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Efficient catalyst reuse by simple dissolution in non-conventional media

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This feature article is a description of the achievements made on the development of attractive sustainable approaches to synthetic organic chemistry, namely, catalyst reuse by simple dissolution in water and ionic liquids and asymmetric transformations induced by readily available chiral ionic liquids.

Introduction

The impact of catalysis transcends the borders of synthetic organic chemistry and affects the way we live in modern societies. Catalysis is a powerful tool that allows the production of complex useful molecules, including chiral ones, in different areas such as pharmaceutical, food, agrochemistry, material chemistry and energy resources.¹ Catalysis plays a central role in the broader topic of green chemistry according to the 12 principles defined by Anastas and Warner.² Catalysis

is also one of the main topics selected by James Clark for the *Clean Technology Pool*: Intensive processing, alternative routes, life cycle assessment, supercritical solvents, microreactors, renewable feedstock's, telescoped reactions, non-volatile solvents, catalysis, alternative energy savers and solventless systems.³ The development of catalytic systems for synthetic methodologies which allow high regio- and enantioselectivities when applied, and in high efficiency (high TON and TOF) is extremely important. However, the ideal application in process chemistry generally requires the possibility to extend the process in order to reuse and recycle the catalytic system, without affecting the main features of the catalyst. The most widely used strategy to catalyst reuse is based on catalyst immobilization, usually by means of chemical immobilization in organic or inorganic supports that allow the easy separation of the catalyst from the reaction products and solvents. In this case, the reaction is usually performed under heterogeneous

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First row (left to right): Afonso, Branco and Candeias; second row (left to right): Gois, Lourenço, Mateus and Rosa.

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Our research laboratory (REQUIMTE, CQFB) focuses mainly on more sustainable synthetic methodologies and development-application of new ionic liquids.

conditions, which in many cases leads to some erosion of the catalyst performance. This limitation can be circumvented by further extensive fine changes on structure and combination of the support–spacer–catalyst which nevertheless requires significant research efforts. In contrast, the catalytic system is usually more efficient under homogeneous conditions. However, the catalyst reuse becomes generally more difficult. One interesting approach is based on immobilization of the catalyst in polymers that are soluble in the reaction medium but insoluble in another solvent media. Other approaches are based on chemical catalyst manipulation by anchoring groups with high affinity to alternative reaction media such as fluorinated solvents (or fluorinated supports),⁴ supercritical CO₂ (*sc*CO₂),⁵ water⁶ and ionic liquids (ILs)⁷ or membrane technology.⁸ In all these situations, in spite of being homogeneous and allowing high catalyst performance during the reuse process, they have the drawback of demanding appropriate chemical manipulation on the catalyst, which can potentially interfere with the original catalyst efficiency. One alternative approach is based on the simple use of original catalytic systems under homogeneous conditions and without any chemical manipulation in such a way that the reaction products can be removed from the reaction media. In this feature article, the efforts made in this research laboratory to develop more environmentally friendly organic synthetic methodologies are presented. These efforts include the reuse of the catalytic system by simple catalyst dissolution in non-conventional solvents (water, ionic liquids) and the development of new ionic liquids, including chiral ones, in which the chiral media acts as chiral inducing agent.

Catalyst immobilization in water

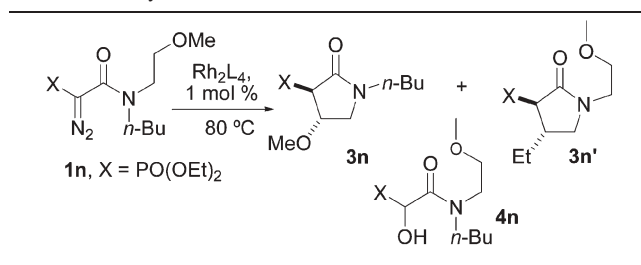
Water is the solvent media used in nature for *in vivo* biological organic functional group transformations. The use of water in synthetic organic chemistry has also some advantages in comparison with the traditional organic solvents not only for being a truly green and readily available solvent, but also for allowing a remarkable induction of reactivity due to “hydrophobic effect”.⁹ There is a considerable range of synthetic transformations performed in pure water or using water as a co-solvent in which it was possible to discover new reagent combination inert to water as solvent.⁶ The absence of desired reactivity of some reagents or intermediates in water is still a limitation in some cases. One example is the carbenoid chemistry in which it has been assumed that Rh and Cu carbenoids and free carbenes react very quickly with X–H labile bonds such as thiols, amines and alcohols as well as water giving preferentially the products resulting from O–H insertions.¹⁰

As part of our ongoing interest on Rh(II) carbenoid C–H insertion of α -diazo- α -phosphorylacetamides **1**¹¹ as an efficient approach to the synthesis of valuable molecules such as β - and γ -lactams, we observed that the C–H insertion was not affected by the use of non-anhydrous 1,2-dichloroethane or wet ionic liquids.^{12,13} These observations prompted us to study this transformation in water (Table 1).¹⁴ In line with these results, Charette and Wurz demonstrated that the cyclopropanation of olefins with diazoacetate catalysed by Rh (also Ru and Co) can

