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Tetrabutylammonium prolinate-based ionic liquids: a combined asymmetric catalysis, antimicrobial toxicity and biodegradation assessment

Nadège Ferlin,[a] Matthieu Courty,[b] Albert Nguyen Van Nhien,[c] Sylvain Gatard,[a] Milan Pour,[d] Brid Quilty,[e] Mukund Ghavre,[f] Annette Haiß,[g] Klaus Kümmerer,[g] Nicholas Gathergood*[f] and Sandrine Bouquillon*[a]

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Chiral ionic liquids (CILs) tetrabutylammonium-(*S*)-prolinate, tetrabutylammonium-(*R*)-prolinate and tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate were investigated as chiral additives in the Pd-catalyzed enantioselective hydrogenation of α,β-unsaturated ketones. These CILs were easily prepared in one step from the aminoacid and tetrabutylammonium hydroxide and characterized (NMR, IR, optical rotation, elemental analysis, DSC, viscosity, decomposition temperature). The research strategy was to assess the antimicrobial toxicity (>20 strains) and biodegradability (OECD 301D) of the CILs at the same time as undertaking the asymmetric catalysis study. The Pd-catalyzed enantioselective hydrogenation of the carbon–carbon double bond of α,β-unsaturated ketones under mild conditions (room temperature, 1 atm of H_2) in different solvents with CILs present. The best results were obtained in *i*-PrOH after 18 hours of reaction with a *i*-PrOH/IL ratio of 5. While all three CILs have low antimicrobial toxicity to a wide range of bacteria and fungi, tetrabutylammonium-(*S*)-prolinate, tetrabutylammonium-(*R*)-prolinate and tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate did not pass the Closed Bottle biodegradation test.

Introduction

Ionic liquids (ILs) consist of an organic cation associated with an anion that may be either organic or inorganic.[1] They are liquids below 100 °C, and many of them are liquids at room temperature (RTILs). The rising interest attracted by ILs in the last two decades is due to their properties: low vapor pressure,[2] high thermal stability and excellent solvation of a wide range of compounds.[3]

Consequently, ILs have been considered as an alternative to volatile solvents in catalytic applications,[4–7] biocatalysis,[8] synthetic chemistry,[9] electrochemistry,[10] analytical applications[11] or for separations and extractions.[12] A number of detailed reviews have expounded the advantages of using ionic liquids as new 'greener' solvent types.[9,13]

Whereas ILs show no toxicity in air because of their negligible vapour pressure and non-inflammability,[14] some are toxic in aqueous media because of their low solubility in water (attributed to high lipophilicity).[3,15] This problem has become a real challenge for IL development and a great number of publications are dealing with the IL toxicity (inc. antibacterial and antifungal),[16,17] Furthermore, toxicity studies involving the nature of the cation and the anion have already been performed on a large number of ILs and they showed that anions containing oxygenated chains and/or tetrabutylammonium cations are less toxic towards many strains.[3,18] However data about IL biodegradation[19] and their bioaccumulation[20] is still lacking for many of the ionic liquids prepared, in particular ammonium salts.

Although limited, some data is available about biodegradability of ammonium based ionic liquids.[21] When mono, di and tri(2-hydroxyethyl)ammonium lactate ionic liquids were tested for biodegradability using BOD method,[22] all were found to be readily biodegradable (60–95%).[23] Similarly, interesting results were obtained when NAILs (naphthenic acid ILs) were screened for biodegradation. Carboxylates of various cores were chosen as anions in ILs. Eight out of ten ILs were found to be 'readily biodegradable' (60–83%), when tested using Closed Bottle test.[24]

[a]*Institut de Chimie Moléculaire de Reims UMR CNRS 7312 – Université de Reims Champagne-Ardenne, Boîte no. 44, B.P. 1039, F-51687 Reims, France. E-mail: sandrine.bouquillon@univ-reims.fr; Fax: +33 3-26-91-31-66; Tel: +33 3-26-91-89-73*

[b]*Laboratoire de Réactivité et de Chimie des Solides UMR CNRS 7314, Université de Picardie Jules Verne, UFR des Sciences, 33 rue Saint Leu, 80039 Amiens Cedex 1, France*

[c]*Laboratoire des Glucides FRE 3517, Université de Picardie Jules Verne, UFR des Sciences, 33 rue Saint Leu, 80039 Amiens Cedex 1, France*

[d]*Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, CZ-500 03, Hradec Králové, Czech Republic*

[e]*School of Biotechnology and National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland*

[f]*School of Chemical Sciences and National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland. E-mail: nick.gathergood@dcu.ie; Fax: +353 170005503; Tel: +353 17007860*

[g]*Institute of Sustainable and Environmental Chemistry, Leuphana University Lüneburg, DE-21335 Lüneburg, Germany*

