

Recent Advances in Asymmetric Baeyer-Villiger Oxidations

Aaron Wroblewski

Department of Medicinal Chemistry, University of Kansas, Lawrence, KS, 66045 USA

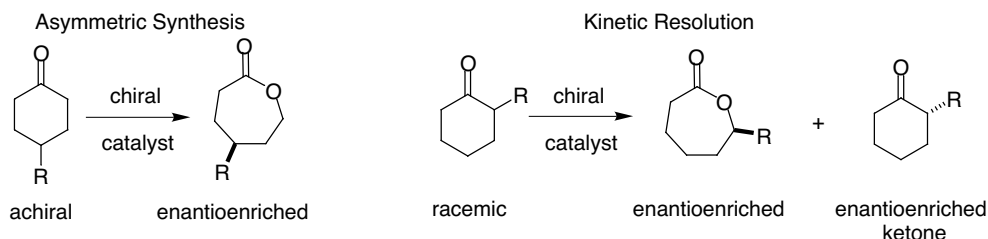
Abstract

Recent progress in developing the asymmetric Baeyer-Villiger oxidation is examined with an emphasis on reactions catalyzed by transition metals, Methods using enzymes, metal catalysts (Cu, Pt, and Ti), or Lewis acid activation of ketals yields lactones in modest to high enantiomeric excess (ee).

Introduction

The development of asymmetric variants of well-established organic reactions is an important and rapidly growing arena of organic chemistry. The demand for enantiopure molecules as precursors and starting materials in asymmetric total syntheses is great in both industrial and academic settings. As one of the classic reactions in organic chemistry, the Baeyer-Villiger oxidation (Scheme 1) is an important target for modification into an asymmetric version.

Scheme 1. Asymmetric Baeyer-Villiger Reaction Systems



In the Baeyer-Villiger oxidation, a peracid is used to insert oxygen in between the ketone carbonyl and an adjacent carbon yielding the corresponding ring-expanded lactone. Without chiral influence, the above reaction generates a racemic lactone from an achiral ketone. However, under the influence of a chiral reagent, this oxidation can be carried out asymmetrically. In other words, an achiral substrate is converted to an enantioenriched product via preferential migration of one of the enantiotopic α carbons. In the case of a chiral, racemic ketone, a chiral catalyst has the potential of performing a kinetic resolution. In this instance, the catalyst preferentially reacts with one enantiomer of the racemate to yield an optically pure lactone. The remaining unreacted racemate can then be isolated in enantioenriched form. These two synthetic methods, asymmetric synthesis and kinetic resolution, will form the basis for the types of asymmetric Baeyer-Villiger oxidations examined in this review.

Enzyme-catalyzed routes towards asymmetric Baeyer-Villiger oxidations have been recently reviewed¹ and will only be briefly summarized. Focus will be directed towards recent developments in metal-assisted asymmetric Baeyer-Villiger oxidations.

Email: adwrobz@eagle.cc.ukans.edu

Enantiopure Lactones via Enzymatic Catalysis

In 1976, the enzyme cyclohexanone oxygenase was reported to carry out asymmetric Baeyer-Villiger oxidations.² At the time, no indication of enantioselectivities were reported. Taschner and Black, in 1988, then communicated the use of the above enzyme in converting achiral cyclohexanones into highly enantioenriched lactones.^{3,4} Since then, cyclohexanone oxygenase (isolated from the bacteria *Acinetobacter* NCIB 9871) has been the most widely studied asymmetric Baeyer-Villiger enzyme.⁵ Genetically engineered *E. coli* have been produced to overexpress the *Acinetobacter* gene for cyclohexanone oxygenase.⁵ Dozens of different ketones have been examined, and in many cases, yields and enantioselectivities for these conversions are extremely high.¹ In the case of Taschner's work, a series of achiral cyclohexanones were converted to lactones in ee's in excess of 98%. This work was supported by other reports describing similar asymmetric conversions in ee's ranging from 75-98%.⁵

Synthesis of optically pure lactones via enzymatic routes is a highly efficient process in terms of yield and enantioselectivity. As will become apparent below, enzymatic routes towards enantiopure lactones are, in most cases, more highly enantioselective than metal catalyzed routes.

