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Chemo-enzymatic Baeyer–Villiger oxidation in the presence of *Candida antarctica* lipase B and ionic liquids

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A new method for the chemo-enzymatic Baeyer–Villiger oxidation of cyclic ketones to lactones has been developed. The influence of reaction parameters and the structure of various ionic liquids were studied. Free *Candida antarctica* lipase B or Novozyme-435 suspended in an ionic liquid was used as the catalytic phase. The reaction was carried out under mild conditions at room temperature using 30% aq. H_2O_2 as the oxidation agent. 1-Butyl-3-methyl bistriflimide was the most effective ionic liquid and increased the reaction rate compared to toluene. Lipase exhibited good stability, and the ionic liquid could be easily reused. Therefore, a general chemo-enzymatic method for the oxidation of cyclohexanones and cyclobutanones to obtain adequate lactones in high yields (79–95%) has been proposed.

Introduction

The Baeyer–Villiger reaction is based on the formation of esters or lactones *via* the oxidation of ketones with peroxide derivatives, primarily peracids, catalysed by acids or enzymes. The resulting esters or lactones are used in the synthesis of antibiotics, steroids, pheromones and monomers for polymerisation.[1–3] The use of enzymes to perform the chemical transformation of ketones to lactones can be carried out using Baeyer–Villiger monooxygenases or *Candida antarctica* lipase B. In the first option, the enzyme catalyses the oxidation of ketones with oxygen and nicotinamide adenine dinucleotide phosphate NADPH as a source of electrons.[4–6] In the second option, the enzyme is used only in one step of the reaction, and therefore, the reaction is called chemo-enzymatic.[7–15] This reaction involves the oxidation of long- or medium-chain carboxylic acids with hydrogen peroxide in the presence of lipase to generate *in situ* peracid, which is used to oxidise ketones to lactones in the second step. An interesting modification of the chemo-enzymatic method that utilises ethyl acetate as a solvent and a peracetic acid precursor has been recently proposed.[9] From this point of view, the chemo-enzymatic approach appears to be a very attractive alternative to avoid the handling of often poorly stable, hazardous and fairly expensive organic percarboxylic acids, which are typical oxidants used in the Baeyer–Villiger reaction.

Although, chemo-enzymatic Baeyer–Villiger reaction conditions are mild, the required reaction times at room temperature

can be as long as several days. The most often used enzyme is *Candida antarctica* lipase B (CALB) immobilised on acrylic resin, which is commercially available as Novozyme-435. In addition, very efficient CALB immobilised as cross-linked enzyme aggregates (CLEAs) has also been used.[12] In our previous study, the high activity of CALB immobilised on siliceous materials with organosilanes terminated with alkyl groups was demonstrated.[13]

Only one report demonstrated that the oxidation of ketones by peracid generated *in situ* in the reaction system catalysed by Novozyme-435 could be significantly accelerated due to the presence of a few hydrogen bond donating ionic liquids.[11] In addition, Novozyme-435 was dissolved in the 1-(3-hydroxypropyl)-3-methylimidazolium nitrate or 1-butyl-3-methylimidazolium nitrate forming gel-like homogeneous liquid. When this method was used, ketones were oxidised with 50% H_2O_2 at 50 °C in 5 h to lactones with moderate to excellent yields.[11]

The properties of enzymes and ionic liquids are complex, and there is no universal method for predicting the appropriate ionic liquid for a specific bioprocess. The challenge of stabilisation or destabilisation of enzymes in an ionic liquid environment occurs in the initial stage. Numerous reports describe the activity and thermal stability of enzymes in ionic liquids and their application in several reactions with considerable success.[16] However, ionic liquids with very similar structures can exhibit different behaviour towards enzymes.[17]

Various properties can influence the catalytic performance of enzymes in ionic liquids including polarity, hydrophobicity, nucleophilicity, hydrogen bonding ability, viscosity, enzyme dissolution, and the surfactant effect.[18–20] In addition, the parameters that quantify the interactions of the proteins and