Table 1 Rh(II) catalyzed insertion of α -diazoacetamides and acetates in water

Entry	Substrate	Catalyst	C-H Insertion		O-H Insertion
			2 : 3 : 4	Yield ^a (%)	
<p>1 $\text{Y} = \text{O}, \text{N-R}'$</p> <p>$\text{X} = \text{PO}(\text{OEt})_2, \text{SO}_2\text{Ph}, \text{Ac}, \text{CO}_2\text{Et}$</p>					
1	1a $\text{X} = \text{PO}(\text{OEt})_2$	Rh ₂ (OAc) ₄	Only 2	75 (>97)	
2	1b $\text{X} = \text{SO}_2\text{Ph}$	Rh ₂ (OAc) ₄	Only 2	73	
3	1c $\text{X} = \text{Ac}$	Rh ₂ (OAc) ₄	Only 2	77 (>97)	
4	1d $\text{X} = \text{CO}_2\text{Et}$	Rh ₂ (OAc) ₄	Only 2	76	
5	1e	Rh ₂ (OAc) ₄	Only 2	79 (>97)	
6	1f	Rh ₂ (OAc) ₄	Only 2	40 (50)	
7	1g	Rh ₂ (OAc) ₄	1 : 10 : —	97 (>97)	
8	1h	Rh ₂ (OAc) ₄	Only 3	59 (63)	
9	1i	Rh ₂ (OAc) ₄	Only 4	78 (90)	
10	1j	Rh ₂ (OAc) ₄	1 : 10 : —	97	
11	1j	Rh ₂ (pfb) ₄	Only 3	97	
12	1k	Rh ₂ (OAc) ₄	Only 4	71	
13	1k	Rh ₂ (pfb) ₄	— : 0.85 : 1	73	
14	1k	Rh ₂ (Ooct) ₄	— : 0.46 : 1	62	
15	1l	Rh ₂ (OAc) ₄	2.3 : — : 1 ^b	82	
16	1l	Rh ₂ (pfb) ₄	Only 2	84	
17	1l	Rh ₂ (Ooct) ₄	Only 2	97	
18	1m	Rh ₂ (OAc) ₄	— : 1 : 2.4 ^b	86	
19	1m	Rh ₂ (pfb) ₄	— : 1 : 0.1 ^b	64	
20	1m	Rh ₂ (Ooct) ₄	Only 3	76	

^a The observed conversion by ³¹P NMR of the crude mixture is given in parentheses. ^b In the isolated product **4** the *t*-Bu group is absent.

Table 2 Catalyst effect on the insertion of **1n** in water

Entry	Solvent	Catalyst	Yield ^a (%)	4n : 3n : 3n'
1	C ₂ H ₄ Cl ₂	Rh ₂ (OAc) ₄	88	— : 1.1 : 1 ^b
2	Water	Rh ₂ (OAc) ₄	85	0.6 : 0.15 : 1 ^b
3	Water	Rh ₂ (pfb) ₄	68	0.5 : 0.5 : 1 ^b
4	Water	Rh ₂ (Ooct) ₄	52	0.3 : 0.86 : 1 ^b

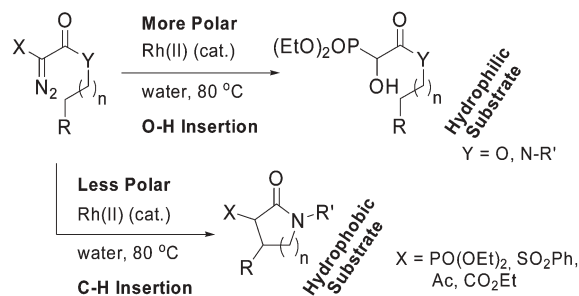
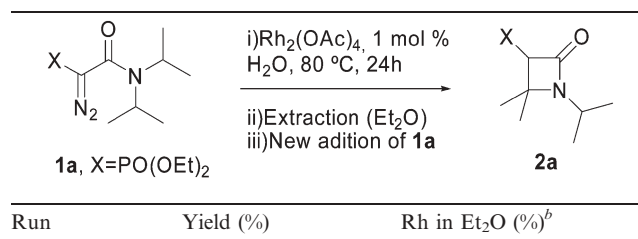
^a Isolated yield as a mixture of **3n**, **3n'** and **4n** (except for entry 1).

^b Observed selectivities of the crude reaction mixture (by ³¹P NMR).

be efficiently performed in water if a more hydrophobic catalyst is used such as Rh₂(C₇H₁₅CO₂)₄.¹⁵ More recently Úbeda and co-workers demonstrated the feasibility of the asymmetric cyclopropanation in water using chiral Rh(II) catalysts.¹⁶ In the same line, Antos and Francis were able to effect the C–H insertion of α -diazoacetates on tryptophan residues catalysed by Rh(II) in aqueous media.¹⁷ Taking advantage of the diazo substrates available in our laboratory, mainly α -phosphoryl- α -diazoacetamides **1**,¹² we studied the diazo decomposition in water using Rh₂(OAc)₄ as the catalyst. For α -phosphono- α -diazoacetates the reaction was less clean as for example the ester **1i** yielded only the product of O–H insertion in detectable amounts (Table 1, entry 9).¹⁸

In contrast, for a considerable range of substrates (entries 1–8, 10–11) exclusive C–H insertion was observed using Rh₂(OAc)₄ as catalyst. Interestingly, these substrates in general were insoluble under the reaction conditions, suggesting that the transformation for reactions occurs under biphasic systems, which is in line with the higher reactivity recently described by Sharpless and co-workers for systems *on water*.⁹ For the substrates **1k–m** partial O–H and C–H insertion occurred, using Rh₂(OAc)₄. However, the C–H insertion can be increased if a more hydrophobic catalyst is used such as Rh₂(pfb)₄ or Rh₂(Ooct)₄ (entries 13–20). Interestingly, the non-symmetric substrate **1n** revealed in C₂H₄Cl₂ some slightly preference for the C–H insertion at the more reactive β -C–H bond due to the effect of the methoxy group. However, in water a preference for the C–H insertion on the less reactive but more hydrophobic *n*-butyl group was observed (Table 2). These results clearly show that the C–H vs. OH insertion is strongly dependent of the rhodium carbenoid structure in water in which preferential C–H insertion occurs for more hydrophobic substrates. The following picture aims to explain our findings according to hydrophobic nature⁹ of the combination catalyst–substrate (Scheme 1).