Pretti *et al.*[25] investigated the toxicity and biodegradation of cyclic ammonium based ILs. Both DABCO and morpholine based ILs containing bromide anion showed low biodegradability when measured by CO_2 headspace test. DABCO based ILs lied in the range of 5–30% whereas morpholinium ILs showed 22–40% biodegradation. Out of these results ethyl substituted ILs (for both DABCO and morpholinium) degraded better than decyl derivatives as expected. Abovementioned results were corroborated by the work of Pernak *et al.*,[26] where benzylmorpholinium cation in ionic liquids did not biodegrade. Authors suggested that functionalised side chain instead of benzyl group would improve biodegradation. Wells *et al.*[27] studies have already shown that the long alkyl or glycol chain ILs show poor or no biodegradability. Recently a temperature study has been performed to enhance the biodegradability of a tetrabutylammonium IL, which was successful and biodegradation was enhanced from 23% at 30 °C to 64% at 45 °C. From other compounds it is known that biodegradation is accelerated when temperature is increased.[28]

Of note, however the majority of biodegradation studies has focused on the effect of substitution of the cation of the ionic liquid.[19] While toxicity studies of a series of ionic liquids with the same cation and varying the anion are widely reported,[17] almost all of these investigations do not include biodegradation data. That is an obvious lack of knowledge on biodegradability and short comings on assessing the 'greenness' of IL.

As ILs are often used as solvent or co-solvent, their synthesis in a quick and efficient manner is required. In addition, making ILs from bio-resources, such as acids derived from biomass, could lead to easily obtained biodegradable and low toxicity ILs. Toxicity screening is thus included in this investigation so any undesirably high toxicity ionic liquids can be identified at an early stage. When combined with biodegradation and catalysis performance data, an assessment of an ionic liquid as 'fit for purpose' can be made.

Results and discussion

Chiral ILs (CILs) comprised of imidazolium cations,[29] phosphonium cations[30] or tetrabutylammonium[31] and amino-acid anions have been described in the literature since 2005. Tetrabutylammonium (*S*)-prolinate (**1**) (Fig. 1), was prepared according to Ohno's method[29b] and characterised through classical analytical methods (NMR, IR, optical rotation, mass and elemental analysis) in agreement with literature data reported by Maschmeyer *et al.*[31] Concerning the tetrabutylammonium (*R*)-prolinate (**2**) and the tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate (**3**) (Fig. 1), although they have been used as solvent or chiral additive in reactions, as described by Zhang *et al.*[32] and Wang *et al.*,[33] their synthesis and characterization are not fully described therein. The synthesis of **2** and **3** is also only briefly outlined in Ohno's papers.[29]

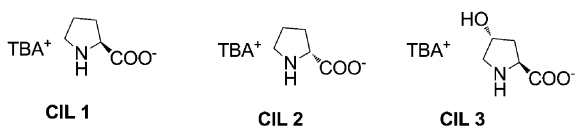


Fig. 1 Tetrabutylammonium (TBA) (*S*)- and (*R*)-prolinate (**1** and **2**) and TBA *trans*-4-hydroxy-(*S*)-prolinate (**3**).

Synthesis and characterization of tetrabutylammonium (*S*)-prolinate (1), tetrabutylammonium (*R*)-prolinate (2) and tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate (3)

The CILs **1**, **2** and **3** were easily obtained with good yields accordingly to the method developed by Ohno *et al.* (Scheme 1).[29]

Viscosity measurements were performed at two different temperatures (Table 1). At room temperature, **1** was very viscous, contrary to **2** and **3** whose viscosities were low. The difference in viscosity between enantiomers **1** and **2** is attributed to the quantity of water present in samples as observed in elemental analysis ($C_{21}H_{44}N_2O_2 \cdot 1.5H_2O$ for **1** and $C_{21}H_{44}N_2O_2 \cdot 2.5H_2O$ for **2**). At 80 °C, for all CILs, the expected decreasing of the viscosity was observed and values were in the range 18.7–39.6 cP. CIL **3**, with a slightly lower water content compared to CIL **2**, has higher viscosity values at both 25 °C and 80 °C due to the presence of the hydroxyl group in the 4 position of the prolinate anion. The glass transition temperature (T_g) was determined by Differential Scanning Calorimetry (DSC) and similar values were obtained for CILs **1** and **2** (−53.9 and −49.6 °C, respectively). A lower T_g (−38.0 °C) value for the 4-hydroxyl derivative **3** was observed. Next, thermogravimetric analyses were performed to determine the decomposition temperature (T_{dec}) of CIL **1–3** and these were in the region of 170 °C allow their use as solvent for many applications.

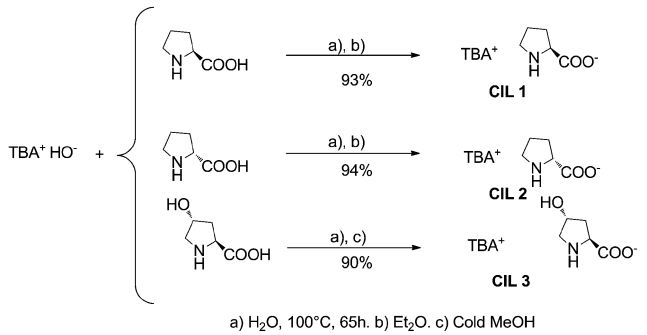
Toxicity of CILs

Regarding the toxicity of CILs **1**, **2** and **3**, preliminary toxicity tests were performed to determine if they presented high antimicrobial toxicity.[7,19b,o,36] The three CILs were screened against four Gram positive organisms (*Staphylococcus aureus* ATCC 6538, *Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08) and four Gram negative organisms (*Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae*-ESBL positive HK14368/08 and *Pseudomonas aeruginosa* ATCC 9027). MIC values for the antibacterial study were defined as 95% inhibition (IC_{95}) of the control growth.[34] For all compounds IC_{95}

