ASYMMETRIC OXIDATION OF KETONES

Margus LOPP[a], Anne PAJU[b], Tõnis KANGER[a], Kadri KRIIS[b],
Kaja ILMARINEN[b], and Tõnis PEHK[c]

[a] Department of Chemistry, Tallinn Technical University, Ehitajate tee 5, 19086 Tallinn, Estonia;
   lopp@chemnet.ee
[b] Institute of Chemistry, Tallinn Technical University, Akadeemia tee 15, 12618 Tallinn, Estonia
[c] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia

Abstract. The Ti(OiPr)$_4$/tartaric acid diethyl ester/t-BuOOH complex (Sharpless catalyst) was successfully used for the direct asymmetric oxidation of ketones resulting in lactones from cyclobutanones; α,β-dihydroxy ketones from β-hydroxy ketones; alkyl lactone carboxylic acids from 3-alkylcyclopentane-1,2-diones; and spiro-γ-dilactone from 3-(2-hydroxyethyl)cyclopentane-1,2-dione in high enantioselectivity and satisfactory yield.

Key words: asymmetric oxidation, ketones, α-hydroxy ketones, spiro-γ-dilactones, chiral catalysts.

INTRODUCTION

Asymmetric oxidation of prochiral and racemic ketones using chiral catalysts has been almost neglected by researchers. Only some examples of asymmetric oxidation of ketones have been published recently [1]. At the same time the enantiomeric derivatives of ketones (α-hydroxy ketones, acids, lactones, etc.) are widely represented among biologically active natural products. In this report a brief summary of the recent results of our group on the use of the Sharpless–Katsuki complex in the direct asymmetric oxidation of ketones is presented.

This article is part of the plenary lecture "Tartaric Acid in the Synthesis of Enantiomeric Compounds" delivered by M. Lopp at the Baltic Conference on Organic Synthesis (BOS 2000) held in Vilnius on 26–29 June 2000.

ASYMMETRIC BAEYER–VILLIGER OXIDATION OF KETONES

Baeyer–Villiger oxidation has been known for more than a hundred years already [2, 3]. Although the first compounds oxidized by these chemists were natural enantiomeric compounds, their work cannot be considered as a beginning of asymmetric Baeyer–Villiger reaction (Fig. 1).
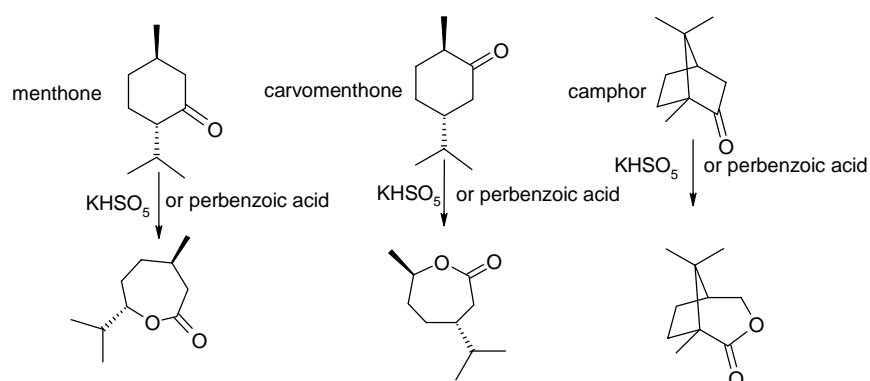

Fig. 1. Baeyer–Villiger oxidation of natural ketones.

The real asymmetric Baeyer–Villiger oxidation was achieved only recently by a few groups. In 1994 Bolm with co-workers published data about using chiral Cu and Ni complexes in catalytic amount together with different oxidation systems [4] in oxidation of α-substituted ketones giving rise to the lactones in stereoselectivity up to 65% *ee* and in yield up to 41% (Fig. 2).
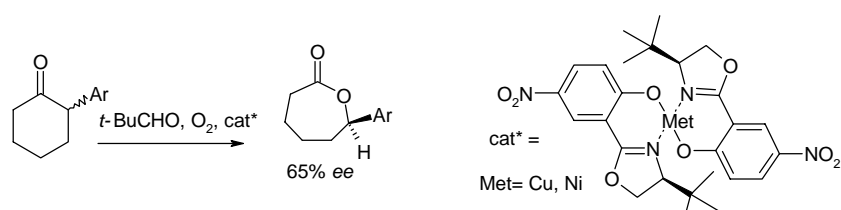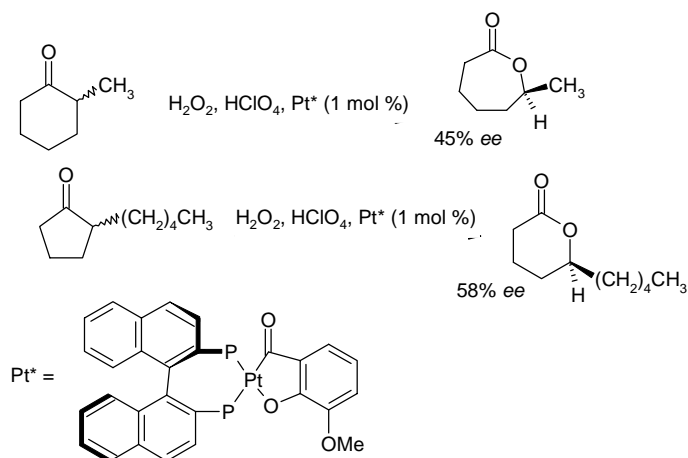

**Fig. 2.** Oxidation of ketones using chiral catalysts.

The same catalytic system was effective also for other substrates [5, 6].