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the aqueous electrolytes, such as cosmotropicity *vs.* chaotropicity, have been proposed for explaining protein behaviour in aqueous ionic liquids. Unfortunately, the anions of ionic liquids do not always strictly follow the Hofmeister series for protein stability.[16] Ionic liquids can also form the so-called organised 'nano-structures,' which are described as hydrogen bonded polymeric supramolecules that have polar and non-polar regions. The structure of the ionic liquids can protect the crucial water in the protein from solvophobic interactions that are necessary to maintain the native protein structure. Ionic liquids that are enzyme compatible and can dissolve substrates which are not soluble in conventional organic solvents are desired for enzyme-catalysed reactions.[21–23]

To summarise, the chemo-enzymatic Baeyer–Villiger reaction is still under intensive studies to investigate its usefulness in biotransformations. The major challenges to overcome include long reaction times, poor stability of lipase in the presence of concentrated H_2O_2 and the modest yields resulting from this method. Therefore, the current work studies the influence of the structure of various ionic liquids on the activity of CALB in the Baeyer–Villiger oxidation of cyclic ketones to lactones. In contrast to Novozyme-435, the lipase was not attached to a solid support but used in the free form. Because the operational stability of native enzymes is rather limited, our intention was to determine if the presence of ionic liquids influences the stability and activity of CALB in the Baeyer–Villiger reaction.

Results and discussion

Selection of the carboxylic acid structure

We aimed to develop a clean Baeyer–Villiger process with facile catalyst separation and reuse by using hydrogen peroxide and ionic liquids. As shown in Scheme 1, the applied chemo-enzymatic method for lactone synthesis involved the use of CALB as the biocatalyst for peracid formation, 30% aq. H_2O_2 as the oxidant (Scheme 1) and an ionic liquid as the solvent. Commercially available water solution of CALB was used.

Only immobilised forms of CALB were used for this process[7–15] (*e.g.*, for Novozyme-435 as a catalyst, the best results were obtained with the long- or medium-chain carboxylic acids). To use free CALB, preliminary studies focused on the appropriate selection of a carboxylic acid for this purpose. This part of the study was carried out at room temperature in toluene, which was the best organic solvent for this process. A comparison of the effectiveness of H_2O_2 for converting

Scheme 1 Chemo-enzymatic Baeyer–Villiger oxidation of 2-methyl-cyclohexanone.

Table 1 Comparative study of the performance of native CALB and Novozyme-435 for the oxidation of 2-methylcyclohexanone[a]

| Entry | Carboxylic acid | Yield of lactone[a] [%] | |
		Native CALB	Novozyme-435
1	Etanoic acid	16	11
2	Propanoic acid	82	16
3	Pentanoic acid	98	81
4	Octanoic acid	98	99
5	Octanoic acid	0[b]	0[b]
6	Nonanoic acid	97	99
7	Tetradecanoic acid	67	96
8	Hexadecanoic acid	65	99
9	Octadecanoic acid	60	98

[a] Reaction conditions: native CALB (0.100 g) or Novozyme-435 (0.025 g), toluene (1 ml), 2-methylcyclohexanone (0.5 mmol), acid (1 mmol), 30% aq. H_2O_2 (1 mmol), 24 h, RT, shaking (250 rpm); yields determined by GC. [b] Reaction without lipase.

various carboxylic acids (from ethanoic to octadecanoic acid) to peracids in the presence of native lipase or Novozyme-435 followed by the subsequent oxidation of model ketone 2-methyl-cyclohexanone to 6-methyl-ε-caprolactone is shown in Table 1. The comparative study was performed using 0.100 g of native lipase (CALB) and 0.025 g of Novozyme-435 for 0.5 mmol of ketone. In both cases, this amount of lipase was sufficient to carry out the reaction in the region where the reaction kinetic is controlled by the formation of lactone, and not by the formation of peracid in the enzyme-catalysed reaction. Therefore, a further increase in the amount of the enzyme did not influence the yield of lactone. In addition, 0.025 g of Novozyme-435 per 0.5 mmol of ketone was used in a previous study.[11] We also used a standard molar excess of acids to ketones (*i.e.*, 2:1). As a result of our study, a lower interval of reactive carboxylic acids (*i.e.*, from pentanoic to nonanoic acids) was observed for native CALB (Table 1). The reaction does not proceed without the lipase catalyst, as also reported by other researchers.[7] Chiral induction was not observed during the reaction. For additional studies, octanoic acid was chosen as the peracid precursor.