Table 1 CILs **1**, **2** and **3**: viscosity, glass transition temperature, decomposition temperature

	Viscosity (cP)			
CIL	25 °C	80 °C	T_g (°C)	T_{dec}[a] (°C)
1	1109	27.8	−53.9	174.3
2	220.2	18.7	−49.6	167.4
3	266	39.6	−38.0	168.6

[a] The values reported correspond to the onset temperature found by heating the compounds from 30 °C to 500 °C with a heating rate of 10 K min^{-1}.



Scheme 1 Synthesis of CILs **1**, **2** and **3**.

values were above the maximum concentration screened in the test (1 mM).

CILs were also tested against yeast strains: *Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258, *Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporan asahii* 1188 and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445). MIC values for antifungal study were defined as 80% inhibition (IC_{80}) of the control growth for yeast and 50% inhibition (IC_{50}) of the control growth for filamentous fungi.[34] The MIC values for fungi were recorded after 24 h and 48 h, except for the dermatophytic strain (*T. mentagrophytes* 445) which was determined after 72 h and 120 h. Results show MIC values (IC_{80}, and IC_{50}) were greater than 1 mM for all fungi strains screened.

CILs **1**, **2** and **3** do not have high toxicity to any of the Gram positive and Gram negative bacteria and fungi (yeasts and filamentous) strains screened.

The next step in the screening strategy was to determine the IC_{50} (mM) values of the CILs for several bacteria strains.[35] The tests were also performed on commercial TBABr and TBAOH for comparison (Table 2).

For *E. coli*, *P. fluorescens* and *P. putida* (CP1), IC_{50} values were obtained in a similar range with all CILs compared to the values found with commercial ILs and, our CILS were as toxic as TBABr and TBAOH. Unfortunately, for *B. subtilis*, CILs values are smaller than the commercial ones, showing that the synthesized CILS are the more toxic for this strain. For *P. putida* (KT2440), the value for **1** was quite the same as the commercial ones (12.50–25.00 mM), whereas **2** and **3** had higher IC_{50} values and so were less toxic. As IC_{50} values varied from strain to strain, our toxicity study showed that it is very important to determine the toxicity of chemical compounds, and more particularly ionic liquids, on different strains.

Biodegradation studies

Concerning the biodegradation of CILs **1**, **2** and **3**, the results are presented in Fig. 2. The biodegradability of these CILs was investigated in the Closed Bottle test.[24] The test was valid according to the test guideline since sodium acetate was biodegraded up to 82% within 14 days (demand of at least 60%) and oxygen concentrations in all bottles did not fall below 0.5 mg L^{-1} at any time. Oxygen depletion in the inoculum blanks after 28 days was 0.82 mg L^{-1} and therefore less than 1.5 mg L^{-1}. The difference of extremes in replicate values of the removal of the test compound was less than 20% in all tests. Previously, the test was performed on commercial tetrabutylammonium bromide (TBA Br) and tetrabutylammonium hydroxide (TBA OH) to compare with the synthesized CILs.[37] Tetraethylammonium and tetramethylammonium bromide (TEA Br and TMA Br) were also included in the study to investigate the effect of alkyl chain length on biodegradation. With biodegradability values below 8%, the commercial ILs failed the Closed Bottle test (OECD 301D)[24] and are not classified readily biodegradable. CILs **1**, **2** and **3** also failed the test, but showed a better biodegradability than the commercial ILs. The increase in CO_2 evolved from CIL **1**, **2** and **3** during the Closed Bottle Test compared to TBABr is 10–16%. This is too low to represent complete degradation of the prolinate anion within the 28 days of the test. We propose the alternative hypothesis, that the prolinate anion of CILs **1–3** is poorly biodegraded during the Closed Bottle test.

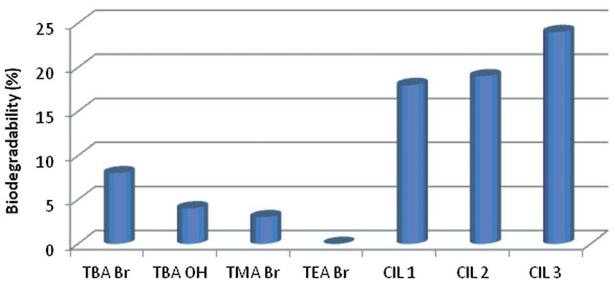


Fig. 2 Biodegradability of CILs **1**, **2** and **3**.

