

Chiral Guanidinium Ionic Liquids for Asymmetric Dihydroxylation of Olefins with Recycling of the Catalytic System by Supercritical CO₂

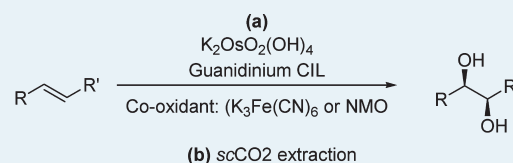
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ABSTRACT: This paper presents the advantages of combining two alternative solvents in asymmetric dihydroxylation (AD) of olefins: chiral ionic liquids (CIL) as chirality-inducing media and supercritical CO₂, as extraction media. Initially, the AD reaction was optimized using 1-hexene as the model substrate and as the chiral source, guanidinium ionic liquids [(di-h)₂dmg] based on chiral anions such as (*S*)-mandelate, (*R*)-mandelate, quinic, L-lactic, (*S*)-camphorsulfonate, BOC-hydroxyproline, and acetylhydroxyproline. In the first approach, chiral ionic liquids [(di-h)₂dmg][quinic] and [(di-h)₂dmg][lactic] were used as unique reaction and chirality-inducing media, allowing for yields and enantiomeric excess comparable to or higher than the conventional systems (using Sharpless chiral ligands). The use of this method offers the additional advantage of performing the reactions without the need for a slow addition of olefins. Several olefins containing aliphatic and aromatic units were tested using the selected CILs with a good performance in terms of yields and ee's. In the second approach, the chiral ionic liquid [(di-h)₂dmg][quinic] was used as a chiral source in combination with nonchiral imidazolium ionic liquids ([C₁₀mim][BF₄] and [C₈mim][PF₆]). Asymmetric dihydroxylation of 1-hexene in [(di-h)₂dmg][quinic] as chiral source and [C₁₀mim][BF₄] as reaction media and using *N*-methylmorpholine-*N*-oxide as co-oxidant was selected as a model system to evaluate the feasibility of recycling the catalytic system (osmium catalyst + CIL) using either organic solvents or supercritical CO₂ (scCO₂) as the extraction medium. The reaction media and catalytic system (osmium + CIL) were successfully recycled and reused by scCO₂ extraction for at least five successive cycles without significant decrease in yield (90%) or enantioselectivity (77%).

KEYWORDS: alkenes, asymmetric catalysis, dihydroxylation, ionic liquids, osmium, supercritical fluids



- ⇒ 6 examples: yields and ee higher or comparable to conventional Sharpless system
- ⇒ No slow addition of olefins is required
- ⇒ Catalytic system efficiently reused for 5 cycles
- ⇒ Very low osmium content into final product

1. INTRODUCTION

The Sharpless asymmetric dihydroxylation (AD) of olefins offers one of the most efficient methods for the preparation of chiral 1,2-diols, which are key intermediaries for many biological and pharmaceutical compounds.¹ Osmium tetroxide (OsO₄), is one of the most selective oxidants known: it dihydroxylates a broad range of olefins, and it reacts only with olefins.² The AD reaction is a route to the synthesis of various chiral drugs, natural products, and fine chemicals.^{3–5}

Several recent approaches have been described, such as replacing very toxic osmium tetroxide by nonvolatile K₂OsO₂(OH)₄ or using methods for osmium catalyst immobilization: micro-encapsulation techniques⁶ with polystyrene polymers or poly-urea microcapsules;⁷ ion exchangers;⁸ anchoring tetrasubstituted olefins in silica,⁹ in polyethylene glycol matrixes, or in Amberlite containing residual vinyl groups;¹⁰ use of gold colloids or nanocrystalline magnesium oxide;¹¹ and more recently, using an aqueous solution of sucrose or generating in situ osmium diamine chelates.¹² Recycling experiments have been successfully performed up to a maximum of six cycles. The use of osmium catalyst derivatives or alternative catalyst based on ruthenium or rhenium species have been recently described.¹³ On the other hand, the immobilization of conventional chiral ligands onto

soluble and insoluble polymers requires an expensive and long synthesis of each chiral ligand, and its application leads to reduction of enantioselectivity. Moreover, osmium leaching was also observed, and thus, recovery and reuse of the catalyst was not completely possible.¹⁴

Reoxidation of osmium in the catalytic system^{15,16} has been performed using various stoichiometric reagents, in particular, *tert*-butyl hydroperoxide (TBHP), *N*-methylmorpholine oxide (NMO), and potassium ferrocyanide; or using peroxide or air as the terminal oxidant. A water/*tert*-butanol (1:1, v/v) mixture has been described as standard medium for many AD reactions, where high enantioselectivity is achieved as simultaneous complete dissolution and effective interaction between the catalytic system and the substrate are ensured.

