THESIS ON NATURAL AND EXACT SCIENCES B125

3-Alkylcyclopentane-1,2-Diones in Asymmetric Oxidation and Alkylation Reactions

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Declaration:
Hereby, I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology, has not been submitted for any other academic degree.

Indrek Reile

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Contents

List of Publications

The thesis is based on the following papers:

I. Reile, I.; Paju, A.; Eek, M.; Pehk, T.; Lopp, M. Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones on Pt/C Catalyst. *Synlett* **2008**, 347-350.

II. Reile, I.; Paju, A.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. Oxidation of cyclopentane-1,2-dione: a study with ^{18}O labeled reagents. *Tetrahedron* **2011**, *67*, 5942-5948.

III. Reile, I.; Paju, A.; Kanger, T.; Järving, I.; Lopp, M. Cyclopentane-1,2-dione bis-Silyl Enol Ether in Asymmetric Organocatalytic Mukaiyama-Michael Reaction. *Tetrahedron Lett.* **2012**, *53*, 1476-1478.

IV. Reile I.; Kalle, S.; Werner, F.; Järving, I.; Kudrjashova, M.; Paju, A.; Lopp, M. Heterogeneous Platinum Catalytic Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones. *Submitted*

Authors Contribution

The contribution by the author to the papers included in the theses is as follows:

I. Participated in the planning of experiments, carried out the experiments, wrote the manuscript draft and participated in final manuscript preparation.

II. Participated in the planning of experiments, carried out the experiments, wrote the manuscript draft and participated in final manuscript preparation.

III. Planned the experiments, carried out the experiments, wrote the manuscript draft and participated in final manuscript preparation.

IV. Planned the experiments, participated in and supervised carrying out the experiments, wrote the manuscript draft and participated in final manuscript preparation.

Abbreviations

Ar	aryl
Bn	benzyl
cat.	catalytic amount
dba	dibenzylideneacetone
E	electrophile
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedianato
Hal	halogen atom
HOMO	highest occupied molecular orbital
in situ	in original location
in vitro	test tube experiment
LUMO	lowest unoccupied molecular orbital
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
OTf	trifluoromethanesulfonate
platinum metal	platinum group metal (i.e. Ru, Rh, Pd, Os, Ir, Pt)
*t*Amyl	*tert*-C_5H_{11}
TBAF	*tetra*-N-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TUT	Tallinn University of Technology
vic	vicinal, neighboring atom

Introduction

Cyclopentane-1,2-diones are a class of simple organic compounds that have been known since the end of the 18th century, when Dieckmann published his condensation reaction[1] and later extended the use of his reaction for the preparation of simple cyclopentane-1,2-diones.[2] Soon after that, cyclopentane-1,2-diones were found in natural sources.[3,4] Following these discoveries, the early research was directed towards the isolation and preparation of cyclopentanedione compounds, which were regarded as promising pesticides.[5,6] Although a considerable effort was put into the synthesis[7] and isolation[8] of cyclopentane-1,2-diones, the tautomeric structure of cyclic α-diketones proved to be a challenging question and early reports led to inconclusive results.[9,10] In fact, the actual solution structure of cyclopentane-1,2-diones was unambiguously proved only after the first practical NMR techniques became available.[11] It was shown that they exist in solution as keto-enols and preferably form the thermodynamically preferred more substituted enol (Figure 1). Such behavior of these compounds did not find theoretical explanation until several decades later.[12,13]

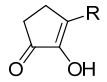


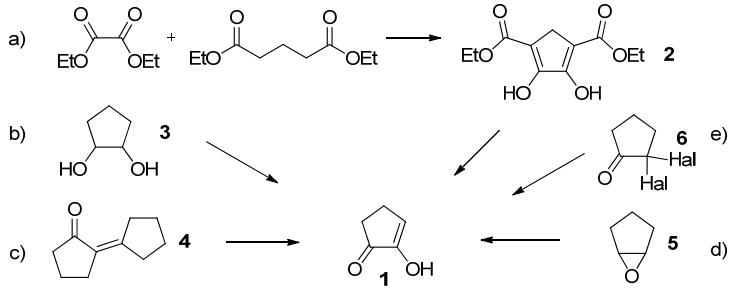
Figure 1. Preferred structure of 3-alkylcyclopentane-1,2-diones in solution

3-Methylcyclopentane-1,2-dione, the simplest member of the 3-alkylcyclopentane-1,2-dione family, has been found in maple syrup[14] and coffee.[15] It constitutes to coffee aroma and has been used as a food-flavoring agent, marketed as *cyclotene*.[16] Also, other structurally similar cyclpentane-1,2-diones have pleasant organoleptic properties.[17] Recent research on the biological effects of the compound has revealed that these structures have anti-inflammatory properties[18] and influence age-related inflammation processes.[19] *In vitro* experiments have shown that cyclopentane-1,2-diones are able to cross-link proteins, an observation that may lead to new therapeutic strategies in the future.[20]

In addition to organoleptic and biological properties, cyclopentane-1,2-diones have gained attention as intermediates in the preparation of various compounds, for instance propellanes[21] and pyrazines.[22] Cyclopentane-1,2-dione has been used as a starting material in the total synthesis of stemona alkaloids[23] and 3-alkylcyclopentane-1,2-diones can be asymmetrically oxidized to produce a natural product homocitric acid[24] or nucleoside analogues with antiviral activity.[25]

Although some of the simpler cyclopentane-1,2-diones are present in plants and can be separated from them,[14,15] the wider use of such diketones as synthetic feedstock has been hindered by the preparation difficulties of cyclic α-dicarbonyl compounds. In most cases, the simple unsubstituted cyclopentane-1,2-dione **1** is prepared by the relatively atom inefficient Dieckmann condensation reaction[2,5,26] (Scheme 1, a). The same methodology can be applied for the preparation of 3-alkylcyclopentane-1,2-diones if the diester intermediate **2** is alkylated prior to decarboxylation.[27,28] Alternatively, cyclopentane-1,2-dione **1** can be prepared by an inconvenient Swern oxidation of the corresponding cyclopentane-1,2-diol **3** (Scheme 1, b). Using this reaction to produce 3-alkyl derivatives of **1** involves separate synthesis of 3-alkyl derivatives of **3**.[29]

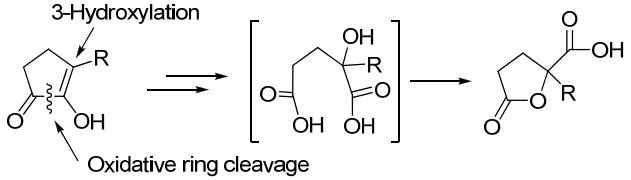
A short selection of additional methods includes ozonolysis of appropriate precursors **4**,[30] oxidation of epoxides **5**[31] and hydrolysis of α-haloketones **6**[32] (Scheme 1, c, d, e respectively). Although acyclic α-diketones can be prepared by oxidation of appropriate alkynes,[33] cyclopentyne is not stable enough to be used as a practical starting material. All of the available methods either do not lend themselves well to the preparation of cyclopentane-1,2-diones with diverse substituents attached to the pentane template or use inefficient chemistry that produces a lot of waste.



Scheme 1. Different strategies for the preparation of cyclopentane-1,2-dione

The present thesis aims to look for improvements in the field of cyclopentane-1,2-dione chemistry regarding the preparation and derivatization of the mentioned dicarbonyl compounds. Based on prior experience in the preparation of 3-alkylcyclopentane-1,2-diones by Swern oxidation,[29] we aimed to develop a more economical method for the oxidation of 3-alkyl analogues of cyclopentane-1,2-diol **3**. Among different alcohol oxidation methods, aerobic oxidation is the most attractive methodology because it uses a cheap and green bulk oxidant – oxygen – that produces water as the only byproduct. Based on these considerations, a metal catalytic aerobic oxidation method for the preparation of cyclopentane-1,2-diones would be of considerable interest. The development of such a method is covered in articles I and IV.

As mentioned earlier, 3-alkylcyclopentane-1,2-diones can be asymmetrically oxidized to produce enantioenriched precursors to biologically active compounds.[24,25] Although asymmetric oxidation is the key reaction in this conversion, its mechanism has not been fully rationalized. It is known that the oxidation of α-dicarbonyl compounds does not follow the same path as the oxidation of simple carbonyl compounds.[34] However, later research has failed to agree upon a universal mechanism for the oxidation of *vic*-diketones[35,36] and there are no examples available that would unambiguously establish the mechanism of the peroxide oxidation of enolizable 3-alkylcyclopentane-1,2-diones (Scheme 2). A clarification of the mechanism of the asymmetric oxidation of cyclopentane-1,2-diones, which will help in further optimization and in the development of additional applications for the reaction, is covered in article II.



Scheme 2. Asymmetric oxidation of enolizable 3-alkylcyclopentane-1,2-diones

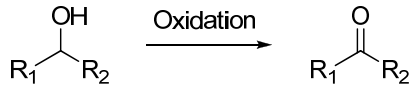
The asymmetric oxidation reaction is known to tolerate various functionalities in the 3-position substituent, including alkyl-,[37] alkoxyalkyl-,[37] ester-[38] and hydroxyl[39] groups. However none of the synthetic approaches depicted on Scheme 1 are compatible with the range of functional groups that one might want to introduce as 3-position substituents in the cyclopentane ring. It is reasonable to assume that the aerobic oxidation of their preceding diols, in order to obtain diketones, would also have limitations regarding the synthetic scope.

One way to circumvent this is to first prepare the cyclopetane-1,2-dione **1** and then functionalize it in the 3-position with a suitable alkylating agent. Direct 3-alkylation of cyclopentane-1,2-dione **1** has been achieved by a Mannich reaction with morpholine and formaldehyde,[40] and by alkylating diketone dienolates with alkylhalides.[41] Both of these methods provide mediocre yields and have been used to introduce very simple alkyl groups; none allow for the introduction of more diverse functional groups, nor do they make it possible to generate stereocenters with controlled configuration during the alkylation reaction. A method that would allow both would be desirable for the preparation of novel substrates for the earlier described asymmetric oxidation reaction. The development of an organocatalytic method that would fulfill these expectations is described in paper III.

1 Literature Overview

1.1 Platinum Metal Catalytic Aerobic Oxidation of Alcohols to Carbonyl Compounds

Organic compounds that bear carbonyl groups, obtained by oxidation of their preceding alcohols, are of enormous importance in the chemical industry and in laboratory research (Scheme 3). Oxidation of alcohols to carbonyl compounds is among the most widely used chemical transformations, with an annual output in excess of $2x10^6$ tons.[42] Traditionally, this reaction has been achieved by systems using corrosive chemical oxidants, such as ClO^-, Cr^{VI}, Cl_2 and peroxy acids.



Scheme 3. Oxidation of alcohols to carbonyl compounds

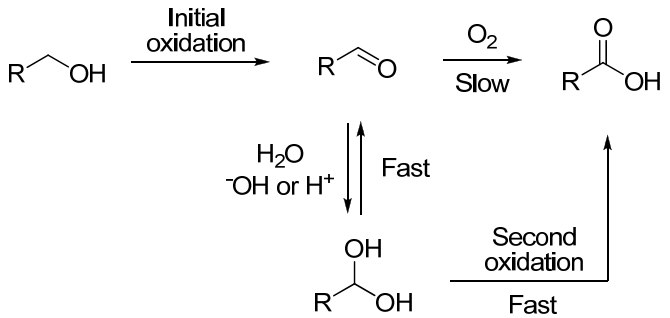
Due to the environmental and economic problems that arise with these reagents, there has been a steady search for greener and more economical alternatives. Ever since the development of the Wacker process[43] in the 1950s, there has been a continuous interest in platinum metal-catalyzed oxidations. Still, further development in this direction was slow due to the somewhat complicated nature of the catalysis.[44] The first successful example of the aerobic oxidation of alcohols to their corresponding carbonyl compounds dates to the late 1970s when Schwartz *et al* reported a homogeneous Pd catalytic aerobic oxidation of secondary alcohols to ketones.[45] Following these successes, the field has seen steady growth, with new applications quickly emerging. Aerobic oxidations are especially attractive from the environmental viewpoint because they generate water as their only byproduct.

Metal catalytic aerobic oxidation systems can be divided into two major categories: homogeneous catalytic systems, where the metal species forms a soluble complex in the reaction environment, and heterogeneous catalysis, where the metal is bound to a non-soluble carrier matrix or used as a finely dispersed metal powder. Homogeneous catalyst systems can be considered advantageous at first glance and the reaction mechanisms of many such catalyst systems have been established.[46,47] As the catalyst and the reagents coexist simultaneously in the same phase, these methods enjoy the benefit of higher activity and also allow enantioselective reactions.[48] For instance homogeneous catalysis has been used for the oxidative kinetic resolution of secondary alcohols.[49]

Heterogeneous catalysts have one crucial advantage over their homogeneous counterparts: easier catalyst recovery and product separation. They can be easily separated from reaction mixtures by filtration, in some cases by centrifuge[50] or, in more exotic cases, by a magnet when magnetic particles are used as catalyst support.[51] Unfortunately such catalysts may be of lower catalyst activity relative to their homogeneous analogues and the durability of the catalyst supports can also be a problem.

As both catalyst types clearly have their advantages, they have been continuously developed. Soluble metal complex catalyzed homogeneous catalysis has been achieved both in water[52,53] and in organic solvents.[54,55,56] Heterogeneous catalyst systems, consisting of traditional solid supported catalysts[57,58] or metal nanoparticles,[59] have been successfully implemented in various reaction media, including common organic solvents,[60] water,[59] supercritical CO_2,[61] and even in solvent free conditions.[62] Metals that are commonly used as catalytic species primarily include such platinum group metals as ruthenium,[58] palladium[63] and platinum.[64] More recently, heterogeneous gold catalysts have been developed for the aerobic oxidation of alcohols.[65] Metal nanoparticles have their own distinctive catalytic properties that can be beneficial for chemical processes.[66]

While many of the mentioned catalytic systems are run in organic or chloroorganic solvents, water as the reaction medium would offer some benefits as it is a safer, cheaper and arguably more environmentally friendly chemical. However, aqueous conditions can be difficult to achieve, as some of the catalytic systems require dry conditions, an intrinsic problem since water is also generated during the reaction. Water may not only interfere with the catalytic process but the presence of water also makes it difficult to obtain aldehyde products that will quickly turn to acids in the presence of water (Scheme 4).[61,67] One interesting idea is to use ionic liquids as a reaction medium, as they can prevent the over-oxidation of aldehydes to acids.[68] Also organic solvents that remove the forming water quickly from the catalyst surface have solved the selectivity issue.[69]



Scheme 4. Water influences product selectivity of metal catalytic aerobic oxidations

Many of the catalysts described above are either relatively expensive or must be separately prepared and may have only a limited shelf-life.[70] For practical reasons, it would be highly beneficial to use catalysts that are inexpensive and commercially available, for instance catalysts that utilize activated carbon as the heterogeneous support.[58] For the same reasons it would be desirable to use atmospheric air rather than pure oxygen as the oxidant source.

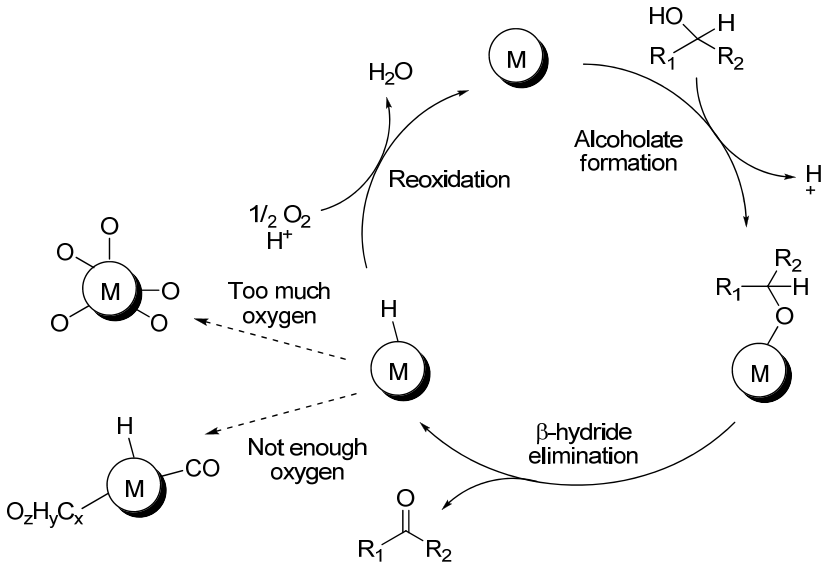
1.1.1 Heterogeneous Metal Catalytic Aerobic Oxidation of Alcohols

The most common solid supports used to carry catalytic species in heterogeneous catalysis include aluminium oxide[57] and activated carbon.[69] Also, other inorganic materials, such as polyoxymetalates[64] and hydrotalcites, [71] have been used. More recent materials include carbon nanotubes[72] and organic polymers and resins. The latter can be used ed to anchor otherwise soluble metal complexes to a heterogeneous support[73] but can also be used for anchoring metal nanoparticles.[59,65] However, polymer supports are not very widely used (compared to inorganic materials), partly due to the questionable stability of organic polymer supports under different reaction conditions. The mechanical durability of polymer supports can also be a problem.

A great deal of effort has been put into examining the mechanism of heterogeneous aerobic oxidations. Grunwaldt *et al* showed that, in the case of supported Pd catalysis, oxidation proceeds *via* two major steps: the oxidation of alcohol by dehydrogenation and the regeneration of the active catalyst by oxidation.[74] Later Ikeda *et al* showed that platinum catalytic oxidation proceeds by the same mechanism[75] and, indeed, most heterogeneous metal-based catalysts are expected to follow similar mechanistic paths (Scheme 5). The reaction starts with the formation of an alkoxy-metal species. Next, the desired carbonyl product is formed by β-hydride elimination on the metal surface, leaving the metal covered in hydride species, which are finally removed by oxygen to complete the catalytic cycle. As with the homogeneous oxidation of primary alcohols, over-oxidation to carboxylic acids can occur (Scheme 4). It has been shown that the product selectivity of the Pt/C catalysts can be tuned to the formation of aldehydes or acids by means of solvent selection.[69]

A common problem in heterogenic aerobic oxidations is catalyst deactivation during the process. This occurs for different reasons,[76] such as aggregation and the sintering of the catalyst particles (irreversible deactivation) or due to modification of the metal surface (reversible deactivation). For instance, if an excess of oxygen is available, the metal surface can oxidize (Scheme 5). This is less of a problem in Pt catalysis because, due to its higher oxidation potential, platinum is less prone to oxidation to metal oxide.[76] On the other hand, under conditions of oxygen deficiency, the catalyst surface can get saturated with strongly coordinating reaction byproducts and with hydrogen subtracted from

the substrate. It has been shown that, if deactivation occurs due to over-oxidation during a batch process, the catalyst can be regenerated afterwards by means of hydrogen reduction.[77] The initial catalyst deactivation can be suppressed by combining different additives on the support surface to stabilize the metal particles, such as polyoxymetallates[64] or promoter metals (Bi, Pb, Sn etc).[67] Also, small amounts of ionic liquids can serve as a rate-enhancing and catalyst-stabilizing additive.[72]



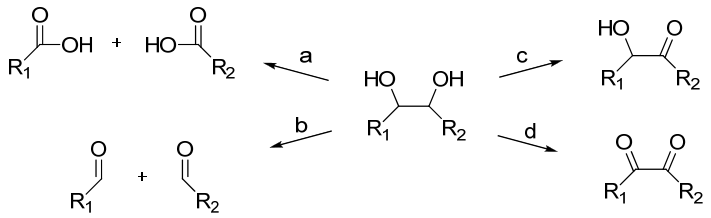
Scheme 5. The mechanism of heterogeneous aerobic oxidation of alcohols

1.1.2 Aerobic Metal Catalytic Oxidation of *vic*-Diols

The majority of aerobic oxidation systems that have been developed can be applied for the conversion of allylic or benzylic alcohols. These oxidations benefit from the resonance stabilization in the product and thus have an additional driving force. Due to industrial interest, the most widely studied polyols from the perspective of aerobic oxidations are such natural compounds as sugars[78] and glycerol,[77,79] or ethylene glycol.[76,67] Examples in which more complex synthetic 1,2-diols have been successfully oxidized to the corresponding *vic*-diketones are scarce.

The common outcome of the oxidation of *vic*-diols is the cleavage of the carbon-carbon bond between the hydroxyl-bearing carbons. This reaction has been known for a long time and has been employed for the preparation of aldehydes[80,81] and carboxylic acids[82] (Scheme 6, a). Similarly, this was the main outcome in early aerobic oxidation methods. When *cis*-cyclohexane-1,2-diol was oxidized on a heterogeneous ruthenium oxide catalyst, cleavage of the cycle was

observed, producing diacids.[83] This is also the usual outcome in heterogeneous Pd and Pt catalyses, but not necessarily in the case of Au catalyses, where no C-C bond cleavage occurs and usually only one of the hydroxyl groups gets oxidized to an acid when the substrate is a terminal 1,2-diol.[84,]



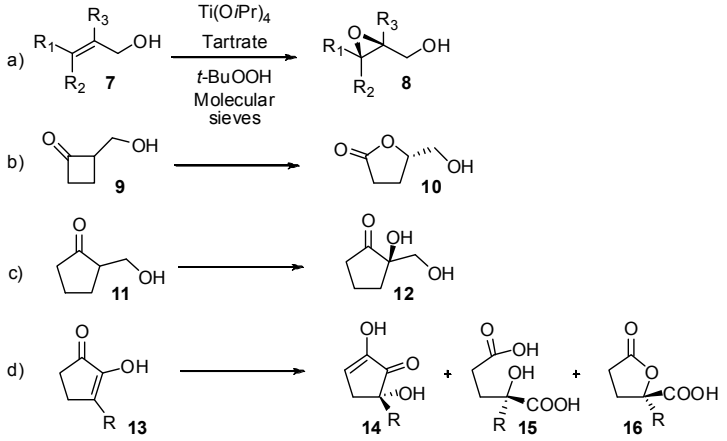
Scheme 6. Possible outcomes of the metal catalytic aerobic oxidation of *vic*-diols

By the appropriate selection of a catalyst and conditions, it is possible to cleave diols to dialdehydes rather than acids over a carbon immobilized Ru catalyst[85] (Scheme 6, b) or to oxidize only one of the two hydroxyl groups, producing an hydroxyketone (Scheme 6, c).[55] Still, there are a small number of examples available where *vic*-diols have been converted to the corresponding dicarbonyls without cleaving the C-C bond (Scheme 6, d)[71] or where cyclic *vic*-diols have been oxidized to diketones over platinum metal catalysts.[42] Some further examples are available in aerobic oxidations *via* radical mechanisms,[86,87] but they remain scarce and there are no known examples available of the aerobic metal catalytic oxidation of cyclopentane-1,2-diols to cyclopentane-1,2-diketones, either *via* radical or the earlier described dehydrogendation mechanisms.

1.2 Mechanism of the Asymmetric Oxidation of Cyclopentane-1,2-diones

Whereas the oxidative cleavage of cyclopentane-1,2-diones was mentioned as an unwanted product degradation process in the previous chapter, it can serve as a valuable and desired reaction under different circumstances. When subjected to a peroxide oxidation reaction in the presence of the titanium isopropoxide-tartrate catalyst discovered by Sharpless,[88] 3-alkyl- and 3-arylcyclopentane-1,2-diones can be cleaved in an enantioselective manner, resulting in chiral nonracemic diacids.

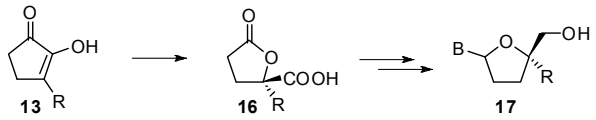
The Sharpless catalyst was initially developed for the asymmetric epoxidation of allylic alcohols **7** (Scheme 7, a), but was soon employed for the asymmetric oxidation of sulfides.[89] Later Lopp *et al* showed that the same catalyst could be used for the asymmetric Bayer-Williger oxidation of cyclobutanones **9** (Scheme 7, b),[90] as well as for the α-hydroxylation of β-hydroxy ketones **11** (Scheme 7, c).[91] Upon further development of the scope of the catalyst system, it was found that 3-alkylcyclopentane-1,2-diones **13** also undergo asymmetric oxidation.[92] As a result, a mixture of an α-hydroxylation product **14**, a ring cleaved diacid product **15** and a lactone acid product **16**, formed from diacid **15**, was obtained (Scheme 7, d). Although the oxidative ring cleavage of cyclopentane-1,2-diones had been observed earlier,[93,94] this was the first known example of doing so in a stereoselective manner.



Scheme 7. a) Sharpless epoxidation; b) asymmetric Baeyer-Williger oxidation; c) asymmetric α-hydroxylation; d) asymmetric oxidation of 1,2-diketones

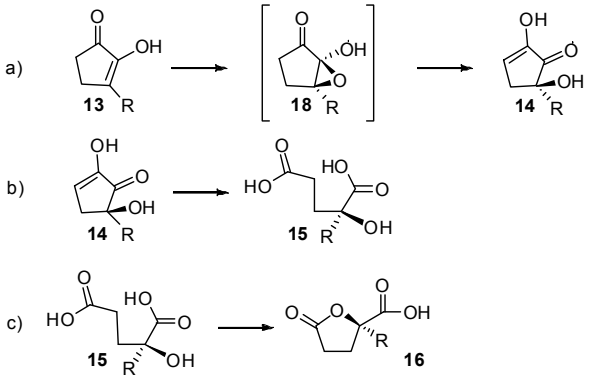
Soon it was found that the reaction could be optimized to the preparation of primarily the 3-hydroxylation product[29] **14** or the lactone acid product[95] **16**, and it was suggested that the process is a three-step domino reaction. The first oxidation step produces the 3-hydroxylated compound **14**, the diacid **15** is

produced during a second oxidation step and the lactone acid forms intramolecularly from the latter. The reaction was optimized further to yield only the lactone acid products in up to 83% yield and up to 96% ee,[37] and it was used for the preparation of biologically active nucleoside analogues **17** (Scheme 8).[96]



Scheme 8. Preparation of 4'-substituted nucleoside analogues; B – nitrogen base

Based on the knowledge that enol ethers can be asymmetrically α-hydroxylated,[97,98] and that an α-hydroxylation product **14** was indeed observed among the reaction products, it is reasonable to assume that the first step in the domino reaction is hydroxylation. Considering that the titanium catalyst is usually used for epoxidation reactions, it can be assumed that, once the starting material becomes coordinated to the metal, it is epoxidized. The epoxide **18** in turn is cleaved to give the α-hydroxylation products (Scheme 9, a). Provided the reaction conditions are appropriate,[37] the intermediate hydroxylation product can undergo a second oxidation step (Scheme 9, b) that cleaves the cyclopentane ring, producing a diacid compound **15** that can be isolated. The latter product can be acid-catalytically cyclized to lactone acids **16** in the third step of the reaction sequence (Scheme 9, c). The enantioselectivity of the whole process is determined during the initial epoxidation, with no racemization occurring in further steps.