Enantiopure Lactones via Transition Metal-Catalyzed Reactions

Numerous systems for generating optically pure lactones based on transition metal-catalysis have been established, and preliminary data suggests this method could lead to highly enantioselective reactions with a broad range of substrates. This review will focus on four oxidizing systems: (1) chiral Cu catalysts, O₂, and an aldehyde as an oxygen acceptor, (2) chiral Pt catalysts and hydrogen peroxide, (3) a modified Sharpless catalyst, and (4) chiral ketals with Lewis acids.

Enantiopure Lactones via Chiral Cu catalysts/O₂/RCHO. In 1994, Bolm and co-workers reported the first metal-catalyzed asymmetric Baeyer-Villiger oxidations.^{6,7} Initial reports concerning this reaction were carried out on racemic 2-aryl substituted cyclohexanones⁶ (Scheme 2, Table 1), and later papers described the reactions of substituted cyclobutanones (Scheme 3).^{7,8}

Scheme 2. Asymmetric Baeyer-Villiger Oxidations of 2-Substituted Cyclohexanones

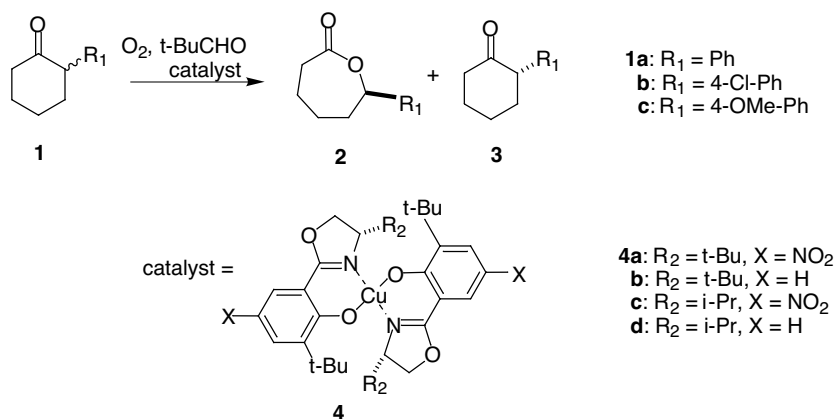
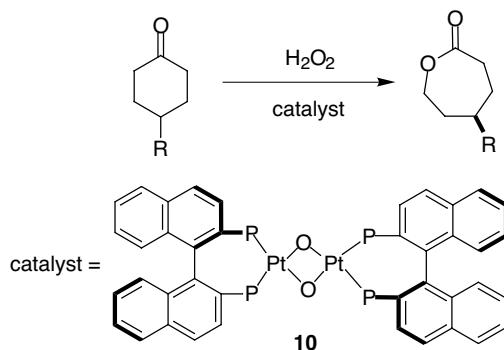


Table 1: Baeyer-Villiger Oxidation of Racemic Cyclohexanones

entry	ketone	catalyst	yield of 2 (%)	ee (%)
1	1a	4a	47	69
2	1b	4a	43	60
3	1c	4a	53	65

Scheme 4. Pt Catalyzed Baeyer-Villiger Oxidation¹¹



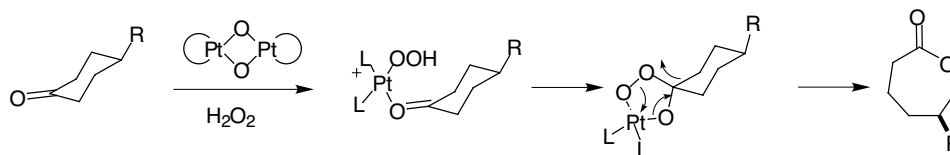
For simplicity, only one of the numerous diphosphine/Pt catalysts (**10**) is shown amongst a few other C_2 symmetric ligands ((*S,S*)diop, (*R,R*)pyrphos, (*R,R*)Me-duphos). However, catalyst **10** was, in general, the most enantioselective of those examined. Table 2 shows the results obtained for Pt catalyzed Baeyer-Villiger reactions vs. those using cyclohexanone oxygenase on a few achiral cyclohexanones.