To find greener methodologies, we described the possibility of performing the AD reaction using a conventional water–organic solvent system or water–surfactant as the reaction media, K₂OsO₂(OH)₄/(DHQD)₂PHAL as the AD catalytic system and K₃Fe(CN)₆ or NMO as co-oxidant.¹⁷ In addition, a membrane

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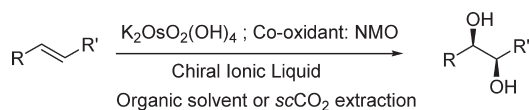


Figure 1. Schematic representation of asymmetric dihydroxylation of olefins using chiral ionic liquid as chirality-inducing media.

nanofiltration process was applied to recycle and reuse the AD catalytic system (osmium catalyst/chiral ligand) as well as the surfactants selected.¹⁷ The choice of ionic liquids as alternative cosolvents^{18–20} or unique solvents²¹ for the AD reactions was proposed as a robust methodology to recycle and reuse the AD catalytic system (osmium + chiral ligand). The product is extracted with either an organic solvent (e.g., diethyl ether) or supercritical CO₂ (scCO₂). When NMO is used as co-oxidant in the conventional Sharpless AD, a slow addition of the olefin is required to eliminate the secondary catalytic cycle effect, which would lead to erosion of the enantioselectivity. Recently, we described the possibility of avoiding this slow addition protocol by simply using specific ionic liquids as a reaction medium.²¹ In a more recent approach, chiral ionic liquids were tested as an alternative chiral promoter, replacing the Sharpless chiral ligand.²²

Herein, we present a more detailed study on the possibility of using chiral guanidinium ionic liquids for asymmetric dihydroxylation of olefins, followed by an organic solvent or supercritical CO₂ product extraction (Figure 1).

Since the first examples of chiral ionic liquids, the number of publications has been growing rapidly, and nowadays, a large pool of CILs is available, bearing either chiral cations, anions, or both, with a wide variety of functionalities.^{23,24} The most common applications of novel CILs are mainly focused on chiral media for asymmetric synthesis, chiral-resolution reagents, and chiral additives in spectroscopic and chromatographic applications.²⁵ Despite the efforts to design new CILs, enantioselectivity performances higher than 80% were only recently described, in particular, for asymmetric Diels–Alder reactions,²⁶ asymmetric Michael and Baylis–Hillman additions,²⁷ asymmetric aldol reaction,²⁸ and enantioselective biotransformations.²⁹

In the perspective of developing novel classes of room temperature ionic liquids, we reported the tetra-alkyl-dimethyl-guanidinium cations (dmg) as a new generation of ILs, with low tendency for crystallization, even in the presence of anions that are persistently solid for different cations.^{22,30} This peculiar property allowed the development of new CILs by simple replacement of the tetra-hexyl-dimethylguanidinium [(di-h)₂dmg]Cl salt with natural or easily functionalized chiral natural anions such as (*S*)-mandelate, quinic, L-lactic, (*S*)-camphorsulfonate, BOC-D-hydroxyproline and acetyl-D-hydroxyproline (Figure 2). The comparatively simple synthesis and the possibility to recycle combined with peculiar ionic liquid properties suggest that CILs could contribute to the application of chiral solvents in asymmetric synthesis.

In recent years, the combination of supercritical scCO₂ with ionic liquids as alternative reaction media has become a focus of intensive research. Blanchard et al.³¹ were the first to suggest that this combination would generate very interesting biphasic mixtures to carry out reaction. The attractive properties of both solvents can bring numerous advantages to chemical processes. Due to their ionic nature and negligible vapor pressure, ionic liquids exhibit no appreciable solubility in scCO₂; at the same time, scCO₂ is remarkably soluble in most ILs and can be used to

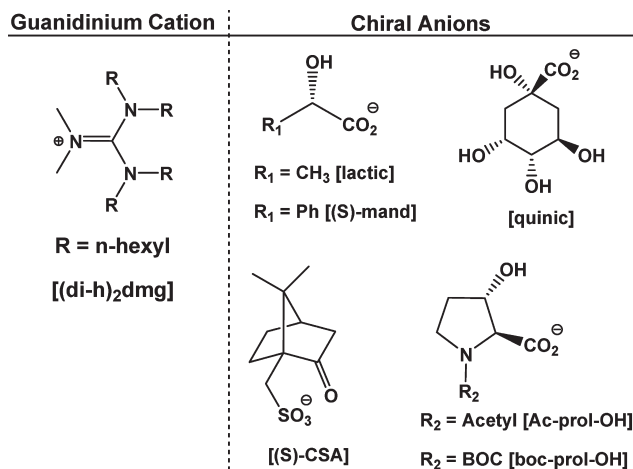


Figure 2. Structure of chiral guanidinium ionic liquids selected for AD reactions.

