Stable Chiral Complexes of Ionic Liquids with Aluminium and Biaryl Ligands as Efficient Catalysts for the Synthesis of Chiral Lactones

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Abstract: A new catalytic system for the asymmetric Baeyer–Villiger oxidation of monosubstituted prochiral cyclobutanones to γ-butyrolactones with high yields (40–99%) and enantioselectivities (45–87%) is described. Aluminium complexes with biaryl ligands and ionic liquids are presented. The incorporation of an ionic liquid in the complex structure was confirmed by the observed four-coordinate nature of the aluminium.

Key words: ionic liquids, lactones, biaryl ligands, aluminium complexes, asymmetric catalysis

The Baeyer–Villiger (BV) reaction is based on the formation of esters and lactones by the oxidation of ketones with peroxide derivatives.[1] Of particular importance are new protocols for the asymmetric version of this reaction for the synthesis of chiral lactones. γ-Butyrolactones are a class of chiral compounds that often occur in an enantiomerically pure form in nature, e.g., Japanese beetle pheromone. Furthermore, the γ-butyrolactone subunit is a valuable building block for the natural synthesis of biologically important substances, such as alkaloids, macrocyclic antibiotics, lignan lactones and antileukemics.[2]

The first reports concerning asymmetric BV reactions catalysed by metal complexes date back to 1994. Since then, syntheses of chiral lactones using chiral catalysts and chiral hydroperoxides have been described.[3] One of these methods uses metal complexes with chiral ligands. Strukul[4] and Bolm[5] described the first examples of the racemic resolution of cyclic alkanones catalysed by platinum or copper compounds, obtaining the corresponding lactones with high ee (up to 69%). Another example of the synthesis of chiral lactones is the application of titanium Sharpless catalysts for the oxidation of prochiral cyclobutanones reported by Lopp.[6] Other metals (Cu, Zr, Hf, Pt, Sn, Zn) and their chiral complexes are known to catalyse the synthesis of lactones with high enantioselectivities (up to 87% ee).[7] One of the most efficient metals for the asymmetric BV oxidation is aluminium.[8] Complexes of this metal with different chiral ligands, e.g., based on BINOL (1,1′-bi-2-naphthol) or VANOL (3,3′-diphenyl-2,2′-bi-1-naphthol), facilitate the synthesis of monosubstituted γ-butyrolactones from prochiral cyclobutanones with high enantioselectivity (77–83%).[8]

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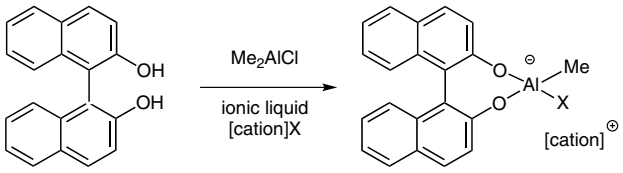
The last two decades have been filled with studies concerning the synthesis and applications of ionic liquids.[9] Our previous work demonstrated that the use of ionic liquids in the Baeyer–Villiger oxidation resulted in improved yields and enhanced reaction rates.[10] Among ionic liquids, chiral analogues are known, bearing the chirality in the cation or anion.[11] Thus far, chiral ionic liquids have been used as solvents and organocatalysts for the asymmetric induction of many types of reactions: Michael addition, aldol, Baylis–Hillman and Diels–Alder reaction.

Herein, we present a new catalytic system for the asymmetric Baeyer–Villiger oxidation of monosubstituted prochiral cyclobutanones with cumyl hydroperoxide (CHP) as the oxidant. To the best of our knowledge, this is the first example of the application of ionic liquids in an asymmetric Baeyer–Villiger reaction.

Our idea relies on the introduction of ionic liquids (ILs) into the structure of an aluminium complex with biaryl ligands, as presented in Scheme 1. For this purpose, new catalytic complexes were synthesised (Table 1). We chose two ligands: BINOL and the vaulted biaryl ligand VANOL and Me_2AlCl was used as the aluminium precursor. For the ionic liquids, a chiral cation {1-[(1′*R*,2′*S*,5′*R*)-(–)-menthoxymethyl]-3-methylimidazolium, (–)[mmmim], or 1-[(1′S,2′R,5′S)-(+)-menthoxymethyl]-3-methylimidazolium, (+)-[mmmim]} and an achiral cation (1-butyl-3-methylimidazolium, [bmim]) were selected, possessing strongly coordinating anions (Cl^-) and weakly coordinating bis(trifluoromethylsulfonyl)imide ([NTf_2]) anions.