Selection of the ionic liquid structure

Because the properties of ionic liquids are primarily determined by the structure of the anion, various ionic liquids were chosen for screening studies. Ionic liquids based on the 1-butyl-3-methylimidazolium [bmim] cation, both hydrophobic with bistriflimide [NTf$_2$] or hexafluorophosphate [PF$_6$] anions or hydrophilic ones based on trifluoromethanosulphate [OTf], trifluoroacetate [TFA], biscyanamide [NCN$_2$], tetrafluoroborate [BF$_4$], methylsulphate [MeSO$_4$] and octylsulphate [OcSO$_4$] anions were used (Fig. 1). Screening oxidation experiments were performed under mild conditions (24 °C, a 1:2 molar ratio of ketone to 30% aq. H_2O_2, with ionic liquid as a solvent) using 2-methylcyclohexanone and octanoic acid. Yields were determined by GC after 24 h. For comparison, the results obtained for Novozyme-435 were also included in the figure.

The influence of hydrophobicity was investigated due to literature reports on the stability and activity of lipase in ionic liquids.[18–20] It is known that Novozyme-435 in hydrophobic
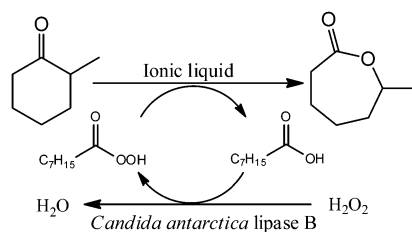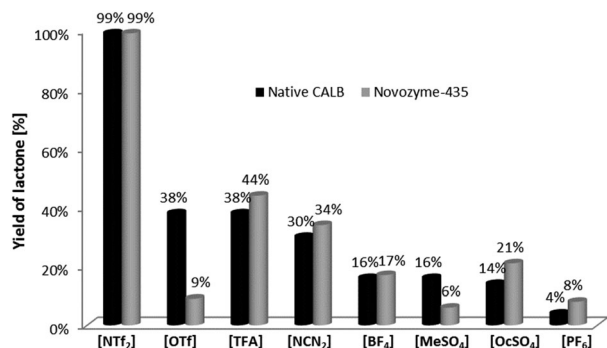
Fig. 1 Influence of the anion structure of 1-butyl-3-methylimidazolium ionic liquids on the yield of 6-methyl-ε-caprolactone.

ionic liquids, such as based on $[NTf_2]$ and $[PF_6]$ anions, can retain its activity even after several reuse cycles.[16] In some reports, Novozyme-435 was dissolved in hydrophilic ionic liquids (*e.g.*, in triethylmethylammonium methylsulphate $[Et_3MeN][MeSO_4]$) and maintained its activity and structure.[20] However, in other reports, the activity of lipase in hydrophilic ionic liquids was substantially decreased.[17,20]

Our results indicate that the best ionic liquid for the chemo-enzymatic Baeyer–Villiger oxidation of 2-methylcyclohexanone was based on the $[NTf_2]$ anion (Fig. 1), which most likely maintains the flexibility of lipase in its active conformation. Other hydrophobic ionic liquid solvents, such as $[bmim][PF_6]$, do not exhibit activity. During the reaction, the water present in the system most likely liberates HF, which is toxic to the enzyme. All hydrophilic ionic liquids have a negative impact on this reaction. The hydrophilic ionic liquids most likely remove essential water from the lipase, which leads to unfolding of the biomolecule upon exposure of the inner hydrophobic residues. Therefore, the anion plays a crucial role in the CALB performance.

Next, the influence of the structure of the cation on the activity of bistriflimide ionic liquids was studied. Therefore, the ionic liquids based on dialkylimidazolium, alkylpyridinium, dialkylpyrrolidinium or trialkylammonium cations were tested. In a series of dialkylimidazolium bistriflimides, the best results were obtained for the 1-butyl-3-methylimidazolium [bmim] cation when native CALB was used as the catalyst. When the slightly acidic C2 hydrogen in the [bmim] cation was substituted with a methyl group (Table 2, entry 5), the reaction time necessary for complete conversion increased from 18 to 42 h. This result may be due to the hydrogen bonding interactions with CALB, which decreases the enzyme activity. A slightly different activity for native CALB compared to Novozyme-435 was observed. In general, native CALB is slightly more active, and the reaction times are shortened by several hours. 3-Methyl-1-butylpyridinium bistriflimide (Table 2, entry 8) was as active as [bmim][NTf_2] and similar in activity to trimethylbutylammonium bistriflimide (Table 2, entry 12). 1-Butyl-1-methylpyrrolidinium bistriflimide exhibited the lowest activity (Table 2, entry 11).

