenewable sources. Although numerous reports are available on the application of carbohydrate derivatives in achiral/chiral synthesis, the reports on carbohydrate derived chiral ionic liquids (CCILs) are very less in number.⁹ Recently, we reported the synthesis of D-ribose and D-galactose based CILs and their







Scheme 1:Chiral Recognition of Racemic Mosher's Acid Salt using D-xylose Derived CILs

application in Michael addition reaction, where they were used as recyclable chiral solvents as well as chiral catalysts.¹⁰ Further the hydrophobic D-galactose based IL was utilized for the effective removal of Pb²⁺ ions from aqueous solution.¹¹ In continuation of our effort to synthesize some of the CCILs and to study their applications in asymmetric transformations, herein we report the synthesis of new imidazolium containing D-xylose derived CILs. The synthesized CCILs were studied for their chiral recognition property using racemic Mosher's acid salt (Scheme 1).

The synthetic route for the CCILs presented in this work is a straightforward protocol starting from naturally originated D-xylose which is cheap and readily available (Scheme 2). The synthesis of D-xylose based CIL began with acid catalyzed protection of D-xylose **1** in dry acetone, followed by selective deprotection using 0.1N HCl solution at room temperature, which resulted (3aS,5S,6R,6aS)-5-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol **3.**¹²

room temperature.

Figure 1: Partial ¹⁹F NMR (376.5 MHz) spectra of CCIL 7 and racemic Mosher's acid salt

complex. Splitting pattern of CF3 signal. (a) 2 equiv. of CCIL 7; (b) 4 equiv. of CCIL 7; (c) 6 equiv. of CCIL 7.

After the successful synthesis of the target CCILs (7- 11, Scheme 2), the chiral discrimination ability was evaluated by studying the diastereomeric interaction between CCIL 7 (10 mg, 0.027 mmol) and racemic Mosher's acid silver salt (4.6 mg, 0.013 mmol) in CD₃CN (0.6 mL). The mixture was analyzed, using ¹⁹F NMR. Clear splitting of CF₃ signal was observed (Figure 1 (a)), which indicating its excellent chiral discrimination property on racemic Mosher's acid salt.¹⁵

Table 2: $\Delta\delta$ Values of CF₃ Signals of Racemic Mosher's acid silver salt in the presence of varied concentrations of CCIL 7.

Entry	CCIL 7 (Equiv.)	Racemic Mosher's Silver salt (Equiv.)	Chemical Shift difference $(\Delta \delta)^{R/S}$ in ppm ^[a]
1	1	1	0.017
2	2	1	0.062
3	4	1	0.074
4	6	1	0.075
-1	10		

^[a]Recorded by ¹⁹F NMR at 376.5 MHz

Broad peaks of CF3 signals were observed when the experiments were performed using the remaining CCILs (8, 9, 10 and 11) at similar condition. In order to get clear splitting, each CCIL was mixed with racemic salt in dry acetonitrile, stirred for 10 min at room temperature, filtered and the filtrate was distilled. The residual compound was dissolved in

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OCH₃ OCH₃ (iv-a) (v)осн (iv-b) 5 OCH₃ OCH₃ OCH₃ OCH 9 X= Tf_N ĊΗ₃ ĊΗ 10 X= OTf 11 X= BF

Scheme 2: Route of Synthesis for D-xylose Derived CCILs

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Reagents and conditions: (i) CuSO₄, H₂SO₄, Me₂CO, 24 h, rt (85%); (ii) HCl, H₂O, 3 h, rt (95%); (iii)p-TsCl, dry DCM, N-methyl imidazole, TEA, reflux (91%); (iv-a) TFA, MeOH, reflux, 10 h (93%); (iv-b) K2CO3, MeOH, 3 h, rt; (v) Imidazole, Cs2CO3, DMF, 120 °C, overnight (90%); (vi) CH₂I, rt, 6 h (91%); LiX, H₂O, 24 h, rt (8-72%, 9-82%, 10-76%, 11-62%)