The combination of exclusive C–H insertion for some diazo substrates catalysed by Rh₂(OAc)₄ and the complete solubility of the catalyst in water allows the development of a simple system for expensive Rh(II) catalyst reuse just by extraction of the reaction mixture with an organic solvent. Table 3 shows the results observed for the model substrate **1a** in which the

**Scheme 1** General dependence of Rh(II) catalyzed C–H vs. OH insertion in water with catalyst and substrate structure.**Table 3** Reuse of the Rh₂(OAc)₄ catalyst using the substrate model **1a**

Run	Yield (%)	Rh in Et ₂ O (%) ^b
1–9	88 ^a	1.6 ^c
10	90	1.1
11	(63) ^d	0.2

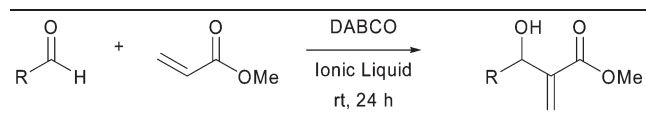
^a Average yield for the combined cycles 1–9. ^b Percentage of rhodium relative to initial amount detected by ICP in the organic phase. ^c Average value for the combined cycles 1–9. ^d Observed conversion by ³¹P NMR (**1a**, 37%; **2a**, 63%).

catalyst was reused efficiently 10 times and with low leaching of catalyst into the organic phase.¹⁴ Similar behaviour was observed for the substrates **1e** and **1j**.¹⁸ Those examples clearly show that this simple system is very robust for catalyst reuse.

Ionic liquids (ILs) as an efficient medium for product separation and catalyst immobilization

Low-temperature melting salts have long been used in electrochemistry applications due to their high electrochemical window and electrolyte properties. The discovery of air-stable and water-resistant low-temperature melting salts, later designated as room temperature ionic liquids (ILs), created, during the last few years, an impressive interest in the scientific community in different research areas¹⁹ such as electrochemistry,²⁰ organic,⁷ inorganic,⁷ organometallic,⁷ polymer²¹ and material chemistry¹⁹ biotransformations,⁷ remediation,²² fuel and solar cells,¹⁹ and separation technology^{19,23} (biphasic, membranes, *sc*CO₂, systems and pervaporation), flotation fluids, lubricants,¹⁹ nanotechnology²⁴ and paint additives.²⁵ Perhaps the reasons for such wide research applications are due to some unique properties such as high conductivity, wide electrochemical window,^{19,20} near non-volatility,²⁶ high thermal stability, low flammability,¹⁹ tunable solubility in water and in common organic solvents, insolubility in *sc*CO₂²⁷ high solubility and in some cases specific affinity for organic, inorganic, organometallic solutes, *sc*CO₂ and other gases²⁸ in

Table 4 Obtained yields for the Morita–Baylis–Hillman reactions in ILs based on the [C₄mim] and [C₄dmim] cations in the presence of DABCO



Aldehyde	Yield ^a (%) in [C ₄ mim]PF ₆	Yield ^a (%) in [C ₄ dmim]PF ₆
PhCHO	65 (63) ^b	(79) ^b
CH ₃ (CH ₂) ₂ CHO	20 (44) ^b	(58) ^b
(CH ₃) ₂ CHCHO	14	
<i>c</i> -C ₆ H ₁₁ CHO	20	
4-ClC ₆ H ₄ CHO	72 (66) ^b	(99) ^b
4-MeOC ₆ H ₄ CHO	39 (39) ^b	(65) ^b
4-MeC ₆ H ₄ CHO	61 (57) ^b	(80) ^b
PhCH=CHCHO	43 (23) ^b	(57) ^b
2-Furaldehyde	68 (38) ^b	(73) ^b
3,4,5-(MeO) ₃ C ₆ H ₂ CHO	72 (70) ^b	(96) ^b

^a Acrylate : aldehyde : DABCO (1.1 : 1 : 1). ^b The observed yields reported by Chu *et al.*³⁵ using acrylate : aldehyde : DABCO (2 : 1 : 2) are given in parentheses.

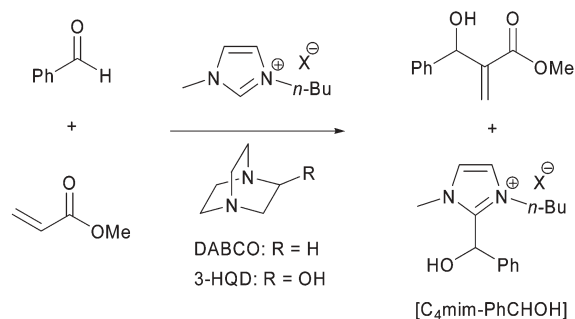
some ILs, and high stability of enzymes in some IL media.^{7,29,30}

We have focused our research mainly on the development of new ionic liquids and in exploring their use as an efficient reaction media for catalyst reuse, product separation and selective transport by membrane technology, although the later topic being outside the scope of this feature article.³¹

Reuse of the IL reaction media

The use of volatile organic solvents (VOCs) in organic synthetic transformations is not in line with environmentally sustainable development trends in modern chemical industry. In contrast, ILs can be potential candidates for the substitution of common VOCs due to their almost non-volatility.³⁶ However, the high cost and toxicity concerns³² have limited their use which, is probably only acceptable if the IL reuse is easily feasible or if the IL medium presents some advantage for the synthetic transformation. One of the first examples studied was the Morita–Baylis–Hillman reaction (MBH) as a potential candidate mainly because involved the formation of zwitterionic intermediates that could probably be stabilized in the IL environment. The MBH reaction is a very important transformation because, apart from being a complete atom economic transformation, it allows the formation in one step of the significant allylic alcohol functional units. The MBH reaction has been the subject of considerable interest mainly because of being generally a slow reaction and for the difficulty in achieving an efficient asymmetric catalytic version.³³ We and others observed that the MBH reaction can be efficiently performed in ILs, of which [C₄mim]PF₆† gave better results (Table 4).^{34–36} Additionally the MBH is faster in ionic liquids than in acetonitrile as the best reported solvent.³⁴ Similar

† Used abbreviators for the ionic liquids based on the imidazolium cation: 1-*n*-butyl-3-methylimidazolium [C₄mim], 1-*n*-octyl-3-methylimidazolium [C₈mim] and 1-*n*-butyl-2,3-dimethylimidazolium [C₄dmim].