Strukul and co-workers oxidized 2-alkylcycloalkanones using hydrogen peroxide in the presence of catalytic amount of chiral Pt catalyst [7] (see Fig. 3).

Fig. 3. Oxidation of 2-alkylcycloalkanones using hydrogen peroxide in the presence of chiral Pt catalyst.

The most famous asymmetric oxidation catalyst is Sharpless–Katsuki complex, which is known as a tool for asymmetric epoxidation of allylic alcohols [8, 9]. A possible structure of the complex is shown in Fig. 4.
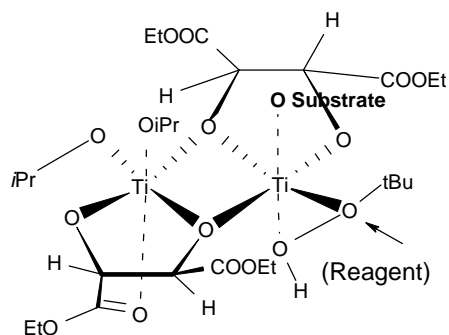
Fig. 4. A possible structure of Sharpless–Katsuki complex (with reagent –*t*-BuOOH and a substrate).

We have found that Sharpless–Katsuki complex is able to oxidize different cyclobutanones resulting in enantiomerically enriched lactones. This is the first example of asymmetric Baeyer–Villiger oxidation of ketones by Sharpless–Katsuki complex [10]. Figure 5 summarizes the obtained results of oxidizing one prochiral and three racemic ketones.
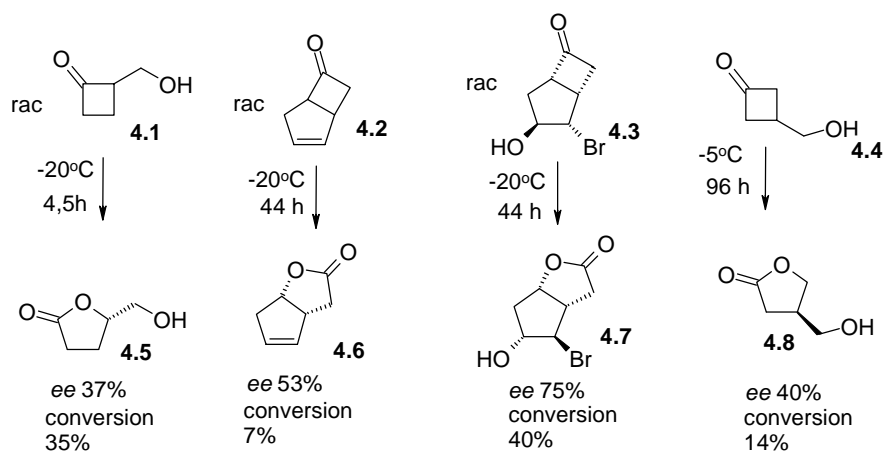
Fig. 5. Oxidation of racemic and prochiral cyclobutanones by the Sharpless–Katsuki complex.

α-Hydroxymethyl cyclobutanone **4.1** is the most readily oxidized substrate in the investigated series. During the oxidation reaction the corresponding lactone was obtained in 4.5 h with moderate enantiomeric excess (*ee* 37%, kinetic resolution of the initial racemic compound occurred). The presence of a hydroxyl group in the molecule enhanced the rate of oxidation (probably because of strong complex formation between the OH group and the catalyst). So from bromohydrin **4.3** lactone (**4.7**) in 40% conversion (44 h) was obtained while the bicyclic structure without the OH group (ketone **4.2**) was oxidized only in 7% conversion (lactone **4.6** formed) during the same time period. Prochiral *β*-hydroxymethyl cyclobutanone **4.4** revealed also low reactivity towards oxidation. The oxidation occurred only at an elevated temperature (−5 °C, usually the reaction temperature is −20 °C) and at prolonged reaction time (96 h). In spite of that, the enantioselectivity of the oxidation was still remarkable (*ee* 40%). The best enantioselectivity was obtained for the most sterically hindered ketone – bromohydrin **4.3** (*ee* 75%).

In order to obtain higher selectivity we tried to modify the Sharpless–Katsuki complex by changing the tartaric acid ester to some other, sterically more hindered, ligands. A well-known tartaric acid derivative that is used as chiral ligand in catalysts is TADDOL [11] (Fig. 6), which was synthesized by Seebach's group and used successfully as a chiral ligand in Diels–Alder reaction [12], carbonyl-ene reaction [13], 1,3-dipolar cycloaddition [14], and nucleophilic addition to carbonyl group [15].

