

Electronic Supporting Information

Hydrophobic vs. Hydrophilic Ionic Liquid Separations Strategies in Support of Continuous Pharmaceutical Manufacturing

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Structure of aliskiren

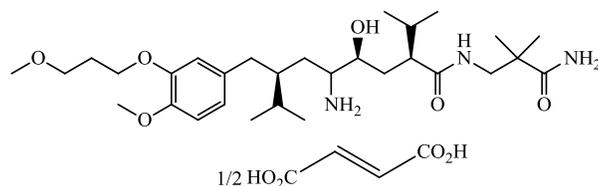


Fig. S1. Structure of aliskiren.

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Crystal structure of **4**

The asymmetric unit of the crystal structure of **4** is shown in Fig. S2. The chiral center alpha to the carboxylate group of 2-ethylhexanoate, C8, shows seemingly trigonal planar geometry. This is probably due to the molecule interconverting between its R and S forms through keto-enol tautomerization, causing the peak for C8 to show up in its average position. Despite the inappropriate geometry a disordered hydrogen atom was placed on C8 to give the crystal structure the correct formula. This assignment is supported by the C-C and C-O bond distances, which show no sign of an enolate anion or any reason for true sp^2 hybridization of C8.

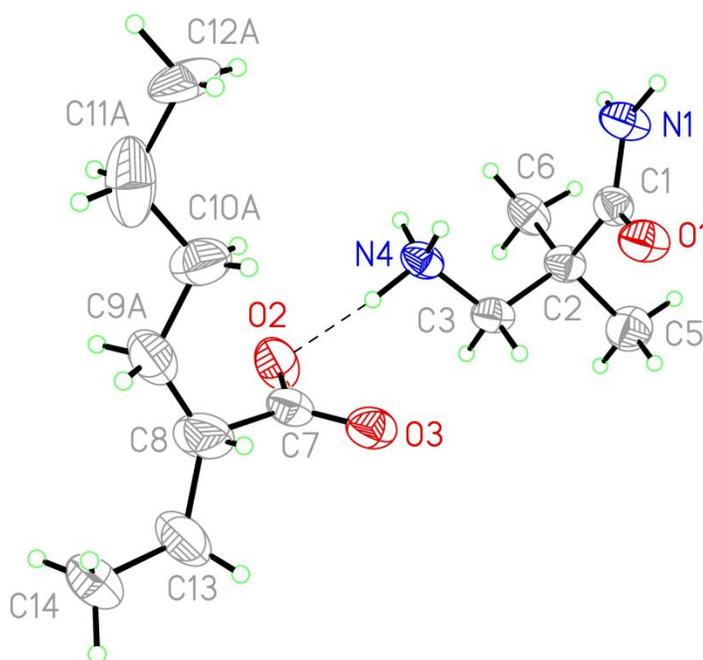


Fig. S2. 50% probability ellipsoid diagram of asymmetric unit of **4** (disorder omitted).

Miscibility and solubility of organic solvents, H₂O in the two ionic liquids

Miscibility and solubility of organic solvents, H₂O in [C₂mim][OAc] and [C₂mim][NTf₂] are summarized in Table S1.

Table S1. Miscibility and solubility of organic solvents, H₂O in [C₂mim][OAc] and [C₂mim][NTf₂].

Solvent	[C ₂ mim][OAc]		[C ₂ mim][NTf ₂]	
	Totally miscible or not	Solubility in IL (mol/mol IL)	Totally miscible or not	Solubility in IL (mol/mol IL)
H ₂ O	√	-	×	0.45
EtOH	√	-	√	-
MeOH	√	-	√	-
Acetone	√	-	√	-
EtOAc	×	0.18	√	-
CHCl ₃	√	-	×	3.5
<i>n</i> -Heptane	×	0.01	×	0.02
Cyclohexane	×	0.01	×	0.02
Toluene	×	0.21	×	1.85
Tetrahydrofuran	×	0.78	√	-
CH ₃ CN	√	-	√	-