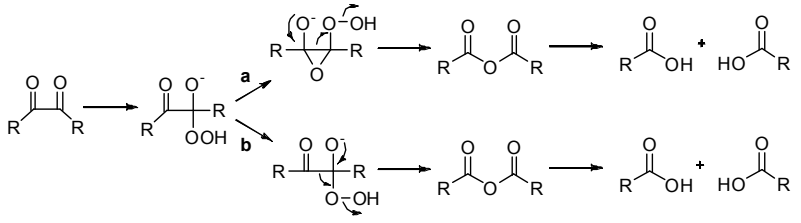


Scheme 9. The formal steps in the reaction sequence

The mechanism of the Sharpless epoxidation reaction has been thoroughly studied[99,100] and is generally agreed upon, although the exact structure of the catalytically active species is not clear. Based on earlier research, it is reasonable to conclude that the α-hydroxylation of 1,2-diones (Scheme 9, a) follows the mechanistic principles of asymmetric epoxidation reactions. On the other hand, the mechanism of the second step of the reaction sequence is unclear. Formally,

the cleavage of the cyclopentane ring is the result of a diketone oxidation reaction. Although, there are a few earlier examples available where *vic*-diketones have been oxidatively cleaved, all of them deal with non-enolizable benzils.

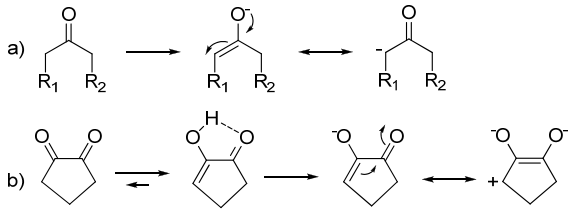
The earlier studies aimed at clarifying the mechanism produced inconsistent results and proposed several different possibilities.[101] Foote *et al* showed that the peroxide cleavage of benzils should proceed *via* the Baeyer-Villiger mechanism (Scheme 10, b).[35] That conclusion was, however, challenged by another study a few years later, which found the Baeyer-Villiger mechanism implausible and supported a different "epoxide" mechanism (Scheme 10, a).[36] Thus the mechanism of C-C bond cleavage in 1,2-diketones has not been unambiguously clarified. Furthermore, there are no previous inquiries into the oxidation mechanism of enolizable *vic*-diketones that can be used to explain the asymmetric oxidation reaction that cleaves 3-alkylcyclopentane-1,2-diones. As a conclusion from the earlier examples, one can observe that both of the mechanisms depicted in Scheme 10 share common intermediates and produce an anhydride intermediate. The mechanistic suggestions differ only in the paths of specific oxygen atoms throughout the reaction sequence.



Scheme 10. Possible mechanisms for benzil cleavage (R = Ph) by peroxide oxidation *via* a) the "epoxide" mechanism or b) the Baeyer-Villiger mechanism

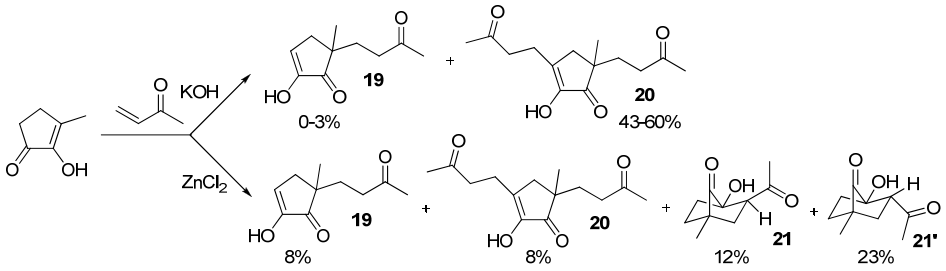
1.3 α-Alkylation of Cyclic Vicinal Diketones

While the α-alkylation of simple carbonyl compounds is a common and well-documented reaction, the α-alkylation of *vic*-diketones has been less explored. The most straightforward method for the electrophilic α-functionalization of carbonyl compounds involves the generation of a nucleophilic enolate species prior to the reaction with an electrophile (Scheme 11, a). However, due to electronic and electrostatic factors, this strategy does not work in the case of small ring vicinal diketones, where the carbonyl moieties are forced to be in the same plane[13] and one of the carbonyls adopts the enol configuration (Scheme 11, b). As a result the dipole repulsions between the coplanar C=O groups are relieved and additional stabilization is obtained from a higher degree of conjugation[102] and from the formation of an intramolecular hydrogen bond between the enol and carbonyl groups.[12] The enolate obtained by deprotonating the keto-enol unit is a relatively weak nucleophile because the neighboring carbonyl group decreases the electron release and thus the nucleophilicity of the enolate.[41]



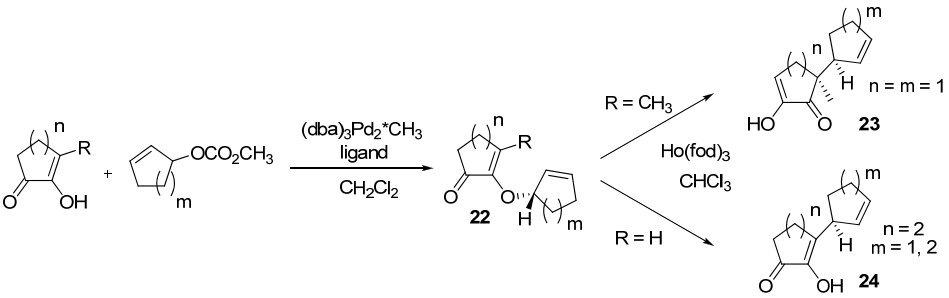
Scheme 11. Generation of enolates and enolate resonance structures for a) carbonyl compounds and b) vicinal dicarbonyls

Despite the electronic effects, cyclopentane-1,2-diones have been found to react with methyl vinyl ketone in a Michael reaction, although in modest yields.[103] A detailed study of the reaction showed that both cyclohexane- and cyclopentane-1,2-diones are suitable nucleophiles, but the product selectivity can be an issue.[104] When potassium hydroxide was used as the base, the main product was a dialkylation product **20** in moderate yields with only trace amounts of the mono Michael product **19** isolated (Scheme 12). If KOH was replaced with $ZnCl_2$, mainly the bicyclic compounds **21** and **21'** that form *via* an intramolecular aldol reaction were obtained. The intramolecular reaction is likely to be facilitated by the Lewis acid properties of $ZnCl_2$. The ability of cyclic 1,2-diones to form multi-cyclic compounds by intramolecular aldol reactions in the presence of Lewis acids has been separately documented.[105] A similar outcome, namely the formation of a bicyclic compound by an intramolecular aldol reaction after a Michael addition, has also been documented in the case of an organocatalytic reaction.[106]



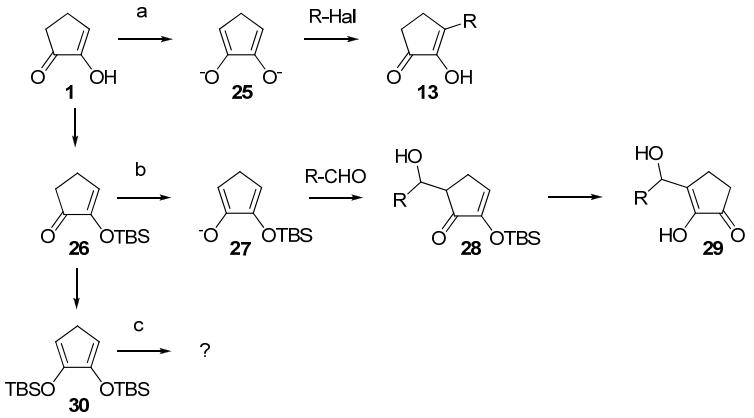
Scheme 12. Michael adducts of 3-methylcyclopentane-1,2-dione and methyl vinyl ketone

Better product selectivity has been achieved in the Heck arylation of cyclohexane-1,2-diones, where only a single product was isolated in reasonably good yields.[107] Alternatively, very good results have been obtained from a combination of asymmetric allylic alkylation and Claisen rearrangement reactions (Scheme 13).[108] In this transformation, the chirality is established in the first O-alkylation step and the second rearrangement step transfers the chirality in **22** to the C-C bond in **23**. It was found that, when the starting diketone **22** was not substituted in the α-position, the product isomerized instantly to its more substituted enol form **24**. This constitutes one of the few known methods for the generation of asymmetric 3-substituted cyclic 1,2-diones from simpler prochiral cyclic 1,2-diones.



Scheme 13. Asymmetric 3-alkylation on cyclic 1,2-diones by asymmetric allylic alkylation – Claisen rearrangement

It can be concluded that in the α-alkylation of cyclic-1,2-diones the yields and product selectivities are usually low. Better selectivity can be achieved by the organocatalytic Michael reaction or by the O-alkylation-Claisen rearrangement procedure. In these cases, the former gives an intramolecular aldol product and the latter is confined to reagents that are susceptible to the rearrangement. Attempts have been made to improve the outcomes of the electrophilic alkylations by converting the diketones **1** to dienolates **25** (Scheme 14, a). As a result the nucleophilicity of the enolate increases (Scheme 11) and the alkylation products **13** in up to 70% isolated yield could be obtained when the dienolate **25** was alkylated with alkyl halides.[41]



Scheme 14. Alkylation of dienolates

The dienolates **25** of cyclopentane-1,2-diones can be easily obtained. However, such dianions have low solubility and are difficult to handle. On the other hand, dione **1** can be converted into a silyl mono-enolate **26** (Scheme 14, b) and then converted to the active mixed silyl-lithium dienolate, to avoid the formation of poorly soluble dianions. Such a strategy was employed for an aldol reaction during a total synthesis of a natural compound (±)-bilobalide.[109] Alternatively, bis-silyl dienolates **30**, which are soluble in organic solvents, can be generated (Scheme 14, c). This approach has been used in Diels Alder reactions[110] and in the preparation of disilyloxy substituted cyclopentadienyl zirconocenes.[111] The bis-silyl dienolates could act as nucleophiles in Mukaiyama-Michael-type reactions. In the case of using dienolates, one of the silyl enolates is consumed during the reaction. The remaining second silyl enolate can serve as a ketone-protecting group, preventing the intamolecular aldol reaction observed in the cases discussed above (see Scheme 12). Quite often in Mykaiyama reactions, the electrophile needs to be activated by a catalyst for the reaction to occur. The catalyst can be either a stereoselective organometallic catalyst or an organocatalyst.

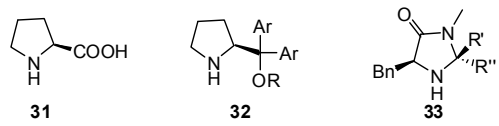
1.3.1 Organocatalytic Reactions

Stereoselective reactions that produce enantiomerically enriched organic compounds are usually facilitated by metal- or enzymatic catalysis, both of which have their drawbacks. The use of enzymes is usually limited to certain chemical transformations and metal catalysts use heavy metal complexes that can be the source of unwanted impurities in the product. Furthermore, metal catalysts quite often require dry and air-free conditions that may be a hindrance in their use. Organocatalysis, on the other hand, offers an alternative between metal-mediated small molecule catalysis and enzymatic catalysis.

Organocatalysts usually do not use metals, are not poisonous and in several cases show selectivities that are close to enzymes.

Although the first organocatalytic reactions were published as early as the mid 1970s,[112] modern organocatalysis took off in the late 1990s, with the work by List and Barbas.[113] Soon after, noticeable contributions were made by others, most noticeably by Jorgensen[114] and MacMillan,[115] who expanded the range of compounds that could be used as organocatalysts and the range of reactions that could be facilitated by organocatalysis. This led to a very rapid development in the early 2000s that has been called the "gold rush" in organic chemistry.[116] However, by the end of the 2000s the "gold rush" was, according to other authors, over[117] and many of the organocatalytic activation modes and mechanisms had been established. Since then, the focus of organocatalytic research has been shifting towards combining different activation modes into cascade reactions[118,119,120] and applying organocatalysis for the synthesis of complex products.[118,121]

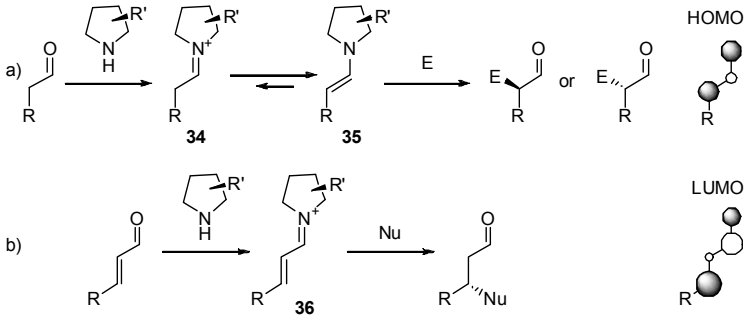
The different activation modes that have been developed for organocatalytic transformations include primary amine catalysis,[122] bifunctional thiourea catalysis[123,124] and N-heterocyclic carbene catalysis.[125] More recently, newer concepts, such as catalysis by chiral counterions[126,127] and radical amino-catalyses,[128] have emerged. However, the most widely used activation mode in modern organocatalysis is secondary amine aminocatalysis, which utilizes chiral secondary amines as the catalytically active species (Scheme 15). The latter can be, according to the precise activation mechanism, divided into either HOMO-raising or LUMO-lowering organocatalysis (Scheme 16).[129]



R = Silyl protecting group; R' = Branched alkyl; R'' = H or Me

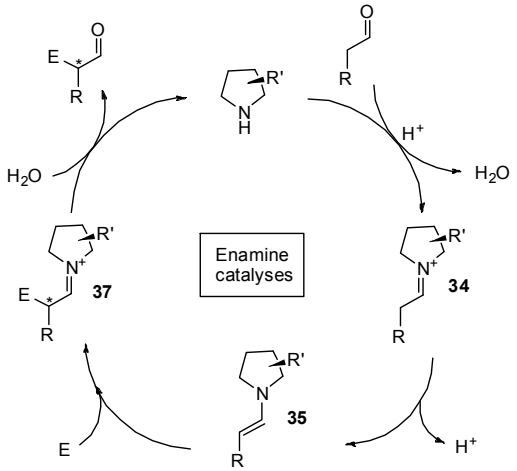
Scheme 15. Common chiral secondary amines employed in aminocatalyses

In the case of HOMO-raising enamine catalysis (Scheme 16, a), the reaction initially starts with the condensation of an aldehyde with an amine to form an iminium ion **34**. Unlike in the case of keto-enol equilibrium, the equilibrium with the iminium ion is shifted towards the more stable enamine **35**, which acts as a nucleophile. The nonbonding lone electron pair on the enamine nitrogen raises the HOMO even further, making the enamine highly nucleophilic in the α-position, readily attacking available electrophiles.



Scheme 16. HOMO-raising enamine catalysis (a) and LUMO-lowering iminium catalysis (b)

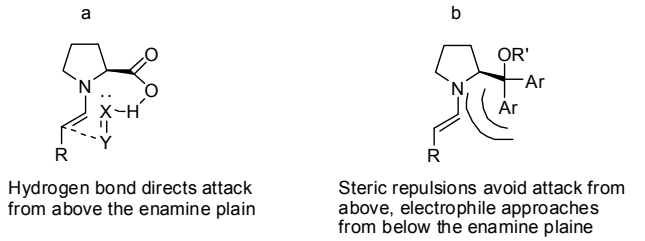
As can be seen in Scheme 17, the catalytic cycle is acid catalytic throughout the first steps, leading to enamine **35**. In the case of proline **31**, the catalyst itself provides the active acidic proton but, in the case of substituted prolinol ethers **32**, the reaction benefits from a protic additive in the reaction environment. Finally, the nucleophilic enamine species **35** reacts with an electrophile and forms an iminium ion **37** that hydrolyzes and releases the α-functionalized carbonyl compound and the catalyst, ready to enter a new catalytic cycle.



Scheme 17. General catalytic cycle of enamine-catalyzed reactions

Stereocontrol can be achieved in two different ways. The enamine **35** depicted in Scheme 17 is always in E configuration, as in Z configuration the R group would be, due to steric repulsions with the catalyst, energetically disfavored. Still, the electrophile can approach the E-enamine from either side. When the reaction is catalyzed by proline **31** or its modifications, the face selection is directed by hydrogen bonding with the carboxylic acid moiety (Scheme 18, a).[130] The hydrogen bonding both activates the electrophile for the reaction with the enamine and directs the electrophile to approach from the "upper side" of the enamine, where it is able to stabilize the transition state. This mode of

electrophile activation and stereocontrol can be applied to a wide range of different electrophiles that have a basic lone pair of electrons interacting with the acid proton. For instance, in the structure described in Scheme 18 a, the electrophilic substrate Y=X (i.e. a carbonyl unit C=O) has the lone pair centered on the heteroatom X.



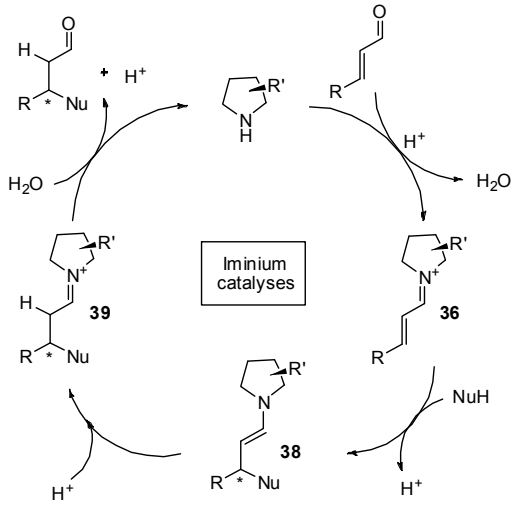
Scheme 18. Hydrogen bonding (a) and sterically directing (b) stereocontrol over enamine-catalyzed reactions.

The other form of face stereocontrol applies to the bulky prolinol derivatives **32** and oxazolidinone derivatives **33** catalyzed reactions (see Scheme 15), which lead to opposite stereogenic control when compared to proline. In this case, the sterically demanding groups of the catalyst shield the "upper side" of the enamine, allowing the electrophile to preferably approach from the "lower" side of the enamine plane (Scheme 18, b).[131] Due to this difference, the two catalyst types lead to different enantiomers, although the catalysts themselves may be of the same absolute configuration.

Utilizing these mechanisms, the enamine catalyses have been used to introduce a variety of different electrophiles to the α-position of carbonyl compounds, with the most well-known example being the enantioselective aldol reaction[113] that may occur both intra- and intermolecularly. The same principles also apply to Mannich reactions.[132] Non-carbon electrophiles can be used, for instance, in α-amination,[133] α-fluorination[134] and chlorination[135] reactions. It is important to note that not only addition but also enantioselective nucleophilic substitution reactions can be catalyzed by secondary amines.[136]

In the LUMO-lowering amine catalysis (Scheme 16, b), the reaction starts with the condensation of an amine and an α,β-unsaturated carbonyl group. But here the iminium ion **36** renders the intermediate more electrophilic in the β-position, so that it will react with an available nucleophile to produce β-substituted carbonyl compounds. Although the mechanism of catalysis is similar to the enamine catalyses described above, there are some important differences. The catalytic cycle (Scheme 19) also starts with the initial condensation, the rate of which is enhanced by the presence of either water or acidic additives that assist the proton transfer from the amine to the forming water molecule. Unlike the enamine catalyses, this reaction step is not followed by tautomerization. Instead, β-addition of a nucleophile occurs, producing a β-substituted enamine **38**, which is in equilibrium with its iminium derivative **39**. The rate of this transformation

is enhanced by proton donor additives. In the final step of the catalytic cycle, the iminium species **39** is hydrolyzed, releasing the β-substituted carbonyl compound and the secondary amine, ready to enter a new catalytic cycle.



Scheme 19. General catalytic cycle for iminium-catalyzed reactions.

The iminium-catalyzed reactions where imidazolidinone catalysts **33** are used include Diels-Alder reactions, which were first reported by MacMillan.[115] Following this discovery, the scope of the catalyses mode was expanded to diarylprolinol ether catalysts **32** and used in [3+2] cycloadditions,[137] Friedel-Crafts alkylations,[138] conjugate additions and hydrogenations of α,β-unsaturated carbonyl compounds.[116] The list of different nucleophiles that have been employed includes C, N, O and S nucleophiles.[139]

Stereocontrol in the iminium catalyses is mainly directed by steric factors.[140] The structures of the reactive iminium intermediates derived from prolinol catalysts (Figure 2) have been identified[141] and shown to usually adopt a configuration where the (silyl) protecting group is closest to the double bonds and thus makes the largest contribution to stereocontrol. Bulky aryl groups (i.e. with *meta*-trifluoromethyl substituents) can additionally contribute to the sterically driven stereoinduction. As in enamine catalyses, these effects both ensure that the iminium ion is in E configuration, which is the most energetically favored state, and that the nucleophile approaches the iminium intermediate preferably from the "lower side" of the alkene-iminium plane.

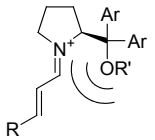
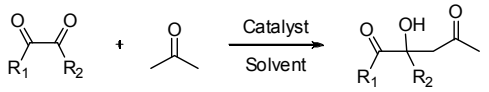


Figure 2. Stereocontrol in iminium-catalyzed β-functionalization of α,β-unsaturated aldehydes

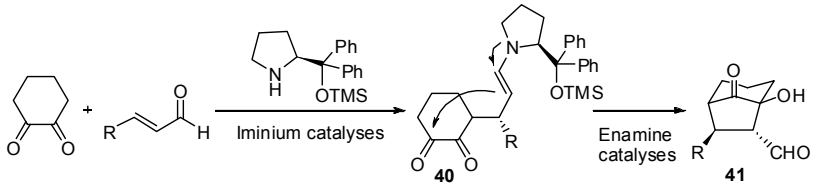
1.3.2 α-Diketones in Organocatalytic Reactions

Despite the considerable and rapid developments in organocatalytic chemistry over the last 10 years, the organocatalytic functionalization of α-diketones has received surprisingly little attention. Most of the few examples available in the literature concentrate on using α-diketones as electrophilic counterparts in organocatalytic reactions. For instance, *vic*-diketones have been used as electrophiles in N-heterocyclic carbene-catalyzed reactions with α,β-unsaturated aldehydes,[142] in thiourea-catalyzed reactions with α-isothiocyanato imides[143] and in proline derivative-catalyzed cross-aldol reactions with ketones (Scheme 20).[144]



Scheme 20. Cross-aldol reaction of 1,2-diketone and acetone

Still, there are some examples available in which α-diketones have been used as nucleophiles in organocatalytic chemistry. Most of these examples utilize bifunctional thiourea catalysis,[145,146,147] in which the diketone acts as a nucleophile in a Michael reaction with an α,β-unsaturated nitro compound[145,146] or benzylidene-malononitriles.[147] Such α-diketones have also proved to be good nucleophiles in secondary amine-catalyzed iminium catalytic Michael reactions with α,β-unsaturated aldehydes.[106] However, in all cases the first Michael adduct *in situ* proceeds to a conjugated secondary reaction, producing bicyclic compounds. In the case of iminium catalysis (Scheme 21), the Michael adduct **40** is an enamine that gives an intramolecular aldol reaction with one of the carbonyl groups in the diketone to give a bicyclic product **41**. Such secondary amine-catalyzed enamine aldol reactions have also been observed in an intermolecular manner.[144]

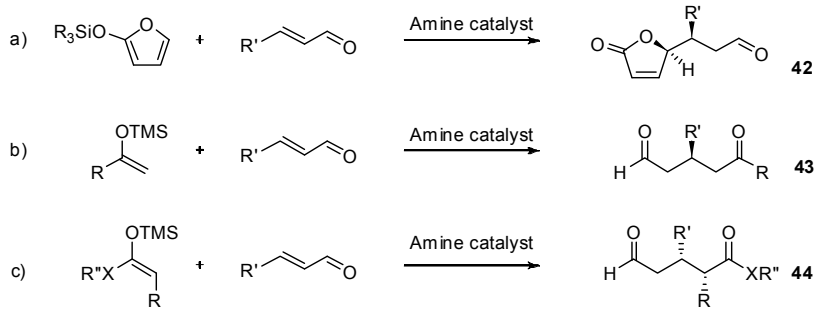


Scheme 21. Secondary amine catalytic iminium-enamine tandem catalyses

1.3.3 Organocatalytic Mukaiyama-Michael Reactions

Mukaiyama-type reactions have long been a useful means of transformation of organic molecules, especially when used in aldol reactions. In Mukaiyama-Michael reactions the α,β-unsaturated carbonyl compounds usually tend to give 1,2-addition products instead of Michael adducts. In 2003 MacMillan reported

the first known organocatalytic Mukaiyama-Michael addition reaction where iminium catalysis was used to overcome the 1,2-regioselectivity problem.[148] In that report, unsaturated aldehydes were combined with silyloxy furans to obtain γ-butenolides **42** (Scheme 22, a), which were used in the synthesis of spiculisporic acid, a natural product. The synthetic utility of this transformation was further demonstrated by others in the synthesis of (+)-compactin.[149]



Scheme 22. a) Mukaiyama-Michael reaction of silyloxyfurans; b) Mukaiyama-Michael reaction of silyl enol ethers; c) Mukaiyama-Michael reaction of silyl ketene acetals; X = heteroatom

Soon an iminium catalytic Mukaiyama-Michael reaction between silyl enol ethers and α,β-unsaturated aldehydes was developed,[150] making it possible to prepare enantiomerically enriched 1,5-dicarbonyl compounds **43** (Scheme 22, b). A few years later, MacMillan extended the scope of the reaction to the use of various silyl ketene acetals as nuclephilic counterparts,[151] further broadening the range of compounds accessible *via* the organocatalytic Mukaiyama-Michael reaction (Scheme 22, c). Thus, it is quite surprising that these reports have not received sufficient attention. The scope of organocatalytic Mukaiyama-Michael reactions has been slowly extended, but these reports remain sparse. Thus, a novel iminium catalytic Mukaiyama-Michael reaction by using cyclopentane-1,2-dione bis-silyldienolates would be of scientific value.