Inspired by the work of Arends *et al.*, who described effective hydrogen bond-donating ionic liquids based on $[NO_3]$ anions dissolving Novozyme-435, cations with H-bonding capability were

Table 2 Influence of the cation structure in bistriflimide ionic liquids[a]

Entry	Cations of bistriflimide ionic liquid	Yield of lactone[b] [%]	
		Native CALB	Novozyme-435
1		80 (24 h)	78 (24 h)
2		81 (10 h) 99 (18 h)	62 (10 h) 99 (24 h)
3		68 (10 h)	88 (24 h)
4		67 (10 h) 81 (18 h) 89 (24 h) 98 (42 h)	84 (24 h)
5		83 (24 h) 98 (42 h)	70 (24 h)
6		63 (24 h)	98 (24 h)
7		87 (10 h) 96 (18 h) 99 (24 h)	89 (24 h)
8		88 (10 h) 96 (18 h) 99 (24 h)	91 (24 h)
9		53 (24 h)	67 (24 h)
10		78 (24 h)	85 (24 h)
11		84 (24 h)	76 (24 h)
12		77 (10 h) 92 (18 h) 98 (24 h)	76 (24 h)
13		48 (18 h) 72 (24 h)	88 (24 h)
14		66 (24 h)	15 (24 h)
15		76 (24 h)	20 (24 h)

[a] Reaction conditions: native CALB (0.100 g) or Novozyme-435 (0.025 g), ionic liquid (1 ml), 2-methylcyclohexanone (0.5 mmol), octanoic acid (1 mmol), 30% aq. H_2O_2 (1 mmol), RT, shaking (250 rpm). [b] Yields determined by GC.

also selected for our study.[10] In each case, the activity of the ionic liquids with –OH groups introduced into the cation structure (Table 2, entries 6, 9 and 13–15) was lower in the reaction catalysed by native CALB compared to that of the same ionic liquids without the –OH groups. This effect was not as dramatic when Novozyme-435 was used. It is important to note that ionic liquids with two –OH groups (Table 2, entries 14 and 15) were extremely viscous, which can influence the reaction rate.

The introduction of a –CN group into the [bmim] structure (Table 2, entry 7) resulted in maintaining the same activity as that without the –CN group. For the 3-methyl-1-butylpyridinium ionic liquid, the presence of a –CN group reduced the activity of the ionic liquid. Therefore, the cation structure also plays an important role in CALB activation.

The influence of process parameters on the model reaction

Next, we studied the key parameters affecting the reaction including the influence of the ketone to hydrogen peroxide molar ratio and the concentration of aq. H_2O_2 on the rate of 2-methylcyclohexanone oxidation. The reaction was carried out with [bmim][NTf$_2$], which is the most active ionic liquid, and native CALB at 45 °C. As shown in Fig. 2, among the different forms of hydrogen peroxide used (*i.e.*, 30 and 50% aq. H_2O_2 and urea hydrogen peroxide (UHP), respectively), the most active form is the 30% aq. H_2O_2. Double molar excess of the ketone to H_2O_2 is sufficient to produce sufficient peracid, and a further increase in the hydrogen peroxide amount does not influence the reaction rate.

The exposure of lipase to a high concentration of aqueous hydrogen peroxide may result in its slow deactivation. There is 9% mass of water in the reaction system when 30% aq. H_2O_2 is used. Water is produced as a by-product, which is introduced into the system with native CALB (which is a water solution) and hydrogen peroxide. When anhydrous UHP is used, the additional water is most likely not introduced into the reaction system, and the water that is crucial for maintaining the protein structure is not achieved.

The increase in the reaction temperature from room temperature to 45 °C resulted in an increase in the reaction rate. In fact, the oxidation of 2-methylcyclohexanone with 30% aq. H_2O_2 in the ionic liquid catalysed by native CALB was completed after 10 h (Fig. 3). The reaction was much slower in toluene and accelerated with temperature. The study on the influence of temperature on the reaction rate indicated that CALB is more active in an ionic liquid environment at higher temperature compared to toluene.

