Enantioselective Metal-catalyzed Baeyer-Villiger Oxidation of Cyclobutanones

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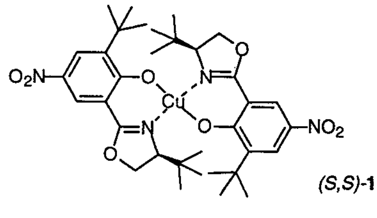
Received 20 June 1997

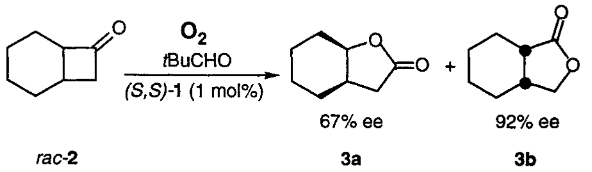
Dedicated to Professor Dr. H. Offermanns on occasion of his 60th birthday

Abstract: Optically active lactones are obtained by metal-catalyzed aerobic oxidation of prochiral cyclobutanones. Starting from 3-monosubstituted substrates lactones with moderate enantioselectivities (up to 47% *ee*) have been obtained. *Kelly*'s tricyclic ketone **8** provides the corresponding lactone with 91% enantiomeric excess.

The Baeyer-Villiger reaction was discovered almost a century ago.[1] The oxygen insertion into the C-C bond α to the carbonyl group of a ketone is usually highly regioselective and stereospecific.[2] Until recently, only biocatalysts were known to perform asymmetric Baeyer-Villiger reactions giving optically active lactones from racemic or prochiral ketones.[3] Both purified enzymes and whole-cell systems from various microorganisms have successfully been used.[4] *Metal-catalyzed* asymmetric Baeyer-Villiger-type oxidations were first reported in 1994.[5-7] The highest enantioselectivities have been achieved in aerobic oxidations catalyzed by copper complex *(S,S)*-**1**. From racemic bicyclic cyclobutanone derivatives such as **2** optically active butyrolactones with enantioselectivities of up to 95% *ee* were obtained.[5] The reaction proceeds in an enantiodivergent manner giving two isomeric lactones **3a** and **3b**.[5,8] A mathematical model correlating the enantiomeric excesses and the quantities of the isomeric products was derived by *Kagan*.[9]

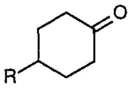


(S,S)-**1**



We now found that copper complex *(S,S)*-**1** is also capable to catalyze *enantioselective* Baeyer-Villiger oxidations of *prochiral* cyclic ketones.

As expected from our previous studies, 4-substituted cyclohexanones **4** (R = methyl, phenyl, *tert*-butyl) did not react under the usual conditions using 1 mol% of *(S,S)*-**1** as catalyst and 0.5 equiv. of pivaldehyde in benzene under an atmosphere of dioxygen at room temperature.[5] Because of ring strain cyclobutanones are more reactive in Baeyer-Villiger reactions than other ketones.[2] We therefore decided to investigate oxidations of 3-monosubstituted cyclobutanones **5**.



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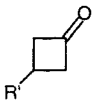

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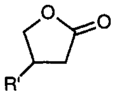


6

Substrates with various substituents R' were used as starting materials, and in all cases the corresponding lactones **6** were formed. In order to obtain high product yields the amount of pivaldehyde was increased from 0.5 to 3 equivalents. Over a period of 3 days the aldehyde was added in three portions consecutively. Analysis by GC or HPLC using chiral columns[10] revealed that lactones **6** were optically active. The enantiomeric excesses, however, were only moderate. A summary of the most significant results is given in the Table. The highest enantioselectivity was achieved in the oxidation of 3-*tert*-butylcyclobutanone providing the corresponding lactone with 47% *ee* (entry 2). Comparison of the optical rotation of the lactone obtained from 3-phenylcyclobutanone (entry 3) with the literature value[11] revealed that the *S*-configured product was formed.[12]

Table. Asymmetric Baeyer-Villiger-type oxidation of cyclobutanones with dioxygen and pivaldehyde catalyzed by 1 mol% of *(S,S)*-**1**

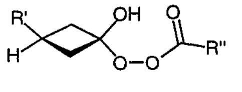
Entry	R' of **5** and **6**	Yield of **6** (%) [a]	*Ee* of **6** (%) [b]
1	octyl	77	31
2	*t*Bu	85	47
3	Ph	88	44
4	Bn	90	29
5	CO_2tBu	92	36
6	CO_2Bn	82	26
7	CH_2OBn	80	23

[a] After column chromatography. [b] See refs. 10 and 12

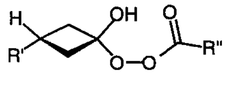
With the objective to increase the enantioselectivity we explored various features of this catalytic system. The enantiomeric excess does not significantly decrease with reaction time indicating that the catalytically active species is not decomposed to achiral catalysts, which then give racemic product. This result was confirmed by an experiment in which three different cyclobutanones were consecutively added to the reaction mixture providing the corresponding lactones with *ee*-values which were almost identical to the ones obtained from three independent runs. Apparently, the chiral catalyst retains its potential to oxidize enantioselectively even after prolonged reaction times.

Other factors, which can be responsible for the moderate enantioselectivity, are related to the presence of highly oxygenated species such as peracids. If they are formed by aldehyde autoxidation, parallel *un*catalyzed Baeyer-Villiger reactions could yield racemic product thereby lowering the overall enantiomeric excess.

Aspects of diastereoselectivity become important when the mechanism involves the formation of peracid/ketone addition products of type **7**. Then two diastereomeric Criegee intermediates (*anti*-**7** and *syn*-**7**) can be expected. If they give opposite enantiomeric products or the Baeyer-Villiger catalyst does not differentiate well enough between the two enantiotopic sides of each diastereomer, the enantioselectivity of the overall process will only be moderate.

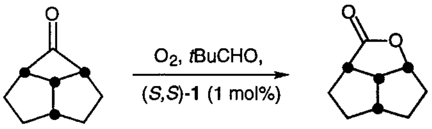


anti-**7**



syn-**7**

On that basis we assumed that a better diastereofacial control in the formation of the Criegee intermediate would improve the performance of the catalyst, and we therefore investigated the Baeyer-Villiger reaction of tricyclic ketone **8**.[13] Supporting our hypothesis, catalysis with 1 mol% of *(S,S)*-**1** in the presence of 0.5 equiv. of pivaldehyde afforded lactone **9** in 62% yield with 91% *ee*. Comparison of its optical rotation with the literature value[13] revealed that the lactone had *2R,8S*-configuration.



8 **9**

In conclusion, we have demonstrated that copper complex *(S,S)*-**1** is capable to catalyze enantioselective Baeyer-Villiger reactions of prochiral cyclobutanone derivatives giving optically active lactones with moderate to good asymmetric induction. Our current efforts are directed towards an improvement of the reaction protocol to increase catalyst activity and enantioselectivity.[14]

Acknowledgment. This research was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm Sauerstofftransfer / Peroxidchemie) and the Fonds der Chemischen Industrie. We are grateful to Dr. D. R. Kelly, Cardiff, for providing samples of **8** and racemic **9**, and we thank Degussa, Hanau, for a gift of amino acids.

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