2 Aims of the Present Work

Cyclopentane-1,2-diones are promising starting compounds for different organic transformations. Up to now, the synthetic potential of these compounds has not received sufficient attention. Based on the literature data and the conclusions and considerations drawn on their basis, the main aims of the present thesis are the following:

- One hindrance that may hold cyclopentane-1,2-diones back from wider use is the lack of good methods for their preparation. Therefore, we aimed to develop a new method for the preparation of cyclopentane-1,2-diones from *vic*-diols using heterogeneous platinum metal-catalytic aerobic oxidation.

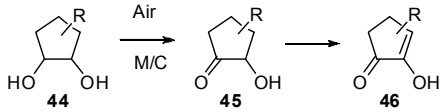
- The asymmetric oxidation of 3-alkylcyclopentane-1,2-diones is a valuable tool in the preparation of chiral γ-lactone acids. The absence of a rational mechanism for this reaction hinders further development and the use of the method in practical applications. The elucidation of the reaction mechanism of the asymmetric oxidation of 3-alkylcyclopentane-1,2-diones was one of the aims of the thesis.

- 1,2-Diketones may act as strong nucleophiles in the form of bis-dienolates. Elucidation of the possiblilities of organocatalytic reactions of these enolates was one of the aims of the work. The first example selected for such investigation was a Mukaiyama-Michael reaction.

3 Results and Discussion

3.1 Platinum-Catalyzed Aerobic Oxidation of Cyclopentane-1,2-diols

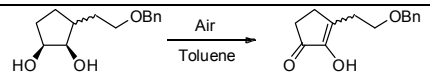
As discussed in chapter 1.1, the oxidation of *vic*-diols may lead to noticeable C-C bond cleavage between oxygen-bearing carbons and there are only a few known oxidation methods for the preparation of cyclic 1,2-diones available. There are no earlier examples of the metal-catalytic aerobic oxidation of cyclopentane-1,2-diols **44** to 1,2-diketones **46** (Scheme 23). Preliminary scanning of activated carbon-supported catalysts showed that the oxidative dehydrogenation of cyclopentane-1,2-diols can be achieved over a heterogeneous platinum catalyst (Table 1). Activated carbon-supported platinum catalysts were used, as they are relatively cheap, durable and easily manipulated.



Scheme 23. Metal-catalytic aerobic oxidation of cyclopentane-1,2-diols

All of the used catalysts contained noticeable amounts of intrinsic water, usually around 50% by weight. It is known that water can have a noticeable influence on aerobic metal-catalytic oxidations. To determine the effect of water, a dried Pt/C catalyst was used for the oxidation in dry toluene and proved to be inactive. Thus, we concluded that water was essential for the dehydrogenation reaction. It has been proposed that water can act as a weak base and help to subtract the OH proton,[152] driving the formation of the alcoholate species in the catalytic cycle (Scheme 5).

Table 1. Activity of different activated carbon supported catalysts



Catalyst	Rh/C	Pd/C	Pt/C	Pd,Pt,Bi/C	Dry Pt/C	Pd/Al	$Pd(OH)_2/Al$
Catalyst activity	Not active	Low activity	Active	Very low activity	Not active	Not active	Not active

Reactions were followed by TLC and activity was evaluated by comparing conversion at equal reaction times.

The initial reaction conditions developed for the oxidation of **44** to **46** over a commercial Pt/C[153] catalyst involved 5 mol% of the metal catalyst (metal basis) in toluene. For the reasons discussed in chapter 1.1.1, the reaction was sensitive to the amount of air available. For experimental simplicity, a method was developed that involved a batch-wise addition of air, i.e. the air atmosphere in a closed reactor was changed in 4 h intervals. Applying fresh air more frequently

increased the formation of undetermined degradation products (presumably ring cleavage products formed by over-oxidizing the diketone). Less frequent ventilation slowed the reaction down and eventually led to earlier catalyst deactivation.

Although these preliminary reaction conditions were suitable for the oxidation of diols **44** with different R groups, quantitative conversion was not achieved and some starting material was always recovered. In all cases a certain amount of intermediate hydroxyketone **45** was detected in the reaction mixture, suggesting that the two hydroxyl groups were oxidized successively.

Although a mixture of a flammable solvent, air and Pt/C catalyst is relatively safe to use in small laboratory scale reactions, it can be seen as a potential safety hazard in bench- and industrial scale preparations. Having established that water is essential for the oxidation to occur, oxidation of water-soluble diols (R = H, Me; see Scheme 23) was performed in water with good results. The developed 4-hourly ventilating procedure reflects the challenges in the method development of heterogeneous oxidations.

3.1.1 Alkali Additives

It is known that inorganic bases can considerably enhance product yields in platinum metal-catalytic aerobic oxidations,[152] presumably by providing an additional driving force for the alcoholate formation. We found that the addition of lithium hydroxide to the oxidation medium rendered the catalyst system less sensitive to the amount of air. It was possible to run the oxidation of diols **44** in a reactor equipped with an open vertical condenser. Good yields were obtained in shorter reaction times, both in toluene and in a 1:1 mixture of acetonitrile and water. The latter was found to be a tunable reaction medium suitable for a wide variety of substrates with different solubilities, and provided better yields than toluene. The optimal amount of alkali was found to be 1 equivalent towards the substrate.

The possibility of recycling the catalyst was evaluated under the developed conditions and it was found that the catalyst could be regenerated by filtration and reused at least once, with only a small reduction in yield. Changing LiOH to CsOH produced a small decrease in product yield, accompanied by a complete loss of recovered starting material. It is possible that CsOH renders the reaction faster but the oxidation product is not stable in the presence of CsOH. Changes in the reaction temperature did not improve the yield: below 60°C the reaction was significantly slower and above 70°C the product started to decompose, suggesting that the optimal temperature was around 60 °C.

3.1.2 Method for the Aerobic Oxidation of Cyclopentane-1,2-diols to 1,2-Diketones

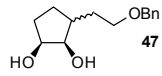
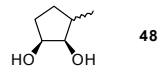
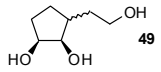
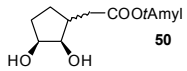
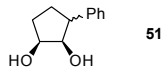
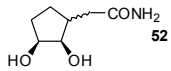
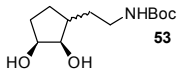
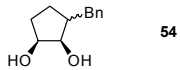
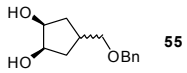
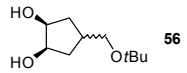
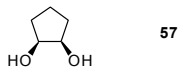
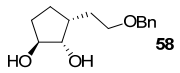
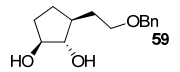
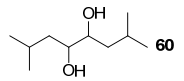
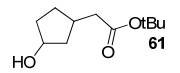
Based on the results and considerations presented above, it was possible to outline a practical method for the aerobic oxidation of cyclopentane-1,2-diols to 1,2-diones. A 1:1 mixture of MeCN and water was used as the reaction medium in the presence of 1 eq of LiOH and 5 mol% of Pt/C catalyst for the oxidation of 3-benzyloxyethylcyclopetane-1,2-diol **47** (Table 2, entry 1). The reaction was run in a reactor that was open to atmospheric air through a vertical condenser. In the presence of LiOH, no more intermediate **45** was observed among the reaction products, indicating that under the achieved conditions the transformation of **45** to **46** is faster than **44** to **45**.

It was found that different diols were suitable as substrates in these reaction conditions (Table 2, entries 3-8). A primary hydroxyl containing substrate **49** (Table 2, entry 4) provided a product with only the secondary hydroxyls selectively oxidized. It is possible that some of the primary alcohol was also oxidized to acid, but this product remained in water and thus was lost during workup.

The ester and amide group containing diols were not good substrates for the oxidation (Table 2, entries 5 and 7). From the ester containing diol **50**, only a low yield of diketone was obtained and the amide group bearing diol **52** provided no product at all. It is possible that the carbonyl groups in the side chains of these substrates coordinated strongly to the metal surface, blocking the desired reactivity of the catalyst. This may give rise to competing undesired reactions – we observed a complete decomposition of the starting material in both cases if the reaction time was extended.

In a further attempt to optimize the reaction conditions, the catalyst loading was lowered to 1 mol% (Table 2, entries 2 and 9). As a result, longer reaction times were required to complete the reaction and slightly lower yields were obtained. However, the five-fold reduction in the catalyst amount signified a rise in the catalyst turnover number from 14-15 to 63 and 72 (Table 2, entries 1-2 and 8-9 respectively), making lower catalyst loading economically feasible. The substrate scope of the reaction was reevaluated with 1 mol% of catalyst and certain trends were revealed. Whereas the position of the alkyl substituent in the diol is not crucial (compare **47** and **55**), the spatial arrangement of the hydroxyl groups is: *cis*-diol **47** is a better substrate than *trans*-diols **58** and **59**. It was also found that the method is not suitable for the oxidation of acyclic *vic*-diols (**60**) but is applicable for the conversion of cyclopentane mono-alcohols (**61)** to ketones. The latter observation is especially noteworthy since the similar diols with ester and amide groups (**50** and **52** respectively) had not provided good results in earlier experiments (Table 2, entries 5 and 7).

Table 2. Aerobic oxidation of diols **44**

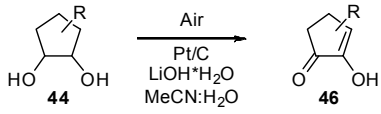
Entry	Diol **44**	Pt/C, mol%	Time, h	**46** yield, %
1	 **47**	5	4	70
2		1	5.5	63
3	 **48**	5	5	74
4	 **49**	5	5	49
5	 **50**	5	1.3	28
6	 **51**	5	3.5	69
7	 **52**	5	3	0
8	 **53**	5	4	76
9		1	4	72
10	 **54**	1	5	65
11	 **55**	1	5	63
12	 **56**	1	5	61
13	 **57**	1	4	19
14	 **58**	1	4	38
15	 **59**	1	4	36
16	 **60**	1	4	0
17	 **61**	1	3.5	28 (+33*)

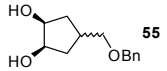
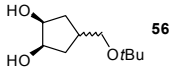
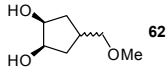
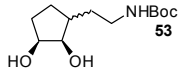
All experiments run in 1:1 MeCN-H_2O at 60 °C in an open glass reactor equipped with a condenser; 1 eq of $LiOH \cdot H_2O$. *Oxidation product with the ester hydrolyzed

3.1.3 Gram-Scale Oxidation

When the reaction was scaled from a 100 mg scale to a gram scale, only 34% of the diketone product was obtained, with most of the starting material left unreacted. Most probably the rate of the unassisted mass transfer of air oxygen through the condenser was not enough, leading to catalyst deactivation (Table 3, entry 1). Thus, additional air was provided by saturating a 0.3 ml/min flow of air with fresh solvent in a different vessel and then bubbling it through the reactor, giving the diketone in 64% yield. Most of the unreacted starting material could be recovered and used in the next batch. A selection of different diketones was prepared in good yields under these conditions. Although quantitative turnover was not achieved, the overall loss in material was small.

Table 3. Gram scale oxidation of diols **44**



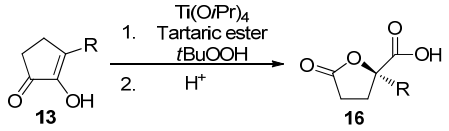
Entry	Substrate **44**	Time, h	**46** yield, %	Regen. **44**, %
1*	 **55**	5	34	62
2		6	64	28
3	 **56**	6	51	46
4	 **62**	6	56	40
5	 **53**	4	66	26

All experiments run in 1:1 MeCN-H_2O at 60 °C with 1 mol% Pt/C catalyst under an open vertical condenser; 1 eq of LiOH·H_2O. A 0.3 ml/min flow of atmospheric air saturated with solvent mixture was maintained through the reactor during the reaction. *Without air flow

In summary, a practical method for the catalytic aerobic oxidation for cyclopentane-1,2-diols to cyclopentane-1,2-diones was developed. The reaction proceeded under relatively mild conditions (60 °C in MeCN/H_2O) in the presence of 1 mol% of a heterogeneous Pt/C catalyst and 1 eq of LiOH. The method tolerated a wide choice of solvent systems, ranging from organic solvents to aqueous mixtures to water. Under the described reaction conditions, the secondary hydroxyl groups were preferably oxidized and various functional groups, including primary hydroxyl, tolerated the reaction conditions. The reaction method could also be scaled up for preparative use.

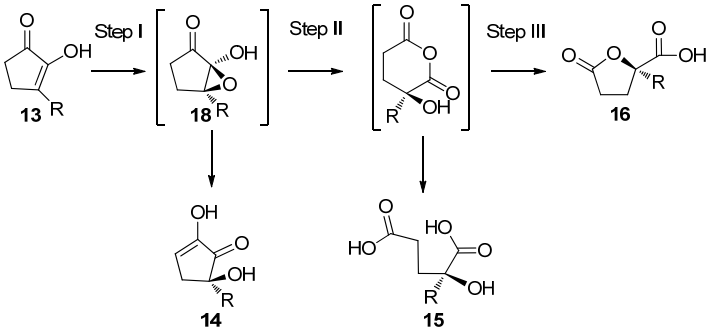
3.2 Mechanism of the Asymmetric Oxidation of 3-Alkylcyclopentane-1,2-diones

The reaction mechanism of the asymmetric oxidation reaction that has been used for the generation of chirality in the preparation of chiral tetrahydrofuran derivatives,[154] homocitric acid[38] and nucleoside analogues[96] is not fully understood. The formal reaction scheme of the domino reaction sequence (Scheme 24) does not reveal all the steps, the intermediates involved or the mechanisms of their interconversion.



Scheme 24. Asymmetric oxidation of 3-alkylcyclopentane-1,2-diones to 2-alkyl-γ-lactone acids

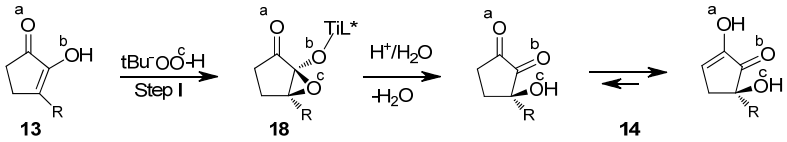
The whole oxidation process can be divided into three formal steps (Scheme 25). In step I the enolic double bond is epoxidized. The epoxide product **18** may rearrange, affording the α-hydroxylated diketone **14**, which has been previously isolated and characterized.[29] In step II, the intermediate epoxide **18** is further oxidized. This step results in C-C bond cleavage, producing an anhydride intermediate. After quenching the reaction mixture by alkaline hydrolysis and acid treatment, diacid **15** is isolated.[37] Finally, in formal step III, the anhydride is acylated (or diacid **15** is cyclisized) to a lactone **16**. The stereogenic center in the lactone acid is created in step I of the reaction sequence and the asymmetry is preserved throughout the following transformations.



Scheme 25. The formal steps in the reaction sequence

The first isolable compound is the 3-hydroxylated product **14**. In analogy to the epoxidation of allylic alcohols, it is reasonable to assume that this compound arises from the cleavage of the epoxide from the epoxidation of the enolic double bond of the compound **13**. However, it has been demonstrated earlier that compound **14** itself cannot be further oxidized into compounds **15** or **16**.[95] **14**

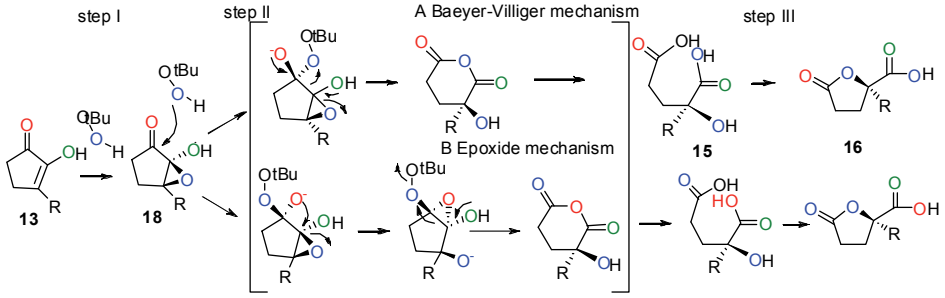
appears upon quenching the reaction mixture that contains the epoxide species **18** (Scheme 26). Thus epoxide **18** must be the substrate for the second oxidation in Step II.



Scheme 26. Step I – the asymmetric epoxidation and hydrolytic cleavage of epoxide

Attempts were made to detect the epoxide species in the reaction mixture under conditions that were optimized for the preparation of **15** and **16**.[95] However no distinctive signals that could be assigned to the epoxide were detected by NMR when the reaction was run in an NMR tube. This suggests that Step I is the rate-limiting step in the reaction sequence and the formed epoxide is quickly consumed by the following Step II. All reaction intermediates exist as a mixture of different titanium complexes, so the NMR spectra does not have characteristic chemical shift bands and is very difficult to interpret.

Based on these considerations and earlier mechanistic insights presented in chapter 1.2, we may propose two possible reaction pathways, as presented in Scheme 27. Both share common intermediates and can only be distinguished by following the paths of individual oxygen atoms throughout the reaction cascade.



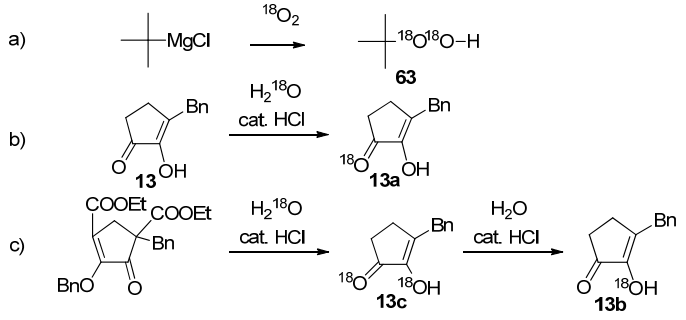
Scheme 27. Proposed mechanisms for the Ti(O*i*Pr)$_4$-*t*BuOOH oxidative cleavage of cyclopentane-1,2-diones

3.2.1. Determination of Labeled Oxygen Atom Pathways

In previous attempts to clarify the mechanism of the oxidation of diketones, isotope-labeled oxygen atoms that are involved in the process have been followed either by mass spectroscopy[35,155] or by NMR.[36] ^{13}C NMR can be used to track ^{18}O atoms in organic molecules because the change of ^{16}O atom to ^{18}O causes a small upfield chemical shift of the carbon attached to the oxygen.[156]

The magnitude of the shift is specific to the functional group.[157,158] Partial ^{18}O saturation on a given oxygen causes the ^{13}C NMR signal to split, and the chemical shift difference between the splitting peaks is specific to the nature of the C-O bond. ^{18}O saturation can be measured by the relative peak heights of different oxygen isotope-bound ^{13}C peaks. As the isotope does not noticeably alter the relaxation time (and hence the peak shape) of the carbon nucleus, the peak heights are as good quantitative measures of the oxygen isotope content as are peak areas.[159]

The labels were introduced into the reactant (*t*BuOOH) and into two different positions in the substrate. The ^{18}O-labeled oxidant *tert*-butyl hydroperoxide **63** was prepared from *tert*-butyl Grignard reagent and $^{18}O_2$ gas according to a known procedure (Scheme 28, a).[160] Differently labeled 3-benzylcyclopentane diones with ^{18}O labels at C1 (compound **13a**) and at C2 (compound **13b**) were prepared separately by means of different synthetic routes. Labeled diketone **13a** was prepared from 3-benzylcyclopetane-1,2-dione by an acid catalytic isotope exchange reaction[161] that could be monitored by NMR (Figure 3). Labeled diketone **13b** was prepared in two steps from a known intermediate of the synthesis of 2-alkylcyclopentane-1,2-diones.[96]



Scheme 28. Preparation of ^{18}O labeled reagents

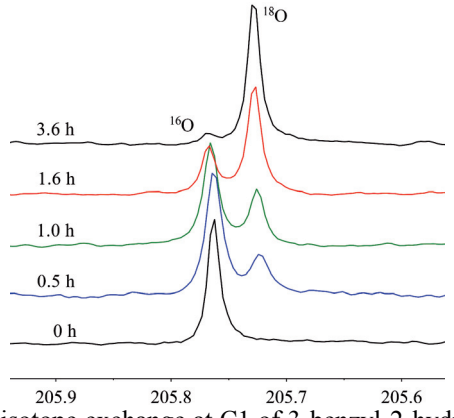


Figure 3. Oxygen isotope exchange at C1 of 3-benzyl-2-hydroxycyclopent-2-ene-1-one **13**, monitored by NMR

3.2.2 Oxidation with Labeled Oxidant

3-Benzyl diketone **13** was subjected to oxidation with the labeled oxidant, and the product from Step II – diacid **15** – was isolated. A ^{13}C NMR analysis of the product revealed distinctive isotope splitting on the carboxylic acid carbons of **15**, both corresponding to roughly 50% ^{18}O saturation (Figure 4, a). According to a mass spectroscopy analysis, the diacid contained two ^{18}O labels, which can be explained by the origin of the labels. One of the labels originated from Step I and was carried on to the C2-OH (Scheme 29) position without dilution of the saturation. Because the saturation was close to 100%, the peak corresponding to the unlabeled hydroxyl was not visible in ^{13}C NMR. The second labeled oxidant was introduced in Step II and was, after the hydrolysis of the anhydride intermediate, found in both of the acid groups in equal probabilities, hence the approximately 50% saturation on both. This situation distinctively corresponds to the Baeyer-Villiger mechanism depicted in Scheme 29. If the reaction proceeded according to the epoxide approach, none of the labeled oxygens should have been found in the C1 acid.

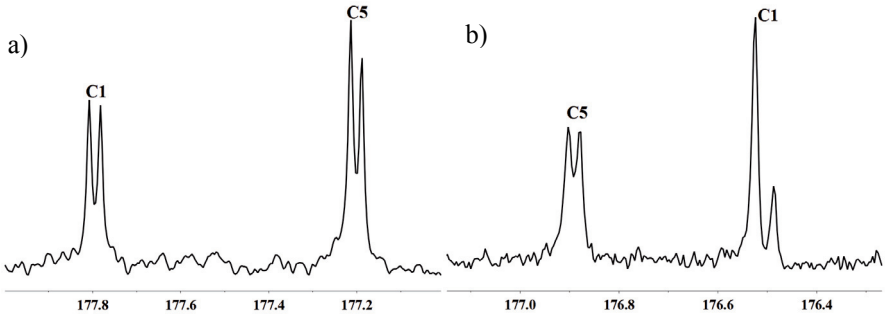
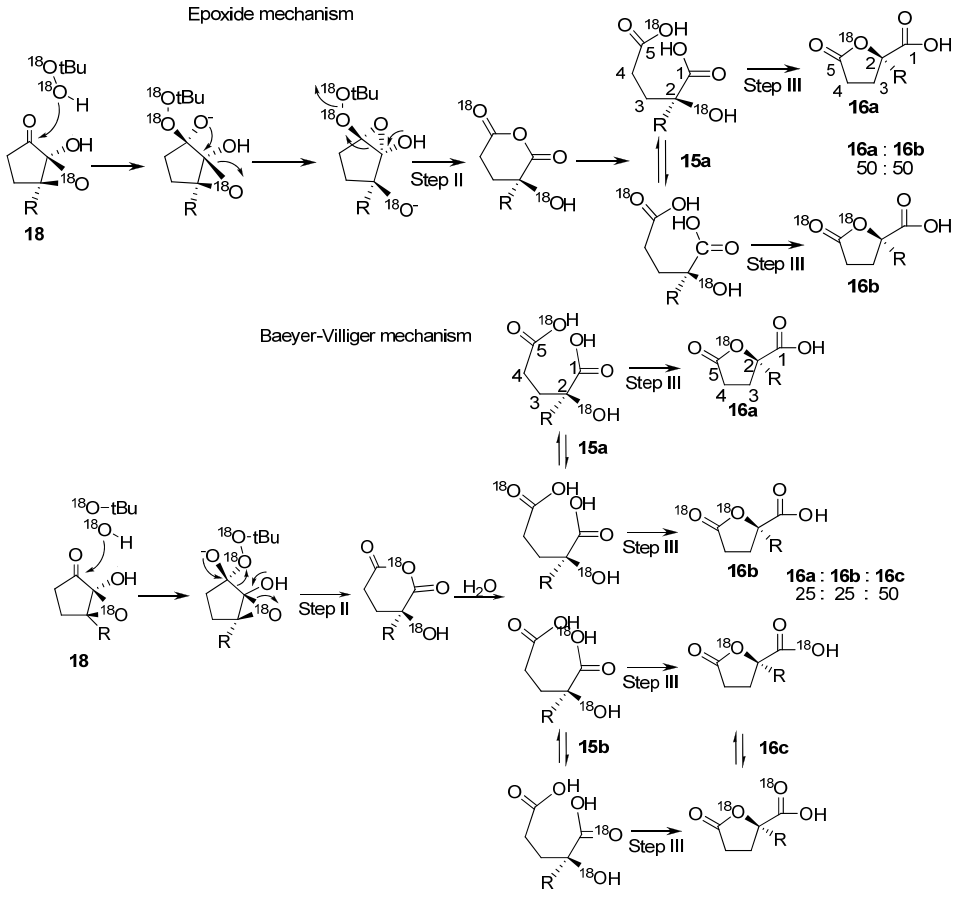


Figure 4. ^{18}O saturation on C1 and C5 of diacid **15** (a) and lactone acid **16** (b) as observed by ^{13}C NMR in labeled compounds derived from labeled oxidant

When the diacid auto-catalytically cyclized to lactone acid **16**, 24% ^{18}O saturation was observed on the C1 acid and close to 50% saturation was retained in the C5 carboxyl group (Figure 4, b). A mass spectroscopy analysis of the product revealed 26% of the compound to contain one label and 73% two labels. This suggests that the Step I epoxide oxygen that had been incorporated into the lactone had retained its isotope saturation. Again these observations support the Baeyer-Villiger mechanism. The epoxide mechanism would not give any labeling on C1 and should produce a 1:1 mixture of mono and dilabeled **16**.



Scheme 29. Proposed reaction mechanisms followed by labeled oxidant

3.2.3 Oxidation of Labeled Diketones

In order to confirm the findings from the experiment with labeled oxidant and to clarify the path of the two oxygen atoms from substrate **13** to the product, differently labeled diketones **13a** and **13b** were separately submitted to oxidation with an unlabeled oxidant. When labeled diketone **13a** was subjected to the oxidation reaction with *t*BuOOH, the isolated diacid showed ^{18}O saturation only at C5 of the molecule when analyzed by NMR (Scheme 30; Figure 5, a). A mass spectroscopy analysis suggested that the compound had only one label, as expected. These observations again support the Baeyer-Villiger mechanism. According to the epoxide mechanism, the label should be equally distributed between C1 and C5. After cyclization to the lactone, a two-fold reduction in the isotope saturation on C5 was observed by NMR and mass spectroscopy (Figure 5, b). This is explained by the lactonization mechanism, where one of the carboxyl oxygens is eliminated from C5.