Upon comparing our results with those obtained by other methods described in the literature, a substantial decrease in the reaction time was observed. Upon using Novozyme-435 and
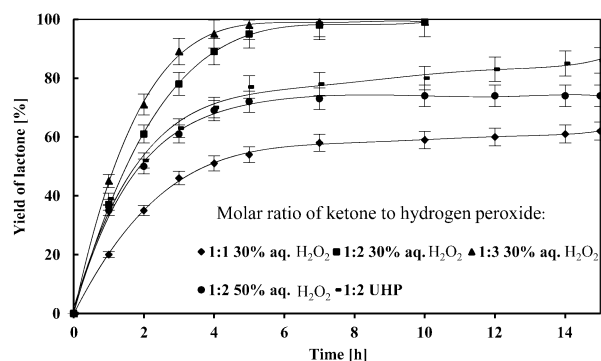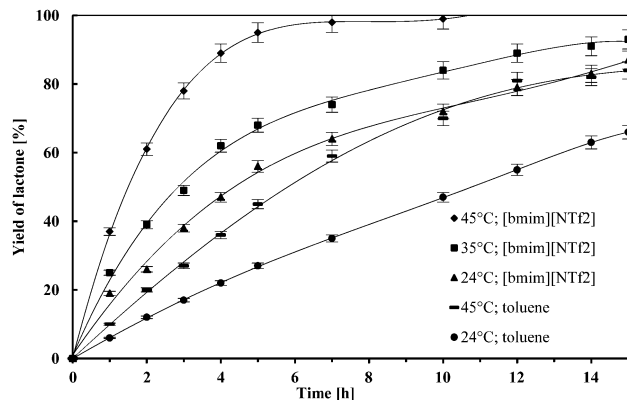
Fig. 3   Influence of temperature on the rate of oxidation of 2-methyl-cyclohexanone.

ethyl acetate as the solvent and the peracid precursor, respectively, 72 h were required for the oxidation of 2-methylcyclo-hexanone to 6-methyl-ε-caprolactone with 95% yield at room temperature.[10] The best results were obtained using CLEA immobilised on a silica support (97% yield after 29 h, RT)[13] or CALB-CLEA (84% yield after 48 h).[12] Our method enabled the full conversion of 2-methylcyclohexanone in 18 h at RT or 10 h at 45 °C.

Recycling study

The recycling of the catalytic phase (*i.e.*, ionic liquid together with native CALB or with Novozyme-435) was studied. In both cases, the enzymes were not dissolved in [bmim][NTf$_2$] to form the second phase. The recycling experiments were carried out at room temperature. For the reactions carried out at higher temperatures, the enzymes were not sufficiently stable to survive the next cycle, and all of the tests of the recycled enzymes after the reaction carried out at 45 °C failed. For the recycling of native CALB with the ionic liquid, the following procedure was used: first, the post-reaction mixture was extracted with toluene to remove the product and the unreacted starting material. The residue was concentrated and used for another reaction cycle. After each catalytic run with Novozyme-435, the post-reaction mixture was dissolved in dichloro-methane, and Novozyme-435 was filtered and washed with ethyl acetate. The filtrate was concentrated under vacuum and extracted with diethyl ether to remove the product and the unreacted starting material. The combined Novozyme-435 and ionic liquid phase was used for another run.

Fig. 4 shows the yields of lactone in four consecutive runs with the application of different catalytic systems (*i.e.*, native CALB or Novozyme-435 in toluene or a [bmim][NTf$_2$] environ-ment). The most important conclusion is that the enzymes lost their activity after the first run when the reaction was carried out in toluene. Better results were obtained with the application of the ionic liquid in the reaction. However, the recycling of the catalytic phase based on native CALB with the ionic liquid was not as efficient as that in the case of Novozyme-435 with the ionic liquid.
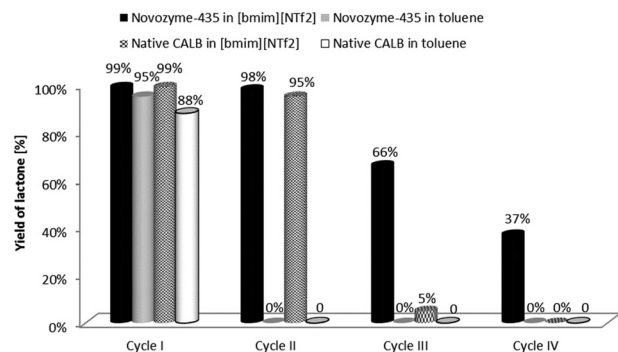
Fig. 2   Effect of the molar ratio of ketones to hydrogen peroxide and concentration of aq. H_2O_2 on the rate of oxidation of 2-methylcyclohexanone.
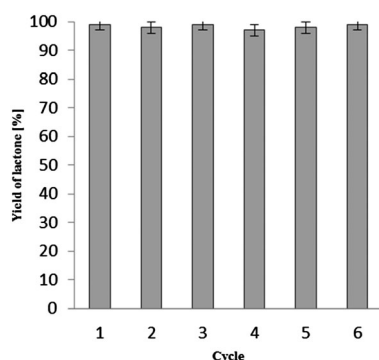
Fig. 4 Recycling of the catalytic phase.