Table 2 CILs **1**, **2** and **3**: toxicity tests

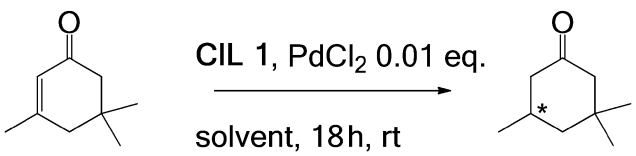
	IC_{50} value (mM)				
IL	*E. coli*	*B. subtilis*	*P. fluorescens*	*P. putida* (CP1)	*P. putida* (KT2440)
TBA Br	03.13–06.25	25.00–50.00	06.25–12.50	25.00–50.00	12.50–25.00
TBA OH	06.25–12.50	12.50–25.00	12.50–25.00	12.50–25.00	12.50–25.00
1	03.13–06.25	12.50–25.00	12.50–25.00	25.00–50.00	12.50–25.00
2	06.30–12.50	06.30–12.50	06.30–12.50	12.50–25.00	25.00–50.00
3	06.30–12.50	06.30–12.50	06.30–12.50	12.50–25.00	25.00–50.00

Catalysis

The performance of CILs **1**, **2** and **3** in organocatalysis was recently demonstrated by different studies over the last ten years. Yamaguchi *et al.*[38] showed first in 1996 the influence of prolinate salts in the asymmetric Michael addition while Iwabuchi *et al.* used **1** in desymmetric aldolization.[39] Jing *et al.*[32] reported asymmetric cycloaddition of CO_2 to epoxides with both **1** and **2**.

As it was proved that the ionic liquid *N*-methylprolinium bis(trifluoromethylsulfonyl)imide, was a chiral agent in enantioselective hydrogenation of dimethylitaconate in the presence of a Rh/racemic BINAP system,[40] we decided to investigate the role of CILs **1**, **2** and **3** in the enantioselective hydrogenation of the carbon–carbon double bond of α,β-unsaturated ketones. Hydrogenation of isophorone was selected as the first study. For this reaction, many organometallic catalytic systems are already described, essentially based on palladium derivatives associated to chiral ligands. These systems consist on black palladium or palladium supported over Al_2O_3, MgO, $BaCO_3$, $SrCO_3$, $CaCO_3$ or modified silica, associated to proline,[41] proline-based chiral modifiers[41h,42] or (−)-dihydroapovincaminic acid ethyl ester in high pressure conditions.[43] Other organometallic systems are used like Ruthenium-[44] or Raney Nickel-based[45] catalytic systems which preferentially lead to trimethylcyclohexanol (TMCH) while Cr–Ni-,[46] Zn[47]- or Rh[48]-based ones yield only the saturated ketone. Theoretical approaches showed the origin of the enantioselectivity in the proline-directed Pd/isophorone system through several techniques[49] (UV, voltammetry) in order to propose mechanisms.[41h,50] The kinetic resolution of TMCH over Pd catalysts in the presence of (*S*)-proline has been also studied.[51] In general, these catalytic systems are performed in harsh reaction conditions, such as very high pressure, and require toxic solvents, including methanol.[41–43] However, the advantageous role of $scCO_2$ as a reaction medium as a replacement for organic solvents was highlighted by enhancing conversion at mild for heterogeneously catalyzed hydrogenation of carvone.[52]

Table 3 Influence of the nature of the solvent[a]



Solvent	Conversion[b] (%)	Selectivity[b] (%)	ee[c] (%)
H_2O	98	94	—
Absolute EtOH	100	70	24 (*S*)
MeOH	100	85	32 (*S*)
t-BuOH	97	62	17 (*S*)
i-PrOH	100	59	47 (*S*)
THF	98	98	—
DMF	89	99	—
1,4-Dioxane	94	98	—

[a] *Conditions*: CIL **1** (400 mg), $PdCl_2$ (0.01 eq.), mass ratio solvent/CIL **1** = 5, 18 h, RT. —: no ee observed. [b] Determined by GC. [c] Determined by GC with a chiral column.

Regarding the application of CILs **1**, **2** and **3** in catalysis, our goal in this study was to realize enantioselective hydrogenation of the carbon–carbon double bond of isophorone in mild conditions. As solvents or co-solvents are commonly used in the literature for such reaction, we studied the influence of the nature of the solvent, considering CIL **1** as chiral additive.

At first, we realized the reaction in water (mass ratio H_2O/CIL **1** = 5) and we observed a good conversion with a good selectivity for trimethylcyclohexanone but without enantioselectivity. Next, as alcohols are commonly used in such enantioselective hydrogenations,[41–43] different alcohols were used (EtOH, MeOH, *t*-BuOH and *i*-PrOH) (Table 3). The conversions are complete with good selectivities and ee between 17 and 47%, the main by-product of the reaction being the trimethylcyclohexanol (TMCH). The best ee is obtained using *i*-PrOH as solvent which is not surprising, considering the literature data.[49] The highest ee is obtained using *i*-PrOH as solvent which is consistent with the literature data.[49] The importance of the nature of the protic solvent on the enantioselectivity could be related to the mechanism proposed by Vida *et al.*[41h] Aprotic solvents, such as THF or DMF, were also trialled and led to good conversions and selectivities but only racemic product (Table 3). Alternative palladium based catalyst ($Pd(OAc)_2$, $Pd(acac)_2$, K_2PdCl_4, $PdCl_2(PhCN)_2$) in *i*-PrOH or MeOH provided no reaction.