We have synthesized several hindered alcohols, esters, amides, and amines from tartaric acid [16, 17] (Fig. 6) and checked the behaviour of some of them as ligands in the Ti-catalyzed oxidation reaction.
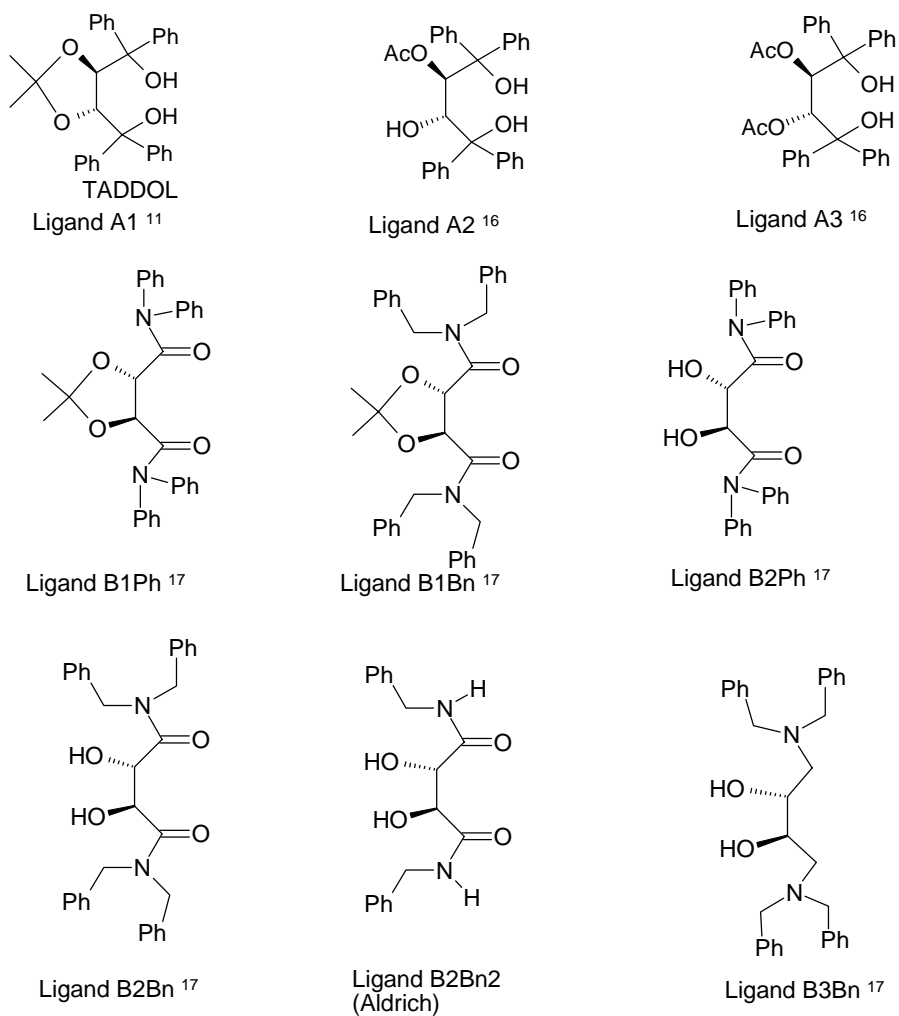
Fig. 6. Synthetic enantiomeric ligands to the oxidation catalyst.

Oxidation of cyclobutanones using a modified TADDOL as a ligand (A1) in the Ti-based oxidation complex (Ti(OiPr)$_4$/t-BuOOH/ligand) resulted, similarly to the Sharpless–Katsuki complex, in enantiomerically enriched lactones [16] (Fig. 7).
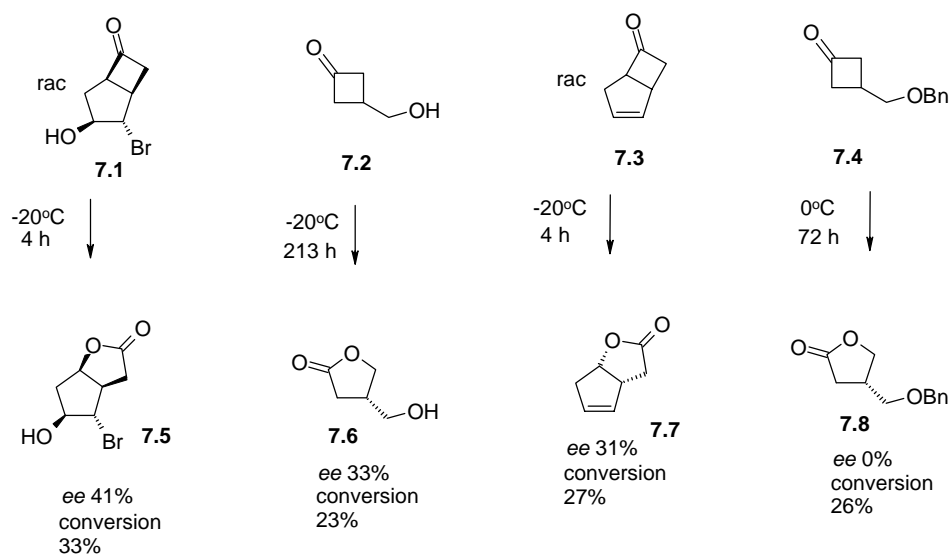
Fig. 7. Oxidation of racemic and prochiral cyclobutanones by a modified catalyst Ti(O*i*Pr)$_4$ /*t*-BuOOH/chiral ligand.

