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USE OF ORGANOCATALYSTS IN STEREOSELECTIVE ORGANIC SYNTHESIS

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Presentata da: Dott.ssa Francesca CAPITTA
Relatori: Prof. Pier Paolo PIRAS, Dott. Jean OLLIVIER

Commissione esaminatrice:

Prof. G. CERIONI Presidente
Prof. G. BASHIARDES Commissario
Prof. L. PELLACANI Commissario Coordinatore dottorato: Prof. M. CASU

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Pr. G. CERIONI	**Président**
Pr. G. BASHIARDES	**Rapporteur**
Pr. L. PELLACANI	**Rapporteur**
Pr. P.P. PIRAS	
Dr. J. OLLIVIER	

Alla mia famiglia

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Introduction

The main topic of thesis is the use of organocatalysis to synthesize cyclobutanones derivatives. Cyclobutanone derivatives are useful molecular building blocks for the construction of complex molecular structures. Surprisingly, however, the use of organocatalysts to functionalize cyclobutanones is rare, especially when the substrate bears substituents. In this thesis, we present the enantioselective transformations and functionalizations of substituted cyclobutanones which employ readily-available amino acids (or derivatives) and thiourea derivatives as organocatalysts.

- The first transformation involves the enantioselective aldol reaction between 2-hydroxy-cyclobutanone with a selection of aromatic aldehydes. The results show that the 2-hydroxycyclobutanone is particularly amenable to solvent-free L-threonine-catalyzed direct aldol reactions with reasonable stereocontrol.

- After, we synthesized 2,3-disubstituted cyclobutanones through direct aldol reactions involving 3-substituted cyclobutanones and aryl aldehydes catalyzed by N-phenylsulfonyl (S)-proline and via asymmetric nitro-Michael reaction of 3-substituted cyclobutanones and several nitrostyrenes catalyzed by thiourea derivatives. In the first case the relative aldol products were obtained with an unprecedented control of all three contiguous stereocenters in the latter the relatives γ-nitro cyclobutanones were obtained in good yields but in modest enantioselectivities.

- The last case concerns the conversion of 3-substituted cyclobutanones into 4-substituted-5-hydroxy-γ-lactam using as electrophile nitrosobenzene and L-proline and its derivatives as catalysts. This reaction involves a ring-expanding *O*-nitroso-aldol–cyclization domino sequence. The synthetic protocol provides access to the five-membered ring system in good yield, and the formation of two new stereogenic centers is achieved with complete stereochemical control.

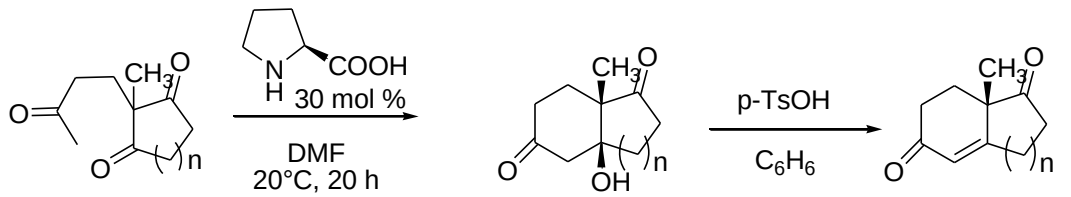
CHAPTER 1

Asymmetric Organocatalysis

General Introduction

The term 'asymmetric organocatalysis' describes the acceleration of chemical reactions through the addition of a catalytic amount of a chiral organic compound.[1] The use of solely organic molecules as chiral catalysts complements the traditional organometallic and biological approaches to asymmetric catalysis. Organocatalysis have several advantages: the reactions can be performed under an aerobic atmosphere with wet solvents, the catalysts are inexpensive, generally nontoxic and often more stable than enzymes or other bioorganic catalysts.

The first example of use of organic molecules as catalysts was reported by two industrial research groups in the early 1971.[2] Hajos and Parrish at Hoffmann La Roche reported that proline-catalyzed intramolecular asymmetric aldol reaction of a triketones **(1)** give aldols **2** in good yields and ees[2a,d] (scheme 1). The aldol condensation products **3** was obtained in a second step through acid-catalyzed dehydration. Eder, Sauer, and Wiechert at Schering shown that the aldol condensation products can also be obtained directly from triketones if the cyclization is performed in the presence of proline and an acid-cocatalyst such as $HClO_4$.[2b,c]



1a n=1
1b n=2

2a n=1 99% yield, 93% *ee*
2b n=2 52%yield, 74% *ee*

3a n=1 99% yield, 87% *ee*
3b n=2 98% yield, 95% *ee*

Scheme 1

This asymmetric proline-catalyzed intramolecular aldol cyclization, now termed Hajos-Parrish-Eder-Sauer-Wiechert reaction,[3] has been applied for the synthesis of steroid and several other natural product (figure 1).[4]

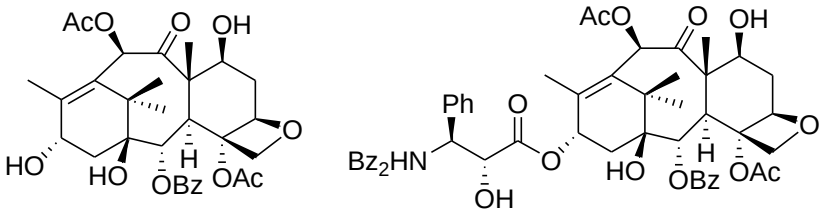
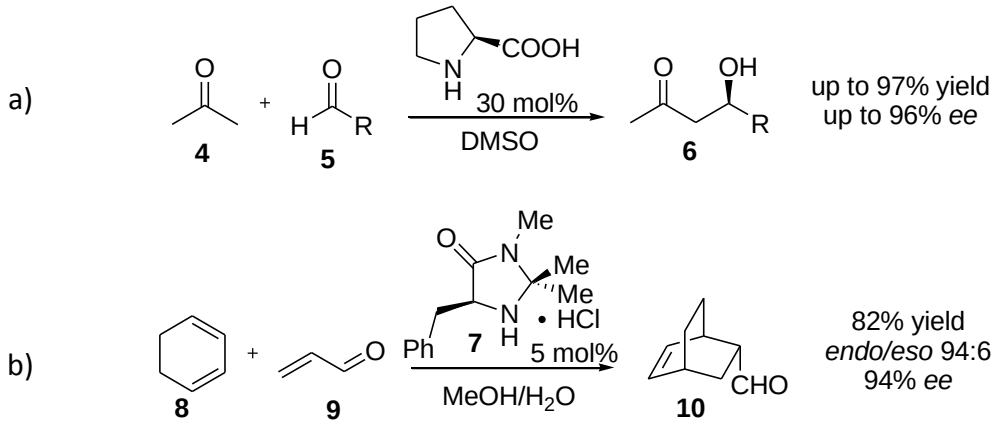


Figure 1

Despite the ketones **3,** prepared through proline catalysis, have been used more or less continuously as a synthetic building block over the past 25 years, its broader implications for asymmetric catalysis were appreciated only in 2000 after two seminal reports by List, Lerner and Barbas,[5] and MacMillan and co-workers[6] on catalysis by chiral secondary amines.

1.1. Enamine and iminium catalysis

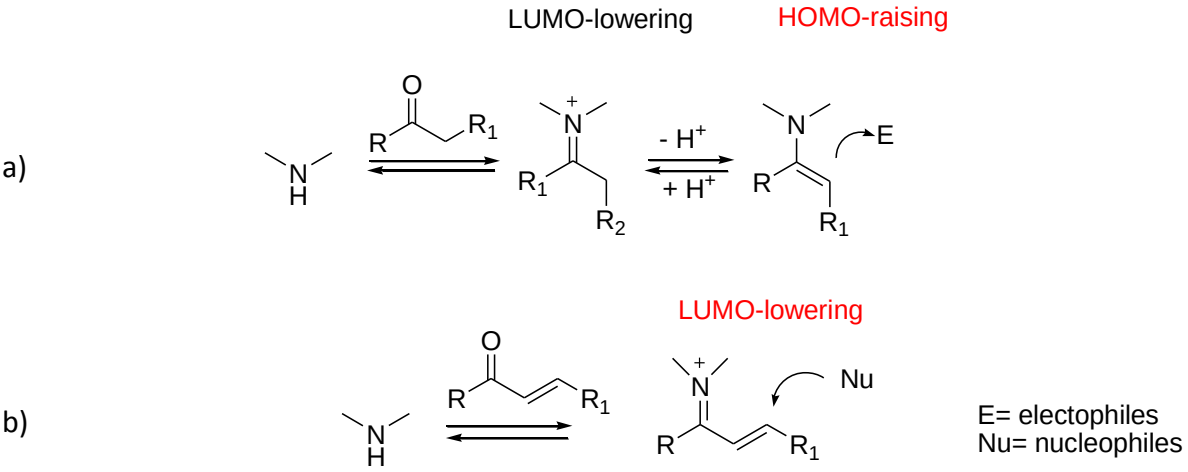
List, Lerner, and Barbas reported that a catalytic amount of the L-proline was able to promote the enantioselective direct aldol reaction between an unmodified ketone, such as acetone **(4)**, and a variety of aldehydes (scheme 2a).[5]



Scheme 2

At the same time MacMillan and co-workers demonstrated the effectiveness of the newly designed imidazolidinone catalyst **(7)** in the activation of α,β-unsaturated aldehydes **(9)** (scheme 2b).[6] These results constituted the basis for two novel organocatalytic activation modes of carbonyl compounds: enamine catalysis[7] and iminium ion catalysis.[8] Both

activation modes were based on covalent active intermediates generated by the condensation of chiral cyclic amines with a carbonyl group. The reversible condensation of a chiral secondary amine with carbonyl compounds to form positively charged iminium ion intermediates induces the energy's lowering of the lowest unoccupied molecular orbital (LUMO). With isolated π-systems, the lowering of LUMO energy increases the acidity of the α proton leading to the generation of the enamine (HOMO activation) (scheme 3a). Instead with conjugate π-systems, the electronic redistribution induced by the iminium intermediates facilitates nucleophilic additions, including conjugate additions and pericyclic reactions (LUMO activation) (scheme 3b).



Scheme 3

By exploiting the HOMO-raising activation (enamine catalysis), several aldehydes and ketones have been α-functionalized with electrophilic reagents. The LUMO-lowering approach (iminium ion catalysis) allowed the asymmetric introduction of different nucleophiles to the β-position of unsaturated aldehydes and ketones.

List described the enamine and iminium ion catalysis, as the Ying and Yang[9] of aminocatalysis, in fact it is apparent that enamine and iminium catalysis are based on the same origin. Enamine catalysis *proceeds via* iminium ion formation and *results* in iminium ion formation. Iminium catalysis *results* in the formation of an enamine intermediate. The two catalytic intermediates are opposites, yet interdependent, and they consume and support each other (figure 2).[10]

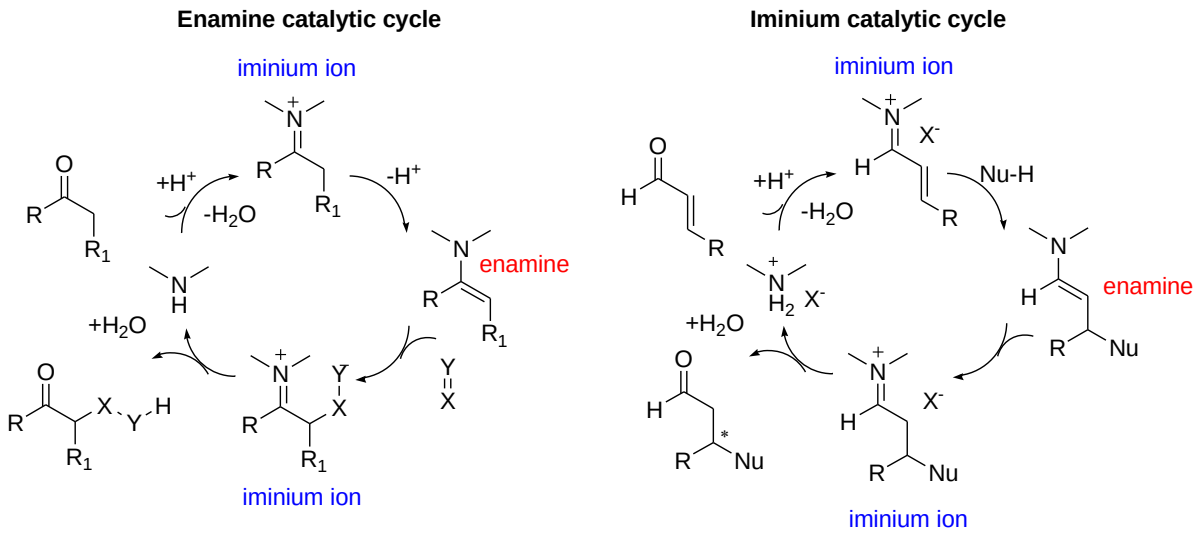
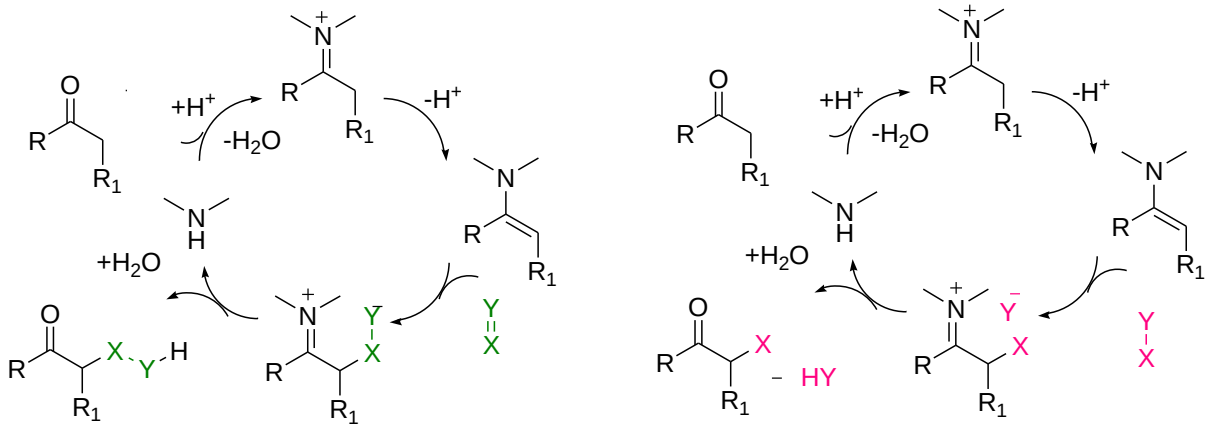


Figure 2

There are two modes of enamine catalysis, depending on the class of electrophile used. The electophiles containing double bound such as aldehydes, imines, Michael acceptors are inserted into the α-C-H bond of the carbonyl compounds via a nucleophilic *addition* reaction of the enamine intermediate, while the electrophile containing single bond, such as alkyl halides, react in a nucleophilic *substitution* reaction.

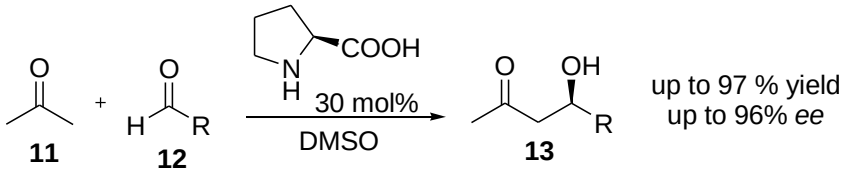


Nucleophilic *addition*

Nucleophilic *substitution*

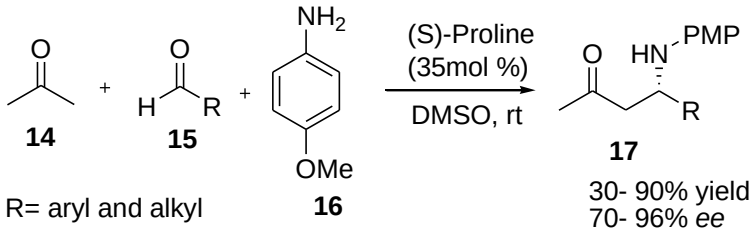
Nucleophilic addition

- Direct Asymmetric Aldol Reaction. In 2000 List and co-workers demonstrated the use of proline as a catalyst for the direct asymmetric aldol reaction between acetone **11** and a variety of aldehydes **12**.[11] The aldol adducts were generated in good to high yield and enantioselectivities.



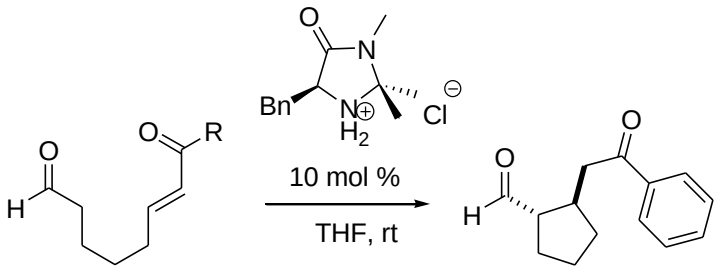
Scheme 4

- Asymmetric Mannich Reaction. The first efficient proline-catalyzed asymmetric three-component Mannich reaction of different ketones with p-anisidine and aldehydes in DMSO was discovered by List.[12] He found that in the presence of 35 mol% (S)-proline, aromatic and α-substituted and α-unsubstituted aliphatic aldehydes (**15**) reacted with acetone to give the corresponding β-amino ketones (**17**) in good yields and excellent enantioselectivities (scheme 5).



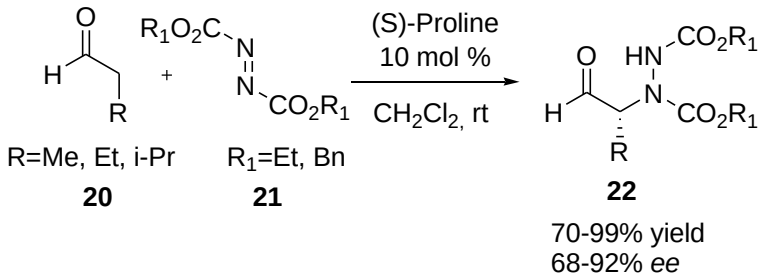
Scheme 5

- Asymmetric Michael Reactions. In 2004, Fonseca and List[13] reported the first catalytic asymmetric intramolecular Michael reaction of formyl enone **18** in the presence of 10 mol% of the commercially available MacMillan imidazolidinone in THF. The Michael addition furnished *trans*-disubstituted cyclic five-membered ketoaldehydes in high yield and with an excellent 97% *ee* (scheme 6).



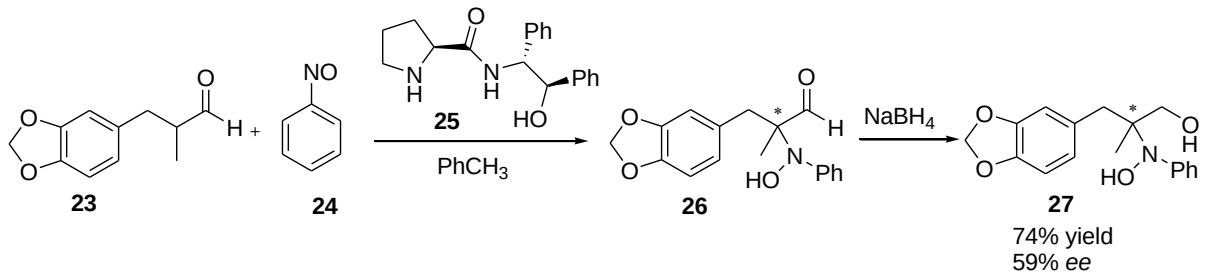
Scheme 6

- Direct Asymmetric α-Amination and α-Oxygenation of carbonyl compounds. The first example was reported simultaneously and independently by Jørgensen *et al*. and List in 2002.[14] Using azodicarboxylates **21** as the nitrogen electrophile with a slight excess of aldehydes **20** and 10 mol% of (S)-proline they obtained the hydrazine aldehydes **22** in moderate to high yields and excellent enantioselectivities (scheme 7).



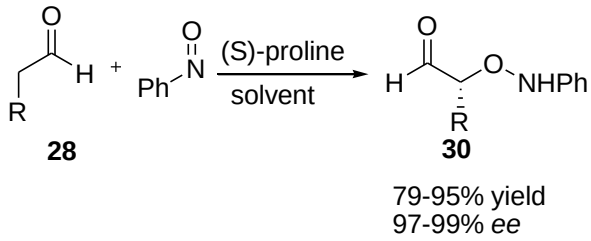
Scheme 7

Gong, Jiang, and co-workers[15] presented for the first time that nitrosobenzene can be used for asymmetric hydroxyamination of carbonyl compounds via enamine catalysis. They observed that the reaction of 2-methyl-3-(3,4-methylenedioxophenyl)propanal **23** with nitrosobenzene **24** in the presence of 10 mol % of **25** give a *N*-selective nitroso aldol adduct **26** with a tertiary stereogenic center as only product which was reduced *in situ* with $NaBH_4$ to produce **27** in moderate yield (scheme 8). No oxyamination product were observed.



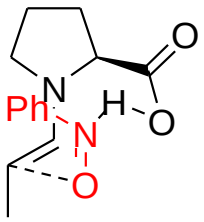
Scheme 8

The oxyamination product was observed almost contemporaneously by Zhong, Hayashi *et al*. and MacMillan and co-workers.[16] They described that in the presence of (S)-proline a series of unbranched aldehydes react with nitrosobenzene to generate the α-aminoxylated aldehydes with excellent enantioselectivity (scheme 9).

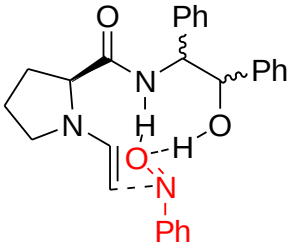


Scheme 9

It is obvious that L-proline and L-prolinamide catalyzed nitroso aldol reaction via different transition states. In the case of proline the oxygen is activated by protonation of the nitrogen of nitrosobenzene with carboxylic acid **TS1**, in the latter case the nitrogen is activated by hydrogen-bonds formed between the oxygen and the amide and hydroxy protons **TS2**.[17]



TS1

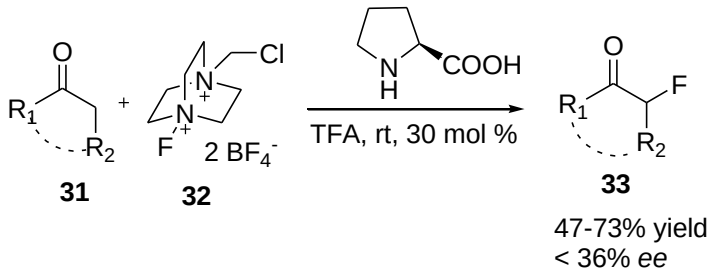


TS2

Nucleophilic substitution

The nucleophilic substitution reactions are inherently more difficult to perform enantioselectively than addition processes as a result of the more flexible nature of the transition state. Some examples are presented in the following section.

- Direct Asymmetric α-Halogenation of Carbonyl Compounds. The first organocatalytic direct α-fluorination of aldehydes and ketones employing Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] as the fluorine source was reported by Enders and Hüttl (scheme 10).[18] For the aldehydes, no enantiomeric excess was reported. In the attempt to perform direct enantioselective α-fluorination of ketones, cyclohexanone was used as the model substrate and a number of chiral amines were tested for their enantioselectivities properties; however, the enantiomeric excess was rather low and in the range of 0 to 36% *ee*.

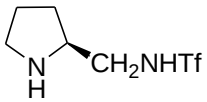


31 **32** **33**

Scheme 10

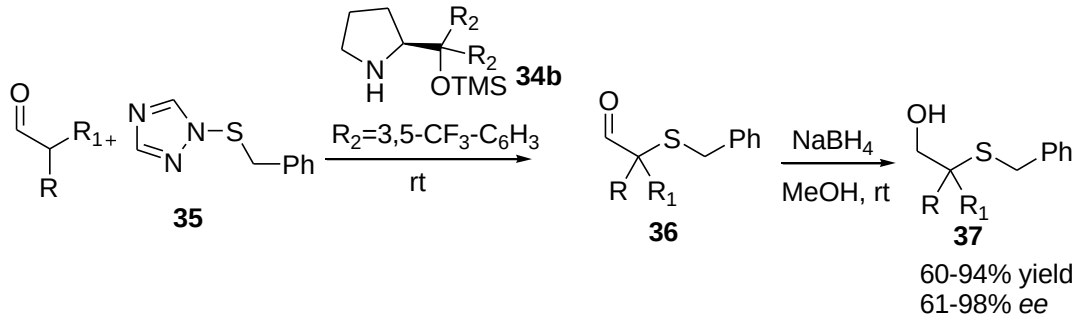
There are also several examples of α-chlorination,[19] α-bromination[20] but scarce examples of the enantioselective α-iodination.[21]

- Direct Asymmetric α-Sulfenylation and α-Selenylation of aldehydes. The direct catalytic approach to α-Sulfenylation was presented recently by Wang *at al.*[22] using catalyst **34a**, which promoted the racemic sulfenylation of aldehydes and ketones using commercially available electrophilic sources.



34a

Almost contemporarily Jørgensen *et al.*[23] presented the first enantioselective version of this transformation by using 1-benzylsulfanyl-1,2,4-triazole **35** as the sulfur source and compound **34b** as catalyst (scheme 11).

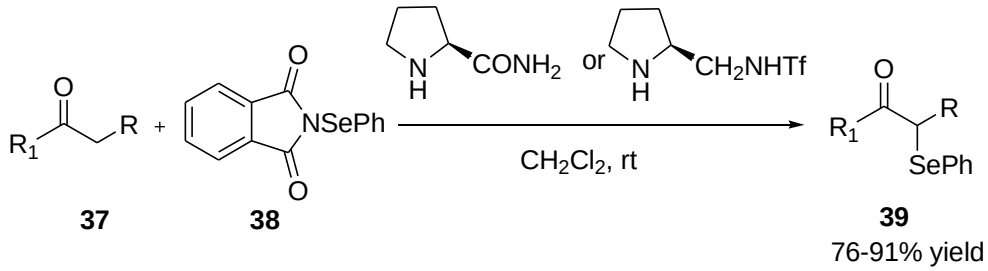


34b **35** **36** **37**

Scheme 11

Catalytic α-Selenylation of carbonyl compounds can be viewed as an extension of the α-Sulfenylation reaction. In 2004, Wang and co-workers reported the first catalytic example of this reaction using chiral secondary amines as catalyst and N-(phenylseleno)phthalimide (**38**)

as the electrophilic selenium source.[24] Different unbranched and some α-branched aldehydes were selenylated rapidly to obtain the product in very high yield (scheme 12).