Next, we observed that the configuration of the resulting ketone is closely related to the nature of the CIL (Table 4), **1** and **3** leading to the (*S*) configuration for the saturated ketone (albeit with very low enantioselectivity for **3**), while TBA (*R*)-prolinate led to the (*R*)-isomer.

The reaction time is also an important factor (Fig. 3). The highest ee with **1** as chiral additive is obtained with a reaction

Table 4 Influence of the nature of IL[a]

CIL	Conversion[b] (%)	Selectivity[b] (%)	ee[c] (%)
—	100	95	—
1	100	59	47 (*S*)
2	100	58	26 (*R*)
3	75	85	3 (*S*)

[a] *Conditions*: CIL (400 mg), $PdCl_2$ (0.01 eq.), *i*-PrOH (2.5 mL), 18 h, RT. —: no ee observed. [b] Determined by GC. [c] Determined by GC with a chiral column.

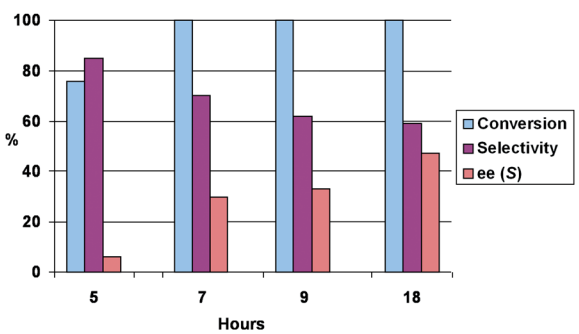


Fig. 3 Influence of the reaction time.

time of 18 h combined with a good conversion and a satisfactory selectivity.

Finally, in order to find the optimal solvent/CIL **1** ratio, several hydrogenation conditions were performed in 7 h to compare rapidly the influence of the ratio on the conversions, selectivities and enantioselectivities. Complete conversion (100%) was obtained after 7 hours of reaction. Increasing the reaction time to 9 and 18 h, gave rise to lower selectivity for trimethylhexanone although an increase in ee was observed.

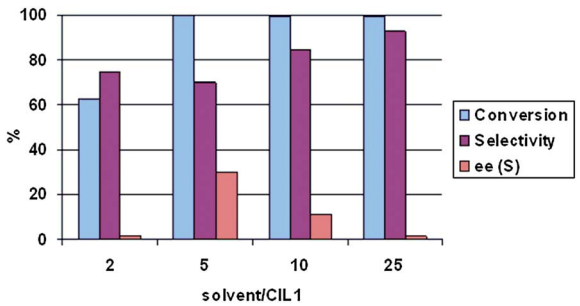
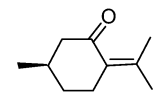
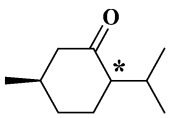
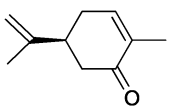
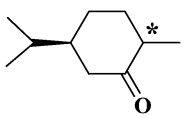
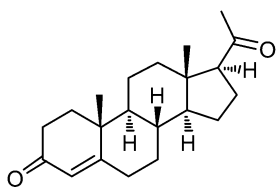
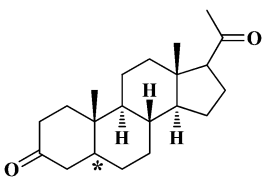
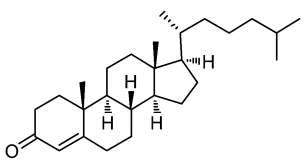
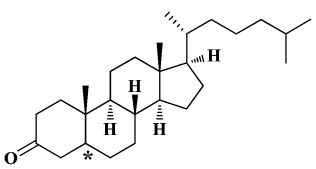


Fig. 4 Influence of the ratio solvent/CIL **1** (reaction time: 7 h).

Fig. 4 shows the best solvent/IL ratio is 5 offering a good compromise between conversion, selectivity and enantioselectivity. A very low quantity of CIL **1** did not allow any enantioselective hydrogenation of the substrate, as no ee was obtained with a solvent/ratio of 25. More surprisingly, with a high proportion of CIL **1**, no ee was measured and the conversion was not total, letting us supposed that a high proportion of CIL **1** inhibited the reaction.

After this study with isophorone as substrate, other α,β-unsaturated ketones ((*R*)-pulegone, (*R*)-carvone, progesterone and 4-cholest-3-one) were tested with our optimized conditions (Table 5). With (*R*)-pulegone, the conversion and the selectivity are complete with a good de in such conditions compared to the literature data.[53] For (*R*)-carvone, the conversion is complete and the selectivity is relatively high (90%), the two carbon–carbon double bonds are hydrogenated and the obtained de is significant (73%). Here again, compared to previously described works,[53b,54] this hydrogenation system is very competitive considering the mild conditions employed. Two other α,β-unsaturated ketones, the progesterone and the 4-cholest-3-one were also used as substrates and their hydrogenation was performed with good yields and de especially for 4-cholest-3-one (67%).

