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Tandem ionic liquid antimicrobial toxicity and asymmetric catalysis study: carbonyl-ene reactions with trifluoropyruvate†

Rohitkumar G. Gore,[a] Thi-Kim-Thu Truong,[a] Milan Pour,[b] Lauren Myles,[c] Stephen J. Connon*[c] and Nicholas Gathergood*[a]

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The asymmetric carbonyl-ene reaction of trifluoropyruvate with five alkenes catalysed by [Pd{(*R*)-BINAP}]-$(SbF_6)_2$ were carried out in good yields and enantioselectivities (up to 96% yield and 96% ee) in low antimicrobial toxicity C2-substituted imidazolium ionic liquids (ILs). Toxicity data was included in the selection criteria for reaction optimisation after a preliminary IL screen. The Pd(II) catalyst immobilised in an IL was recycled and reused up to 7 times without decrease of either yield or ee. One IL prepared, which was determined to be of high antimicrobial toxicity was assigned a low priority for future applications.

Introduction

The enantioselective carbonyl-ene reaction[1] has gained much attention in the past two decades as an atom-economic, reliable and convenient process for generating homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds.[2,3] The achievement of high enantioselectivity has been reported, initially in 1988, when Yamamato presented the first asymmetric carbonyl-ene reaction using modified Al-BINAP complexes.[4] Subsequently Mikami and other groups developed Ti-BINOL catalysts,[5] while Evans and co-workers reported that both Cu-Box[6] and Sc-PyBox[7] were efficient catalysts. Other metal complexes derived from Pd and Pt,[8] Co,[9] Ni,[10] Cr,[11] In[3] and several lanthanides[12] have also been used to catalyse this reaction. Mikami and co-workers obtained high enantioselectivities (between 84% and 98% ee) in the reactions of ethyl trifluoropyruvate and alkenes catalysed by a 'naked' palladium(II) complex with the chiral *atropos*-SEGPHOS and an *atropos*-platinum complex with BIPHEP.[8b,n–o] Doherty *et al.* reported a comparative study of the carbonyl-ene reaction between a range of 1,1′-disubstituted or trisubstituted alkenes and ethyl trifluoropyruvate catalysed by Lewis acid-platinum group metal complexes of the type $[M\{(R)\text{-BINAP}\}]^{2+}$ (M = Pt, Pd, Ni).[8k] This study revealed subtle but significant differences in the reactivity of these catalysts. For instance, the palladium-based Lewis acid $[Pd\text{-}\{(R)\text{-BINAP}\}]^{2+}$ catalyses the ene reaction between methylene cycloalkanes and ethyl trifluoropyruvate to afford the expected α-hydroxy ester in good yield and excellent diastereo- and enantioselectivity. In contrast, under the same conditions, the corresponding $[M\{(R)\text{-BINAP}\}]^{2+}$ (M = Pt, Ni) catalyses both the isomerisation of methylene cycloalkane and the ene reaction of the resulting mixture of methylene cycloalkane and 1-methylcycloalkene at similar rates to afford a range of α-hydroxy esters in high regioselectivity, good diastereoselectivity, and good to excellent enantioselectivity. In addition, $[Pt\{(R)\text{-BINAP}\}]^{2+}$ also catalyses post-reaction isomerisation of the ene product as well as consecutive ene reactions to afford a double carbonyl-ene product.[8k] In another study by this research group, with the same reaction model, it revealed that platinum complexes of enantiopure conformationally flexible *tropos* NUPHOS diphosphines either rival or outperform their atropisomeric enantiopure BINAP counterparts.[8p] Recently, Luo and co-worker reported that the Pd(II)-BINAPHANE catalyst afforded both good yields and excellent enantiomeric excess as high as 99.6% in the case of the carbonyl-ene reaction between ethyl trifluoropyruvate and alkenes.[8m]

Chiral transition metal complexes in asymmetric catalysis often (when well designed) promote the formation of products with high enantioselectivity, however, many are expensive. Therefore recycling of these catalysts has attracted great interest in industrial applications.[13] Immobilisation of chiral catalysts with either solid supports or polymers is a representative method to recover and reuse catalysts.[13] However, often solid

[a]*School of Chemical Sciences and National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland. E-mail: Nick.Gathergood@dcu.ie; Fax: +35 317005503*

[b]*Centre for New Antivirals and Antineoplastics, Department of Inorganic and Organic Chemistry, Charles University, Faculty of Pharmacy, Heyrovskeho 1203, CZ-500 03, Hradec Kralove, Czech Republic*

[c]*Trinity Biomedical Sciences Institute, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland. E-mail: connons@tcd.ie; Fax: +35 316712826*

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supported catalysts resulted in decreased enantioselectivity and/or activity.[13d] Recently, ionic liquids (ILs) have been shown to extend catalyst lifetime in a variety of asymmetric catalytic reactions[14] such as dihydroxylation,[14a–c] Diels–Alder,[14d] allylic amination,[14e] Michael,[14f] fluorination,[14f] epoxidation,[14g] hydrogenation,[14h] and aldol reactions.[14i] Facile product isolation by either extraction with non-polar solvents or distillation, if realised, can be a major advantage associated with IL-based methods. However, the environmental impact due to the utilization of these solvents should also be included in any life cycle assessment (LCA). There can also be benefits from a selectivity standpoint: For instance, in enantioselective carbonyl-ene reactions between various alkenes and either ethyl- or phenylglyoxal catalysed by chiral platinum complexes, the product ee obtained in 1-ethyl-2-methylimidazolium bis(trifluoromethylsulfonyl)amide is higher (up to 95%), or at least comparable, to those obtained in dichloromethane.[8j] Recycling of the IL phase, afforded after three runs, the same enantioselectivity with decreased product yield. Recently, Luo and coworkers reported that the chiral Lewis acidic palladium(II) catalyst incorporating (*R*)-BINAP is stable in 1-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide and could be recycled 21 times with retention of high enantioselectivity in each recycle.[8l]

Due to the wide range of applications and versatility, possible uses of ILs[15] have triggered an issue of waste management. Hence it is important to study the environmental impact of such ILs, especially with the potential for accidental release into the natural environment. Due to their very low vapour pressure, ILs have a low possibility of air pollution. However, ILs due to their ionic interactions, they are highly soluble in water[16–18] (except in a few cases, *e.g.* NTf_2^- and PF_6^-) which presents a viable route these ILs can be transported and interact with the environment. Therefore, in order to evaluate the biocompatibility of ILs (or ideally any chemical), toxicity, eco-toxicity, biodegradation, bioaccumulation and persistence studies should be carried out. There is however, a counter argument, that extensive assessment of the environmental impact of every IL investigated as part of a new technology, would stifle the project progress towards meeting performance goals.[19] A balance should be found, where limited assessment of the impact of the IL on the environment is performed.[19,20] If, during this preliminary screen, the IL was determined to be a high toxicity biocide, in our opinion it would be unwise to continue optimising a methodology using this as the solvent. With this in mind, ILs can be categorised in the pattern of '*Traffic Signal Lights*' as discussed at the BATIL (biodegradation and toxicity of ionic liquids) meeting in DECHEMA, Frankfurt, 2009.[19] As we start classifying ILs in three colours (Red, Yellow and Green), we can find that most ILs assessed by Stephens *et al.*[19] are in the undesirable Red and Yellow regions, although this information was solely based on toxicity data.[19] For an IL to be classified more accurately by a 'Traffic Signal Lights' pattern, detailed information about the toxicity, biodegradation and synthesis[21,22] are required.[23] A similar classification system has been applied to commonly used organic solvents, with for instance, benzene and dichloromethane rated Red.[24] In addition, the environmental impact due to the utilization of volatile solvents, during the IL synthesis and product isolation, ideally should also be included in a life cycle assessment (LCA) of the catalyzed reaction under study.