Separation of standard mixture using [C₂mim][NTf₂]/H₂O or [C₂mim][OAc]/EtOAc

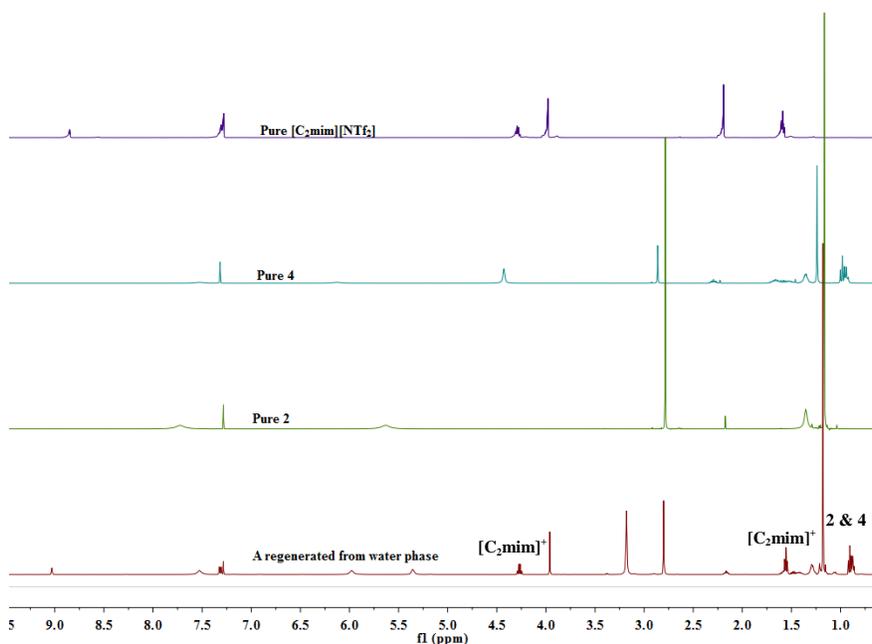


Fig. S3. ¹H NMR spectra of A (see Fig. 1) regenerated from the standard mixture using [C₂mim][NTf₂]/H₂O, pure **2**, **4**, and [C₂mim][NTf₂] in CDCl₃.

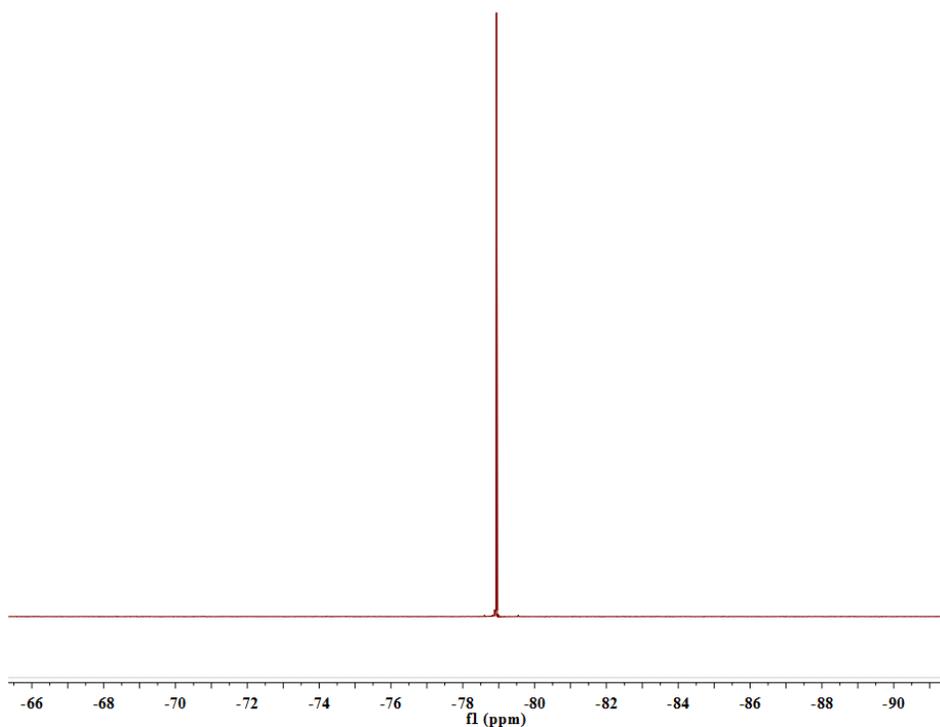


Fig. S4. ¹⁹F NMR spectrum of A (see Fig. 1) regenerated from the standard mixture using [C₂mim][NTf₂]/H₂O in CDCl₃.