Table 5 Hydrogenation of other α,β-unsaturated ketones[a]

Substrate	Conversion[b] (%)	Selectivity[b] (%)	de[c] (%)	Product
 (*R*)-pulegone	100	100	29 (2*S*,5*R*)	
 (*R*)-carvone	100	90	73 (3*R*,6*S*)	
 Progesterone	100	87	25 (5*R* epimer)	
 4-cholest-3-one	100	100	67 (5*R* epimer)	

[a] *Conditions*: **1** (400 mg), $PdCl_2$ (0.01 eq.), *i*-PrOH (2.5 mL), 18 h, RT. [b] Determined by GC. [c] Determined by GC with a chiral column.

Experimental

All reagents were commercially available and used as received (TBAOH·30H_2O, (*R*)-proline, (*S*)-proline and *trans*-(*S*)-hydroxyproline from ACROS). ^{1}H and ^{13}C NMR spectra were recorded on an AC 250 Bruker with acetone-d_6 as solvent and as reference (δ 2.05 for ^{1}H and 30.6 for ^{13}C spectra). The infrared spectra were recorded with Spectrafile IR™ Plus MIDAC. C, H and N analyses were performed on a Perkin-Elmer 2400 CHN equipment.

GC analyses were recorded on a Hewlett-Packard HP-6890 gas chromatograph, fitted with DB-1 capillary column (25 m, 0.32 mm), a flame ionization detector and HP-3395 integrator under the following conditions: helium as vector gas (5×10^4 Pa), temperature of injector: 250 °C, temperature of the oven: isotherm 150 °C, 5 min, then 150–300 °C (10 °C min^{-1}) and isotherm 300 °C, 5 min.

GC/MS analyses were recorded on a THERMOQUEST Draw GC on 2000 Series by using the techniques of chemical ionization under the following conditions: capillary column DB1 (length: 25 m, diameter: 0.32 mm), vector gas: helium (0.5 bar), temperature injector: 250 °C.

ee were determinated with a β-cyclodextrines-based chiral gaz chromatography column and by-products by GC/MS.

Thermogravimetric analyses coupled with a mass spectrometer were performed between 30 °C and 500 °C under a constant flow of dry argon (50 mL min^{-1}) using a Simultaneous Thermal Analyzer STA 449C Jupiter from Netzsch, and a heating rate of 10 K min^{-1}. The isothermal drift and sensitivity values are 0.6 μg h^{-1} and 0.1 μg, respectively. Alumina crucibles were loaded with 10–20 mg of sample powder.

The mass spectrometer is a quadrupole QMS 403 Aëolos® with a stainless steel capillary and a SEV detector (Channeltron). The counting time for mass spectrometer is of 20 ms per *m*/*z* values (scanning width: m/z = 10–150 amu) with a resting time of 1 s.

The DSC experiments were carried out on a Netzsch DSC 204F1 heat flux differential calorimeter at a heating/cooling rate of 10 K min^{-1} under a constant argon flow with 200 mL min^{-1}. The crucibles were loaded with 10–20 mg of sample powder/liquid. Samples were weighed in aluminum sample pans covered with a pierced lid. An empty aluminum sample pan with a pierced lid was used as a reference.

The viscosities measurements in cP (or mPa.s) were performed with a Brookfield LV-DVII + PRO viscometer using a CP51 cone spindle. The instrument was connected to a HUBER-ministat circulation-type thermo-regulated water bath, and measures were realized between 298.15 and 353.15 K. The repeatability of the viscometer was of 0.20% with an uncertainty in the viscosity measurements of 1.00% of the full scale range, declared by the manufacturer.

General procedure for the synthesis of CILs 1–3

In a 500 mL round-bottom flask, the prolines (6 mmol) are dissolved in distilled water (50 mL). An aqueous solution of TBAOH·30H_2O (5 mmol in 100 mL) was added and the mixture is stirred under reflux for 65 hours. After cooling, the solvent is evaporated under reduced pressure and the crude product was washed with diethyl ether or precipitated in cold methanol. The final material was dried *in vacuo* at 50 °C for 48 hours.

Tetrabutylammonium (*S*)-prolinate CIL 1. The general procedure was followed with 1.051 g of (*S*)-proline and 4.024 g TBAOH·30H_2O. The crude product was washed with ether (3 × 20 mL). A brown-orange oil was obtained (2.501 g, 93%).

IR (film) cm^{-1}: 3500–3100, 29569, 2939, 2871, 1642, 1587, 1485, 1461, 1383, 1171, 1151, 1106, 1069, 1028.

NMR ^{1}H (250 MHz, $CDCl_3$) δ: 3.48 (m, 1H, H-1′), 3.15 (m, 8H, H-1), 3.01 (m, 1H, H-4′a), 2.76 (m, 1H, H-4′b), 1.98 (m, 1H, H-2′a), 1.80 (m, 1H, H-2′b), 1.50 (m, 10H, H-3, H-3′), 1.32 (hex, 8H, $J_{2-3} = J_{3-4} = 7.2$ Hz), 0.89 (t, 12H, H-4, $J_{3-4} = 7.2$ Hz).

NMR ^{13}C (63 MHz, $CDCl_3$) δ: 180.9 (C═O), 63.04 (C-1′), 59.4 (C-1), 47.6 (C-4′), 32.2 (C-2′), 26,7 (C-3′), 24.7 (C-2), 20.6 (C-3), 14.1 (C-4).