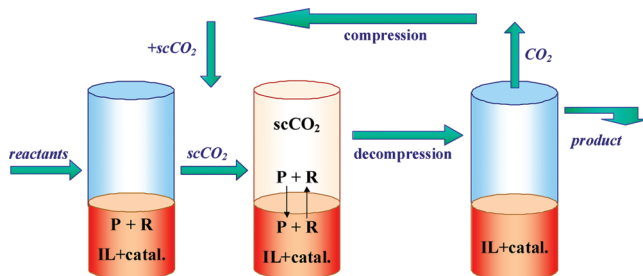


Figure 3. Ionic liquid/catalyst phase recycle and product recovery using scCO₂–IL biphasic system.

extract numerous organic substances from them without any IL contamination in the final product.³² Another advantage of this system is that ionic liquid phase containing the catalyst can then be reused in subsequent reaction/extraction cycles, as presented in Figure 3. Previous work of this group on Sharpless asymmetric dihydroxylation using imidazolium-based ILs, followed by scCO₂ extraction of different solutes²¹ proved that this concept provides a very efficient, simple, and robust method for the immobilization of the catalytic system and allows for a cleaner process with high product quality as well as easy product recovery.

2. RESULTS AND DISCUSSION

2.1. Performance Screening of Chiral Ionic Liquids. The new chiral guanidinium ILs were prepared combining the tetra-hexyl-dimethylguanidinium cation with readily available chiral anions, such as (*S*)-mandelate, (*R*)-mandelate, quinic, L-lactic, (*S*)-camphorsulfonate, BOC-hydroxyproline, and acetyl-hydroxyproline. Initially, we performed a screening of synthesized chiral ionic liquids as a unique reaction and chirality-inducing media for Sharpless dihydroxylation of 1-hexene. All experiments were performed by adding the olefin all at one time (normal addition) to the reaction mixture.

Interestingly, using the CILs [(di-h)₂dmg][quinic] and [(di-h)₂-dmg][L-lactic] (Table 1, entries 3 and 4) in the absence of the Sharpless chiral ligand and without slow addition of the olefin, product (*R*)-1,2-hexanediol was obtained in high yields and high enantiomeric excess. It is important to note that these

Table 1. AD Reaction of 1-Hexene as Model Substrate, Using NMO As Co-oxidant, $K_2OsO_2(OH)_4$ as Osmium Catalyst, and Chiral ILs as Chiral Reaction Media^{a,b}

entry	chiral ionic liquid (CIL)	yield (%)	ee (%) ^c
1	[(di-h) ₂ dmg][(S)-mandelic] ^d	78	74 (71 ^e)
2	[(di-h) ₂ dmg][(R)-mandelic] ^f	75	70 (68 ^e)
3	[(di-h) ₂ dmg][quinic] ^d	95	85
4	[(di-h) ₂ dmg][L-lactic] ^d	93	81
5	[(di-h) ₂ dmg][(S)-CSA] ^d	65	58
6	[(di-h) ₂ dmg][BOC-prol-OH] ^d	70	48
7	[(di-h) ₂ dmg][Ac-prol-OH] ^d	55	72

^aIn stoichiometric conditions. ^bIn a typical experiment, co-oxidant NMO (1.3 mmol), selected chiral guanidinium ionic liquid (0.3 mL, 1 mol equiv), $K_2OsO_2(OH)_4$ (0.5 mol %), and substrate 1-hexene (0.5 mmol) were added and stirred at room temperature for 24 h. ^cEnantiomeric excess determined by GLC. ^dThe product (R)-1,2-hexanediol was obtained. ^eEnantiomeric excess determined by NMR. ^fThe product (S)-1,2-hexanediol was obtained.

