Enantioselective Baeyer-Villiger Oxidations Catalyzed by Chiral Magnesium Complexes

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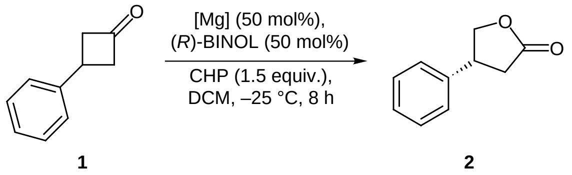
Abstract: Catalytic enantioselective Baeyer-Villiger oxidations of 3-substituted cyclobutanones with cumene hydroperoxide as oxidant have successfully been performed in the presence of chiral magnesium catalysts. The combination of enantiopure BINOL and a variety of Mg reagents is able to promote the oxidation of ketones with good enantiomeric excesses. MgI_2 or MeMgI as metal source were found to give the best enantioselectivities.

Key words: asymmetric catalysis, Baeyer-Villiger reaction, BINOL, lactones, magnesium, oxidation

In recent years, many catalytic reactions have been established that involve a Lewis acid as the chiral mediator.[1] Among these, the use of magnesium has received much attention in 1,3-dipolar cycloadditions[2] and Diels-Alder reactions,[3] but to the best of our knowledge, only a single Mg-catalyzed oxidation has been reported,[4] to which we wish to add another example, viz an asymmetric variant of the Baeyer-Villiger oxidation.

Several metal-catalyzed[5] and biocatalytic[6] versions of asymmetric Baeyer-Villiger reactions using racemic or prochiral ketones for the synthesis of optically active lactones have been developed. Systems that employ Lewis acids consist, e.g., of copper[7] or platinum[8] complexes or a zirconium species,[9] which proved able to mediate the oxidation of cyclic ketones to enantiomerically enriched lactones. Another variant, which is in some respect the most efficient one, relies on an aluminum-BINOL catalyst.[10] We here present a novel system,[11] in which a chiral Mg(II) species prepared from Grignard reagents as well as from alkylmagnesium compounds or Mg salts with readily available enantiopure BINOL serves as an effective Lewis acid.

In our initial evaluation of Mg(II)-based mediators, we used as the model reaction the oxidation of 3-phenylcyclobutanone (**1**) by cumene hydroperoxide (CHP) in the presence of a complex derived from $MgBu_2$ and a chiral chelating ligand.[12] Among several ligands tested, only enantiopure BINOL was successful leading to full conversion of the substrate affording the corresponding lactone with 33% enantiomeric excess (ee).



Scheme 1

This result encouraged us to focus on a screening of different metal sources and to examine their applicability in the oxygen transfer to prochiral substrates. Interestingly, and in contrast to what we had noticed in the case of the aluminum system,[10] in which only Me_2AlCl was found to be suitable for the asymmetric Baeyer-Villiger oxidation, many organomagnesium compounds gave products with notable enantiomeric excess. The precise nature of the Mg(II) compound strongly influenced both activity and enantioselectivity. Among the various reagents surveyed, MeMgI and MgI_2 afforded the best results, i.e., full conversion and ee values up to 60% and 65%, respectively (Table 1). However, when magnesium triflate was employed as precursor, the conversion of **1** to lactone was only 20% and no asymmetric induction was observed. With the use of both anhydrous $MgCl_2$ and $MgSO_4$ the oxidation was completely inhibited. The superiority of MgI_2 may be attributed to the easier dissociation of an iodide anion from species such as L_2MgI_2 as already proposed by Corey et al.[3g] On the other hand, the counterion may be fundamental in determining the geometry of the active complex, as Desimoni had suggested with respect to Mg-catalyzed dipolar cycloadditions.[2c]

Table 1 Asymmetric oxidation of **1** mediated by various Mg reagents in combination with enantiopure BINOL[a]

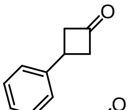
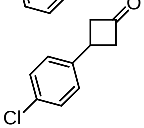
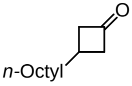
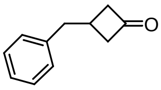
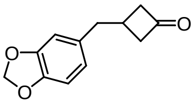
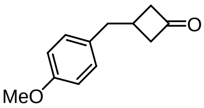
Entry	Magnesium source	Conv. (%)[b]	Ee (%)[c]
1	Bu_2Mg	100	33
2	MeMgBr	100	49
3	PhMgBr	70	58
4	MeMgI	100 (93)	61
5	$Mg(OTf)_2$	20	rac
6	$MgBr_2 \cdot OEt_2$	80	50
7	MgI_2	100 (91)	65

[a] Conditions: [Mg] (50 mol%), *(R)*-BINOL (50 mol%), $PhC(CH_3)_2OOH$ (1.5 equiv.), CH_2Cl_2, −25 °C, 8 h. [b] Determined by GC. The values in parentheses refer to yields of pure lactone isolated by column chromatography. [c] Determined by GC using chiral columns.