Our research effort is directed towards the development of *environmentally friendly* ILs which can also offer performance advantages over established methods.[25] As a part of our interest in performing asymmetric catalysis (*e.g.* Diels–Alder[26] and hydrogenation[27]) in ILs, we present herein enantioselective carbonyl-ene reactions of ethyl trifluoropyruvate and alkenes catalysed by chiral Pd(II)-BINAP complexes carried out in IL solvent. While we design the ILs to have low antimicrobial toxicity, it is only by tandem toxicity screening to supplement the catalysis studies that we can direct the research program towards 'greener' ILs where possible. The Pd(II)-BINAP catalyst class was chosen for this carbonyl-ene reaction because it gives the expected α-hydroxy ester in good yield and excellent diastereo- and enantioselectivity.[8k] In addition, when using Pd(II)-BINAP as the catalyst, enantioselectivities for carbonyl ene products typically are observed up to 90% ee. Thus, if our ILs have a synergistic effect on the enantioinduction conferred by the catalyst, this can be evaluated. This cannot be determined if using the Pd(II)-BINAPHANE catalyst which affords almost enantiopure product when using CH_2Cl_2 as the solvent.[8m] Furthermore, to the best of our knowledge, the use of chiral Pd(II)-BINAP catalysed carbonyl-ene reactions of ethyl trifluoropyruvate and alkenes in ILs with recovery and reuse of the chiral catalysts has not been previously reported. The performance of these ILs in comparison with common organic solvents, and the recycling of the catalyst/IL media are investigated.

Results and discussion

Synthesis of ILs

In order to design 'green' ILs, factors such as toxicity, ecotoxicity and biodegradation have been considered.[19–23,28] There are some commonly used cations such as imidazolium, pyridinium, phosphonium, and sulphonium ions. Among these classes of ILs, imidazolium have been studied in the most detail due in part to their facile preparation, low viscosity and low melting points.[29] The Gathergood and Scammells groups have previously described how the incorporation of oxygen-based functionality into the side-chain of imidazolium-derived ILs such as esters[20c,30] and ethers[31] can reduce antimicrobial toxicity. ILs with long hydrocarbon side chains have been reported to be very toxic to bacteria and fungi due to their lipophilicity.[32] According to these guidelines above, achiral ILs with ester and amide functionality in the side chains have been selected as a target for this work.

Our objective was to design low antimicrobial toxicity ILs and to use them in carbonyl-ene reactions as solvent. A series of achiral 1,2-dimethylimidazolium ILs were selected instead of 1-methylimidazolium analogues, so as to block the free acidic position at C2 and minimise any inhibiting effects on

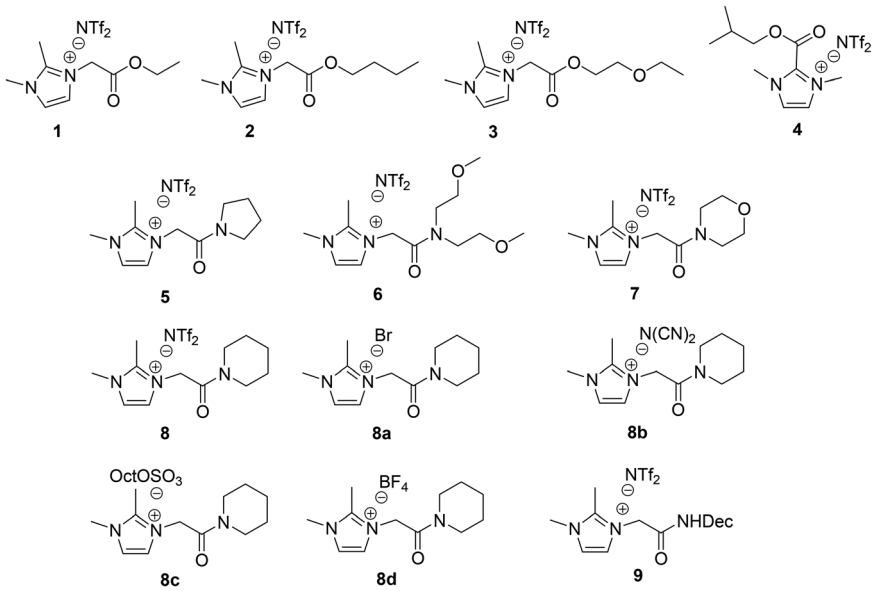


Fig. 1 ILs used as reaction solvents.

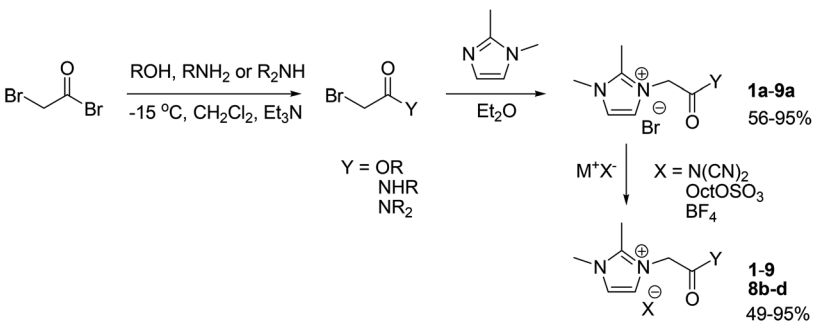
the carbonyl-ene reaction. Several amide side chain-based ILs were synthesised along with analogues incorporating ester side chains, due to unknown stability of the more labile later class of ILs under the target reaction conditions (Fig. 1).

Preparation of these ILs was carried out in three steps (Scheme 1). The first step was preparation of alkylating reagents by treatment of bromoacetyl bromide with either alcohols or amine, in presence of base.[31] The methyl and ethyl bromoacetate were commercially available. Low temperature −15 °C was used during the addition of bromoacetyl bromide. Verifying by ^{1}H-NMR spectroscopic analysis, the α-bromoesters prepared were found to be of high purity. α-Bromoamides were prepared from decylamine, pyrrolidine, piperidine, morpholine, and bis(2-methoxyethyl)amine[31] (Scheme 1).

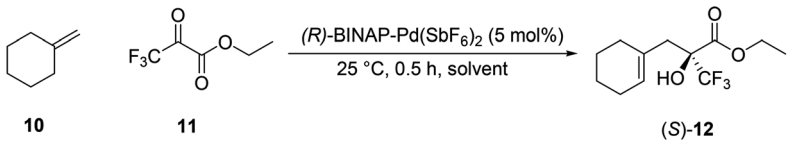
The second step, *i.e.* alkylation of the heterocycle with α-bromoesters/amides, gave the IL bromide (*e.g.* **8a**, Fig. 1) salts. 1,2-Dimethylimidazole was added to a solution of α-bromoester/α-bromoamide in diethyl ether at room temperature (RT) under inert atmosphere. Product precipitated from the reaction mixture and was easily isolated, then dried *in vacuo*. The bromide salts (**1a–9a**) formed were solid at room temperature in most cases (except **3a**) in yields ranging from 56–95%. The last step, anion metathesis, was performed on imidazolium bromide salts to obtain bistriflimide (NTf_2), tetrafluoroborate (BF_4), dicyanamide ($N(CN)_2$), and octyl sulfate ($OctOSO_3$) anion analogues. The yields for this last step were **1** 85%, **2** 91%, **3** 49%, **6** 68%, **7** 85%, **8** 80%, **8b** 94%, **8c** 95%, **8d** 79% and **9** quantitative (Scheme 1, also see Experimental section). IL **4**[33] (with an iso-butyl ester at the C2-position) and **5**[27] were prepared according to literature procedure (Fig. 1).