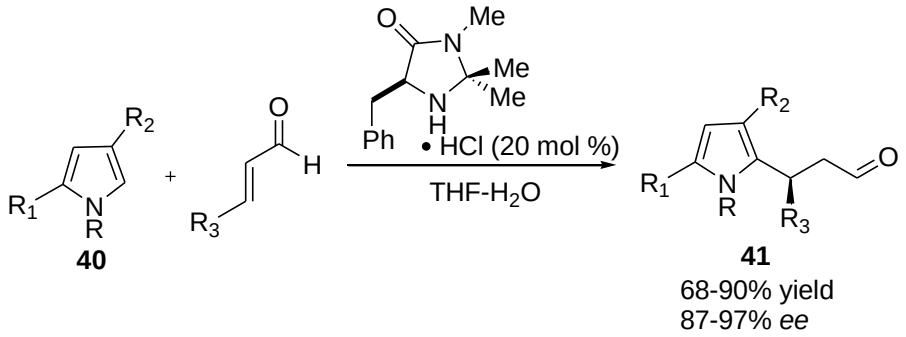


Scheme 12

About the organocatalytic iminium activation strategy, this has been applied in several reactions such as:

- Cycloaddition Reactions. In 2000, MacMillan disclosed the first highly enantioselective amine-catalyzed cycloaddition reaction (Diels-Alder reaction) (see page 2).

- 1,4-Addition Reactions. To further demonstrate the value of iminium catalysis, MacMillan and co-workers undertook the development of asymmetric catalytic Friedel-Crafts alkylations.[25] As such, amine-catalyzed 1,4-addition of aromatics and heteroaromatics to α,β-unsaturated aldehydes were investigated. They focused initial studies on the use of pyrrole (**40**) as substrate to generate β-pyrrolyl carbonyls (**41**) (scheme 13).



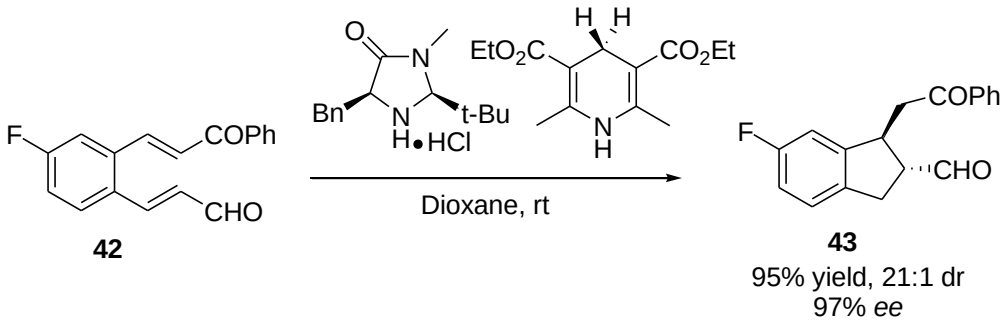
Scheme 13

Chiral imidazolidinone catalyst can also catalyze the addition of silyloxy furans to α,β-unsaturated aldehydes to provide γ-butenolides,[26] the asymmetric Michael addition of carbogenic reagents to α,β-unsaturated carbonyl compounds,[27] the chiral hydrogenation

reactions[28] and almost certainly there are many new powerful enantioselective transformations waiting to be discovered using this mode of activation .

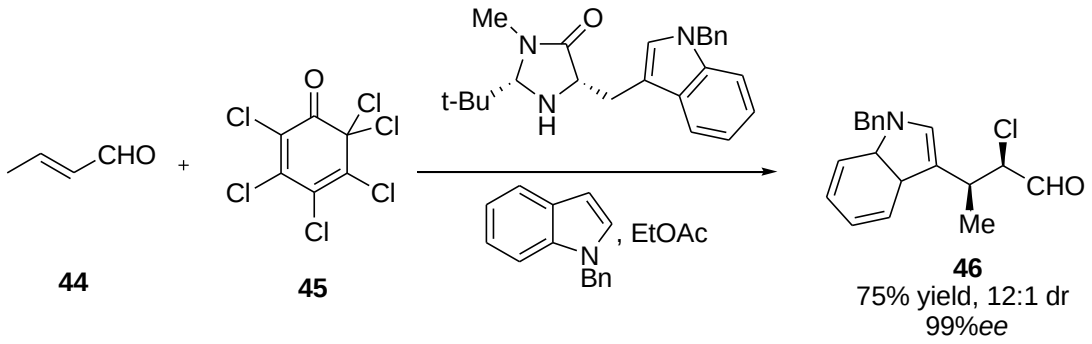
1.2 Tandem iminium-enamine catalysis

The two catalytic principles (enamine and iminium catalysis) were combined in a tandem sequence. List disclosed an efficient asymmetric Michael cyclization consisting of an iminium catalytic conjugate reduction followed by an enamine catalytic intramolecular Michael reaction (scheme 14).[29]



Scheme 14

The MacMillan group discovered a similar sequence which is initiated by an iminium catalytic conjugate addition and terminate in an enamine catalytic α-halogenation (scheme 15).[30]



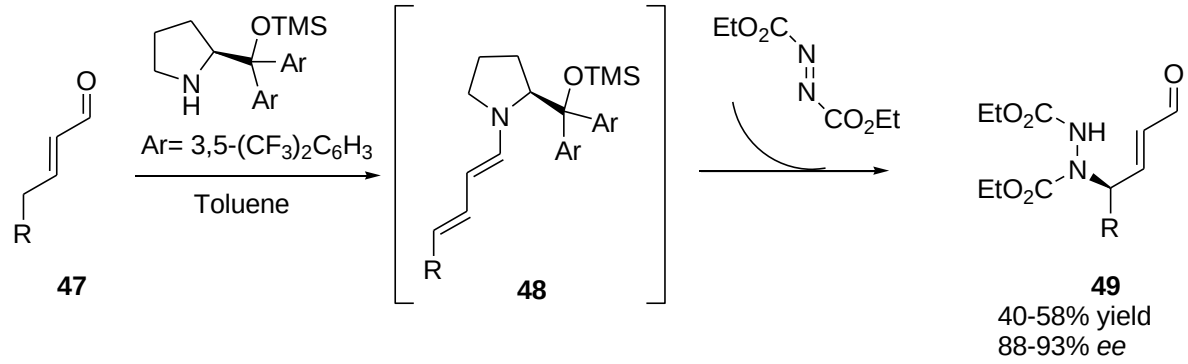
Scheme 15

This tandem sequence turn out to be useful strategies to the formation of molecules of even higher complexity.

Recently two new methods for the enantioselective functionalization of carbonyl compounds have been described: dienamine catalysis[31] and singly occupied molecular orbital (SOMO) catalysis.[32]

1.3 Dienamine catalysis

About the dienamine catalysis the first example was presented by Jørgensen group.[31] They disclosed that the proline derivatives can invert the usual reactivity of α,β-unsaturated aldehydes, allowing a direct γ-amination of the carbonyl compound using azodicarboxylates as the electrophilic nitrogen-source. The ^{1}H-NMR spectroscopic investigations showed that the reaction between (E)-pentenal (**47a**, R= Me) and the chiral catalyst did not give the 'expected' iminium-ion but the dienamine **48** as most abundant compound in solution. The [4+2]-cycloaddition reaction between the diethyl azodicarboxylate and the chiral dienamine gave product **49** in moderate yield and with good enantiomeric excess (scheme 16).



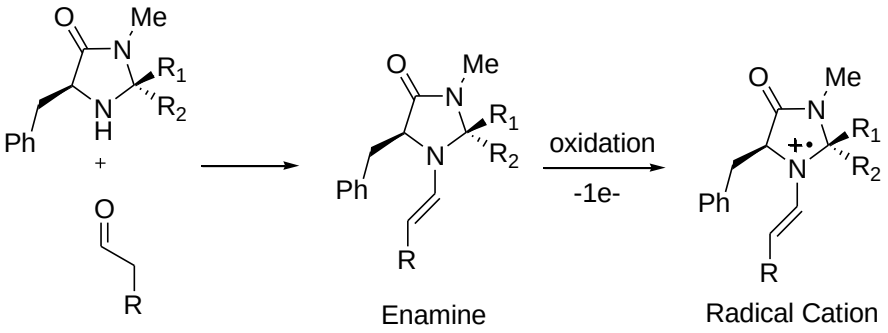
Scheme 16

The research group of Hong applied dienamine catalysis to highly enantioselective Robinson annulations of α,β-unsaturated aldehydes.[33] M. Christmann *et al.*[34] in 2008 applied dienamine catalysis to the asymmetric cyclization of tethered α,β-unsaturated carbonyl compounds. Thus dienamine catalysis offers a number of new possibilities to synthetic chemists.

1.4 SOMO catalysis

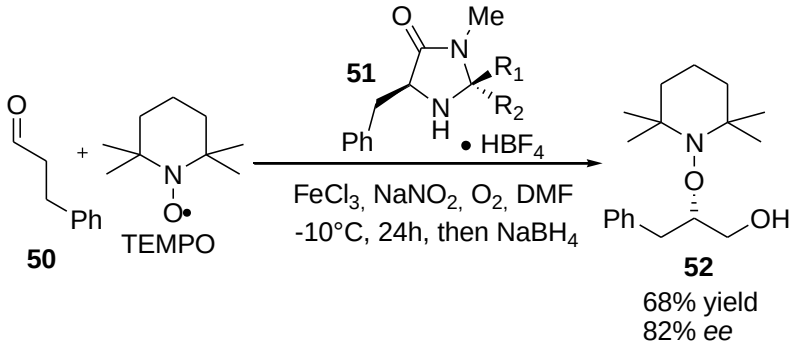
The SOMO catalysis is based on radical intermediates, this represents a link between two different areas: organocatalysis and radical chemistry. The SOMO catalysis exploits the

susceptibility of the transient enamine (generated by condensation of aldehydes and chiral amines) to undergo selective oxidation relative to other reaction components. It thus generates a radical cation with a singly occupied molecular orbital that is activated toward a range of enantioselective catalytic transformations (scheme 17).[32]



Scheme 17

Sibi and Hasegawa[32c] applied the aminocatalytic SOMO activation for the enantioselective α-oxyamination of aldehydes. They used the MacMillan catalyst (**51**) and a catalytic amount of $FeCl_3$ for single electron transfer (SET) in the presence of $NaNO_2/O_2$ as a cooxidant to regenerate the radical active intermediate from the enamine. The TEMPO intercepts the radical cationic species affords the adduct **52** (scheme 18).



Scheme 18

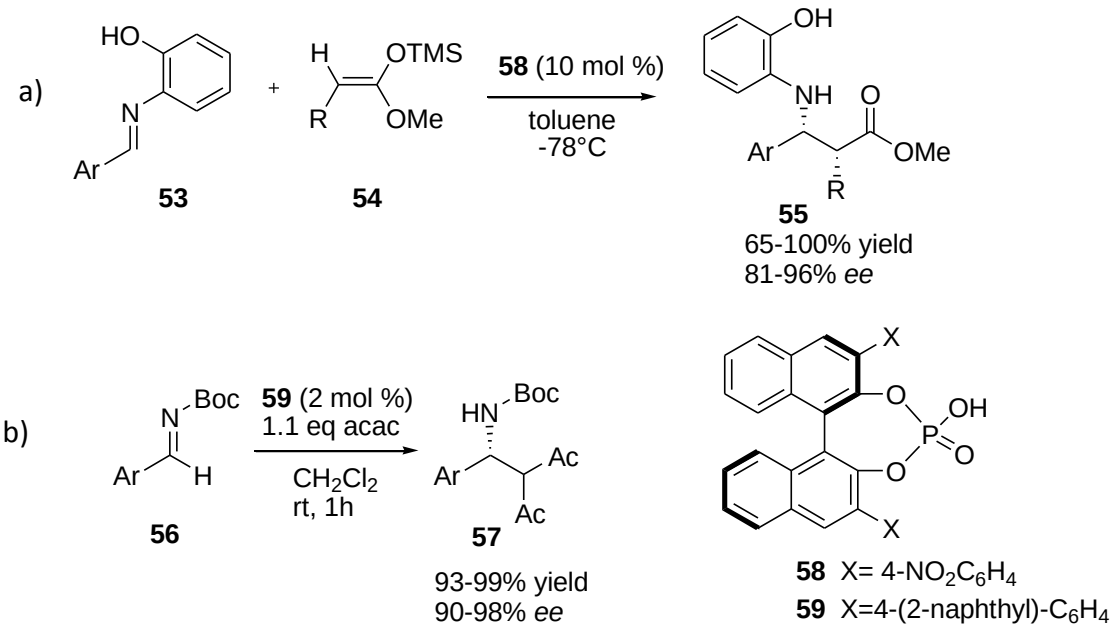
SOMO catalysis was applied to asymmetric α-allylation[32a] and α-enolation[32b] of aldehydes and also to α-arylation by using N-Boc-protected pyrrole as the somophile.[32a]

These four types of organocatalysis (enamino, iminium, dienamine and SOMO catalysis) based on the use of chiral amine as catalysis (asymmetric aminocatalysis), represent the vast majority of organocatalytic reactions. Other different types of organocatalysis involve the

use of Brønsted acids and bases, Lewis acids, hydrogen bond-mediated catalysis, phase transfer and N-heterocyclic carbene catalysis.

1.5 Brønsted acids catalysis

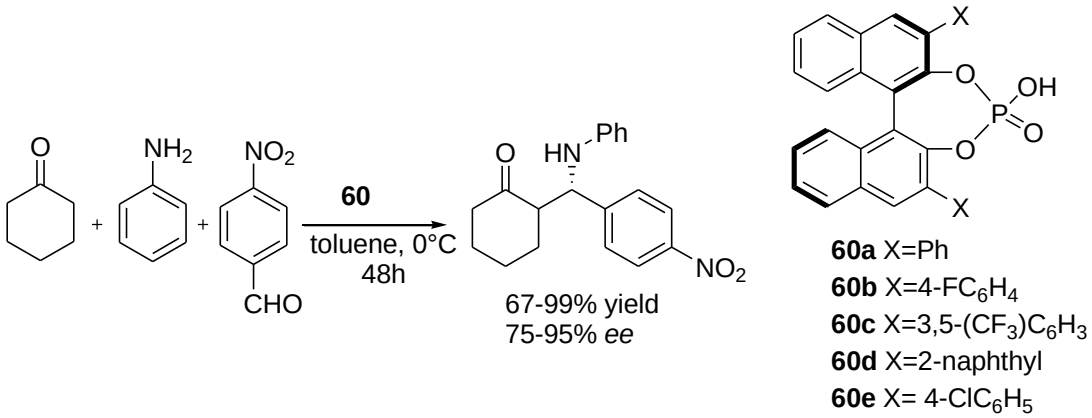
During the last few years, catalysis by Brønsted acids has emerged as a powerful tool in asymmetric synthesis, due to their high activity and selectivity.[35] Brønsted acids such as phosphoric, carboxylic and sulfonic acids work protonating the substrate giving a more electrophilic species that can in turn easily react with a nucleophilic reagent. In 2004 Akiyama[36] and Terada[37] independently reported the use of axially chiral phosphoric acid in the asymmetric Mannich reaction (scheme 19a,b).



Scheme 19

The good activity of phosphorus acids is due not only to the rigid structure around the phosphorus atom and the appropriate acidity that should catch up the imine through hydrogen bonding without loose ion-pair formation but also to the phosphoryl oxygen which is a potential Lewis base. This bifunctional behavior of phosphoric Brønsted acids has been

exploited some years later by Gong and co-workers[38] in the direct asymmetric three component Mannich reaction (scheme 20).



Scheme 20

Although binaphthol-based phosphoric acids are good catalysts for activated imine-derivatives, their acidity is not sufficient for the activation of less reactive substrates such as carbonyl compounds. In 2006, Nakashima and Yamamoto[39] synthesized the BINOL-based triflyl-phosphoramide as stronger Brønster acids to promote the asymmetric Diels-Alder reaction of α,β-unsaturated ketones with silyloxy dienes. Recently, Ishihara and co-workers catalyzed the enantioselective Mannich reaction between aldimine and 1,3-diones using the 1,1'-binaphthyl-2,2'-disulfonic acid (figure 3) in combination with the achiral Brønsted base 2,6-diphenylpyridine.[40]

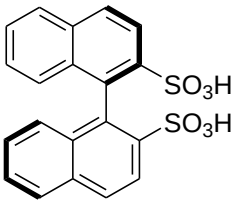
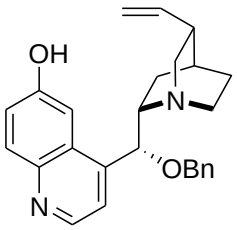


Figure 3

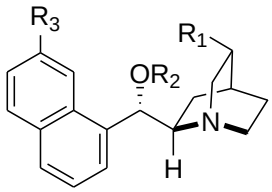
1.6 Brønsted bases catalysis

The family of *Cinchona* alkaloids probably have been the first kind of organocatalysis.[41] They act as a Brønsted bases, in fact the quinuclidine nitrogen can be partially or totally

protonated by a nucleophilic substrate, forming a chiral intermediate able to stereodirect the following attack to the electrophile. Furthermore, *Cinchona* alkaloids possess other functionalities such as the OH or NH_2 group in the C(9) position, and the OR group in the C(6) position that can add further stabilizing interaction thus working as a bifunctional catalysis (figure 4).



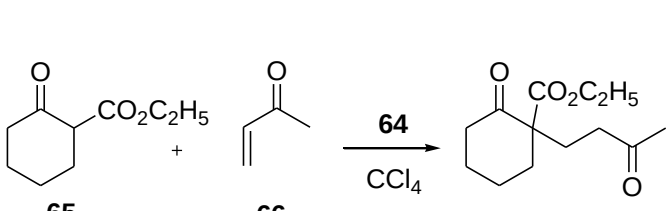
62



63a R_1=$CH_2CH_2SiPh_3$, R_2=H, R_3=H
63b R_1=CH=CH_2, R_2=Ac, R_3=OH

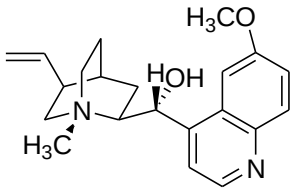
Figure 4

In 1978 Hermann and Wynberg[41b] reported the pioneering work of the use of quinine methohydroxide **64** in a enantioselective Michael reactions of substituted cyclohexanone **65** and methyl vinyl ketone **66**. The yield was excellent (98%) but the enantiomeric excess was not too high (17 % ee) (scheme 21).



65 **66** **67**

88-100% yield
5-25% *ee*

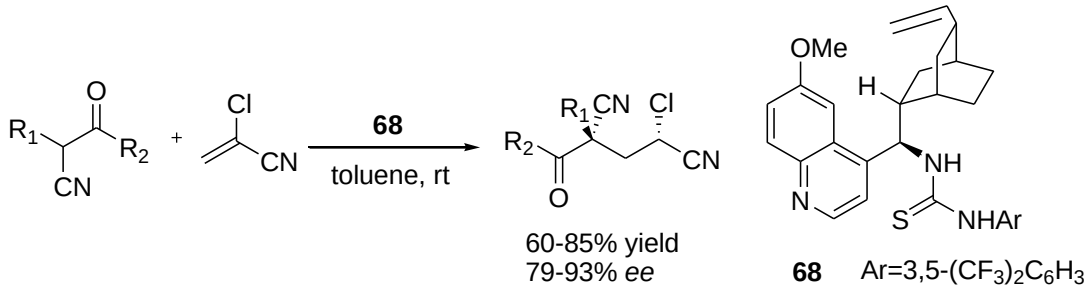


64

Scheme 21

Since that time, several approaches have been directed toward expanding the synthetic utility of this methodology, and, in the last few years, impressive progress has been achieved. In this context, Deng and co-workers[42] described the use of catalyst **68** in a tandem asymmetric reaction involving catalytic conjugate addition of α-cyanoketones with

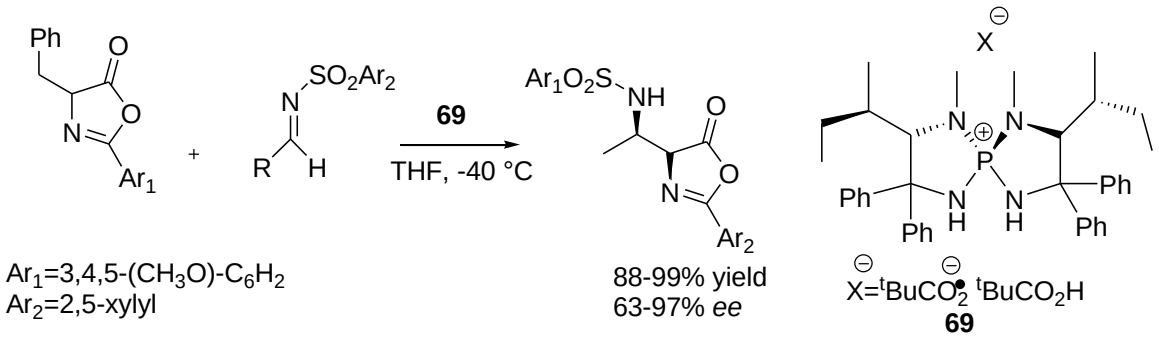
α-chloroacrylonitrile and followed by an asymmetric conjugate addition-protonation (scheme 22).



Scheme 22

1.7 Lewis acids catalysis

Lewis acids catalyze reactions through electrophilic activation of organic groups, such as carbonyl compounds, imines or epoxides, towards nucleophilic attack. Firstly, the Lewis acid forms a chiral complex between the nucleophile substrate, hence the reaction between the ion pair complex and the substrate affords the enantioenriched ion pair intermediate which generates the product and releases the catalyst for the next turn over. In 2008, Ooi *et al.*[43] presented a chiral tetraaminophosphonium carboxylate **69** as a ion pair catalyst for the enantioselective direct Mannich reaction of azlactones with sulfonyl aldimines (scheme 23).

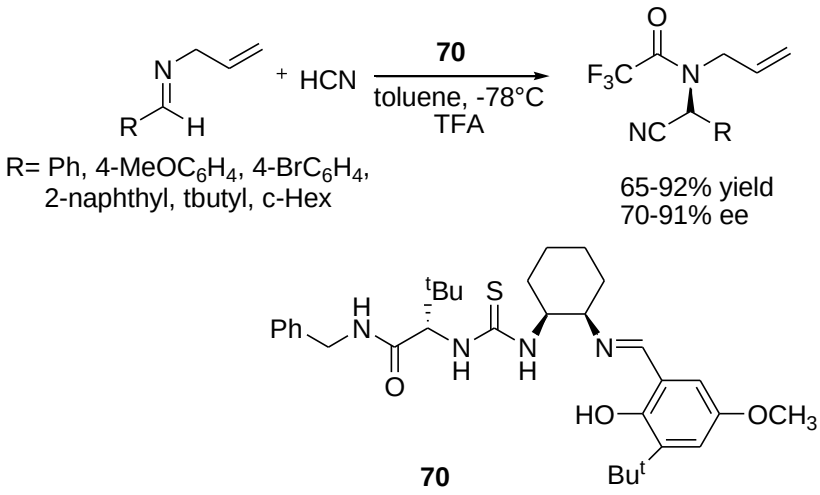


Scheme 23

1.8 Hydrogen bonding catalysis

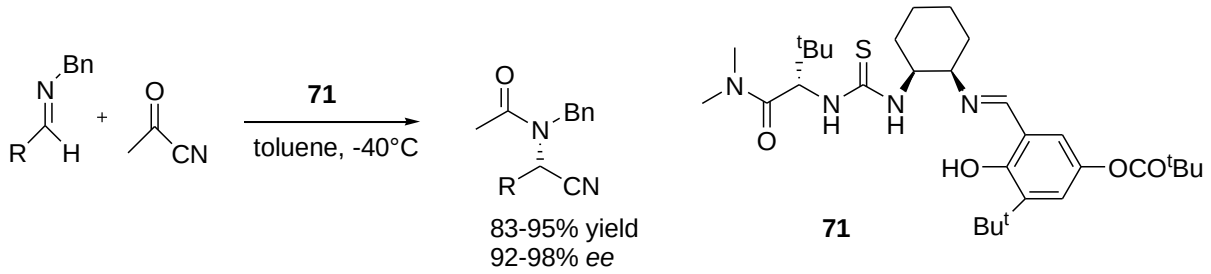
The hydrogen bonding catalysis is the most recent trends in asymmetric organocatalysis. The H-bond between the catalyst and the electrophile substrate results in a diminished electron density for the latter, making easier the nucleophile attack. In 1998 Sigman and Jacobsen[44]

reported the first example using a series of resin-supported and homogeneus Schiff-base organocatalysts for the asymmetric Strecker reaction. They demostrated that the thiourea[45] **70** was able to promote the hydrocyanation of amines with moderate to high enantioselectivity and yield (scheme 24).



Scheme 24

A similar reaction was reported by List *at al*.[46] in 2007, they developed an efficient and potentially useful new reaction, namely the acylcyanation of benzyl aldimines with acetyl cyanide adopting thiourea **71** as catalyst (scheme 25).

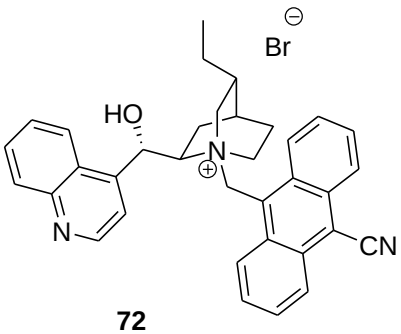


Scheme 25

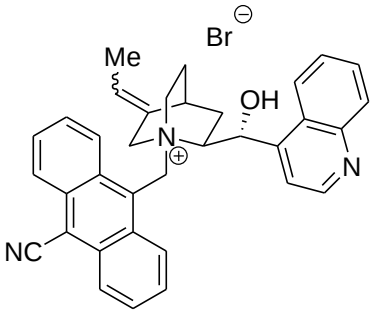
1.9 Phase transfer catalysis

Phase transfer catalysis (PTC)[47] is an attractive alternative for organic reactions in which charged intermediates are involved. Reactions are carried out in two- or three- phase systems, generally in vigorously stirred aqueous/apolar solvent mixture. The most used

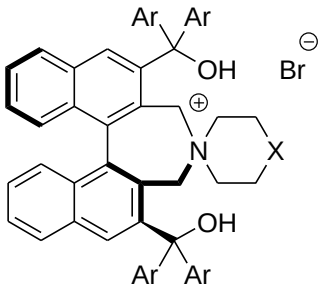
asymmetric phase transfer catalysts are quaternary ammonium salts generated by: i) *Cinchona* alkaloids based on the N-anthracenylmethyl substituted structure (**72**, **73**) or ii) a chiral binaphthyl core possessing a spiro structure or flexibile straight-chain alkyl groups (**74**).