As to the solvent, the use of coordinating media such as ether led to low conversion. In dichloroethane and chlorobenzene, the product had 60% and 55% ee, respectively. The solvent of choice, however, was dichloromethane, which allowed the formation of **2** with 65% ee.

Table 2 relates the ee values of lactones that were obtained by complete oxidation of the corresponding prochiral cyclobutanones.[13] The oxidation of compounds with an alkyl or a benzyl group in position 3 led to results comparable with the one of 3-phenyl cyclobutanone.

Table 2 Mg-catalyzed asymmetric oxidation of various cyclobutanones[a]

Entry	Substrate	Ee (%) of the lactone[b]	Config.	Ref.
1		65	(–)-(*R*)	14a
2		63	(–)-(*R*)	14b
3		52	(–)	15
4		64	(–)-(*S*)	14c
5		61	(–)-(*S*)	14d
6		56	(–)-(*S*)	14e

[a]Conditions: MgI_2 (50 mol%), *(R)*-BINOL (50 mol%), CHP (1.5 equiv.), CH_2Cl_2, −25 °C, 8 h; all substrates showed full conversion to lactones according to GC analysis. [b]Determined by GC using chiral columns.

In order to vary the Mg complex further, several additives were tested. The addition of 1 equivalent of iodine, which had been shown to be benign for Diels-Alder reactions involving MgI_2, due to the dissociation of the iodide as a iodinate,[3g] resulted in a small decrease in enantiomeric excess (62% instead of 65%). Also the addition of molecular sieves entailed a detrimental effect, in contrast to the observations of Jørgensen and Desimoni, who assumed that molecular sieves represented a necessary part of their magnesium catalyst system.[2a,c] DBU and $AgSbF_6$, which proved advantageous in asymmetric Diels-Alder reactions,[3b] effected a shutdown of the oxidation reaction. Only the presence of $AgNO_3$ allowed a slightly higher enantioselectivity (66% ee).

Attempts to increase the asymmetric induction by modifying the substitution pattern of the BINOL ligand failed. For instance a BINOL derivative bearing bromo substituents in position 3 and 3' vicinal to the hydroxyl groups inhibited the oxidation of **1** while the same substituent in position 6 and 6´ caused the ee to decrease to 56%. The use of mono or diprotected BINOL (methoxy instead of hydroxy groups) as well as 2,2'-diaminobinaphthyl and BINAP afforded racemic products. Finally, an oxidation in the presence of Li di-BINOLate gave **2** with 33% ee.

As the use of only 50 mol% of Mg-BINOL was as effective as the stoichiometric variant of the oxidation a further reduction of the catalyst loading was tried. Indeed, an experiment with 3-phenyl cyclobutanone (**1**) as substrate confirmed that complete conversion and an ee value of still 63% was attainable by employing only 25 mol% of the chiral mediator.

In summary, we have disclosed a novel, main group metal-based asymmetric Baeyer-Villiger system that furnishes appreciable enantioselectivities at high conversion. In view of the state of the art in metal-catalyzed Baeyer-Villiger oxidation, these are promising results which prompt us to continue our investigation.

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(12) In a typical oxidation experiment the chiral active species was prepared by stirring the solution of ligand and Mg precursor (ligand:Mg = 1:1, 50 mol%) in CH_2Cl_2 under an Ar atmosphere at room temperature for 30 minutes. The ketone (0.2 mmol) was added and the solution cooled down to −25 °C before the reaction was eventually started by injection of the hydroperoxide (0.3 mmol). The mixture was allowed to warm in the cooling bath during 8 h, then quenched with a 0.5 N solution of aqueous HCl. The organic phase was extracted with MTBE, and washed with 5 wt% aqueous $Na_2S_2O_3$, water and brine. After being dried over $MgSO_4$ the crude products solution was either directly subjected to GC analysis or purified by column chromatography to determine the yields.

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