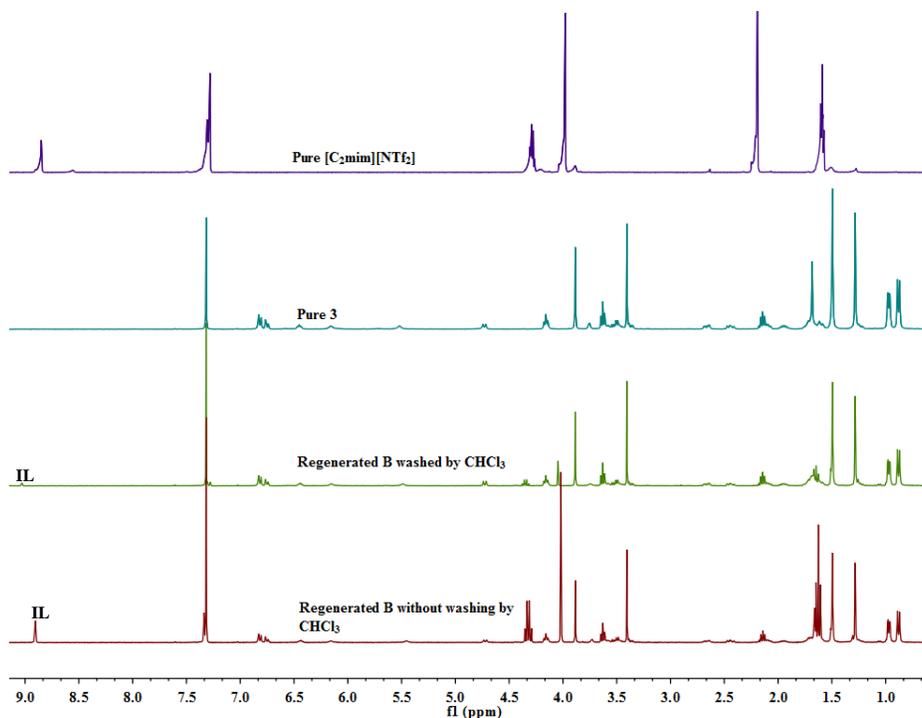


Fig. S5. ¹H NMR spectra of B (see Fig. 1) regenerated from the standard mixture using [C₂mim][NTf₂]/H₂O, pure **3**, and [C₂mim][NTf₂] in CDCl₃.

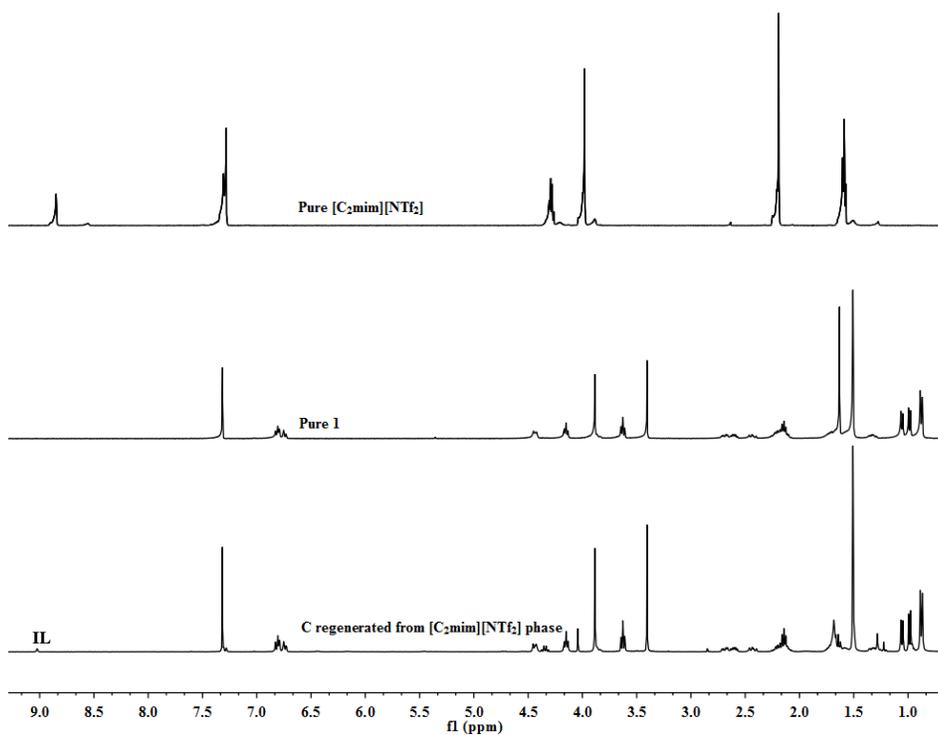


Fig. S6. ¹H NMR spectra of C (see Fig. 1) regenerated from the standard mixture using [C₂mim][NTf₂]/H₂O, pure **1**, and [C₂mim][NTf₂] in CDCl₃.