72

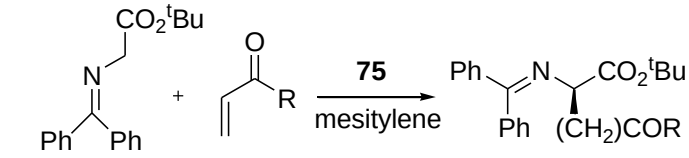


73



74

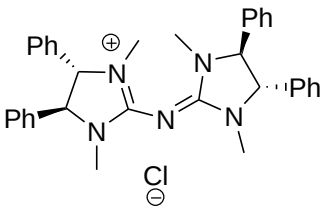
More recently, new structures like **75** have been proposed. This novel chiral species, namely pentaindinium, was used by Tan and co-workers[48] in the Michael addition of **76** with vinyl ketones and acrylates **77** (scheme 26).



76 **77** **78**

R= Me, Et, n-Bu, Ph, OEt, OBn

50-97% yield
88-97% *ee*



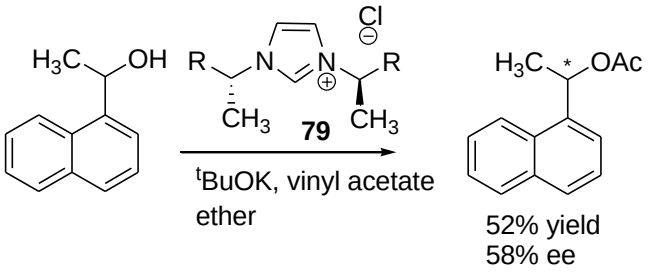
75

Scheme 26

1.10 *N*-Heterocyclic carbenes

The first report of stable nucleophilic carbenes was presented by Bertrand and co-workers and Arduengo *at al*.[49] in the late 1980s. The use of carbenes organocatalysts has emerged as an exceptionally fruitful research area in synthetic organic chemistry. An early example of

the use of chiral N-etherocyclic carbenes (NHCs) was reported by Suzuki and co-workers.[50] They described the use of several NHCs **79** as catalysts for kinetic resolution of secondary alcohols (scheme 27).



Scheme 27

In summary in the last few years the asymmetric organocatalysis has emerged as a significant synthetic tool; surprisingly, however the use of organocatalysts to functionalize cyclobutanones is rare, despite the fact that cyclobutanones are important intermediates in the synthesis of natural products and various complex organic molecules.

CHAPTER 1

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CHAPTER 2

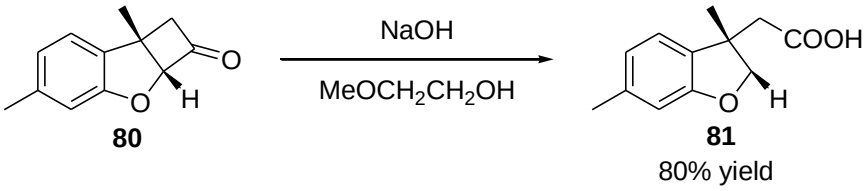
Reactivity of cyclobutanones

General Introduction

Due to their previously mentioned importance in organic synthesis and our involvement in the field of strained carbocycles[51] we report in this thesis the results of a study on the interaction between organocatalysts[1] and cyclobutanones.[52] They reveal interesting characteristics such as high electrophilicity and ring tension which make them good substrates for ring transformation reactions. Functionalized cyclobutanones have been the subject of studies which describe their reactivity with nucleophiles to induce ring opening, ring contraction and ring expansion.

2.1. Ring-Opening Reactions [53]

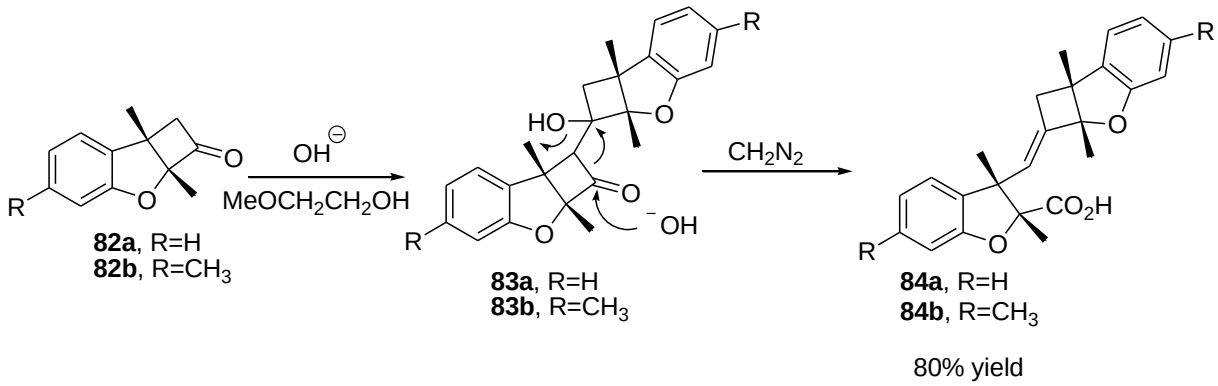
In 1998, Venkateswaran *et al*.[54] reported the ring opening of the cyclobutanones fused to benzofurans of the type **80** upon treatment of sodium hydroxide in 2-methoxyethanol. On base treatment **80** furnished the oxabicyclic carboxylic acid **81** through regioselective C-C cleavage directed by the furanoid oxygen (scheme 28).



80 **81**
80% yield

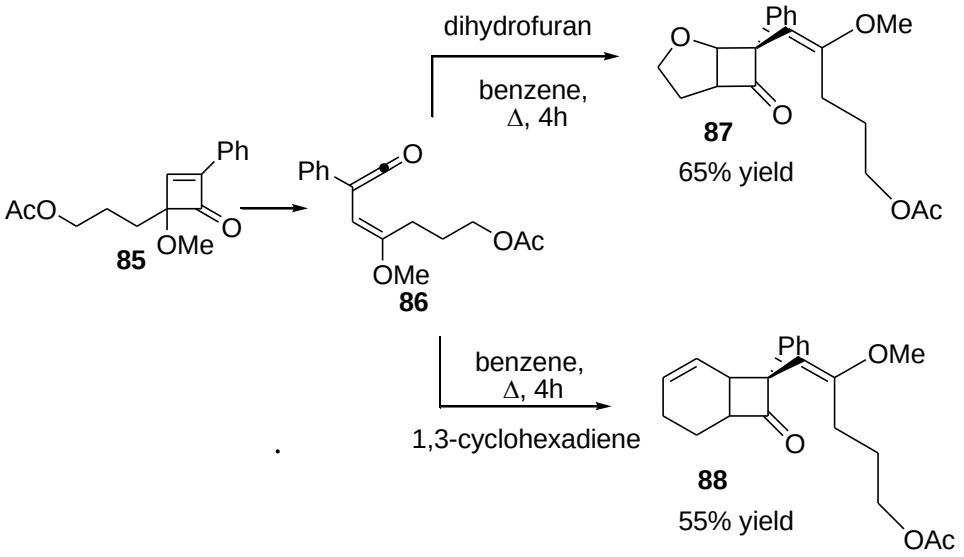
Scheme 28

In sharp contrast to **80**, the cyclobutabenzofuranones with quaternary angular carbon centres **82a,b** took a multievent route and furnished **84a,b** via an initial self-condensation to the ketol **83a,b** followed by fragmentation of the cyclobutanone ring (scheme 29).



Scheme 29

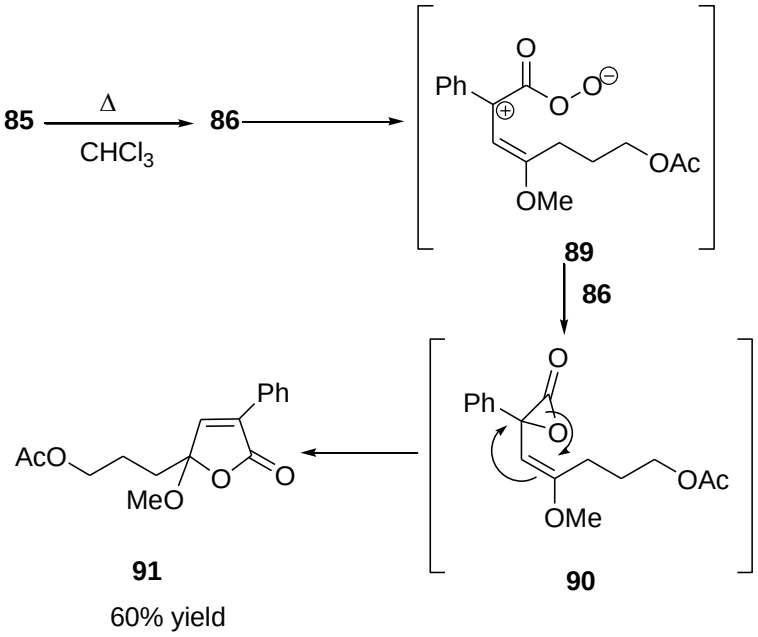
Hassner and co-workers[55] observed that when cyclobutenone **85** was refluxed in benzene with dihydrofuran for 2 h a cycloadduct **87** was obtained. Heating **85** with 1,3 cyclohexadiene in refluxing benzene overnight provided the unsaturated cyclobutanone **88** as a single isomer. Both cyclobutanones are achieved with (2+2)-cycloaddition of vinylketene **86**, generated from **85**, with dihydrofuran and 1,3-cyclohexadiene, respectively (scheme 30).



Scheme 30

An unexpected product was obtained when cyclobutenone **85** was refluxed for 4 h in a dilute solution of $CDCl_3$. The obtained product **91** contains an additional oxygen. A plausible mechanism for the formation of **91** is an electrophilic attack by the oxygen on the vinylketene **86**, generated by electrocyclic ring opening of cyclobutenone **85**, to form a dioxetanone (cyclic peroxide), which opens to a zwitterionic intermediate **89**. This

intermediate acts as a Prileschajew reagent[56] for a second molecule of vinylketene **86**, leading the α-lactone **90**, which rearranges to γ-lactone **91** (scheme 31).

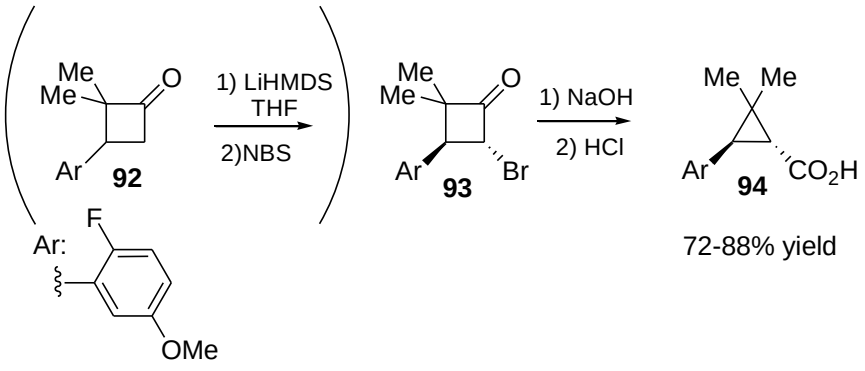


Scheme 31

2.2 Ring-Contraction Reactions[57]

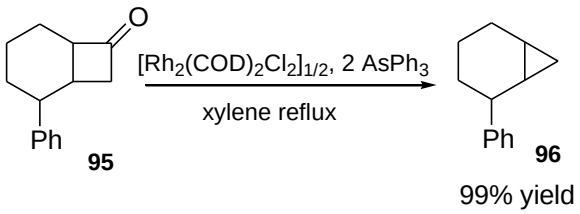
The ring contraction reactions of cyclobutanone derivatives have minor relevance because it is easier to build up a cyclopropane ring from an acyclic precursor than to contract a larger ring. Yet, there are different examples of this reaction.

Chen and Ahmad[58] developed a new facile method for the preparation of *trans*-2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids **94**. This method involved a base–induced ring contraction of an in situ formed 2-bromocyclobutanone **93** (scheme 32).



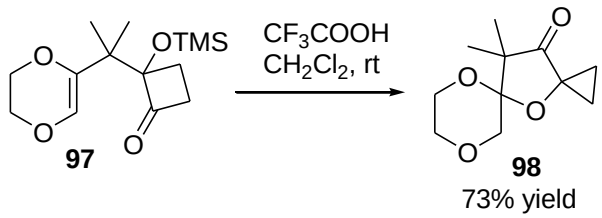
Scheme 32

In 1996, Murakami *et al*.[59] described a synthetic transformations involving selective breaking of the C-C bond α to the carbonyl group of cyclobutanones to give the corresponding cyclopropanes. Decarbonylation took place on treatment of annelated cyclobutanone **95** with only 5 mol % of dirhodium biscyclooctadiene dichloride with two molecules of triphenylarsine as stabilizing ligand (scheme 33).



Scheme 33

An acid-catalyzed transformation of a 2-silyloxycyclobutanone derivative was reported by Hanna and Ricard.[60] Exposing the cyclobutanone **97** to trifluoroacetic acid in CH_2Cl_2 for 1 h at room temperature led to the spirocyclopropyltetrahydrofuran **98** in 73% yield (scheme 34).



Scheme 34

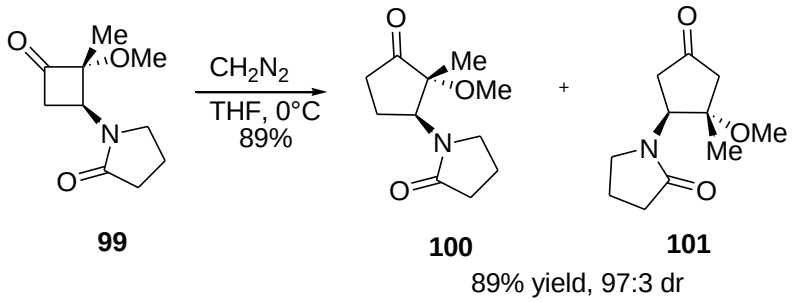
2.3 Ring-Expansion Reactions

Ring-enlargement reactions provide efficient access for the formation of five-[61] and six-[62] membered ring systems, but seven-,[63] eight-,[64] and nine-[65] membered ring systems can be synthesized via intra- or intermolecular sequential reaction modes.

- Five-Membered Rings[61]

Hegedus and co-workers[66] studied the diazomethane induced ring expansion of differently β-substituted-α-methyl-α-methoxycyclobutanones to the corresponding cyclopentanones.

For example the functionalized cyclobutanone **99** led a mixture of regioisomeric cyclopentanones **100** and **101** (scheme 35).

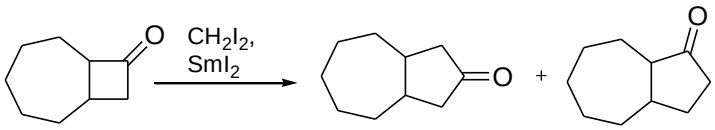


99 **100** **101**

89% yield, 97:3 dr

Scheme 35

Fukuzawa and Tsuchimoto[67] developed a facile, one pot synthesis of cyclopentanones from cyclobutanones upon treatment with CH_2I_2/SmI_2 at room temperature. This reaction involves an iodomethylation and rearrangement sequence. For example, the octahydroazulenones **103** and **104** were obtained from the annelated cyclobutanone **102** in 82% yield (scheme 36).



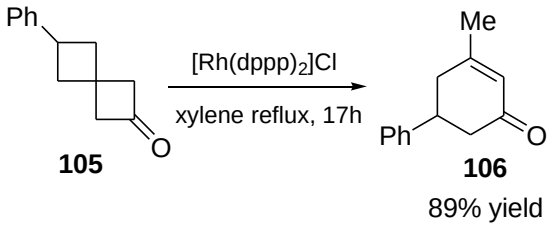
102 **103** **104**

73% yield, 97:3 dr

Scheme 36

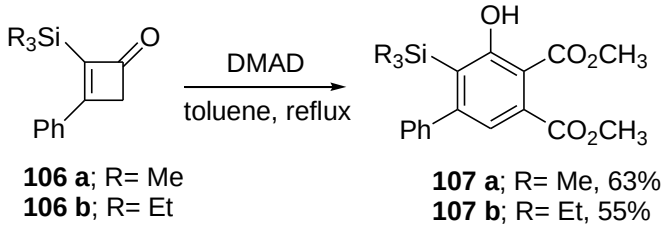
- Six-Membered Rings[62]

In 1997, Ito *et al.*[68] reported the ring-enlarging rearrangement of spyrocyclobutanones **105** to disubstituted-cyclohexenone **106** with a rhodium catalyst (scheme 37). They developed a new tandem sequence in which two C-C bonds are cleaved, the first through the insertion of rhodium and the second by subsequent β-carbon elimination.



Scheme 37

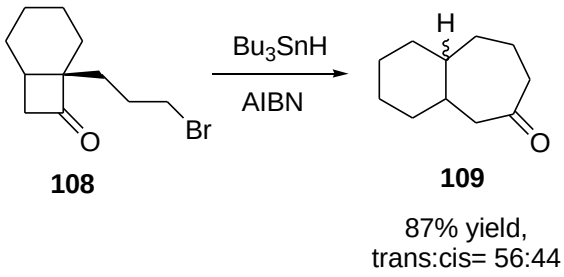
In 1998, Danheiser *et al.*[69] published that heating 2-silylcyclobutenones **106 a,b** in toluene at reflux in the presence of a reactive dienophile such as dimethyl acetylenedicarboxylate (DMAD) affords phenols **107 a,b** in good yield, probably via electrocyclic ring opening to generate (trialkylsilyl)vinylketenes followed by a Diels-Alder reaction (scheme 38).



Scheme 38

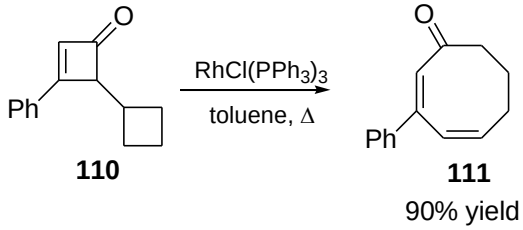
- Seven-, eight-,nine-Membered Rings [63,64,65]

Dowd *et al*. [70] reported a free radical ring expansion of fused-cyclobutanones to provide a variety of ring expanded, seven- and eight- membered systems. Free radical ring expansion of bromoalkyl and iodoalkyl cyclobutanones is carried out in refluxing benzene solution by slow addition of 1.5 eq. of tributyltin hydride with a catalytic amount of azobisisobutyronitrile (AIBN). For example, the bicyclo[3.2.0]heptanone **108** afforded the octahydroazulen-3-one (**109**) in 73% yield as a mixture of isomers (scheme 39).



Scheme 39

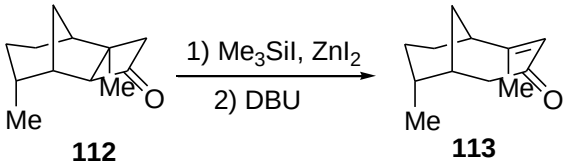
In 1993, Huffman and Liebeskind[71] reported the rhodium(I)-catalyzed ring fusion of 4-cyclobutyl-3-phenylcyclobut-2-enone **110** to 3-phenylcycloocta-2,4-dienone **111** in 90% yield (scheme 40).



110 **111**
90% yield

Scheme 40

Dowd *et al.*[72] prepared a bicyclic decenone (**113**) via a ring opening of annelated cyclobutanone (**112**) with trimethylsilyl iodide (scheme 41).



112 **113**
92% yield

Scheme 41

CHAPTER 2

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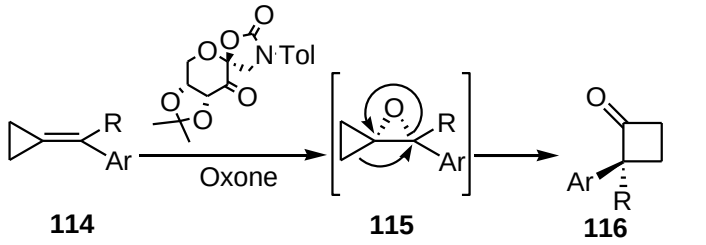
CHAPTER 3

Synthesis of 2,2-disubstituted cyclobutanones

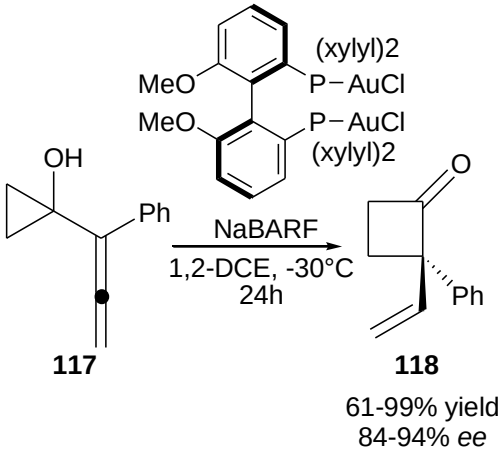
General Introduction

Despite the relevance of chiral 2,2-disubstituted cyclobutanones only a limited number of reports have appeared on the preparation of such derivatives in non racemic form.[73,74] Shi *et al*.[75] described an enantioselective synthesis of optically active cyclobutanones using the N-tolyl-substituted oxazolidinone-containing ketone as catalyst and Oxone[76] as oxidant via a sequential asymmetric epoxidation of benzylidenecyclopropanes **114** followed by ring expansion (scheme 42).



Scheme 42

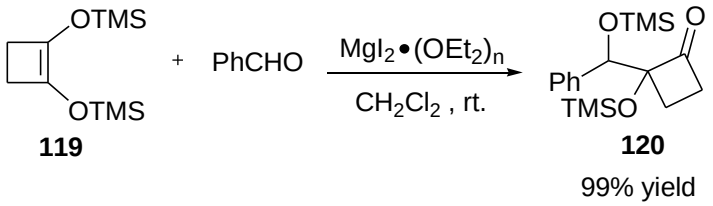
In 2009, Toste and co-workes[77] developed an asymmetric ring expansion reaction of 1-allenylcyclopropanols using chiral gold(I)-phosphine complexes (scheme 43).



Schema 43

The gold(I) catalyst coordinates the internal double bond of the allene moiety in **117** and it triggers a ring expansion to give the related cyclobutanone **118.**

2,2-disubstituted cyclobutanones can also be synthesized via Mukaiyama-type aldol coupling of 1,2-bis(trimethylsilyloxy)cyclobutane **119** with aryl aldehydes in the presence of 5 mol % of MgI_2 etherate[78] (scheme 44).

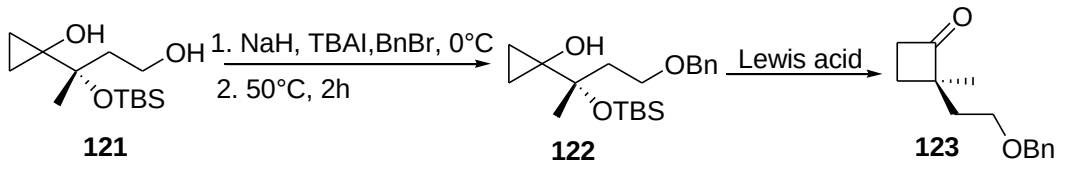


119 **120**

99% yield

Scheme 44

Another method to synthesize 2,2-disubstituted cyclobutanones involves the pinacol rearrangement of protected cyclopropanol **122** (scheme 45).[79a]



121 **122** **123**

TBAI= tetrabutylammonium iodide

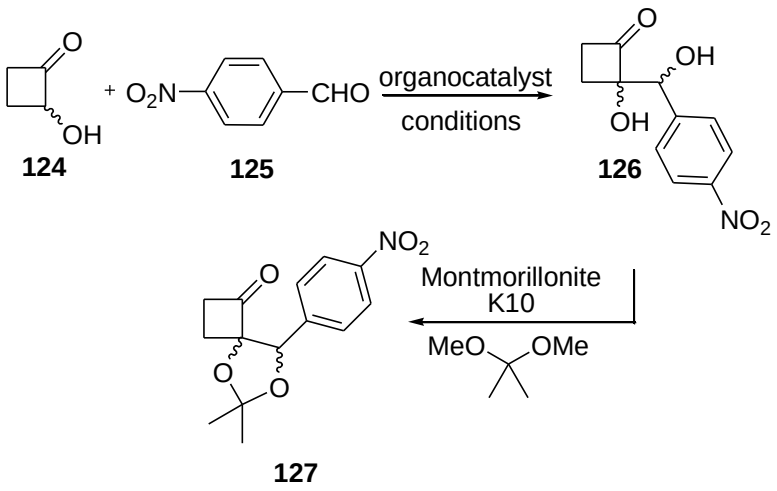
89-97% yield
65-95% *ee*

Scheme 45

3.1 Result and discussion[79b,c]

Our method for the synthesis of 2,2-disubstituted cyclobutanones involves the use of organocatalysts[80]. Asymmetric organocatalysis has emerged as a significant synthetic tool in recent years, and the stereoselective functionalization of cyclic ketones has been a prominent area of activity in the field;[81] surprisingly, however, the use of organocatalysts to functionalize cyclobutanones is rare.[80]

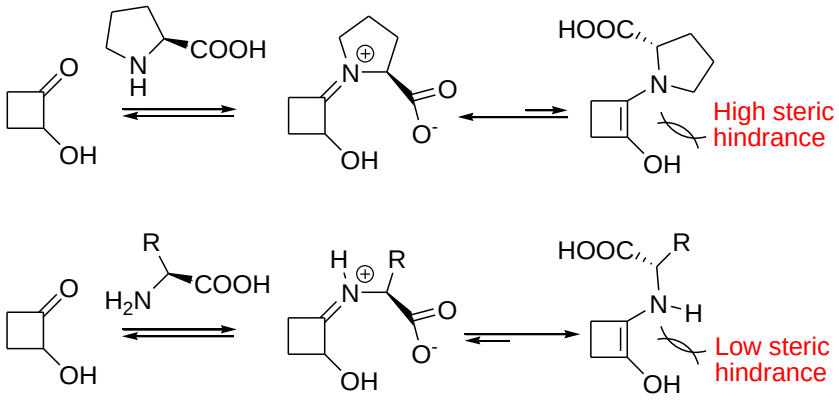
As first we examined the direct aldol reaction between the readily available 2-hydroxycyclobutanone **124** and a model aldehyde, 4-nitrobenzaldehyde **125** (Scheme 46).