The enantioselectivity of the oxidation was close to that obtained with the original catalyst. Only in the case of bromohydrin **7.1** the enantioselectivity was slightly lower. Achiral compound **7.4**, which does not have any free OH group, oxidizes into lactone **7.8** without enantioselectivity, while the corresponding free OH compound **7.2** oxidizes with similar stereoselectivity to that obtained with the Sharpless–Katsuki complex (*ee* 33% vs. *ee* 40%). The catalytic activity of the complex with ligand A1 was considerably higher than that of the Sharpless complex that enables to get satisfactory conversions with all substrates already at −20°C and to reach preparatively acceptable isolated yields also for the less reactive ketone **7.2**. The results of the oxidation of cyclobutanones using the modified complexes with ligands A1, A2, A3, B2Bn, and B2Bn2 are presented in Table 1 [16].

Table 1. Results of the oxidation of cyclobutanones with the modified complexes

Complex	Time, h	Conversion, %	Selectivity, *ee*%
A1 (0.6 eq *t*-BuOOH)	4	33	41
A2 (1.0 eq *t*-BuOOH)	6	30	0
A3 (1.0 eq *t*-BuOOH)	1.5	10	6.5
B2Bn (1.5 eq *t*-BuOOH)	116	16	37
B2Bn2 (1.5 eq *t*-BuOOH)	46	12	10

α-HYDROXYLATION OF KETONES

The chiral α-hydroxy compounds are frequently found among bioactive natural compounds. Therefore, methods that enable a direct α-hydroxylation of racemic or prochiral ketones are of great importance. The asymmetric generation of α-hydroxy ketones has been achieved by oxidation of silyl enolates of ketones by using salen-type catalysts [18] and oxidants such as NaOCl, N-oxides, etc. (Fig. 8).
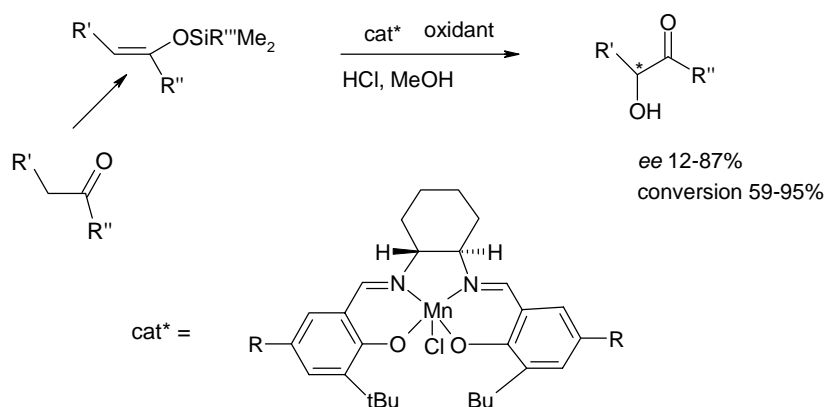
Fig. 8. Asymmetric α-hydroxylation of silyl enolates using a salen-type catalyst.

Also, the oxidation of alkyl enolates using hindered salen-type catalysts with different oxidizing agents has been successfully applied in order to get α-hydroxy ketones (Fig. 9) [19].
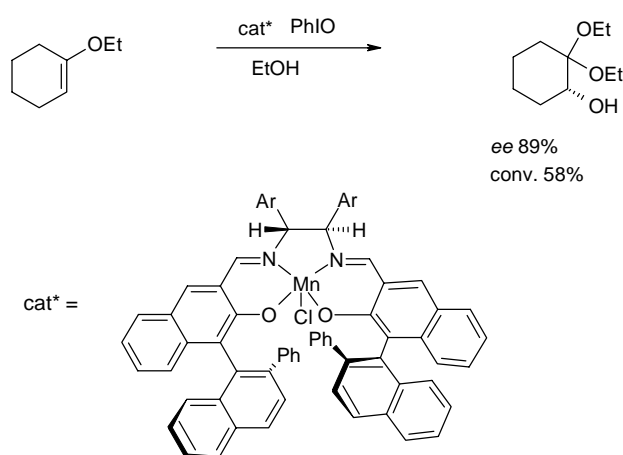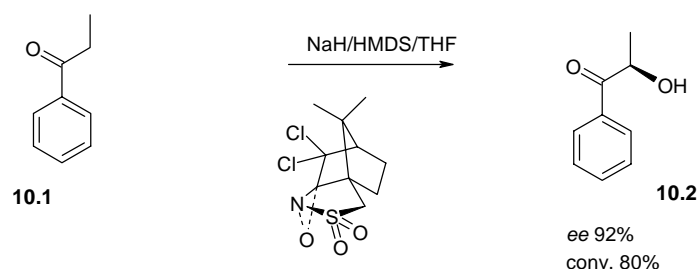
Fig. 9. Asymmetric α-hydroxylation of alkyl enolates using a salen-type catalyst.

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Several examples of direct asymmetric oxidation of ketones have also been published in the review [20]. Usually, ketones are oxidized by chiral oxaziridine at basic conditions (the initial compound that is oxidized is certainly the corresponding metal enolate (e.g. Fig. 10 [21]).

Fig. 10. Direct asymmetric oxidation of ketones by chiral oxaziridine.