The synthesis of the complexes was based on the combination of equimolar amounts of Me_2AlCl with enantiopure BINOL or VANOL under a dry, inert atmosphere at −15 °C in anhydrous dichloromethane followed by the addition of equimolar amounts of ionic liquid.[12]



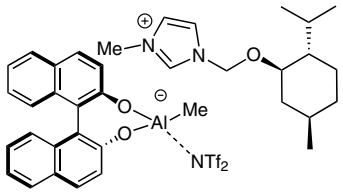
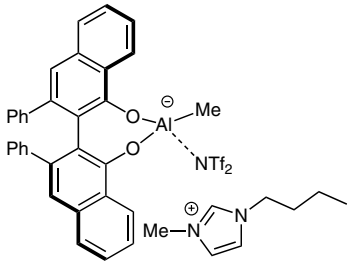
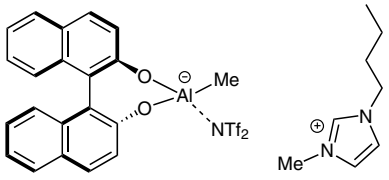
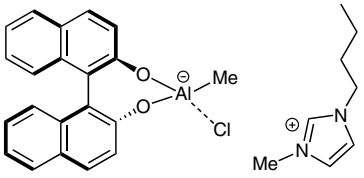
Scheme 1 The proposed structures of the biaryl ligand–aluminium promoter–IL complexes

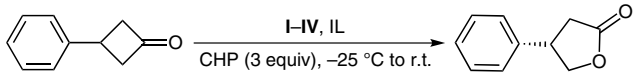
The complexes were characterised by ^1H NMR, ^{13}C NMR, and ^{27}Al NMR spectroscopy and mass spectrome-

try (Supporting Information). In the organoaluminium compounds, the chemical shift δ (^{27}Al) is an indicator of the coordination number of the aluminium atom. A lone signal was observed in the solid-state ^{27}Al NMR spectra of the complexes **I**–**IV**, with a chemical shift of approximately 60–90 ppm. No signals generated by three-fold coordinated aluminium atoms (280–210 ppm) were seen. This fact confirms the change of the coordination number for aluminium from three to four and the incorporation of the ionic liquid into the complex structure. The structures of all the complexes synthesised were also confirmed by electrospray ionisation mass spectrometry (ESI–MS). In the positive ESI (+) mode *m*/*z* signals belonging to [bmim]/[mmmim] cations were found. Similarly, in the negative ESI (–) mode, signals belonging to the anionic fragments were identified (Supporting Information).

All the synthesised complexes were tested as catalysts for the asymmetric Baeyer–Villiger reaction (Scheme 2). We used the optimal reaction conditions reported in the literature for the aluminium-catalysed oxidation of prochiral 3-substituted cyclobutanones.[8] As a model reaction, the oxidation of 3-phenylcyclobutanone with CHP was performed with complexes **I**–**IV** (molar ratio of complex to ketone 0.5) and an ionic liquid as the solvent (Table 2). The highest enantioselectivity of 3-phenyl-γ-butyrolactone was achieved in the reaction with the application of complex **II** and [bmim][NTf_2] as a solvent (74% ee; Table 2, entry 1). Acceptable enantioselectivity of 67% ee was also achieved using complex **III** with BINOL ligand and [bmim][NTf_2] as a solvent (Table 2, entry 2). Unfortunately, the replacement of the [bmim] cation in complex **III** with chiral [(+)mmmim] cation and the application of this new complex **I** with chiral ionic liquid as a solvent caused a drop in the enantioselectivity of the product to 52% ee (Table 2, entry 3). Complex **IV**, with the strongly coordinating anion [Cl^-], had a detrimental effect on the catalysis, leading to a racemic product and lower yields. The results clearly demonstrate that the main influence on the study of asymmetric Baeyer–Villiger reaction is the structure of biaryl ligand and the solvent.

