Vaulted Biaryls: Efficient Ligands for the Aluminum-Catalyzed Asymmetric Baeyer–Villiger Reaction

Carsten Bolm,*[a] Jean-Cédric Frison,[a] Yu Zhang,[b] William D. Wulff[b]

[a] Institut für Organische Chemie der RWTH Aachen, Professor Pirlet-Str. 1, 52056 Aachen, Germany
Fax +49(241)8092391; E-mail: Carsten.Bolm@oc.RWTH-Aachen.de

[b] Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, USA

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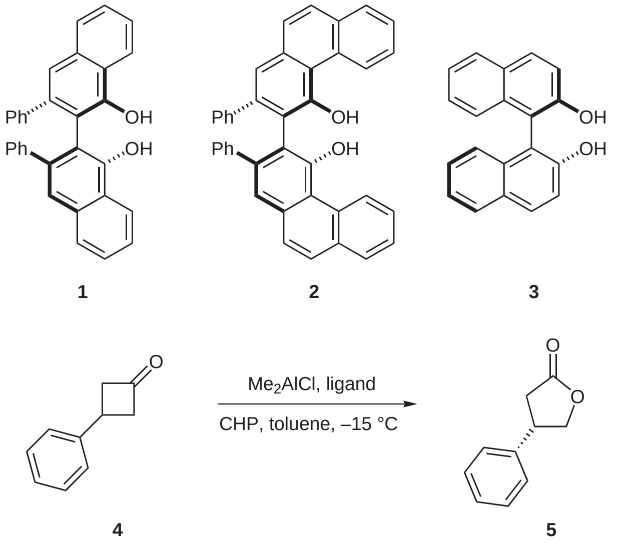
Abstract: Vaulted biaryls (VANOL and VAPOL) have been applied in the aluminum-catalyzed asymmetric Baeyer–Villiger reaction of prochiral 3-substituted cyclobutanones. Optically active γ-butyrolactones are obtained in high yields with enantioselectivities of up to 84% ee.

Key words: aluminium, asymmetric catalysis, Baeyer–Villiger reaction, biaryls, lactones

The Baeyer–Villiger reaction is a synthetically highly useful oxidative rearrangement of ketones into lactones or esters.[1] Recently, much effort has been devoted to the search of metal-catalyzed variants of this transformation.[2] Although several metals were found to promote the reaction,[2] only very few of them proved useful for the development of asymmetric variants. To date, the application of chiral Lewis acids represents the most successful approach allowing the conversion of prochiral (or racemic) cycloalkanones into enantioenriched lactones.[3]

We recently reported that the use of dialkylaluminum reagents in combination with enantiopure BINOL catalyzed the reaction of prochiral cyclobutanones yielding the corresponding lactones in high yields and enantioselectivities up to 77% ee.[4] With the goal to find aluminum-based catalysts with improved properties, we screened the use of several chiral biphenol derivatives, whose syntheses are well-documented in the literature.[5] While 6,6′-disubstituted BINOLs provided more efficient catalysts, both the activity and the enantioselectivity of the resulting catalysts were dramatically reduced, when 3,3′-disubstituted BINOLs were applied as ligands.[4] Beside these linear biaryls, we decided to test the vaulted derivatives VANOL (**1**) and VAPOL (**2**), which had been introduced by Wulff and co-workers.[6] Both compounds are readily available[7] and have successfully been applied as ligands in various asymmetric catalyses including aziridinations,[8] Mannich type reactions,[9] and cycloadditions.[6] In all of those catalyses, the use of VANOL and VAPOL provided more efficient catalysts than BINOL leading to better activities and improved enantioselectivities.