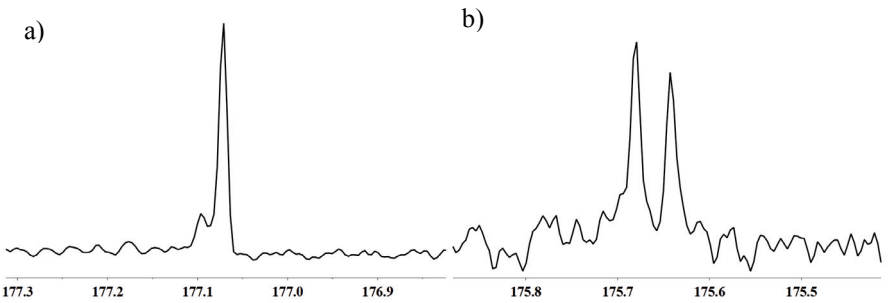
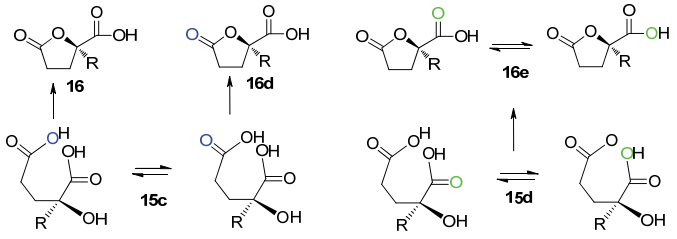


Figure 5. ^{18}O saturation on C5 of diacid **15** (a) and lactone acid **16** (b) as observed by ^{13}C NMR in labeled compounds derived from **13a**

Using the labeled diketone **13b** as the asymmetric oxidation substrate provided diacid **15d** with good ^{18}O saturation at C1 (Scheme 30). When this compound was cyclized, compound **16e** with a label in C1 carboxylic moiety was observed with only a marginal loss in isotope saturation. A mass spectroscopy analysis of both compounds supported these findings. The experiments with labeled diketone **13b** did not reveal additional information about the reaction mechanism. The results corresponded exactly to the expected outcome and there was no conflict with findings from the earlier experiments with other labeled starting materials.



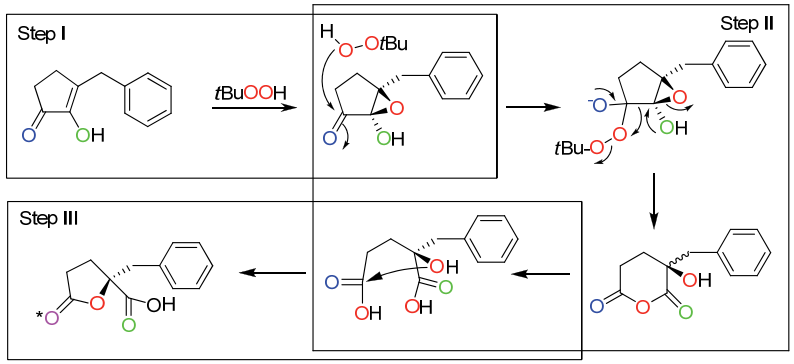
Scheme 30. Oxidation of ^{18}O labeled diketones

3.2.4 Conclusions About the Mechanism

Based on the findings above, we can confirm the "Baeyer-Villiger mechanism" as depicted in Scheme 31. The first step of the oxidative reaction cascade for 3-alkylcyclopentane-1,2-dione **13** – asymmetric epoxidation – is a key step in the whole process that stereoselectively generates a chiral center and also appears to be the reaction rate limiting step. The oxidation was very similar to the asymmetric oxidation of allylic alcohols developed by Sharpless *et al*[88] and the formed stereogenic center retained its configuration throughout the rest of the reaction cascade. The reaction continued with the Baeyer-Villiger oxidation of the formed epoxide **18**, with a second equivalent of *t*-butyl hydroperoxide. At this point, the process was quenched by aqueous alkali hydrolysis. As a result,

the diacid was formed and isolated. In the third step, the diacid was cyclized to γ-lactone acid.

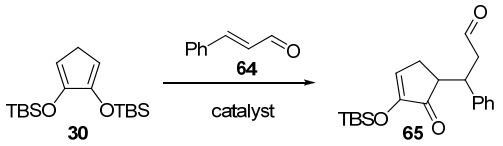
It has to be remembered that throughout Step I and Step II the reagents are coordinated to a titanium complex. The chirality is generated in the rate-limiting Step I and the chiral intermediate proceeds to Step II instantly. At this point the titanium complexes are hydrolyzed, producing the diacid which can be isolated. Finally, in Step III, the diacid is acid-catalytically cyclized, forming the chiral γ-lactone acid product in excellent yield and stereoselectivity. The ^{18}O labeled experiments unambiguously demonstrate that the second oxidation, the cleavage of the cyclopentane ring, proceeds by the Baeyer-Villiger type mechanism.



Scheme 31. Reaction mechanism. * Note that the magenta colored carbonyl oxygen in the lactone can have ^{18}O labels both from the substrate diketone and from the *t*BuOOH oxidant

3.3 Organocatalytic Mukaiyama-Michael Reaction of Cyclopentane-1,2-dione bis-Silyldienolate with α,β-Unsaturated Aldehyde – Access to Enantioenriched 3-Alkylcyclopentane-1,2-diones

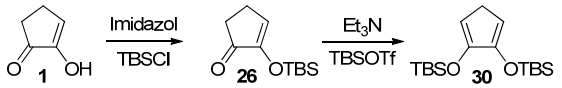
An organocatalytic Mukaiyama-Michael reaction of bis-silyldienolate **30** with an α,β-unsaturated aldehyde **64** was examined (Scheme 32). Bis-silyldienolate **30** was used as the nucleohilic counterpart because, as discussed in chapter 1.3, cyclic vicinal dicarbonyls decrease each other's nucleophilicity and thus additional activation was needed to complement organocatalysis.



Scheme 32. Organocatalytic Mukaiyama-Michael reaction.

3.3.1 Preparation of the Nucleophilic Dienolate

The bis-silyl dienolate **30** is a known compound that had previously been prepared in a single step[162] or in two steps.[111] Although both of these protocols did indeed work, they utilize highly hygroscopic lithium salts, which makes them cumbersome to use. Better results were obtained by preparing **26** in conditions analogous to the earlier example[111] and subsequently converting it to **30** in a reaction with Et_3N and TBSOTf (Scheme 33), inspired by an example by Reetz.[110]

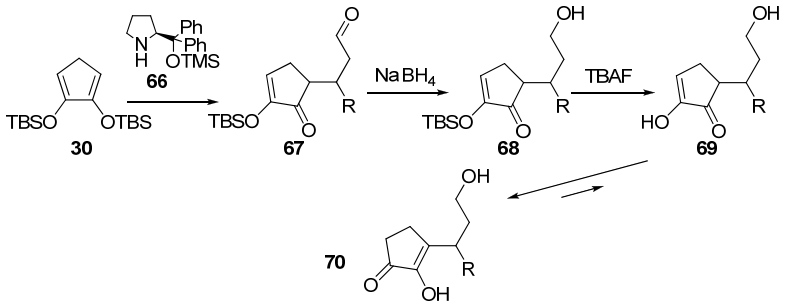


Scheme 33. Preparation of 2,3-bis-(*t*-butyldimethylsilyloxy)-cyclopenta-1,3-diene

3.3.2 Preliminary Experiments

First the mono silyl enolate **26** was subjected to a Mukaiyama-Michael reaction with *trans*-cinnamaldehyde **64** using a protected prolinol catalyst, but the reaction was found to be extremely slow. Dienolate **30**, on the other hand, proved to be a good nucleophile. In the presence of 20 mol% of catalyst **66**, all of cinnamaldehyde reacted in 6 h (Scheme 34). Being concerned about the hydrolytic stability of **30**, the initial experiments were run in dry conditions in the presence of molecular sieves. Also, acid co-catalysts were avoided because such additives may contribute to the decomposition of silyl enolates in organocatalytic Mukaiyama type reactions.[150]

The product **67** formed as a 1:2 mixture of diastereomers, but was too unstable to be reproducibly isolated. In order to prepare α-substituted cyclopentane-1,2-diones and to obtain stable results, aldehyde **67** was reduced *in situ* to a relatively stable alcohol **68** by $NaBH_4$. Following an aqueous workup, the crude mixture was treated with TBAF to remove the remaining silyl group. Although, the product is initially formed in the enol form **69**, it quickly rearranges to a thermodynamically more stable enol **70**.[11]



Scheme 34. Organocatalytic Mukaiyama-Michael reaction.

Usually such organocatalytic reactions offer good enantioselectivities when run with an appropriate catalyst in suitable reaction conditions. Diastereoselectivity, however, depends much more on the reaction conditions and can be difficult to control, often leading to poor selectivity. In the present case, the diastereoselectivity during the transformation of **30** to **67** was low. Instead of separating the diastereomers, both were converted to a single product during the isomerization of **69** to **70**. Thus the stereoselectivity of the reaction sequence was only determined by the enatioselectivity of the process.

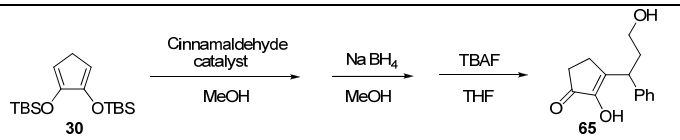
Utilizing this reaction methodology, the 3-substituted cyclopentane-1,2-dione **65** was obtained from a reaction with *trans*-cinnamaldehyde **64** in 24% yield with a respectable 88% ee in the presence of 5% of organocatalyst **66** (Table 4, entry 1). After 13 h of reaction time, all of the reactant **30** was consumed, leaving a substantial amount of aldehyde unreacted. Thus, the initial amount of **30** was increased until a total consumption of aldehyde was observed, with some **30** still present in the reaction mixture (Table 4, entry 3).

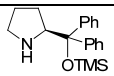
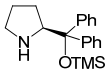
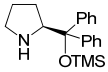
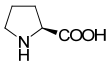
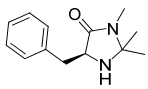
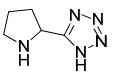
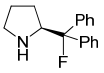
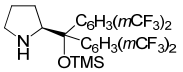
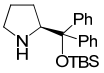
3.3.3 Catalyst Screening

While scanning different catalysts for the reaction, it was found that simple proline **31** was not active, with most of the aldehyde and some **30** left after 116 h, and no desired product observed (Table 4). Also catalyst **71** proved to be inactive. This is not a surprising result, for imidazolidinone catalysts are usually active in iminium catalysis only if combined with an acid co-catalyst.[163] The tetrazole catalyst **72** was more active than **66** but with poor selectivity, while the

fluorine containing prolinol derivative **73** was of low activity and selectivity. The sterically more demanding catalyst **74** proved to be of very low activity and also showed moderate selectivity after an extended reaction time. The hydrolytically more stable and bulkier **75** was slow to react but in the end provided both the highest yield and selectivity.

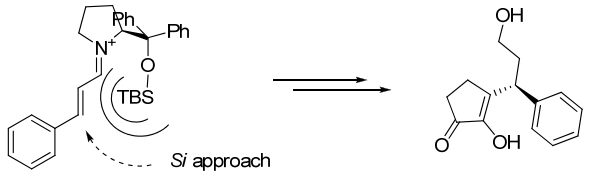
Table 4. Optimization of the two-pot three-step reaction sequence



Entry		Catalyst	**30** eq	Reaction time, h	**70** yield %	ee %
1	**66**		1,3	13	24	88
2	**66**		1,6	13	34	87
3	**66**		2	15	50	87
4	**31**		2	116	-	-
5	**71**		2	100	-	-
6	**72**		2	9	56	21
7	**73**		2	65	39	30
8	**74**		2	100	11	79
9	**75**		2	70	59	92

Reaction conditions - Step 1: 5 mol% of catalyst, 0.15 M solution of aldehyde, 100 mass% MS4Å; Step 2: 1 eq of $NaBH_4$ based on cinnamaldehyde; Step 3: 0,05 M solution in THF, 4 eq of TBAF based on cinnamaldehyde, 2 eq based on **30**.

The small differences in selectivity between catalysts **66** and **75** were expected, as in silyl protected diarylprolinol catalysts most of the facial selectivity is owed to the silyl protecting group that will be closest to the iminium ion and provide most of the facial shielding.[141] Thus the potentially H-donor and hydrogen bonding properties of **72** are not able to enhance enantioselectivity in Mukaiyama-Michael reactions. In a meta-substituted diarylprolinol catalyst **74**, the large aryls contribute to the shielding, which in this case significantly lowered the catalyst activity. Fluorine substituted catalyst **73** should provide a similar transition structure to **74**, but with less shielding.[164] Hence, the higher activity and lower selectivity of catalyst **73**. We can assume that the OTBS group of **75** provides the optimal conditions for the addition, shielding the *Re* face of the formed iminium intermediate and directing the silyl enolate nucleophile to attack from the *Si* face (Scheme 35).[165] The end product **65** should be produced in S configuration.



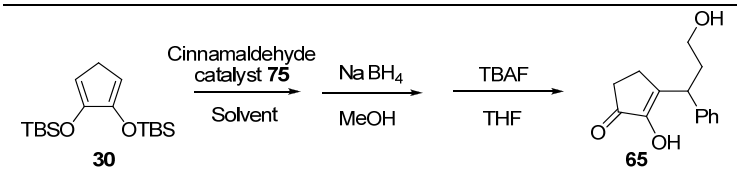
Scheme 35. Proposed stereoinduction in the addition reaction

3.3.4 Solvent Screening

In the presence of catalyst **75** the process was found to be noticeably faster if no precautions were taken to exclude water from the reaction environment (Table 5). Unfortunately the selectivity was slightly lower and the decomposition of **30** was noticeably faster with no excess dienolate left by the end of the reaction time. Using 10 mol% of the catalyst restored some of the yield and selectivity.

No reaction was observed when the addition was performed in chloroform, toluene and HPLC grade acetonitrile. Surprisingly, a reasonable yield, although with lower selectivity, was observed in reagent grade (i.e. not dry) acetonitrile. It is possible that the intrinsic moisture in the latter played a role in the reaction. Further solvent screening established alcohols as the optimal environment. The reaction was slower but provided the highest selectivity in isopropanol. 96% ethanol as a solvent gave the optimal combination of reactivity and selectivity. In ethanol, it was possible to reduce the catalyst loading back to 5 mol% with a minimal decrease in yield and selectivity.

Table 5. Solvent scan for catalyst **75**; reagent grade solvents used



Entry	Solvent	Catalyst loading	Reaction time	Yield	ee
1	MeOH	5	11	56	88
2	MeOH	10	14	60	90
3	PhMe	10	11	0	-
4	$CHCl_3$	10	15	0	-
5	MeCN*	10	23	0	-
6	MeCN	10	23	57	86
7	iPrOH	10	23	54	92
8	EtOH	10	9	56	93
9	EtOH	5	9	55	92

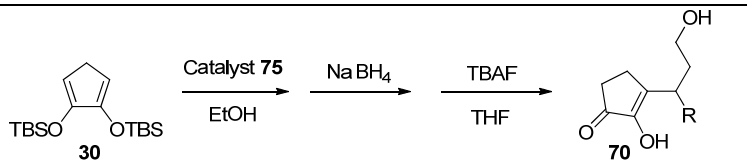
Reaction conditions - Step 1: 0.15 M solution of aldehyde, 2 eq of **30**; Step 2: 1 eq of $NaBH_4$ based on cinnamaldehyde; Step 3: 0.05 M solution in THF, 4 eq of TBAF based on cinnamaldehyde.
* Dry HPLC grade solvent

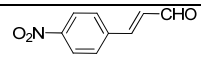
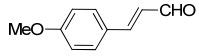
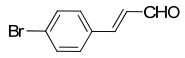
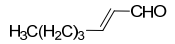
3.3.5 Reaction Scope

In addition to cinnamaldehyde **64**, other α,β-unsaturated aldehydes were subjected to the optimal reaction conditions (Table 6). Both the electron-poor *p*-nitrocinnamaldehyde and the electron-rich *p*-methoxycinnamaldehyde reacted well. While the results from the electron-poor counterpart were comparable to the results from cinnamaldehyde, the *p*-methoxy compound (Table 6, entry 2) provided a slightly lower yield. This result is not very surprising, as such electron-poor aldehydes are known to give slightly lower yields also in other organocatalytic reactions.[166] In an attempt to produce crystals that would be suitable for X-ray diffraction analysis, the *p*-bromocinnamaldehyde was subjected to the reaction with good results. Although the product was a solid at

room temperature, it failed to give workable single crystals. Also an α,β-unsaturated aldehyde with an aliphatic chain gave good results. Unfortunately, all of the products proved to be somewhat unstable in contact with silica gel, which made it difficult to obtain analytical samples in high purity.

Table 6. Synthetic scope of the Mukaiyama-Michael reaction



Entry	Aldehyde	Reaction time	Yield	ee
1		9	57	94
2		20	40	87
3		10	66	90
4		9	63	91

Reaction conditions. Step 1: 0.15 M solution of aldehyde in EtOH, 2 eq of **30**; Step 2: 1 eq of $NaBH_4$ based on aldehyde; Step 3: 0.05 M solution in THF, 4 eq of TBAF based on aldehyde.

Conclusions

The following problems regarding the preparation and reactions of cyclopentane-1,2-diones were explored and solved in the course of the present study:

- A method for the aerobic oxidation of cyclopentane-1,2-diols to their corresponding cyclopentane-1,2-diones was developed. The method utilized a commercial activated carbon-supported platinum catalyst and used atmospheric air oxygen as the bulk oxidant in an aqueous reaction environment. It was possible to prepare unsubstituted, 3-alkyl- and 4-alkylcyclopentane-1,2-diones in good yields without carbon-carbon bond cleavage between the forming carbonyl groups.

- ^{18}O isotope-labeled substrates and reagent were used to establish the mechanism of the asymmetric oxidation of 3-alkylcyclopentane-1,2-diones with the $Ti(O\textit{i}Pr)_4$/tartrate ester/*t*BuOOH catalytic complex. It was found that this cascade reaction proceeded via the following main steps: (I) enantioselective epoxidation of the enolic double bond of the cyclopentane-1,2-dione; (II) Baeyer-Villiger oxidation of the carbonyl group, followed by rearrangement of the intermediates and (III) intramolecular acylation, resulting in γ-lactone acids.

- A method for the preparation of enantiomerically enriched chiral 3-alkylcyclopentane-1,2-diones was developed. The method used a bis-silyl dienolate derived from unsubstituted cyclopentane-1,2-dione as the nucleophile in an organocatalytic C-C bond formation by a Mukaiyama-Michael reaction. The reaction tolerated both electron-rich and electron-poor aromatic α,β-unsaturated aldehydes, as well as aliphatic α,β-unsaturated aldehydes as the electrophilic counterparts to give chiral 3-alkylcyclopentane-1,2-diones in up to 66% yield and up to 94% ee over three reaction steps

Acknowledgements

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I owe big thanks to Dr. Anne Paju who taught me most of the practical laboratory tricks I know and who was always around to help and to discuss the latest results. I am also indebted to all of the coworkers and fellow students of the chair of organic chemistry who generated a pleasant atmosphere and without whom this work would not have been possible. Thank you!

I am grateful to professor Paul G. Williard who gave me the opportunity to briefly work in his group and helped me to understand what doing science is all about. I would also like to thank Dr. Andrus Tasa and Dr. Olga Tšubrik from TBD-Biodiscovery who inspired me to evolve into a productive synthetic chemist during my short apprenticeship in Tartu.

Above all I am deeply grateful to Eliise, to my parents and to my friends for their continued support and understanding throughout the ups and downs of my doctoral studies.

Abstract

3-Alkylcyclopentane-1,2-diones are a group of compounds that occur in nature and that can be biologically active on their own. They can be used as starting materials for the synthesis of various biologically active compounds. Although some simpler 3-alkylcyclopentane-1,2-diones can be isolated from natural sources, the preparation of more complex synthetic analogues of these compounds can be challenging.

One of the known ways of preparing cyclopentane-1,2-diones involves the oxidation of their preceding diols to the desired dicarbonyl compounds, while avoiding the oxidative cleavage of the diketones. This calls for mild and selective oxidation methods: for instance Swern oxidation has been used for the transformation. In order to devise a more effective and less waste-producing alternative, an aerobic oxidation method was developed in the course of this thesis. The method makes use of a commercial and reusable Pt/C catalyst in aqueous solvents and uses atmospheric air oxygen as the oxidant. A variety of unsubstituted, 3-alkyl- and 4-alkylcyclopentane-1,2-diols were oxidized to diketones. The reaction tolerated a variety of different functionalities in the substituents of the cyclopentane ring.

Although the oxidative cleavage of cyclopentane-1,2-diones can be seen as an undesired degradation process, it can also be carried out in an asymmetric manner and used for the preparation of chiral γ-lactone acids. The process employs a Ti(O*i*Pr)$_4$/tartrate ester/*t*BuOOH complex and involves two successive oxidations by two equivalents of the oxidant. While the first oxidation is believed to proceed by a mechanism similar to the Sharpless epoxidation, the mechanism of the second oxidation that cleaves the cyclopentane ring has been unresolved. In the present work, isotopic labeling experiments were used to demonstrate that the oxidative cleavage of cyclopentane-1,2-diones proceeds by the Baeyer-Villiger oxidation mechanism.

In order to prepare chiral diketones, a secondary amine-catalyzed organocatalytic Mukaiyama-Michael reaction was developed, which in combination with primary product reduction and deprotection made it possible to prepare enantiomerically enriched 3-alkylcyclopentane-1,2-diones. The reaction utilized α,β-unsaturated aldehydes and the bis-silyl dienolate of cyclopentane-1,2-dione as starting materials and allowed access to chiral 3-alkylcyclopentane-1,2-diones in good yields and enantioselectivities.

Kokkuvõte

3-alküültsüklopentaan-1,2-dioonid on looduses esinevad bioloogiliselt aktiivsed ühendid, mida saab kasutada lähteainetena keerukamate bioloogiliselt aktiivsete ainete sünteesil. Ükskuid lihtsamaid 3-alküültsüklopentaan-1,2-dioone saab looduslikest allikatest eraldada, kuid keerukamate sünteetiliste analoogide valmistamine võib olla tülikas.

Üheks võimalikuks tsüklopentaan-1,2-dioonide saamise viisiks on vastavate dioolide dikarbonüülühenditeks oksüdeerimine, vältides tekkivate diketoonide täiendavat oksüdeerumist ja lagunemist. See on võimalik vaid pehmete ja selektiivsete oksüdeerimismeetoditega, näiteks Swerni oksüdeerimist kasutades. Käesoleva doktoritöö üheks eesmärgiks oli efektiivsema ja vähem jääke tootva aeroobse oksüdeerimismeetodi väljatöötamine. Saadud meetod kasutab kaubanduslikku taaskasutatavat Pt/C katalüsaatorit, reaktsioonikeskkonnana vett või vettsisaldavaid solvendisegusid ning oksüdeerijana õhuhapnikku. Meetod sobib erinevate asendamata, 3-asendatud- ja 4-asendatud tsüklopentaan-1,2-dioolide vastavateks diketoonideks oksüdeerimiseks ning sobib paljusid erinevaid funktsioonaalrühmi sisaldavate lähteainetega.

Kuigi tsüklopentaan-1,2-dioonide oksüdeerimise teel lõhustumine võib olla nimetatud ühendite lagunemisprotsessiks, saab 3-alküültsüklopentaan-1,2-dioone sihilikult lõhustada ka asümmeetrilise oksüdeerimise teel, saades kiraalseid γ-laktoonhappeid. Nimetatud protsess kasutab Ti(O*i*Pr)$_4$/viinhappe estri/*t*BuOOH kompleksi ning hõlmab lähteaine kahte järjestikust oksüdeerimist kahe ekvivalendi oksüdeerijaga. Neist esimese oksüdeerimisetapi mehhanism sarnaneb Sharplessi epoksüdeerimisega, kuid teise etapi, mis lõhub tsüklopentaani tsükli, mehhanism oli seni teadmata. Käesolevas töös näidati isotoopidega märgistamise abil, et 3-alküültsüklopentaan-1,2-dioonide asümmeetriline oksüdatiivne lõhustamine kulgeb Baeyer-Villigeri oksüdeerimise mehhanismi järgi.

Kiraalsete diketoonide sünteesimiseks töötati välja sekundaarse amiini katalüütiline Mukaiyama-Michael-i reaktsioon, mis kombinatsioonis esmase reaktsiooniprodukti taandamise ning vaheühendilt kaitsva rühma eemaldamisega võimaldab saada enantiomeerselt rikastatud 3-alküültsüklopentaan-1,2-dioone. Reaktsiooni lähteaineteks on α,β-küllastamata aldehüüdid ja tsüklopentaan-1,2-diooni bis-silüüldienolaat ning produktidena saadakse heade saagiste ja enantioselektiivsustega kiraalseid 3-alküültsüklopentaan-1,2-dioone.

References

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Article I

Reile, I.; Paju, A.; Eek, M.; Pehk, T.; Lopp, M. Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones on Pt/C Catalyst. *Synlett* **2008**, 347-350.

Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones on Pt/C Catalyst

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Abstract: A new method for the aerobic oxidation of cyclopentane-1,2-diols to corresponding 1,2-diones using heterogeneous Pt/C catalyst in the presence of LiOH is described. Different functional groups tolerate the oxidation conditions. Yields of 1,2-diones up to 76% were achieved.

