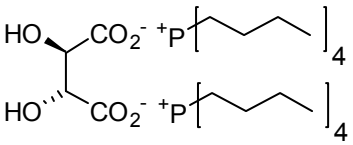
Electronic supplementary information

Purification of [PBu_4][OH] and synthesis of [PBu_4]$_2$[(*R,R*)-Trtr]:

During the study of the partition of previously prepared [PBu_4]-[(*R,R*)-Trtr] in water/CH_2Cl_2 and in water/$CHCl_3$ biphasic mixtures it was found that from 15 to 20 wt% of ionic liquid distributes to organic phase, and this distribution happens only during the first extraction, when all following extractions are not able to extract anymore. ^{1}H NMR study of the extracted compound showed the presence of tetrabutylphosphonium cation but without tartaric acid. It was proposed that extracted compound represents the residual tetrabutylphosphonium chloride or bromide, which was used in the preparation of commercial [PBu_4][OH]. Indeed, it was proven by the Beilstein test, which was positive for extracted compound, for starting IL and for tetrabutylphosphonium hydroxide, but negative for the extracted water solution of IL (extracted 4 times with CH_2Cl_2 or $CHCl_3$ and dried under reduced pressure to eliminate traces of organic solvents).
Finally, commercial [PBu_4][OH] was purified from residual [PBu_4][Cl] by multiple extractions with CH_2Cl_2 and drying under reduced pressure. To determine the exact concentration of [PBu_4][OH], it was titrated with 1M HCl to define the concentration and verified with the Beilstein test to confirm the absence of halogens.
To (*R,R*) tartaric acid was added the appropriate volume of [PBu_4][OH] aqueous solution. The resulting mixture was stirred for 15 minutes, evaporated to dryness under reduced pressure and dried under the vacuum line.

Tetrabutylphosphonium (2*R*,3*R*)-tartrate; [PBu_4]$_2$-[(*R,R*)-Trtr]:



$C_{36}H_{76}O_6P_2$
M = 666.93 g.mol^{-1}
White wax
Yield: overall 100%.
DSC = -62.1°C (glass transition).
[α] $_D^{20}$ = +7.7 (c 1, H_2O).
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.03 (t, 24 H, J=7.2 Hz); 1.50-1.71 (m, 32 H); 2.20-2.35 (m, 16H); 4.41 (s, 2H).
^{13}C NMR (75.48 MHz, D_2O), ppm: 12.5 (s); 17.6 (d, J= 48.5 Hz); 22.7 (d, J= 4.5 Hz); 23.3 (d, J= 15.2 Hz), 72.83 (s); 178.40 (s).
^{31}P NMR (121.49 MHz, D_2O), ppm: 33.24 (s).
Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.
IR (CaF_2, cm^{-1}): 3351, 2959, 1609, 1350.
Water content (Karl Fisher): 13.9%.
Traces Cl: 968 ppm.
Elemental Analysis, Calculated for $C_{36}H_{76}O_6P_2 \cdot 6H_2O$: C, 55.79; H, 11.14. Found: C, 56.20; H, 11.31.

ILICM general procedure:

To the IL [bmim][NTf_2] or [omim][NTf_2] (15 equiv.) was added bis-(tetrabutylphosphonium)-(*R,R*)-tartrate (1 equiv.) and water (33 equiv.). The resulting mixture was stirred overnight, decanted. After separation of the aqueous phase, water was evaporated and the resulting material was dried under vacuum line.

[bmim]$_2$-[(*R,R*)-Trtr]:
100%, $C_{20}H_{34}N_4O_6$, M = 426.50 g.mol^{-1}, light yellow oil. DSC = -58°C (glass transition with relaxation). $[\alpha]_D^{20}$ = +11.7 (c 1, H_2O). **^{1}H NMR** (300.18 MHz, D_2O): 0.72 (t, 6H, J=7.4 Hz); 1.13 (m, 4H); 1.67 (m, 4H); 3.71 (s, 6H); 4.03 (t, 2H, J=7.1 Hz); 4.14 (s, 2H); 7.24 (m, 2H); 7.30 (m, 2H); 8.53 (s, 2H). **^{13}C NMR** (75.48 MHz, D_2O): 12.6; 18.7; 31.2; 35.5; 49.2; 73.8; 122.1; 123.4; 178.4. **^{31}P NMR** (121.49 MHz, D_2O): no signal detected. **MS** IS- (H_2O/MeOH): 280, 212, 149. IS+ (H_2O/MeOH): 139. **Water content** (freshly dried sample, Karl Fischer): <2%. **Anal** calc for $C_{20}H_{34}N_4O_6$, $3H_2O$: C: 49.99; H: 8.39; N: 11.66; found: C: 49.71; H: 8.52; N: 11.67.