We performed a direct asymmetric α-oxidation of ketones using the Sharpless–Katsuki complex. We found that this complex is able to oxidize cyclic and acyclic β-hydroxy ketones in very high enantioselectivity and in satisfactory yield (Fig. 11 [22]).
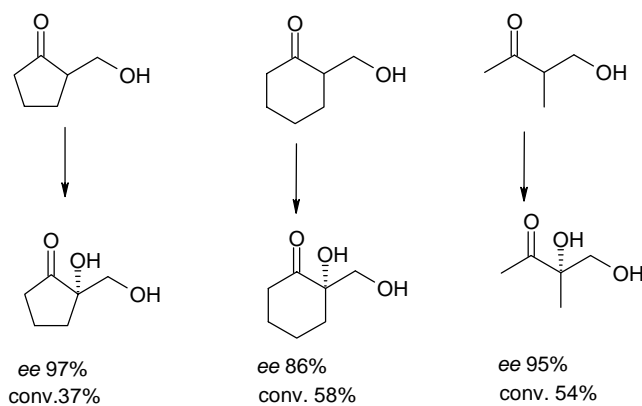

Fig. 11. Direct asymmetric α-oxidation of ketones by the Sharpless–Katsuki complex.

Conversions over 50% without considerable loss in stereoselectivity hint to the possible formation of an achiral intermediate from the racemic starting ketone and that enantioselection rather than kinetic resolution takes place. It may be assumed that the oxidation occurs via an intermediate enolate giving rise to an allylic structure. Such allylic system oxidizes according to an ordinary Sharpless oxidation process resulting first in an epoxide as an intermediate that rearranges subsequently into an α-hydroxy compound. This suggestion is supported by the

fact that other α-branched ketones that do not have an OH group, e.g. 2-methylcyclopentanone and 2-methylcyclohexanone, do not oxidize at our ordinary oxidation conditions. This suggestion may be rationalized as follows (Fig. 12 [22]):
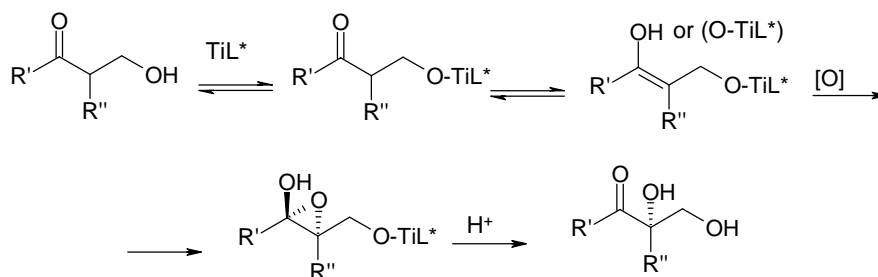
Fig. 12. A possible mechanism of α-hydroxylation.

A simplified model of the intermediate complex that explains the reasons of the obtained selectivity in terms of favoured/unfavoured conformations is represented in Fig. 13.
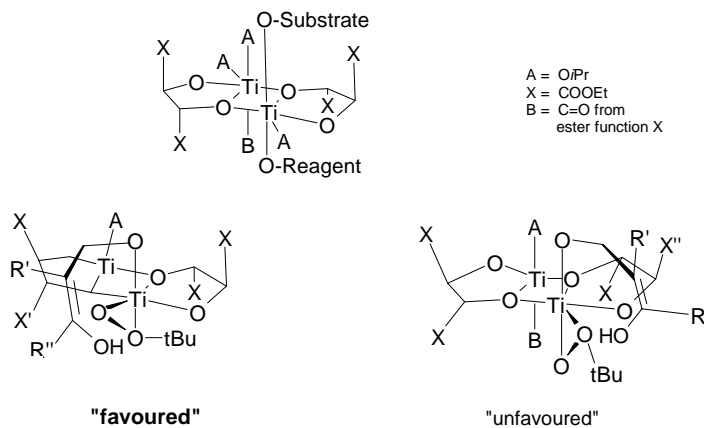

Fig. 13. A simplified model of the structure of the intermediate complex.

From simple Dreiding mechanical molecular models it can be seen that the ester group X′ in the "favoured" configuration is sterically not hindering double bond of the enolate and this determines the face of oxidation, while the ester group X in the other conformation makes it "unfavoured".

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ASYMMETRIC OXIDATION OF
3-ALKYL-1,2-CYCLOPENTANEDIONES

There are only a few examples of non-asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones [23–25] and not any about asymmetric oxidation of those compounds. In order to elucidate the scope and limitation in the direct asymmetric oxidation of ketones for the choice of substrates, we investigated the asymmetric oxidation of 3-methyl-, 3-ethyl-, and 3-hydroxyethyl-1,2-cyclopentanediones using the Sharpless–Katsuki complex. The oxidation results in two classes of compounds: α-hydroxylation products and ring cleavage products (Fig. 14).
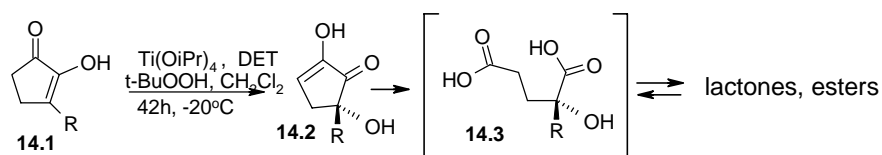
Fig. 14. Direct asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones using the Sharpless–Katsuki complex.

Below we discuss the formation of these two groups separately.