Key words: diols, ketones, heterogeneous catalysis, oxidation, platinum

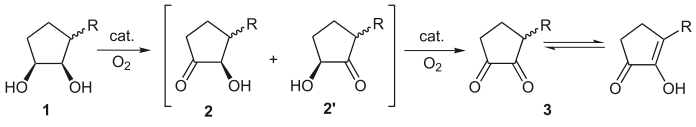
Catalytic dehydrogenation is a common method for the oxidation of alcohols to ketones. The use of atmospheric air oxygen as an oxidant is preferred due to its 'green' nature. The first reports on the platinum-metal-catalyzed aerobic oxidations of alcohols date back to the seventies.[1] Since then a variety of such oxidation methods have been developed for the conversion of allylic and benzylic alcohols, as well as of nonactivated primary and secondary aliphatic alcohols, into carbonyl compounds. Both, the homogeneous catalysis using metal complexes in organic solvents[2] or in water[3] and the heterogeneous catalysis using easily recoverable traditional catalysts[4] or metal nanoparticles[5] are used. Oxidation has been carried out in different solvents: common organic solvents,[5a,6] water,[4a,5b] and supercritical carbon dioxide.[7]

There are only a few methods for oxidizing diols to diones[6b,8] and no methods for the catalytic aerobic oxidation of cyclopentane-1,2-diols to the corresponding 1,2-diketones available in literature. Cyclopentane-1,2-diones were of interest to us as substrates for the asymmetric domino oxidation, leading to tertiary hydroxyketones and lactone acids,[9] which are useful as the building blocks for natural compounds.[10]

In the present paper we reveal our results on a new method of aerobic oxidation of vicinal cyclopentane diols to 1,2-diketones using a heterogeneous Pt/C catalyst (Scheme 1).

We have found that aerobic oxidation on a commercially available Pt/C catalyst[11] at 60 °C converts *cis*-1,2-diols **1** into the corresponding 1,2-diones **3**. In our preliminary experiments toluene was used as a solvent for hydrophobic substrates, water for hydrophilic substrates, and a mixture of MeCN and H_2O as a universal medium for both types of substrates. In these cases some amount of hydroxyketone **2** was also isolated, indicating that the oxidation occurred in the succession: diol – hydroxyketone – dione. In the case of **1a** intermediate hydroxy ketone **2a** was isolated and identified by NMR. Presence of a minor amount of the regioisomeric hydroxy ketone **2a′** was also observed in the spectrum.

The process is strongly dependent on the amount of oxygen available to the reaction medium. We established that the amount of oxygen that was present in the solvent and in the catalyst converts approximately 30% of the substrate into the product. Therefore, additional oxygen is needed to complete the process. On the other hand, unrestricted access of air to the reaction system lowers the yield of the product, presumably by overoxidizing the



R = **a** CH_2CH_2OBn
b CH_2CH_2OH
c Me
d $CH_2COOt\text{-}C_5H_{11}$
e CH_2CH_2NHBoc
f Ph
g CH_2CONH_2

Scheme 1

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product to carboxylic acids.[8b] Thus, better results were obtained when the reactor was periodically flushed with fresh air (in ca. 4 h intervals) during 16–20 hours. Using this procedure with 10 mol% of Pt/C catalyst, the oxidation of diol **1a** resulted in 76% of dione **3a** in toluene and 66% in acetonitrile–water mixture (1:1), the oxidation of diol **1c** resulted in dione **3c** in 67% in water. It should be noted that solubility of oxygen in these media is different (8.7 mM in toluene and 8.1 mM in acetonitrile compared to 1.3 mM in water at 20 °C[12]). We may suggest that the amount of oxygen in water-containing solvents is not sufficient for the reaction that slightly reduces the yield.

There is a slight difference in the reactivity of *all-cis* and *cis*-diol-*trans*-alkyl compounds. In the case of **1d** we observed that *cis*-diol-*trans*-alkyl compounds react slower.

Inorganic base additives to the oxidation system have been recommended by Bäckvall for heterogeneous catalytic dehydrogenations[13] and Mueller et al. for aerobic oxidations.[14] In our case the addition of alkali significantly influenced the process by considerably increasing the reaction rate. This enabled us to reduce the amount of catalyst to 5 mol%. It is noteworthy that in the presence of base hydroxyketone **2** was no longer detected among the reaction products. Thus, in acetonitrile–water without alkali, the yields of **2a** and **3a** were 16% and 60%, respectively, within 16 hours, while in the presence of one equivalent of alkali the only reaction product was **3a** in 70% yield within four hours. We may suggest that in the presence of alkali the conversion of **2** into **3** is faster than the conversion of **1** into **2**. In the presence of base the process was also less sensitive to the oxygen concentration. A part of this effect can probably be caused by the complex nature of the oxidation process, as discussed by Steinoff and Stahl.[12b] By adding LiOH we achieved a stable process in acetonitrile–water when access of atmospheric air was not restricted.

In order to establish the necessary amount of alkali, substrate **1a** was oxidized in a 1:1 mixture of acetonitrile–water in the presence of different amounts of LiOH. The obtained results are presented in Figure 1. We can note that already starting from 0.5 equivalent of LiOH the yields of the isolated product are close to maximum (ca. 70%).

Using a reactor with unrestricted air access through an open condenser, acetonitrile–water (1:1) as a solvent and LiOH as an additive, we performed the aerobic oxidation of alkyl, substituted alkyl, and aryl diols **1a**–**g**[15] on the Pt/C catalyst. The obtained results are presented in Table 1.[16]

In most cases 1,2-diones **3**[17] were obtained in good yield (around 70%). There are some exceptions: hydroxyalkyl substrate with unprotected OH group **1b** resulted in a modest yield of **3b** (49%, Table 1, entry 6). It is also noteworthy that only the secondary OH groups of the substrate were oxidized leaving the primary alcohol group untouched. The oxidation of *tert*-amylcarbonyloxy diol (**1d**) proceeded quickly over about one hour, until a yield of **3d** of 28% was reached and then the reaction stopped

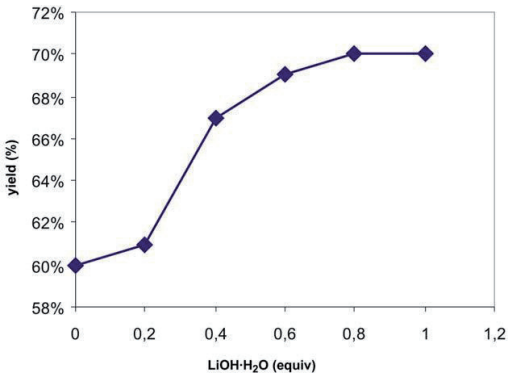

Figure 1 The effect of different amounts of $LiOH \cdot H_2O$ on the isolated yield of **3a**. *Reaction conditions*: MeCN–H_2O (1:1); 60 °C; 4 h; 5 mol% Pt/C catalyst.

Table 1 Aerobic Oxidation of diols **1** to diones **3** in the Presence of Pt/C Catalyst

Entry[a]	Substrate	LiOH (equiv)	Time (h)	Yield (%)
1	**1a**	0.2	4	61
2[b]	**1a**	0.4	4	67
3	**1a**	0.6	4	69
4	**1a**	1.0	4	70
5[c]	**1a**	1.0	4	68
6	**1b**	1.0	5	49
7	**1c**	1.0	5	74
8	**1d**	1.0	1.3	28
9	**1e**	1.0	4	76
10	**1f**	1.0	3.5	69
11	**1g**	1.0	3	0

[a] All experiments were run at 60 °C with 5 mol% Pt/C catalyst in an open glass reactor equipped with a condenser. MeCN–H_2O (1:1) used as solvent unless stated otherwise.
[b] In toluene.
[c] Regenerated catalyst used in the experiment.

(Table 1, entry 8); diol **1g**, which bears an amido group, did not afford the expected dione **3g**. At the same time Boc-aminoalkyl substrate **1e** resulted in the best isolated yield of dione **3e** (76%, Table 1, entry 9). In all these cases no hydroxyketone intermediates **2** were observed.

When the catalyst was filtered from the reaction mixture and reused for the oxidation of diol **1a**, only a minor decrease in the yield was observed and the product dione **3a** was isolated in 68% yield (Table 1, entry 5). Thus the catalyst can be reused at least once without noticeable decrease in the catalyst activity and the TON for a batch remains approximately 14.

We may conclude that a new, safe, and easy to use Pt/C catalytic aerobic oxidation method for the oxidation of cyclopentane-1,2-diols to the corresponding 1,2-diones was developed. The method is viable in the presence of a variety of functional groups, including benzyl ethers, alkyl-, Boc-amino-, hydroxyl-, and phenyl groups. A wide choice of solvents ranging from toluene to water–acetonitrile mixture to water makes it possible to oxidize many other substrates by this method.

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(15) **Preparation of Substrates**
(a) Substrates **1a**,**b** and **1d**–**f** were prepared from the corresponding alkenes according to the following dihydroxylation procedure: Alkene was dissolved in a H_2O–*t*-BuOH mixture (1:3), and NMO (1.3 equiv) and fiber bound OsO_4 catalyst (0.1 mol%) were added. The reaction mixture was stirred at 60 °C for an appropriate time (the reaction was monitored by TLC), the catalyst filtered, rinsed with EtOAc, and the filtrate quenched with an aqueous solution of $Na_2S_2O_3$ (10%). The aqueous layer was extracted with EtOAc, the organic extracts combined, dried over $MgSO_4$, the solvent evaporated and the crude product purified by flash chromatography, to afford the corresponding diol. Due to the synthetic route always the *cis*-diol was obtained as two isomers at the 3-position and used as a mixture. (b) Diol **1c** is a commercial product[18] and was used without purification. (c) Alkenes preceding diols **1a** and **1b** were prepared from 2-cyclopentene-1-acetic acid.[9a] (d) The alkene preceding diol **1d** was prepared from 2-cyclopentene-1-acetic acid ethyl ester by transesterification, as reported by: Frei, U.; Kirchmayr, R. EP 0278914, **1988**. (e) Alkenes preceding diols **1e** and **1g** were prepared from 2-cyclopentene-1-acetic acid according to: Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (f) The alkene preceding diol **1f** was prepared according to: Büchner, I. K.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 5381.

(16) **General Procedure for the Catalytic Aerobic Oxidation of Diols**
Diol (0.424 mmol), catalyst (5 mol%), $LiOH·H_2O$ (1.0 equiv) and solvent [2 mL, MeCN–H_2O (1:1)] were added to a 10 mL glass reactor, equipped with a condenser and stirred at 60 °C for an appropriate time. Consumption of the substrate was monitored by TLC. When the substrate was consumed the catalyst was filtered, rinsed with EtOAc (15 mL), EtOAc (10 mL) was added and the obtained two-phase solution was washed with 0.025 M HCl aq soln (20 mL). The separated aqueous layer was extracted once with EtOAc (20 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuum. The solid crude product was purified by flash chromatography [EtOAc–PE (2.5:10)] to give the diketone as a white crystalline solid.

(17) All products have been fully characterized by ^{1}H NMR and ^{13}C NMR. The analyses of known compounds are in agreement with published data. The characteristics of compounds are as follows:
Compound **2a**: ^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.48 (m, 4 H, Bn *o*-, *m*-), 7.43 (m, 1 H, Bn *p*-), 4.67 and 4.65 (2d, *J* = 11.8 Hz, 2 H, Bn CH_2O), 3.74 (dd, *J* = 1.8, 10.9 Hz, 1 H, H-2), 3.69 (td, *J* = 2 × 5.0, 9.6 Hz, 1 H, H-7), 3.65 (ddd, *J* = 4.5, 8.5, 9.6 Hz, 1 H, H-7), 2.41 (ddddd, *J* = 0.6, 1.4, 1.9, 9.2, 19.6 Hz, 1 H, H-5), 2.20 (dddd, *J* = 0.4, 9.6, 11.0, 19.6 Hz, 1 H, H-5), 2.09 (ddddd, *J* = 0.5, 1.4, 6.2, 9.6, 13.1 Hz, 1 H, H-4), 1.97 (m, 2 H, H-3,6), 1.86 (m, 1 H, H-6), 1.51 (dddd, *J* = 9.1, 11.0, 11.6, 13.1 Hz, 1 H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.4 (C-1), 137.6 (C-9), 128.3 (C-11), 127.7 (C-10, C-12), 81.1 (C-2),73.1 (C-8), 68.9 (C-7), 42.5 (C-3), 34.2 (C-6), 34.0 (C-5), 23.3 (C-4). This structure was confirmed by 2D FT correlation diagrams and ^{1}H–^{1}H coupling constants from H-2 and H-5 (19.6 Hz geminal coupling). The assignment of *trans*-configuration results from the comparison of ^{13}C chemical shifts with *cis*- and and *trans*-isomers of 3-[2-(benzyloxy)ethyl]cyclopentane-*cis*-1,2-diol.

Compound **2a′**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5 H, Bn *o*-, *m*-, *p*-), 4.46 (s, 2 H, H-8), 4.01 (tdd, *J* = 2 × 0.5, 8.3, 11.8 Hz, 1 H, H-5), 3.57 and 3.54 (m, 2 H, H-7), 2.37 and 1.60 (m, 2 H, H-4), 2.30 (m, 1 H, H-2), 2.15 and 1.49 (m, 2 H, H-3), 2.02 and 1.75 (m, 2 H, H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 219.6 (C-1), 138.1 (C-9), 128.2 (C-11), 127.4 (C-10, C-12), 75.5 (C-5), 72.7 (C-8), 67.3 (C-7), 43.3 (C-2), 30.2 (C-6), 29.3 (C-4), 22.9 (C-3). Large coupling constants of C-5 carbinol proton point to a methylene group bonded to C-5.
Compound **3a**: data available in ref. 9a. Compound **3b**: data available in ref. 9a. Compound **3c**: data are in accordance with commercial compound purchased from Aldrich.
Compound **3d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85 (s, 1 H, OH), 3.38 (s, 2 H, CH_2CO), 2.53 (m, 2 H, H-5), 2.43 (m, 2 H, H-4), 1.75 (q, *J* = 7.3 Hz, 2 H, CH_2CH_3), 1.42 (s, 6 H, $(CH_3)_2$), 0.86 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.16 (C-3), 168.80 (COO), 150.04 (C-2), 138.61 (C-1), 84.24 [$OC(Me)_2$], 35.42 (CH_2CO), 33.36 (CH_2CH_3), 32.01 (C-4), 25.36 [$OCMe_2$ and C-5], 8.09 (CH_3CH_2). IR: ν = 3315, 2979, 2937, 2885, 1727, 1699, 1665, 1465, 1386, 1193, 1149 cm^{-1}.
Compound **3e**: ^{1}H NMR [500 MHz, $CDCl_3$, broadened spectrum (*E*/*Z* exchange of Boc)]: δ = 6.40 (br s, 1 H, OH), 4.89 (br s, 1 H, NH), 3.41 (br m, 2 H, H-7), 2.59 (t, *J* = 2 × 6.6 Hz, 2 H, H-6), 2.47 (br m, 2 H, H-5), 2.41 (br m, 2 H, H-4), 1.41 (br s, 9 H, H-11). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.21 (C-3), 155.96 (C-9), 149.57 (C-2), 144.18 (C-1), 79.33 (C-10), 37.82 (C-7), 31.90 (C-4), 29.88 (C-6), 28.32 (C-11), 25.51 (C-5). IR: ν = 3371, 3326, 3008, 1689, 1657, 1524, 1451, 1393, 1367, 1249, 1169, 1119 cm^{-1}.
Compound **3f**: Ramage, R.; Griffiths, G. J.; Shutt, F. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, *7*, 1531.

(18) 3-Methylcyclopentane-1,2-diol was purchased from Alfa Aesar as a mixture of diastereomers, 95%.

Article II

Reile, I.; Paju, A.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. Oxidation of cyclopentane-1,2-dione: a study with ^{18}O labeled reagents. *Tetrahedron* **2011**, *67*, 5942-5948.

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Oxidation of cyclopentane-1,2-dione: a study with ^{18}O labeled reagents

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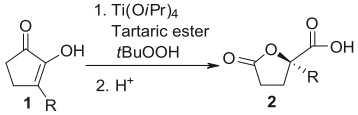
ABSTRACT

The asymmetric oxidation of 3-alkyl-cyclopentane-1,2-diones with the Ti(O^iPr)$_4$/tartaric ester/*t*-BuOOH complex, which gives, in a cascade process, highly enantiomerically enriched γ-lactone acids, was studied by ^{18}O isotopic labeling in the substrate and in the oxidant. The path of the labeled atoms was followed by ^{13}C NMR spectroscopy. It was found that the oxidative ring cleavage of 1,2-dione proceeds via a Baeyer–Villiger-type oxidation mechanism.

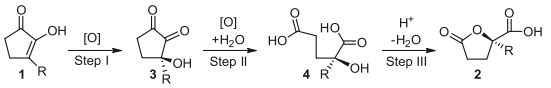
1. Introduction

Asymmetric oxidation of 3-alkyl- and 3-aryl-cyclopentane-1,2-diones **1** with the Ti(O^iPr)$_4$/tartaric ester/*t*-BuOOH complex[1] is an efficient tool in organic synthesis that provides γ-lactone acids **2**[2,3] in high optical purity and good yield (Scheme 1). These γ-lactone acids have been used in the synthesis of natural products as homocitric acid,[4] alkyl-,[5] and aryl-[6] substituted nucleoside analogues, and have high potential for many other applications.



Scheme 1. Asymmetric oxidation of 3-alkyl-cyclopentane-1,2-diones to 2-alkyl-γ-lactone acids.

The transformation of 3-alkyl-cyclopentane-1,2-diones to 2-alkyl-γ-lactone acids includes several chemical reactions and can be outlined on the basis of identified intermediates as presented in Scheme 2. The first oxidation step determines the stereochemical outcome of the whole reaction and is formally an asymmetric 3-hydroxylation of substrate **1** (intermediate **3** has been isolated and identified by us as described,[7,8] Scheme 2, Step I). In the second step, the cyclopentane ring is oxidatively cleaved, yielding intermediate diacid **4** (Scheme 2; Step II). Subsequent esterification of the diacid affords γ-lactone acid **2** and other esters of the diacid[2] (Scheme 2; Step III). The formal reaction scheme does not reveal neither all the chemical reactions nor the mechanisms of the transformations. Thus, more detail information is needed about the whole multi-step process.



Scheme 2. Formal reaction steps according to isolated and identified intermediates.

The mechanism of the oxidation of 1,2-diketones has been studied on the model of non-enolizable 1,2-diphenyl-1,2- ethanedione[9,10] (benzil). Contradictions in the obtained experimental results do not make it possible to establish whether the oxidative C–C bond cleavage proceeds via a Baeyer–Villiger-type reaction, which is a well-studied and established reaction for oxidizing ketones[11] (Scheme 5), or via the formation of an intermediate epoxide[12] (Scheme 6). There is no data on the mechanism of oxidation of enolizable 1,2-diketones in the literature. The mechanistic uncertainty is an obstacle in generating efficient oxidation processes for these compounds.

Herein, we present the results of a detailed study of the Ti(O^iPr)$_4$/tartaric ester catalyzed transformations of 3-alkyl-cyclopentane-1,2-diones (enols **1**) with labeled *t*-Bu$^{18}O^{18}OH$ **5**, and labeled enols **1a** and **1b** with *t*-BuOOH (Fig. 1), in order to elucidate how the oxidation proceeds and to understand whether the

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oxidative cleavage of 1,2-diones is a Baeyer–Villiger-type transformation. ^{18}O Labeled *t*-Bu$^{18}O^{18}OH$ **5** and labeled enols **1a** and **1b** were prepared and subjected to the reaction. Heavy oxygen isotope-induced changes in chemical shifts in natural abundance ^{13}C NMR[13] were used to track the position of ^{18}O in the reaction intermediates and products originating from differently labeled cyclopentane diones **1**, **1a** or **1b** or from ^{18}O labeled *tert*-butyl hydroperoxide **5**. NMR data were further confirmed by LC/MS/MS.

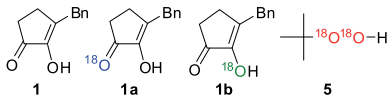


Fig. 1. Labeled substrates **1a** and **1b** and labeled reagent **5**.

2. Results and discussion

2.1. Preparation of the labeled reagent and substrates

The labeled oxidation reagent di-^{18}O-*tert*-butyl hydroperoxide **5** was prepared from a commercial *tert*-butyl Grignard reagent and $^{18}O_2$ gas, according to a known procedure.[14] The differently labeled 3-benzyl-cyclopentane diones with ^{18}O labels at C1 (compound **1a**) and at C2 (compound **1b**) were prepared separately by means of different synthetic routes.

Labeled ketoenol **1a** was obtained by subjecting unlabeled ketoenol **1** to an acid-catalyzed (HCl in $H_2{}^{18}O$) isotope exchange reaction[15] in dioxane-d_8 at room temperature. The reaction was run and the transformation monitored by ^{13}C NMR spectroscopy in an NMR tube (Fig. 2).[16] According to NMR, the formation of **1a** (95% of ^{18}O) was almost complete in 4 h. Surprisingly, none of the differently labeled compound **1b** (isotope exchange of the enolic oxygen) or the di-labeled compound **1c** with both oxygen atoms exchanged for ^{18}O were observed.[17]

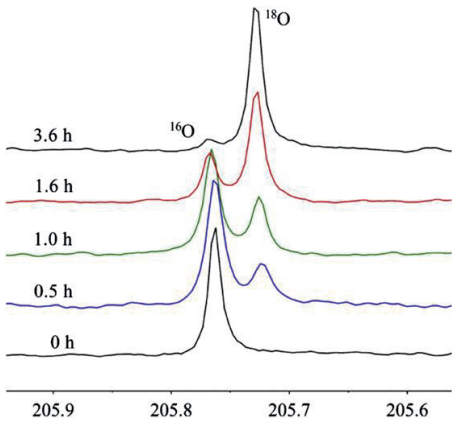
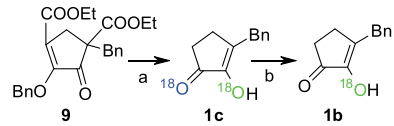


Fig. 2. Time dependence of oxygen isotope exchange at C1 of 3-benzyl-2-hydroxycyclopent-2-ene-1-one **1**, monitored by NMR.

To prepare ketoenol **1b**, we took advantage of the different mobility of the oxygen atoms attached to C1 and C2 in ketoenol **1a**. Thus, intermediate **9** from the synthesis scheme of ketoenol **1**[5] was decarboxylated in a mixture of dry dioxane and $H_2{}^{18}O$ in the presence of HCl, resulting in di-labeled ketoenol **1c** (Scheme 3). Then the ^{18}O atom at C1 was replaced with ^{16}O, using an acid-catalyzed isotope exchange with $H_2{}^{16}O$, under the same conditions that were used for the preparation of compound **1a**. As a result, mainly compound **1b** with ^{18}O saturation at C2 was obtained. According to NMR and GC/MS, the obtained product contained 1% of **1a**, 81% of **1b**, 5% of di-labeled **1c**, and 13% of **1** without any labels.[18]



Scheme 3. Preparation of 2-labeled 3-benzyl-2-hydroxycyclopent-2-en-1-one. (a) Dioxane, $H_2{}^{18}O$, cat. HCl, reflux; (b) Dioxane, H_2O, cat. HCl.

2.2. Oxidation of ketoenol 1 with labeled oxidation reagent 5

In order to follow the path of the oxygen atoms from the oxidation reagent, unlabeled diketone **1** was oxidized with labeled *t*-Bu$^{18}O^{18}OH$ reagent **5**. The oxidation products diacid **4** and lactone acid **2** were analyzed by ^{13}C NMR and LC/MS/MS. According to ^{13}C NMR, there was no isotope shift observed at C2, which was due to the high ^{18}O saturation (close to 100%) at this position.

The intermediate diacid **4** had an almost equal distribution of ^{18}O at C1 and C5 (which corresponds to **4a** and **4b** in Scheme 5; Fig. 3; Table 1) according to ^{13}C NMR. In LC/MS/MS spectra, diacid **4** revealed 95% with two ^{18}O isotopes. This result is in good agreement with NMR data.

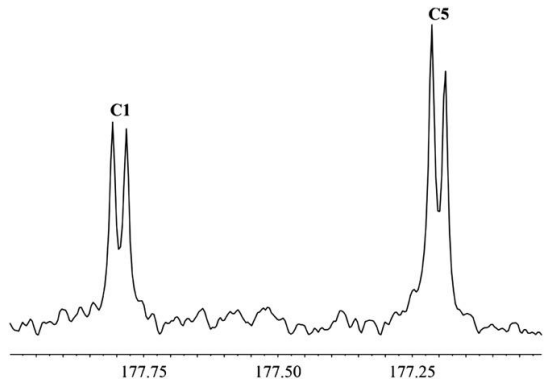


Fig. 3. ^{13}C NMR shifts for C1 and C5 of the labeled diacids **4a** and **4b**.

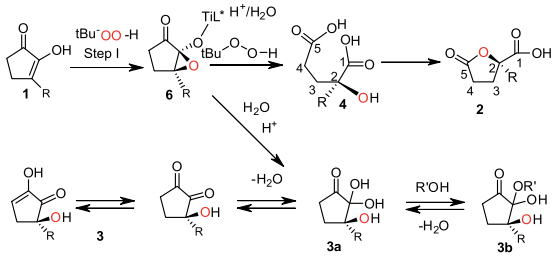
Table 1
Distribution of ^{18}O labels at C1 and C5 in intermediate **4** and product **2**, according to ^{13}C NMR from the oxidation of ketoenol **1** with labeled *t*-Bu$^{18}O^{18}OH$

Product	Calcd[a]	Calcd[b]	Exptl[c]
4a	50	100	43
4b	50	0	48
2a	25	50	24
2b	25	50	24
2c	50	0	49

[a] Calculated distribution based on expected isotope paths in the 'Baeyer–Villiger-type' mechanism.
[b] Calculated distribution based on expected isotope paths in the 'epoxide-type' mechanism.
[c] Experimental value determined by NMR.

It is very likely that the first oxidation is a typical Sharpless process,[19,20] similar to the epoxidation of allylic alcohols, yielding intermediate **6**. The intermediate affords, in hydrolytic conditions, 3-hydroxylated product 3[7] (Scheme 4). Our attempts to detect epoxide **6** by NMR were not successful. This was probably due to

epoxidation being the rate-limiting step and epoxide **6** transforming fast in the following reaction cascade sequence. Still, the hydrolysis products **3**, that we have isolated, identified, and reported previously,[2,7] could have been formed from epoxide **6** and indirectly hint at its existence. In addition to enol **3** we have also isolated hydrate **3a** and hemiacetal **3b** from the reaction mixture in certain conditions.[7]



Scheme 4. Step I—epoxidation of the double bond according to a Sharpless mechanism.

Our main interest was directed to the next oxidation step: further transformations leading to **4** and **2**. The substrate for these transformations may either be epoxide **6** or diketone derivatives **3a** and **3b**. All these intermediates lead to the same oxidation products **4** and **2**. Diketone **3**, which according to NMR is exclusively in its enol form in solution, does not oxidize further under present reaction conditions and remains unaffected.[8] It means that the second oxygen atom adds to the C1 carbonyl carbon. The intermediate compounds **3a** and **3b** can not be formed under the oxidation conditions. Thus we may suggest that the second oxidation proceeds directly from epoxide **6**.