[omim]$_2$-[(*R,R*)-Trtr]:
100%, $C_{28}H_{50}N_4O_6$, M = 538.72 g.mol^{-1}, light yellow oil. **DSC** = -43°C (glass transition with relaxation). $[\alpha]_D^{20}$ = +7.5 (c 1, H_2O). **^{1}H NMR** (300.18 MHz, D_2O): 0.85 (t, 6H, J=6.9 Hz); 1.27 (m, 20H); 1.86 (m, 4H); 3.88 (s, 6H); 4.18 (t, 2H, J=7.0 Hz); 4.31 (s, 2H); 7.41 (t, 1H, J=1.7 Hz); 7.46 (t, 1H, J=1.7 Hz); 8.69 (s, 1H). **^{13}C NMR** (75.48 MHz, D_2O): 13.4; 21.9; 25.2; 28.0; 28.1; 29.1; 30.9; 35.5; 49.5; 73.8; 122.1; 123.4; 178.4. **^{31}P NMR** (121.49 MHz, D_2O): no signal detected. **MS** IS+ (H_2O/MeOH)**:** 195. **Water content** (freshly dried sample, Karl Fischer): <2%. **Anal** calc for $C_{28}H_{50}N_4O_6$, $3H_2O$: C: 56.73; H: 9.52; N: 9.45; found: C: 56.46; H: 9.27; N: 9.36.

(*R,S*)-*N*-(2,6-dimethylphenyl)piperidinium-2-carboxamide bis-(trifluoromethylsulfonyl)imide [HPip][NTf_2]:
(*R,S*)-Pipecoloxylidide (1 equiv.) was dissolved in acetonitrile and bis-(trifluoromethylsulfonyl)imide (1 equiv.) was added. The resulting solution was stirred for 30 min., then concentrated to dryness and the resulting material dried under vacuum line.
100%, $C_{16}H_{21}F_6N_3O_5S_2$, white solid, mp = 204°C. **^{1}H NMR** (300.18 MHz, MeOD): 3.02 (m, 3H); 3.55 (s, 6H); 3.61 (m, 1H); 4.39 (m, 1H); 4.80 (m, 1H); 5.38 (m, 1H); 8.33 (broad s, 1H); 8.51 (m, 3H); 9.51 (s, 1H). **^{13}C NMR** (75.48 MHz, MeOD): 16.9; 21.5; 21.8; 27.7; 43.6; 57.8; 113.7-126.1 (q, 2C, J=319 Hz); 127.5; 127.9; 132.9; 135.3; 167.5. **^{19}F NMR** (282.37 MHz, MeOD): -79.51. **MS** CI+ (NH_3): 233. CI- (NH_3): 280. **Anal** calc C: 37.43; H: 4.12; N: 8.18; found: C: 37.33; H: 3.80; N: 8.08.