Scheme 2 Side reaction reported by Aggarwal *et al.*³⁹ between the imidazolium cation and the aldehyde under DABCO or 3-HQD catalysed MBH reaction.

results were observed by Ko and co-workers³⁶ and more recently by Tsai and co-workers.³⁷ In addition, Eberlin and co-workers observed by electrospray ionization mass spectrometry the formation of supramolecular species containing the IL which are strongly dependent of the [C₄mim]X used and the order of formation was CF₃CO₂ > BF₄ >> PF₆.³⁸

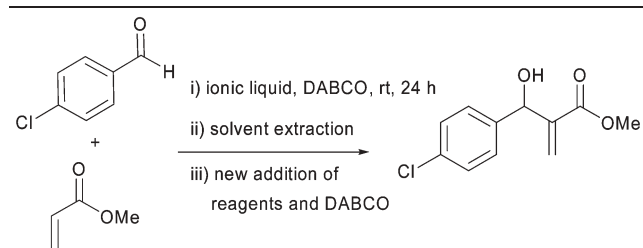
Later, Aggarwal *et al.* reported that in case of [bmim]Cl a reversible adduct [C₄mim–PhCHOH] X was formed in 49% between the imidazolium cation and the benzaldehyde in the presence of 3-HQD (Scheme 2).^{39,‡} We later observed that the adduct formation is quite dependent of the anion (Cl > BF₄ > PF₆ > NTf₂) and while in case of PF₆ the adduct formation was of 16%, for Cl it was considerably higher (44%).⁴⁰ Interestingly the formation of the MBH product is also quite dependent of the solvent in the order [C₄mim]X; X = BF₄ > PF₆ > Cl > NTf₂ > [C₄dmim]PF₆ > CH₃CN. Probably the nature of the C(2)–H hydrogen bond which is absent in case of [C₄dmim]PF₆ plays an important role in facilitating the formation of new C(2)–CHOHPh bond induced by the base DABCO and in the formation of the MBH product by stabilising the zwitterionic intermediates formed during the MBH reaction^{34,41} which is in line with some reported examples in several reactions and affinity studies in ILs.⁴²

The IL reaction media can be reused in the MBH reaction (Table 5). While in case of [C₄mim]PF₆ the formation of the adduct limits their reuse for different substrates,^{34,35} but in case of [C₄dmim] cation this side reaction is suppressed as was firstly demonstrated by Chu and co-workers.^{35,40}

The nucleophilic substitution on saturated carbons is certainly an important method for the formation of new C–C and C–heteroatom bonds, including chiral biphasic systems. One reliable and efficient approach is based on two-phase systems consisting of aqueous and organic phases and using an efficient phase-transfer catalyst (PTC) which is generally an organic cation.⁴³ Due to the ionic nature of the IL, we tested their use as simultaneous reaction media and

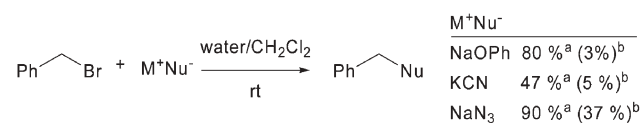
‡ According to Aggarwal *et al.*,³⁹ the formation of the adduct [C₄mim–PhCHOH]X was not exclusive for [C₄mim]Cl since *other* imidazolium salts behaved similarly, such as [C₄mim]PF₆, [emim]OTf, [emim]Cl, [emim]PF₆ and [emim]BF₄ (using 3-HQD or DABCO). In the course of our studies,³⁴ we also followed the reaction by ¹H NMR using net [C₄mim]PF₆, while Aggarwal *et al.*³⁹ used a solution in CDCl₃. So at that time, in our case due to the broad signals of the [C₄mim] unit we did not notice the competitive formation of the adduct.

Table 5 Observed yields for the Morita–Bayliss–Hillman reaction by reuse of the ionic liquid^{34,35,40}

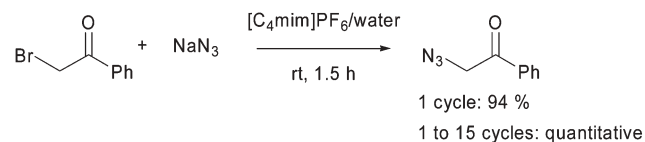


Cycle	Yield ^a (%) in [C ₄ mim]PF ₆	Yield (%) in [C ₄ dmm]PF ₆
1	53	77 ^b (94) ^c
2	69	83 ^b (95) ^c
3	59	76 ^b (95) ^c
4	76	74 ^b (98) ^c

^a Acrylate : aldehyde : DABCO (1.1 : 1 : 1). ^b Acrylate : aldehyde : DABCO (1.1 : 1 : 0.5), rt, 24 h. ^c The observed yields reported by Chu and co-workers³⁵ using acrylate : aldehyde : DABCO (2 : 1 : 2) are given in parentheses.



Scheme 3 Ionic liquid as a phase-transfer catalyst for nucleophilic substitution reactions: ^a) [C₄mim]PF₆ (0.5 eq.); ^b) in the absence of IL.



Scheme 4 Reuse of the IL [C₄mim]PF₆ for azide formation.

phase-transfer promoter in a two-liquid phase system.⁴⁴ As expected, was observed that the IL [C₄mim]PF₆ acts as a phase-transfer catalyst for simple substitution of benzyl bromide by several nucleophiles such as PhO⁻, CN⁻ and N₃⁻ in the water–dichloromethane biphasic system (Scheme 3).^{44§}

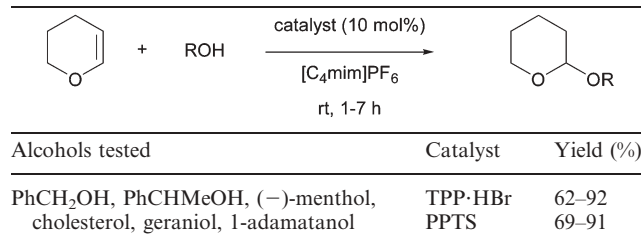
The use of IL instead of the organic volatile solvent and the PTC is desirable. We observed that high conversion under mild conditions occurs for substitution of alkyl chlorides, bromides and iodides by several nucleophiles such as Schiff bases, phenoxides, I⁻, CN⁻ and N₃⁻. This method appears very attractive for azide formation in which no erosion on the yield was observed for the maximum of 15 cycles tested (Scheme 4).⁴⁴ Other efficient nucleophilic substitutions in ILs were reported as has been pointed out recently by Jorapur and Chi.⁴⁵

Reuse of the catalytic system immobilised in ILs

The tetrahydropyranilation of alcohols was studied using the efficient catalysts *p*-toluenesulfonic acid (TsOH), triphenylphosphine hydrobromide (TPP·HBr) and pyridinium

§ While we were performing this study, Eckert *et al.*⁶⁴ demonstrated the advantage of use the IL for solid–liquid biphasic nucleophilic substitution of cyanide on benzyl chloride.