Table 1 Synthesis of the Complexes from Me_2AlCl (1 mmol), Biaryl Ligand (1 mmol) and IL (1 mmol) at –15 °C in Dichloromethane

Ionic liquid/ligand	Complex	Yield (%)
(+)[mmmim][NTf_2]/(*R*)-BINOL	 **I**	99
[bmim][NTf_2]/(*R*)-VANOL	 **II**	95
[bmim][NTf_2]/(*R*)-BINOL	 **III**	90
[bmim][Cl]/(*R*)-BINOL	 **IV**	95



Scheme 2 Oxidation of 3-phenylcyclobutanone to 3-phenyl-γ-butyrolactone

Table 2 Oxidation of 3-Phenylcyclobutanone (0.5 mmol) to 3-Phenyl-γ-butyrolactone with CHP (1.5 mmol) in the Presence of Complexes **I**–**IV** (0.25 mmol) and Ionic Liquid (0.8 g) at –25 °C to Room Temperature

Entry	Complex	IL (solvent)	Yield (%)[a]	ee (*R*) (%)
1	**II**	[bmim][NTf_2]	99	74
1a	**II** (recycle)	[bmim][NTf_2]	50	57
2	**III**	[bmim][NTf_2]	89	67
3	**I**	[(+)mmmim][NTf_2]	99	52
4	**IV**	[bmim][Cl]	70	0

[a] Determined by GC.

We next tested the reusability of the aluminium complexes in the standard reaction with complex **II** to check whether the complex was still active after the reaction cycle. To this aim, the post-reaction mixture was extracted with dibutyl ether to isolate the product, unreacted CHP and other by-products. After evaporation of the dibutyl ether, the ionic liquid with the immobilised complex (catalytic phase) was used in another reaction cycle without any addition of fresh portion of complex **II** or Me_2AlCl (Table 2, entry 3). Unfortunately, we observed a decrease in the enantioselectivity and yield of the product indicating that the complex had partially lost activity.

To improve these promising results further, we decided to create the complex in situ. The order of reagents, the quantity of reagents and the temperature of each step of the reaction has an influence on the enantioselectivity.[13] Based on the results from Table 2 [mmmim][NTf_2] and [bmim][NTf_2] were used as solvents. The molar ratio of the complex/ketone was recalculated with the assumption that the complex is created from an equimolar ratio of biaryl ligand/$MeAlCl_2$/IL. Increasing the complex/ketone molar ratio from 0.1 to 0.5 and the concentration of ketone, resulted in a high yield and relatively high ee values (Table 3, entries 1 and 2). Different combinations of chiral IL (+)/(–) [mmmim][NTf_2] with (*R*)-BINOL or (*R*)-VANOL did not influence the ee value (Table 3, entries 2, 3 and 7). However, (*S*)-BINOL had a detrimental effect on the ee value (Table 3, entry 4). The best results, full conversion of the ketone and high ee, were obtained using [bmim][NTf_2] with (*R*)-VANOL (ee 87%, Table 3, entry 6) and [bmim][NTf_2] with (*R*)-BINOL (ee 75%, Table 3, entry 5). These results are comparable to those found in the literature.[8] Among the organoanions, acetate and lactate were also examined with [bmim] and (+)/(–)[mmmim] cations. These anions possess slightly different properties to those of the [NTf_2] anion. They are basic, capable of hydrogen bonding, and are strongly coordinating towards metal ions (Table 3, entry 8). The low activity of these complexes caused racemic mixtures and low yields of lactone. Tests for recycling the catalytic phase were performed in the same manner as presented in Table 2 (without any addition of fresh Me_2AlCl) and showed a relatively small decrease in ee and lower yields (Table 3, entry 5a and 6a). To show the stability of the new aluminium complexes, the ^{27}Al NMR spectroscopy of the catalytic phase used for the second cycle was performed. The presence of a signal from aluminium with a coordination number of four was found which confirmed the presence of the active complex in the recycled mixture.

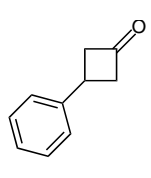
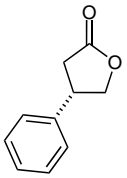
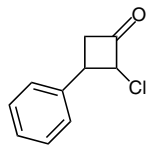
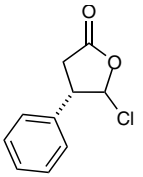
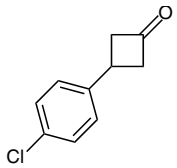
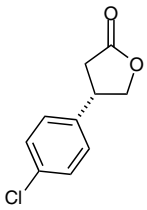
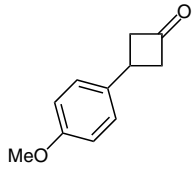
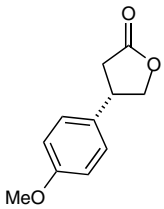
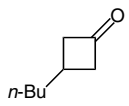
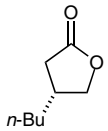
Table 3 Oxidation of 3-Phenylcyclobutanone (0.5 mmol) to 3-Phenyl-γ-butyrolactone with CHP (1.5 mmol) in the Presence of Me_2AlCl (0.25 mmol), Biaryl Ligand (0.25 mmol) and Ionic Liquid (0.8 g) at –25 °C to Room Temperature (Reaction Time: 22 h)