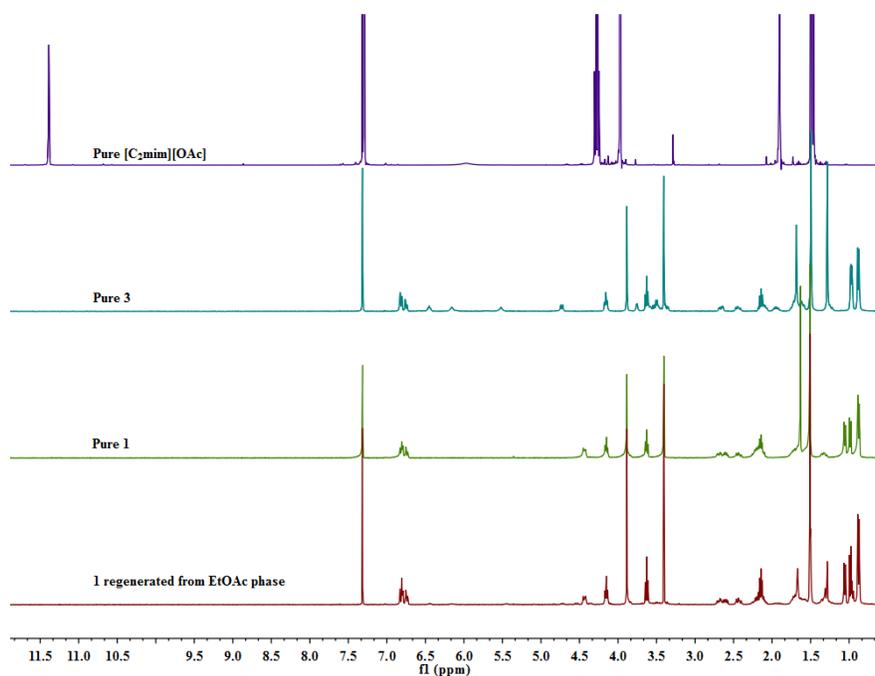


Fig. S7. ¹H NMR spectra of **1** regenerated from the standard mixture by [C₂mim][OAc]/EtOAc, pure **1**, **3**, and [C₂mim][OAc] in CDCl₃.

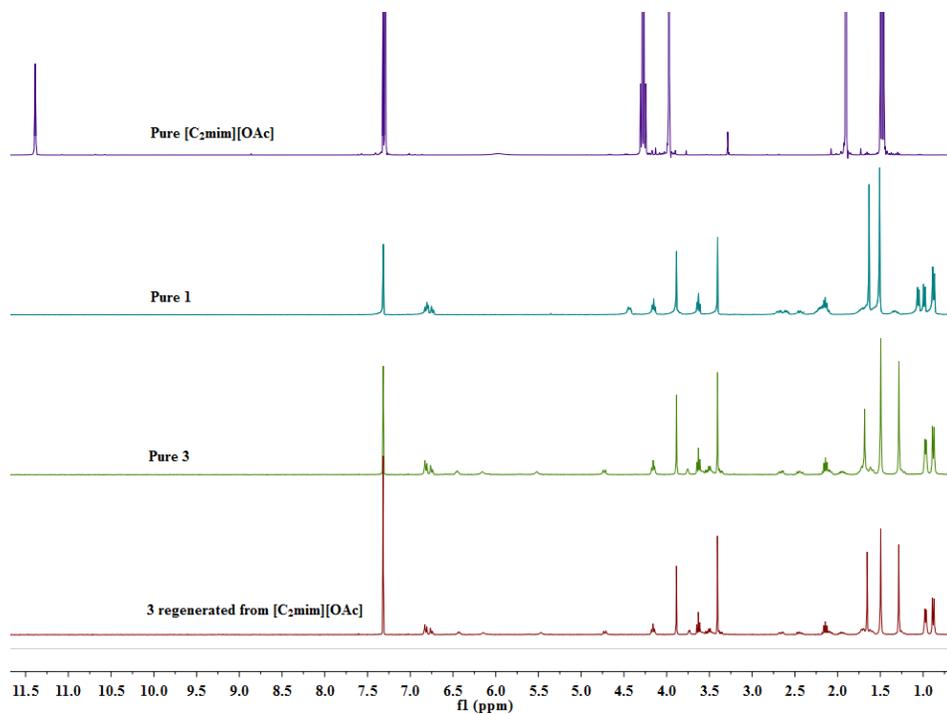


Fig. S8. ¹H NMR spectra of **3** regenerated from the standard mixture by [C₂mim][OAc]/EtOAc, and pure **1**, **3**, and [C₂mim][OAc] in CDCl₃.