Fig. 5 Recycling of the ionic liquid.

Based on these results, we attempted to recycle the neat ionic liquid [bmim][NTf$_2$] (Fig. 5). In six consecutive runs, almost no mass loss of the ionic liquid was observed (95–98% of recovery). Although the yield of lactone appeared to decrease slightly, it remained within the error bars of the measurement for all six runs (mean yield = 98%, Fig. 5).

Substrate scope

Finally, the most active reaction system was examined in the chemo-enzymatic Baeyer–Villiger synthesis of various lactones from the corresponding ketones to determine its practical potential. As shown in Table 3, the oxidation processes proceeded very efficiently at 45 °C. In fact, cyclic ketones were readily oxidised to their corresponding lactones in high yields (79–96%) under mild conditions in reasonable reaction times. As model reactants, we chose strained ketones, such as cyclobutanones that form lactones in high yields, and non-strained ketone cyclohexanones, which are much more difficult to oxidise. The most reactive of these ketones were cyclobutanones, which oxidised to γ-butyrolactones with 98% yield in 1.5 h, and cyclohexanones, which yielded 85% ε-caprolactone after 15 h. Cyclobutanones are very reactive molecules because their ring strain is very high, and therefore, very fast oxidation was expected. The oxidation of 2-adamantanone and norcamphor yielded their corresponding lactones in high yields. Extremely unreactive cycloheptanone did not undergo oxidation under these conditions.

Table 3 Oxidation of selected cyclic ketones to lactones[a]

Entry	Ketone	Lactone	Time [h]	Yield of lactone in [bmim][NTf$_2$] [%]
1			10	83
			15	85 (80)[b]
			20	65 (toluene)
2			10	99 (96)[b]
			20	95 (toluene)
3			10	80
			15	94 (89)[b]
4			2	71
			4	88
			6	93
			8	99 (95)[b]
5			2	45
			4	61
			8	70
			15	85 (79)[b]
6			1	86
			1.5	99 (96)[b]
			2	91 (toluene)
7			2	91
			3	99 (95)[b]
			4	93 (toluene)
8			2	88
			3	98 (95)[b]
			4	90 (toluene)
9			48	8

[a] Reaction conditions: native CALB (0.4 g), [bmim][NTf$_2$] (4 ml), ketone (2 mmol), octanoic acid (4 mmol), 30% aq. H$_2$O$_2$ (4 mmol), 45 °C, shaking (250 rpm); yields were determined by GC. [b] Isolated yields.

According to the literature method, the oxidation of cyclohexanone in 1-(3-hydroxypropyl)-3-methylimidazolium nitrate or choline nitrate[11] with 50% H$_2$O$_2$ at 50 °C after 5 h yielded 45–62% ε-caprolactone. In our method, 83% yield of lactone was produce after 10 h.

Experimental

Materials

1-Methylimidazole, 1,2-dimethylimidazole, 3-picoline, 1-chlorobutane, 1-chlorohexane, 30% and 50% aq. H$_2$O$_2$ and urea hydrogen peroxide, respectively, were purchased from Acros Organics. 1-butyl-3-methylimidazolium dicyanamide, 1-butyl-3-methylimidazolium octylsulphate, 1-butyl-3-methylimidazolium methylsulphate, 1-butyl-3-methylimidazolium triflate, lithium bis(trifluoromethanesulphate)imide, 1-methyl-3-octylimidazolium bromide and 1-butyl-1-methylpyrrolidinium bis(trifluoromethanesulphate)imide were purchased from Merck. Cyclic ketones,

carboxylic acids, 1-butyl-3-methylimidazolium hexafluorophosphate and native CALB [5, 000 LU/G] were purchased from Sigma Aldrich. Novozyme-35 was donated by Novozymes. Quarterisation reactions of 1-methylimidazole or 1,2-dimethylimidazole,[24] 3-picoline,[25] and aliphatic amines,[26] the metathesis reaction,[27] and the synthesis of 3-substituted cyclobutanones[14] were performed according to literature methods.