MS: (+) 242.2 (−) 114.1.

Elemental analysis calculated for $C_{21}H_{44}N_2O_2 \cdot 1.5H_2O$, C: 66.14%; H: 11.81%; N: 7.35%.

Found C: 66.33%; H: 11.90%; N: 7.26%.

Tetrabutylammonium (*R*)-prolinate CIL 2. The general procedure was followed with 1.106 g of (*R*)-proline and 4.070 g of TBAOH·30H_2O. The crude product was washed with ether (3 × 20 mL). A brown oil was obtained (1.705 g, 94%).

$[\alpha]_D^{20} = 28.50$ (c 10, H_2O).

IR (film) ν: 3600–3000 (OH, N^+), 2966 (CH_2), 2939 (CH_3), 2877 (CH_2), 1598 (COO^-), 1485, 1458, 1386, 1171, 1151, 1106, 1035, 878 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.44 (m, 9H, H-1, H-1′), 3.05 (m, 1H, H-4′a), 2.78 (m, 1H, H-4′b), 1.88 (m, 2H, H-2′), 1.80 (quint, 8H, H-2, $J = 7.4$ Hz), 1.59 (quint, 2H, H-3′, $J = 6.7$ Hz), 1.45 (hex, 8H, H-3, $J = 7.3$ Hz), 0.96 (t, 12H, H-4, $J = 7.3$ Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 178.6 (C═O), 64.0 (C-1′), 60.1 (C-1), 48.6 (C-4′), 32.7 (C-2′), 27.5 (C-3′), 25.4 (C-2), 21.3 (C-3), 14.9 (C-4).

MS: (+) 242,1 (−) 114,0.

Elemental analysis calculated for $C_{21}H_{44}N_2O_2 \cdot 2.5H_2O$, C: 62.80%; H: 12.30%; N: 6.97%.

Found C: 62.34%; H: 12.40%; N: 7.10%.

Tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate CIL 3. General procedure with 805.4 mg of 4-hydroxy-(*S*)-proline and 4.052 g of TBAOH·30H_2O. The crude product was dissolved in methanol and let to stay in a fridge for 5 hours. The white formed solid was evacuated by filtration and the filtrate again put in the fridge for one night. The formed solid was eliminated by filtration and the filtrate evaporated under reduced pressure. An orange oil was obtained (1.680 g, 90%).

$[\alpha]_D^{20} = -7.83$ (c 12, H_2O).

IR (film) ν: 3600–3000 (OH, N^+), 2965 (CH_3), 2936 (CH_3), 2877 (CH_2), 1588 (COO^-), 1489, 1465, 1379, 1202, 1168, 1096, 1052, 10331171, 1151, 1106, 1035, 881 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.20 (quint, 1H, H-3′, $J = 4.9$ Hz), 3.46 (m, 1H, H-1′), 3.44 (m, 8H, H-1), 3.15 (dd, 1H, H-4′a, $J =$ 5.5 Hz, $J = 10.7$ Hz), 2.64 (m, 1H, H-4′b), 1.93 (dd, 2H, H-2′, $J =$ 4.4 Hz, $J = 7.5$ Hz), 1.78 (quint, 8H, H-2, $J = 7.4$ Hz), 1.43 (hex, 8H, H-3, $J = 7.4$ Hz), 0.97 (t, 12H, H-4, $J = 7.4$ Hz)

^{13}C NMR (63 MHz, $CDCl_3$) δ: 177.7 (C=O), 72.2 (C-3′), 61.9 (C-1′), 58.7 (C-1), 55.4 (C-4′), 41.3 (C-2′), 24.0 (C-2), 19.9 (C-3), 13.5 (C-4).

Elemental analysis calculated for $C_{21}H_{44}N_2O_3 \cdot 2.1H_2O$, C: 61.46%; H: 11.84%; N: 6.83%.

Found C: 61.48%, H: 11.27%; N: 6.69%.

General procedure for hydrogenation

In a Schlenk tube, ionic liquid (400 mg) and $PdCl_2$ (3.5 mg, 0.02 mmol, 0.01 eq.) were introduced. After 10 minutes under vacuum, isophorone (300 μL, 2 mmol, 1 eq.) in 2 g of solvent was added under argon. A hydrogen atmosphere was filled into the reactor with the help of a gas bag and the mixture was stirred at room temperature during the required time. Then, distillated water (2 mL) was introduced and the aqueous layer was extracted three times with 5 mL of diethyl ether. The organic layers were gathered, dried over $MgSO_4$ and filtered through cotton. 1 μL of the organic phase was injected in a gas chromatography to determine the conversion. Enantiomeric excess (ee) were determined with a β-cyclodextrines-based chiral gas chromatography column and by-products by GC/MS.

Closed Bottle test (CBT)

The CBT is one of six test methods described in the OECD Test Guidelines[24] to determine the ready biodegradability of organic chemicals. With a low nutrient content and a low bacterial density the CBT simulates the conditions of environmental surface water. One can assume that substances classified as "readily biodegradable" are biodegradable in sewage treatment plants and therefore are not expected to reach or accumulate in the aquatic environment.