Enantioselective catalytic carbonyl-ene reactions in ILs

With the goal of demonstrating *environmentally friendly* ILs are compatible and beneficial in asymmetric reactions, we investigated their effect in the catalytic carbonyl-ene reaction of ethyl trifluoropyruvate (**11**) and methylenecyclohexane (**10**) with the *in situ* prepared catalyst $[Pd\{(R)\text{-BINAP}\}](SbF_6)_2$ (Scheme 2). This reaction proceeds effectively in dichloromethane (100% chemoselectivity, >99% conv., 93% ee).[8k] However, dichloromethane is not a sustainable solvent because of its high vapour pressure and high toxicity.[24] In this study, screening for alternative solvents was thus examined as shown in



Scheme 1 Synthetic route to ILs with either an ester or an amide group in the side chain.



10 11 (S)-12

Scheme 2 Enantioselective carbonyl-ene reactions catalysed by {[(*R*)-BINAP]Pd}$(SbF_6)_2$.

Table 1 Screening of solvent for the enantioselective carbonyl-ene reaction[a] of **11** with **10**

Entry	Solvent	Yield[b] (%)	ee (%)
1	CH_2Cl_2	93	90
2	Et_2O	68	98
3	PhMe	84	96
4	THF	0	nd[c]
5	**1**	76	85
6	**2**	78	90
7	**3**	77	89
8	**4**	89	91
9	**5**	89	92
10	**6**	85	89
11	**7**	87	90
12	**8**	89	91
13	**8a**	0	nd
14	**8b**	0	nd
15	**8c**	0	nd
16	**8d**	10	0
17	**9**	90	80

[a] Conditions: methylenecyclohexane (**10**) 0.25 mmol, ethyl trifluoropyruvate (**11**) 0.375 mmol (1.5 equiv.), {[(*R*)-BINAP]Pd}$(SbF_6)_2$ 0.0125 mmol (5 mol%), IL 0.25 mmol (1 equiv.) or 2 mL of conventional solvent (entries 1–4), RT, 30 min. [b] Isolated yield after flash column chromatography. [c] nd: not determined.

Table 1. The reaction was conducted with **11** (1.5 equiv.), in the presence of IL (1.0 equiv.), and catalyst [Pd{(*R*)-BINAP}]-$(SbF_6)_2$ (5 mol%) at RT for 30 min.

As illustrated in Table 1, reaction in diethyl ether and toluene resulted in good enantioselectivity (96–98% ee) and lower yield (68% and 84% respectively) in comparison to reaction in dichloromethane (entries 1 *vs.* 2 and 3). Our results in dichloromethane are in good agreement with those obtained by Doherty *et al.*[8b] under identical reaction conditions (100% conv., 93% ee). Tetrahydrofuran solvent gave 0% conversion (entry 4) which may be explained by competitive complexation to the catalyst system. The use of IL **1** gave **12** in only 76% yield and 85% ee (entry 5), while the use of ILs **2** and **3** as the solvent afforded the product **12** with similar enantioselectivity (89–90% ee, entries 6 and 7) to that obtained in dichloromethane (entry 1), although the yield decreased dramatically (77–78%). The results of carbonyl-ene reaction in ILs **4** and **5** (89% yield, 91–92% ee, entries 8 and 9) were comparable with that in dichloromethane.

The use of ILs **6** and **7** resulted in similar levels of product enantiomeric excess (89–90% ee) to reactions performed in dichloromethane, although the yield decreased slightly (85–87%, entries 10 and 11). The results of carbonyl-ene reaction in ILs **8** (89% yield, 91% ee, entry 12) were comparable with those in dichloromethane. Thus, lower yields were obtained in the reactions using ILs containing an ester side chain at C1 **1–3** (76–78% yield, entries 5–7 *vs.* entry 1).

The effect of cation and counterion structure can also be evaluated. Reactions in amide side chain-based ILs **5–8** gave higher product yields than results in the ester side chain ILs **1–3**, although the structure of cation for ILs **5–8** had no significant impact on either yield or enantioselectivity. To investigate the anion effect, ILs with commonly used anions, such as Br, BF_4, NTf_2, $OctOSO_3$ and $N(CN)_2$ were studied. From the series of **8–8d**, only the NTf_2 IL **8** gave a comparable result (89% yield, 91% ee) to that obtained in dichloromethane (entry 11 *vs.* entry 1). No conversion was observed in the case of IL **8a**, **8b**, **8c** with Br, $N(CN)_2$ and $OctOSO_3$ anions, respectively (entries 13–15). This could be explained by either an exchange of those anions with SbF_6 which could result in catalyst deactivation or due to the hydrophilic properties of **8a–c** compared to the hydrophobic NTf_2 ILs **1–8**. The use of IL **8d** (with the BF_4 counterion), led to just 10% yield of racemic product **12** (entry 16). To study the effect of a long linear alkyl chain, the decyl amide IL **9** was screened. While the yield of **12** was the same as when the reaction carried out in ILs **4**, **5** and **8**, a decrease in ee of **12** by 10% is observed in **9** (entry 17 *vs.* entries 8, 9 and 12).

On the basis of the results in Table 1 and antimicrobial toxicity data (*vide infra*) the ester IL **4** was selected for further reaction optimisation, and substrate scope studies. The amide-based IL **5** was also included for comparison in stability/recycling studies.

Catalyst optimisation study

Optimisation of reaction conditions was carried out, and the results shown in Table 2. The first parameter investigated was the amount of IL, as a reduction in the quantity required would lead to a significant benefit in the overall 'greenness' of the reaction. We were pleased to find that decreasing the amount of IL from 1 equiv. to 0.5 equiv. (Table 2 entry 1 *vs.* 2) lead to an increase in the yield from 89% to 96%, while retaining high enantioselectivity (91% ee). However, 1.5 equiv. of ethyl trifluoropyruvate (**11**) was required for a high yield, with yields of only 78% and 68% attained when 1 equiv. present (entries 3 and 4). Decreasing the catalyst loading from 5 mol% to 2 mol%, gave a slight (6%) decrease in yield, however a further dramatic 39% decrease in yield was observed at 10 mol% catalyst loading (entry 2 *vs.* entries 5 and 6). The enantioselectivity did not significantly change throughout this catalyst loading study (87–91% ee). At 10 mol% catalyst loading (entry 6), the reaction mixture was very viscous, and efficient stirring a problem, which we attribute to the low yield. Adjusting the

Table 2 Condition optimisation for the enantioselective carbonyl-ene reaction of **11** with **10** in IL **4** catalysed by {[(*R*)-BINAP]Pd}$(SbF_6)_2$

Entry	**10** (equiv.)	**11** (equiv.)	Catalyst (equiv.)	IL **4** (equiv.)	Temperature (°C)	Time (min)	Yield[a] (%)	ee (%)
1	1	1.5	0.05	1	25	30	89	91
2	1	1.5	0.05	0.5	25	30	96	91
3	1	1	0.05	0.5	25	30	78	89
4	1.5	1	0.05	0.5	25	30	68	91
5	1	1.5	0.02	0.5	25	30	90	87
6	1	1.5	0.10	0.5	25	30	51	88
7	1	1.5	0.05	0.5	40	30	92	87
8	1	1.5	0.05	0.5	0	30	93	90
9	1	1.5	0.05	0.5	25	60	88	87
10	1	1.5	0.05	0.5	25	120	93	87
11	1	1.5	0.05	0.5	25	15	90	88

[a] Isolated yield.

reaction temperature (40 °C or 0 °C, entries 7 and 8) and reaction time (15, 60 or 120 min, entries 9–11) did not lead to an increase in either the yield or ee.[33] The optimal conditions in Table 2 are given in entry 2, and were selected for use in the substrate scope study.