Scheme 46

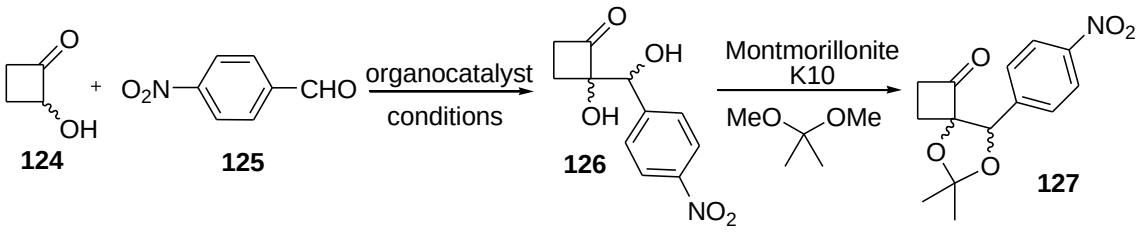
The target aldol structure **126** has a 2-hydroxymethyl-2-hydroxycyclobutanone core, which has been widely exploited in the preparation of other complex molecules, but for which an enantioselective preparation remains a considerable challenge.[82]

The first catalyst tested was L-Proline,[83] that is an established organocatalyst for intermolecular asymmetric aldol reactions. L-Proline gave only traces of the diol **126**. We hypothesized that the low efficiency of L-Proline in the aldol reaction originated from relatively slow formation of the Z-enamine intermediates due to steric interaction (scheme 47). On the basis of these considerations, we reasoned that the use of primary amino acids[84] could offer the possibility to overcome the inherent difficulties of L-Proline in generating the congested enamine intermediate. Moreover, the presence of an extra N-H in the enamine intermediate derived from the primary amino group may facilitate the control of the enamine structure and directs the reaction to occur with increased reactivity and specific selectivity, which may not be attainable *via* proline catalysis.[83c]



Scheme 47

We therefore evaluated a variety of natural acyclic primary amino acids including: L-tryptophan, L-alanine, L-threonine, L-serine, L-valine. To our delight, when a DMF solution of 2-hydroxycyclobutanone was reacted with 4-nitrobenzaldehyde in the presence of L-tryptophan as a catalyst the reaction took place, after 5 days, with moderate conversion and enantioselectivity and good diastereoselectivity (table 1, entry 2). Assessment of the enantiomeric excess of each diastereomer of **126** was not possible, so the mixture of aldol adducts was transformed into the corresponding mixture of acetonides **127** (Scheme 46), which could be analyzed by chiral HPLC. Use of higher temperature (35°C) yielded a noticeable drop in chemical yield (table 1, entry 3). However, when the reaction was performed in DMF containing 8 vol% water, an acceleration of the reaction was observed and the corresponding aldol product was obtained in 60% yield, after seven days, with 74:26 *dr*, albeit with loss in *ee* (table 1, entry 4). As other natural acyclic amino acids did not provide significant improvement of reactivity or stereoselectivity, (table 1, entries 5, 6, 7, 8), we decided to continue this study using L-tryptophan as our best catalyst.



124 **125** **126** **127**

Table 1. Catalyst screening for the aldol reaction of 2-hydroxycyclobutanone with *p*-nitrobenzaldehyde.

entry	cat. (mol%)	Solvent	t (ºC)	yield, %	*ee*, % *anti/syn*	*dr*, % *anti/syn*	time (d)
1	I(20)	DMSO	20	Traces	n.d.	n.d.	3
2	L-Tryptophan (20)	DMF	20	30	67/46	91:9	5
3	L-Tryptophan (30)	DMF	35	Traces	n.d.	n.d.	3
4	L-Tryptophan (30)	DMF/H_2O 2.2 mmol.	20	60	14/34	74:26	7
5	L-Alanine (30)	DMF/H_2O 2.2 mmol.	20	64	0/30	80:20	7
6	L-Valine (30)	DMF/H_2O 2.2 mmol.	20	42	28/32	73:27	7
7	L-Threonine (30)	DMF/H_2O 2.2 mmol.	20	25	38/60	77:23	7
8	L-Serine (30)	DMF/ H_2O 2.2 mmol	20	50	2/30	75:25	7

Reactions were run using 0.5 ml of DMF. Cyclobutanone (1 mmol), 4-nitrobenzaldehyde (0.5 mmol), and L-tryptophan (0.15 mmol), H_2O (2.2 mmol) at room temperature.

Another point worth to be consideration was the role of water concentration both on the reaction rate and enantioselectivity of the model reaction (table 2). This study showed that increasing the water concentration beyond 8 vol% in DMF caused a decreased enantioselectivity as did the reduction of water concentration to 4, 2 and 1 vol%, while no reaction was observed using water as the reaction solvent. This unreactivity could be due to the fact that 2-hydroxycyclobutanone is a water-miscible ketone and therefore, it was mainly dissolved in water and could not contact the organocatalyst rather hydrophobic and moreover slightly soluble in water. In a further effort to improve reaction rates and stereoselectivities, we also evaluated the role of different solvents and additives (table 3). We performed a solvent screening using L-tryptophan with 8 vol% of water as a fixed additive. A slight enhancement of the reactivity was observed using CH_3CN and 2-PrOH (table 3, entries 4, 5), while the use of other solvents as well as different additives (AcOH, Imidazole) was not particularly advantageous.

Table 2. Effect of water concentration on aldol reaction of 2-hydroxycyclobutanone with *p*-nitrobenzaldehyde.

Entry	amount of H_2O		yield, %	*ee*, %	*dr*, %
	vol%	mmol		*anti/syn*	*anti/syn*
1	0	0	30	67/46	91/9
2	1	0.27	70	4/16	47/53
3	2	0.55	74	8/12	56/44
4	4	1.1	48	12/12	66/34
5	8	2.2	60	14/34	74/26
6	16	4.4	60	6/14	44/56
7	100	22	0	-	-

Reactions were run using 0.5 ml DMF. Cyclobutanone (1 mmol), 4-nitrobenzaldehyde (0.5 mmol), and L-tryptophan (0.15 mmol) at room temperature for 7 days.

Table 3. Solvent and additive screening for the aldol reaction of 2-hydroxycyclobutanone with *p*-nitrobenzaldehyde.

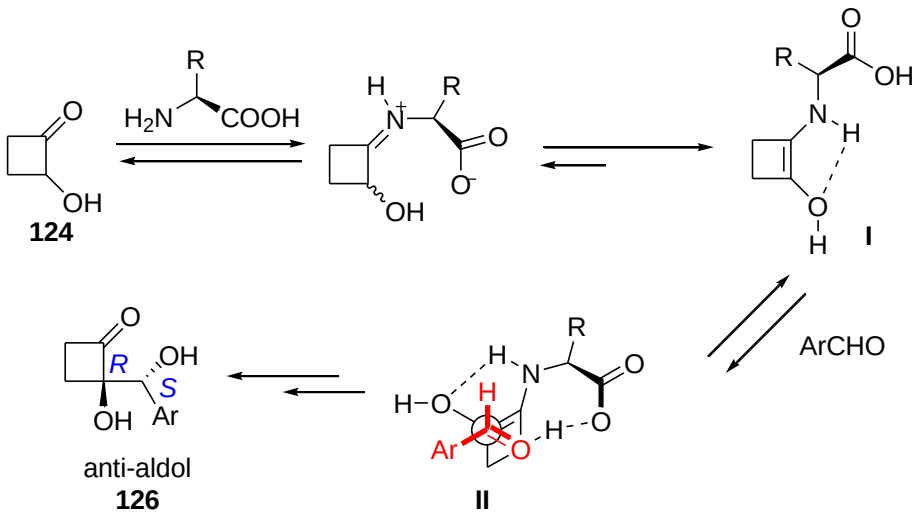
Entry	Solvent	Additive	time (d)	yield, %	*ee*, % *anti/syn*	*dr*, % *anti/syn*
1[a]	DMF	-	7	60	14/34	74/26
2[a]	DMSO	-	7	32	36/n.d.	60/40
3[a]	NMP	-	7	39	0/28	72/28
4[a]	CH_3CN	-	4	75	10/28	62/38
5[a]	2-PrOH	-	4	74	6/44	66/34
6	DMF	AcOH (0.15mmol)	7	68	2/26	76/24
7	DMF	Imidazole (0.15mmol)	7	80	40/n.d.	57/43

[a]Reactions were run using 0.5 ml of solvent. Cyclobutanone (1 mmol), 4-nitrobenzaldehyde (0.5 mmol), and L-tryptophan (0.15 mmol), H_2O (2.2 mmol) at room temperature.[b]Cyclobutanone (0.75 mmol), 4-nitrobenzaldehyde (0.25 mmol), and L-tryptophan (0.075 mmol) at room temperature.

For the stereochemical assignement of the diastereomers of **126** a single crystal of the major acetonide derivative **127** was grown from EtOH and examined by X-ray diffraction[85] (Figure 5). The crystal contained the racemate, but the relative configuration of the major isomer of **127** (and thus **126**) was unambiguously established as *anti.*

Figure 5. X-ray crystal structure of the major diastereomer of **127**

The general selectivity trends can be rationalized as follows (Scheme 48). Firstly, the regioselective formation of the more substituted enamine **I** results from stabilization due to hydrogen-bond formation between the N-H in the enamine intermediate and the cyclobutanone-bound alcohol. This key interaction has been evoked previously to explain the regioselective enamine formation between primary amino acids (or derivatives) and hydroxyacetone.[86] The approach of the aldehyde is facilitated by the carboxylate function, and in the transition state **II** the aryl moiety is preferentially oriented to minimize steric repulsion, leading to an *anti* configuration of the aldol. In recent reports of organocatalyzed aldol reactions of two acyclic substrates, hydroxyacetone, and dihydroxyacetone,[86] the *syn*-aldol adducts were preferred; the switch in diastereoselectivity in the cyclic substrate here may be due to the localized steric hindrance imposed by the four-membered ring in the lower part of the transition-state model **II** (Scheme 48). The absolute configuration of the major enantiomer of *anti*-**126** has not been established unambiguously, but in analogy with the above-mentioned results using primary L-amino acids to catalyze (di)hydroxyacetone aldol reactions,[86] the *R* configuration at the cyclobutane α-carbon is predicted, as illustrated in scheme 48.



Scheme 48

To further develop this original deracemizing reaction of **124**, also in the light of better green conditions, we decided to examine the direct aldol reaction in solvent-free conditions.[87] Some organocatalyzed solvent-free direct aldol reactions have been described,[88] but not with respect to ketone substrates having neither a four-membered ring skeleton nor an α–hydroxy function. We tested the reactivity of **124** toward different aliphatic amino acids in solvent free conditions and the results are reported in table 4.

The reaction in the presence of L-valine resulted in the negligible formation of the aldol (10% after 6h), (table 4, entry 5). L-Serine gave results comparable with those of L-tryptophan (table 4, entry 4) while the best results appeared to be those obtained using L-threonine. In wet DMF at room temperature, the reaction using L-threonine was very sluggish (25% yield of aldol **126** after one week) mainly giving the *anti* isomer (table 1, entry 7) while in solvent-free conditions at 20 °C the aldol was obtained in 70% yield in only 6 h. At lower reaction temperature (0°C) we observed slightly increased chemical yields (72%) and more interestingly a switch in the diastereoselectivity (anti:syn=39:61) and comparable *ee* (anti *ee*=56; syn *ee*=82) (table 4, entry 3).

Table 4. Catalyst screening for the aldol reaction of 2-hydroxycyclobutanone **124** with *p*-nitrobenzaldehyde in solvent-free conditions[a].

entry	cat. (mol%)	time (h)	t (ºC)	yield, %	*ee*, % *anti/syn*	*dr*, % *anti/syn*
1	L-tryptophan (30)	15	20	87	20/62	66/34
2	L-threonine (30)	6	20	70	36/81	60/40
3[b]	L-threonine (20)	27	0	72	56/82	39/61
4	L-serine (30)	6	20	68	26/68	74/26
5	L-valine (30)	6	20	10	n.d.	n.d.

[a]Reactions were run in solvent-free conditions. Cyclobutanone (0.75 mmol), 4-nitrobenzaldehyde (0.25 mmol), and catalyst (0.075 mmol) at room temperature. [b]Cyclobutanone (1.25 mmol), 4-nitrobenzaldehyde (0.25 mmol), and catalyst (0.05 mmol) at 0°C

The reaction was then extended to different aldehydes and different hydroxyketones in solvent free conditions with L-threonine as catalyst, the results are reported in Table 5.

Benzaldehyde proved to be an unsuitable substrate for the threonine-promoted direct aldol reaction, and no reaction product was observed (table 5, entry 6).

The presence of an electron-withdrawing substituents in the aromatic ring of benzaldehydes increases the enantioselectivity of the aldol reaction. [54% *ee* (4-CN), 72% *ee* (4-CF_3), 82% *ee* (4-NO_2 and 4-F) to 84% *ee* (2,4-Cl_2)]. This protocol was further applied to other cycloalkyl and acyclic 2-hydroxyketones. In the case of 2-hydroxycyclopentanone the aldol product could be obtained in moderate yield as a 31:69 mixture of two *anti:syn* diastereoisomers although after 5 days at room temperature with moderate enantioselectivity (table 5, entry 7). An attempted reaction with 2-hydroxycyclohexanone (table 5, entry 8) and 2-hydroxybutanone (table 5, entry 9) lacking ring strain failed to occur.

These results could confirm that the increased reactivity of the ketonic carbonyl group of cyclobutanone toward enamine formation could be attributed to the strained four-membered ring structure.[89]

This remarkable different behavior of the cyclobutyl moiety represents a further evidence of the effect of small strained rings on chemical reactivity and in determining the outcome of chemical transformations.

Table 5. Direct asymmetric aldol reaction of 2-hydroxyketones with various aldehydes catalyzed by L-threonine[a].

Entry	ketone	R	Product	time (h)	yield, %[b]	*ee*, % *anti/syn*[c]	*dr*, % *anti/syn*[d]
1		4-NO_2-C_6H_4	**126a**	27	72	56/82[e]	39/61
2		4-F-C_6H_4	**126b**	48	50	n.d./82	15/85
3		4-CF_3-C_6H_4	**126c**	48	50	48/72	16/84
4		2,4-Cl_2-C_6H_3	**126d**	48	60	n.d/84	30/70
5		4-CN-C_6H_4	**126e**	48	64	52/54	22/78
6[f]		C_6H_5	**126f**	48	0	-	-
7[f]		4-$NO_2C_6H_4$	**126g**	120	53	48/70	31/69
8[g]		4-$NO_2C_6H_4$	**126h**	120	0	-	-
9[g]		4-$NO_2C_6H_4$	**126i**	120	0	-	-

[a]Reactions were run in solvent-free condition. Cyclobutanone (1.25 mmol), aldehyde (0.25 mmol),catalyst (0.05 mmol)0°C. [b]Yield isolated product. [c]Determined by HPLC. [d]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.[e]After conversion into the corresponding acetonide **127**, *ee* was determined by HPLC. [f]Ketone (0.75 mmol), aldehyde (0.25 mmol),catalyst (0.075 mmol) at rt. [g]Reactions were run using 0.5 ml of DMSO. Ketone (0.75 mmol), 4-nitrobenzaldehyde (0.25 mmol), and catalyst (0.075 mmol) at rt.

Collectively, these results show that 2-hydroxycyclobutanone **124** is particularly amenable to solvent-free L-Thr-catalyzed direct aldol reactions with reasonable stereocontrol. The prevalence of a *syn* selectivity is consistent with Barbas' transition state model for L-proline-catalyzed aldol reactions of α-hydroxyacetone;[90] the alcohol function on the Thr side chain may help to location the water molecule removed then returned for enamine hydrolysis (Figure 6). The *R* configuration at the quaternary chiral center is assumed by analogy with previous observations on product **126** obtained in a solution-state aldol reaction[91]. Development of this deracemizing "green chemistry" approach to highly-functionalized derivatives of **124** and further synthetic exploitation thereof should now be facilitated

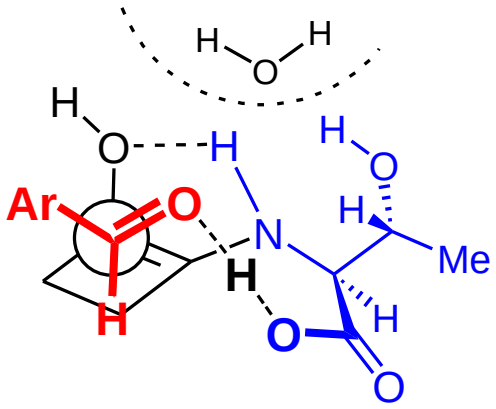


Figure 6

CHAPTER 3

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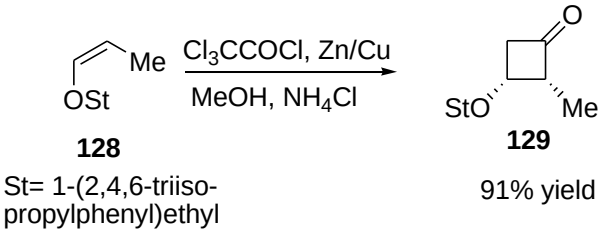
CHAPTER 4

Synthesis of 2,3-disubstituted cyclobutanones via organocatalyzed enantioselective aldol reaction and via asymmetric nitro-Michael reaction.

General Introduction

There are some examples reported in the literature about the synthesis of 2,3-disubstituted cyclobutanones.

The synthesis of enantiopure 2,3-disubstituted cyclobutanones could involve an efficient [2+2] cycloaddition of dichloroketene with chiral enol ethers (**128**) followed by in situ dechlorination reaction[92] (scheme 49). The diastereomerically enriched (92/8) *cis*-cyclobutanone **129** could thus obtained in 91% overall yield.



128

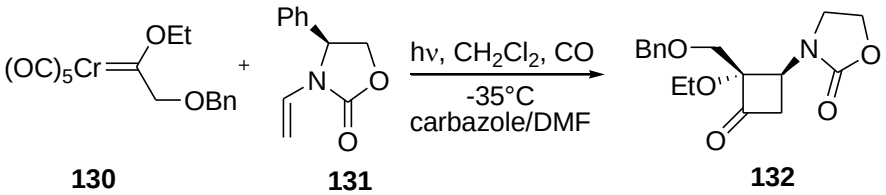
St= 1-(2,4,6-triiso-propylphenyl)ethyl

129

91% yield

Scheme 49

Hegedus *et al*.[93] developed an efficient synthesis of optically active cyclobutanones by photolysis of chromium carbene complex **130** in the presence of ene carbamate **131**, the desired cyclobutanone **132** was obtained in 79% yield with 97% enantiomeric excess (scheme 50).

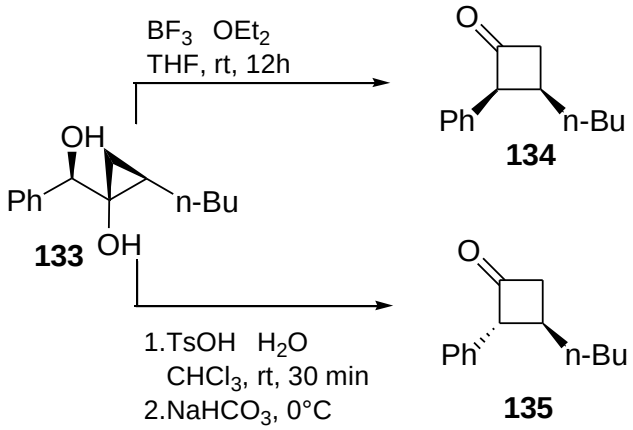


130 **131** **132**

79% yield
97% *ee*

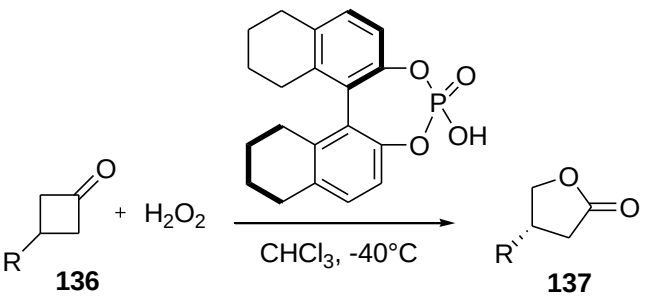
Scheme 50

In the literature is also reported an acid-catalyzed pinacol-type rearrangement of α-hydroxycyclopropylcarbinols (**133**) to 2,3-disubstituted cyclobutanones.[94] This approach involve the use of $BF_3 \bullet OEt_2$ in THF to obtain the *cis* diastereoisomer **134** in 17:1 dr and 80% yield and the use of TsOH to achieve the trans-2,3-disubstituted cyclobutanone **135** (scheme 51).



Scheme 51

Our method for the synthesis of 2,3-substituted cyclobutanones involves the organocatalyzed[95] desymmetrizations of prochiral 3-substituted cyclobutanones. Until now the organocatalyzed desymmetrizations of prochiral 3-substituted cyclobutanones have been strictly limited to a Baeyer-Villiger oxidation[96] and a lactam-forming ring expansion.[97-99] Un example the catalytic asymmetric Baeyer-Villiger[96] oxidation of 3-substituted cyclobutanones involves the use of chiral organophosphoric acid based on enantiopure 1,1'-bi-2-naphthol derivatives with aqueous H_2O_2 as the oxidant, this conditions afford the corresponding lactone **137** in excellent yield with enantiomeric excess values up to 93% (scheme 52).



R= various aryl or alkyl groups

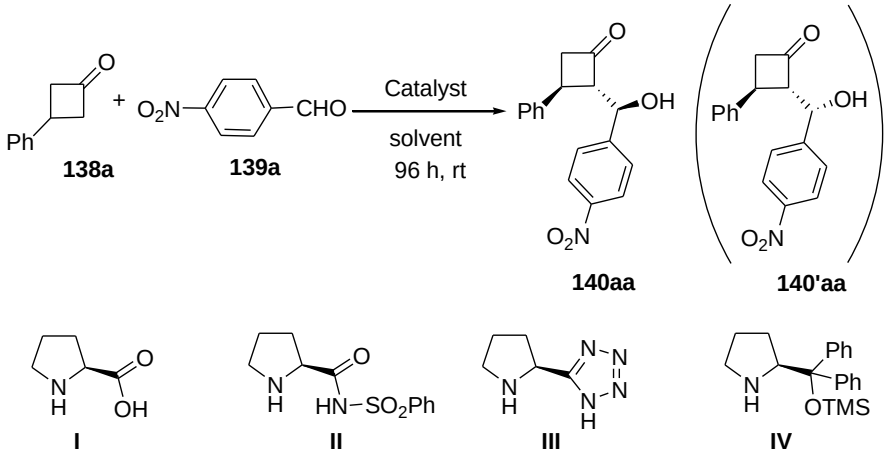
Scheme 52

To get the 2,3-substituted cyclobutanones we considered the possibility of using an enantioselective desymmetrization of variously 3-substituted prochiral cyclobutanones via direct aldol reaction[100] and via asymmetric nitro-Michael reaction.[101]

4.1 Result and discussion

Synthesis of 2,3-disubstituted cyclobutanones via organocatalyzed enantioselective aldol reaction

The reaction between the 3-phenylcyclobutanone **138a** and 4-nitrobenzaldehyde **139a** was chosen as a model reaction for catalyst screening (scheme 53), the results are summarized in Table 6. The first catalyst tested was (*S*)-Proline (**I**) in DMSO. Unfortunately the relative aldol product was obtained only in 31% yield (entry 1) but with high diastereoselectivity, in fact only two of the four possible isomers, designated **140aa** and **140'aa**, were observed, with the first predominating. Furthermore, chiral hplc analysis showed the major diastereoisomer **140aa** to be highly enantiomerically enriched. When the same catalyst was employed in dichloromethane (entry 2), the reaction yield decreased, but the stereoselectivity was even better: only a single diastereoisomer **140aa** was formed and was >99% enantiomerically pure.



Scheme 53

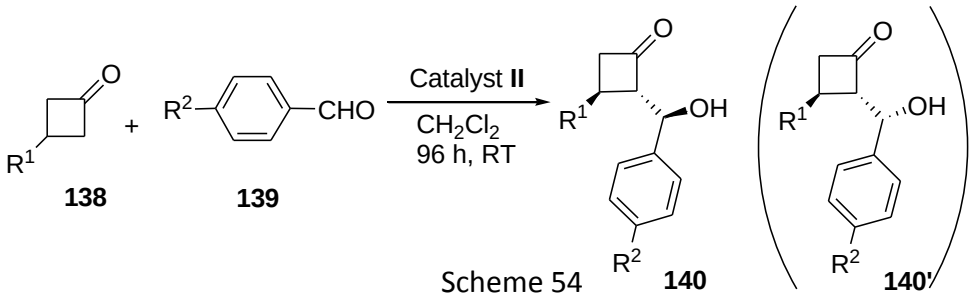
Table 6. Optimization of the reaction condition[a]

Entry	Cat.	Solvent	Yield 60 (%)[b]	dr[c] 60:60'	ee 60 (%)[d]
1	**I**	DMSO	31	82:18	96
2	**I**	CH_2Cl_2	10	99:1	>99
3	**II**	CH_2Cl_2	71	98:2	>99
4	**III**	CH_2Cl_2	80	78:22	>99
5	**IV**[e]	CH_2Cl_2	92	37:63	26

[a]Cyclobutanone **138a** (10 mmol), aldehyde **139a** (0.5 mmol), catalyst **I**-**IV** (20 mol %), solvent (2 mL), 96 h, room temperature. [b]Total yield of all isomers of **140aa**. [c]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]Benzoic acid (20 mol %) was included in the reaction mixture

On the basis of these results we continued the study of the model reaction using other (*S*)-proline-derived catalysts, **II-IV** (Table 6). When we carried out the reaction with catalysts **II** and **III** in dichloromethane (entries 3 and 4), the requisite aldol product was obtained in good yield with good-to-excellent diastereoisomeric excesses, and with complete enantiomeric control in the formation of the major **140aa** isomer. Catalyst **IV**, used in conjunction with a Brønsted acid, also provided an excellent yield of aldol but the stereoselectivity of the reaction was greatly reduced - indeed, the second diastereomer **140aa** became the major component (entry 5). With the encouraging lead result using catalyst **II** in hand, the desymmetrization of various 3-substituted cyclobutanones with several aldehyde was then investigated, the results are shown in Table 7. Firstly, we extended these reaction conditions to different aryl aldehydes using **138a** as the representative cyclobutanone. Similarly to the reaction of **139a** in standard conditions (entry 1), other aldehydes bearing an electron-withdrawing group, **139b-139e**, reacted with **138a** to give good yields of the corresponding aldols **140ab-140ae**, with very good-to-excellent diastereo- and enantioselectivities (entries 2-5). At most, only very small amounts of one other diastereoisomer (**140'ab-140'ae**) were detected. The less reactive benzaldehyde (entry 6), however, failed to provide any aldol adduct. Then, the tolerance of the substituent of the cyclobutanone **138** was investigated in a series of aldolization experiments (entries 7-11) using **139a** as the aryl aldehyde. The reactions of **138b-138f** proceeded with uniform chemical yields to give the corresponding aldol adducts **140ba-140fa**. Once again, one diastereoisomer always predominated, with dr values going up to 99:1, and in each case, this diastereoisomer was obtained with high ee, in

the range 83% to >99%. The cyclobutanone tolerates many groups as substituents including both aromatic and aliphatic chains at the 3-position. Some other combinations of diversely substituted cyclobutanones and aryl aldehydes completed the survey (entries 12-14) and confirmed the scope and high stereoselectivity of the reaction. These organocatalyzed aldolization reactions invariably provided one stereoisomer of the product **140** with excellent selectivity.