Table 2: Asymmetric Baeyer-Villiger on Achiral Cyclohexanones

entry	cyclohexanone	ee (%) for Pt ¹¹	enzyme ee (%) ³
1	4-methyl-	53	>98
2	4-pheny-	68	-
3	<i>cis</i> -2,6-dimethyl-	79	>98

Mechanistically, the copper and platinum catalytic systems differ in the type of oxidant used. Scheme 5 shows the conversion of an achiral ketone to an optically pure lactone using a generalized Pt catalyst and H_2O_2 . Coordination of Pt and peroxide to the carbonyl leads to the formation of a metallocycle that decomposes to the lactone product. Chiral ligands associated with Pt allow for diastereomeric transition states which then discriminate between the two possible migrating carbon atoms resulting in enantioselectivity.

Scheme 5: Mechanism of Pt Catalyzed Baeyer-Villiger Oxidation¹¹



Enantiopure lactones via a modified Sharpless catalyst. Shortly after Bolm's and Strukul's development of their versions of the asymmetric Baeyer-Villiger reaction, Pehk and co-workers formulated a method based on the catalytic system created by Sharpless.^{12,13} Similar to the work presented above, this "new" catalytic system was tested on racemic and achiral cyclobutanones (Scheme 6, Table 3). Since work by Pehk et al. showed that the standard Sharpless catalyst was capable of inducing an asymmetric Baeyer-Villiger using cyclobutanones,¹² a modified version of the catalyst was developed to examine whether enantioselectivities of the oxidation reaction could be increased. As depicted in Scheme 6, the major modification of the catalytic system was altering the chiral ligand. The standard Sharpless catalyst utilizes chiral tartaric acid derivatives complexed with $Ti(O-iPr)_4$ and tertiary butyl

peroxide as an oxidant.¹⁴ The modified version of the catalyst makes use of a TADDOL ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol) ligand while maintaining the use of $\text{Ti}(\text{O}-i\text{Pr})_4$ and tertiary butyl peroxide.¹³

Scheme 6. Asymmetric Baeyer-Villiger Oxidation Using Tartrate-Derived Titanium Catalysts¹³

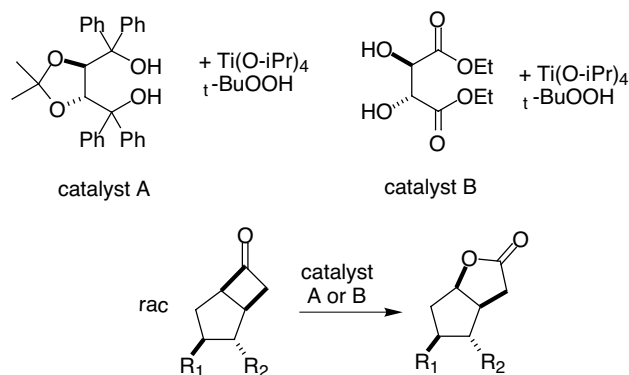


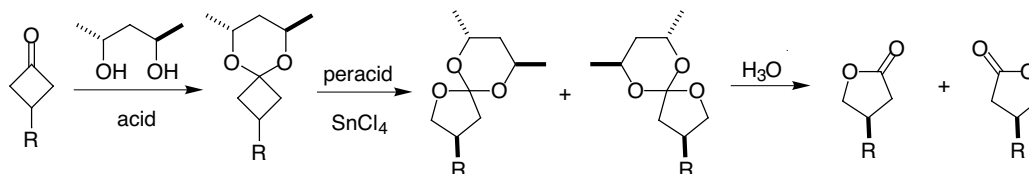
Table 3: Comparison of Catalyst A vs. B Enantioselectivity

entry	R ₁	R ₂	cat. A ee	yield	cat B. ee	yield
1	OH	Br	41	33	75	40
2	OH	Ph	39	20	59	31
3	Ph	OH	31	35	-	-