Table 6 Tetrahydropyranilation of alcohols catalysed by TPP·HBr and PPTS in [C₄mim]PF₆



p-toluenesulfonate (PPTS) immobilised in ILs.⁴⁶ In this case, the ionic liquid [C₄mim]PF₆ allows a slightly faster reaction providing an efficient catalytic system for a range of substrates (Table 6). This catalytic system can be efficiently reused for up to 17 cycles just by simply extraction of the reaction mixture with the appropriate organic solvent (Table 7). Due to partial extraction of the catalyst and the IL by the solvent, the extraction process and nature of the solvent used is crucial for the catalytic system reuse performance. More recently Varma and co-workers⁴⁷ and Deng and co-workers⁴⁸ described another approach using ionic liquids based on the imidazolium cation as Lewis and Brønsted acids, respectively.

In another example we demonstrated that the enantioselective addition of alkynes to imines catalysed by Cu(I)-bis(oxazoline) can be performed just by using the appropriate IL⁴⁹ instead of the solvent systems developed by Wei and Li⁵⁰ consisting of toluene or water (Table 8). In this case the ionic liquid [C₄mim]NTf₂ was the most appropriate for the transformation and catalyst reuse (Table 8). By extraction of the reaction mixture with *n*-hexane less than 0.3% of Cu was detected in the organic phase.

Was also demonstrated that the Rh₂(OAc)₄ catalysed C–H insertion of α -diazophosphonates, can be efficiently performed in the IL [C₄mim]PF₆ allowing an efficient catalyst reuse simply by extraction of the reaction mixture with organic solvent (Table 9).¹³

The Sharpless asymmetric dihydroxylation (AD) is a very powerful methodology for the synthesis of a considerable range of 1,2-diols in very high optical purity.⁵¹ However, the use of this methodology in large scale presents some limitations mainly due to the high toxicity of osmium and osmium/chiral ligand costs. To circumvent these limitations, several approaches have been developed to reuse the catalytic

Table 7 Reuse of the catalytic system for the tetrahydropyranilation of alcohols

i) [C₄mim]PF₆, catalyst (10 mol%),
rt, 1 h
ii) Extraction (Et₂O)
iii) New addition of reagents

Cycle	Catalyst	Conversion (%)	Cycle	Catalyst	Conversion (%)
1	PPTS	93.7	1	TPP·HBr	96.4
2–11		94.8 ^a	2–16		96.1 ^a
12		86.0	17		92.3

^a Average conversion.

Table 8 Enantioselective addition of alkynes to imines in [C₄mim]NTf₂ catalysed by CuOTf/box and catalytic system reuse

Ar	Yield (%)	ee (%)
Ph, 4-MeC ₆ H ₄ , 4-CF ₃ C ₆ H ₄ , 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 2-naphthyl	74–91	86–99
Ph, Cycle 1–6	82 ^a	94–88

^a Average yield obtained by extraction of the reaction mixture in each cycle with *n*-hexane; 34% more of product was isolated in cycle 6 by further extraction with diethyl ether.

system by anchoring the chiral ligand, osmium or both in different supports under homogeneous or heterogeneous reaction conditions.⁵² One method is based on immobilization of chiral ligands onto soluble and insoluble polymers. However, this approach has shown the need of long syntheses of each chiral ligand, erosion of the enantioselectivity, and/or incomplete recovery and reuse of the osmium–ligand catalytic system, due to the occurrence of osmium leaching.⁵³ Other efficient approaches have been described: microencapsulation of osmium catalyst in polystyrene,⁵⁴ polyurea (achiral version),⁵⁵ anchoring in poly(ethylene glycol) matrices,⁵⁶ silica tetrasubstituted olefins,⁵⁷ ion exchangers,⁵⁸ nanocrystalline magnesium oxide⁵⁹ anchoring in Amberlite containing residual vinyl groups,⁶⁰ gold colloids,⁶¹ biphasic system containing dendrimer-bound (achiral version)⁶² or fluorosilane (achiral version)⁶³ osmium catalyst.

Table 10 Selection of best results for the asymmetric dihydroxylation of representative olefins using ionic liquids as solvent or co-solvent^a