Substrate scope

The scope of the carbonyl-ene reaction was next studied under the optimised reaction conditions described in Table 2, entry 2 (1 equiv. alkene, 1.5 equiv. of **11**, 0.5 equiv. of IL **4**, 5 mol% catalyst, 25 °C, 30 min). A range of aliphatic, aromatic and cycloalkene substrates were screened in the reaction with ethyl trifluoropyruvate (**11**) (Table 3).

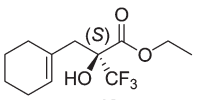
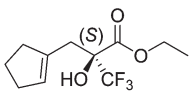
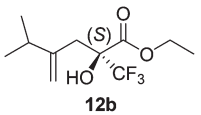
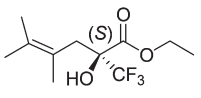
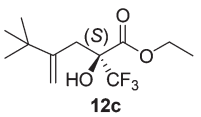
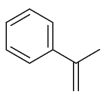
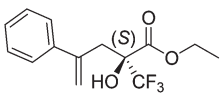
Excellent isolated yield and good enantiomeric excess were observed for the product in the reaction involving methylene cyclohexane (**10**) (96% yield, 91% ee, entry 1). Good isolated yield and excellent enantiomeric excess for the product were observed when using methylene cyclopentane (**10a**) as the substrate in the carbonyl ene reaction (82% yield, 96% ee, entry 2).

In reactions involving 2,3-dimethyl-1-butene **10b**, two products (**12b** and **12b′**) were observed with 80% combined yield (ratio **12b**/**12b′** = 1.8) and 94% ee for both compounds (Table 3, entry 3). This mixture of products can be explained by the reported possible catalytic mechanism due to the availability of two different C–H bonds alpha to the carbon–carbon double bond.[8m] Furthermore, both 2,3-dimethyl-1-butene (**10b**) and ethyl trifluoropyruvate (**11**) are small compounds which can easily access the Pd-catalyst to allow **10b** to approach the coordinated ethyl trifluoropyruvate **11** in two different ways.[8m] Alkene **10c** gave product **12c** in 81% yield and 96% ee. With α-methylstyrene (**10d**), moderate yield and enantioselectivity were observed (71% yield, 75% ee, entry 5, Table 3). The results in Table 3 also show that the enantioselectivities obtained using aliphatic alkenes (**10–10c**) were higher than associated with the conjugated aromatic substrate **10d** (91–96% >75% ee).

In comparison with the reaction in CH_2Cl_2, the result obtained on reaction with either methylene cyclohexane (**10**) (96% yield, 91% ee, entry 1 *vs.* 96% yield, 93% ee in CH_2Cl_2),[8k] or 2,3-dimethyl-1-butene (**10b**) (80% yield, 94% ee, entry 3 *vs.* 87% yield, 95% ee in CH_2Cl_2) in IL **4** were similar.[8k]

In the case of either methylene cyclopentane (**10a**) (82% yield, 96% ee, entry 2 *vs.* 100% conv., 96% ee in CH_2Cl_2),[8k] or α-methylstyrene (71% yield, 75% ee *vs.* >99% conversion, 78% ee) the enantiomeric excess of the products are similar to when the reaction is performed in either CH_2Cl_2 or IL **4**,

Table 3 Substrate scope for the enantioselective carbonyl-ene reaction[a] of **11** to alkenes **10–10d** in IL **4** catalysed by {[(*R*)-BINAP]Pd}$(SbF_6)_2$

Entry	Alkene	Product	Yield[b] (%)	ee (%)
1	 **10**	 **12**	96	91[c]
2	 **10a**	 **12a**	82	96[c]
3	 **10b**	 **12b**	80 (**12b**/**12b′** = 1.8)[d]	94[c]
		 **12b′**		94[c]
4	 **10c**	 **12c**	81	96[c]
5	 **10d**	 **12d**	71	75[e]

[a] Conditions: alkene 0.25 mmol (1 equiv.), ethyl trifluoropyruvate (**11**) 0.375 mmol (1.5 equiv.), catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$ 0.0125 mmol (5 mol%), IL **4** 0.125 mmol (0.5 equiv.), 25 °C, 30 min. [b] Isolated yield. [c] Determined by chiral GC. [d] Ratio of products was determined by ^{1}H- and ^{19}F-NMR spectroscopic analysis. [e] Determined by chiral HPLC.

Table 4 Enantioselective carbonyl-ene reaction[a] of **11** to **10** in either recycled catalyst/IL **4** or **5**

	Reaction in ester side chain IL **4**		Reaction in amide side chain IL **5**	
Cycle	Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	96	91	90	93
2	92	91	88	92
3	90	92	84	89
4	92	93	75	86
5	92	93	69	73
6	90	92	—	—
7	92	91	—	—
8	77	84	—	—

[a] Conditions: methylenecyclohexane (**10**) 0.25 mmol (1 equiv.), ethyl trifluoropyruvate (**11**) 0.375 mmol (1.5 equiv.), catalyst {[(*R*)-BINAP]Pd}-$(SbF_6)_2$ 0.0125 mmol (5 mol%) for the first cycle, IL 0.125 mmol (0.5 equiv.) for the first cycle, RT, 30 min. [b] Isolated yield. [c] Determined by chiral GC.

however, comparison of the isolated yield is not possible, as only conversion (albeit >99%) was reported.

The recyclability of catalyst [Pd{(*R*)-BINAP}]$(SbF_6)_2$/IL media was also evaluated (Table 4). After 30 min the reaction mixture was extracted into diethyl ether (2 mL × 3), and the product **12** isolated by column chromatography. The ether-immiscible phase, including the IL and catalyst was dried under vacuum to remove residual solvent. Then, to this recycled IL immobilised catalyst was added new substrates and the reaction repeated. Using this procedure, the IL **4** and immobilised catalyst could be recycled and reused 7 times, maintaining both similar activity and enantioselectivity. From cycle 8 onwards, a slight drop in yield and enantiomeric excess was observed.

Due to the susceptibility of ester groups to undergo hydrolysis, we were pleased that IL **4** performed effectively over 7 cycles. Our expectation was that the amide IL **5** would give superior recycling performance, due to the susceptibility of the ester bond to hydrolysis, however, this was not the case. On cycle 4 in amide IL **5**, the yield had dropped to 75%, and by cycle 5 the enantioselectivity decreased to 73% ee (Table 4).

Antifungal and antibacterial toxicity

The NTf_2 based ILs **1–9** performed well as the solvent in the enantioselective catalytic carbonyl-ene reactions of ethyl trifluoropyruvate (**11**) and alkenes, in several examples leading to results comparable to those obtained in CH_2Cl_2. Our research philosophy is to provide antimicrobial toxicity data for ILs we prepare, thus antifungal and antibacterial properties were studied concurrently for all ILs (Tables 5 and 6). ILs are not omitted from the toxicity screening due to poor performance (**8a–d**) in the carbonyl ene reactions studied, as **1–7**, **8–8d** and **9** may find use in other applications. With toxicity data available, a decision can be made on whether they can be recommended for further study or not. The antifungal toxicity results (Table 5) and antibacterial toxicity results (Table 6) reveal that all ILs (except **9**), did not exhibit high toxicity in the test system up to 2000 μM concentration (or the solubility limit in media), irrespective of the incorporation of either ester or amide side chains. Due to the low solubility of ILs **1**, **8** and **9** the maximum concentration achieved was only 1000 μM in the media for antibacterial toxicity screening and 1000 μM for **1** and **9** in the media for antifungal toxicity screening.