Entry	Biaryl ligand	Ionic liquid	x[a]	Yield (%)[b]	ee (%)[b]
1	(*R*)-BINOL	1.6 g (+) [mmmim][NTf_2]	0.1	66	45 (*R*)
2	(*R*)-BINOL	0.8 g (+) [mmmim][NTf_2]	0.5	98	68 (*R*)
3	(*R*)-BINOL	0.8 g (–) [mmmim][NTf_2]	0.5	98	69 (*R*)
4	(*S*)-BINOL	0.8 g (+) [mmmim][NTf_2]	0.5	98	57 (*S*)
5	(*R*)-BINOL	0.8 g [bmim][NTf_2]	0.5	98	75 (*R*)
5a				65 (recycle)	59 (*R*)
6	(*R*)-VANOL	0.8 g [bmim][NTf_2]	0.5	98	87 (*R*)
6a				50 (recycle)	77 (*R*)
7	(*R*)-VANOL	0.8 g (+) [mmmim][NTf_2]	0.5	98	68 (*R*)
8	(*R*)-BINOL	0.8 g [bmim][OAc] or [bmim][lactate] or (+)/(–) [mmmim][lactate]	0.5	<60	0

[a] Molar ratio of complex/ketone calculated with the assumption that the complex is created in situ with an equimolar ratio of biaryl ligand–$MeAlCl_2$–ionic liquid.
[b] Determined by GC with a precision of ±1%.

Next, the optimal conditions with the (*R*)-BINOL ligand, [bmim][NTf_2] ionic liquid, Me_2AlCl as aluminium source and cumyl hydroperoxide as oxidant were examined in the BV oxidation of various 3-substituted cyclobutanones to determine its scope (Table 4). Cyclobutanones used in this study were synthesised by means of a [2+2]-cycloaddition of dichloroketene and an olefin, followed by subsequent dehalogenation.[14]

Table 4 Oxidation of 3-Substituted Cyclobutanone (0.5 mmol) to 3-Substituted γ-Butyrolactone with CHP (1.5 mmol) in the Presence of Me_2AlCl (0.25 mmol), (*R*)-BINOL (0.25 mmol) and [bmim][NTf_2] (0.8 g) at –25 °C to Room Temperature

Entry	Ketone	Lactone	Yield (%)	ee (*R*) (%)
1			99[a]	75[a]
2			99[b]	86[b]
3			40[b]	45[b]
4			70[b]	62[b]
5			99[a]	48[a]

[a] Yields were determined by GC; enantioselectivities were determined chiral GC.
[b] Yields and enantioselectivities after 22 h were determined by chiral HPLC.

In practical terms, 3-substituted cyclobutanones were readily oxidised to their corresponding lactones in high yields (40–99%) and enantioselectivities (54–75%). Variation of the substitution pattern in the phenyl substituent of the cyclobutanone with electron-withdrawing group showed reduction in enantioselectivity. Neither the introduction of chlorine atom in *para* position of the phenyl ring nor the replacement of a phenyl group with an alkyl group at C-3 position had a detrimental effect (45% and 48% ee respectively, Table 4, entries 3 and 5). A good level of enantioselectivity was achieved in the oxidation of *p*-methoxyphenylcyclobutanone (62% ee, Table 4, entry 4), while a cyclobutanone bearing the chlorine substituent in C-2 position provided a high enantioselection (86% ee, Table 4, entry 4).

Finally, it is worth noting that imidazolium-based ionic liquids can interact by various means, e.g. electrostatic interactions, π–π stacking, hydrogen bond donation, and the formation of hydrophobic (possible Van der Waals interactions) and hydrophilic domains. Anions of ionic liquids also play important roles as hydrogen-bond acceptors or Lewis bases. Several ionic liquids applied for the creation of chiral complexes of biaryl ligand with aluminium presented in this work, possessing anions such as lactate, acetate or chloride had a detrimental effect on the catalysis. These anions are strongly coordinating towards metal ions. Based on this observation it can be proposed that Lewis acidity of the aluminium atom is important for this transformation. Presumably, the more acidic the metal, the lower the activity of the complex in the BV reaction. A similar effect was observed by Bolm[8a] when investigating the relationship between the electronic properties of the biaryl ligand and the enantioselectivity of the BV reaction.