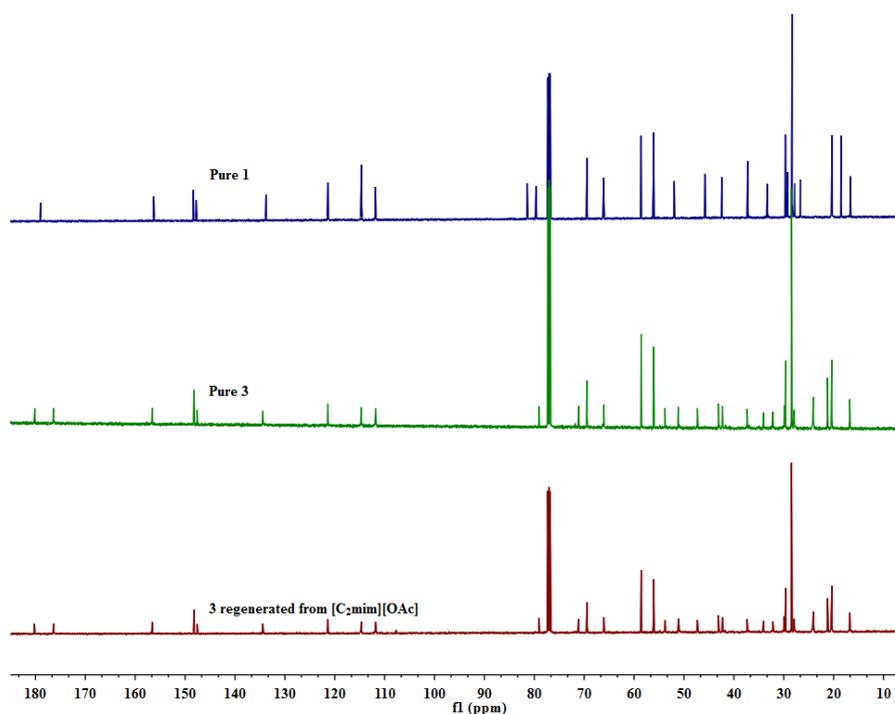


Fig. S9. ^{13}C NMR spectra of **3** regenerated from the standard mixture by $[\text{C}_2\text{mim}][\text{OAc}]/\text{EtOAc}$, pure **1**, and **3** in CDCl_3 .

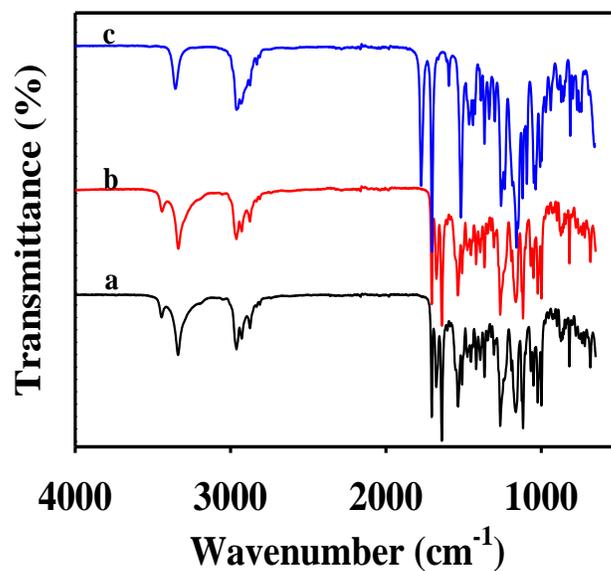


Fig. S10. FT-IR spectra of **3** regenerated from the standard mixture by $[\text{C}_2\text{mim}][\text{OAc}]/\text{EtOAc}$ (a), pure **3** (b), and **1** (c).