Substrate	Solvent	Co-oxidant	Ligand ^b	Yield (ee) ^c
Styrene	[C ₄ mim]NTf ₂	NMO	AQN ^d	95 (99)
	[bdmim]NTf ₂	NMO	AQN ^d	96 (99)
α -Methylstyrene	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PHAL	88 (97)
	[bdmim]NTf ₂	NMO	PHAL	94 (89)
1-Hexene	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PHAL	83 (92)
	[C ₈ mim]PF ₆ –H ₂ O– <i>t</i> -BuOH (1 : 1 : 2)	K ₃ Fe(CN) ₆	PHAL	89 (97)
1-Methylcyclohexene	[bdmim]NTf ₂	NMO	AQN ^d	97 (99)
	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PYR	93 (94)
<i>trans</i> -Stilbene	[C ₄ mim]NTf ₂	NMO	PHAL	99 (98)
	<i>t</i> -BuOH/H ₂ O (1 : 2)	NMO	PHAL	87 (99)
<i>trans</i> -Stilbene	[C ₈ mim]PF ₆ –H ₂ O– <i>t</i> -BuOH (1 : 1 : 2)	K ₃ Fe(CN) ₆	PYR	89 (96)
	[C ₄ mim]PF ₆ –H ₂ O– <i>t</i> -BuOH (1 : 1 : 2)	K ₃ Fe(CN) ₆	PHAL	92 (99)
<i>trans</i> -5-Decene	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PHAL	89 (96)
	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PYR	94 (87)
<i>trans</i> -5-Decene	[C ₄ mim]PF ₆ –H ₂ O– <i>t</i> -BuOH (1 : 1 : 2)	K ₃ Fe(CN) ₆	PYR	92 (96)
	[C ₄ mim]NTf ₂	NMO	PHAL	94 (99)
<i>trans</i> -Methylcinnamate	[bdmim]NTf ₂	NMO	PHAL	89 (98)
	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PHAL	94 (94)
<i>trans</i> -Methylcinnamate	<i>t</i> -BuOH–H ₂ O (1 : 2)	NMO	PHAL	98 (80)
	[C ₄ mim]PF ₆ –H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PYR	78 (93)
<i>trans</i> -Methylcinnamate	[C ₈ mim]PF ₆ –H ₂ O (1 : 2)	NMO	PYR	70 (92)
	<i>t</i> -BuOH–H ₂ O (1 : 2)	K ₃ Fe(CN) ₆	PHAL	88 (80)
<i>trans</i> -Methylcinnamate	<i>t</i> -BuOH–H ₂ O (1 : 2)	NMO	PYR	89 (89)

^a Olefin (0.5 or 1.0 mmol), catalyst: K₂OsO₂(OH)₄ (0.5 mol%), ligand (1.0 mol%), co-oxidant: K₃Fe(CN)₆ (3.0 mol eq.), K₂CO₃ (3.0 mol eq.) or NMO (1 mol eq.), solvent, rt, 24 h; olefin added at once for K₃Fe(CN)₆; olefin added slowly using NMO except in case of using IL as the only solvent. ^b PHAL or PYR refers respectively to (DHQD)₂PHAL and (DHQD)₂PYR. ^c Yield and enantiomeric excess (in parentheses) of the diol (%). ^d Used (DHQD)₂AQN.

Table 9 Catalyst reuse on the C–H insertion of α -diazophosphonoacetamide **1h** catalysed by Rh₂(OAc)₄ immobilised in the IL [C₄mim]PF₆

Run	Yield (%) (extraction with <i>n</i> -hexane)	Run	Yield (%) (extraction with TBME)
1–6	82 ^a	1–5	87 ^a

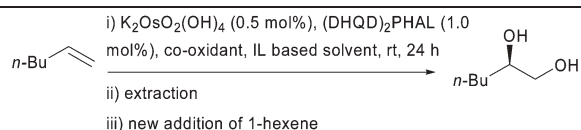
^a Average yield for the combined cycles.

Our preliminary observation of high solubility of the chiral ligand (DHQD)₂PHAL in [C₄mim]PF₆ prompted us to test the AD reaction in ILs. In fact we were pleased to observe that the AD reaction could be efficiently performed in biphasic IL–water and monophasic IL/water–*t*-butanol solvent systems for a range of substrates,⁶⁴ using the co-oxidants K₃Fe(CN)₆ or *N*-methylmorpholine oxide (NMO).⁶⁵

For each substrate, it was possible to find one solvent system that afforded similar or higher yields and enantioselectivities than the traditional *t*-BuOH–water solvent system (Table 10).

More importantly, the use of IL as a co-solvent allows the very efficient reuse of the catalytic system just by separation of the ionic liquid containing the osmium/chiral ligand and removing the products from the aqueous and organic phases (Table 11). In the case of [C₄mim]PF₆ as co-solvent it was possible to reuse the catalytic system for 9 cycles observing only a 5% yield reduction from the first cycle (overall yield of 87%, TON = 1566). Additionally, for each cycle, the osmium

Table 11 Reuse of the catalytic system for the AD of 1-hexene and *trans*-cinnamate (last example) using $K_3Fe(CN)_6$ and NMO as co-oxidants and ionic liquid as solvent or co-solvent



Solvent system (substrate)	Cycle	Yield (%)	ee (%)	Os in water (%)	Os in product (%)
[C ₄ mim]PF ₆ -H ₂ O (1 : 2) ^b (1-hexene)	1–8	75 ^a	88–81	14–3	≤ 3 ^d
	9	70	83	3	≤ 3 ^d
[C ₄ mim]PF ₆ -H ₂ O (1 : 2) ^c (1-hexene)	1–8	75 ^a	96–76	2	≤ 3 ^d
	9	50	70	1	≤ 3 ^d
[C ₈ mim]PF ₆ -H ₂ O (1 : 2) ^b (1-hexene)	1–8	61 ^a	82–60	2	≤ 3 ^d
	9	39	41	3	≤ 3 ^d
[C ₄ mim]PF ₆ -H ₂ O- <i>t</i> -BuOH (1 : 1 : 2) ^b (1-hexene)	1–10	86 ^a	92–82	6–3	≤ 3 ^d
	11	63	75	4	≤ 3 ^d
[C ₄ mim]PF ₆ -H ₂ O- <i>t</i> -BuOH (1 : 1 : 2) ^c (1-hexene)	1–8	80 ^a	85–72	5–1	≤ 3 ^d
	9	60	71	1	≤ 3 ^d
[C ₈ mim]PF ₆ -H ₂ O- <i>t</i> -BuOH (1 : 1 : 2) ^b (1-hexene)	1–7	70 ^a	96–59	5–3	≤ 3 ^d
	8	12	33	2	≤ 3 ^d
[C ₄ mim]NTf ₂ ^c (1-hexene)	1–13	96 ^a	96–93	— ^e	1.8–1.2 ^d
	14	92	92	— ^e	1.3 ^d
[C ₄ dmm]NTf ₂ ^c (1-hexene)	1–13	92 ^a	96–89	— ^e	2.0–1.1 ^d
	14	88	87	— ^e	1.3 ^d
[C ₈ mim]PF ₆ ^c (methyl <i>trans</i> -cinnamate) ^g	1–5	75 ^a	79–81	— ^e	≤ 0.05 ^d
	6	79 ^f	81	— ^e	≤ 0.05 ^d

^a Average yield for the combined cycles. ^b $K_3Fe(CN)_6$ as co-oxidant. ^c NMO as co-oxidant. ^d Extraction with Et₂O. ^e No water extraction was used. ^f More diol (52%) was isolated from the remaining IL by flash chromatography. ^g (DHQD)₂PYR as chiral ligand.

content in the organic phase which contains the AD product and in the aqueous phase was respectively in the range of the ICP detection limit (≤ 3%, ≤ 7 ppb) and to 3–6% of initial amount, while the recovered IL phase contains more than 90% of the osmium contents of the previous cycle (Table 11).