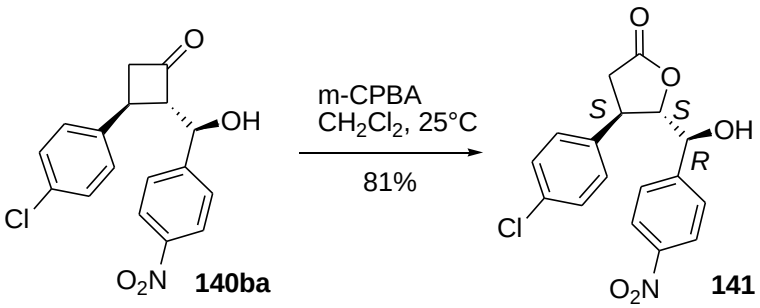
Scheme 54

Table 7. Asymmetric aldol reactions between diverse 3-substituted cyclobutanones and aryl aldehydes.[a]

Entry	R^1	R^2	Product	Yield (%)[b]	dr[c] 60:60´	ee (%)[d] 60 (major)
1	Ph-	-NO_2	**140aa**	71	98:2	>99
2	Ph-	-CN	**140ab**	76	97:3	96
3	Ph-	-Cl	**140ac**	64	98:2	>99
4	Ph-	-F	**140ad**	66	96:4	74
5	Ph-	-CF_3	**140ae**	51	98:2	90
6	Ph-	-H	**-**	0	-	-
7	4-Cl-C_6H_4-	-NO_2	**140ba**	77	89:11	84
8	4-Br-C_6H_4-	-NO_2	**140ca**	63	96:4	94
9	4-CH_3-C_6H_4-	-NO_2	**140da**	74	93:7	86
10	*n*-C_6H_{13}-	-NO_2	**140ea**	70	98:2	>99
11	$PhCH_2CH_2$-	-NO_2	**140fa**	60	99:1	98
12	4-Cl-C_6H_4-	-CF_3	**140be**	70	90:10	84
13	*n*-C_6H_{13}-	-CN	**140eb**	60	98:2	83
14	4-Br-C_6H_4-	-CN	**140cb**	64	96:4	89

[a]Cyclobutanone **138** (10 mmol), arylaldehyde **139** (0.5 mmol), catalyst II (20 mol %), CH_2Cl_2 (2 mL), 96 h, room temperature. [b]Total yield of all isomers of **140**. [c]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d]Determined by HPLC analysis.

In order to establish the absolute configuration at the three newly-formed stereocenters, the aldol product **140ba** was transformed by a Baeyer-Villiger oxidation (81% yield) into the crystalline lactone **141** (Scheme 55).



Scheme 55

Single crystal X-ray diffraction analysis established the absolute configuration of compound **141** as *R,S,S* (Figure 7).[102] It was thus deduced that compound **140ba** had the same configuration and, by analogy, the *R,S,S* configuration was attributed to each major stereoisomer of the suite of aldols **140**.[103]

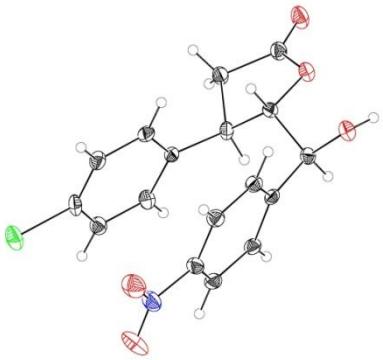


Figure 7

On the basis of previous models for (*S*)-proline catalyzed aldol reactions, supported by both experiments and DFT calculations,[104] the stereochemical course of the reactions described here can be rationalized in terms of the favored transition state model shown in Figure 8. The lowest energy transition state for proline-type Brønsted acid mediated intermolecular aldol reaction implicates *re* attack on an *anti* enamine, with the aryl moiety of the aldehyde oriented away from the steric bulk (in the equatorial position of the Zimmerman-Traxler 6-membered ring chair-like model).[104] Two diastereoisomeric enamines are likely to coexist; however, only one—designated the *S,S*-enamine, assuming for the sake of argument that the

3-substituent has nomenclature priority—allows unhindered approach of the aldehyde to the *re* face of the *anti* enamine. This model leads to the *R,S,S* configuration in the aldol product.

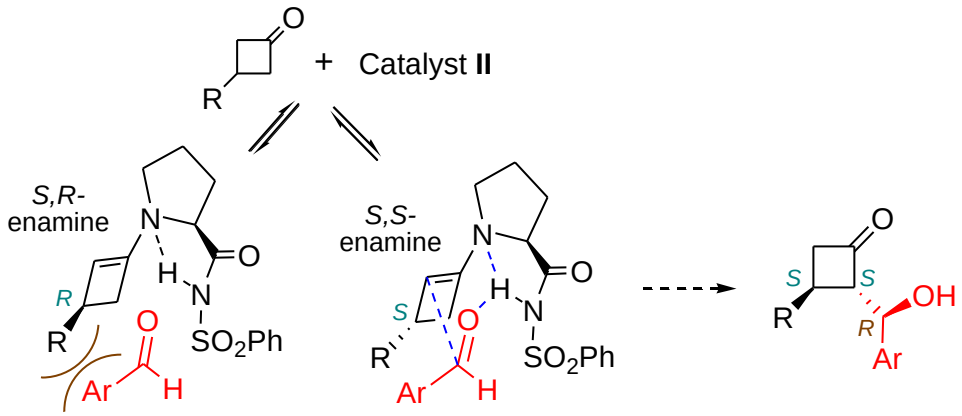


Figure 8

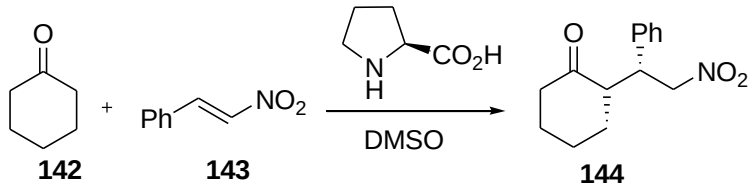
In conclusion, the **II**-catalyzed aldol reaction allows desymmetrization of 3-substituted cyclobutanones **138** to give aldol products with unprecedented control of all three contiguous stereocenters. The aldol adducts with *trans* ring substitution and an *anti* aldol geometry are obtained with high enantioselectivity.

4.2 Result and discussion

Synthesis of 2,3-disubstituted cyclobutanones via asymmetric nitro-Michael reaction

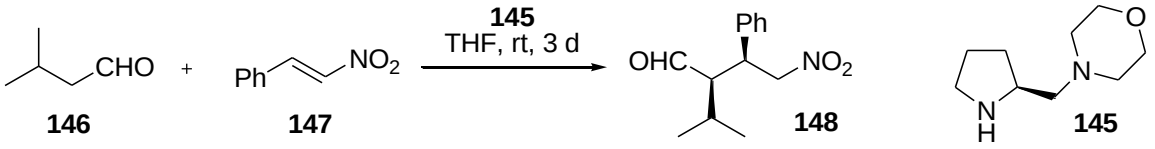
The Michael addition[105] is generally recognized as one of the most efficient carbon-carbon bond forming reaction in organic synthesis. Among the Michael acceptors, nitroalkenes[106] are very attractive, in fact the nitro group is the most electron-withdrawing group known. Often it is described as a 'synthetic chameleon' because it can be transformed to other important organic functional groups.[107] The Michael additions of carbonyl compounds to nitro alkenes can be catalyzed by small organic molecules[108] via enamines and iminium ions as active intermediates. The first catalytic version of this transformation was independently developed by List *et al.*,[109] and Betancort and Barbas.[110] List described the proline-catalyzed Michael addition of unmodified ketones to nitro olefins. Symmetrically substituted ketones such as

cyclohexanone **(142)** were treated with (*E*)-nitrostyrene **143** in the presence of L-proline to give γ-nitro ketones in excellent yield but in modest enantioselectivity (scheme 56).



Scheme 56

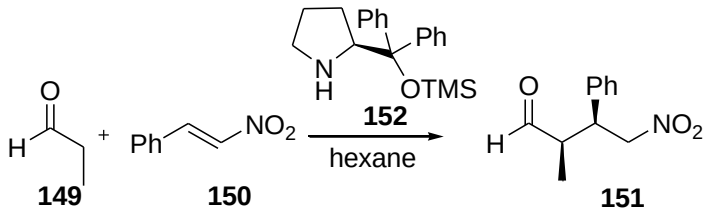
Barbas *et al*. developed a highly diastereoselective direct catalytic Michael reaction involving the addition of aldehydes with β-nitrostyrene employing chiral diamine **145** (scheme 57).



Scheme 57

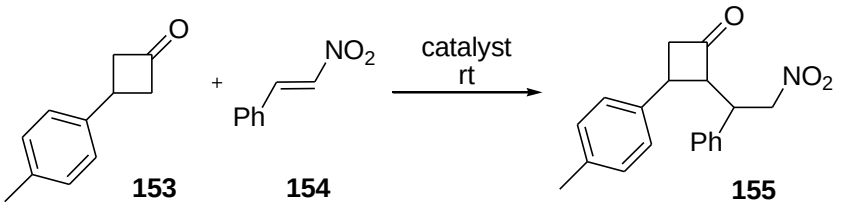
The reactions proceed in good to high yield (up to 96%) and in highly *syn*-selective manner (up to 98:2), with up to 91% *ee* values.

In 2005, Jørgensen and co-workers,[111] and Hayashi *et al*.[111] discovered that diphenylprolinol silyl ether is a very active catalyst for a variety of transformations. Hayashi and coworkers showed that the diphenyl siloxy proline **152** is an efficient organocatalyst for the asymmetric Michael reaction of aldehydes (**149**) and nitroalkenes (**150**) (scheme 58). The reaction was completed at room temperature and the adduct **151** was afforded in good yield (82%) and with excellent enantioselectivity (99% *ee*).



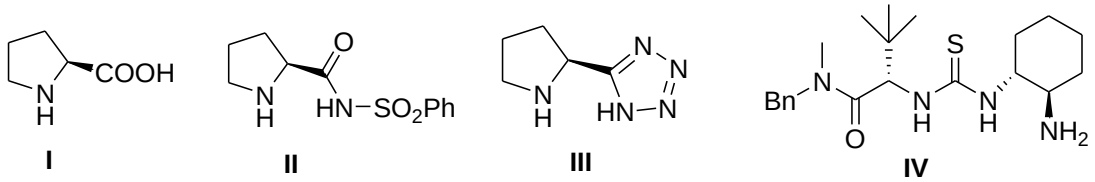
Scheme 58

In our work the reaction of cyclobutanone **153** and nitrostyrene **154** was selected as a model reaction for catalyst screening and the results are summarized in table 8.



153 **154** **155**

Scheme 59



I **II** **III** **IV**

Table 8. The effect of the catalyst in the Michael reaction of 3-p-tolylcyclobutanone and nitrostyrene.[a]

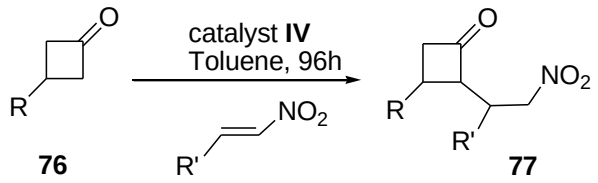
Entry	Cat. [mol%]	time (h)	Solvent	Yield, [%][b]	*Ee.*[%]dia. *maj.*[d]	dr.[%]*maj./min.*[c]
1	I(20)	48	DMSO	68	6	87/13
2	II(20)	48	DMSO	42	-10	93/7
3	III(20)	48	DMSO	93	10	90/10
4	IV(10)	48	Toluene	29	88	96/4
5	IV(20)	48	Toluene	41	38	80/20
6	IV(10)	48	CH_3CN	17	40	86/14
7	IV(10)	48	$CHCl_3$	72	74	80/20
8	IV(10)	48	THF	41	78	99/1
9	IV(10)	48	DMF	28	nd	80/20
10	IV(10)	96	Toluene	76	80	80/20

[a]Cyclobutanone **153** (1.5 mmol), nitrostyrene **154** (0.5 mmol), solvent (1.5 mL), room temperature. [b]Total yield of all isomers of **155**. [c]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d]Determined by chiral HPLC analysis.

The first catalysts examined, proline and proline derivatives **I-III**, led to the desired product in modest to good yield but with low enantioselectivity. These results prompted the study of model reactions using different types of catalysts, and so, Tsogoeva and Wei,[112] reported recently the successful application of primary amine thiourea catalysts to the addition of

ketones to nitroalkenes, we evaluated the catalytic efficiency of the chiral thiourea **IV** in the addition of the 3-p-tolylcyclobutanone to nitrostyrene. Solvent screening studies indentified toluene as the optimal solvent for the reaction as the adduct **155** was obtained after 48 h with excellent diastereomeric excesses and good enantiomeric control (entry 4, table 8), in modest yield. In order to improve the yield the reaction was carried out for 96 h. To our delight the adduct **155** was obtained in 76 % and with slightly reduced good stereoselectivity (entry 11, table 8).

Due to the encouraging result obtained using catalyst **IV**, we retained this catalyst for the study of the scope of the reaction. Organocatalyzed addition to a series of 3-substituted cyclobutanones was examined, and results are shown in Table 9.



Scheme 60

Table 9. Catalytic asymmetric Michael reaction of 3-substituted cyclobutanones and nitrostyrene.[a]

Entry	R	R'	Product	Yield[%]	*E.e.*[%] dia. *maj.*	d.r.,[%]*maj./min.*
1	C_6H_5	Ph	**157a**	63	50	66/34
2	*p*-ClC_6H_4	Ph	**157b**	86	64	66/34
3	$PhCH_2CH_2$	Ph	**157c**	50 conv.	32	84/16
4	*p*-BrC_6H_4	Ph	**157d**	83	64	77/23
5	Cyclohexyl	Ph	**157e**	63	59	80/20
6	*p*-$CH_3C_6H_5$	*p*-$BnOC_6H_4$	**157f**	55	40	81/19
7	*p*-$CH_3C_6H_5$	2,4-$Cl_2C_6H_3$	**157g**	56	34	73/27

[a]Cyclobutanone **156** (1.5 mmol), nitrostyrene (0.5 mmol),catalyst **IV** (10% mol), solvent (1.5 mL), 96 h, room temperature. [b]Total yield of all isomers of **157**. [c]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d]Determined by chiral HPLC analysis.

Although the enantioselectivities are still moderate, these preliminary results obtained form the basis for further developments.

CHAPTER 4

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[103] Single crystal x-ray diffraction analysis of the minor diastereoisomer from the same aldol reaction, **140ba´**, was also carried out. The crystal contained racemic material, but the relative configuration was established as that of a *trans* 2,3-cyclobutanone ring substitution and a *syn* aldol geometry. CCDC 796934 contains the supplementary crystallographic data for compound **140ba´**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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CHAPTER 5

Desymmetrizing nitroso-aldol reactions of 3-substituted cyclobutanones

General introduction

Nitrosobenzene[113] exhibits a high reactivity of the nitroso group. The polarization of the nitrogen-oxygen bond, similar to the carbon-oxygen bond in carbonyl group, result in a susceptibility of the –N=O group to additions of nucleophiles. This compound exists as a monomer-dimer equilibrium. In the solid state, it exists as dimeric, azodioxy form but in solution the equilibrium is largely in favour of the monomer and rather high concentrations are required to obtain an appreciable fraction of dimer (figure 9).[114]

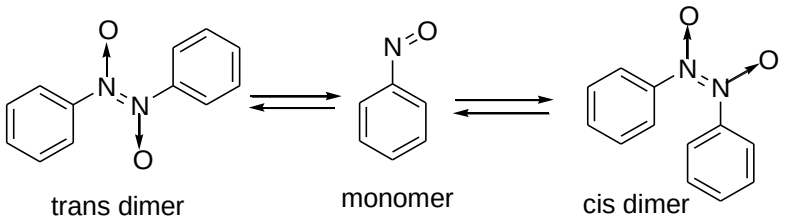
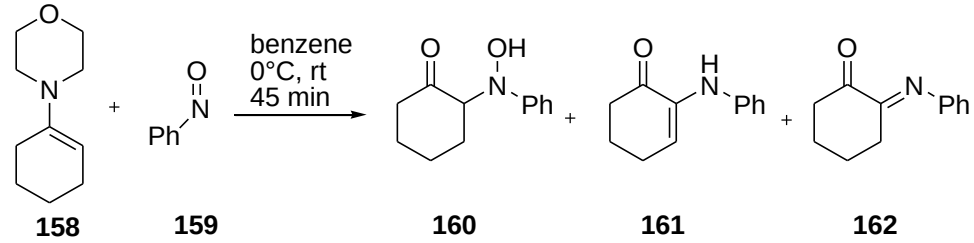


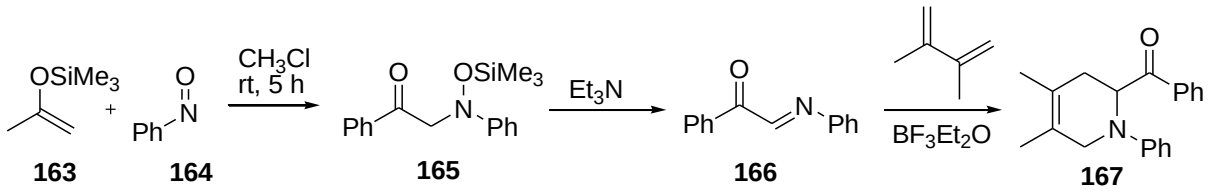
Figure 9

Lewis *at al.*[115] in 1972 reported the reaction of nitrosobenzene **159** with 1-Morpholin-1-ylcyclohexene **158**. The reaction yielded the corresponding α-hydroxyaminoketone **160** in 30% yield (scheme 61).



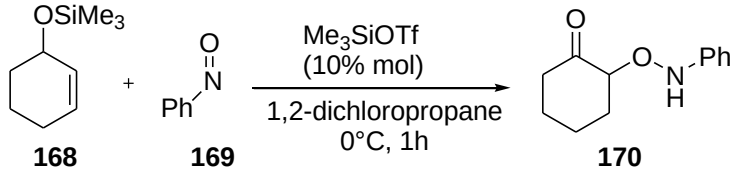
Scheme 61

This strategy was extended at various silyl enol ether by Sasaki and Ohno.[116] Their study revealed that reactive silyl enol ethers **163** led to siloxyamino ketones **165** which were further transformed to the heterocyclic derivatives **167** (scheme 62).



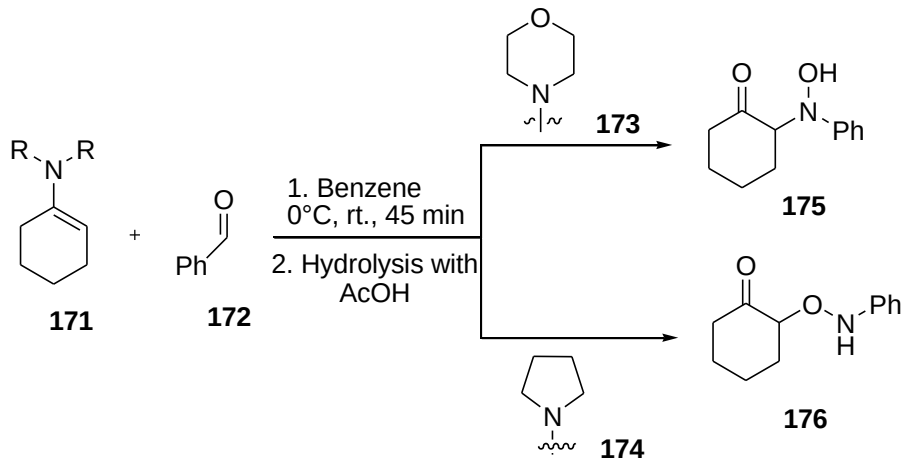
Scheme 62

Significant contribution to the nitroso group chemistry was the discovery of O-selective nucleophilic attack of silyl enol ethers to nitrosobenzene catalyzed by acid. The first regioselective synthesis of aminooxy ketones from silyl enol ethers and nitrosobenzene promoted by acid catalyst was reported by Yamamoto and co-workers in 2002[117] (scheme 63). Unexpectedly, the only product isolated was the α-aminooxy ketone (**170**).



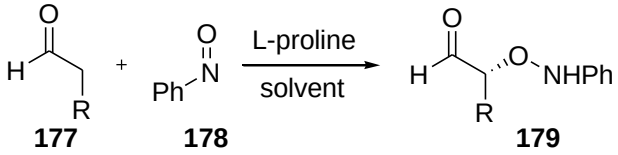
Scheme 63

After this discovery they obtained the α-aminooxy carbonyl compound using enamine as nucleophile.[118] The reaction between 1-pyrrolidin-1-ylcyclohexene and nitrosobenzene in acetic acid gives rise to the aminooxy ketone almost exclusively. The observed discrepancies with the results reported by Lewis derived from the structural difference of enamines. In fact, when the reaction was conducted with morpholine enamine the product isolated was the hydroxyamino ketone (scheme 64).



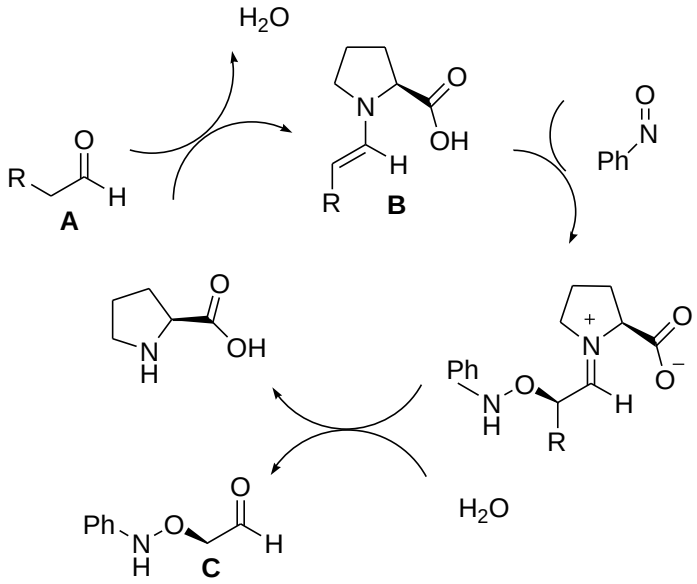
Scheme 64

MacMillan and coworkers, Zhong, and Hayashi *et al.*[119] independently reported the enantioselective nitroso aldol reaction of nitroso benzene and simple aldehyde using proline catalyst (scheme 65).



Scheme 65

The aldehyde **A** reacts with proline, yielding highly reactive enamine intermediate **B**, O-selective nucleophilic attack of enamine on the nitrosobenzene provides the α-aminoxy product **C** (scheme 66).

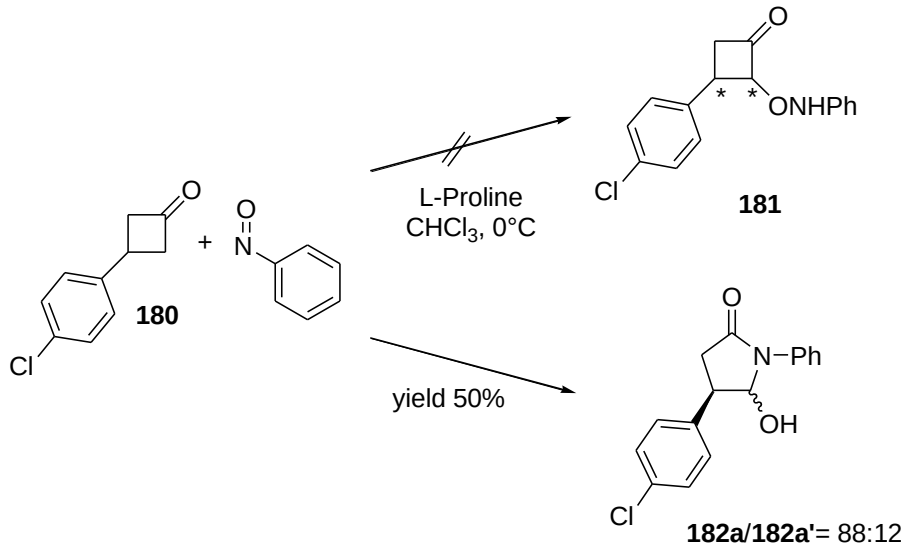


Scheme 66

5.1 Result and discussion[120a]

Following our involvement in the chemistry of small carbocylic derivatives,[120b] we were intrigued by the possibility of preparing optically active 2,3-disubstituted cyclobutanones by an enantio- and diastereoselective organocatalytic[121] desymmetrization of 3-substituted prochiral cyclobutanones with nitrosobenzene.

So we decided to examine the reaction of suitable prochiral cyclobutanones **180** with nitrosobenzene in the presence of different organocatalysts[122] (Scheme 67).



Scheme 67. Attempted synthesis of α-aminoxylated cyclobutanone **182**.