The long alkyl (*i.e.* decyl) amide side chain in IL **9** was demonstrated to be the structural feature leading to the high toxicity of **9** in most of the fungi and bacterial strains, especially with IC_{80} values of 15.6 μM to *Candida krusei E28* and *Candida tropicalis 156* and IC_{95} values of 62.5 μM to

Table 5 Antifungal toxicity screening of ILs (MIC IC_{80} or IC_{50})

		IL (μM)			
Strain	Time (h)	**1**	**2–7, 8a–d**	**8**	**9**
Candida albicans ATCC 44859[a]	24 h	1000	>2000	>2000	250
	48 h	>1000	>2000	>2000	250
Candida albicans ATCC 90028[a]	24 h	1000	>2000	>2000	250
	48 h	>1000	>2000	>2000	250
Candida parapsilosis ATCC 22019[a]	24 h	>1000	>2000	>2000	62.5
	48 h	>1000	>2000	>2000	125
Candida krusei ATCC 6258[a]	24 h	>1000	>2000	>2000	31.25
	48 h	>1000	>2000	>2000	31.25
Candida krusei E28[a]	24 h	>1000	>2000	>2000	15.62
	48 h	>1000	>2000	>2000	31.25
Candida tropicalis 156[a]	24 h	>1000	>2000	>2000	15.62
	48 h	>1000	>2000	>2000	31.25
Candida glabrata 20/I[a]	24 h	>1000	>2000	>2000	62.5
	48 h	>1000	>2000	>2000	125
Candida lusitaniae 2446/I[a]	24 h	>1000	>2000	>2000	250
	48 h	>1000	>2000	>2000	250
Trichosporon beigelii 1188[a]	24 h	>1000	>2000	>2000	250
	48 h	>1000	>2000	>2000	500
Aspergillus fumigatus 231[b]	24 h	>1000	>2000	>2000	250
	48 h	>1000	>2000	>2000	500
Absidia corymbifera 272[b]	24 h	>1000	>2000	>2000	>1000
	48 h	>1000	>2000	>2000	>1000
Trichophyton mentagrophytes 445[b]	72 h	>1000	>2000	>2000	250
	120 h	>1000	>2000	>2000	250

[a] MIC = IC_{80}. [b] MIC = IC_{50}.

Table 6 Antibacterial toxicity screening of ILs (MIC IC_{95})

		IL (μM)			
Strain	Time (h)	**1**	**2–7, 8a–d**	**8**	**9**
Staphylococcus aureus	24 h	>1000	>2000	>1000	62.5
ATCC 6538	48 h	>1000	>2000	>1000	62.5
Staphylococcus aureus	24 h	>1000	>2000	>1000	125
HK 5996/08	48 h	>1000	>2000	>1000	125
Staphylococcus	24 h	>1000	>2000	>1000	250
epidermidis HK 6966/08	48 h	>1000	>2000	>1000	250
Enterococcus sp.	24 h	>1000	>2000	>1000	62.5
HK 14365/08	48 h	>1000	>2000	>1000	125
Escherichia coli	24 h	>1000	>2000	>1000	250
ATCC 8739	48 h	>1000	>2000	>1000	250
Klebsiella pneumonia	24 h	>1000	>2000	>1000	250
HK 11750/08	48 h	>1000	>2000	>1000	250
Klebsiella pneumonia	24 h	>1000	>2000	>1000	250
ESBL HK 14368/08	48 h	>1000	>2000	>1000	250
Pseudomonas aeruginosa	24 h	>1000	>2000	>1000	1000
ATCC 9027	48 h	>1000	>2000	>1000	>1000

Staphylococcus aureus and *Enterococcus* sp. IL **1** has inhibited both *Candida albicans* strains at 1000 μM concentration after 24 h, which was eventually suppressed over the period of 48 h, and may be due to hydrolysis of the ester. In summary, the antimicrobial toxicity data supported the further study of ILs **4** and **5** (combined with Table 1 results) in the catalyst optimisation screening investigation and support the assignment of low priority to IL **9** for future applications.

Conclusions

A series of imidazolium-based ILs substituted at the C2-position of the heterocycle and incorporating either ester or amide groups have been synthesised. Tandem assessment of their performance in the enantioselective catalytic carbonyl-ene reactions of ethyl trifluoropyruvate (**11**) and methylenecyclohexane (**10**) with the *in situ* prepared catalyst [Pd{(*R*)-BINAP}]-$(SbF_6)_2$ and antimicrobial toxicity have been studied. By including toxicity data of ILs as a parameter in the selection criteria for reaction optimisation, ILs with undesirable high toxicity (antimicrobial screened herein) can be avoided. We determined that the *n*-decylamide derivative **9**, was the only IL in the study of high antimicrobial toxicity (IC_{80} values of 15.6 μM to *Candida krusei E28* and *Candida tropicalis 156* and IC_{95} values of 62.5 μM to *Staphylococcus aureus* and *Enterococcus* sp.) Although this gave the carbonyl ene product in yields similar to those obtained in CH_2Cl_2 solvent, the enantioselectivity was *ca.* 10% lower. Therefore there was no clear reason to continue with this IL in the current study. All the other ILs prepared were demonstrated to be of acceptable low antimicrobial toxicity, based on the scope (20 strains) of the screen. Ester- and amide-based ILs (**4** and **5** respectively) were selected for further reaction optimisation and recycling studies based on the initial results of the asymmetric carbonyl-ene reaction screen.

Excellent yields and enantioselectivities (up to 96% yield and 94% ee) were obtained using IL **4** as the solvent. During the optimisation study, reducing the volume of IL by 50%, lead to an increase of yield if 1.5 equiv. of ethyl trifluoropyruvate was used. These results were either superior or comparable to those associated with conventional volatile solvents (*e.g.* CH_2Cl_2). Substrate scope studies revealed identical enantioselectivity when using methylenecyclopentane in either IL **4** or CH_2Cl_2.[8k] Furthermore, the IL **4** immobilised catalyst [Pd{(*R*)-BINAP}]$(SbF_6)_2$ reaction medium was recycled and reused up to 7 times without loss of activity. Overall, several ILs were found to be a good solvent as a replacement for harmful VOCs (dichloromethane) and to be an efficient trap for the chiral Pd catalyst used in these carbonyl-ene reactions of ethyl trifluoropyruvate. However, the environmental impact due to the utilization of volatile solvents, during the IL synthesis and product isolation, ideally should also be included in a LCA of the catalyzed reaction under study. The *n*-decylamide based IL **9** was determined to be of high antimicrobial toxicity 'Red', and is given a low priority for future applications. Conversely, ILs **1–8d** are classed 'Yellow' under the 'Traffic Signal Light' categorisation and warrant further toxicity, eco-toxicity and biodegradation evaluation and hold promise for consideration in IL based technologies.