While we were performing the AD studies two communications reported the reusable OsO₄-catalyzed olefin dihydroxylation using the co-oxidant NMO in [C₄mim]PF₆-water-*t*-butanol.⁶⁶ Later we⁶⁴ and Song *et al.*⁶⁷ simultaneously reported a simple and practical approach to reuse the catalytic system of the AD reaction using the ionic liquid [C₄mim]PF₆ as a co-solvent. Later, Sheldon and co-workers⁶⁸ described the AD on *trans*-stilbene using the [C₄mim]PF₆-H₂O-acetone (1 : 2 : 3) solvent system and the chiral ligand (DQ)₂PHAL in which the initial terminal olefins in the (DQ)₂PHAL unit after being dihydroxylated increased affinity to the IL phase. Additionally, Bäckvall and co-workers⁶⁹ and Zhang and co-workers⁷⁰ described the possibility to perform the AD reaction in [C₄mim]PF₆ respectively using H₂O₂ as oxidant in the presence of a electron transfer mediator as co-catalyst and by the catalyst TentaGel-OsO₄.

In the course of our further studies on the AD reaction, was observed that the AD reaction can be efficiently performed using IL as the only solvent. After screening several ILs, it was possible to obtain even better yields and enantioselectivities than previously using the IL as a co-solvent (Table 10).⁷¹ Additionally, was demonstrated that after the AD reaction using NMO as the co-oxidant, is possible to extract the product with *sc*CO₂ using the appropriate conditions and reuse the catalytic system (Table 12).⁷¹ Another observed advantage of *sc*CO₂ approach is that the osmium contamination in the product is inferior to earlier systems based on organic solvent

extraction (Tables 11 and 12). This approach was further optimised to the more important substrate methyl *trans*-cinnamate since the corresponding diol is a precursor of the Taxol side chain (Table 12).⁷²

The research performed by us^{64,65,71,72} and by other groups^{67–70} clearly demonstrates that the AD reaction having ILs as reaction media is a simple, efficient and robust method for catalyst reuse by immobilisation of the catalytic system in the IL which allows easy product isolation and nearly without osmium contamination.

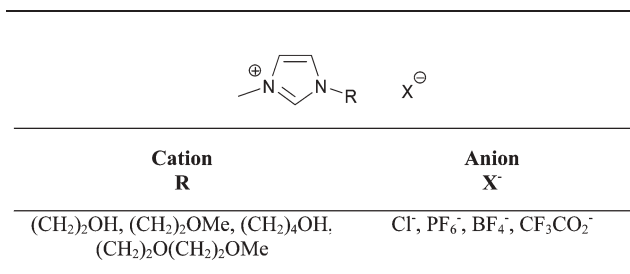
Development of new room temperature ionic liquids

In the course of our studies to use ILs as reaction media for organic transformations, we noticed that all ILs available in the laboratory based on the 1-methyl-3-alkylimidazolium cation were less prone to solubilise hard Lewis acids and primary ammonium salts, including amino acids. To circumvent this limitation we studied the possibility to find other ILs based on the methylimidazolium cation [mim] by introducing other functional groups such as hydroxyl, and ether expecting

Table 12 Reuse of the catalytic system for the AD of 1-hexene and methyl *trans*-cinnamate using $K_2OsO_2(OH)_4$ (0.5 mol%)- (DHQD)₂PYR (1.0 mol%), NMO as co-oxidants and ionic liquid as solvent followed by extraction with *sc*CO₂

Substrate	Solvent system	Cycle	Yield (%)	ee (%)	Os in product (%)
1-Hexene	[C ₄ mim]NTf ₂	1–8	80 ^a	96–87	0.4–0.2
		9	56	80	0.4
Methyl <i>trans</i> -cinnamate	[C ₈ mim]PF ₆	1–5	89 ^a	85–77	≤ 0.05
		6	85	84	≤ 0.03

^a Average yield for the combined cycles.



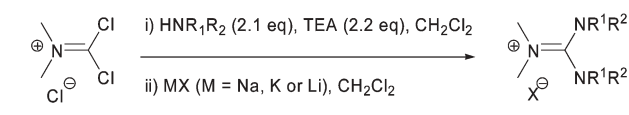
Scheme 5 Structure of room-temperature ionic liquids of the series [C_nO_mmim][X].

that these groups could improve the interaction of the [mim] cation with other solutes. In fact the structures presented in Scheme 5 are liquid at room temperature, moderately viscous and by performing solubility studies using the inorganic salts LiCl, HgCl₂ and LaCl₃ as representative model salts, specific high solubilities were observed (up to 18 and 5 times) respectively for LaCl₃ and HgCl₂.⁷³ Bazureau and co-workers,⁷⁴ Dzyuba and Bartsch⁷⁵ and Pernak and co-workers⁷⁶ described similar ILs and later Rogers and co-workers developed a more efficient IL containing the bis-imidazolium cation and ethylene glycol spacer ether functionality for efficient partition of Hg²⁺ to the IL phase in an IL–aqueous biphasic mixture.⁷⁷

Asymmetric transformations induced by chiral ionic liquids based on natural chiral anions