experiments were performed using CILs as unique reaction media (stoichiometric conditions), and the isolated product yields (93–95%) and enantioselectivities (72–85%) were similar to the ones obtained using the chiral ligand [DHQD]₂PHAL in *t*-BuOH/H₂O (1:2) by adding the olefin all at one time (catalytic conditions). Other CILs gave poor results for AD of 1-hexene, providing yields of 55–78% and ee's of 48–74% (Table 1, entries 1, 2, 5, and 6). CILs [(di-h)₂dmg][(S)-mandelic] and [(di-h)₂dmg][(R)-mandelic] were tested as chiral reaction media for AD of 1-hexene to evaluate the stereochemistry of the final product. In the case of (R)-mandelate as the chiral anion of CIL, the final product was obtained with the opposite stereochemistry. The corresponding enantioselectivities were determined by GLC and NMR as indicated in Table 1.

2.2. Optimization of Reaction Conditions Using Chiral Ionic Liquids As Reaction and Chirality Inducing Media. Encouraged by these preliminary results, we tested the asymmetric dihydroxylation using six different olefins (containing aliphatic and aromatic units) that were selected as representative substrates: 1-hexene, *trans*-5-decene, 1-methylcyclohexene, styrene, α -methylstyrene and methyl *trans*-cinnamate. The CILs [(di-h)₂dmg][quinic] and [(di-h)₂dmg][L-lactic] were selected as best chiral source. The results obtained for asymmetric dihydroxylation are presented in Table 2.

In general, for all olefins tested, the novel chiral guanidinium ILs based on quinic and L-lactic anions allowed us to obtain yields and enantioselectivities comparable to or better than for conventional systems (using conventional chiral ligands). Particularly relevant is the case of [(di-h)₂dmg][quinic] for substrates methylstyrene, 1-methylcyclohexene, and *trans*-5-decene (86–94% yields and 80–93% ee's) and [(di-h)₂dmg][L-lactic] for substrate styrene (81% yield and 86% ee). Despite the lower efficiency in the case of *trans*-methyl cinnamate, the observed performance is comparable to results previously described in the literature for ionic liquids/chiral ligands or conventional systems. In the case of 1-hexene as a model substrate, it was possible to perform the AD reaction with both CILs using the inorganic co-oxidant potassium ferrocyanide, $K_3Fe(CN)_6$, instead of NMO (Table 2, last entry).

2.3. Optimization of Reaction Conditions Using Chiral Ionic Liquids in Catalytic Amount. To reduce the amount of CIL required for the AD transformation as a chiral promoter,

Table 2. AD Reaction of Olefins Using NMO as Co-oxidant and the CILs [(di-h)₂dmg][quinic] and [(di-h)₂dmg]-[L-lactic] As Chiral Reaction Media^{a,b}

olefin	chiral IL	yield (%)	ee (%) ^c
1-hexene (from Table 1)	[(di-h) ₂ dmg][quinic]	95	85
	[(di-h) ₂ dmg][L-lactic]	93	81
styrene	[(di-h) ₂ dmg][quinic]	92	72
	[(di-h) ₂ dmg][L-lactic]	81	86
α -methylstyrene	[(di-h) ₂ dmg][quinic]	93	80
	[(di-h) ₂ dmg][L-lactic]	75	74
1-methyl-1-cyclohexene	[(di-h) ₂ dmg][quinic]	94	86
	[(di-h) ₂ dmg][L-lactic]	81	78
<i>trans</i> -5-decene	[(di-h) ₂ dmg][quinic]	86	93
	[(di-h) ₂ dmg][L-lactic]	61	80
<i>trans</i> -methylcinnamate	[(di-h) ₂ dmg][quinic]	76	74
	[(di-h) ₂ dmg][L-lactic]	62	60
1-hexene ^d	[(di-h) ₂ dmg][quinic]	88	80
	[(di-h) ₂ dmg][L-lactic]	77	89

^aIn stoichiometric conditions. ^bIn a typical experiment, co-oxidant NMO (1.3 mmol, 1 equiv), [(di-h)₂dmg][quinic], or [(di-h)₂dmg]-[L-lactic] (0.3 mL, 1 mol equiv), $K_2OsO_2(OH)_4$ (0.5 mol %), and selected substrate (0.5 mmol) were added and stirred at room temperature for 24 h. ^cEnantiomeric excess determined GLC or HPLC analysis. ^dUsing $K_3Fe(CN)_6$ (3 equiv) and K_2CO_3 as co-oxidant instead of NMO.

we also explored the possibility of using chiral IL [(di-h)₂dmg]-[quinic] as a chirality-inducing media dissolved in a conventional IL media, in particular, [(C₈mim)[PF₆] and [(C₁₀mim)[BF₄]]. It is known that for some specific cases, the use of novel CILs under catalytic conditions, dissolved in other ionic liquid media, can be useful to improve the complete dissolution of different components and decrease the viscosity of the mixture.¹⁶ For the studies of AD reaction in which [(di-h)₂dmg][quinic] is used as chiral source, nonchiral imidazolium ionic liquids [(C₈mim)[PF₆] or [(C₁₀mim)[BF₄]] were used as the reaction solvent, NMO as co-oxidant, and 1-hexene was again selected as model substrate.