The test was performed in the dark at a room temperature of 20 ± 1 °C in the laboratories of the Institute of Sustainable and Environmental Chemistry at Leuphana University Lüneburg as described in details elsewhere[55] It consisted of four different test series. All series were run as duplicates. The "blank series" contained only mineral medium and inoculum. The "quality control" was prepared additionally with readily biodegradable sodium acetate to monitor the activity of the microorganisms. The "test series" included besides medium and inoculum the test compound as only organic compound while the "toxicity control" series contained additionally sodium acetate. The amount of sodium acetate and of each test compound corresponded to a theoretical oxygen demand (ThOD) of 5 mg L^{-1}. All test vessels contained the same mineral salt solution and were inoculated with two drops of inoculum from the effluent of the municipal sewage treatment plant in Lüneburg (Abwasser, Grün und Lüneburger Service GmbH, Germany; 250.000 population equivalents).

According to the guidelines, at least 60% decomposition of the reference substance sodium acetate is required within 14 days. Toxicity was assessed by comparing oxygen consumption as measured in the toxicity control bottles with the predicted level computed from the oxygen consumption in the quality control and in the test vessel containing only the test compound, respectively. A compound is labeled toxic if the difference between the predicted amount of oxygen consumption and the measured one exceeds 25%.[24]

The process of aerobic biodegradation was monitored by measuring the biological oxygen demand of the microorganisms in accordance with international standard methods[56] at day 0, 0 (after 3 hours), 1, 7, 14, 21 and 28 using sensor spots in the bottles and an oxygen electrode (Oxi 196 with EO 196-1.5 WTW Weilheim, Germany).[57]

Antifungal activity

In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical yeast isolates (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three ATCC strains were used as the quality control strains. All of the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by modified CLSI standard of microdilution format of the M27-A3 and M38-A2 documents.[34] Dimethyl sulfoxide (100%) served as a diluent for all compounds; the final concentration did not exceed 2%. RPMI 1640 (Sevapharma, Prague) medium supplemented with L-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 M NaOH was used as the test medium. The wells of the microdilution tray contained 200 μL of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (1000 to 0.244 μmol L^{-1} for the new compounds) and 10 μL of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu mL^{-1}. The trays were incubated at 35 °C and MICs were read visually after 24 h and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 h and 120 h. The MICs were defined as 80% inhibition (IC_{80}) of the control growth for yeasts and as 50% inhibition (IC_{50}) of the control growth for filamentous fungi. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

Antibacterial activity

In vitro antibacterial activities[34] of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University,

Hradec Králové, Czech Republic. The above-mentioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton agar prior to being tested.

Dimethyl sulfoxide (100%) served as a diluent for all compounds; the final concentration did not exceed 2%. Mueller-Hinton agar (MH, HiMedia, Čadersky-Envitek, Czech Republic) buffered to pH 7.4 (±0.2) was used as the test medium. The wells of the microdilution tray contained 200 μL of the Mueller-Hinton medium with 2-fold serial dilutions of the compounds (1000 to 0.244 μmol L^{-1}) and 10 μL of inoculum suspension. Inoculum in MH medium was prepared to give a final concentration of 0.5 McFarland scale (1.5×10^8 cfu mL^{-1}). The trays were incubated at 37 °C and MICs were read visually after 24 h and 48 h. The MICs were defined as 95% inhibition of the control growth. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

Toxicity studies

IC_{50} values for the compounds were determined at The School of Biotechnology, Dublin City University using a modification of the broth microdilution method described by Amsterdam.[35] Strains were grown in nutrient broth overnight, washed with 0.01 M sodium phosphate buffer and the cell number adjusted to give an optical density reading of 0.07 at 660 nm. The antimicrobial activity of the ILs were tested in 96 well microplates. 180 μL of Mueller-Hinton broth was pipetted into column 1 of the wells and 100 μL into the other wells. 20 μL of the chemical solution was transferred into column 1 giving a concentration of 200 mM. 100 μL of the solution from column 1 was then transferred to the next column and mixed. The procedure was repeated to give a series of two-fold dilutions. Each well was inoculated with 5 μL of bacterial culture. Wells containing medium only were used as blanks and wells containing medium and culture only were used as positive controls. The microplates were incubated overnight at 37 °C for *E. coli* and 30 °C for all other bacteria. The presence or absence of growth was determined by measuring the optical density of the wells at a wavelength of 405 nm using a plate reader. The IC_{50} values were determined as the concentration or range of concentrations that caused a 50% reduction in growth.

Conclusions

To summarize, tetrabutylammonium prolinates, and particularly CIL **1**, are good chiral modifiers for the hydrogenation of carbon–carbon double bond of α,β-unsaturated ketones in *i*-PrOH under mild conditions. Investigations towards other substrates and the possibility to recover the catalytic system are currently ongoing in our group. CILs **1–3** all do not have high antimicrobial toxicity to the 20 bacteria and fungi strains screened. Additional screening against 5 bacteria gave IC_{50} values between 3 and 50 mM for the CILs and demonstrates low toxicity to these bacteria strains. CILs **1–3** failed the biodegradability closed bottle test but showed slightly better biodegradability than the commercial starting ammonium salts.

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