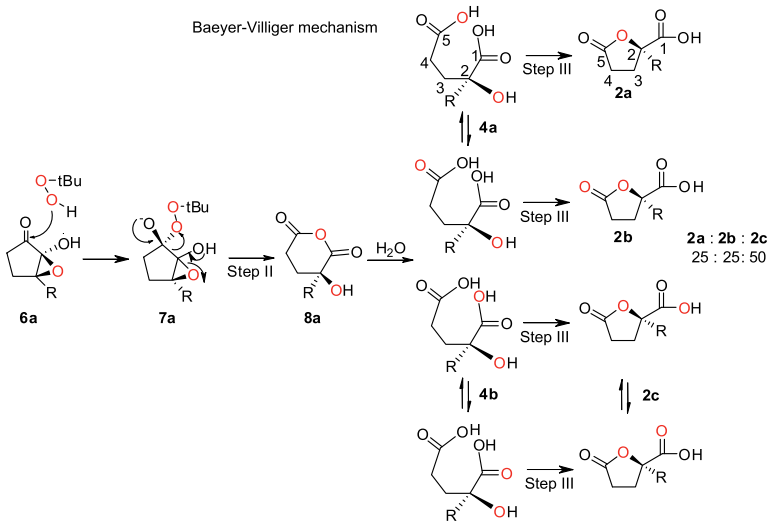
The process may proceed either via a Baeyer–Villiger-type rearrangement[9] or via a pathway involving the formation of a second epoxide,[12] as in the case of the oxidation of benzil. If the second oxidation proceeds via the classic Baeyer–Villiger approach (Scheme 5) in accordance with the Doering and Dorfman labeling experiments,[21] that confirmed the mechanism suggested by Criegee,[22] the second oxygen atom from **5**, which is involved in the ring cleavage reaction, should appear in one of the carboxylic groups of diacid **4** and either in the carboxylic group of **2c** or **2b**. Also, at a 25% extent, one of the labeled carboxylic oxygen atoms from **4** is eliminated during the lactonization, which yields product **2a**. As a result, the ratio of mono-labeled compound **2a** to di-labeled compounds **2b** and **2c** should be 1:3. If the reaction proceeds according to an epoxide formation pathway, the labels should appear only in the furanone ring (Scheme 6).

When compound **4a** is cyclized to the lactone acid, we should obtain a mixture of compound **2a** (one label) and compound **2b** (two labels); when **4b** cyclizes, compound **2c** (two labels) should form, with the ratio of **2a**, **2b**, and **2c** being 25:25:50. Indeed, such a distribution was observed by NMR[23] (and was supported by LC/MS/MS), with the ratio of **2a**/**2b**/**2c** being 22:22:43. The result corresponded to that expected from the 'Baeyer–Villiger-type' mechanism (Table 1).

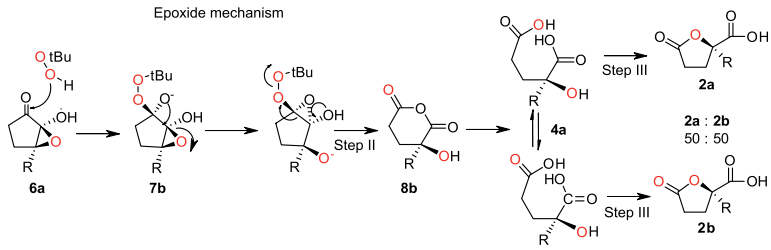
2.3. Oxidation of labeled substrates

In order to elucidate the path of the two oxygen atoms from substrate **1** to the product, and confirm the conclusions drawn from the labeled reagent experiments, we performed oxidation experiments with the labeled substrates **1a** and **1b**. Thus, labeled diketone **1a** was subjected to the oxidation reaction with unlabeled *t*-BuOOH, and the isolated diacids **4** were analyzed. The NMR spectra showed clear ^{18}O saturation at C5 of the molecule, which corresponded to compound **4c** (Table 2). No ^{18}O shift was observed at other carbon atoms in the compound. The lactonization of **4c** resulted in a mixture of compounds **2** and **2d** (Table 2), which facilitated a two-fold loss in the ^{18}O saturation on C5 in the ^{13}C spectra of the mixture of products.[24] The obtained results were confirmed by LC/MS/MS and were in good accordance with the 'Baeyer–Villiger-type' mechanism (Scheme 5, Fig. 2), which suggests that **1a** will produce a diacid **4c** with the isotope label solely at the C5 carboxyl group and should lose 50% of the label during the lactonization step, giving rise to equal amounts of lactone acids **2** with no label and **2d** with the label on C5 (Fig. 4).

Using the labeled diketone **1b** as the asymmetric oxidation substrate provided diacid **4d** with good ^{18}O saturation at C1. When compound **4d** was cyclized, there was no isotope effect observable



Scheme 5. The path of oxygen labels from the labeled oxidant **5** in the reaction cascade, according to the 'Baeyer–Villiger-type' mechanism.



Scheme 6. The path of different oxygen labels in the reaction cascade, according to the 'epoxide-type' mechanism.

Table 2
Distribution of ^{18}O labels in intermediate **4** and product **2**, according to ^{13}C NMR, from the oxidation of labeled ketoenols **1a** and **1b** with *t*-BuOOH

Product	Substrate					
	1a			**1b**		
	Calcd[a]	Calcd[b]	Exptl[c]	Calcd[a]	Calcd[b]	Exptl[c]
4c	100	50	84	0	0	0
4d	0	50	0	100	100	76
2	50	25	54	0	0	0
2d	50	25	46	0	0	0
2e	0	50	0	100	100	76

[a] Calculated distribution based on expected isotope paths in the 'Baeyer–Villiger-type' mechanism.
[b] Calculated distribution based on expected isotope paths in the 'epoxide-type' mechanism.
[c] Experimental value determined by NMR.

Table 3
Upfield ^{18}O isotope shifts on ^{13}C chemical shifts of labeled compounds in ppb

Compound	C1	C2/C4	C5
1a[a]	41		
1b[b]	38	C2 10	
1c[b]	42		
2a–c[b,d]	23		38
2d[b]		C4 07	38
2e[b,d]	23		
4a–b[c]	26		25
4c[c]			25
4d[c]	26		

[a] Dioxane-d_8.
[b] $CDCl_3$.
[c] CD_3OD.
[d] Spectra obtained at sub ambient temperatures.

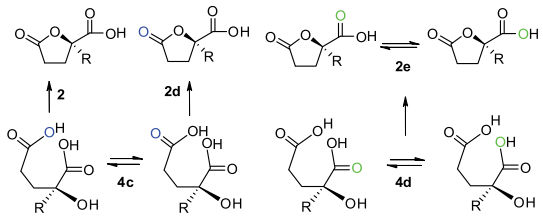


Fig. 4. Expected isotope ^{18}O location from labeled substrates **1a** and **1b**, according to the Baeyer–Villiger mechanism.

in the C1 of the lactone acid **2e** at room temperature. When the sample was cooled to 248 K, labeling in the carboxylic moiety, with no loss in isotope saturation when compared to **4d**, was observed (Table 2).

As expected from a Baeyer–Villiger-type mechanism, the enolic oxygen from **1b** appeared in the carboxylic acid group in the end product **2e** and the carbonylic oxygen from **1a** either appeared in the furanone carbonyl group or was eliminated in half of the cases (Scheme 5, Fig. 4).

3. Conclusion

The first step of the oxidative reaction cascade for 3-benzyl-1,2-cyclopentanedione **1**—asymmetric epoxidation—is a key step in the whole process, which selectively generated a stereogenic center at C2 of diacid **4** and lactone acid **2**. This step is similar to the asymmetric oxidation of allylic alcohols developed by Sharpless et al.[1] The formed stereogenic center retains its configuration throughout the following reaction cascade: the labeled oxygen from the reagent appeared in the hydroxyl group of the intermediate diacid **4** and in the furan oxygen atom in lactone acid **2**. The cascade continues with the second oxidation reaction with *tert*-butyl hydroperoxide. In all cases with labeled substrates **1a** and **1b** and reagent **5**, the isotope distribution in the intermediate diacid **4** and lactone acid **2** unambiguously confirmed that the oxidative cleavage of the cyclopentane ring proceeds by a Baeyer–Villiger-type mechanism.

4. Experimental section

4.1. General experimental details

All reagents were purchased from common suppliers and used without further purification. ^{18}O Labeled organic compounds were stored at −80 °C. CH_2Cl_2 was distilled from CaH_2, toluene and dioxane were distilled from Na. Silica gel 40–100 μm was used for column chromatography for compounds **1a–c** and **2**, **2a–e**; silica gel 100–160 μm was used for chromatography for compounds **4a–d**. All NMR spectra were obtained at room temperature unless noted otherwise. NMR spectra were normalized according to solvent peaks, except for ^1H NMR spectra measured in $CDCl_3$ that was normalized by internal standard (TMS δ=0.00). ^{13}C chemical shifts are given in three decimal numbers where isotopes are observed, otherwise in two decimal numbers. Mass spectra and HRMS of substrates were recorded using EI. LC/MS/MS spectra and HRMS of products were recorded using ESI.

4.2. General procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one 1 with *tert*-butyl hydroperoxide

An Ar-filled Schlenck tube was charged with CH_2Cl_2 (0.167 M compared to the substrate). MS 4 Å powder (100 mg/mmol) and 1 equiv of $Ti(O^iPr)_4$ were added, followed by dropwise addition of 1.6 equiv of (+)-diethyl tartrate at −20 °C. The mixture was stirred

for 20 min, then 1 equiv of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one was added dropwise as a 0.5 M solution in CH_2Cl_2 and stirred for a further 30 min, followed by the slow addition of 2.5 equiv of *tert*-butyl hydroperoxide. The reaction was stirred for 20 min and then left to stand at −20 °C for 68h. The reaction was quenched with 6 ml/mmol of H_2O and stirred for 2 h; then, 1.2 ml/mmol of 30% NaOH solution in brine was added and stirred for a further 1.5 h. The mixture was filtered through Celite and rinsed with CH_2Cl_2; the phases were separated and the aqueous phase was acidified and extracted with EtOAc. All of the organics were combined, dried over $MgSO_4$ and the product was purified by column chromatography over silica gel (3:10 to 4:10 acetone/petroleum ether) to give 2-benzyl-2-hydroxy-pentanedioic acids **4**, which at ambient temperature spontaneously cyclize to lactone acids **2**. Samples of **4** always contained increasing amount of **2** and, therefore, were fully characterized after cyclization as lactone acids **2**.

4.3. General procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids

An Ar-filled round bottom flask was charged with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid and toluene; the material did not dissolve completely. The reaction was stirred at 100 °C for 2 h, the now homogeneous mixture was allowed to cool to room temperature and the solvent was removed on a rotary evaporator to give ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid.

4.4. Preparation of C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1a

An oven dried NMR tube was filled with Ar and charged with 101 mg (0.538 mmol) 3-benzyl-2-hydroxycyclopent-2-enone, 480 μl of $H_2{}^{18}O$, 0.5 ml of dioxane-d_8, and 0.1 ml of dioxane. After the substrate was dissolved 20 μl of 22.8% HCl in $H_2{}^{18}O$ (prepared by bubbling dry HCl into $H_2{}^{18}O$) was added. The reaction was run at room temperature and monitored by ^{13}C NMR. After 60 h the NMR revealed 95% of ^{18}O saturation at C1. Reaction mixture ^1H NMR (400 MHz, dioxane-d_8/dioxane/$H_2{}^{18}O$) δ=7.14–7.04 (m, 5H, Ph), 3.52 (br s, 2H, Ph–CH_2–), 2.11 (br s, 4H, H-4, H-5); ^{13}C NMR (400 MHz, dioxane-d_8/dioxane/$H_2{}^{18}O$) δ=205.766 (C^{18}O), 205.725 (CO), 149.98 (C–OH), 148.81 (C-3), 139.13 (*s*), 129.80 (*o*), 129.55 (*m*), 127.41 (*p*), 35.27 (Ph–CH_2–), 32.85 (C-5), 25.41 (C-4). The reaction mixture was extracted with CH_2Cl_2 (5×1 ml), dried over a small amount of $MgSO_4$, and concentrated to give (99 mg, 96%) 95% saturated C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone **1a** as yellowish solid. An analytical sample was crystallized from CH_2Cl_2/petroleum ether to give **1a** as white crystals, mp 95–97 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.32–7.21 (m, 5H, Ph), 6.59 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.39–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.71 (C^{18}O), 148.78 (C–OH), 146.33 (C-3), 137.73 (*s*), 128.95 (*o*), 128.67 (*m*), 126.61 (*p*), 34.88 (Ph–CH_2–) 31.96 (C-5), 24.75 (C-4); IR: 3320, 2924, 1682, 1641, 1385, 1218, 1107, 762, 699 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=190 (100, M^+), 188 (5.1), 172 (3.4), 159 (16.4), 142 (25.3), 129 (32.2), 117 (44.8), 104 (21.6), 91 (46.6). C1 ^{18}O saturation 95% based on MS. HRMS (EI): M^+ *m*/*z* calcd for $C_{12}H_{12}O^{18}O$ 190.0880; found 190.0874.

4.5. Preparation of C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1b

1-Benzyl-4-benzyloxy-5-oxo-cyclopent-3-ene-1,3-dicarboxylic acid diethyl ester (422 mg, 1 mmol) was dissolved in 2 ml of dioxane and 1 ml of 22.8% HCl in $H_2{}^{18}O$ was added. The reaction was stirred at 105 °C under Ar overnight. The reaction mixture was extracted with CH_2Cl_2 (6×1 ml), all extracts combined, concentrated, and purified by column chromatography over silica gel (2:10 EtOAc/petroleum ether) to give 132 mg of di-labeled 3-benzyl-2-hydroxycyclopent-2-enone **1c** as white crystals, mp 94–97 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.33–7.22 (m, 5H, Ph), 5.82 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.40–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.421 (CO), 203.379 (C^{18}O), 148.617 (C–^{18}OH), 145.66 (C-3), 137.80 (*s*), 129.08 (*o*), 128.85 (*m*), 126.81 (*p*), 35.01 (Ph–CH_2–) 31.97 (C-5), 24.89 (C-4); IR: 3308, 2923, 1679, 1638, 1378, 1194, 1098, 762, 699 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=192 (100, M^+), 190 (35.1), 188 (2.8), 172 (5.1), 170 (1.2), 161 (24.9), 159 (3.9), 142 (31.5), 129 (38.9), 117 (59.9), 104 (26.0), 91 (55.3). HRMS (EI): M^+ *m*/*z* calcd for $C_{12}H_{12}{}^{18}O_2$ 192.0922; found 192.0926.

Di-labeled 3-benzyl-2-hydroxycyclopent-2-enone **1c** (104 mg, 0.538 mmol) was dissolved in 650 μl of dioxane, 500 μl of H_2O and 20 μl of 22% HCl was added. The reaction was left overnight at room temperature, then extracted with CH_2Cl_2 (8×1 ml), all extracts combined, dried over $MgSO_4$, and purified by chromatography over silica gel (2:10 EtOAc/petroleum ether) to give crude C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone **1b** (83 mg, 81%) as yellowish crystals. ^1H NMR (400 MHz, $CDCl_3$) δ=7.25–7.15 (m, 5H, Ph), 6,19 (br s, 1H, –O*H*), 3.67 (br s, 2H, Ph–CH_2–), 2.32–2.26 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.619 (*C*O), 203.581 (*C*^{18}O), 148.793 (*C*–OH), 148.783 (*C*–^{18}OH), 146.02 (C-3), 137.84 (*s*), 129.08 (*o*), 128.82 (*m*), 126.77 (*p*), 35.01 (Ph–CH_2–), 32.03 (C-5), 24.89 (C-4). An analytical sample was crystallized from CH_2Cl_2/petroleum ether to give **1b** as white crystals, mp 92–95 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.33–7.22 (m, 5H, Ph), 6.08 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.39–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.540 (CO), 148.705 (C–^{18}OH), 145.86 (C-3), 137.82 (*s*), 129.08 (*o*), 128.83 (*m*), 126.79 (*p*), 35.00 (Ph–CH_2–), 32.01 (C-5), 24.88 (C-4); IR: 3308, 2922, 1695, 1655, 1379, 1194, 1099, 762, 699 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=192 (6.4), 190 (100, M^+), 188 (14.3), 170 (3.4), 161 (23.5), 142 (51.2), 129 (52.1), 117 (81.8), 104 (46.3), 91 (99.9). HRMS (EI): M^+ *m*/*z* calcd for $C_{12}H_{12}O^{18}O$ 190.0880; found 190.0884.

4.6. Preparation of di-^{18}O-*tert*-butyl hydroperoxide 5

A reaction setup consisting of a 250 ml round bottom flask connected to a 98% ^{18}O gas cylinder through a needle and capillary tubing was charged with 60 ml of Et_2O in argon atmosphere. The flask was cooled to −78 °C and ^{18}O gas was slowly bubbled through (~1 bubble/s) the solvent for 10 min to saturate the solvent with labeled oxygen. Then 60 ml of 0.52 M *t*-BuMgCl solution in Et_2O was added dropwise, a noticeable amount of white precipitate formed. The reaction was stirred for 10 min at −78 °C, then allowed to warm to room temperature and poured into a flask containing ice. The mixture was acidified with 6 M HCl, the phases separated and the aqueous phase extracted twice with 30 ml of Et_2O. All organics were combined, dried over $MgSO_4$, and concentrated to 50 ml on a rotary evaporator (30 °C, 0.5 atm). Further Et_2O was removed by distillation through a 20 cm Vigreux column to give 2 g of clear solution. The solution was dissolved with 10 ml of hexane and 10 ml of azeotrope was removed by Dean–Stark apparatus to give 2.1 ml of clear colorless solution that contained 1.56 M of *t*-Bu^{18}O^{18}OH **5** by titration.

4.7. Oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one 1 with di-^{18}O-*tert*-butyl hydroperoxide 5

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1** with *tert*-butyl hydroperoxide with 6 ml of CH_2Cl_2, 100 mg of MS 4 Å powder, Ti(O^iPr)$_4$ (300 μl,

1 mmol), (+)-diethyl tartrate (270 μl, 1.6 mmol), 3-benzyl-2-hydroxy-cyclopent-2-en-1-one (188 mg, 1 mmol) solution in 1.8 ml of DCM and di-^{18}O-*tert*-butyl hydroperoxide **5** (1.6 ml, 1.56 M, 1.5 mmol) and quenching the reaction with 6 ml of H_2O followed by 1.2 ml of 30% NaOH solution in brine gave, after extraction and purification, a mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4a** and **4b** (149 mg, 61%) as a yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.29–7.19 (m, 5H, Ph), 3.08 and 2.92 (2d, J=13.5 Hz, 2H, Ph–CH_2–), 2.56–2.46 and 2.26–2.12 (m, 2H, H3), 2.56–2.46 and 2.00–1.91 (m, 2H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.684 (C1–OOH), 177.658 (C1–^{18}OOH), 177.090 (C5–OOH), 177.065 (C5–^{18}OOH), 137.49 (*s*), 131.48 (*o*), 128.94 (*m*), 127.66 (*p*), 78.30 (C2), 46.49 (Ph–CH_2–), 35.33 (C3), 29.77 (C4); LC/MS/MS (ESI): m/z (%)=243 (2.6, $[M-H]^-$), 241 (100, $[M-H]^-$), 239 (4.5, $[M-H]^-$), 237 (0.8, $[M-H]^-$); Fragments of 241 (ESI): m/z (%)= 223 (100), 221 (36.3), 219 (0.9), 179 (0.9), 177 (10.6), 175 (9.1), 131 (6.3).

4.8. Cyclization of the mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids 4a and 4b into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acids 2a, 2b, and 2c

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with the mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4a** and **4b** (39 mg, 0.162 mmol) and 2 ml of toluene gave a mixture of ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acids **2a**, **2b**, and **2c** (34 mg, 100%) as yellow oil that solidified at cooling into the yellowish-white crystals, mp 106–108 °C: ^{1}H NMR (400 MHz, $CDCl_3$, 244 K) δ=9.48 (*s*, 1H, COO*H*), 7.35–7.29 (m, 5H, Ph), 3.42 and 3.16 (2d, J=14.4 Hz, 2H, Ph–CH_2–), 2.58–2.48 and 2.40–2.28 (m, 2H, H3), 2.58–2.48 and 2.23–2.11 (m, 2H, H4); ^{13}C NMR (100 MHz, $CDCl_3$, 244 K) δ=176.901 (C1–OOH), 176.878 (C1–^{18}OOH), 176.524 (C5–O), 176.486 (C5–^{18}O), 133.33 (*s*), 130.67 (*o*), 128.72 (*m*), 127.67 (*p*), 85.90 (C2), 41.73 (Ph–CH_2–), 30.00 (C3), 28.05 (C4); IR: 3059, 1769, 1734, 1707, 1496, 1462, 1408, 1178, 1033, 919, 709 cm^{-1}; LC/MS/MS (ESI): m/z (%)=223 (100, $[M-H]^-$), 221 (35.7, $[M-H]^-$), 219 (2.3, $[M-H]^-$); Fragments of 223 (ESI): m/z (%)=179 (7.6), 177 (98.1), 175 (79.5), 131 (100). HRMS (ESI): calcd for $C_{12}H_{12}O_4$ $[M+H]^+$ 221.0808; found 221.0798. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ $[M+H]^+$ 223.0851; found 223.0840. HRMS (ESI): calcd for $C_{12}H_{12}O_2{}^{18}O_2$ $[M+H]^+$ 225.0893; found 225.0881.

4.9. Oxidation of C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1a with *tert*-butyl hydroperoxide

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1** with *tert*-butyl hydroperoxide with 1.5 ml of DCM, 15 mg of MS 4 Å powder, Ti(O^{i}Pr)$_4$ (75 μl, 0.25 mmol), (+)-diethyl tartrate (67.5 μl, 0.4 mmol), C1 ^{18}O labeled 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1a** (47 mg, 0.25 mmol) solution in 0.5 ml of DCM and *tert*-butyl hydroperoxide (90 μl, 6.8M in decane, 0.6 mmol) and quenching the reaction with 1.25 ml of H_2O followed by 0.3 ml of 30% NaOH solution in brine gave, after extraction and purification, a mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4c** (10 mg, 17%) as a light brown oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.30–7.17 (m, 5H, Ph), 3.08 and 2.92 (2d, J=13.5 Hz, 2H, Ph–CH_2–), 2.51–2.46 and 2.26–2.12 (m, 2H, H3), 2.51–2.46 and 2.01–1.91 (m, 2H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.72 (C1–OOH), 177.096 (C5–OOH), 177.071 (C5–^{18}OOH), 137.50 (*s*), 131.48 (*o*), 128.94 (*m*), 127.65 (*p*), 78.34 (C2), 46.49 (Ph–CH_2–), 35.34 (C3), 29.78 (C4); LC/MS/MS (ESI): m/z (%)=239 (100, $[M-H]^-$), 237 (9.8, $[M-H]^-$); Fragments of 239 (ESI): m/z (%)=221 (100), 219 (93.8), 177 (2.9), 175 (31.9), 131 (12.8).

4.10. Cyclization of the mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids 4c into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid 2d and unlabeled acid 2

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4c** (4 mg, 0.018 mmol) and 0.5 ml of toluene gave a mixture of ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2d** and unlabeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2** (8 mg) as a light brown solid, mp 103–105 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.99 (*s*, 1H; COO*H*), 7.24–7.11 (m, 5H, Ph), 3.32 and 3.08 (2d, J=14.4 Hz, 2H, Ph–CH_2–), 2.46–2.37 and 2.25–2.16 (m, 2H; H3), 2.46–2.37 and 2.11–2.00 (m, 2H, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ=176.06 (C1–OOH), 175.927 (C5–O), 175.889 (C5–^{18}O), 133.68 (*s*), 130.74 (*o*), 128.79 (*m*), 127.75 (*p*), 86.14 (C2), 42.26 (Ph–CH_2–), 30.07 (C3), 28.11 (C4); IR: 3032, 2925, 1784, 1750, 1714, 1496, 1456, 1419, 1192, 1042, 931, 699 cm^{-1}; LC/MS/MS (ESI): m/z (%)=221 (95.5, $[M-H]^-$), 219 (100, $[M-H]^-$); Fragments of 221 (ESI): m/z (%)=177 (5.1), 175 (100), 131 (37.7). HRMS (ESI): calcd for $C_{12}H_{12}O_4$ $[M+H]^+$ 221.0808; found 221.0813. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ $[M+H]^+$ 223.0851; found 223.0855.

4.11. Oxidation of C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1b with *tert*-butyl hydroperoxide

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-ones **1** with *tert*-butyl hydroperoxide with 2.5 ml of DCM, 39 mg of MS 4 Å powder, Ti(O^{i}Pr)$_4$ (116 μl, 0.391 mmol), (+)-diethyl tartrate (109 μl, 0.625 mmol), C2 ^{18}O labeled 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1b** (86 mg, 0.391 mmol) solution in 0.8 ml of DCM and *tert*-butyl hydroperoxide (160 μl, 6.15M in decane, 0.977 mmol) and quenching the reaction with 2.34 ml of H_2O followed by 0.5 ml of 30% NaOH solution in brine gave, after extraction an purification, ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid **4d** (27 mg, 29%) as a yellowish oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.29–6.19 (m, 5H, Ph), 3.08 and 2.92 (2d, J=13.5 Hz, 2H, Ph–CH_2–), 2.54–2.46 and 2.27–2.13 (m, 2H, H3), 2.54–2.46 and 2.01–1.90 (m, 1H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.688 (C1–OOH), 177.662 (C1–^{18}OOH), 177.08 (C5–OOH), 137.49 (*s*), 131.48 (*o*), 128.94 (*m*), 127.66 (*p*), 78.32(C2), 46.49 (Ph–CH_2–), 35.33 (C3), 29.78 (C4); LC/MS/MS (ESI): m/z (%)= 239 (100, $[M-H]^-$), 237 (20.8, $[M-H]^-$); Fragments of 239 (ESI): m/z (%)=221 (100), 219 (13.5), 177 (11.5), 175 (4.2), 131 (5.1).