Analyzing the results of Table 3, it can be observed that the amount of CIL [(di-h)₂dmg][quinic] as cosolvent dissolved in ILs [(C₈mim)[PF₆] or [(C₁₀mim)[BF₄]] influences significantly the final enantioselectivity (35–79%). On the other hand, the corresponding yields differ only mildly (84–93%) for different amounts of CIL [(di-h)₂dmg][quinic]. Reaction media (i.e., ILs [(C₈mim)[PF₆] or [(C₁₀mim)[BF₄]]) did not have a significant influence on the reaction efficiency (yields and ee's). For the following studies, the use of 50 mol % of CIL [(di-h)₂dmg]-[quinic] dissolved in IL [(C₁₀mim)[BF₄]] (90% of yield and 79% of ee) was chosen as corresponding to optimal experimental conditions.

2.4. Recycling and Reuse of the Reaction System (Osmium + Chiral IL + Nonchiral IL) by Organic Solvent Extraction. After optimizing the reaction conditions, the important issue of the possibility to reuse the catalytic system (osmium + CILs) was also evaluated. In the previous studies of AD of olefins in ionic liquids, we proved the possibility to reuse the conventional catalytic system consisting of osmium and a chiral ligand.^{19,20} One possible approach is the use of organic solvents, such as *n*-alkanes or ethers, to extract selectively the reaction products without extracting the ionic liquid in the catalytic system.

To test this possibility, the AD reaction of 1-hexene was performed using the best selected reaction conditions (50 mol % of

Table 3. AD Reaction of 1-Hexene in the Presence of [(di-h)₂dmg][quinic]^a as the Chiral Source Dissolved in RTILs [C₈mim][PF₆] and [C₁₀mim][BF₄] and AD Reaction of *trans*-Stilbene Using [(di-h)₂dmg][L-lactic]^b Dissolved in [C₁₀mim][BF₄]^c

olefin	IL media	[(di-h) ₂ dmg][X] ^d	yield (%)	ee (%) ^e
1-hexene	[C ₈ mim][PF ₆]	[X] = quinic, 1 mol %	93	35
		10 mol %	84	61
		50 mol %	92	73
1-hexene	[C ₁₀ mim][BF ₄]	[X] = quinic, 1 mol %	88	37
		10 mol %	89	64
		50 mol %	90	79
<i>trans</i> -stilbene	[C ₁₀ mim][BF ₄]	[X] = L-lactic, 50 mol %	68	82

^a 1, 10, or 50 mol % relative to the reaction media. ^b 50 mol % relative to the reaction media. ^c In a typical experiment, addition of co-oxidant NMO (100 mg; 1.3 mmol) to imidazolium ionic liquid, [C₁₀mim][BF₄] or [C₈mim][PF₆] (0.5 mL) was followed by addition of [(di-h)₂dmg]-[quinic] (1, 10, or 50 mol % relative to the reaction media) or [(di-h)₂dmg][L-lactic] (50 mol % relative to the reaction media), K₂OsO₂(OH)₄ (0.5 mol %), and 1-hexene or *trans*-stilbene (0.5 mmol), and the reaction mixture was allowed to stir at room temperature for 24 h. ^d Quantity of chiral guanidinium IL added to reaction mixture (1, 10, or 50 mol % relative to the reaction media). ^e Enantiomeric excess determined by GLC (1-hexene) or HPLC (*trans*-stilbene).

CIL [(di-h)₂dmg][quinic] relative to the reaction media dissolved in the IL [C₁₀mim][BF₄] and either *tert*-butyl methyl ether (TBME) or *n*-hexane as extraction solvents. These organic solvents were selected mainly because of the limited solubility of both ionic liquids and organometallic catalyst in them. After removing the product, fresh quantities of substrate 1-hexene and NMO co-oxidant were added to the reaction mixture (ionic liquid + osmium catalyst + chiral ionic liquid), and the reaction was run again.