Table 1: Δδ Values of CF₃ Signals of Racemic Mosher's acid Silver Salt in the Presence of 2 equiv. of CCILs (7-11)

Entry	CCIL	CCIL Anion	Solvent	Chemical Shift difference $\left(\Delta\delta\right)^{\text{R/S}}$ in ppm $^{[a]}$	
1	7	[1]	CD₃CN	0.062	
2	8	$[PF_6]$	CDCl ₃	0.031	
3	9	$[Tf_2N]$	CDCl ₃	0.045	
4 ^[b]	10	[OTf]	CDCl ₃	NS	
5	11	[BF ₄]	CDCl₃	0.047	
^[a] Recorded by ¹⁹ E NMR at 376 5 MHz ^{, [b]} NS [,] No splitting for CE ₂ signal					

Then compound 3 was converted to ditosylated compound ((3aS,5S,6R,6aS)-2,2-dimethyl-5-

((tosyloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl 4methylbenzenesulfonate) 4 using *p*-TSCl and Nmethylimidazole. The oxirane derivative of D-xylose ((1R, 2R, 5R)-2-(dimethoxymethyl)-3, 6-dioxabicyclo [3.1.0] hexane) 5 was synthesized from compound 4 by acid promoted ring transposition followed by treating with potassium carbonate in methanol at room temperature.13 The epoxide ring of compound 5 was opened by nucleophilic attack of imidazole in the presence of Cs₂CO₃ at 120 °C to produce (2R, 3R, 4S)-2-(dimethoxymethyl)-4-(1H-imidazol-1-yl) tetrahydrofuran-3-ol 6. Finally compound 6 was quarternized using methyl iodide at room temperature, affording target CCIL 7 (1-((3S,4R,5R)-5-(dimethoxymethyl)-4-hydroxytetrahydrofuran-3-yl)-3-methyl-1H-imidazol-3-ium iodide)¹⁴ in good overall yield (56%) starting from D-xylose. Furthermore, the iodo anion of compound 7 was exchanged with different fluorine containing anions by simple anion metathesis in aqueous medium with very good C Advances Accepted Mar

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CDCl₃ and ¹⁹F NMR was recorded. CClLs **8**, **9** and **11** have shown very good splitting for CF₃ signal of racemic Mosher's acid salt, while in case of CClL **10** no splitting was observed. The results are summarized in table- **1.** Among all, CClL **7** have shown excellent optical resolution property using less equivalents (2 equiv.) in CD₃CN itself. Next, we analyzed the splitting pattern of racemic Mosher's acid salt using CClL **7** by ¹H and ¹³C NMR. In case of ¹H NMR, only broad peak (OMe of Mosher's acid salt) was observed and no clear splitting was noticed by ¹³C NMR.



Figure 2: Effect of concentration of CCIL 7 on s signal splitting of racemic Mosher's acid salt.



Figure 3: Determination of ee values of non-racemic Mosher's acid salt by ¹⁹F NMR. (*R/S*)= 1:2 (a); 1:4 (b) approximately.

Further, CCIL **7** was employed in varied concentrations with respect to racemic salt and the details are summarized in table 2.¹⁶ From the table 2, it is evident that 2 equiv. (0.0450 mol/L) of CCIL was sufficient enough for clear separation of racemic mixture and almost saturation point was reached while using 4, 6 equiv. of CCIL **7** (Table 2 and Figure 1). The concentration effect of CCIL **7** on the magnitude of CF₃ signal splitting is represented in figure 2. The highest splitting for CF₃ signal of racemic Mosher's acid salt using CCILs have been rarely reported in

the literature (except Malhotra and coworkers in 2007).

Since, CCIL **7** have shown an excellent chiral discrimination property, used for the determination of enantiomeric excess values of non-racemic Mosher's acid salt mixtures. Two different ratio of non-racemic mixtures were prepared by adding (*S*)-Mosher's acid salt to racemic Mosher's acid salt ((*R*/*S*) = 1:2 and 1:4 approximately). The ee value can be determined from integration of CF₃ signal by ¹⁹F NMR (Figure 3).