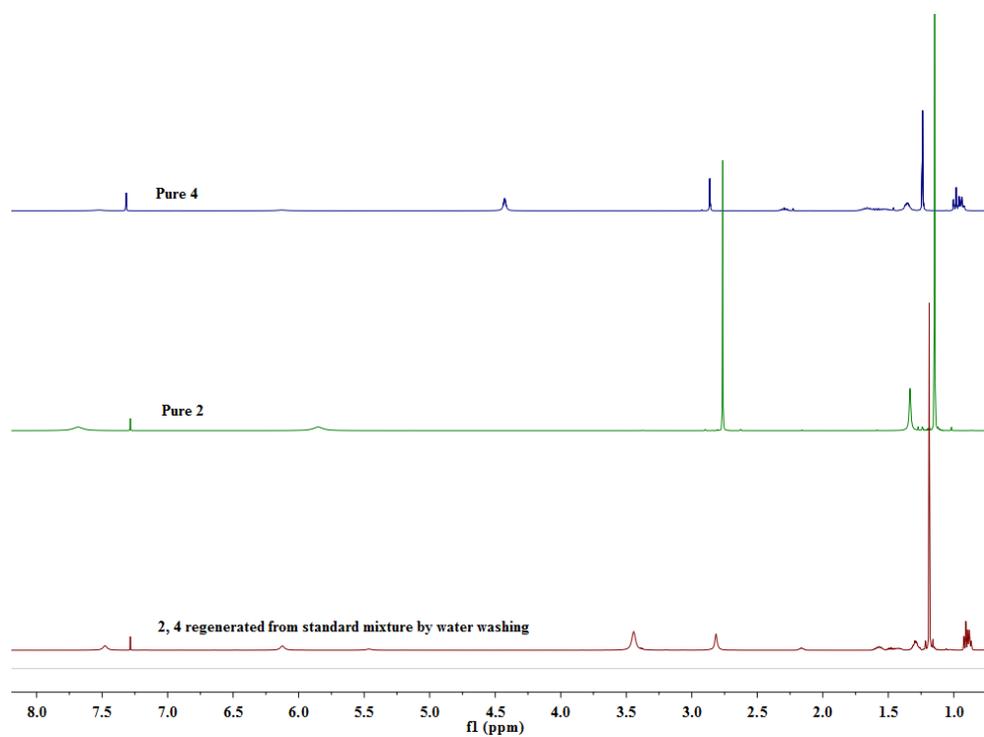


Fig. S11. ¹H NMR spectra of **2** and **4** regenerated from the standard mixture by washing with water, pure **2**, **4** in CDCl₃.

Separation of the reaction mixture using [C₂mim][OAc]/EtOAc

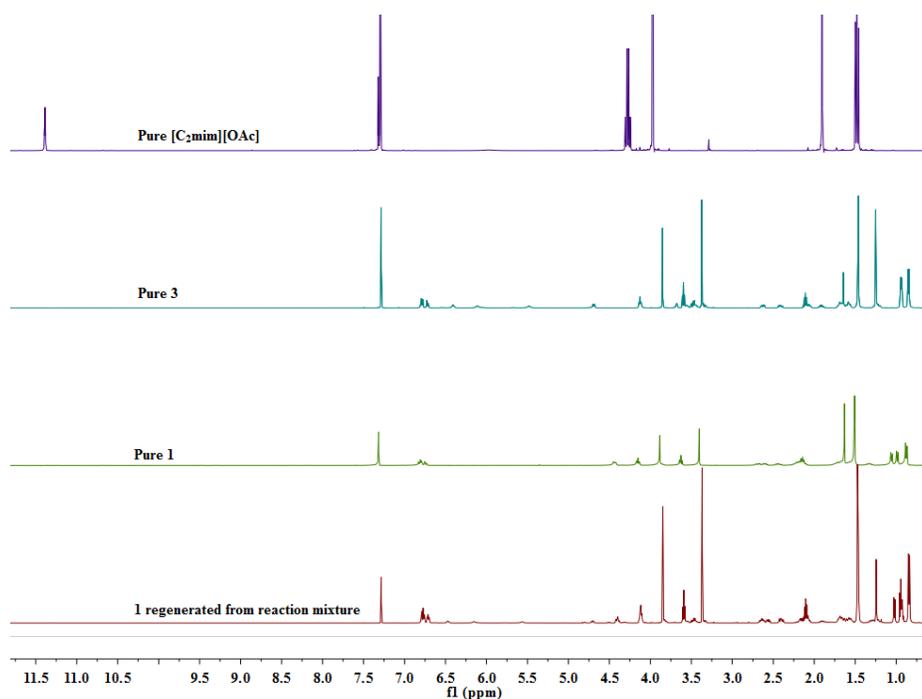


Fig. S12. ¹H NMR spectra of **1** regenerated from the reaction mixture by [C₂mim][OAc]/EtOAc, and pure **1**, **3**, and [C₂mim][OAc] in CDCl₃.