Scheme 1

In order to ensure that the vaulted biaryls were also applicable in asymmetric Baeyer–Villiger reactions, a test system with 3-phenylcyclobutanone (**4**) as substrate, dimethylaluminum chloride as metal source and either VANOL (**1**), VAPOL (**2**), or BINOL (**3**) as ligand was established (Scheme 1). Using cumene hydroperoxide (CHP, 1.2 equiv) as oxidant and 20 mol% of a 1:1 mixture of Me$_2$AlCl and the ligand in toluene at –15 °C lactone **5** was obtained selectively in all three cases. The *R*-configured ligand led to the formation of the *R* enantiomer of the product in all three cases. The enantioselectivity, however, differed significantly. Whereas use of VANOL gave **5** with 80% ee reactions with VAPOL and BINOL afforded the lactone with only 14% and 68% ee, respectively. Apparently, the catalyst bearing the vaulted biaryl VANOL was superior over the one prepared from BINOL. The fact that the VANOL-based system gave a higher enantioselectivity than its VAPOL counterpart was expected and in good agreement with our previous observations, since it was found that increased steric bulk at the 3,3′-positions of the biaryl led to a reduced enantioselectivity. In all three Baeyer–Villiger reactions the absolute configuration of the major enantiomer of the product was identical.

The promising result with the catalyst obtained from **1** prompted us to investigate this particular system in more detail. Assuming that the enantioselectivity increased in catalyses at lower temperatures, the Baeyer–Villiger

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reaction with **4** was performed at –30 °C. Gratifyingly, the ee of the corresponding lactone was now raised to 83% ee, and **5** was obtained in 91% yield after column chromatography. Attempts to further increase the enantioselectivity by reducing the temperature remained unsuccessful. Thus, below –30 °C the reaction became rather slow, and even after prolonged reaction times it did not go to completion. Furthermore, the ee of the product remained unchanged.[10]

Beside the temperature, the catalyst loading is known to have a significant influence on the enantioselectivity of the aluminum-catalyzed Baeyer–Villiger reaction. In the original system using BINOL (**3**) as ligand, 50 mol% of Me_2AlCl and the ligand (in a 1:1 ratio) were required to achieve enantioselectivities >70% ee.[4] To our delight we found that such high catalyst loading was not essential in the VANOL-based system. Here, the Baeyer–Villiger reaction of **4** with 20 mol% of Me_2AlCl/VANOL gave almost the same result as the one with 50 mol% of the catalyst (83% versus 84% ee). In both cases full conversion of the substrate was achieved, albeit the reaction was faster when more catalyst was applied (Table 1, entries 1 and 2). Reducing the catalyst loading to 10 mol% or even 5 mol% led to incomplete conversion and lower ee values of **5**.

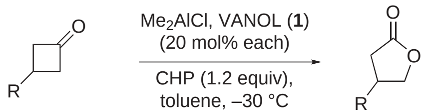
Table 1 Influence of the Catalyst Loading on the Asymmetric Baeyer–Villiger Reaction of Cyclobutanone **4**[a]

Entry	Catalyst (mol%)	Conversion (%)[b]	ee (%)[c]
1	50	100[d]	84
2	20	100[e]	83
3	10	83	43
4	5	43	14

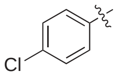
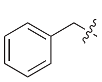
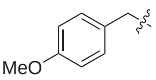
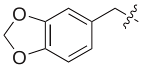
[a] The reaction was performed at –30 °C in toluene (0.05 M in ketone).
[b] Determined by GC.
[c] Determined by GC using a chiral column (Lipodex B).
[d] The reaction was complete after 4 h.
[e] The reaction was complete after 12 h.

Next, the substrate scope was evaluated by using various cyclobutanones as starting materials. Under the optimized conditions (20 mol% of each Me_2AlCl and VANOL in toluene at –30 °C and CHP as oxidant),[11] 3-substituted derivatives **6** afforded optically active lactones with up to 84% ee. As shown in Table 2 (entry 1), 3-*p*-chlorophenylcyclobutanone (**6a**) gave the corresponding lactone with (almost) the same ee (84%) as phenyl-substituted **4** (83% ee). Cyclobutanones with benzylic substituents in the 3-position led to lactones with enantiomeric excesses in the range of 34–41% (entries 2–4).[12] Alkyl-substituted derivative **6e** afforded the product with remarkable 69% ee.