The results presented in Table 4 show that the same reaction medium can be reused only once. In fact, in run 3, the enantiomeric excess dropped to 37% (using TBME) and 25% (using *n*-hexane). This drop in the enantiomeric excess after only one reuse is probably due to the extraction of the chiral guanidinium ionic liquid by the organic solvents. This fact was supported by the observation of CIL peaks in the ¹H NMR spectra of the crude extracted product. In addition, using TBME and *n*-hexane did not prove efficient in terms of product yield because of the poor solubility of 1,2-hexanediol in these organic solvents.

2.5. Recycling and Reuse Studies of Reaction System (Osmium + Chiral IL + Nonchiral IL) by Supercritical CO₂ Extraction. To achieve a more efficient reuse process, several recycle experiments were performed using supercritical carbon dioxide (scCO₂).

Provided that the AD reaction proceeds efficiently in ionic liquids, the application of the IL-supercritical CO₂ separation approach requires that scCO₂ be selective toward the reaction products and that it will not extract the catalytic system (osmium catalyst and chiral ionic liquid). The strategy was to use scCO₂ at the lowest possible density (and therefore pressure) at which it can still dissolve the reaction products but does not carry any catalyst out of the ionic liquid solution. The extraction procedure was performed at 40 °C and a constant pressure of 120 bar. When the extraction was finished, fresh quantities of substrate 1-hexene and co-oxidant NMO were added to the ionic liquid so that a new reaction/extraction cycle could start. Extraction samples were in ethanol and divided into two equal parts: one was used for the determination of osmium content by ICP, and the other was used

Table 4. Recycling AD Reaction of 1-Hexene Using the Best Reaction Conditions and *tert*-Butyl Methyl Ether or *n*-Hexane As Extraction Solvents^a

extraction solvent	cycles	yield (%)	ee, % ^b
<i>tert</i> -butyl methyl ether (TBME)	1	90	73
	2	89	57
	3	78	37
<i>n</i> -hexane	1	80	69
	2	69	60
	3	77	25

^a A typical recycling procedure was performed by addition of NMO (1.3 mol equiv), [C₁₀mim]BF₄ (1 mL), [(di-h)₂dmg][quinic] (50 mol %), K₂OsO₂(OH)₄ (1.0 ± 0.1 mg; 0.5 mol %), and 1-hexene (0.5 mmol) and stirring for 24 h at room temperature. The final reaction mixture was then extracted with either TBME or *n*-hexane. Then, more 1-hexene (0.5 mmol) and NMO (100 mg; 1.3 mol equiv) was added to the reused ionic liquid, and the cycle was repeated. ^b Enantiomeric excess determined by GLC.

Table 5. Yield, Enantiomeric Excess, and Osmium Content in Recycling Experiments, for AD Reaction of 1-Hexene, in [C₁₀mim][BF₄] Solvent and [(di-h)₂dmg][quinic] Chiral Source, Extracting the Product with scCO₂ at 40 °C and 120 bar^a

cycles	yield, (%)	ee, % ^b	osmium content, % ^c
1	90	76	0.04
2	93	75	0.08
3	91	81	0.04
4	89	77	0.03
5	87	74	0.03

^a In a typical recycling experiment, [C₁₀mim][BF₄] (2 mL) combined with [(di-h)₂dmg][quinic] (50 mol % relative to the reaction media), K₂OsO₂(OH)₄ (0.5 mol %), NMO (1.3 mol equiv), and 1-hexene (0.5 mmol) were added into the high-pressure cell, and the reaction was carried out for 24 h (*p* = 1 atm, *t* = 25 °C). After the reaction was finished, scCO₂ (*p* = 120 atm, *t* = 40 °C) was added. A fresh quantity of NMO and 1-hexene were added to the remaining IL phase after the scCO₂ extraction. After the reaction time of 24 h, a new scCO₂ extraction at 120 atm was carried out. ^b Enantiomeric excess was determined by GLC analysis. ^c Osmium content was determined by ICP.

for the isolation of the 1,2-hexanediol and the determination of the enantiomeric excess.

As described in the previous studies, the use of NMO as co-oxidant and ionic liquid solvent avoided the need to add olefins slowly to the reaction medium. Comparison of the results obtained using scCO₂ extraction (Table 5) with previous studies using organic solvents (Table 4) shows that a significant improvement in terms of efficiency is clear, as product yield (87–93%) and enantioselectivity (74–81%) remain high in the first 5 cycles. Another relevant advantage of scCO₂ extraction process is the fact that the osmium leaching was always very low and close to the detection limit of the ICP method (0.03–0.08%).