ASYMMETRIC 3-HYDROXYLATION OF
3-ALKYL-1,2-CYCLOPENTANEDIONES

The formation of 3-hydroxylated products when oxidizing 3-alkyl-1,2-cyclopentanediones has not been observed before and not cited in the literature. However, we have found that 3-alkyl-1,2-cyclopentanediones when oxidized with the complex of Ti(OiPr)$_4$/(+)diethyl tartrate/t-BuOOH in the ratio of 1:1.6:1.5, resulted in 3-hydroxylated products in high enantioselectivity (Fig. 15 [26]).
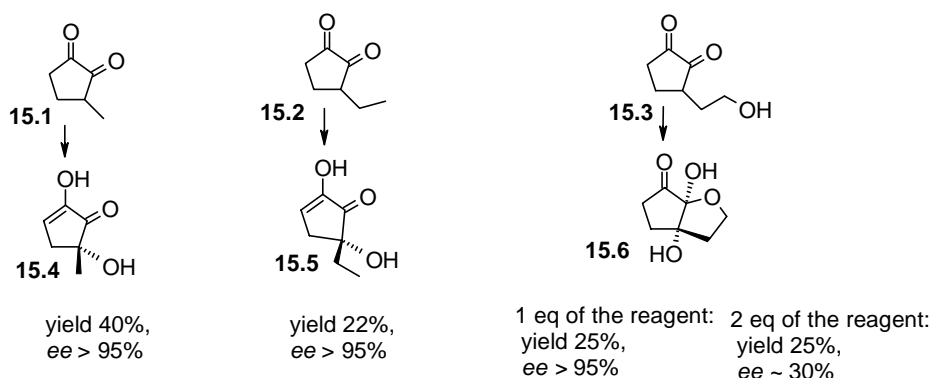
Fig. 15. Asymmetric 3-hydroxylation of 3-alkyl-1,2-cyclopentanediones.

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If the reaction conditions are properly chosen it is possible to obtain enantiomeric 3-hydroxylated products preparatively (in the case of **15.1** the isolated yield of **15.4** was as high as 40%). In the case of **15.3** the corresponding 3-hydroxylated product was separated as a hydroxylated intramolecular acetal **15.6.**

A possible mechanism of the formation of α-hydroxylated products is rationalized in Fig. 16.
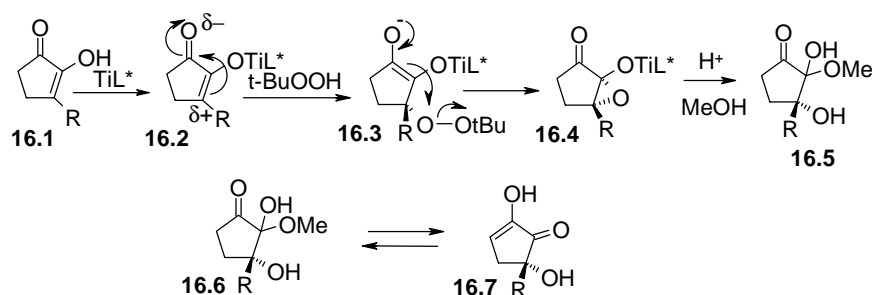

Fig. 16. A possible mechanism of the formation of α-hydroxylated products.

The initially formed hemiacetal **16.5** transforms, depending on the conditions, into a hydrate, hemiacetal, or enol form (Fig. 17).
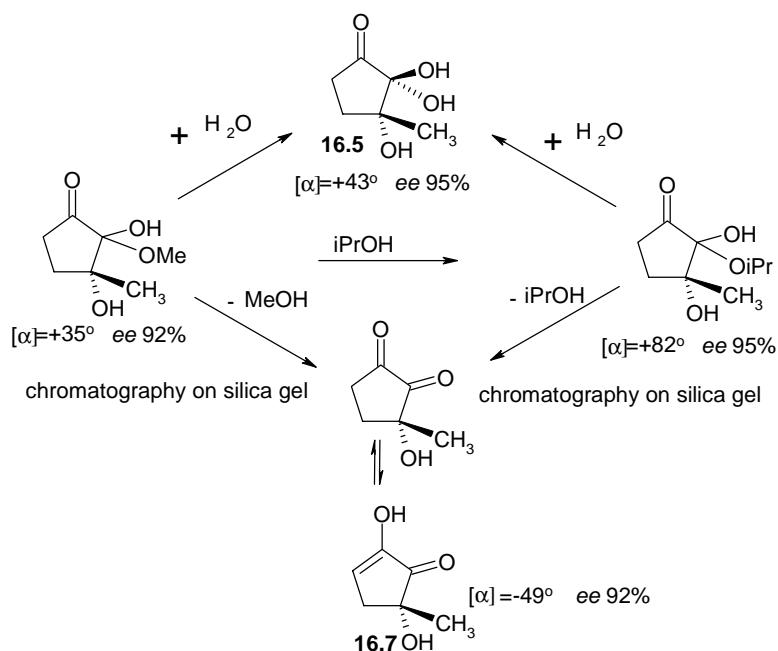

Fig. 17. Transformations of the 3-alkyl-1,2-cyclopentanediones.