4.12. Cyclization of the mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid 4d into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid 2e

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid **4d** (11 mg, 0.046 mmol) and 1.0 ml of toluene gave ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2e** (19 mg) as white crystals, mp 107–110 °C: ^{1}H NMR (800 MHz, $CDCl_3$, 248 K) δ=10.39 (*s*, 1H, COO*H*), 7.26–7.19 (m, 5H, Ph), 3.33 and 3.08 (2d, J=14.5 Hz, 1H, Ph–CH_2–), 2.46–2.40 and 2.26–2.22 (m, 2H, H3), 2.46–2.40 and 2.11–2.05 (m, 2H, H4); ^{13}C NMR (200 MHz, $CDCl_3$, 248 K) δ=176.780 (C1–OOH), 176.757 (C1–^{18}OOH), 176.28 (C5–O), 133.46 (*s*), 130.70 (*o*), 128.75 (*m*), 127.71 (*p*), 85.98 (C2), 41.97 (Ph–CH_2–), 30.04 (C3), 28.06 (C4); IR: 3060, 1769, 1497, 1461, 1421, 1180, 1042, 946, 706 cm^{-1}; LC/MS/MS (ESI): m/z (%)=221 (100, $[M-H]^-$), 219 (26.0, $[M-H]^-$); Fragments of 221 (ESI): m/z (%)=177 (100), 175 (51.3), 131 (69.7). HRMS (ESI):

calcd for $C_{12}H_{12}O_4$ $[M+H]^+$ 221.0808; found 221.0818. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ $[M+H]^+$ 223.0851; found 223.0844.

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Supplementary data

NMR spectra and graphic representation of isotope exchange in **1**—**1a**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.06.036.

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16. ^{13}C NMR is used to track ^{18}O atoms in organic molecules because of exchanging an ^{16}O atom for ^{18}O causes a small upfield chemical shift of the carbon attached to the oxygen.[13,15] The magnitude of the shift is specific to functional group,[25] which allows good interpretation of experimental data: in our case the shift is 41 ppb,[17] which is typical for a conjugated carbonyl unit.
17. ^{18}O saturation was measured by the relative peak heights of different oxygen isotope bound ^{13}C peaks. As the change of the isotope does not noticeably alter the relaxation time (and hence the peak shape) of the carbon nucleus, the peak heights are as good quantitative measurements as peak areas.[26]
18. The isotope shift at C2 is noticeably smaller than at C1 and also smaller than typical values for allylic alcohols, which is probably due to the electronic effects from the adjacent carbonyl group (Table 3).
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23. Sample was cooled down to render the isotope shifts observable; shifts were smaller than in **2d** and **2e** (Table 3).
24. Interestingly, in the NMR spectrum, isotope shift was also observed on C4 carbon of the furanone ring when the sample was cooled to 259 K (Table 3).
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Article III

Reile, I.; Paju, A.; Kanger, T.; Järving, I.; Lopp, M. Cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether in asymmetric organocatalytic Mukaiyama–Michael reactions. *Tetrahedron Letters* **2012**, *53*, 1476-1478.

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Cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether in asymmetric organocatalytic Mukaiyama–Michael reactions

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ABSTRACT

Cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether readily undergoes organocatalytic reactions with α,β-unsaturated aldehydes resulting in Mukaiyama–Michael adducts which, after reduction of the aldehyde group and deprotection result in chiral 1,2-diketones (in mono-enolic form) in good yields (up to 66%) and with high stereoselectivity (up to 94% ee).

The enantio- and diastereoselective organocatalytic Mukaiyama–Michael reaction of silyl enol ethers with α,β-unsaturated aldehydes was introduced by MacMillan for silyloxy furan[1] and later extended to acyclic ketone enol ethers[2] and silyl ketene acetals.[3]

In continuation of our work on organocatalytic C–C bond forming reactions[4–7] and on the elaboration of polyfunctional chiral building blocks and natural compounds from cyclopentane-1,2-diketones,[8–12] we were interested in applying organocatalytic C–C bond forming reactions for the synthesis of chiral non-racemic substituted cyclopentane-1,2-diketones (in mono-enolic form) for further transformations.

Cyclohexane-1,2-diones have been successfully used as nucleophiles in iminium-catalyzed[13] and bifunctional thiourea catalyzed[14–16] Michael reactions, and as electrophiles in organocatalytic aldol reactions with ketones.[17] 3-Methyl-cyclopentane-1,2-dione does not react when thiourea is used as the catalyst.[14] To the best of our knowledge, cyclopentane-1,2-dione silyl enol ethers have not been used as Mukaiyama-type nucleophiles in asymmetric addition reactions, although their non-asymmetric alkylations,[18] aldol reactions[19] and Diels–Alder cycloaddition reactions[20] have been reported.

In the Mukaiyama–Michael reaction of diketone bis-silyl enol ethers with α,β-unsaturated aldehydes two stereogenic centers can be generated in one step. Hence, both the enantioselectivity and diastereoselectivity of the reaction have to be considered. It is generally known that the *syn/anti* selectivity of the reaction is dependent on the choice of solvent, acid co-catalyst, and temperature.[1] At the same time, the almost planar structure of diketone bis-silyl enol ethers may afford good enantioselectivity in the organocatalytic addition step. This reaction can be more easily controlled by means of selection of suitable organocatalysts.[21] On the other hand, the problem of separation of the diastereomers formed could be circumvented by taking advantage of the keto-enol tautomerism of cyclic-1,2-diketones: it is known that 3-alkyl substituted cyclopentane-1,2-diones enolize preferably to the thermodynamically more stable isomer with an alkyl group at the enol double bond.[22] This means that, after the addition step, the resulting diastereomeric mixture can be deprotected, causing migration of the double bond to the position shown in isomer **5**. In this case the second stereogenic center is lost and the product with one stereogenic center is obtained. The stereoisomeric composition of the reaction mixture is determined only by the enantioselectivity of the addition reaction (Scheme 1).

In the present study we investigated the organocatalytic addition of cyclopentane-1,2-dione bis-silyl enol ether **1** to α,β-unsaturated aldehydes **3** by using iminium activation. Bis-silyl enol ether **1** was prepared according to a literature process in one[23] or two steps[24] from cyclopentane-1,2-dione. The best results were obtained using a two-step procedure, modified according to Reetz et al.[20]

Our preliminary experiments with prolinol derivative **6** (Fig. 1) as the catalyst (20 mol %) revealed that bis-silyl enol ether **1**

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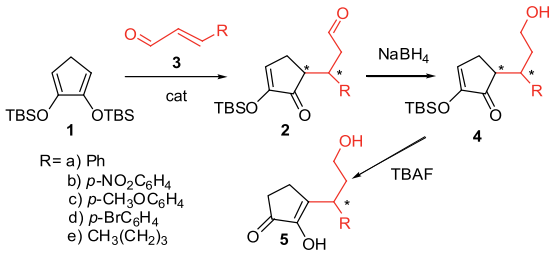


Scheme 1. Mukaiyama–Michael addition of cyclopentane-1,2-dione bis-silyl enol ether to α,β-unsaturated aldehydes.

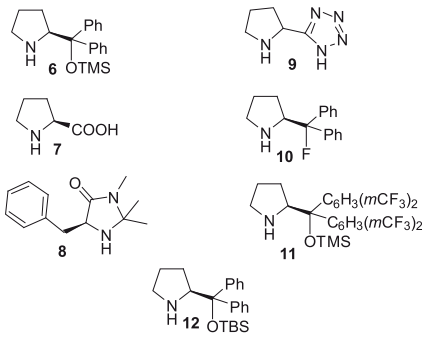


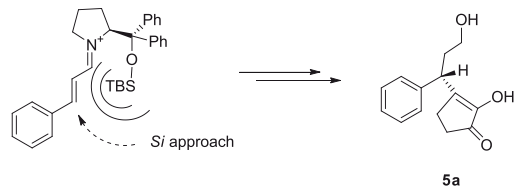
Figure 1. The organocatalysts used in the present work.

reacted with cinnamaldehyde (**3a**) in the presence of 4 Å molecular sieves such that all the aldehyde was consumed within 6 h. The product **2** obtained was an inseparable mixture of diastereomers which was not stable enough to be reproducibly isolated and fully characterized. To obtain stable products the adduct **2** was reduced in situ with $NaBH_4$ to alcohol **4**. Removal of the protecting TBS group with TBAF caused the double bond migration and afforded stable alcohol **5a** with one stereogenic center (Scheme 1). After lowering the amount of the catalyst **6** to 5 mol %, dione **5a** was isolated in a 24% yield after 13 h (Table 1, entry 1). In the present case, the intramolecular adduct, which is the main product in the reaction of free cyclopentane-1,2-dione and cinnamaldehyde,[13] did not form because the intermediate enamine could not add to the second carbonyl group of the 1,2-diketone, being in the form of silyl enol ether **2**, and thus protected from nucleophilic attack. Also, monosilyl enol ether **2** is not nucleophilic enough to be involved

Table 1
Organocatalytic reaction of cinnamaldehyde (**3a**) with cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether (**1**) in the presence of different catalysts[a]

Entry	Catalyst	**1** (equiv)	Time (h)	Yield of **5a** (%)	ee (%)
1	**6**	1.3	13	24	88
2	**6**	1.6	13	34	87
3	**6**	2	15	50	87
4	**7**	2	116	—	—
5	**8**	2	100	—	—
6	**9**	2	9	56	21
7	**10**	2	65	39	30
8	**11**	2	100	11	79
9	**12**	2	70	59	92

[a] Reaction conditions: dienol ether **1** (2 equiv); aldehyde **3a** (1 equiv, 0.15 M in methanol); catalyst (5 mol %); $NaBH_4$ (1 equiv); TBAF (4 equiv, 0.05 M in THF).



Scheme 2. Possible stereoinduction in the addition reaction.

Table 2
Selection of the solvent for the Mukaiyama–Michael addition of dienolate **1** to cinnamaldehyde (**3a**) with catalyst **12**[a]

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield of **5a** (%)	ee (%)
1	MeOH	5	11	56	88
2	EtOH[b]	5	9	55	92
3	MeOH	10	14	60	90
4	EtOH[b]	10	9	56	93
5	PhMe	10	11	0	—
6	MeCN	10	23	57	86
7	MeCN[c]	10	23	0	—
8	$CHCl_3$	10	15	0	—
9	*i*PrOH	10	23	54	92

[a] Reaction conditions: dienol ether **1** (2 equiv); aldehyde **3a** (1 equiv, 0.15 M in the solvent); catalyst **12**; $NaBH_4$ (1 equiv); TBAF (4 equiv, 0.05 M in THF).
[b] 96% EtOH was used.
[c] HPLC grade MeCN.

in an intramolecular aldol reaction with the aldehyde group under these reaction conditions.

We assumed that the low yield of product **5a** might be connected with the poor stability of **1** in protic solvents such as MeOH. Increasing the relative amount of **1** with respect to substrate **3a** from 1.3 to 2 equiv (Table 1, entries 2 and 3) resulted in an increase in the isolated product yield. With 2 equiv of **1**, compound **5a** was obtained in a 50% isolated yield (the total yield over three subsequent steps).

Using these conditions the organocatalysts listed in Figure 1 were tested in this reaction and compared with that obtained with catalyst **6**. The results are presented in Table 1.

We found that proline **7** was substantially less active than **6** leaving most of the aldehyde **3** and some dienol ether **1** unreacted after 116 h (Table 1, entry 4). The catalyst **8** was also inactive in this reaction (Table 1, entry 5). This result was expected, as imidazolidone catalysts of type **8** are active only together with an acid co-catalyst.[25] However, we were concerned about acidic additives in the reaction mixture, as according to the observations of Wang,[2] acids contribute to the decomposition of silyl enol ethers and therefore need to be avoided. Tetrazole catalyst **9** appeared to be more active than **6** but demonstrated poor selectivity (Table 1, entry 6). The fluorine-containing prolinol derivative **10** was of both low activity and selectivity (Table 1, entry 7). The sterically demanding catalyst **11** showed very low activity but moderate selectivity after an extended reaction time (Table 1, entry 8). Finally, the stable and sterically demanding catalyst **12** afforded the highest yield and selectivity among the investigated catalysts.

It is most probable that the OTBS group of catalyst **12** shields the *Re* face of the double bond in the iminium intermediate and directs the silyl enol ether **1** to attack from the *Si* face producing the Mukaiyama–Michael adduct **5a** with *S* configuration. (Scheme 2).[26,27] Confirmation of the absolute configuration of **5a** by comparing the measured and calculated vibrational circular dichroism spectra[28,29] is currently underway and will be published separately in due course.

Table 3
Synthetic scope of the Mukaiyama–Michael addition[a]

Entry	Aldehyde	Time (h)	Yield of **5** (%)	ee (%)
1	**3a**	9	55	92
2	**3b**	9	57	94
3	**3c**	20	40	87
4	**3d**	10	66	90
5	**3e**	9	63	91

[a] Reaction conditions: dienol ether **1** (2 equiv); aldehyde **3** (1 equiv, 0.15 M in EtOH); catalyst **12** (5 mol %); $NaBH_4$ (1 equiv); TBAF (4 equiv, 0.05 M in THF).

We found that the reaction was faster in 96% ethanol than in methanol (anhydrous) (Table 2, entries 1 and 2). Taking into account the relative instability of **1** under hydrolytic conditions, we increased the catalyst amount to 10 mol % and obtained only slightly improved results (Table 2, entries 1 and 2 vs 3 and 4). Toluene and chloroform were not suitable solvents as no reactions were observed. In reagent grade acetonitrile (not dried) a slower reaction with lower selectivity was observed (Table 2, entry 6) while in dry HPLC grade acetonitrile no product was formed at all (Table 2, entry 7). Of the alcohols used, isopropanol provided the best selectivity, but a lower reaction rate than that of ethanol (Table 2, entry 9). On the basis of these results we selected 96% ethanol in the presence of 5 mol % of the catalyst **12** for the subsequent experiments, affording fast reactions with good stereoselectivity.

To evaluate the scope of this iminium-catalyzed Mukaiyama–Michael type addition we performed the reaction with different α,β-unsaturated aldehydes **3**. The electron-withdrawing substituent on the benzene ring of *p*-nitrocinnamaldehyde **3b** provided the addition product **5b** in good isolated yield (57%) and in excellent selectivity (94% ee) (Scheme 1, Table 3, entry 2). The *p*-methoxycinnamaldehyde **3c** reacted slowly and gave a lower yield and selectivity (Table 3, entry 3). The same trend had been observed before for the organocatalytic aldol reaction of *p*-methoxybenzaldehyde with acetone.[30] The results obtained with *p*-bromo derivative **3d** were in between the previous two in terms of selectivity, but the isolated yield of **5d** was higher (Table 3, entry 4). It is also noteworthy that the aliphatic unsaturated aldehyde *trans*-hept-2-enal (**3e**) gave the addition product **5e** in good yield and selectivity (Table 3, entry 5).

In summary, cyclopentane-1,2-dione bis-silyl enol ether readily undergoes the organocatalytic Mukaiyama–Michael reaction with α,β-unsaturated aldehydes in good yield and high stereoselectivity. The results demonstrate a convenient method to obtain chiral 3-substituted 1,2-diketone structural subunits from easily accessible starting compounds. These fragments are present in many biologically active compounds.[31–33] Also, the obtained 1,2-diketones (mono-enolic form) could be transformed into lactone acids via oxidative ring cleavage to afford a wide variety of products as we have demonstrated earlier.[34–37]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.041.

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Article IV

Reile, I.; Kalle, S.; Werner, F.; Järving, I.; Kudrjashova, M.; Paju, A.; Lopp, M. Heterogeneous Platinum Catalytic Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones, *submitted*.

Heterogeneous Platinum Catalytic Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones

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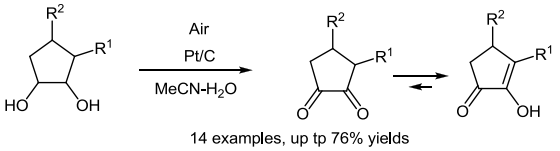
Abstract

A method for the aerobic oxidation of cyclopentane-1,2-diols to diketones over a commercial heterogeneous Pt/C catalyst is described. Under optimized reaction conditions (atmospheric air, 1 mol% of catalyst, 1 eq of LiOH, aqueous solvents and 60 °C temperature) unsubstituted, 3- and 4-substituted cyclopentane-1,2-diols oxidized to 1,2-dicarbonyl compounds in good yields. The method is applicable for producing cyclopentane-1,2-diketones.

Graphical abstract



Highlights

Method for aerobic oxidation of cyclopentane-1,2-diols to their corresponding diketones. Oxidation of cyclopentane vic-diols over a heterogeneous Pt/C catalyst in aqueous solvents. Up to 76% of isolated yields. The method is applicable both at milligram and gram scales.

Keywords: dehydrogenation, diols, heterogeneous catalysis, 1,2-diketones, oxidation, platinum

1. Introduction

Oxidative catalytic dehydrogenation is a common way of selectively converting alcohols to their carbonyl derivatives. Catalytic oxidation, especially the catalytic aerobic oxidation, is preferred over the traditional stoichiometric oxidation processes, since it

does not produce hazardous by-products.[1] Since the 1970s, when the first reports of the metal-catalyzed aerobic oxidations appeared,[2] steady progress in this field has occurred.[3] Several catalyst systems, such as homogeneous metal complexes dissolved in water,[4,5] ionic liquids[6] or organic solvents,[7] and heterogeneous systems, containing solid supported metal catalysts[8] or metal nanoparticles[9] in organic solvents,[10] water[9] and supercritical CO_2[11] have been developed. In addition to the platinum metal catalysts,[12] other metals, including palladium,[13] ruthenium,[14] gold[15] and bimetallic systems,[16,17] have also been used.

While most of the known methods can be applied for the conversion of allylic or benzylic alcohols, only a few of them can be used for the oxidation of non-activated aliphatic alcohols.[8] Furthermore, there are even fewer aerobic oxidation methods suitable for the oxidation of *vic*-diols to their corresponding diketones[18,19,20] because of the easy cleavage of the carbon-carbon bond between the hydroxyl groups under oxidative conditions.[21,22,23] In our preliminary report, we described the first experiments on aerobic metal catalysed oxidation of cyclopentane-1,2-diols to their corresponding cyclopentane-1,2-diones, which were isolated as their mono enol tautomers.[24] Here, we summarize the results of our study on the oxidation method, concerning optimization of the reaction conditions and broadening of the selection of alcohols as the reaction substrates.

2. Experimental

2.1 General remarks

All reagents purchased from common suppliers were used without further purification. All solvents were distilled according to common procedures prior to use. Silica gel 40 – 100 μm was used for column chromatography. All NMR spectra were measured at room temperature on a Bruker Avance III 400 MHz instrument. MS (EI) spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer, FT-IR spectra were recorded on a Perkin-Elmer Spectrum BX spectrometer, HRMS (APCI-MS) measurements were performed on a Agilent Technologies 6450 UHD Accurate-Mass Q-TOF LC/MS instrument. Single crystal X-ray diffraction data were collected on a Bruker SMART X2S. The supplementary material contains additional synthetic procedures for the preparation of oxidation substrates, NMR spectra and the crystallographic data for this paper (compounds **4j** and **4k**, deposited with the Cambridge Crystallographic Data Centre (CCDC 833165 (**4j**) and 833166 (**4k**)).

2.2 Preparation of oxidation substrates

Diols **1b** and **1l** were purchased from Aldrich. The preparation of diols **1a** and **1c**-**1g** was described earlier.[24,25] Diols **1h** – **1k** were prepared from their preceding cyclopentenes by the general dihydroxylation procedure described below. The preparation of the above mentioned cyclopentenes is described in the supplementary material. The preparation of diols **1m**, **1n**, **5** and alcohol **6** is described in the supplementary material.

2.2.1 General procedure for the dihydoxylation of cyclopentenes used for the preparation of diols 1h – 1k

4 mmol of the corresponding cyclopentene was dissolved in 13 ml of 3:1 mixture of *t*-BuOH and water. 1.1 ml of 50% w/w aqueous NMO solution (5.2 mmol) and 13.5 mg of 7.5% solid supported OsO_4 catalyst (0.004 mmol) were added. The mixture was stirred at 60 °C until no more of the corresponding cyclopentene was observed in the reaction mixture. The catalyst was filtered off, 20 ml of EtOAc was added and the mixture was washed with 10 ml of 10% $Na_2S_2O_3$. The aqueous phase was separated and extracted with EtOAc. All organics were combined and dried over $MgSO_4$, the solvent was evaporated and the product was purified by column chromatography over silica gel.

2.2.2 Characterization of the prepared diols 1

3-Benzylcyclopentane-*cis*-1,2-diol 1h was obtained by the general dihydroxylation procedure over 3 days in 93% yield as a 1:0.6 mixture of diastereomers (white crystals, m.p. 46-47 °C). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.16 (m, 5 H, Ph), 4.09 – 4.05 (dd, *J* = 8.8, 5.3 Hz, 1 H, H1), 3.65 – 3.62 (t, *J* = 5.6 Hz, 1 H, H2), 2.90 – 2.85 (dd, *J* = 13.5, 6.3 Hz, 1 H, Bn), 2.61 – 2.56 (dd, *J* = 13.5, 8.5 Hz, 1 H, Bn), 2.42 (broad s, 1 H, O*H*1), 2.25 – 2.16 (m, 2H, H3, O*H*2), 2.01 – 1.82 (m, 2 H, H4, H5), 1.68 – 1.57 (m, 1 H, H5), 1.25 – 1.14 (m, 1 H, H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.82 (Ph), 128.98 (Ph), 128.57 (Ph), 126.18 (Ph), 78.88 (C2), 73.03 (C1), 45.49 (C3), 39.81 (Bn), 30.38 (C5), 26.48 (C4). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.16 (m, 5 H, Ph), 4.16 – 4.10 (m, 1 H, H1), 3.84 – 3.82 (t, *J* = 4.0 Hz, 1 H, H2), 2.95 – 2.89 (dd, *J* = 13.5, 7.9 Hz, 1 H, Bn), 2.68 – 2.63 (dd, *J* = 13.6, 7.6 Hz, 1 H, Bn), 2.42 (broad s, 1 H, O*H*2), 2.34 (broad s, 1 H, O*H*1), 2.14 – 2.02 (m, 1 H, H3), 2.01 – 1.82 (m, 1 H, H5), 1.68 – 1.57 (m, 3 H, H4, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.55 (Ph), 128.90 (Ph), 128.45 (Ph), 125.94 (Ph), 74.73 (C1), 74.34 (C2), 44.30 (C3), 36.03 (Bn), 30.87 (C5), 27.31 (C4). IR: 3409, 2924, 1604, 1495, 1453, 1341, 1100, 1038, 752, 701 cm^{-1}; MS (EI): *m*/*z* = 192, 174, 156, 145, 130, 117, 91, 83. Anal. calcd. for $C_7H_{14}O_3$: C 74.97; H 8.39. Found: C 74.95; H 8.44.

4-(Benzyloxymethyl)cyclopentane-*cis*-1,2-diol 1i was prepared by the general dihydroxylation procedure over 2 days in 98% yield (1:2.8 mixture of diastereomers). The preceding cyclopentene was prepared from 3-cyclopentene carboxylic acid according to a known procedure.[26] Compound **1i** was obtained as a white crystalline material with spectral and physical properties matching literature values.[27]

4-(*t*-Butoxymethyl)cyclopentane-*cis*-1,2-diol 1j was obtained by the general dihydroxylation procedure over 3 days in 62% yield as a colourless oil (1:2.5 mixture of diastereomers). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 – 4.04 (m, 2 H, H1, H2), 3.91 (broad s, 2 H, 2x OH), 3.18 – 3.16 (d, *J* = 6.3 Hz, 2 H, -C*H*$_2$O-), 2.48 – 2.37 (m, 1H, H4), 1.89 – 1.79 & 1.62 – 1.56 (m, 2 x 2 H; H3, H5), 1.16 (s, 9 H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.69 (C1, C2), 72.21 (-*C*(CH$_3$)$_3$), 65.76 (-*C*OH-), 34.69 (C4), 34.41 (C3, C5), 27.42 (*t*Bu). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (broad s, 4 H, 2x OH, H1, H2), 3.31 – 3.30 (d, *J* = 3.4 Hz, 2 H, -C*H*$_2$O-), 2.31 – 2.23 (m, 1 H, H4), 2.07 – 2.00 & 1.53 – 1.47 (m, 2 x 2 H, H3, H5), 1.21 (s, 3.6 H, *t*Bu'). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.03 (C1, C2), 73.49 (-*C*(CH$_3$)$_3$), 64.34 (-*C*OH-), 33.91 (C4), 33.52 (C3, C4), 27.25 (*t*Bu). IR: 3405, 2973, 1391, 1363, 1200, 1083, 1021 cm^{-1}; MS (EI): *m*/*z* = 188, 173, 155, 131, 113, 102, 97, 83, 69, 57. APCI-MS: *m*/*z* observed 192.1145, calcd. for $C_7H_{14}O_3$ 192.1150.

4-(Methoxymethyl)cyclopentane-*cis*-1,2-diol 1k was obtained by the general dihydroxylation procedure over 2 days in 56% yield as a colourless oil (1:0.4 mixture of diastereomers). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10 – 4.08 (t, *J* = 4.8 Hz, 2 H, H1, H2), 3.33 (s, 3 H, OMe), 3.24 – 3.22 (d, *J* = 6.5 Hz, 2 H, -C*H*$_2$OMe), 2.57 – 2.51 (tt, *J* = 9.2, 6.5 Hz, 1 H; H4), 1.88 – 1.81 (m, 2 H, H3, H5), 1.64 – 1.57 (m, 2 H, H3, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.29 (-*C*H$_2$OMe), 73.87 (C1, C2), 58.84 (OMe), 34.63 (C3, C5), 34.51 (C4). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 – 3.89 (q, *J* = 5.5 Hz, 2 H, H1, H2), 3.40 (s, 3H, OMe), 3.34 – 3.33 (d, *J* = 4.0 Hz, 2 H, -C*H*$_2$OMe), 2.30 – 2.20 (m, 1 H, H4), 2.10 – 2.02 (m, 2 H, H4, H5), 1.54 – 1.48 (dt, *J* = 13.9, 5.5 Hz, 2 H, H4, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.38 (-*C*H$_2$OMe), 74.11 (C1, C2), 59.06 (OMe), 34.23 (C5), 34.01 (C3, C4). IR: 3396, 2930, 1442, 1388, 1338, 1115, 927 cm^{-1}; MS (EI): *m/z* = 146, 128, 114, 101, 96, 83, 69, 55, 45. APCI-MS: *m/z* observed 146.0942, calcd. for $C_7H_{14}O_3$ 146.0943.