The mechanism of the BV reaction in the presence of complexes reported in this work probably involves initial formation of the chiral complex, for example of type **III**, and then coordination of the ketone and cumyl hydroperoxide to the aluminium atom (Figure 1, structure **A**). The next step involves Criegee intermediate formation (Figure 1, structure **B**), which then stereoselectively rearranges to the lactone. Probably, if the Lewis acidity of the aluminium atom is too high, the rearrangement step is hindered.

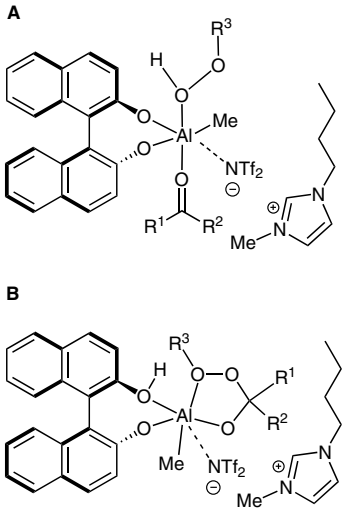


Figure 1 Postulated chiral intermediates

In conclusion, new aluminium complexes with biaryl ligands and ionic liquids are presented. The incorporation of an ionic liquid in the complex structure was confirmed by observation of the four-coordinate nature of the aluminium using ^{27}Al NMR spectroscopy. Subsequently, the new complexes were used as catalysts for the asymmetric Baeyer–Villiger oxidation of 3-substituted cyclobutanones. The most effective catalytic system was composed of (*R*)-VANOL, Me_2AlCl and [bmim][NTf_2]. Careful choice of ionic liquid and reaction conditions allowed the synthesis of 3-substituted γ-butyrolactones in high yields and enantioselectivities. Several important parameters have been studied, and the results of this work have provided useful insights into understanding how ILs may be used in the asymmetric BV oxidation. Further studies are currently under investigation.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Synthesis of the Complexes I–IV**: Me_2AlCl (1 mmol), biaryl ligand (1 mmol), ionic liquid (1 mmol) and anhyd CH_2Cl_2 (1 mL) were placed in a round-bottom flask under a dry, inert atmosphere at –15 °C. The contents of the flask were stirred for 1 h. After this time, evaporation of the solvent gave complexes **I–IV** in high yields (90–99%). Complex **II**: ^{1}H NMR (600 MHz, DMSO): δ = 0.89 (t, *J* = 8.5 Hz, 3 H), 1.25 (sextet, *J* = 8.2 Hz, 2 H), 1.75 (p, *J* = 8.2 Hz, 2 H), 3.85 (s, 3 H), 4.15 (t, *J* = 8.2 Hz, 2 H), 6.67–6.75 (m, 4 H), 6.80–6.89 (m, 4 H), 6.90–7.02 (m, 2 H), 7.15 (s, 2 H), 7.29–7.35 (m, 1 H), 7.43–7.50 (m, 4 H), 7.61–7.71 (m, 1 H), 7.75–7.81 (m, 2 H), 8.25–8.35 (m, 2 H), 9.05 (s, 3 H, $AlCH_3$), 9.15 (s, 1 H). ^{13}C NMR (150 MHz, DMSO): δ = 13.22, 18.73, 31.31, 35.70, 48.46, 116.17, 117.25, 119.62 (q, [$(CF_3SO_2)_2N$], 122.24, 123.59, 123.91, 124.81, 125.09, 126.05, 126.60, 126.89, 128.70, 133.49, 136.50, 141.13, 141.90, 151.47, 159.57. ^{27}Al NMR (400 MHz): δ = 60.13. ESI–MS: *m*/*z* = 139 ([bmim]$^+$), 437 ([VANOL]$^-$), 280 ([$(CF_3SO_2)_2N$]$^-$).
(13) **General Procedure for the Synthesis of 3-Phenyl-γ-butyrolactones**: The sequence of the reagent addition was as follows: first the ketone (0.5 mmol), then biaryl ligand (0.25 mmol), followed by the addition of ionic liquid (0.8 g) were placed in a round-bottom flask under a dry, inert atmosphere and cooled to –15 °C. After the addition of Me_2AlCl (0.25 mmol), the contents of the flask were stirred for 1 h. Next, CHP (1.5 mmol) was added at –25 °C and the reaction was allowed to warm to r.t. and left for 22 h. Yields and enantioselectivities of lactone were determined by GC.
(14) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.