Experimental section

General information

The NMR spectra were recorded in $CDCl_3$. ^{1}H-NMR spectra were recorded at 400 MHz. The chemical shifts (δ) are reported in part per million, relative to TMS as internal standard. *J* values are given in hertz. ^{13}C NMR spectra were recorded at 100 MHz. TLC experiments were carried out in 0.2 mm thick silica gel plates (GF254) and visualization was accomplished by UV light or phosphomolybdic acid solution. The columns were hand-packed with silica l60 (200–300 mesh). All reagents and solvents were purchased from commercial sources (Acros, Aldrich) and were used without further purification. α-Bromoesters/amides were prepared according to literature methods. Compounds **4** and **5** were prepared according to literature.[27,34]

1*H*-Imidazolium-1,2-dimethyl-3-(2-ethoxy-2-oxoethyl)-1-methyl bis(trifluoromethanesulfonimide) (1). A round bottom flask was charged with ethyl bromoacetate (1.00 g, 5.90 mmol) and diethyl ether (20 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (0.575 g, 5.90 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid. The product was then washed with diethyl ether (10 × 10 mL), then solvent was removed on the rotary evaporator. Product 1*H*-imidazolium,1,2-dimethyl-3-(2-ethoxy-2-oxoethyl)-1-methyl-, bromide (**1a**) was dried *in vacuo* for 72 h to give a white solid at RT in 95% yield (1.50 g, 5.60 mmol). Melting point: 130–131 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.93 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 5.49 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 2.75 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.28, 145.62, 123.00, 122.41, 62.89, 50.01, 36.10, 14.10, 11.26. ES-MS (+ve) *m*/*z*: Found $[M - Br^-]^+$ 183.1127, $C_9H_{13}N_2O_2^+$ requires 183.1128. A flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl-, bromide (1.00 g, 0.38 mmol) and distilled water (5 mL). $LiNTf_2$ (1.09 g, 0.38 mmol) in distilled water (5 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed and IL washed with water (3 × 10 mL). Water was removed on the rotary evaporator and the product dried *in vacuo* for 72 h to give the title compound **1** as a colourless liquid at RT in 85% yield (1.51 g, 0.326 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 4.95 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 2.59 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.73, 145.55, 122.42, 122.30, 119.72 (q, *J* = 320 Hz, 2 CF_3), 63.21, 49.34, 35.58, 13.91, 9.90. ES-MS (+ve) *m*/*z*: Found $[M - NTf_2^-]^+$ 183.1130, $C_{11}H_{19}N_2O_2^+$ requires 183.1128.

1*H*-Imidazolium,1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl-, NTf_2 (2). A flask was charged with butyl bromoacetate (8.17 g, 41.9 mmol) and diethyl ether (150 mL) under nitrogen. To this

solution was added 1,2-dimethylimidazole (4.02 g, 41.9 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, and washed with diethyl ether (10 × 100 mL). The solvent was removed on the rotary evaporator, and the product was dried *in vacuo* for 72 h to give 1*H*-imidazolium,1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl-bromide (**2a**) as a white solid at RT in 71% yield (8.66 g, 29.75 mmol). Melting point: 75–76 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.91 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 5.47 (s, 2H), 4.18 (t, J = 6.8 Hz, 2H), 3.97 (s, 3H), 2.74 (s, 3H), 1.69–1.60 (m, 2H), 1.41–1.31 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.33, 145.60, 122.97, 122.44, 66.68, 49.98, 36.09, 30.35, 18.96, 13.65, 11.26. ES-MS (+ve) m/z: Found $[M - Br^-]^+$ 211.1453, $C_{11}H_{19}N_2O_2^+$ requires 211.1441. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl-bromide (**2a**) (3.00 g, 10.3 mmol) and distilled water (15 mL). Lithium bis(trifluoromethanesulfonimide) (2.96 g, 10.3 mmol) in distilled water (10 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed and IL washed with water (3 × 40 mL). Water was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give the title compound **2** as a colourless liquid at RT in 91% yield (4.61 g, 9.39 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 4.85 (s, 2H), 4.14 (t, J = 6.6 Hz, 2H), 3.75 (s, 3H), 2.48 (s, 3H), 1.63–1.55 (m, 2H), 1.36–1.26 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.79, 145.48, 122.40, 122.35, 119.72 (q, J = 320 Hz, 2 CF_3), 66.95, 49.22, 35.53, 30.25, 18.89, 13.56, 9.81. ES-MS (+ve) m/z: Found $[M - NTf_2^-]^+$ 211.1449, $C_{11}H_{19}N_2O_2^+$ requires 211.1441.

1*H*-Imidazolium,1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl-, NTf_2 (3). A RB flask was charged with 2-ethoxyethyl bromoacetate (3.51 g, 16.58 mmol) and diethyl ether (75 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (1.75 g, 18.24 mmol). The reaction mixture was stirred vigorously for 24 h and the product separated as a brown liquid phase. The product was then washed with diethyl ether (10 × 100 mL), solvent removed on the rotary evaporator and dried *in vacuo* for 72 h to give 1*H*-imidazolium,1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl-bromide (**3a**) as a brown liquid at RT in 61% yield (3.11 g, 10.13 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 5.42 (s, 2H), 4.31–4.27 (m, 2H), 3.90 (s, 3H), 3.62–3.59 (m, 2H), 3.47 (q, J = 7.1 Hz, 2H), 2.67 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.38, 145.70, 122.95, 122.48, 67.77, 66.67, 65.62, 49.94, 36.09, 15.12, 11.16. ES-MS (+ve) m/z: Found $[M - Br^-]^+$ 227.1397, $C_{11}H_{19}N_2O_3^+$ requires 227.1390. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl-bromide (**3a**) (2.00 g, 6.5 mmol) and distilled water (9 mL). Lithium bis(trifluoromethanesulfonimide) (1.87 g, 6.5 mmol) in distilled water (9 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed, the IL washed with water (3 × 40 mL). The excess water was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give the title compound **3** as a colourless liquid at RT in 49% yield (1.605 g, 3.16 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 4.88 (s, 2H), 4.31–4.27 (m, 2H), 3.75 (s, 3H), 3.60–3.58 (m, 2H), 3.46 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.76, 145.56, 122.39, 122.30, 119.72 (q, J = 320 Hz, 2 CF_3), 67.62, 66.66, 65.90, 49.20, 35.53, 15.03, 9.78. ES-MS (+ve) m/z: Found $[M - NTf_2^-]^+$ 227.1392, $C_{11}H_{19}N_2O_3^+$ requires 227.13902.

1*H*-Imidazolium,1,2-dimethyl-3-[2-[bis(2-methoxyethyl)amino]-2-oxoethyl]-, NTf_2 (6). A RB flask was charged with 2-bromo-*N*,*N*-bis(2-methoxyethyl)-acetamide (1.00 g, 3.93 mmol) and diethyl ether (25 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (3.78 g, 3.93 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid and was washed with diethyl ether (10 × 25 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give 1*H*-imidazolium-1,2-dimethyl-3-[2-[bis(2-methoxyethyl)amino]-2-oxoethyl]-bromide (**6a**) as a white solid at RT in 85% yield (1.17 g, 3.34 mmol). Melting point: 119–120 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (d, J = 2.4 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 5.70 (s, 2H), 3.93 (s, 3H), 3.74 (t, J = 4.8 Hz, 2H), 3.57 (t, J = 4.8 Hz, 2H), 3.53 (t, J = 4.8 Hz, 2H), 3.49 (t, J = 4.8 Hz, 2H), 3.36 (s, 3H), 3.31 (s, 3H), 2.64 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.47, 145.69, 122.90, 121.96, 70.46, 69.97, 59.18, 58.89, 50.70, 48.55, 46.55, 35.93, 10.68. ES-MS (+ve) m/z: Found $[M - Br^-]^+$ 270.1816, $C_{13}H_{24}N_3O_3^+$ requires 270.1812. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-[bis(2-methoxyethyl)amino]-2-oxoethyl]bromide (**6a**) (1.00 g, 2.85 mmol) and distilled water (4 mL). Lithium bis(trifluoromethanesulfonimide) (0.819 g, 2.85 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 × 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give the title compound **6** as a colourless liquid at RT in 68% yield (1.07 g, 1.94 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 5.26 (s, 2H), 3.81 (s, 3H), 3.65 (dd, J = 4.8, 4.4 Hz, 2H), 3.59–3.56 (m, 4H), 3.53–3.50 (m, 2H), 3.40 (s, 3H), 3.34 (s, 3H), 2.52 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.17, 145.74, 122.68, 121.65, 119.76 (q, J = 320 Hz, 2 CF_3), 70.52, 69.68, 59.10, 58.88, 50.14, 48.31, 46.39, 35.38, 9.69. ES-MS (+ve) m/z: Found $[M - NTf_2^-]^+$ 270.1823, $C_{12}H_{20}N_3O^+$ requires 270.1812.