In conclusion, new D-xylose derived CILs have been synthesized by simple modifications starting from D-xylose with good overall yields. Studied their chiral recognition property using racemic and non-racemic Mosher's acid silver salts, excellent discrimination was observed with very less quantities of CCILs. The high resolution property of the CCILs for racemic salt indicates their potential application as NMR chiral shift reagents for various racemic carboxylic acids. Further applications of these CCILs as chiral solvent and chiral catalyst for various asymmetric transformations are being underway in our laboratory.

Acknowledgements

Funding from DST/SR/FT/CS-93/2011 (FAST-TRACK-SCHEME), Govt. of India is gratefully acknowledged. We thank the DST-FIST and VIT-SIF for providing FT-NMR facilities. We would like to extend our sincerest thanks to Dr. V. Jayathirtha Rao (Head & Chief scientist, CFC-division) and Mr. M. Sasi kumar, CSIR-IICT-Hyderabad for their support.

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- 14 1-((3S, 4R, 5R)-5-(dimethoxymethyl)-4hydroxytetrahydrofuran-3-yl)-3-methyl-1H-imidazol-3-ium iodide (7):To a stirred solution of compound 6 (641 mg, 2.808 mmol) in dry acetonitrile (2 mL), charged methyl iodide (598 mg/ 0.26 mL, 4.212 mmol). Stirred the reaction mass at room temperature for 6 h. Upon completion of the reaction, removed the solvent by vacuum distillation. The

crude compound was dissolved in 50% methanol/chloroform and passed through neutral alumina, afforded colorless liquid compound **7** in 91% yield.

Yield: 90%, Light brown colour liquid; $[\alpha]_{D}^{25} = +88.8 (c 1, MeOH);^{1}$ H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.72 (t, *J* = 2.0 Hz, 1H), 7.17 (t, *J* = 2.0 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 4.61 (d, *J* = 4.8 Hz, 1H), 4.51 (d, *J* = 3.6 Hz, 1H), 4.30 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.20 (d, *J* = 11.2 Hz, 1H), 4.00 (s, 3H), 3.98 (dd, *J* = 4.8, 3.2 Hz, 1H), 3.46 (s, 3H), 3.44 (s, 3H); ¹³C NMR (100 MHz, Chloroform-*d*) δ 137.50, 122.69, 121.37, 103.66, 85.67, 78.69, 70.92, 68.34, 55.99, 55.55, 36.91; HRMS (ESI) exact calculated mass for [M+] (C₁₁H₁₉O₄N₂)requires *m/z* 243.1339, found *m/z* 243.1336; LR-MS (ESI) ES⁺: 243.2, ES⁻: 126.9.

- 15 The racemic Mosher's acid silver salt (4.6 mg, 0.013 mmol) was mixed with CCIL 7 (10 mg, 0.027 mmol) in 0.6 mL of CD₃CN and stirred for 10 min at room temperature to exchange anions. The formed Agl precipitate was filtered and filtrate was analyzed by ¹⁹F NMR (376.5 MHz). For CCILs 8-11, the racemic salt (1 equiv.) was mixed with each CIL (10 mg, 2equiv.) separately in dry ACN and stirred for 10 min. Filtered the formed salts and concentrated the filtrate under reduced pressure using rotary evaporator. The residual compound was dissolved in CDCl₃ and analyzed by ¹⁹F NMR.
- 16 Effect of CCIL 7 concentration: In another set of experiment, each time different concentrations of CCIL 7 (1 eq, 4 eq, and 6 eq) was mixed with racemic salt and studied the effect of concentration of CCIL 7 for chiral discrimination by ¹⁹F NMR.

DOI: 10.1039/C6RA02792J

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A remarkable chiral recognition of racemic mosher's acid salt by naturally derived chiral ionic liquids using ¹⁹F NMR

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