The preliminary reaction of **180a** with nitrosobenzene (3.0 equiv.) in the presence of 30% L-proline gave, instead of the expected α-aminoxylated cyclobutanone **181**, good yields (50%) of the α-hydroxy-γ-lactam **182** as a mixture of two diastereoisomers **182a/182a'** (dr= 88/12), that we considered, at this stage, as a *trans/cis* mixture (44% and 70% *ee* respectively) of a single regioisomer. This was an unprecedented result and its importance was further increased by the fact that 2-pyrrolidinones[123] and their derivatives are very interesting compounds for the pharmaceutical industry. Moreover the 5-hydroxy substituted 2-pyrrolidinones show several versatile applications[124] and are also the precursors of the highly reactive cyclic α-acyliminium ion.[125] Intrigued by this preliminary result, we sought to establish reaction conditions that would give improvement in yield and stereoselectivity.

The reaction of cyclobutanone **180** and nitrosobenzene was investigated as a model and the effect of a number of known catalyst **I**-**V**, different solvents and reaction conditions were examined with the results summarized in table 10.

Among the catalysts probed, **I** and **IV** were the best promoters for the process (table 10, entries 2 and 8) in terms of both chemical yield and stereoselectivity and the use of other solvents as well as reaction temperatures was not advantageous.

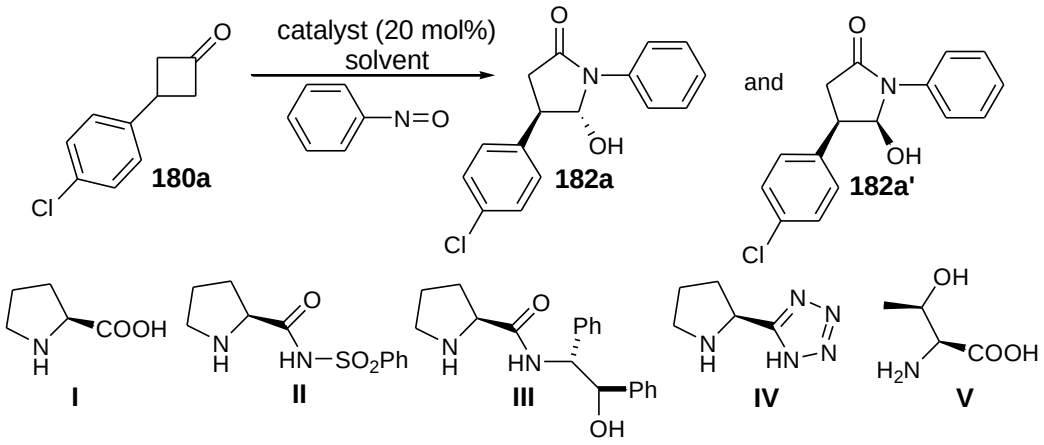


Table 10. Optimization Studies[a]

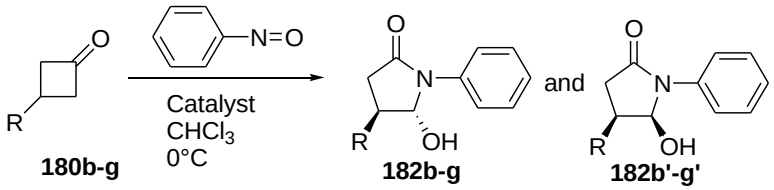
Entry	Catalyst	Solvent	Temp (°C)	Yield[b]	ee *trans* (%)[c]	dr(%)[d] *trans/cis*
1[e]	**I**	$CHCl_3$	0	50	44	88/12
2[f]	**I**	$CHCl_3$	0	65	50	70/30
3	**II**	$CHCl_3$	0	40	52	>99/<1
4	**II**	$CHCl_3$	-10	30	>99	>99/<1
5	**II**	$CHCl_3$	-20	-	-	-
6	**III**	$CHCl_3$	0	-	-	-
7	**III**	Toluene	0	-	-	-
8	**IV**	$CHCl_3$	0	55	58	>99/<1
9	**IV**	CH_2Cl_2	0	30	60	>99/<1
10	**IV**	DMSO	RT	0	-	-
11	**IV**	DMF	0	0	-	-
12	**IV**	Toluene	0	0	-	-
13	**V**	$CHCl_3$	0	0	-	-

[a] Unless otherwise noted, all the reactions were carried out with 3.0 equiv of nitrosobenzene relative to prochiral cyclobutanone and 20 mol% of catalyst at 0°C for 96h. [b]Yield of isolated product (sum of diastereomers). [c] Determined by chiral HPLC analysis.

[d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] 30 mol% of L-proline was used.[f] The reaction was carried out by slow addition (48h) of nitrosobenzene to 5 eq. of cyclobutanone **180** in the presence of 30 mol % of L-proline.

As catalyst **I** and **IV** gave the best results in $CHCl_3$, we extended this reaction to different cyclobutanones **180b-g** using $CHCl_3$ as a solvent at 0°C and the results are summarized in table 11.

Table 11. Asymmetric synthesis of 4-substituted-5-hydroxy-γ-lactams **182**.[a]

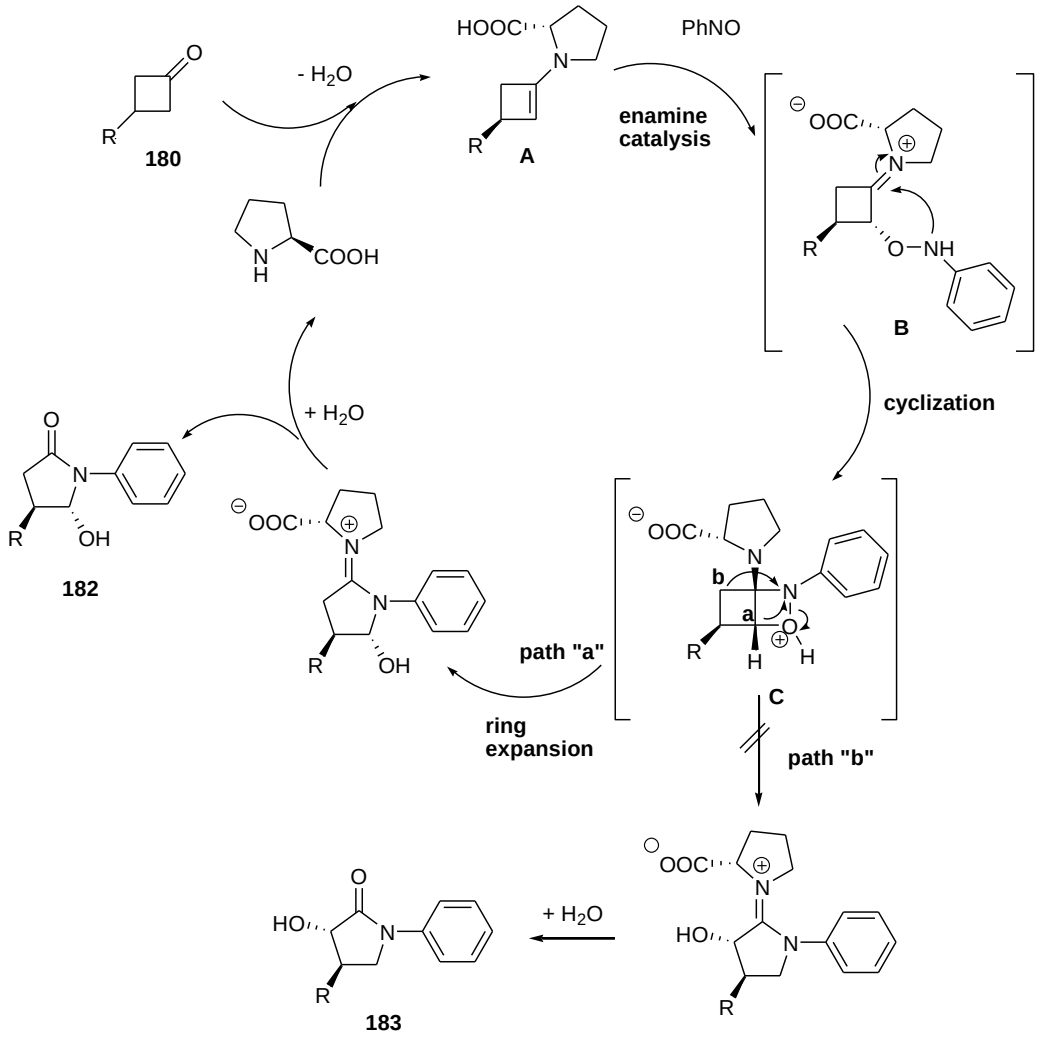


Entry	R (product)	Catalyst	Yield[b]	ee *trans* (%)[c]	dr(%)[d] *trans/cis*
1	C_6H_5	**I**	40	20	95/5
	(**182b/182b'**)	**IV**	45	30	79/21
2	*p*-BrC_6H_4	**I**	57	27	73/27
	(**182c/182c'**)	**IV**	20	4	>99/<1
3	*p*-$CH_3C_6H_4$	**IV**	30	40	77/23
	(**182d/182d'**)				
4	$PhCH_2CH_2$	**I**	65	51	93/7
	(**182e/182e'**)	**IV**	40	42	94/6
5	*n*-C_6H_{13}	**I**	60	38	67/33
	(**182f/182f'**)	**IV**	40	60	99/1
6	Cyclohexyl	**I**	48	37	85/15
	(**182g/182g'**)	**IV**	41	56	72/28

[a] The reactions were carried out in $CHCl_3$, with 3.0 equiv of nitrosobenzene relative to prochiral cyclobutanone and 20 mol % of catalyst **IV** or by slow addition (48h) of nitrosobenzene to 5 eq. of cyclobutanone **180** in the presence of 30 mol % of L-proline, at 0°C for 96h.[b]Yield of isolated product (sum of diastereomers). [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

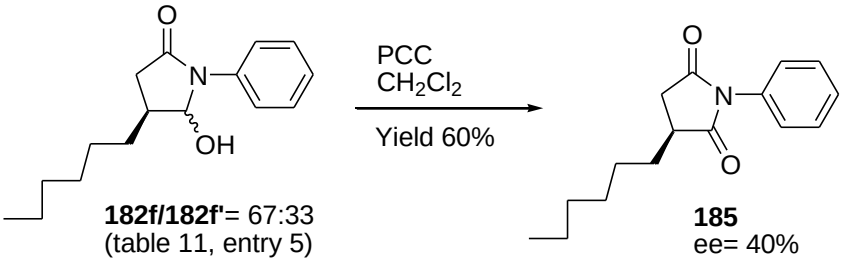
The reaction can be rationalized by assuming the mechanism shown in scheme 68, based on a catalytic cycle through a cascade reaction initiated by an O-nitroso aldol-cyclization domino reaction ending with a cyclobutyl ring expansion. Chiral L-proline catalyzes the

formation of the enamine **A** with a not high asymmetric induction. Subsequent nucleophilic addition to nitrosobenzene furnishes the α-aminoxylated cyclobutyl iminium intermediate **B** with excellent diastereoselectivity. **B** undergoes intramolecular nucleophilic 1,2 addition followed by rearrangement of the bicyclic intermediate **C**, either into the 5-hydroxy-γ-lactam **182** by migration of the more substituted terminus (path a) or into the 3-hydroxy-γ-lactam **183** by migration of the less substituted terminus (path b).



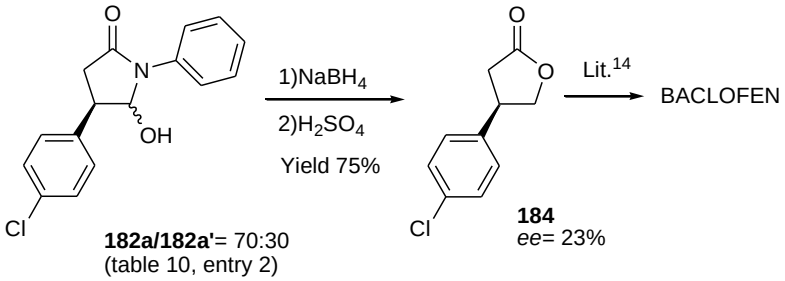
Scheme 68. Proposed catalytic cycle of the domino organocatalytic asymmetric synthesis of γ-lactams **182**. (Only the *trans* isomer is showed)

On the basis of this mechanism we could be dealing either with two geometric isomers of a single regioisomer or with two regioisomer with the same geometry. To solve the above mentioned uncertainty we carried out the oxidation of the inseparable mixture of diastereoisomers **182f** and **182f'** (Scheme 69). The fact that we obtained only the product **185** (ee= 40%) was taken as a conclusive evidence that mixture **182f/182f'** was a *trans/cis* mixture of a single regioisomer (5-hydroxy-γ-lactams).



Scheme 69

The geometry of compounds **182a-g** and **182a'-g'** was assigned on the basis of the coupling constant value of C4-H and C5-H as well as by comparison with literature data.[126] On the other hand, the absolute stereochemistry of the major isomer of compounds **182a-g** could be assigned by analogy with that assigned to **182a/182a'**after its conversion to the (R)-lactone **184** (ee= 23%) that is a known precursor[127] of the aminoacid Baclofen (Scheme 70).



Scheme 42. Reactions of two γ-lactams **182** to assign their relative and absolute configurations.

In summary we have developed an organocatalyzed desymmetrization of 3-substituted cyclobutanones using as electrophile nitrosobenzene that led to the discovery of the first direct organocatalysed enantioselective “ring expansion-terminated O-nitroso aldol-cyclization domino reaction”. Two are the focal points of this reaction sequence: a) for the first time, we could successfully combine enamine organocatalysis with a cyclization- ring expansion-terminated reaction in a tandem sequence,[128] b) the fundamental role of the strained cyclobutyl ring that easily expands to originate the pyrrolidinone derivatives. This is a powerful approach for the generation of optically active nitrogen containing molecules.

CHAPTER 5

References and notes

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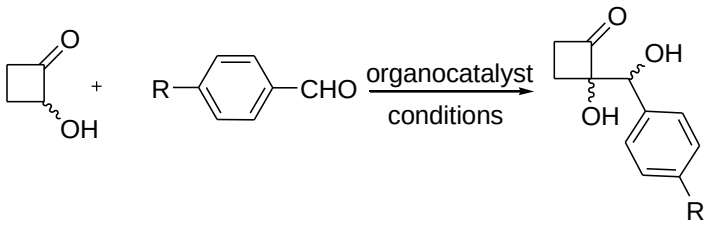
GENERAL CONCLUSION AND PERPECTIVES

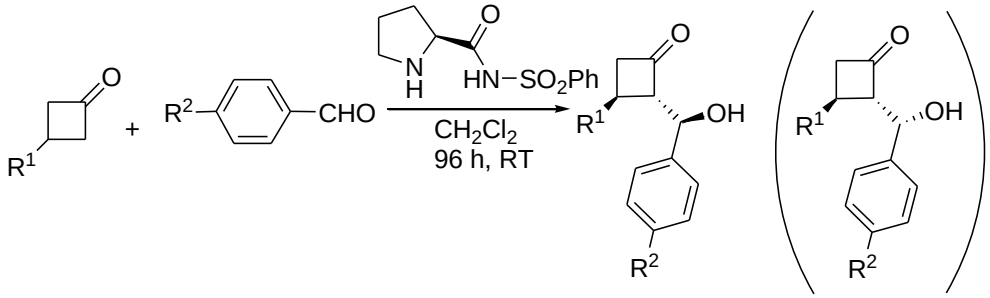
During this work, we developed four enantioselective transformations of substituted cyclobutanones. We investigated the direct aldol reaction of 2-hydroxycyclobutanone with *p*-nitrobenzaldehyde in the presence of selected primary L-amino acids. In wet DMF solvent, the reaction furnishes the relative adduct with noteworthy regio- and stereoselectivities, with the *anti* diastereomer predominating. To develop this original deracemizing reaction, we decided to examine the direct aldol reaction of 2- hydroxycyclobutanone with a selection of aromatic aldehydes in solvent-free conditions. Using L-threonine, deracemized aldol adducts featuring a chiral quaternary center were obtained in good yields with *syn* selectivity (scheme 43).



Scheme 43

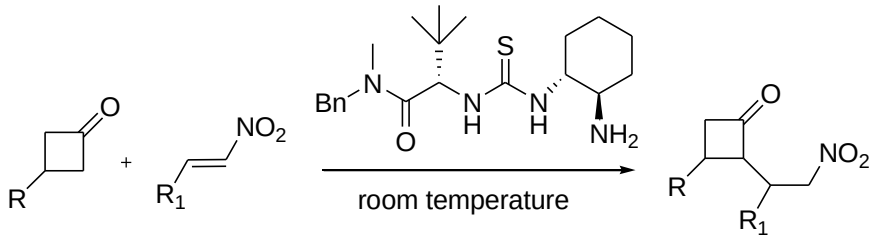
We synthetized 2,3-substituted cyclobutanones with two different modes:

- through direct aldol reactions of 3-substituted cyclobutanones and several aryl aldehydes catalyzed by N-phenylsulfonyl (S)-proline. This desymmetrization process provides highly functionalized cyclobutanones with control over three contiguous stereogenic centers (scheme 44).



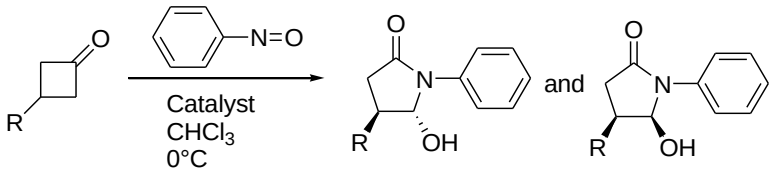
Scheme 44

- via asymmetric nitro Michael reaction of 3-substituted cyclobutanones and several nitrostyrenes catalyzed by thiourea derivatives. The relatives γ-nitrocyclobutanones were obtained in good yields but in modest enantioselectivity (scheme 45).



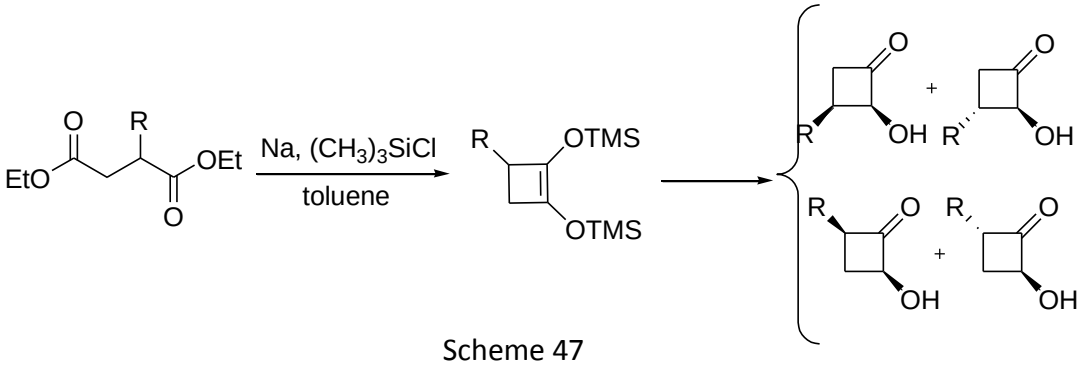
Scheme 45

In the end we presented an unexpected formation of optically 4- substituted 5-hydroxy-γ-lactams via organocatalyzed enantioselective desymmetrization reaction of 3-substituted cyclobutanones with nitrosobenzene. Despite the moderate enantioselectivities, our result add new knowledge because the mechanistic model proposed represents an extension for existing concepts in the chemistry of cyclobutanones and enamine catalysis (scheme 46).



Scheme 46

Future perpectives can involve the synthesis of 2-hydroxy-3-substituted cyclobutanones as substrates for the aldolic reaction with several aldehydes (scheme 47).



Scheme 47

Experimental section

Materials and methods.

^{1}H NMR spectra were recorded on VARIAN 250, 300 or 500 MHz spectrometers at ambient temperature with $CDCl_3$ as solvent and TMS as internal standard. Data are reported as follows: chemical shifts (δ), multiplicity, integration and coupling constants. ^{13}C NMR spectra were recorded on the same instruments, operating respectively, at 62, 75 or 124 MHz at ambient temperature with $CDCl_3$ as solvent. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low resolution mass spectral analyses were recorded on an Agilent 5973N (Cpsil 32m) in E.I. (70 eV) or C.I. (NH_3) mode. Relative intensities are given in parentheses. High resolution mass spectra (HRMS) was recorded on a Finnigan MAT-95 spectrometer using Positive Electro Ionization (ESI) mode. Enantiomeric excesses of aldol products were determined by hplc on a HITACHI L7100 instrument fitted with a HITACHI L-7400 UV detector, using a Diacel Chiralpac AD-H, Chiralcel OD-H or Chiralcel OJ analytical column with *i*-PrOH/hexane as eluent, using authentic racemic samples for reference comparison. Optical rotation values were obtained on a Perkin-Elmer 241 or a PolAAr 32 polarimeter. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 70-200 mesh Merk silica gel. Yields refer to chromatographically pure materials. Where a compound has been obtained as a mixture of diastereomers, the NMR data and the chiral hplc data (*ee* values) are reported for the major component.

(±)-Proline and aldehydes were obtained commercially. (2*S*)-*N*-(2-Pyrrolidine-2-carbonyl)-benzenesulfonamide (**II**) was prepared by the literature procedure.[1] 3-Substituted cyclobutanones were prepared by the literature procedures.[2]

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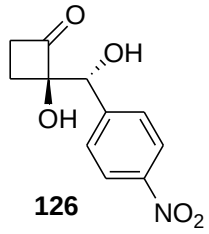
CHAPTER 3

General procedure for the synthesis of authentic racemic samples: To a solution of aldehyde (0.5 mmol) and 2-hydroxycyclobutanone (1 mmol) in DMSO (2 mL) was added (±)-proline (0.05 mmol). The resulting mixture was stirred at room temperature for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted several times with EtOAc (2 $\times$ 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography to give the corresponding aldol product .

General procedure for the synthesis of enantiomeric enriched samples To a solution of 4-nitrobenzaldehyde (0.5 mmol) in DMF (0.5 mL) was added 2-hydroxycyclobutanone (1 mmol) followed by *L*-tryptophan (0.15 mmol), and H_2O (2.2 mmol). The reaction was stirred at r.t. for 7 d, then diluted with EtOAc, and washed with half-sat. NH_4Cl solution. The aqueous phase was further extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified by flash chromatography (PE-Et_2O = 1:1).

2-Hydroxy-2-[1-hydroxy(4-nitrophenyl)methyl]cyclobutanone (126)



126

FW 237
$C_{11}H_{11}NO_5$

White solid

IR (KBr): 3360, 1760 cm^{-1}.

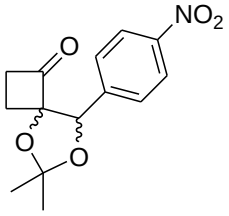
^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.62 (q, 1 H, *J* = 10.5 Hz, *anti*), 1.91 (q, 1 H, *J* = 10.3 Hz, *syn*), 2.29-2.45 (m, 3 H, *syn*), 2.63-2.85 (m, 3 H, *anti*), 4.82 (d, 1 H + 1 H, *J* = 5.0 Hz, *anti* + *syn*), 6.15 (d, 1 H, *J* = 5.0 Hz, *anti*), 6.19 (d, 1 H, *J* = 5.0 Hz, *syn*), 6.24 (s, 1 H, *syn*), 6.31 (s, 1 H, *anti*), 7.63 (d, 2 H, *J* = 8.5 Hz, *syn*), 7.71 (d, 2 H, *J* = 8.8 Hz, *anti*), 8.20 (d, 2 H, *J* = 8.5 Hz, *syn*), 8.23 (d, 2 H, *J* = 8.8 Hz, *anti*).

^{13}C NMR (62 MHz, DMSO-d_6): δ = 23.0 (*anti*), 25.9 (*syn*), 40.9 (*syn*), 41.8 (*anti*), 72.0 (*anti*), 74.5 (*syn*), 93.8 (*anti*), 94.2 (*syn*), 122.8 (*syn*), 122.9 (*anti*), 128.9 (*anti*), 129.4 (*syn*), 147.2 (*anti*), 149.8 (*syn*), 149.9 (*anti* + *syn*), 212.1 (*syn*), 214.2 (*anti*).

MS: *m/z* (%) = 219 $[M - H_2O]^+$ (100), 163 (83), 151 (54), 150 (60), 149 (70), 133 (30), 105 (25), 77 (41).

Anal. Calcd for $C_{11}H_{12}NO_5$: C, 55.46; H, 5.08; N, 5.88. Found: C, 55.59; H, 5.15; N, 5.71.

Preparation of 6,6-Dimethyl-8-(4-nitrophenyl)-5,7-dioxaspiro[3.4]octan-1-one (127). The aldol product **126** was dissolved in dry acetone (2 mL) and Montmorillonite K10 (40% w/w), and 2,2-dimethoxypropane (2 equiv) were added. The mixture was stirred at r.t. for 12 h. After filtration through a glass filter, the filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (PE-Et_2O, 3:1) to afford the requisite acetonide products **47** (yield ca. 95%).



127

$C_{14}H_{15}NO_5$
FW 277

Compound *syn*-127:

white solid.

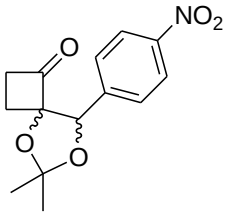
IR (mull): 1785 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.54 (s, 3 H), 1.58-1.73 (m, 1 H), 1.95-2.11 (m, 1 H), 2.18-2.38 (m, 1 H), 2.75-2.89 (m, 1 H), 5.27 (s, 1 H), 7.50 (d, 2 H, *J* = 8.8 Hz), 8.29 (d, 2 H, *J* = 8.8 Hz).

^{13}C NMR (62 MHz, $CDCl_3$): δ = 23.8, 25.7, 27.1, 41.8, 80.1, 98.2, 111.2, 123.9, 127.4, 143.3, 148.1, 208.4. MS: *m/z* (%) = 249 $[M - 28]^+$ (2), 219 (7), 163 (100), 149 (11), 133 (23), 89 (8).

The ee was determined by chiral HPLC [Chiralcel OJ-H column, hexane-EtOH (90:10), flow rate 1 mL/min, λ = 254 nm]: t_R = 17.5 min (major enantiomer), t_R = 26.8 min (minor enantiomer).

6,6-Dimethyl-8-(4-nitrophenyl)-5,7-dioxaspiro[3.4]octan-1-one (127)



127

$C_{14}H_{15}NO_5$
FW 277

Compound *anti*-127:

white solid.

IR (mull): 1785 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.73 (s, 3 H), 1.90-2.00 (m, 1 H), 2.32-2.60 (m, 3 H), 5.23 (s, 1 H), 7.61 (d, 2 H, *J* = 8.5 Hz), 8.23 (d, 2 H, *J* = 8.5 Hz).