Two general trends were observed when comparing catalysts A and B for the entries noted above and for various other cyclobutanones. First, reaction times for catalyst A were notably shorter than B (~4 hr vs. ~48hr). Secondly, enantioselectivities were poorer when using catalyst A vs. B. Contrary to the results obtained with reactions of cyclobutanones with copper catalysts, the reactions promoted with titanium catalysts gave only the regioisomer coming from migration of the more substituted carbon.

Enantiopure lactones via chiral ketals/Lewis acids. A conceptually different method for inducing an asymmetric Baeyer-Villiger reaction involves conversion of the carbonyl of an achiral cyclobutanone to a chiral ketal.¹⁵ Subsequent reaction of the ketal with a peracid (*m*-CPBA) and SnCl_4 produces an orthoester which upon acidic work-up generates the lactone (Scheme 7).

Scheme 7: Optically Pure Lactones via Oxidation of Chiral Ketals



Activation of the ketal with a Lewis acid allows the peracid to attack the activated species and insert oxygen in a manner similar to the standard Baeyer-Villiger. The above reaction was

optimized extensively in the case where R = Ph. Using 2 equivalents of *m*-CPBA and 5 equivalents of SnCl₄ at -100° C gave the *S* configured lactone in 89% ee.

Concluding Remarks

The Baeyer-Villiger reaction emerged over 100 years ago, but not until recently has it been demonstrated that an asymmetric version is possible. The most efficient processes to date rely upon cyclohexanone oxygenase enzymes isolated from microbial sources. In the past 6-7 years, however, various research groups around the world have demonstrated the ability to carry out this important reaction using transition metal-catalysts. Previously listed results indicate that enzymatic routes towards optically pure lactones are still more efficient than any organometallic method developed. However, metal-catalyzed asymmetric Baeyer-Villiger oxidations are early in development, and the recent advances presented are beginning to approach the efficiency seen in enzymatic systems. One route that has not received significant attention is the use of chiral peracids in generation of enantiopure lactones. It may be that the chiral center of the peracid is too far removed from the reactive center of the intermediate to induce any significant enantioselectivity. Since a vast majority of the literature reports studies on cyclobutanone and cyclohexanone systems, it remains to be seen whether the above catalytic methods will prove to be as effective on other cyclic ketones.

References

1. Stewart, J.D. *Curr. Org. Chem.* **1998**, *2*, 211-232.
2. Donoghue, N; Norris, D.; Trudgill, P.W. *Eur. J. Biochem.* **1976**, *63*, 175.
3. Taschner, M.J.; Black, D.J. *J. Am. Chem. Soc.* **1988**, *110*, 6892-6893.
4. Taschner, M.J.; Black, D.J.; Chen, Q.-Z. *Tetrahedron: Asymmetry* **1993**, *4*, 1387-1390.
5. Mihovilovic, M.D.; Chen, G.; Wang, S.; Kyte, B.; Rochon, F.; Kayser, M.M.; Stewart, J.D. *J. Org. Chem.* **2001**, *66*, 733-738.
6. Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848-1849.
7. Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247-1248.
8. Bolm, C.; Luong, K.K.; Schlingloff, G. *Synlett* **1997**, 1151-1152.
9. Murahashi, S.; Oda, Y.; Naota, T. *Tetrahedron Lett.* **1992**, *33*, 7557-7560.
10. Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G. *Organometallics*, **1994**, *13*, 3442-3451.
11. Paneghetti, C.; Gavagnin, R.; Pinna, F.; Strukul, G. *Organometallics* **1999**, *18*, 5057-5065.
12. Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583-7586.
13. Kanger, T.; Kriis, K.; Paju, A.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4475-4482.
14. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
15. Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *34*, 6019-6022.