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl]-, NTf_2 (7). A RB flask was charged with *N*-(bromoacetyl)morpholine (1.00 g, 4.80 mmol) and diethyl ether (25 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (0.466 g, 4.80 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, then washed with diethyl ether (10 × 25 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl]bromide (**7a**) as a white solid at RT in 77% yield (1.12 g, 3.68 mmol). Melting point: 199–200 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.67 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 5.85 (s, 2H), 3.83 (s, 3H), 3.79 (dd, J = 5.2, 4.4 Hz, 2H), 3.68 (dd, J = 5.2, 4.4 Hz, 2H), 3.65 (dd, J = 5.2, 4.4 Hz, 2H), 3.52 (dd, J = 5.2, 4.4 Hz, 2H), 2.68 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.12, 146.25, 123.22, 121.51, 66.75, 66.44, 51.04, 45.59, 42.64, 35.78, 11.17. ES-MS (+ve) m/z: Found $[M - Br^-]^+$ 224.1395, $C_{11}H_{18}N_3O_2^+$ requires 224.1393. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl]bromide (**7a**) (1.10 g, 3.62 mmol) and distilled water (4 mL). Lithium bis(trifluoromethane) sulfonamide (1.04 g, 3.62 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed; the IL washed with water (3 × 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give the title compound **7** as a colourless liquid at RT in 85% yield (1.56 g, 3.09 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.23 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 5.11 (s, 2H), 3.82 (s, 3H), 3.77 (dd, J = 5.2, 4.4 Hz, 2H), 3.72 (dd, J = 5.2, 4.4 Hz, 2H), 3.60 (dd, J = 5.2, 4.4 Hz, 2H), 3.54 (dd, J = 5.2, 4.4 Hz, 2H), 2.53 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 162.51, 145.96, 122.76, 121.74, 119.71 (q, J = 319 Hz, 2 CF_3), 66.43, 66.25, 49.75, 45.09, 42.65, 35.42, 9.92. ES-MS (+ve) m/z: Found $[M - NTf_2^-]^+$ 224.1389, $C_{12}H_{20}N_3O^+$ requires 224.1393.

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, NTf_2 (8). A RB flask was charged with 2-bromo-1-(piperidin-1-yl)ethanone (4.61 g, 48.0 mmol) and diethyl ether (400 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (9.00 g, 43.6 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, then washed with diethyl ether (10 × 100 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, bromide (**8a**) as a white solid at RT in 56% yield (7.36 g, 24.45 mmol). Melting point: 123–124 °C. ^{1}H-NMR (400 MHz, CD_3CN): 7.45 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 5.26 (s, 2H), 3.79 (s, 3H), 3.51 (t, J = 5.6 Hz, 2H), 3.45 (t, J = 5.2 Hz, 2H), 2.49 (s, 3H), 1.70–1.67 (m, 4H), 1.56–1.55 (br m, 2H). ^{13}C-NMR (100 MHz, CD_3CN): 163.76, 147.67, 123.75, 123.24, 51.14, 47.01, 44.42, 36.46, 27.23, 26.63, 25.32, 10.90. ES-MS (+ve) m/z: Found $[M - Br^-]^+$ 222.1610, $C_{12}H_{20}N_3O^+$ requires 222.1601. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-bromide (**8a**) (0.700 g, 2.30 mmol) and distilled water (4 mL). Lithium bis(trifluoromethanesulfonimide) (0.665 g, 2.30 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 × 40 mL). Residual water was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give the title compound **8** as a colourless liquid at RT in 80% yield (0.93 g, 1.85 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.10 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 1.8 Hz, 1H), 4.98 (s, 2H), 3.72 (s, 3H), 3.47 (t, J = 6.0 Hz, 2H), 3.37 (t, J = 5.4 Hz, 2H), 2.44 (s, 3H), 1.61–1.58 (m, 4H), 1.52–1.50 (br m, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$): 161.79, 145.93, 122.96, 122.75, 119.76 (q, J = 319.5 Hz, 2 CF_3), 50.04, 45.95, 43.67, 35.39, 26.07, 25.35, 24.09, 9.96. ES-MS (+ve) m/z: Found $[M - NTf_2^-]^+$ 222.1609, $C_{12}H_{20}N_3O^+$ requires 222.1601.

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, $N(CN)_2$ (8b). A flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, bromide (**8a**) (1.00 g, 3.30 mmol) and acetone (5 mL) under a nitrogen atmosphere. Sodium dicyanamide (0.442 g, 4.96 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 × 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then dried *in vacuo* for 2 days to give the title compound **8b** as a white solid at RT in 99% yield (0.950 g, 3.20 mmol). Melting point: 84–85 °C. ^{1}H-NMR (600 MHz, CD_3CN): 7.34 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 5.14 (s, 2H), 3.77 (s, 3H), 3.51 (t, J = 5.4 Hz, 2H), 3.43 (t, J = 6.0 Hz, 2H), 2.46 (s, 3H), 1.69–1.67 (m, 4H), 1.56–1.54 (m, 2H). ^{13}C-NMR (150 MHz, CD_3CN): 163.48, 147.84, 123.90, 123.45, 121.20, 47.16, 44.63, 36.62, 27.38, 26.79, 25.49, 10.98. ES-MS (+ve) m/z: Found $[M - N(CN)_2^-]^+$ 222.1616, $C_{12}H_{20}N_3O^+$ requires 222.1601.

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, octylsulfate (8c). A flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, bromide (**8a**) (1.00 g, 3.3 mmol) and distilled water (10 mL). Sodium octylsulfate (0.768 g, 3.30 mmol) in distilled water (5 mL) was added in one portion and the suspension was stirred vigorously for 24 h at RT. The water was removed on the rotary evaporator and residue was dissolved in chloroform (10 mL) and washed with water. Organic layer was dried over anhydrous magnesium sulphate, filtered and solvent removed by rotary evaporation. The product was dried *in vacuo* for 72 h to give the title compound **8c** as a white wax at RT in 79% yield (1.12 g, 2.60 mmol). Melting point: 40–42 °C ^{1}H-NMR (600 MHz, $CDCl_3$): 7.39 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 5.34 (s, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.77 (s, 3H), 3.46 (t, J = 6.0 Hz, 4H), 2.52 (s, 3H), 2.44 (s, 3H), 1.64–1.50 (m, 8H), 1.29–1.20 (m, 10H). ^{13}C-NMR (150 MHz, $CDCl_3$): 162.65, 146.02, 123.03, 121.65, 68.03, 50.28, 46.14, 43.58, 35.46, 31.84, 29.49, 29.38, 29.28, 26.17, 25.89, 25.40, 24.20, 22.67, 14.13, 10.40. ES-MS (+ve) m/z: Found $[M - OctOSO_3^-]^+$ 222.1602, $C_{12}H_{20}N_3O^+$ requires 222.1601.