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The reasons for obtaining such a high enantioselectivity may be described in terms of "favoured" and "unfavoured" conformations in the substrate–catalyst complex according to the Sharpless simplified oxidation model (presented in Fig. 13).
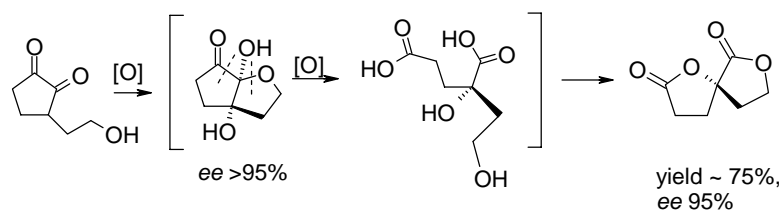
RING CLEAVAGE OF 3-ALKYL-3-HYDROXY-1,2-CYCLOPENTANEDIONES

The symmetric version of ring cleavage of 1,2-diones is well known. This reaction results in diacids. However, only a few examples describe the formation of 2-hydroxy-2-methyl-pentanediacid when oxidizing 3-methylcyclopentane-1,2-dione (one of those by Re catalyst [23] and another by photooxidation [24, 25]). The asymmetric version described by us is the first example of obtaining enantiomeric hydroxylated diacids from 3-alkylcyclopentane-1,2-diones [26]. By changing the reaction conditions it is possible to obtain a "single-oxidation" version (3-hydroxylated products) or a "double-oxidation" version (ring cleavage products) of the oxidation. So, we have obtained the ring cleavage products up to 75% isolated yield in excellent enantiopurity (Fig. 18).
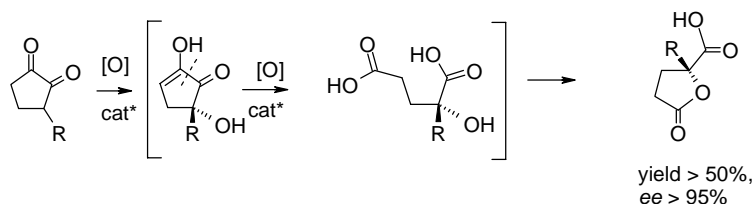
Fig. 18. Oxidative ring cleavage of 3-alkyl-3-hydroxy-1,2-cyclopentanediones.

An especially interesting compound – spirodilactone – is formed in the ring cleavage oxidation of 3-hydroxyethyl-1,2-cyclopentanedione (Fig. 19).

Fig. 19. Formation of spirodilactone in the ring cleavage oxidation of 3-hydroxyethyl-1,2-cyclopentanedione.

CONCLUSIONS

The scope of the application of the Sharpless–Katsuki complex can be extended to the asymmetric oxidation of ketones. Thus, **cyclobutanones**

undergo Baeyer–Villiger oxidation resulting in lactones with enantioselectivity up to 30–40% *ee*. The reactivity of the complex can be increased by the use of TADDOL-type chiral ligands. However, this replacement reduces slightly the enantioselectivity of the process. In the case of racemic cyclobutanones kinetic resolution occurs resulting in lactones up to 75% *ee* (at conversion extent ~40%). *β*-Hydroxyketones undergo an *α*-hydroxylation reaction in very high enantioselectivity (>86–97% *ee*). 3-Alkyl-1,2-cyclopentanones undergo *α*-hydroxylation at the branched carbon in high enantioselectivity (95% *ee* and higher). Also, 3-hydroxy-3-alkyl-1,2-cyclopentanediones undergo ring cleavage resulting in α-hyroxydiacids and the corresponding lactones in high enantiomeric purity. A simplified Sharpless complex model in terms of "favoured" and "unfavoured" complexes can be applied to rationalize the selectivity factors. The developed oxidation method is of preparative value.

REFERENCES

1. Bolm, C. & Beckmann, O. Baeyer–Villiger reaction. In *Comprehensive Asymmetric Catalysis II* (Jacobsen, E. N., Phaltz, A. & Yamamoto, H., eds.). Springer, Berlin, 1999, 803–810, and references cited therein.
2. Baeyer, A. & Villiger, V. Einwirkung des Caro´schen Reagens auf Ketone. Ber. *Dtsch. Chem. Ges.*, 1899, **32**, 3625–3633.
3. Baeyer, A. & Villiger, V. Benzoylwasserstoffsuperoxyd und die Oxydation des Benzaldehyds an der Luft. Ber. *Dtsch. Chem. Ges.*, 1900, **33**, 1569–1585.
4. Bolm, C., Shingloff, G. & Weickhardt, K. Optically active lactones from a Baeyer–Villiger-type metal-catalyzed oxidation with molecular oxygen. *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1848–1849.
5. Bolm, C. & Shingloff, G. Metal-catalyzed enantiospecific aerobic oxidation of cyclobutanones. *J. Chem. Soc., Chem. Comm.*, **1995**, 1247–1248.
6. Bolm, C., Loung, T. K. & Shingloff, G. Enantioselective metal-catalyzed Baeyer–Villiger oxidation of cyclobutanones. *Synlett*, **1997**, 1151–1152.
7. Gusso, A., Baccin, C., Pinna, F. & Strukul, G. Platinum-catalyzed oxidations with hydrogen peroxide: Enantiospecific Baeyer–Villiger oxidations of cyclic ketones. *Organometallics*, 1994, **13**, 3442–3451.
8. Woodward, S. S., Finn, M. G. & Sharpless, K. B. Mechanism of asymmetric epoxidation. 1. Kinetics. *J. Am. Chem. Soc.*, 1991, **113**, 106–113.
9. Finn, M. G. & Sharpless, K. B. Mechanism of asymmetric epoxidation. 2. Catalyst structure. *J. Am. Chem. Soc.*, 1991, **113**, 113–126.
10. Lopp, M., Paju, A., Kanger, T. & Pehk, T. Asymmetric Baeyer–Villiger oxidation of cyclobutanones. *Tetrahedron Lett.*, **1996**, 7583–7586.
11. Seebach, D., Weidmann, L. & Widler, L. In *Modern Synthetic Methods*, Vol. 3 (Scheffold, R., ed.). J. Wiley, New York, 1983, 217–353.
12. Seebach, D., Dahinden, R., Marti, R. E., Beck, A. K., Plattner, D. A. & Kühnle, F. N. M. On the Ti-TADDOLate-catalyzed Diels–Alder addition of 3-butenoyl-1,3-oxazolidin-2-one to cyclopentadiene. General features of Ti-BINOLate- and Ti-TADDOLate-mediated reactions. *J. Org. Chem.*, 1995, **60**, 1788–1799.
13. Mikami, K., Matsukawa, S., Volk, T. & Terada, M. Self-assembly of several components into a highly enantioselective Ti catalyst for carbonyl-ene reactions. *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2768–2771.