(1S,2S,3R)-3-(2-(Benzyloxy)ethyl)cyclopentane-*trans*-1,2-diol 1m was obtained as white crystals, m.p. 34 - 35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.25 (m, 5H, Ph), 4.50 (s, 2 H, Bn), 4.07 – 4.04 (tt, *J* = 4.3, 2.3 Hz, 1 H, H1), 3.90 – 3.88 (dd, *J* = 5.3, 2.3 Hz, 1 H, H2), 3.61 – 3.56 (m, 1 H, CH$_2$C*H*$_2$OBn), 3.49 – 3.42 (m, 1 H, CH$_2$C*H*$_2$OBn), 2.18 – 2.03 (m, 2 H, H3, H5), 1.88 – 1.77 (m, 2 H, H4, C*H*$_2$CH$_2$OBn), 1.69 – 1.61 (m, 1 H, C*H*$_2$CH$_2$OBn), 1.48 – 1.33 (m, 2 H, H4, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.85 (Ph), 128.50 (Ph), 127.80 (Ph), 127.76 (Ph), 79.70 (C2), 78.95 (C1), 73.35 (Bn), 70.10 (-*C*H$_2$C*H*$_2$OBn), 40.96 (C3), 31.68 (C5), 29.35 (-*C*H$_2$C*H*$_2$OBn), 28.26 (C4); (assignment of diasteromers based on γ-syn effect between C2-OH and -CH$_2$CH$_2$OBn groups when comparing ^{13}C chemical shifts of compounds **1m** and **1n**). IR: 3375, 2937, 1454, 1364, 1095, 956, 738, 698 cm^{-1}; MS (EI): *m/z* = 236, 218, 200, 174, 156, 145, 127, 107, 91. APCI-MS: *m/z* observed 236.1412, calcd. for $C_{14}H_{20}O_3$ 236.1412.

(1S,2S,3S)-3-(2-(Benzyloxy)ethyl)cyclopentane-*trans*-1,2-diol 1n was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5 H, Ph), 4.50 (s, 2 H, Bn), 3.97 – 3.92 (q, *J* = 7.3 Hz, 1 H, H1), 3.60 – 3.55 & 3.53 – 3.49 (m, *2* H, -CH$_2$C*H*$_2$OBn), 3.48 – 3.43 (m, 1 H, H2), 1.98 – 1.89 (m, 1 H, H5), 1.87 – 1.68 (m, 3 H, H3, H4, -C*H*$_2$CH$_2$OBn), 1.64 – 1.57 (m, 1 H, -CH$_2$C*H*$_2$OBn), 1.55 – 1.46 (m, 1 H, H5), 1.40 – 1.32 (m, 1 H, H4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.72 (Ph), 128.49 (Ph), 127.83 (Ph), 127.81 (Ph), 84.32 (C2), 78.12 (C1), 73.14 (Bn), 69.95 (-*C*H$_2$*C*H$_2$OBn), 42.60 (C3), 34.36 (C5), 29.03 (-*C*H$_2$CH$_2$OBn), 26.41 (C4); (assignment of diasteromers based on γ-syn effect between C2-OH and -*C*H$_2$CH$_2$OBn groups when comparing ^{13}C chemical shifts of compounds **1m** and **1n**). IR: 3368, 2869, 1454, 1363, 1099, 738, 699 cm^{-1}; MS (EI): *m/z* = 236, 218, 200, 174, 156, 145, 127, 107, 91. APCI-MS: *m/z* observed 236.1415, calcd. for $C_{14}H_{20}O_3$ 236.1412.

2,7-Dimethyloctane-4,5-diol 5 was prepared from isovaleric aldehyde by pinacol coupling,[28] the compound was obtained as white needles, m.p. 72 – 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.46 – 3.41 (ddd, *J* = 7.7, 3.1, 1.7 Hz, 2 H, H4, H5), 2.52 (broad s, 2 H, 2 x O*H*), 1.86 – 1.81 (m, 2 H, H2, H7), 1.44 – 1.37 (ddd, *J* = 14.0, 9.4, 4.6 Hz, 2 H, H3, H6), 1.25 – 1.19 (ddd, *J* = 12.5, 9.5, 3.0, 2 H, H3, H6), 0.95 – 0.91 (dd, *J* = 10.2, 6.6 Hz, 12 H, 4 x Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.04 (C4, C5), 42.71 (C3, C6), 24.50 (C2, C7), 23.76 & 21.71 (4 x Me). IR: 3347, 2957, 1469, 1367, 1058, 844, 719 cm^{-1}; MS spectra coincides with public database values.[29]

***tert*-Butyl-(3-hydroxycyclopentyl)acetate 6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 – 4.22 (m, 1 H, *C*-OH), 2.28 – 2.26 (m, 2 H, *C*H$_2$COO*t*Bu), 2.23 – 2.07 (m, 2 H, H1, H2), 1.80 – 1.66 (m, 2 H, H4, H5), 1.64 – 1.56 (m, 1 H, H4), 1.46 – 1.38 (m, 1 H, H5), 1.37 (s,

9 H, *t*Bu), 1.23 – 1.14 (m, 1 H, H2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.63 (*C*OO), 79.15 (*C*(CH_3)$_3$), 72.60 (C3), 40.93 (*C*H_2COO*t*Bu), 40.65 (C2), 34.49 (C4), 33.76 (C1), 28.85 (C5), 27.10 (*t*Bu). MS (EI): *m*/*z* = 200, 144, 127, 109, 81.

2.3 General procedure for the catalytic aerobic oxidation of diols

Diol (0.424 mmol), Pt/C catalyst (1 or 5 mol% metal loading compared to diol)[30], LiOH·H_2O (1.0 eq, 0.424 mmol) and solvent (2 mL, MeCN–H_2O 1:1) were added to a 10 mL glass reactor, equipped with a condenser and stirred at 60 °C for the appropriate time. The reaction progress was monitored by TLC. When the product formation had stopped, the catalyst was filtered off and rinsed with EtOAc (3x3 mL), resulting in a biphasic solution. The aqueous phase was acidified to pH 5 with 1M HCl and the layers were separated. The aqueous layer was extracted twice with EtOAc (20 mL). All organics were combined and dried over $MgSO_4$ and were concentrated in a vacuum. The crude product was purified by column chromatography (EtOAc-petroleum ether or MeOH-CH_2Cl_2) to give the product diketone as its ketoenol tautomer **4**.

2.4 General procedure for larger scale catalytic aerobic oxidation of diols

Diol (9 mmol) was dissolved in 45 ml of solvent (MeCN–H_2O 1:1) and the Pt/C catalyst catalyst[30] was added (1 mol% metal loading based on diol), followed by 1 eq of LiOH·H_2O (9 mmol). A 0.3 ml/min flow of solvent-saturated air was bubbled through the reaction mixture and the reaction was stirred at 60 °C for 6 h. The catalyst was filtered from the reaction mixture, rinsed three times with 10 ml of EtOAc and the biphasic solution was adjusted to pH 5 with 1.0 M HCl. The phases were separated and the aqueous phase was extracted twice with 20 ml of EtOAc. All organics were combined and dried over $MgSO_4$, the solvent was evaporated and the product and the regenerated starting material were purified by column chromatography (MeOH-CH_2Cl_2).

2.5 Characterization of Oxidation Products

2-Hydroxy-3-(2-benzyloxyethyl)-2-cyclopenten-1-one 4a: The compound spectral properties coincided with a literature example.[25]

2-Hydroxy-3-methyl-2-cyclopenten-1-one 4b: The compound was identical to a commercial sample.

2-Hydroxy-3-(2-hydroxyethyl)-2-cyclopenten-1-one 4c: The compound spectral properties coincided with a literature example.[26]

2-Hydroxy-3-oxo-1-cyclopentene-1-acetic acid-1,1-dimethylpropyl ester 4d: The compound spectral properties coincided with a literature example.[31]

N-[2-(2,3-Dioxocyclopentyl)ethyl]-carbamic acid-1,1-dimethylethyl ester 4e: The compound spectral properties coincided with a literature example.[24]

2-Hydroxy-3-phenyl-2-cyclopenten-1-one 4f: The compound spectral properties coincided with an authentic sample.[32]

2-Hydroxy-3-(benzyl)-2-cyclopenten-1-one 4h: The compound spectral properties coincided with an authentic example.[33]

4-[(Benzyloxy)methyl]-2-hydroxycyclopent-2-en-1-one 4i: The compound was obtained, following the general procedures described above, as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.26 (m, 5 H, Ph), 6.53 – 6.52 (d, *J* = 3.0 Hz, 1 H, H3), 5.73 (broad s, 1 H, -O*H*), 4.53 (s, 2 H, Bn), 3.50 – 3.40 (m, 2 H, -C*H*$_2$O-), 3.12 – 3.06 (m, 1 H, H4), 2.62 – 2.56 (dd, *J* = 19.4, 6.0 Hz, 1 H, H5), 2.24 – 2.19 (dd, *J* = 19.4, 1.6 Hz, 1 H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.28 (C1), 153.37 (C2), 137.98 (Ph), 130.45 (C3), 128.60 (Ph), 127.94 (Ph), 127.81 (Ph), 73.44 (Bn), 73.20 (-*C*H$_2$O-), 36.50 (C5), 35.37 (C4). IR: 3343, 2860, 1686, 1654, 1455, 1395, 1198, 1100, 740, 700 cm^{-1}; MS (EI): *m*/*z* = 218, 200, 188, 172, 160, 145, 134, 121, 107, 91. APCI-MS: *m/z* observed 218.0937, calcd. for $C_{13}H_{14}O_3$ 218.0943.

4-(*t*-Butoxymethyl)-2-hydroxycyclopent-2-en-1-one 4j: The compound was obtained, following the general procedures described above, as colourless crystals, m.p. 64 – 66 °C: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 – 6.56 (d, *J* = 3.0 Hz, 1 H, H3), 6.04 (broad s, 1 H, -O*H*), 3.38 – 3.28 (m, 2 H, -C*H*$_2$O-), 3.00 – 2.95 (m, 1 H, H4), 2.61 – 2.55 (dd, *J* = 19.4, 6.0 Hz, 1 H, H5), 2.20 – 2.15 (dd, *J* = 19.4, 1.6 Hz, 1 H, H5), 1.18 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.83 (C1), 153.26 (C2), 131.51 (C3), 73.19 (-*C*(CH$_3$)$_3$), 65.24 (-*C*H$_2$O-), 36.74 (C5), 35.81 (C4), 27.57 (*t*Bu). IR: 3334, 1707, 1644, 1395, 1375, 1193, 1077, 1058, 842 cm^{-1}; MS (EI): *m*/*z* = 184, 169, 153, 128, 111, 98, 87, 80, 57. APCI-MS: *m/z* observed 184.1103, calcd. for $C_{10}H_{16}O_3$ 184.1099.

4-(Methoxymethyl)-2-hydroxycyclopent-2-en-1-one 4k: The compound was obtained, following the general procedures described above, as colourless crystals, m.p. 46 – 48 °C: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 – 6.52 (d, *J* = 3.0 Hz, 1 H, H3), 6.46 – 6.21 (broad s, 1H, -O*H*), 3.41 – 3.33 (m, 2 H, -C*H*$_2$OMe), 3.37 (s, 3 H, OMe), 3.08 – 3.05 (m, 1 H, H4), 2.62 – 2.55 (dd, *J* = 19.4, 6.0 Hz, 1 H, H5), 2.24 – 2.18 (dd, *J* = 19.3, 1.6 Hz, 1 H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.46 (*C*O), 153.56 (*C*OH), 130.71 (C3), 75.84 (-C*H*$_2$OMe), 59.18 (OMe), 36.49 (C5), 35.22 (C4). IR: 3222, 2910, 1705, 1654, 1394, 1200, 1099, 957, 860 cm^{-1}; MS (EI): *m*/*z* = 142, 112, 97, 83, 69, 45. APCI-MS: *m/z* observed 142.0629, calcd. for $C_7H_{14}O_3$ 142.0630.

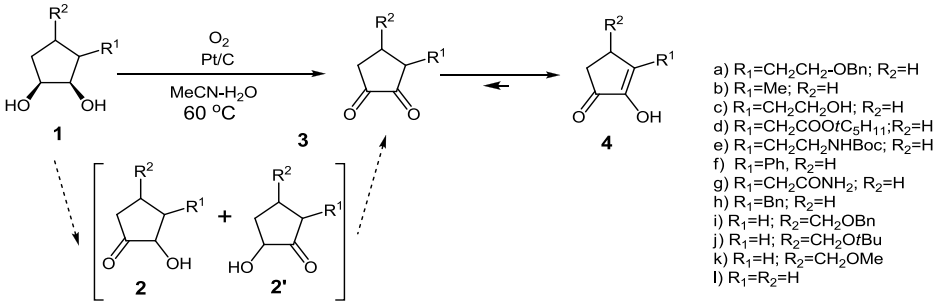
2-Hydroxy-2-cyclopenten-1-one, 4l: The compound spectral properties coincided with an authentic sample.[34]

3-oxo-Cyclopentaneacetic acid-*t*-butyl ester 7: The compound was obtained, following the general procedures described above, as a yellow oil. Compound **7** had been isolated earlier.[35] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 – 2.45 (m, 1 H, H1), 2.43 – 2.36 (m, 1 H, H2), 2.35 – 2.27 (m, 2 H, -C*H*$_2$COO-), 2.27 – 2.19 (m, 1 H, H4), 2.19 – 2.07 (m, 2 H, H4, H5), 1.85 – 1.78 (ddd, *J* = 18.2, 10.1, 1.4 Hz, 1 H, H2), 1.56 – 1.45 (m, 1 H, H5), 1.38 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.68 (C3), 171.46 (-*C*OO-), 80.75 (-*C*(CH$_3$)$_3$), 44.68 (C2), 41.18 (-*C*H$_2$COO-), 38.40 (C4), 33.79 (C1), 29.25 (C5), 28.17 (*t*-Bu); IR: 2976, 1729, 1458, 1368, 1154, 842 cm^{-1}; MS (EI): *m*/*z* = 183, 142, 125, 97, 83, 57.

3-oxo-Cyclopentaneacetic acid 7': The compound was obtained, following the general procedures described above, as a yellow oil. Compound **7'** had been isolated by others earlier.[36] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 – 2.57 (m, 1 H, H1), 2.56 – 2.44 (m, 3 H, H2, -C*H*$_2$-COOH), 2.36 – 2.15 (m, 3 H, H4, H5), 1.94 – 1.87 (ddd, *J* = 18.3, 10.2, 1.4 Hz, 1 H, H2), 1.67 – 1.54 (m, 1 H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.68 (C3), 177.16 (*C*OOH), 44.71 (C2), 39.56 (-*C*H$_2$-COOH), 38,47 (C4), 33.38 (C1), 29.31 (C5). IR:3352, 3209, 2963, 1733, 1660 1403, 1161, 757 cm^{-1}; MS (EI): *m*/*z* = 142, 113, 97, 85, 83, 60, 55, 41.

3. Results and discussion

In testing different activated carbon supported platinum group metal catalysts for dehydrogenation, we found that cis-1,2-diols **1** (Scheme 1) can be converted to 1,2-diones **3** by an aerobic oxidation reaction over a commercially available Pt/C catalyst[30] at 60 °C. The presence of water in the catalyst and/or in the reaction medium is essential for the reaction to occur. Out of several commercial Pt/C catalysts tested, only those two that contained around 50% (w/w) of water were active. When the catalyst was dried before use and the reaction was run in dry toluene, a complete loss of activity was observed.



Scheme 1. Aerobic oxidation of cyclopentane-1,2-diols over Pt/C catalyst.

In selecting a solvent, we found that such solvents as toluene, H_2O or a mixture of MeCN and H_2O can be used if the substrate dissolves in the selected media. When running the reaction in toluene, small amounts of hydroxyketones **2** and **2'** were also detected among the reaction products,[24] indicating that the hydroxyl groups were oxidized in two steps *via* the intermediate hydroxyketones.

The yield of ketoenol **4** depended on the amount of air available. The activated carbon supported catalyst initially contains some oxygen and dissolved oxygen is usually present in solvents. We have previously observed that these oxygen sources are not sufficient for the optimal conversion of **1** to **4**. At the same time, we observed that an unrestricted access of atmospheric air might hinder the oxidation of diols, probably due to the excessive oxidation of the catalyst surface.[26] As a result, the conditions for a stable dehydrogenation procedure were not reached.

The beneficial effect of adding inorganic bases as additives to the oxidation system has been described by Bäckvall for the heterogeneous catalytic dehydrogenations[37] and Mueller et al. for the aerobic oxidations.[38] Following these suggestions, we found that the addition of an inorganic base significantly influenced the process by increasing the reaction rate and the catalyst turnover, allowing us to reduce the reaction time and the catalyst loading. In the presence of a base, the process was also less sensitive to higher oxygen concentration, which made it possible to use free oxygen access and obtain stable yields. The sensitivity drop towards oxygen concentration was similar to that discussed by Steinoff and Stahl for the aerobic homogeneous Pd catalysis.[39] Our observations are in good accordance with earlier findings on the role of the base in the dehydrogenation process[40]: the base facilitated the β-hydrogen elimination step during the reaction.[41] By adding 1 eq of LiOH, we achieved a stable process in acetonitrile–water, with free access of atmospheric air to the reaction medium.

When the substrate **1a** was oxidized in a 1:1 mixture of acetonitrile–water in the presence of different amounts of LiOH and 5 mol% Pt/C loading (Table 1, entries 2-6), it was found that the optimal amount of alkali was around 1 molar equivalent compared to the substrate. In the presence of the base, no hydroxyketone **2** was detected. Alkali considerably enhanced the reaction rate: without alkali we obtained 66% of product **4a** in 20 h, while adding 1 equivalent of LiOH provided 70% of product **4a** in 4 h (Table 1, entries 1 and 6).

Table 1. Scope and reaction conditions

Entry	Substrate	Alkali eq	Time h	Product yield, %
1[24]	**1a**	0	20	66
2	**1a**	0.2	4	61
3	**1a**	0.4	4	67
4	**1a**	0.6	4	69
5	**1a**	0.8	4	70
6	**1a**	1	4	70
7*	**1a**	1	4	68
8	**1b**	1	5	74
9	**1c**	1	5	49
10	**1d**	1	1.3	28
11	**1e**	1	4	76
12	**1f**	1	3.5	69
13	**1g**	1	3	0

All experiments were run in 1:1 MeCN-H_2O at 60 °C with 5 mol% Pt/C catalyst loading in an open glass reactor equipped with a condenser ; 1eq of LiOH*H_2O.
*Regenerated catalyst[24]

When the Pt/C catalyst was filtered from the reaction mixture and reused for the oxidation of diol **1a** under the conditions described above, only a minor decrease of yield was observed and the product **4a** was isolated in 68% yield (Table 1, entry 7). Thus the catalyst could be reused at least once without a noticeable decrease in the catalyst activity.[24]

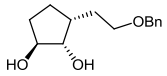
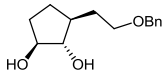
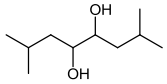
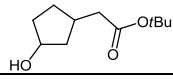
The substrate scope of the reaction was studied by oxidizing 1,2-diols with different structures in the presence of 5 mol% of Pt/C catalyst (Table 1). In most cases, 1,2-diones **4** were obtained in good yield (around 70%). In the case of hydroxyalkyl substituent **1c** with an unprotected OH group, a modest yield of compound **4c** was observed (49%, Table 1, entry 9). However, it is noteworthy that only the secondary OH groups in the cyclopentane moiety in the substrate **1c** were oxidised, leaving the primary hydroxyl group in the hydroxyethyl side chain intact. The oxidation of *tert*-amylcarbonyloxydiol **1d** proceeded quickly during one hour, until a yield of **4d** reached 28% after no further conversion was observed (Table 1, entry 8). The diol **1g** bearing methyl carbamoyl group did not oxidise and the expected dione **4g** was not formed (Table 1, entry 13). At the same time, Boc-aminoalkyl substrate **1e** (also bearing an amido group) resulted in the best isolated yield of dione **4** (76%, Table 1, entry 11).

The reduction of the catalyst loading to 1 mol% slightly decreased the yield when compared with 5 mol% as well as prolonged the reaction time (Table 1, entry 6 *vs* Table 2, entry 1; 63% in 5.5 h). At the same time, the TON value increased from 14 to 63, making the lower catalyst loading highly feasible. The same tendency was observed for all substrates, with the highest observed TON being approximately 72 (Table 2, entry 4) in the case of substrate **1e**. In the investigated cases, the unreacted starting material was easily separated and recovered. The reduction of catalyst loadings below 1 mol% resulted in an excessive decrease in the yield.

The yield of the product with 1 mol% of Pt/C catalyst depended, similarly, on the amount of LiOH, as with 5 mol% of the catalyst. However, with lower catalyst loadings the yield was more sensitive to the alkali amount (Table 2, entry 3). The change of LiOH to CsOH resulted in a small reduction in the product yield (to 59%), accompanied by a complete loss of starting material (Table 2, entry 2). We suggest that CsOH does greatly influence the reaction, but the product **4a** decomposes with CsOH under these conditions. The optimal reaction temperature was around 60-70°C: below 60°C the reaction became significantly slower and above 70°C the product started to decompose, resulting in reduced yields.

The oxidation of different diols with substituents in the cyclopentane ring was studied (Tables 1 and 2). Both 3- and 4-substituted diols were successfully oxidized with good yields. Oxidation of the 4-substituted diols **1j** and **1k** afforded the corresponding diketones **4j** and **4k** which readily formed single crystals suitable for diffraction (Figure 1). The low yield in the case of unsubstituted cyclopentane-1,2-dione **4l** was probably due to the loss of the volatile product during the standard work-up and purification steps.

Table 2. Aerobic oxidation of alcohols to carbonyl compounds over 1 mol% Pt/C catalyst.

Entry	Substrate	Time h	Product yield, %
1	**1a**	5.5	63
2[a]	**1a**	4	59
3[b]	**1a**	5.5	39
4	**1e**	4	72
5	**1h**	5	65
6	**1i**	5	63
7	**1j**	5	61
8	**1l**	4	19
9	**1m** 	4	38
10	**1n** 	4	36
11	**5** 	4	0
12	**6** 	3.5	28 (+33[c])

All experiments were run in 1:1 MeCN-H_2O at 60 °C with 1 mol% Pt/C catalyst loading in an open glass reactor equipped with a condenser ; 1eq of LiOH*H_2O.

[a]1.0 eq of CsOH was used

[b]0.5 eq of LiOH*H_2O was used

[c]yield of corresponding carboxylic acid **7'**

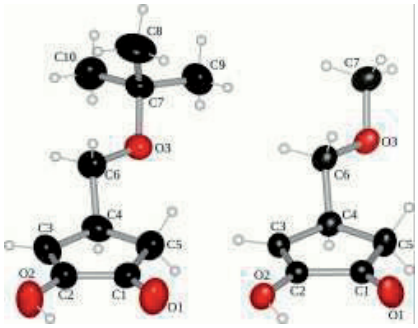


Figure 1. Molecular moieties in the crystal structures of the racemic enols **4j** (left) and **4k** (right). Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

A non-cyclic *vic*-4,5-diol **5** (Figure 2) was completely consumed after 4 h of the oxidation time, but did not afford any expected dicarbonyl compound. Instead, formation of a complex mixture of different carbonyl compounds was observed (Table 2, entry 11). When cyclic compound **6** (Figure 2)with a single secondary hydroxyl group was subjected to oxidation, we obtained the 3-oxo-cyclopentyl acetic acid *t*Bu ester **7** in 28% yield and the corresponding carbocyclic acid **7'** in 33% yield (Table 2, entry 12). The total yield of the dehydration reaction was 61%. This confirms that the oxidation procedure can also be applied to cyclopentanols for the synthesis of cyclic ketones.

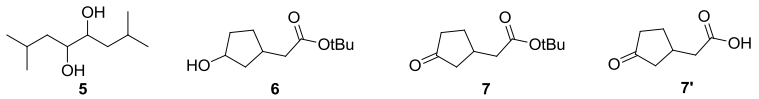


Figure 2. Substrates that were different from template **1**.

The spatial arrangement of the substituents in the cyclopentane ring influenced the reactivity of the substrate. We observed that *trans*-diol afforded a lower yield than the *cis*-diol (Table 2, entry 1 *vs*. entries 9 and 10). At the same time, no noticeable difference was observed when the alkyl substituent was either *cis* or *trans* with the α–hydroxyl group.

Attempts were made to scale up the reaction volume from around 100-milligram scale to gram scale. When the larger reaction volumes were simply run in larger reaction vessels, the obtained reaction yield was low and most of the starting material was left unreacted (Table 3, entry 1), probably due to insufficient oxygen transfer from the surrounding atmosphere into the reaction mixture.

Table 3. Scaled up oxidation of diols **1** to diketones **4**.

Entry	Substrate	Time h	Product yield, %	Regen. **1** %
1*	**1i**	5	34	62
2	**1i**	6	64	28
3	**1j**	6	51	46
4	**1e**	4	66	26
5	**1k**	6	53	40

All experiments were run in 1:1 MeCN-H_2O at 60 °C with 1 mol% Pt/C catalyst in an open glass reactor equipped with a condenser. A 0.3 ml/min flow of atmospheric air saturated with solvent mixture was maintained through the reactor during the reaction.
*without additional air flow

Thus an additional air flow of 0.2-0.3 ml/min was applied by bubbling air (through a separate vessel filled with the reaction solvent) through the reactor. As a result, a constant flow of air (saturated with solvent) was sufficient to successfully oxidise 1,2-diols to 1,2-

diones with a reasonable yield (Table 3). The unreacted material was recovered and separated in all cases. Thus, although quantitative turnover could not be achieved, overall loss in material was small and the regenerated substrate could be reused in the next batch.

4. Conclusions

In summary a practical method for the catalytic aerobic oxidation for cyclopentane-1,2-diols to cyclopentane-1,2-diones was achieved. The reaction was run under relatively mild conditions (60 °C in MeCN/H_2O) in the presence of 1 mol% of a heterogeneous Pt/C catalyst. The method tolerated a wide choice of solvent systems, ranging from organic solvents to aqueous mixtures to water. Under the described reaction conditions, only secondary hydroxyl groups were selectively oxidised. A number of different functional groups in the substrate tolerated oxidation. The reaction method could also be scaled up for preparative use.

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- Reile, I.; Paju, A.; Eek, M.; Pehk, T.; Lopp, M. Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones on Pt/C Catalyst; *30th Estonian Chemistry Days, Abstracts of Scientific Conference*; Rinken, A., Ed. Tartu, **2007**; p. 131; Oral presentation.

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