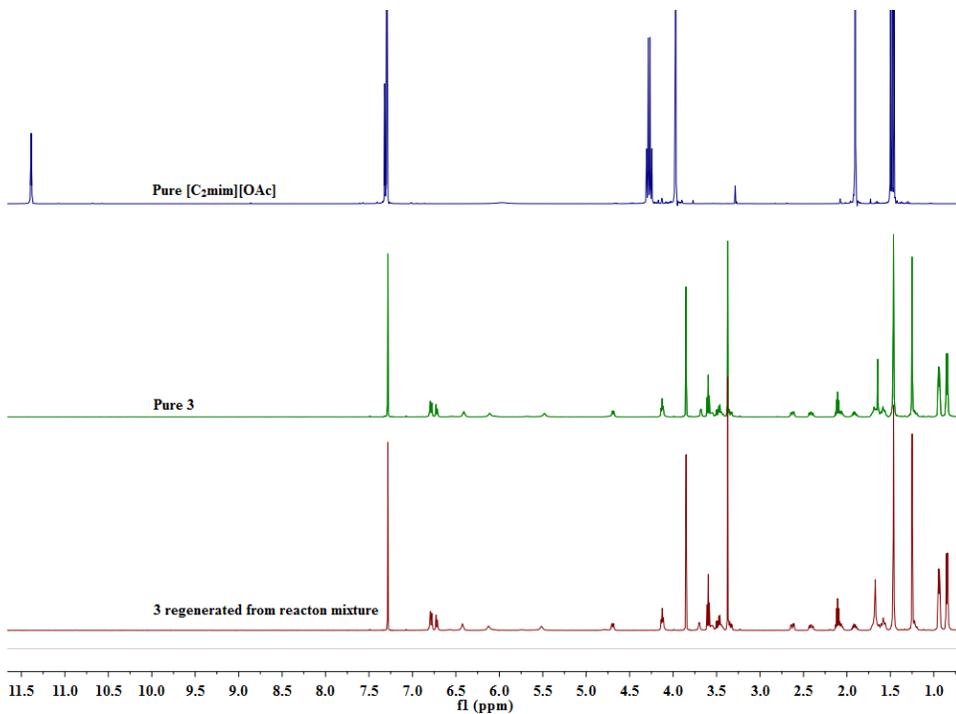


Fig. S13. ¹H NMR spectra of **3** separated from the reaction mixture with [C₂mim][OAc]/EtOAc (further washed by *n*-heptane), and pure **3**, [C₂mim][OAc] in CDCl₃.