Table 2 Substrate Scope of the Asymmetric Baeyer–Villiger Reaction Catalyzed by Mixtures of Me_2AlCl and VANOL (**1**)

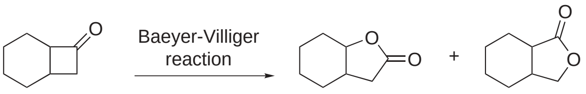


6 **7**

Entry	R	Substrate	Yield (%) of **7**[a]	ee (%) of **7**[b,c]
1		**6a**	92	84
2		**6b**	84	41
3		**6c**	96	34
4		**6d**	93	37
5	*n*-octyl	**6e**	86	69

[a] As determined by NMR spectroscopy.
[b] Determined by GC using a chiral column (Lipodex B).
[c] Using (*R*)-VANOL as ligand, (–)-(*R*)-**7a** and (–)-**7e** (entries 1 and 5, respectively) were obtained. The absolute configurations of products **7b**–**d** remained undetermined.

Besides achiral cyclobutanones, such as those listed in Table 2, racemic (bicyclic) cyclobutanone derivatives such as **8** are also known to undergo asymmetric Baeyer–Villiger reactions giving optically active lactones (Scheme 2).[3] To our surprise we found that the new VANOL-based catalyst was entirely unreactive towards **8** and that almost no conversion of the substrate occured (under the standard conditions described above). Even after 48 hours reaction time only traces of (the 'normal') lactone **9** were formed, and the enantiomer ratio analysis by HPLC using a chiral column revealed that the product was racemic. In the light of the results obtained with the BINOL/aluminum-system this observation is surprising, since there **8** was readily converted into the ring-expanded products **9** and **10** with the latter ('abnormal') lactone being the major isomer formed with high ee. Presumably, the difference between the two systems is caused by steric hindrance of the ligand in the VANOL-based one, which hampers the coordination of the bulky substrate to the Lewis-acidic metal center. The lack of activation then results in the observed uneffectiveness of the catalysis.



8 **9** **10**

Scheme 2

In summary, vaulted biaryls have successfully been applied in the aluminum-catalyzed asymmetric Baeyer–Villiger reactions of 3-substituted cyclobutanones. Enantiomerically enriched lactones with up to 84% ee were obtained. For catalyzed conversions of such simple substrates these enantioselectivities are among the best ever achieved.[3,4,13,14] Furthermore, compared to the original BINOL-based system the catalyst loading for achieving full ketone conversion could significanly be reduced from 50 mol% to only 20 mol% of catalyst. Our current efforts are directed towards further catalyst optimizations.

Acknowledgment

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(10) After 72 h at –40 °C the reaction was quenched to give the lactone with 84% ee in 40% yield.

(11) **Experimental Procedure for the Al-Catalyzed Asymmetric Baeyer–Villiger Reaction.**
To a solution of (*R*)-VANOL (26.4 mg, 0.06 mmol) in toluene (2.5 mL) was added dropwise Me_2AlCl (0.06 mmol, 60 μL, 1 M solution in hexanes) at r.t. The mixture was stirred for 30 min and then cooled at –30 °C. After 15 min at this temperature, a solution of the ketone (0.3 mmol) in toluene (0.5 mL) was added. Stirring was continued for 15 min, cumene hydroperoxide (technical grade 80%, 1.2 equiv, 75 μL) was then added in one portion. Subsequently, the reaction mixture was stirred at –30 °C until full conversion of the ketone (as monitored by GC). The solvent was then evaporated, and the crude product absorbed onto silica gel. Extraction with Et_2O afforded the crude product, which was analyzed by GC or HPLC using chiral columns (for details of the enantiomeric ratio determinations and assignments of absolute configurations, see ref. 4 and references therein).

(12) Slightly better results can be obtained for benzyl-substituted substrates when 50 mol% of the BINOL/Me_2AlCl catalyst system are applied (comp. ref. 4a). Thus, conversions of **6c** and **6d** give lactones with 73% and 58% ee, respectively.

(13) For other recent examples of metal-catalyzed asymmetric Baeyer–Villiger reactions focusing on the conversions of cyclobutanones, see: (a) Uchida, T.; Katsuki, T.; Ito, K.; Akashi, S.; Ishii, A.; Kuroda, T. *Helv. Chim. Acta* **2002**, *85*, 3078. (b) Ito, K.; Ishii, A.; Kuroda, T.; Katsuki, T. *Synlett* **2003**, 643; and references therein.

(14) To the best of our knowledge there is only a single report with a higher ee. Katsuki et al. found a zirconium catalyst bearing a complex salen ligand to give 87% ee in the conversion of **4** to **5**. See: Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 4481.