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, BF_4 (8d). A flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]-, bromide (**8a**) (1.00 g, 3.30 mmol) and acetone (10 mL) under a nitrogen atmosphere. Sodium tetrafluoroborate (0.472 g, 4.30 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetone (2 × 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then dried *in vacuo* for 2 days to give the title compound **8d** as a white solid in 100% yield (1.02 g, 3.30 mmol). Melting point: 119–120 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): 7.26 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 5.15 (s, 2H), 3.79 (s, 3H), 3.53 (t, J = 5.4 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H), 2.51 (s, 3H),

1.70–1.69 (m, 4H), 1.60–1.58 (m, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$): 162.39, 146.00, 122.59, 121.75, 49.60, 45.90, 43.53, 35.19, 25.96, 25.37, 24.16, 9.74. ES-MS (+ve) *m*/*z*: Found $[M - BF_4^-]^+$ 222.1597, $C_{12}H_{20}N_3O^+$ requires 222.1601.

1*H*-Imidazolium,1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl]-, NTf_2 (9). A RB flask was charged with 2-bromo-*N*-decyl-acetamide (3.00 g, 10.78 mmol) and diethyl ether (50 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (1.04 g, 10.78 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, then washed with diethyl ether (10 × 50 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give 1*H*-imidazolium,1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl]bromide (**9a**) as a white solid at RT in 67% yield (2.70 g, 7.21 mmol). Melting point: 95–96 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.68 (dd, J = 5.6, 5.2 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 5.23 (s, 2H), 3.84 (s, 3H), 3.15 (t, J = 6.0 Hz, 2H), 2.75 (s, 3H), 1.55–1.47 (m, 2H), 1.23–1.17 (m, 14H), 0.80 (t, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 164.31, 145.40, 122.76, 121.92, 51.06, 40.05, 35.89, 31.90, 29.59, 29.57, 29.32, 29.26, 29.14, 27.07, 22.69, 14.14, 11.08. ES-MS (+ve) *m*/*z*: Found $[M - Br^-]^+$ 294.2542, $C_{17}H_{32}N_3O^+$ requires 294.2545. A RB flask was charged with 1*H*-imidazolium,1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl]bromide (0.600 g, 1.60 mmol) and distilled water (4 mL). Lithium bis(trifluoromethanesulfonimide) (0.460 g, 1.60 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 × 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give the title compound **9** as a colourless liquid at RT in 94% yield (0.867 g, 1.51 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.85 (t, J = 5.6 Hz, 1H), 4.77 (s, 2H), 3.73 (s, 3H), 3.18–3.12 (m, 2H), 2.52 (s, 3H), 1.48–1.40 (m, 2H), 1.19–1.18 (br m, 14H), 0.80 (t, J = 7.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.75, 145.53, 122.42, 121.92, 119.78 (q, J = 319 Hz, 2 CF_3), 50.42, 40.21, 35.43, 31.89, 29.55, 29.50, 29.31, 29.21, 29.03, 26.83, 22.69, 14.13, 9.94. ES-MS (+ve) *m*/*z*: Found $[M - NTf_2^-]^+$ 294.2531, $C_{12}H_{20}N_3O^+$ requires 294.2545.

General procedure of enantioselective catalytic carbonyl-ene reactions in IL

To a solution of (*R*)-BINAP–$PdCl_2$ (10 mg, 0.0125 mmol) in CH_2Cl_2 (2.0 mL) was added silver hexafluoroantimonate $AgSbF_6$ (9.4 mg, 0.0275 mmol) under argon atmosphere. After the mixture was stirred at room temperature for 30 min, the *in situ* activated catalyst solution in dichloromethane was transferred through a small filter into small flask which was already charged with IL (0.5 or 1 mmol). After removing the dichloromethane under vacuum, ethyl trifluoropyruvate **11** (50 μL, 0.375 mmol) and methylenecyclohexane (30 μL, 0.25 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 30 minutes.

Then the reaction mixture was extracted with diethyl ether (2 mL × 3). Removal of the ether gave a residue which was loaded onto a silica gel column and eluted with hexane–ethyl acetate (5/1) to give ene product as a colourless oil. The isolated material was characterised by ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz). The enantiomeric excess was determined by GC or HPLC with a chiral column and optical rotation measured.

Recycle procedure

Following extraction of the products from the IL, the IL (containing the catalyst) was dried under vacuum to remove the residual. Fresh substrates were then added to the system and the reactions recommenced as described.

(*S*)-Ethyl 2-(cyclohexenylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate (12). The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[8b] $[\alpha]_D^{20}$ = −22.5 (*c* 1.0, CH_2Cl_2), 91% ee in agreement with literature.[8b] The enantiomeric excess was determined by chiral GC (column, CP-cyclodextrin-beta-2,3,6-M-19, i.d. 0.25 mm × 25 m, VARIANT; carrier gas, helium 1 mL min^{-1}; column, 120 °C; injection temp, 150 °C, detector: 230 °C), (*R*)-enantiomer rt_1: 11.04 min (minor), (*S*)-enantiomer rt_2: 11.40 min (major).

(*S*)-Ethyl 2-(cyclopentenylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate (12a). The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[8k] $[\alpha]_D^{20}$ = −25.0 (c 1.0, CH_2Cl_2), 96% ee in agreement with literature.[8b] The enantiomeric excess was determined by chiral GC (column, CP-cyclodextrin-beta-2,3,6-M-19, i.d. 0.25 mm × 25 m, VARIANT; carrier gas, helium 1 mL min^{-1}; column, 110 °C; injection temp, 150 °C, detector: 230 °C), (*R*)-enantiomer rt_1: 7.26 min (minor), (*S*)-enantiomer rt_2: 7.50 min (major).

Ethyl 2-hydroxy-5-methyl-4-methylene-2-(trifluoromethyl)-hexanoate (12b) and ethyl 2-hydroxy-4,5-dimethyl-2-(trifluoromethyl)-4-hexenoate (12b′). The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[8m] The enantiomeric excess was determined by chiral GC (column, CP-cyclodextrin-beta-2,3,6-M-19, i.d. 0.25 mm × 25 m, VARIANT; carrier gas, helium 1 mL min^{-1}; column, 70 °C; injection temp, 150 °C, detector: 230 °C), **12b** rt_1: 23.63 min (minor), rt_2: 24.22 min (major), **12b′** rt_1: 36.83 min (minor), rt_2: 39.05 min (major). Diastereomers could not be separated by column chromatography. Absolute stereochemistry determined based on comparison with Tan *et al.* reaction conditions in dichloromethane.[8m]

(*S*)-Ethyl 2-hydroxy-5,5-dimethyl-4-methylene-2-(trifluoromethyl)-hexanoate (12c). The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[8m] The enantiomeric excess was determined by chiral GC (column, CP-cyclodextrin-beta-2,3,6-M-19, i.d. 0.25 mm × 25 m, VARIANT; carrier gas, helium 1 mL min^{-1}; column, 100 °C; injection temp, 150 °C, detector: 230 °C), (*R*)-enantiomer rt_1: 8.48 min (minor), (*S*)-enantiomer rt_2: 8.77 min (major).

(*S*)-Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (12d). The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[8m] The enantiomeric excess was determined by HPLC with a Chiralpak AS column (1%

2-propanol in hexane, flow 0.5 mL min^{-1}, (*R*)-enantiomer rt_1: 9.37 min (minor), (*S*)-enantiomer rt_2: 10.16 min (major).

Antifungal activity – experimental method

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 isolates of yeasts (*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 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.[35,36] 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 (2000 to 0.488 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 growth of control for yeasts and as 50% inhibition (IC_{50}) of the growth of control 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 – experimental method

In vitro antibacterial activities[37] 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 (2000 to 0.488 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 growth of control. 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.

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