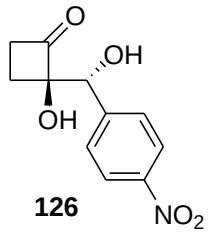
^{13}C NMR (62 MHz, $CDCl_3$): δ = 22.5, 26.3, 27.2, 40.6, 83.3, 99.5, 111.8, 123.8, 127.7, 141.8, 148.0, 206.6.

MS: *m/z* (%) = 249 $[M - 28]^+$ (2), 219 (6), 163 (100), 149 (14), 133 (23), 89 (9).

The ee was determined by chiral HPLC [Chiralcel OJ-H column, hexane-EtOH (90:10), flow rate 1 mL/min, λ = 254 nm]: t_R = 20 min (major enantiomer), t_R = 43.6 min (minor enantiomer

General procedure for the synthesis of 2,2 disubstituted -hydroxy-ketones (126a-126g). A mixture of aldehyde (0.25 mmol), α-hydroxyketone (1.25 mmol) and L-threonine (0.075 mmol) was stirred at 0-5 °C for the requisite time. The mixture was diluted with AcOEt and washed with half-saturated ammonium chloride solution. The water phase was further extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, concentrated and purified by column chromatography (petroleum ether/ether 1:1) to afford the desired aldol product as an inseparable *syn*:*anti* mixture. The *dr* was determined by GC analysis. For *ee* determination, chiral HPLC analysis was used. When indicated, the aldol was first converted into the corresponding acetylated products in effectively quantitative yield, to facilitated signal separation.

2-((4-fluorophenyl)(hydroxy)methyl)-2-hydroxycyclo-butanone (126b)



126

FW 237
$C_{11}H_{11}NO_5$

Data obtained for a 85:15 *syn*:*anti* mixture.

White solid.

IR (nujol): 3455, 1701 cm^{-1}.

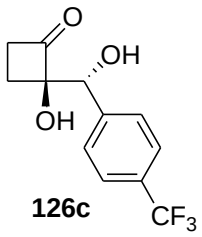
^{1}H NMR (250 MHz, DMSO-d_6): δ: 1.40-1.80 (m, 1 H, *syn*), 2.11-2.32 (dd, 1 H, *J* = 9.7 Hz, 10.7 Hz, *anti*), 2.31-2.51 (m, 3 H, *syn + anti*), 3.55-2.75 (m, 3 H, *syn + anti*), 4.57 (d, 1 H, *J* = 3.75 Hz, *syn*), 4.72 (br s, 1 H, *anti*), 5.72 (s, 1 H, *syn*), 5.94 (m, 1 H, *anti*), 6.40-6.51 (m, 2 H, *syn + anti*), 7.00-7.09 (m, 2 H, *syn + anti*), 7.25-7.38 (m, 2 H, *syn + anti*).

^{13}C NMR (62 MHz, DMSO-d_6): δ: 23.3 (*anti*), 25.7 (*syn*), 38.7 (*syn*), 41.4 (*anti*), 72.5 (*anti*), 74.8 (*syn*), 94.5 (*syn*), 95.1 (*anti*), 114.8 (*syn*), 115.1 (*anti*), 129.9 (*syn*), 130.1 (*anti*), 130.3 (*syn*), 130.4 (*anti*), 138.3 (*anti*), 138.6 (*syn*), 212.3 (*syn*), 214.7 (*anti*).

EI-MS *m/z*: 192 [M^+–18] (66), 149 (15), 136 (69), 122 (100), 97 (50), 94 (54), 77 (22), 58 (28).

After acetylation, the *ee* was determined using a Daicel Chiralcel OJ column (hexane/*i*-PrOH = 93:7, flow rate 1.1 mL/min, λ = 254 nm) *syn*: t_R = 15.3 min (major), t_R = 17.4 min (minor).

2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl)-2-hydroxy-cyclobutanone (126c)



126c

FW 260
$C_{12}H_{11}FO_3$

Data obtained for a 84:16 *syn*:*anti* mixture.

White solid.

IR (nujol): 3470, 1703 cm^{-1}.

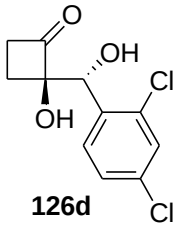
^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.41-1.58 (m, 1 H, *syn*), 1.58-1.79 (m, 1 H, *anti*), 2.08-2.42 (m, 4 H, *syn + anti*), 2.50-2.80 (m, 2 H, *syn + anti*), 4.63 (d, 2 H, *J* = 4.75 Hz, *syn + anti*), 5.87 (d, 2 H, *J* = 4.75 Hz, *syn +anti*), 6.02 (s, 1 H, *anti*), 6.08 (s, 1 H, *syn*), 7.28-7.62 (m, 8 H, *syn + anti*).

^{13}C NMR (62 MHz, DMSO-d_6) δ: 23.4 (*anti*), 26.2 (*syn*), 38.7 (*anti*), 42.2 (*syn*), 72.7 (*syn*), 75.2 (*anti*), 94.4 (*syn*), 94.8 (*anti*), 123.3 (*anti*), 125.1 (*syn*), 125.3 (*anti*), 127.6 (*anti*), 128.4 (*syn*), 129.0 (*syn +anti*), 129.4 (*syn*), 147.2 (*syn + anti*), 212.1 (*syn*), 214.3 (*anti*).

EI-MS *m/z*: 242 [M^+–18] (47), 186 (63), 173 (61), 172 (100), 145 (80), 127 (59), 58 (30).

After acetylation, the *ee* was determined using a Daicel Chiralcel OJ column (hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, λ = 254 nm) *syn*: t_R = 28 min (major), t_R = 38 min (minor); *anti*: t_R = 26 min (minor), t_R = 49.7 min (major).

2-((2,4-dichlorophenyl)(hydroxy)methyl)-2-hydroxycy-clobutanone (126d)



126d

FW 260
$C_{11}H_{10}Cl_2O_3$

Spectral data worked out from the 70:30 *syn*:*anti* mixture.

White solid.

IR (KBr): 3479, 1723 cm^{-1}.

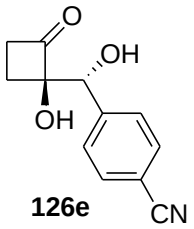
^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.69 (q, 1 H, *J* = 10. 5 Hz, *syn*), 1.82 (q, 1 H, *J* = 10. 4 Hz, *anti*), 2.30 (dq, 1 H, *J* = 5.0, 11.3 Hz, *anti*), 2.51 (q, 1 H, *J* = 11.3 Hz, *syn*), 2.66-2.80 (m, 4 H, *syn +anti*), 5.02 (d, 1 H, *J* = 4.00 Hz, *syn*), 5.05 (d, 1 H, *J* = 3.3 Hz, *anti*), 5.87 (d, 1 H, *J* = 4.75 Hz, *syn*), 6.02 (s, 3 H, *syn +anti*), 7.34-7.61 (m, 6 H, *syn +anti*).

^{13}C NMR (62 MHz, DMSO-d_6) δ: 23.7 (*anti*), 25.4 (*syn*), 40.3 (*syn*), 40.8 (*anti*). 68.2 (*anti*), 70.1 (*syn*), 94.1 (*anti*), 94.2 (*syn*), 126.7 (*syn +anti*), 127.8 (*syn*), 127.9 (*anti*), 131.0 (*anti*), 131.2 (*syn*), 132.3 (*syn +anti*), 133.2 (*anti*), 133.4 (*syn*), 138.2 (*syn*), 138.3 (*anti*), 210.8 (*syn*), 211.4 (*anti*).

EI-MS *m/z*: 242 [M^+–18] (36), 186 (59), 174 (80), 172 (100), 111 (49), 75 (27).

After acetylation, the *ee* was determined using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, λ = 254 nm) *syn*: t_R = 8.9 min (major), t_R = 11.6 min (minor).

4-[hydroxy-(1-hydroxy-2-oxo-cyclobutyl)-methyl]-benzonitrile (126e)



126e

FW 217
$C_{12}H_{11}NO_3$

Data obtained for a 78:22 *syn*:*anti* mixture.

Colorless oil.

IR (neat): 3388, 2236, 1941, 1785 cm^{-1}.

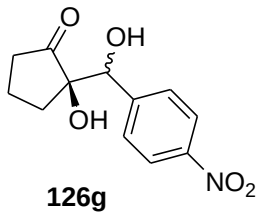
^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.76-1.84 (m, 1 H, *anti*), 1.92 (q, 1 H, *J* = 11.0 Hz, *syn*), 1.98-2.07 (m, 1 H, *syn*), 2.08-2.17 (m, 1 H, *anti*), 2.27 (dt, 1 H, *J* = 5.0, 12.0 Hz, *syn*), 2.35 (dt, 1 H, *J* = 5.0, 12.5 Hz, *anti*), 2.38-2.84 (m, 4 H, *syn + anti*), 4.20-4.80 (m, 2 H, *syn + anti*), 4.90 (s, 2 H, *syn + anti*), 7.49-7.62 (m, 8 H, *syn + anti*).

^{13}C NMR (124 MHz, $CDCl_3$) δ: 21.3 (*anti*), 23.2 (*syn*), 41.2 (*syn*), 41.7 (*anti*), 73.9 (*syn*), 81.6 (*anti*), 93.4 (*syn + anti*), 111.8 (*syn + anti*), 118.4 (*syn + anti*), 127.8 (*anti*), 128.0 (*syn*), 132.0 (*anti*), 132.1 (*syn*), 143.4 (*syn*), 144.2 (*anti*), 210.4 (*syn*), 211.4 (*anti*).

EI-MS *m/z*: 199 [M^+–18] (27), 143 (37), 130 (48), 129 (56), 115 (21), 102 (29), 77 (14), 40 (100).

The *ee* was determined using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm) *syn*: t_R = 39.9 min (major), t_R = 25.9 min (minor); *anti*: t_R = 27.8 min (minor), t_R = 32.8 min (major).

2-hydroxy-2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone (126g)



126g

FW 251
$C_{12}H_{13}NO_5$

Data obtained for a 69:31 *syn*:*anti* mixture, obtained using the modified conditions stated in Table 5 (footnote f).

Orange oil.

IR (neat): 3422, 1750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24-2.43 (m, 12 H), 4.87 (s, 1 H), 4.93 (s, 1 H), 7.53-7.57 (m, 4 H), 8.19-8.22 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.1, 29.6, 30.8, 32.1, 36.1, 37.2, 74.7, 74.8, 79.1, 79.7, 104.1, 104.8, 123.1, 123.3, 128.0, 145.0, 147.0, 216.4, 217.1.

EI-MS *m/z*: 234 [M^+-17] (1), 165 (10), 150 (10), 100 (100), 77 (30), 55 (16), 43 (16).

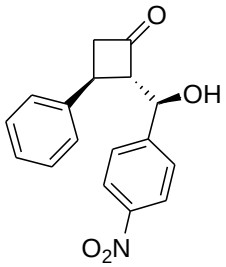
The *ee* was determined using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 92:8, flow rate 0.8 mL/min, λ = 254 nm) *syn*: t_R = 24.1 min (major), t_R = 25.0 min (minor); *anti*: t_R = 21.8 min (major), t_R = 36.7 min (minor).

CHAPTER 4

General procedure for the synthesis of authentic racemic samples: To a solution of aldehyde **139** (0.5 mmol) and 3-substituted cyclobutanone **138** (10 mmol) in DMSO (2 mL) was added (±)-proline (0.05 mmol). The resulting mixture was stirred at room temperature for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted several times with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography to give the corresponding aldol product **140** .

General procedure for the enantioselective organocatalyzed aldol reactions: To a solution of aldehyde **139** (0.5 mmol) and 3-substituted cyclobutanone **138** (10 mmol) in anhydrous CH_2Cl_2 (2 mL) was added (2*S*)-*N*-(2-Pyrrolidine-2-carbonyl)-benzenesulfonamide **II** (0.05 mmol). The resulting mixture was stirred at room temperature for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography to give the corresponding aldol product **140**.

2-(hydroxy(4-nitrophenyl)methyl)-3-phenyl-cyclobutanone (140aa)



140aa

FW 297
$C_{17}H_{15}NO_4$

Purified using flash column chromatography (hexane/ether, 1:1) to give the title compound (71% yield) as a mixture of diastereoisomers (dr = 98:2).

Orange oil.

IR (neat): 3460, 1700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.24 (ddd, 1H, *J* = 2.4 Hz, *J* = 8.4 Hz, *J* = 18.0 Hz), 3.41 (ddd, 1H, *J* = 1.8 Hz, *J* = 9.0 Hz, *J* = 17.4 Hz), 3.55 (q, 1H, *J* = 8.4 Hz), 3.70-3.76 (m, 1H), 5.13 (d, 1H, *J* = 6.6 Hz), 7.07-7.29 (m, 5H), 7.54 (d, 2H, *J* = 8.7 Hz), 8.14 (d, 2H, *J* = 9.0 Hz).

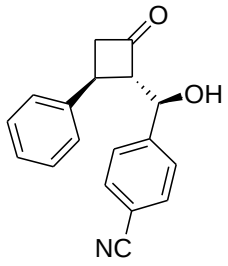
^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.7, 52.5, 72.3, 72.8, 123.7, 126.3, 126.9, 127.2, 128.7, 141.5, 147.5, 147.9, 206.7.

MS *m/z*: 297 (M^+-18 (80)), 251 (14), 234 (63), 204 (100), 189 (44), 165 (18), 115 (100), 89 (34).

Anal. Calcd. for $C_{17}H_{15}NO_4$; C, 68.88; H, 5.09; N, 4.71. Found: C, 68.80; H, 5.12; N, 4.62.

The *ee* was determined to be >99% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 26.68 min, t_R(minor) = 24.79 min.

2-(hydroxy(4-cyanophenyl)methyl)-3-phenyl-cyclobutanone (140ab)



140ab

FW 277
$C_{18}H_{15}NO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (76 % yield) as a mixture of diastereoisomers (dr = 97:3).

Orange oil.

IR (neat): 3450, 1720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.08 (br s, 1H), 3.22 (ddd, 1H, *J* = 2.1 Hz, *J* = 8.1 Hz, *J* = 17.4 Hz), 3.37 (ddd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, *J* = 17.7 Hz), 3.52 (q, 1H, J = 8.7 Hz), 3.67-3.73 (m, 1H), 5.05 (d, 1H, *J* = 6.3 Hz), 7.06 (d, 2H, *J* = 6.6 Hz), 7.18-7.30 (m, 3H), 7.47 (d, 2H, *J* = 8.1 Hz), 7.57 (d, 2H, *J* = 6.6 Hz).

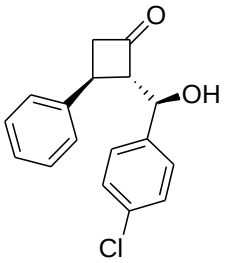
^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.6, 52.4, 72.5, 72.9, 111.7, 118.5, 126.3, 126.9, 127.1, 128.7, 132.3, 141.6, 146.0, 206.7.

MS *m/z*: 259 (M^+-18 (40)), 230 (20), 216 (15), 190 (9), 104 (100), 78 (10).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.91; H, 5.49; N, 5.09.

The *ee* was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 20.61 min, t_R(minor) = 19.18 min.

2-(hydroxy(4-chlorophenyl)methyl)-3-phenyl-cyclobutanone (140ac)



140ac

FW 286
$C_{17}H_{15}ClO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (64 % yield) as a mixture of diastereoisomers (dr = 98:2).

Yellow oil.

IR (neat): 3440, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.25 (ddd, 1H, *J* = 2.7 Hz, *J* = 8.7 Hz, *J* = 15 Hz), 3.35 (ddd, 1H, *J* = 1.8 Hz, *J* = 8.7 Hz, *J* = 17.4 Hz), 3.50 (q, 1H, *J* = 8.4 Hz), 3.69-3.73 (m, 1H), 4.99 (d, 1H, *J* = 6.3 Hz), 7.04-7.45 (m, 9H).

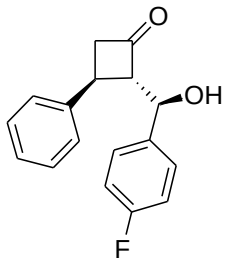
^{13}C NMR (124 MHz, $CDCl_3$) δ: 32.6, 52.0, 72.8, 73.3, 126.4, 126.8, 128.0, 128.6, 128.7, 131.5, 139.2, 141.9, 207.4.

MS *m/z*: 268 (M^+-18 (38)), 233 (87), 205 (75), 189 (40), 164 (43), 136 (34), 104 (100), 78 (15).

Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 71.28; H, 5.21.

The *ee* was determined to be 90% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 11.82 min, t_R(minor) = 12.53 min

2-(hydroxy(4-fluorophenyl)methyl)-3-phenyl-cyclobutanone (140ad)



140ad

FW 270
$C_{17}H_{15}FO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (66 % yield) as a mixture of diastereoisomers (dr = 96:4).

Yellow oil.

IR (neat): 3454, 1780 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.17 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz, *J* = 17.5 Hz), 3.30 (ddd, 1H, *J* = 2.0 Hz, *J* = 9.0 Hz, *J* = 17.5 Hz), 3.42 (q, 1H, *J* = 8.5 Hz), 3.63-3.66 (m, 1H), 4.91 (d, 1H, *J* = 6.5 Hz), 6.91-7.32 (m, 9H).

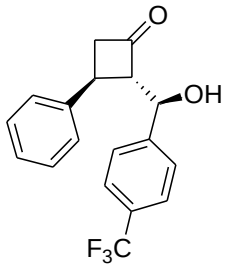
^{13}C NMR (124 MHz, $CDCl_3$) δ: 32.7, 51.9, 72.9, 73.5, 126.6, 126.9, 128.4 (d, *J* = 8.1 Hz), 128.6, 129.1 (d, *J* = 3.5 Hz), 136.5 (d, *J* = 3.2 Hz), 141.9, 162.5 (d, *J* = 2.4 Hz), 207.6.

MS *m/z*: 270 (M^+-18 (3)), 207 (4), 161 (22), 125 (100), 105 (33), 91(20), 77 (19).

Anal. Calcd. for $C_{17}H_{15}FO_2$: C, 75.54; H, 5.59. Found: C, 75.50; H, 5.61.

The *ee* was determined to be 74% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 29.30 min, t_R(minor) = 22.44 min.

2-((4-(trifluoromethyl)phenyl)(hydroxy)methyl)-3-phenyl-cyclobutanone (140ae)



140ae

FW 320
$C_{18}H_{15}FO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (51 % yield) as a mixture of diastereoisomers (dr = 98:2).

Yellow oil.

IR (neat): 3441, 1775 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.23 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.4 Hz, *J* =17.5 Hz), 3.36 (ddd, 1H, *J* = 2.0 Hz, *J* = 9.0 Hz, *J* = 17.5 Hz), 3.50 (q, 1H, *J* = 8.5 Hz), 3.7-3.75 (m, 1H), 5.06 (d, 1H, *J* = 6.5 Hz), 7.04 (d, 2H, *J* = 7.0 Hz), 7.19-7.25 (m, 3H), 7.48 (d, 2H, *J* = 8.5 Hz), 7.56 (d, 2H, *J* = 8.0 Hz).

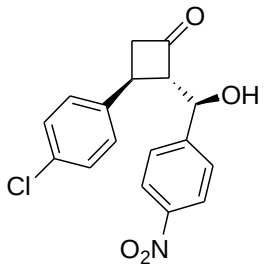
^{13}C NMR (124 MHz, $CDCl_3$) δ: 32.6, 52.1, 72.7, 73.2, 125.5, 125.53, 126.4, 126.8, 126.89, 128.6, 128.7, 129.1, 144.6 (d, *J* = 1.3 Hz), 207.1.

MS *m/z*: 320 (M^+-18 (15)), 301 (4), 161 (40), 145 (9), 127 (11), 104 (100), 77 (12).

Anal. Calcd. for $C_{18}H_{15}F_3O_2$: C, 67.5; H, 4.72. Found: C, 67.3; H, 4.70.

The *ee* was determined to be 91% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 11.57 min, t_R(minor) = 13.74 min.

3-(4-chlorophenyl)-2-(hydroxy(4-nitrophenyl)methyl)cyclobutanone (140ba)



140ba

FW 331
$C_{17}H_{14}ClNO_4$

Syn and *anti* diastereomers were separated by flash column chromatography (hexane/ether, 5:1→1:1) to yield two samples.

***Anti*-140ba** (69 % yield).

Yellow oil.

IR (neat): 3460, 1700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.20 (ddd, 1H, *J* = 1.8 Hz, *J* = 6.3 Hz, *J* = 13.2 Hz), 3.39 (ddd, 1H, *J* = 1.5 Hz, *J* = 6.6 Hz, *J* = 13.2 Hz), 3.54 (q, 1H, *J* = 8.7 Hz), 3.68-3.72 (m, 1H), 5.13 (d, 1H, *J* = 6.0 Hz), 7.04 (d, 2H, *J* = 6.3 Hz), 7.23 (d, 2H, *J* = 6.3 Hz), 7.54 (d, 2H, *J* = 6.6 Hz), 8.15 (d, 2H, *J* = 6.6 Hz).

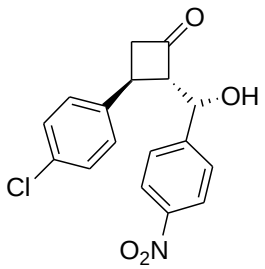
^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.1, 52.4, 72.1, 72.8, 123.7, 127.2, 127.7, 128.8, 132.7, 140.1, 147.5, 147.8, 206.0.

MS *m/z*: 313 (M^+-18 (13)), 296 (11), 278 (9), 203 (19), 189 (20), 138 (100), 101 (18), 75 (8).

Anal. Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.55; H, 4.25; N, 4.22. Found: C, 61.51; H, 4.30; N, 4.18.

The *ee* was determined to be 98% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 38.84 min, t_R(minor) = 48.35 min.

3-(4-chlorophenyl)-2-(hydroxy(4-nitrophenyl)methyl)cyclobutanone (140ba)



140'ba

FW 331
$C_{17}H_{14}ClNO_4$

***Syn*-140ba'** (8 % yield).

White solid, mp: 144 °C.

IR (KBr): 3487, 1780 cm^{-1}.

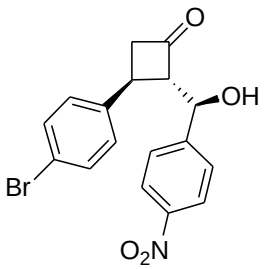
^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.59 (d, 1H, *J* = 4.25 Hz), 3.16 (ddd, 1H, *J* = 2.7 Hz, *J* = 8.0 Hz, *J* = 17.7 Hz), 3.43 (ddd, 1H, *J* = 2.2 Hz, *J* = 9.2 Hz, *J* = 17.5 Hz), 3.66-3.72 (m, 1H), 3.81 (q, 1H, *J* = 8.0 Hz), 5.38 (t, 1H, *J* = 4.0 Hz), 6.87 (d, 2H, *J* = 8.2 Hz), 7.14 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 8.7 Hz).

^{13}C NMR (62 MHz, $CDCl_3$) δ: 30.0, 52.9, 69.8, 73.5, 123.8, 126.4, 127.8, 128.7, 132.7, 140.7, 147.4, 148.3, 206.2.

MS *m/z* (CI, NH_3): 349 (M^++18 (100)), 331 (4), 284 (9), 242 (8), 139 (17), 137 (38), 122 (22).

HRMS (ESI) calcd for M-H ($C_{17}H_{14}ClNO_4$): 330.0539; found 330.0543.

3-(4-bromophenyl)-2-(hydroxy(4-nitrophenyl)methyl)cyclobutanone (140ca)



140ca

FW 375
$C_{17}H_{14}BrNO_4$

Purified using flash column chromatography (hexane/ether, 1:1) to give the title compound (63 % yield) as a mixture of diastereoisomers (dr = 96:4).

Yellow solid.

IR (neat): 3505, 1784 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) 3.18-3.21 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.0 Hz, *J* = 17.5 Hz), 3.38 (ddd, 1H, *J* = 2.0 Hz, *J* = 9.5 Hz, *J* = 18.0 Hz), 3.50 (q, 1H, *J* = 8.5 Hz), 3.67-3.70 (m, 1H), 5.11 (d, 1H, *J* = 6.5 Hz), 6.96 (d, 2H, *J* = 8.5 Hz), 7.38 (d, 2H, *J* = 8.5 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 8.16 (d, 2H, *J* = 8.5 Hz).

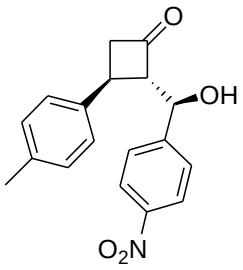
^{13}C NMR (124 MHz, $CDCl_3$) δ: 32.3, 52.5, 72.3, 72.8, 120.8, 123.7, 126.4, 127.3, 128.1, 131.8, 140.6, 147.5, 147.7, 205.8.

MS *m/z*: 377 (M^+(2)), 360 (5), 358 (5), 240 (10), 242 (11), 184 (94), 182 (100), 150 (22), 115 (24), 103 (63), 77 (81), 51 (60), 43 (26).

Anal. Calcd. For $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.47.; H, 3.65; N, 4.80.

The *ee* was determined to be 89% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 48.13 min, t_R(minor) = 45.54 min.

2-(hydroxy(4-nitrophenyl)methyl)-3-(*p*-tolyl)cyclobutanone (140da)



140da

FW 311
$C_{18}H_{17}NO_4$

Purified using flash column chromatography (hexane/ether, 1:1) to give the title compound (74 % yield) as a mixture of diastereoisomers (dr = 93:7).

Yellow solid.

IR (neat): 3521, 1781 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 3.19 (ddd, 1H, *J* = 2.4 Hz, *J* = 8.4 Hz, *J* = 17.4 Hz), 3.36 (ddd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, *J* = 17.4 Hz), 3.49 (q, 1H, *J* = 8.4 Hz), 3.65-3.72 (m, 1H), 5.10 (d, 1H, *J* = 6.6 Hz), 6.95 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 7.2 Hz), 7.53 (d, 2H, *J* = 8.7 Hz), 8.14 (d, 2H, *J* = 8.7 Hz).

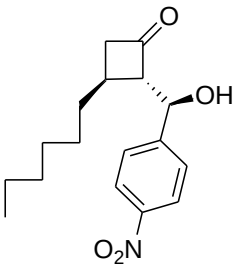
^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 32.4, 52.6, 72.4, 72.7, 123.7, 125.3, 126.2, 127.2, 129.3, 136.6, 138.4, 147.9, 207.0.

MS *m/z*: 293 (M^+-18 (35)), 278 (14), 218 (8), 202 (20), 118 (100).

