Metal-catalysed Enantiospecific Aerobic Oxidation of Cyclobutanones

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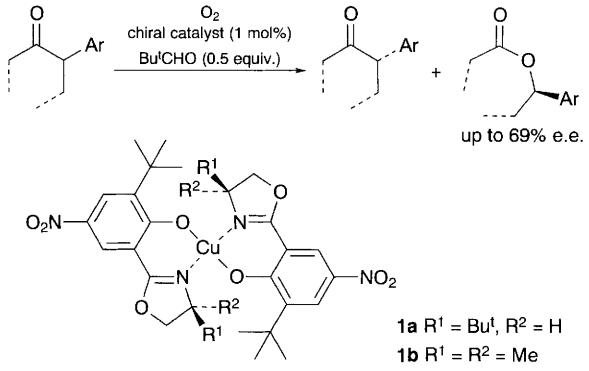
The metal-catalysed aerobic oxidation of substituted racemic cyclobutanones provides optically active lactones with enantioselectivities of up to 95% e.e.

Enantioselective oxidations are of paramount interest owing to the importance of optically active oxygenated compounds as synthetic intermediates or natural products.[1] Until recently, asymmetric Baeyer–Villiger reactions[2] remained a domain of biocatalysis.[3] Enzymes from various microorganisms were found to be capable of catalysing an enantiospecific (or enantioselective) insertion of an oxygen atom into racemic or prochiral ketones giving lactones with high optical purities.[4] In 1994, we[5] and others[6] reported on the first metal-catalysed asymmetric Baeyer–Villiger-type oxidations. In the presence of copper catalyst (*S,S*)-**1a** aerobic oxidation[7] of racemic 2-arylcycloalkanones afforded the corresponding lactones with enantioselectivities of up to 69% e.e. (Scheme 1). Alkyl-substituted ketones and positional isomers did not react when **1a** was used as catalyst.



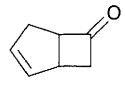
Scheme 1

With the objective of exploring the potential of this new catalytic system we investigated the asymmetric metal-catalysed oxidation of chiral cyclobutanones.[8] Optically active butyrolactones were obtained in an enantiodivergent manner and enantioselectivities of up to 95% e.e. were achieved.

Initial studies using commercially available unsaturated bicyclic ketone **2** as test substrate confirmed the capability of **1a** to catalyse oxidative transformations of cyclobutanones. However, a complex product mixture was obtained from **2**, presumably consisting of the desired lactones and products derived from oxidation of the double bond.

Thus, saturated cyclobutanones were examined. Various methods for their synthesis have been reported[9] and the corresponding γ-lactones are valuable synthetic intermediates. Whereas **3a** and **3b** did not react, ketones **4**–**7** led to clean lactone formation when 1 mol% of **1a** and 0.5 equiv. of pivaldehyde was used in benzene under an atmosphere of dioxygen at room temperature.†

In all cases, two isomeric lactones were obtained. This behaviour is reminiscent of microbiological transformations studied earlier.[4] Both lactones differ in three major aspects. Firstly, they result from oxygen insertion at either side of the carbonyl group. Secondly, their enantiomeric excesses are



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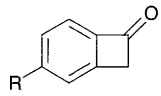
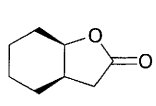
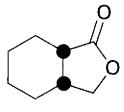


3a R = Me
3b R = OMe

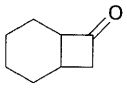
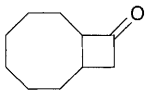
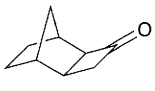
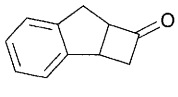
Table 1 Asymmetric Baeyer–Villiger-type oxidation of cyclobutanones catalysed by 1 mol% of (*S,S*)-**1a**