The results suggest that most of the product is extracted with the first 60 cm³ of carbon dioxide (CO₂/product molar ratio ~ 400). This high CO₂/product ratio is the consequence of low extraction pressure, which was chosen to obtain higher CO₂ selectivity toward the desired diol product. On lowering the pressure, carbon dioxide density and solvent power decrease,

so it is necessary to use a higher amount of CO₂ to fully recover the product.

Comparing the results presented in Table 5 with the studies previously published with the same substrate,^{19,21} using conventional Cinchona chiral ligands, it is clear that the chiral guanidinium ionic liquids allowed for similar or higher reaction yields (run 5: 87% with chiral ionic liquid, compared with 75% using the cinchona alkaloid ligand), with slightly lower enantiomeric excess (run 5: 74% using chiral ionic liquid, compared with 88% using the cinchona alkaloid ligand). This result is encouraging because for the first time in the literature, a combination of one ionic liquid as a reaction medium and one chiral ionic liquid as the chirality-inducing medium was successfully applied to the asymmetric dihydroxylation reaction and reused four times utilizing supercritical carbon dioxide for a clean and efficient product separation.

3. CONCLUSIONS

This study presents for the first time the use of chiral ionic liquids as novel chirality-inducing media for AD of olefins. Chiral guanidinium ILs based on quinic and L-lactic as chiral anions can be efficiently used for this approach.

The use of CILs as the unique reaction media offers an alternative chiral inducing agent for the AD reaction previously optimized by Sharpless with conventional chiral ligands based on Cinchona alkaloids. Yields and enantioselectivities obtained through this methodology were higher than or comparable to those obtained in conventional system. In addition, when using the new proposed medium with NMO as co-oxidant, slow addition of olefin into the reaction medium is no longer required to obtain high ee's.

Another attractive advantage is related to the possibility to perform AD reactions using a CIL dissolved in the nonchiral imidazolium ionic liquid.

Supercritical CO₂ was presented as a useful medium to extract and to isolate the product from the toxic osmium catalyst, allowing for reuse of the catalytic system (osmium + ionic liquids) over successive reaction/extraction cycles. Organic solvents such as TBME and *n*-hexane were not good extraction media for the recycling process, mainly because they might also extract the chiral guanidinium ionic liquid.

In summary, asymmetric dihydroxylation of olefins using guanidinium chiral ionic liquids as unique reaction and chirality-inducing media, or chiral source dissolved into nonchiral IL media, provides a very robust, efficient, and simple methodology. Combining ionic liquid reaction media with scCO₂ extraction allows efficient reuse of the osmium catalyst and CIL without any catalyst or ionic liquid contamination of the product.

4. EXPERIMENTAL SECTION

General Description. The following chemicals were purchased from Aldrich and used as supplied: styrene, α -methylstyrene, 1-hexene, 1-methylcyclohexene, trans-5-decene, K₂OsO₂(OH)₄, K₃[Fe(CN)₆], *N*-methyl-morpholine oxide (NMO). All aqueous solutions were prepared using distilled water. ¹H, ¹³C, and ³¹P NMR spectra were recorded on a Bruker AMX 400 spectrometer. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethylsilane reference for ¹H and ¹³C NMR and from external H₃PO₄ for ³¹P NMR. IR spectra were recorded on a Mattson Instruments model Satellite FTIR as thinly dispersed films. Gas liquid chromatography (GLC), HPLC and inductively coupled plasma spectroscopy (ICP) analysis were performed according to previous publications.²²

Chiral ionic liquids, including tetra-hexyl dimethylguanidinium [(di-h)₂dmg] cation combined with chiral anions (*S*)-mandelate, (*R*)-mandelate, quinic, L-lactate, camphorsulfonate, acetyl hydroxyproline, and BOC-hydroxyproline, were prepared according to a reported procedure.²² Ionic liquids [C₁₀mim][BF₄] and [C₈mim][PF₆] were purchased from Solchemar Lda.