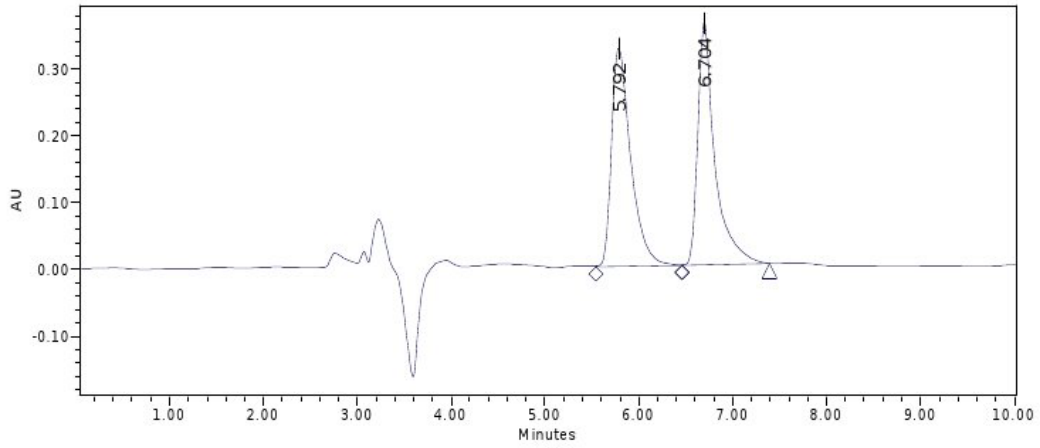
***EWILE* procedure:**

The biphasic chiral extraction system was established in 5 mL test tubes by adding [PBu_4]$_2$-[(*R,R*)-Trtr] (0.25 equiv., 66,7 mg) to [omim][NTf_2] (10 equiv., 951 mg). The IL phase was enriched by (*R,S*)-[HPip][NTf_2] (1 equiv., 208 mg) and the system was stirred for 2 hours at 50°C. After cooling the mixture, distilled water (20 equiv.) was added, and the biphasic system was stirred for 12 additional hours. The water layer was separated, concentrated to dryness and the residue obtained dried under vacuum line to give (*S*)-[HPip]$_2$-[Trtr]. To perform chiral HPLC analysis, 1 mg of dry extract was dissolved in the mixture of 0.5 mL *i*-PrOH/0.5 mL heptane/10 □L diethylamine. Analytical Chiral HPLC analyses were run with an Alliance Waters 2695 Separation module and UV Waters 2996 Photodiode array detector, Empower Software. Column Chiracel OJ-H (250mmx4.6mm), eluent heptane/diethylamine/*i*-PrOH =90/0.1/10, flow 1 mL/min, sample concentration 1 mg/mL, detection UV 230 nm.

Enantiomeric excess of 30% was determined (minor (*R*)-enantiomer: 5.75 min.; major (*S*)-enantiomer: 6.61 min.).

Influence of various parameters of *ELLE* process:

Model compound: (*R,S*)-pipecoloxylidide



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.792		326834	4660532	50.35	VV		
2	6.704		363252	4595745	49.65	Vb		

HPLC chromatogram of the racemic pipecoloxylidide

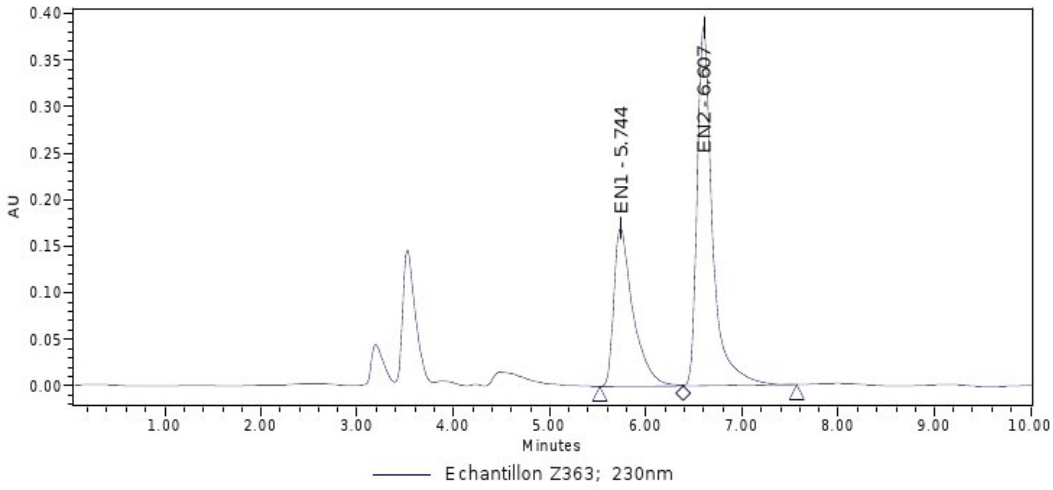
First parameter to check was the role of co-solvent IL. Two extractions were performed without [omim][NTf_2] between 1 equiv. of pipecoloxylidide and 0.5 equiv. of [PBu_4]$_2$-[(*R,R*)-Trtr]. Extraction media was stirred for 12 hours with 100 equivalents of water to yield zero % ee. To confirm the importance of co-solvent IL for *ELLE*, previous extractions were repeated without co-solvent IL and only with 0.25; 0.5; 0.75; 1 and 2 equiv. of [PBu_4]$_2$-[(*R,R*)-Trtr] (10 extractions in total). No ee was observed in all examples. This observation confirms the important role of co-solvent IL for the efficiency of *ELLE*. This can be explained by the increasing of stability of ion pair host/substrate by putting them into IL media and by lowering down the speed of exchange between ion pairs.