Instrumentation

^{1}H NMR and ^{13}C NMR spectra of the lactones were recorded at 300 MHz in CDCl$_3$ (Varian Unity Inova plus spectrometer using a TMS internal standard). All of the lactones were characterised by comparing their NMR spectra with those of standard samples. GC analysis was performed using a Perkin Elmer Clarus 500 chromatograph SUPELCOWAX™10 column (30 m × 0.2 mm × 0.2 μm) using *n*-decane as an external standard.

Methods

General method for Baeyer–Villiger oxidation

4 ml of the ionic liquid and 0.1 g of Novozyme-435 or 0.4 g of native CALB were introduced into a 25 ml round-bottomed flask. Next, the ketone (2 mmol) and the carboxylic acid (4 mmol) were added, and the contents of the flask were shaken. 30% aqueous H$_2$O$_2$ (1 mmol) was added in one portion. The flask was sealed with a septum and mixed in a thermostat shaker (±0.5 °C) with orbital stirring at 250 rpm at 24 °C, 35 °C or 45 °C for 1.5–24 h depending on the reaction rate. Periodically, 20 μl of the samples diluted with 1.5 ml of dichloromethane were collected during the reaction to monitor the progress of the reaction by GC. When the reaction with native CALB was completed, the post reaction mixture was extracted with toluene (6 × 2 ml) to remove the product and the unreacted starting material. The extract was washed with 5 ml of a 10% NaHCO$_3$ solution in water, dried over anhydrous MgSO$_4$ and concentrated under vacuum. The post reaction mixtures with Novozyme-435 were dissolved in dichloromethane (5 ml), and Novozyme-435 was filtered. The filtrate was concentrated under vacuum and extracted with toluene (6 × 2 ml) to extract the product and the unreacted starting material. The extract was washed with 5 ml of a 10% NaHCO$_3$ solution in water, dried over anhydrous MgSO$_4$ and concentrated under vacuum. The yields of the lactones after purification by column chromatography when necessary (with a hexane : ethyl acetate ratio of 4 : 1 as an eluent) were in the range of 79–96%.

Recycling of the catalytic phase or ionic liquid

After completion of the reaction, for the recycling of native CALB with the ionic liquid, the following procedure was used: first, the post reaction mixture was extracted with toluene (6 × 2 ml) to remove the product and the unreacted starting material. The residue was then concentrated and used for another reaction cycle. After each catalytic run with Novozyme-435, the post reaction mixture was dissolved in dichloromethane (5 ml), and Novozyme-435 was filtered and washed with ethyl acetate (3 × 5 ml). The filtrate was concentrated under vacuum and extracted with toluene (6 × 2 ml) to remove the product and the unreacted starting material. The combined Novozyme-435 and ionic liquid phase was used for another run.

Conclusions

In summary, we demonstrated the potential of ionic liquids as lipase carriers and considered the Baeyer–Villiger reaction as an exemplary enzyme-catalysed reaction of major importance. Since the early 2000s, ionic liquids have been proposed as solvent replacements for biocatalytic applications due to their low vapour pressure and ability to stabilise protein structures. The proposed environmentally benign chemo-enzymatic Baeyer–Villiger process avoids the use of a relatively unstable peracid, which in the proposed method is generated *in situ* in the reaction system during the enzymatic stage, and the rate of its synthesis, which affects the rate of the Baeyer–Villiger process, can be effectively controlled by the applied biocatalysts.

The catalytic activity of the lipases (*i.e.*, native CALB or Novozyme-435) is highly dependent on the characteristics of the ionic liquids. The best results were obtained for 1-butyl-3-methylimidazolium bistriflimide, which is a hydrophobic ionic liquid that was efficiently recycled several times. The new method allows for the reduction of reaction times compared to the use of classical solvents in this reaction. The presented method is an example of a green biotransformation process in promising nonaqueous media.

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