General Reaction Procedure for AD Reaction of Olefins Using CIL as Chiral Source (Method A) or CIL as Cosolvent Dissolved into Imidazolium IL (Method B). **Method A.** In a typical experiment, a 2 mL flask was charged with co-oxidant NMO (100 mg; 1.3 mmol), followed by addition of a selected chiral guanidinium ionic liquid (0.3 mL, 1 mol equiv) under argon atmosphere. The catalyst K₂OsO₂(OH)₄ (0.5 mol %) and substrate (0.5 mmol) were added, and the reaction mixture was allowed to stir vigorously at room temperature for 24 h. The obtained mixture was dissolved in a small amount of dichloromethane (2 mL) and purified by flash chromatography to give the corresponding (*R*)-diol, except in the case of the CIL [(di-h)₂dmg][(*R*)-mandelate] experiment, in which (*S*)-diol was obtained. Enantioselectivities were determined by GLC, HPLC, and NMR according to the previous optimized conditions.²¹

Method B. In a typical experiment, a 5 mL flask was charged with imidazolium ionic liquids [C₁₀mim][BF₄] or [C₈mim][PF₆] (0.5 mL), and co-oxidant NMO (100 mg; 1.3 mmol), followed by addition of a selected chiral guanidinium ionic liquid (1, 10, or 50 mol % relative to the reaction media) under argon atmosphere. The catalyst K₂OsO₂(OH)₄ (0.5 mol %) and substrate 1-hexene (0.5 mmol) were added, and the reaction mixture was allowed to stir vigorously at room temperature for 24 h. The obtained mixture was dissolved in a small amount of dichloromethane (2 mL) and purified by flash chromatography to give the corresponding diol.²¹ Enantioselectivities were determined by GLC according to the previous optimized conditions.²¹

General Procedure for the Reuse of the Catalytic System (Osmium and CIL) by Extraction with TBME or *n*-Hexane. A 5 mL flask was charged with NMO (100 mg; 1.3 mol equiv) and [C₁₀mim][BF₄] (1 mL), and under stirring, the chiral ionic liquid [(di-h)₂dmg][quinic] (50 mol % relative to the reaction media) and the catalyst K₂OsO₂(OH)₄ (1.0 ± 0.1 mg; 0.5 mol %) were added under argon atmosphere. 1-Hexene (0.5 mmol) was then added all at one time, and the resulting mixture was stirred for 24 h at room temperature. The final reaction mixture was then extracted with *tert*-butyl methyl ether (2 × 5 mL) or *n*-hexane (2 × 5 mL). The combined organic phase was dried (MgSO₄), evaporated in vacuo, and purified by flash chromatography (eluent: ethyl acetate/*n*-hexane (1:3)). Then, more 1-hexene (0.5 mmol) and NMO (100 mg; 1.3 mol equiv) was added to the reused ionic liquid, and the cycle was repeated. This recycling process was repeated twice.

General Procedure for the Reuse of the Catalytic System (Osmium and CIL) by Extraction with Supercritical CO₂. The ionic liquid [C₁₀mim][BF₄] (2 mL) combined with chiral ionic liquid [(di-h)₂dmg][quinic] (50 mol % relative to the reaction media), K₂OsO₂(OH)₄ (0.5 mol %), NMO (1.3 mol equiv) and substrate 1-hexene (0.5 mmol) were added to the high-pressure cell. The reaction was carried out for 24 h at atmospheric pressure and room temperature.²¹ After the reaction was finished, the high-pressure cell was connected to the scCO₂ extraction apparatus and placed in a temperature-controlled bath at 40 °C. Supercritical CO₂ at 120 bar was added, and when the system equilibrated, scCO₂ extraction at constant pressure was performed. The cold traps were cooled with a mixture of liquid nitrogen and ethanol,

and samples were collected in ethanol at different points of extraction. This was done to determine the amount of CO₂ needed to extract most of the product. Samples were then divided into two equal parts. One was used for the determination of the osmium content by ICP, and the other, for the isolation of the product and for the determination of the enantiomeric excess as described before.²¹ The samples were collected as described above. A fresh quantity of NMO and 1-hexene was added to the ionic liquid phase that remained in the high-pressure cell after the extraction. After the reaction time of 24 h, the new scCO₂ extraction at 120 bar was carried out. This reaction–scCO₂ extraction method was repeated four times.

General Procedure for the Determination of Os in Each Phase of the Recycling and Reuse Experiments. For the determination of the osmium content, ICP was used following a reported procedure.²¹ However, to achieve a lower detection limit, a calibration curve was drawn using standard solutions (0.10, 0.25, 0.50, 1.00, 5.00, 10.00, and 20.00 ppm). After each recycling experiment, the organic phases (after extraction with Et₂O or scCO₂) was removed and diluted in 10 mL of distilled water.

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