Anyways, cross-metathesis works perfectly leading tartaric acid to extract the pipecoloxylidide in the form of [HPip]$_2$-[(*R,R*)-Trtr]. Hemi-tartrate [PBu_4]-[(*R,R*)-Trtr] extracted pure [HPip]-[(*R,R*)-Trtr] when tartrate was added in the quantity up to 0.75 equivalents. Compound [PBu_4]$_2$-[(*R,R*)-Trtr] makes possible to extract pure [HPip]$_2$-[(*R,R*)-Trtr] only when its ratio does not exceed 0.25 equiv. When tetrabutylphosphonium tartrates were more concentrated that mentioned above ratios, tartrates with fractional stoichiometry were extracted.

Next parameter to check was to determine the minimal quantity of co-solvent IL [omim][NTf_2] when our extractions still produce enantiomeric excess. In 7 different tests, one equiv. of [HPip][NTf_2] was mixed with 0.25; 0.5; 0.75; 1; 2; 4 and 5 equiv. of [omim][NTf_2] respectively. After 3 hours of mixing, each solution was extracted by 20 equiv. of water.

In the range from 0.25 to 0.75 equiv. of [omim][NTf_2] no ee was observed. From 1 to 4 equiv. [omim][NTf_2] values of ee about 4% were observed. Only small improvement of 1% ee was observed when using 4 equiv. of [omim][NTf_2].

Also, in this series (*S,S*)-enantiomer of tartrate was used to check the possibility to invert the discrimination order of Pip. As it was expected, the inversion of preferentially extracted enantiomer was observed.
To eliminate the version of possible influence of [omim][NTf_2] on ee, the next experiment was done. Ionic liquid [omim][NTf_2] was changed to [b2,3mim][NTf_2] (1-Butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imide). The last one in amount of 5 equiv. was mixed with 1 equivalent of [HPip][NTf_2] and 0.25 equiv. of [PBu_4]$_2$-[(*R,R*)-Trtr] and mixed for 2 hours. After 12h of extraction with 20 equivalents of water 2% of ee was observed.
Another checked parameter was the effect of temperature. In 8 different tests, one equivalent of [HPip][NTf_2] was mixed with 5 equiv. of co-solvent IL [omim][NTf_2] and heated or cooled for 2 hours at 0; 30; 50; 80; 100; 125; 150 and 180°C respectively. Experiment performed at 0°C, was extracted at the same temperature. All others experiments were cooled to the room temperature and each solution extracted by 20 equiv. of water.
Obtained results were promising. Apparently, heating increases dramatically enantiomeric excess, reaching the maximum at 50°C. Further increasing of temperature slightly decreases ee. At 150°C reaction mixture starts to turn yellow and becomes completely black at 180°C due to degradation of CIL or substrate. At 0°C no ee was observed (see HPLC below).



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.744	EN1	170252	2360092	35.48	BV		
2	6.607	EN2	386522	4292619	64.52	VB		

The best example of ELLE showing ee = 30% after 2h at 50°C

To prove that observed effect of increasing ee with temperature is not related to deracemization of our racemic substrate in chiral medium the next experiment was performed. The mixture of 5 equiv. of [PBu_4]$_2$-[(*R,R*)-Trtr] was mixed with 1 equiv. of pipecoloxylidide and let to interact for 2 days at 50°C. No enantiomeric enrichment was observed.
To check the version of possible role of temperature on [PBu_4]$_2$-[(*R,R*)-Trtr], it was heated at 150°C for 2 hours with 5 equivalents of [omim]NTf_2, and after cooling to the RT, [HPip][NTf_2] and water were added. After 12h of extraction with 20 equivalents of water no ee was determined. This observation proves the importance of incubation time between tartrate CIL and [HPip][NTf_2].