'normal' lactone **a**



'abnormal' lactone **b**

Ketone	e.e. of **a** (%)	e.e. of **b** (%)	G.C. ratio **a**:**b**	Yield (%) (**a**:**b**)[a]
4 	67	92	55:45	61 (3:1)
5 	61	94	—	74 (2:1)
6 	76	95	60:40	32 (3:2)
7 	59	93	48:52	59 (1:1.3)

[a] Ratio after work-up and product isolation.

different, and thirdly, both lactones result from enantiomeric ketones. Thus, metal-catalysed oxidation of *rac*-**4** with (*S,S*)-**1a** led to the formation of the two regioisomeric lactones **4a** and **4b** in an approximate 1:1 ratio (GC analysis from the reaction mixture). Work-up and product isolation gave **4a** and **4b** in a ratio of 3:1 (61% yield). The 'normal' Baeyer–Villiger product **4a** where the oxygen had inserted between the more substituted carbon atom and the carbonyl group was formed with an enantiomeric excess of 67%. Its regioisomer, **4b**, however, was obtained with 92% e.e.‡ Lactones **4a** and **4b** also differ in stereochemistry. Thus, **4a** has the *R*-configuration at the bridgehead carbon atom attached to the oxygen, whereas **4b** has the *S*-configuration at the carbon α to the carbonyl group.§ Recovered ketone **4** was almost racemic (≤6% e.e.). Apparently, metal catalyst (*S,S*)-**1a** transforms the enantiomeric ketones into different regioisomeric lactones **4a** and **4b**.

Table 1 summarizes the results of other oxidations. In all cases, the 'abnormal' Baeyer–Villiger products were formed with enantioselectivities (92–95% e.e.) exceeding those of the 'normal' lactones (59–76% e.e.),‡ presumably owing to competing uncatalysed pathways giving the latter as racemates. The highest asymmetric inductions were observed in the oxidation of tricyclic ketone **6**. The corresponding lactones **6a** and **6b** were formed with 76 and 95% e.e., respectively.§

Interestingly, almost the same enantiomeric excess of **4a** and **4b** was found when the amount of catalyst was reduced to 0.1 mol% of (*S,S*)-**1a** (71 and 94% e.e., respectively). However, now the chemical yield was slightly lower (43%, GC ratio, 55:45). In the presence of 1 mol% of catalyst, slow addition of 1 equiv. of pivaldehyde (24 h, syringe pump) did not significantly change the e.e. of the products (37% yield; GC ratio, 45:55; 68 and 94% e.e.). The low chemical yield of the latter reaction was improved to 64% when 1 equiv. of aldehyde was subsequently added in two portions (64 and 94% e.e. for **4a** and **4b**, respectively).

Our current efforts are directed towards a refinement of this unprecedented metal catalysis and an understanding of the underlying principles. This research was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm Sauerstofftransfer/Peroxidchemie, SFB 260, and Graduiertenkolleg). We are grateful to Degussa Hanau, for generously providing amino acids and to Professor D. Belluš, Ciba, for support. We also thank Ms Ling Guo for her help.

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Footnotes

† The aldehyde was added as a 0.25 mol dm^{-3} benzene solution to a mixture of ketone (0.67 mol dm^{-3}) and catalyst in the same solvent. The use of water-saturated benzene resulted in lower chemical yields of lactone. Further experimental details will be reported in a full account.

‡ The extent of asymmetric induction was determined by GC or HPLC using chiral columns (Lipodex E, Chiraldex B-PH or Chiralcel OD, respectively). Peak assignments were confirmed by analysing racemic product samples synthesized by reacting the ketone with MCPBA (yielding predominantly the 'normal' Baeyer–Villiger lactones **a**) or performing the metal-catalysed aerobic oxidation with the achiral Cu complex **1b** giving mixtures of racemic regioisomeric lactones.

§ The absolute configurations of **4a** and **4b** were determined by comparison of optical rotations with literature values.[10] Those of the other lactones remained unspecified.

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