In the course of our search for other ionic liquids based on different structures from the imidazolium cation, we became interested on the guanidinium cation unit mainly due to its stability by charge delocalization between four atoms and the possibility to introduce six different alkyl chains. Also in a seminal work described in 1984 by Kanthlechner and co-workers, they reported the preparation of a large number of hexaalkylguanidinium salts, which in two cases were described as oils.⁷⁸ Additionally, ILs based on the [alkyl-DBU] cation has also been reported.⁷⁹ Starting from commercial available *N,N*-dimethylphosgeniminium chloride different guanidinium chlorides were prepared in one step following a general reported method,⁸⁰ which allows the preparation of different ionic liquids resulted of further chloride exchange (Scheme 6).⁸¹ These ILs present moderate viscosity, high thermal stability and complementary stability to the ILs based on the imidazolium cation. More importantly, despite the high number of carbon atoms, *e.g.* 27 for tetra-*n*-hexyl-dimethyl-guanidinium [(di-*h*)₂dmg] cation they are less prone to crystallise even in the presence of anions which persistently become solid when combined with different cations. In contrast to ILs based on the [im] cation, this notable property of the [dmg] cation opens the opportunity to create a new generation of chiral ionic liquids from the recent reported ones⁸² just by simple exchange of the [dmg]Cl salt with natural or easily functionalised chiral natural anions. Scheme 7 shows representative examples such as mandelate, lactate, camphor-sulfonate and carboxylates of boc-alanine and quinic acid.⁸³

¶ These ILs are also commercially available from the *Solchemar* company (<http://www.solchemar.com>).



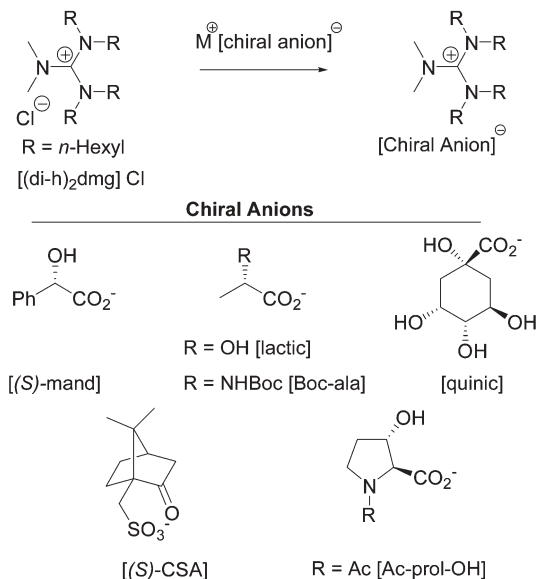
R ¹	R ²	X
Me	<i>n</i> -Bu	PF ₆
Et	<i>n</i> -Bu	BF ₄ , NTF ₂
<i>n</i> -Hexyl	<i>n</i> -Hexyl	Cl, PF ₆ , BF ₄ , NTF ₂
<i>n</i> -Octyl	<i>n</i> -Octyl	Cl, PF ₆ , BF ₄

Scheme 6 ILs based on the dimethylguanidinium [dmg] cation.

The possibility to use this chiral media was explored by taking advantage of our ongoing research on Rh(II) catalysed C–H insertion of α -diazoacetamides and on the Sharpless asymmetric dihydroxylation (AD) (Scheme 8). Interestingly, for both transformations was possible to achieve yields and enantioselectivities similar or higher to the ones using chiral ligands. This new chiral media, due to the diversity of chiral anions available, being ionic, moderately viscous, almost non-volatile and potentially reusable, opens new opportunities not only to induce chirality by performing different reactions in the media but also in other areas such as new materials, chiral resolution by chromatographic methods and membrane technologies.

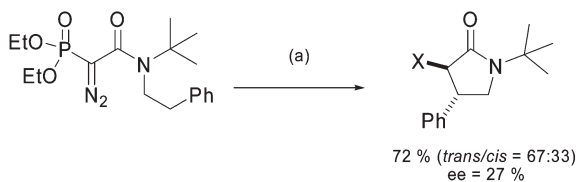
Concluding remarks

In this laboratory, we have been continuously trying to develop environmentally friendly synthetic methodologies with special emphasis on catalyst reuse. We hope that our contribution to this research area has been useful for the scientific community. Our research will continue in this area, perhaps with a bigger focus on the use of our recent chiral

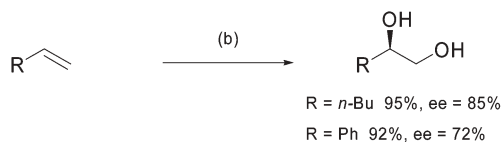


Scheme 7 Chiral ionic liquids prepared by combination of readily accessible chiral anions with [(di-*h*)₂dmg] cation.

i) Rh(II) carbenoid asymmetric C-H insertion



ii) Sharpless asymmetric dihydroxylation (AD)



Scheme 8 Induction of chirality by chiral ionic liquids (CILs) in: (i) C-H insertion of α -diazoacetamides catalyzed by $\text{Rh}_2(\text{OAc})_4$ and (ii) Sharpless AD. *Reagents and conditions:* (a) $\text{Rh}_2(\text{OAc})_4$ (1 mol%), [(di-h)₂dmg][(R)-mand] (0.3 g), diazo (0.15 mmol), 110 °C, 3 h; (b) alkene (0.5 mmol), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.5 mol%), NMO (1 eq.), [(di-h)₂dmg][quinic] (0.3 mL), rt, 24 h.

ionic liquids based on the guanidinium cation as a source of chiral induction in different synthetic applications.

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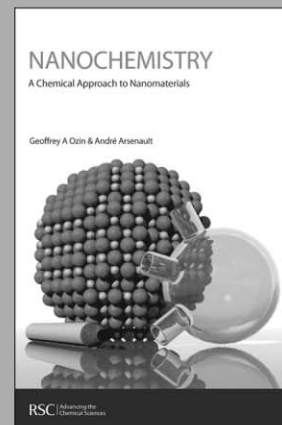
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