14. Gothelf, K. V. & Jorgensen, K. A. On the *trans-cis* controversy in Ti-TADDOLate-catalysed cycloadditions. Experimental indications for the structure of the reactive catalyst-substrate intermediate. *J. Chem. Soc., Perkin Trans.*, 1997, **2**, 111–115.

15. Duthaler, R. O. & Hafner, A. Chiral titanium complexes for enantioselective addition of nucleophiles to carbonyl groups. *Chem. Rev.*, 1992, **92**, 807–832.

16. Kanger, T., Kriis, K., Paju, A., Pehk, T. & Lopp, M. Asymmetric oxidation of cyclobutanones: Modification of the Sharpless catalyst. *Tetrahedron: Asymmetry*, **1998**, 4475–4482.

17. Ilmarinen, K., Kriis, K., Paju, A., Pehk, T. & Lopp, M. Synthesis of new chiral tetrasubstituted derivatives of *R,R*-tartaric acid and their use as ligands in chiral oxidation catalysts. *Proc. Estonian Acad. Sci. Chem.*, 2001, **50**, 147–155.

18. Adam, W., Fell, R. T., Stegmann, V. R. & Saha-Möller, C. R. Synthesis of optically active α-hydroxy carbonyl compounds by the catalytic enantioselective oxidation of silyl enol ethers and ketene acetals with (salen)manganese(III) complexes. *J. Am. Chem. Soc.*, 1998, **120**, 708–714.

19. Fukuda, T. & Katsuki, T. Mn-salen-catalyzed asymmetric oxidation of enol derivatives. *Tetrahedron Lett.*, **1996**, 4389–4392.

20. Davis, F. A. & Chen, B.-C. Asymmetric hydroxylation of enolates with N-sulfonyloxaziridines. *Chem. Rev.*, 1992, **92**, 919–934.

21. Gala, D., DiBenedetto, D. J., Merselsberg, J. & Kugelman, M. Total chiral synthesis of azole antifungals via α-hydroxylation of ketones. *Tetrahedron Lett.*, **1996**, 8117–8120.

22. Lopp, M., Paju, A., Kanger, T. & Pehk, T. Direct asymmetric α-hydroxylation of β-hydroxyketones. *Tetrahedron Lett.*, **1997**, 5051–5054.

23. Abu-Omar, M. M. & Espenson, J. H. Oxidations of cyclic β-diketones catalyzed by methylrhenium trioxide. *Organometallics*, 1996, **15**, 3543–3549.

24. Utaka, M., Nakatani, M. & Takeda, A. Dye-sensitized photooxygenation of 1,2-cyclopentane-diones in methanol. *J.Org. Chem.*, 1986, **51**, 1140–1141.

25. Kwon, B.-M. & Foote, C. C. Chemistry of singlet oxygen. 53. Environmental effects on the photooxygenation of 2-methoxy-3-methyl-2-cyclopenten-1-one. *J. Org. Chem.*, 1989, **54**, 3878–3882.

26. Paju, A., Kanger, T., Pehk, T. & Lopp, M. Asymmetric oxidation of 1,2-cyclopentanediones. *Tetrahedron Lett.*, **2000**, 6883–6887.

KETOONIDE ASÜMMEETRILINE OKSÜDATSIOON

Margus LOPP, Anne PAJU, Tõnis KANGER, Kadri KRIIS, Kaja ILMARINEN ja Tõnis PEHK

Ti(O*i*Pr)$_4$/viinhappe dietüülester/*t*-BuOOH kompleks (Sharplessi katalüsaator) on edukalt rakendatav ketoonide asümmeetriliseks oksüdeerimiseks, mis annab kõrge enantioselektiivsusega (kuni 98%) ja rahuldava saagisega (kuni 75%) enantiomeerseid laktoone tsüklobutanoonidest, α,β-dihüdroksüketoone β-hüdroksü-ketoonidest, alküüllaktoonkarboksüülhappeid 3-alküültsüklopentaan-1,2-dioonist ning spiro-γ-dilaktoone 3-(2-hüdroksetüül)tsüklopentaan-1,2-dioonist. Uus meetod võimaldab sünteesida mitmeid hüdroksüleeritud bioaktiivseid ühendeid.