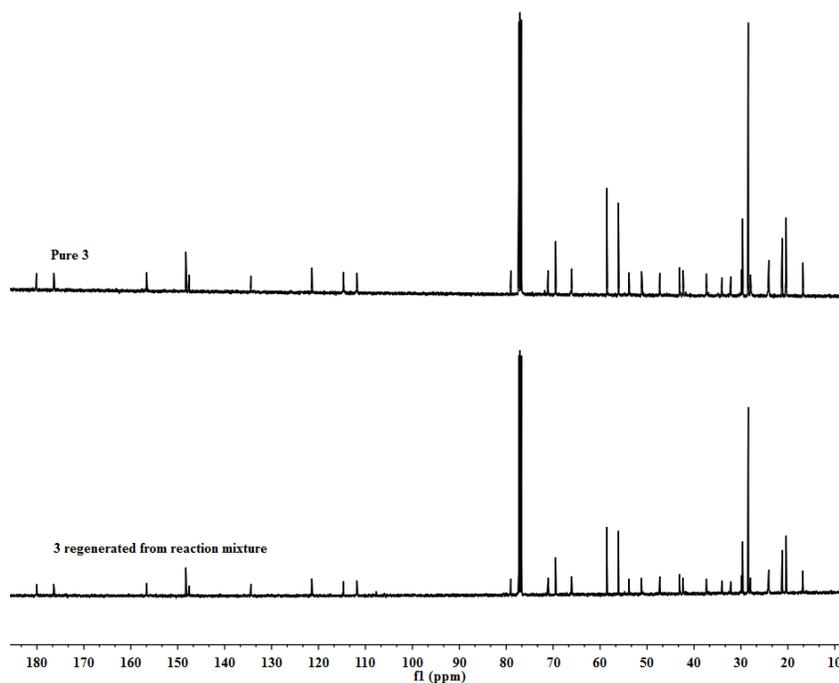


Fig. S14. ^{13}C NMR spectra of **3** regenerated from the reaction mixture by $[\text{C}_2\text{mim}][\text{OAc}]/\text{EtOAc}$ (further washed by *n*-heptane), and pure **3** in CDCl_3 .

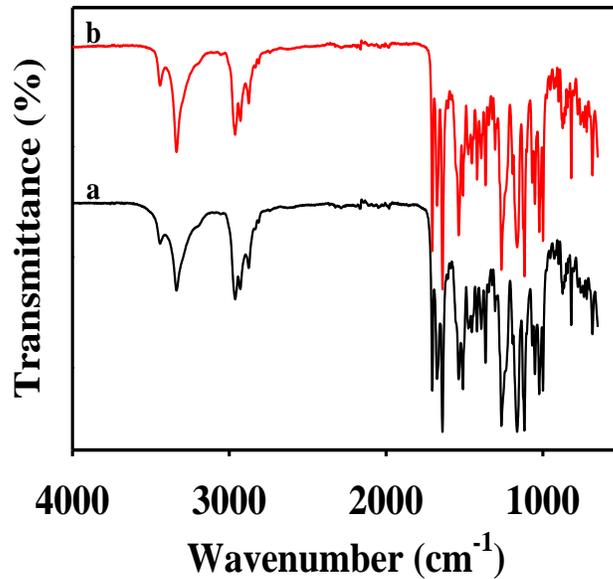


Fig. S15. FT-IR spectrum of **3** regenerated from the reaction mixture (a) and that of pure **3** (b).

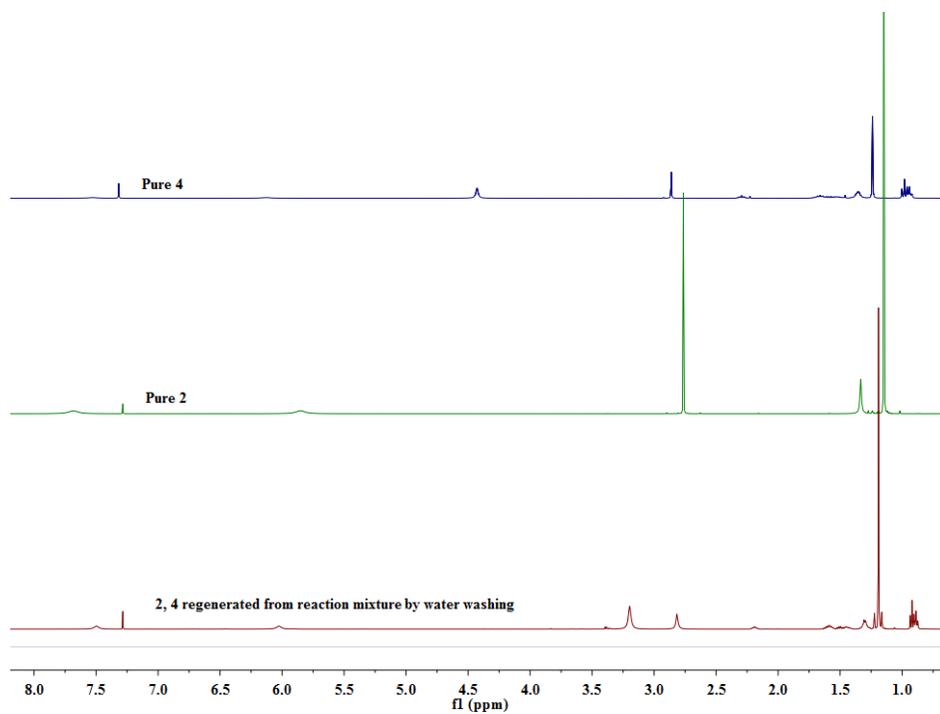


Fig. S16. ^1H NMR spectra of **2** and **4** regenerated from the reaction mixture by water washing, pure **2**, **4** in CDCl_3 .