Anal. Calcd. For $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.21; H, 5.38; N, 4.80.

The *ee* was determined to be 84% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 16.77 min, t_R(minor) = 11.99 min.

3-*n*-hexyl-2-(hydroxy(4-nitrophenyl)methyl)cyclobutanone (140ea)



140ea

FW 305
$C_{17}H_{23}NO_4$

Purified using flash column chromatography (hexane/ether, 1:1) to give the title compound (70 % yield) as a mixture of diastereoisomers (dr = 98:2).

Orange oil.

IR (neat): 3440, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (t, 3H, *J* = 7.5 Hz), 0.88-1.44 (m, 10H), 2.22 (q, 1H, *J* = 7.5 Hz), 2.69 (ddd, 1H, *J* = 2.4 Hz, *J* = 7.5 Hz, *J* = 17.4 Hz), 2.70-2.85 (m, 1H), 3.04-3.17 (m, 2H), 4.97 (d, 1H, *J* = 7.5 Hz), 7.56 (d, 2H, *J* = 9.0 Hz), 8.23 (d, 2H, *J* = 9.0 Hz).

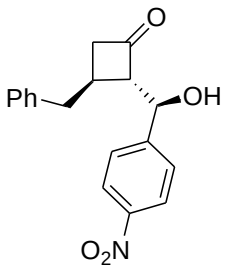
^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.4, 27.6, 28.2, 28.8, 31.5, 35.8, 50.6, 71.1, 72.9, 123.8, 127.1, 147.6, 148.3, 208.5.

MS *m/z*: 287 (M^+-18 (25)), 270 (100), 241 (28), 217 (15), 175 (16), 128 (68), 101 (14).

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.89; H, 7.50; N, 4.68.

The *ee* was determined to be >99% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 85:15, flow rate 1.5 mL/min, λ = 254 nm) t_R(major) = 6.76 min, t_R(minor) = 5.87 min.

2-(hydroxy(4-nitrophenyl)methyl)-3-phenethyl-cyclobutanone (140fa)



140fa

FW 312
$C_{18}H_{17}NO_4$

Purified using flash column chromatography (hexane/ether, 1:1) to give the title compound (60 % yield) as a mixture of diastereoisomers (dr = 99:1).

Orange oil.

IR (neat): 3486, 1773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56-1.79 (m, 2H), 2.14-2.27 (m, 1H), 2.35-2.45 (m, 1H), 2.50-2.59 (m, 1H), 2.67 (ddd, 1H, *J* = 4.8 Hz, *J* = 7.5 Hz, *J* = 17.4 Hz), 3.05 (ddd, 1H, *J* = 2.4 Hz, *J* = 8.7 Hz, *J* = 17.4 Hz), 3.11-3.18 (m, 1H), 4.89 (d, 1H, *J* = 7.5 Hz), 7.02 (d, 2H, *J* = 6.9 Hz), 7.19-2.29 (m, 3H), 7.43 (d, 2H, *J* = 8.4 Hz), 8.16 (d, 2H, *J* = 8.7 Hz).

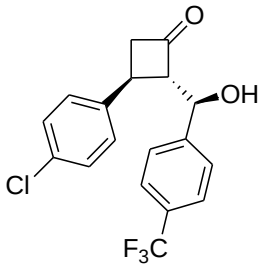
^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.0, 57.4, 60.6, 73.9, 94.4, 95.9, 147.2, 148.8, 149.6, 150.4, 151.6, 151.9, 164.2, 171.7, 231.3.

MS *m/z*: 307 (M^+-18 (23)), 290 (58), 203 (42), 142 (25), 128 (49), 105 (22), 91 (100), 65 (12).

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.85; H, 5.63; N, 4.70.

The *ee* was determined to be 98% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 10.48 min, t_R(minor) = 9.73 min.

3-(4-chlorophenyl)-2-((4-(trifluoromethyl) phenyl)(hydroxy) methyl) cyclobutanone (140be)



60be

FW 354
$C_{18}H_{14}ClF_3O_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (70 % yield) as a mixture of diastereoisomers (dr = 90:10).

Yellow oil.

IR (neat): 3450, 1740 cm^{-1}.

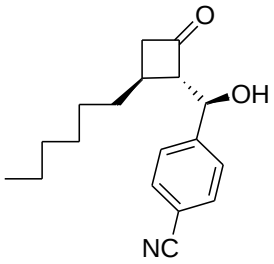
^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.19 (ddd, 1H, *J* = 2.7 Hz, *J* = 8.4 Hz, *J* = 17.4 Hz), 3.36 (ddd, 1H, *J* = 2.4 Hz, *J* = 8.7 Hz, *J* = 17.7 Hz), 3.48 (q, 1H, *J* = 8.7 Hz), 3.66-3.72 (m, 1H), 5.07 (d, 1H, *J* = 6.6 Hz), 6.96 (d, 2H, *J* = 8.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.1, 52.0, 72.6, 73.3, 125.6 (d, *J* = 14.7 Hz), 126.8, 127.8, 128.5, 128.7, 132.2, 140.2, 144.5, 206.4.

MS *m/z*: 336 (M^+-18 (36)), 301 (11), 267 (26), 204 (17), 189 (14), 138 (100), 103 (17).

Anal. Calcd. for $C_{18}H_{14}ClF_3O_2$; C, 60.94; H, 3.98. Found: C, 60.99; H, 3.90. The *ee* was determined to be 84% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1.2 mL/min, λ = 254 nm) t_R(major) = 19.81 min, t_R(minor) = 18.22 min.

4-[(2-Hexyl-4-oxo-cyclobutyl)-hydroxy-methyl]-benzonitrile (140eb)



140eb

FW 285
$C_{18}H_{23}NO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (60 % yield) as a mixture of diastereoisomers (dr = 98:2).

Orange oil.

IR (neat): 3450, 1760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, 3H, *J* = 7.2 Hz), 0.96-1.45 (m, 10H), 2.19 (q, 1H, *J* = 7.8 Hz, *J* = 15.0 Hz), 2.67 (ddd, 1H, *J* = 2.4 Hz, *J* = 7.5 Hz, *J* = 17.4 Hz), 3.02-3.15 (m, 2H), 4.90 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 2H, *J* = 8.7 Hz), 7.66 (d, 2H, *J* = 8.4 Hz).

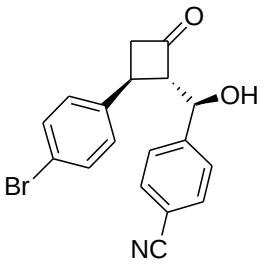
^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.4, 27.6, 28.1, 28.8, 31.5, 35.7, 50.5, 71.1, 73.0, 111.8, 118.5, 127.0, 132.3, 146.4, 208.6.

MS *m/z*: 267 (M^+-18 (58)), 197 (29), 183 (47), 168 (32), 154 (100), 140 (35), 127 (82), 101 (8), 55 (15).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 28.12; N, 4.91. Found: C, 75.69; H, 28.20; N, 4.97.

The *ee* was determined to be 83% *ee* by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 99:1, flow rate 1 mL/min, λ = 254 nm) t_R(major) = 20.36 min, t_R(minor) = 25.30 min.

4-{[2-(4-bromo-phenyl)-4-oxo-cyclobutyl]-hydroxy-methyl}-benzonitrile (140cb):



140cb

FW 355
$C_{18}H_{14}BrNO_2$

Purified using flash column chromatography (hexane/ether, 5:1→1:1) to give the title compound (64 % yield) as a mixture of diastereoisomers (dr = 96:4).

Yellow oil.

IR (neat): 3441, 1771 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.10 (ddd, 1H, *J* = 2.5 Hz, *J* = 8.0 Hz, *J* = 17.5 Hz), 3.29 (ddd, 1H, *J* = 2.0 Hz, *J* = 9.0 Hz, *J* = 17.5 Hz), 3.41 (q, 1H, *J* = 8.5 Hz), 3.58-3.64 (m, 1H), 4.98 (d, 1H, *J* = 6.0 Hz), 6.88 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 2H, *J* = 8.5 Hz).

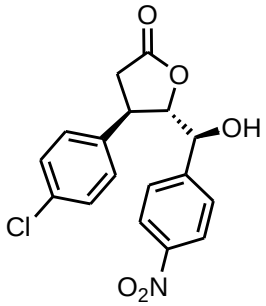
^{13}C NMR (124 MHz, $CDCl_3$) δ: 32.0, 52.2, 72.3, 72.9, 111.9, 118.4, 120.0, 127.2, 128.0, 132.4, 132.5, 140.7, 145.9, 206.0.

MS *m/z*: 355 (M^+-18 (3)), 339 (22), 258 (16), 230 (56), 182 (100), 127 (18), 103 (23).

Anal. Calcd. for $C_{18}H_{14}BrNO_2$; C, 60.69; H, 3.96; N 3.93 Found: C, 60.67; H, 3.97; N 3.91.

The *ee* was determined to be 89% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 75:25, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 31.18 min, t_R(minor) = 46.53 ml.

The synthesis of 4-(4-chlorophenyl)-dihydro-5-(hydroxy(4-nitrophenyl)methyl)furan-2(*3H*)-one (141)



141

FW 347
$C_{17}H_{14}ClNO_5$

To solution of **140ba** (131 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) were added $NaHCO_3$ (87 mg) and m-CPBA (270 mg, 1.5 mmol). The mixture was stirred at 25 °C until the reaction was complete (monitored by TLC). The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give **141** (140 mg) as a white solid in 81% yield; mp: 148-150 °C. $[\alpha]_D^{20}$= +18 (*c* 0.33, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.65 (dd, 1H, *J* = 8.4 Hz, *J* = 18.5 Hz), 2.99 (dd, 1H, *J* = 9.0 Hz, *J* = 18.0 Hz), 3.77 (dd, 1H, *J* = 6.9 Hz, *J* = 8.7 Hz), 4.62 (dd, 1H, *J* = 3.3 Hz, *J* = 6.9 Hz), 4.88 (br s, 1H), 7.11 (d, 2H, *J* = 7.2 Hz), 7.31 (d, 2H, *J* = 7.5 Hz), 7.5 (d, 2H, *J* = 7.8 Hz), 8.14 (d, 2H, *J* = 7.5 Hz) .

^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.4, 42.6, 73.4, 88.7, 124.15, 128.08, 128.2, 128.7, 134.2, 138.3, 146.6, 148.2, 174.3. MS *m/z*: 195 (M^+-120 (27)), 153 (100), 103 (26), 77 (22), 51 (16).

Anal. Calcd. for $C_{17}H_{14}ClNO_5$: C, 58.72; H, 4.06; N, 4.03. Found: C, 58.60; H, 4.31; N, 4.42.

Single-crystal X-ray structure analyses for 141 and 140ba'.

Details of the crystal data, data collection and refinement are given in Table 1. The diffraction intensities were collected with graphite-monochromated MoKα radiation (λ = 0.71073 Å). Data collection and cell refinement were carried out using a Bruker Kappa X8 APEX II diffractometer. The temperature of the crystal was maintained at the selected value (100 ± 1 K) by means of a 700 Series Cryostream cooling device. Intensity data were corrected for Lorenz-polarization and absorption factors. The structures were solved by direct methods using SHELXS-97,[3] and refined against F^2 by full-matrix least-squares methods using SHELXL-97[4] with anisotropic displacement parameters for all non-hydrogen atoms. All calculations were performed by using the crystal structure crystallographic software package WINGX.[5] The structures were drawn (Figures 1 and 2) using ORTEP3.[6] Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters.

The cif files CCDC 752280 (compound **141**) and CCDC 796934 (compound **140ba'**) contain the crystallographic data for this compounds. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif.

[3] G. M. Sheldrick, SHELXS-97, *Program for crystal structure solution*, University of Göttingen, Göttingen, Germany, 1997.
[4] G. M. Sheldrick, SHELXL-97, *Program for the refinement of crystal structures from diffraction data*, University of Göttingen, Göttingen, Germany, 1997.
[5] L. J. Farrugia, *J. Appl. Cryst*., 1999**,** **32**, 837.
[6] L. J. Farrugia, *J. Appl. Cryst*., 1997, **30**, 565.

Table 1. Crystal data and structure refinement for compounds **141** and **140ba'**.

Compound	**141**	**140ba'**
Empirical formula	C_{17} H_{14} Cl N O_5	C_{17} H_{14} Cl N O_4
Crystal size (mm^3)	0.12 × 0.05 × 0.02	0.31 × 0.12 × 0.02
Formula weight (g mol^{-1})	347.74	331.74
Temperature (K)	100(1)	100(1)
Crystal system	Monoclinic	monoclinic
Space group	*P* 2_1	*P –1*
Unit cell dimensions		
a (Å)	9.2365(4)	8.7119(13)
b (Å)	9.7935(4)	12.7240(18)
c (Å)	17.7681(8)	15.850(2)
α (°)	90	66.646(3)
β (°)	101.569(3)	80.311(3)
γ (°)	90	70.794(3)
V ($Å^3$)	1574.61(12)	1521.8(4)
Z	4	4
$D_{calc.}$ ($Mg.m^{-3}$)	1.467	1.448
Absorption coefficient (mm^-	0.270	0.271
F (0 0 0)	720	688
Index ranges	–13 < h < 13, –14 < k < 13, –25 < l < 25	–12 < h < 13, –17 < k < 20, –25 < l < 21
Reflections collected	37 446	25 995
Independent reflections	9 323 (0.0938)	11 075 (0.0288)
Observed reflections [*I* >	5 216	7 614
Refinement method	Full matrix least squares on F^2	Full matrix least squares on F^2
Final *R* indices [$I > 2\sigma I$]	*R1* = 0.0671, *wR2* = 0.1311	*R1* = 0.0484, *wR2* = 0.1216
S	1.023	1.044
Flack Parameter[7]	0.01(9)	/
$(\Delta/\sigma)_{max}$	0.000	0.002
$(\Delta \rho)_{max, min}$ [e $Å^{-3}$]	0.682 ; –0.731	0.581 ; –0.394

[7] H. D. Flack, *Acta Cryst.* 1983, **A39**, 876.

Crystal structure of compound 141.

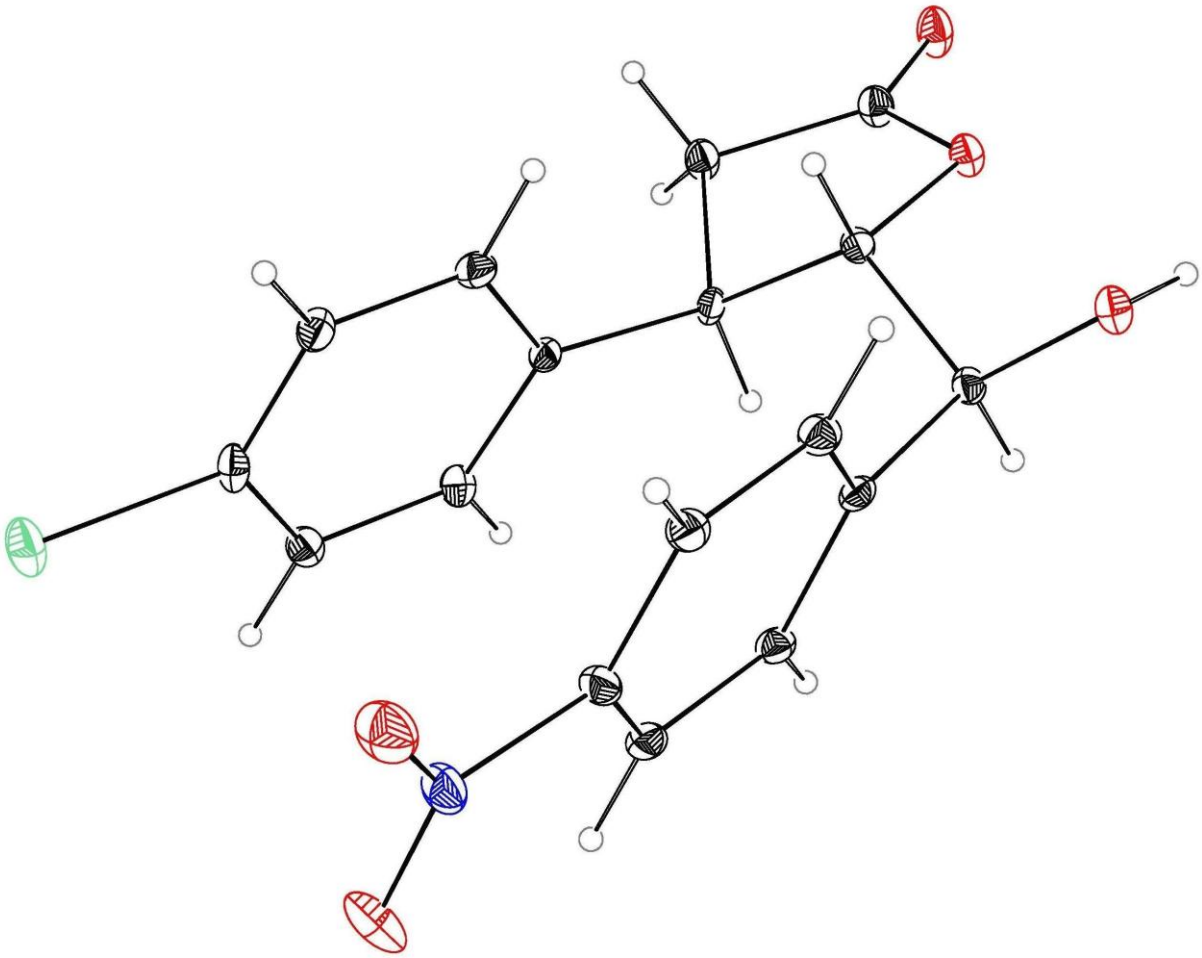


Fig. 1. Displacement ellipsoids are drawn at the 50% probability level. Only one molecule is shown for the sake of clarity.

Crystal structure of compound 140ba’

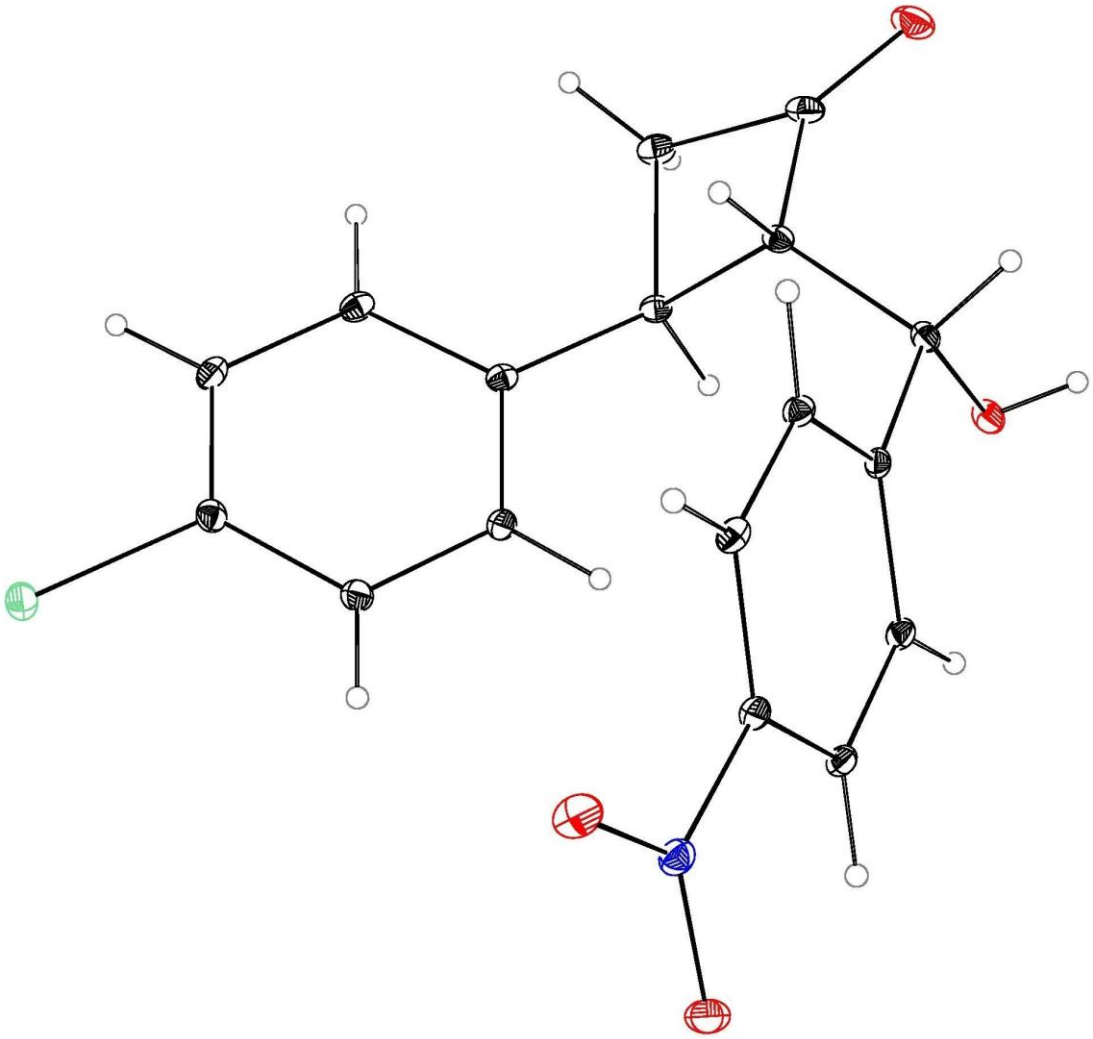
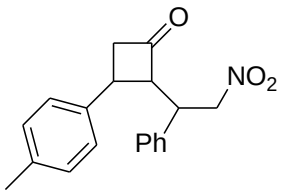


Fig. 2. Displacement ellipsoids are drawn at the 50% probability level. Only one molecule is shown for the sake of clarity.

General procedure for the synthesis of authentic racemic samples: To a solution of prochiral cyclobutanone (1.5 mmol) and nitrostyrene (0.5 mmol) in DMSO (2 mL) was added (±)-proline (0.05 mmol). The resulting mixture was stirred at room temperature for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted several times with EtOAc (2×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography to give the corresponding product.

General Procedure. To a toluene (2.7 mL) solution of the prochiral cyclobutanone **156** (1.5 mmol) and catalyst (10% mmol) was added nitrostyrene (0.5 mmol) and the mixture was stirred for 96 h at that temperature. The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, hexane-Et_2O).

2-(2-nitro-1-phenylethyl)-3-p-tolylcyclobutanone (155)



155

FW 309
$C_{19}H_{19}NO_3$

Yield 76%;

yellow oil.

IR (film): ν = 3030, 1777cm^{-1}.

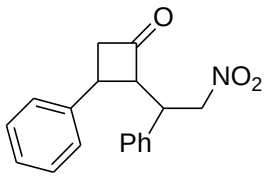
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 1 H), 3.13-3.27 (m, 3 H), 3.26-3.33 (m, 1 H), 3.51-3.44 (m, 1 H), 3.81-3.73 (m, 1 H), 4.61-4.54 (m, 1H), 4.98 (dd, J=12.9, 4.8 Hz), 6.64 (d, 2 H, J= 8.1 Hz), 6.88-7.18 (m, 7H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 20.9, 34.7, 44.6, 51.5, 68.9, 77.7, 110.0, 110.3, 126.1, 127.9, 128.1, 128.9, 129.1, 129.6, 136.2, 136.4, 138.5, 206.7.

MS: *m/z* (%) = 206 (100) [M^+ - 28], 281 (1,4), 267 (15), 220 (87), 205 (60), 129 (30), 105 (50), 91 (74)'.

The ee was determined to be 80% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 95:05, flow rate 1.0 mL/min, λ = 254 nm): t_R(major) = 12.1 min; t_R(minor) = 15.3 min.

2-(2-nitro-1-phenylethyl)-3-phenylcyclobutanone (157a)



77a

FW 295
$C_{18}H_{17}NO_3$

Yield 63%;

White solid.

IR (film): ν = 3029, 1778cm^{-1}.

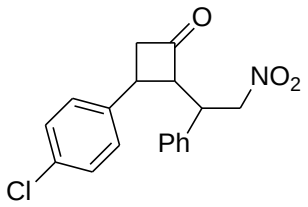
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.23-3.40 (m, 3 H), 3.59-3.62 (m, 1 H), 3.84-3.89 (m, 1 H), 3.73-3.81 (m, 1 H), 4.64-4.69 (m, 1H), 5.07 (dd, 1 H J=13, 5 Hz), 6,85 (d, 2 H, J= 7), 7.10-7.23 (m,8 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 35.0, 44.5, 51.4, 68.9, 77.7, 126.2, 126.7, 127.8, 128.1, 128.4, 128.9, 136.0, 141.5, 206.5

MS: *m/z* (%) = 206 (100) [M^+ - 42], 253 (9), 191 (11), 129 (17), 115 (30), 91 (57), 77 (11).

The ee was determined to be 50% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 98:02, flow rate 0.8 mL/min, λ = 254 nm): t_R(major) = 38.4 min; t_R(minor) = 48.9 min.

3-(4-chlorophenyl)-2-(2-nitro-1-phenylethyl)cyclobutanone (157b)



157b

FW 329
$C_{18}H_{16}ClNO_3$

Yield 86%;

White solid.

IR (film): ν = 3031, 1779cm^{-1}.

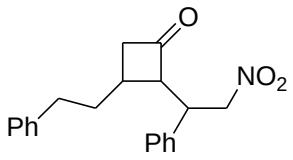
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19-3.28 (m, 2 H), 3.34-3.40 (m, 1 H), 3.52-3.56 (m, 1 H), 3.81-3.86 (m, 1 H), 4.63-4.68 (m, 1H), 5.08 (dd, 1 H J=12.5, 4.5 Hz), 6,72 (d, 2 H, J= 8.5 Hz), 7.07-7.12 (m, 4H), 7,23-7,26 (m, 3H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 34.7, 44.6, 51.3, 69.13, 77.6, 127.6, 127.7, 128.2, 128.5, 129.0, 132.5, 135.9, 139.9, 205.9

MS: *m/z* (%) = 205 (100) [M^+ - 42], 287 (15), 240 (52), 138 (62), 115 (32), 103 (25), 91 (41).

The ee was determined to be 64% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 24.3 min; t_R(minor) = 33.6 min.

2-(2-nitro-1-phenylethyl)-3-phenethylcyclobutanone (157c)



157c

FW 323
$C_{20}H_{21}NO_3$

Conversion 50 %.

IR (film): ν = 3029, 1778cm^{-1}.

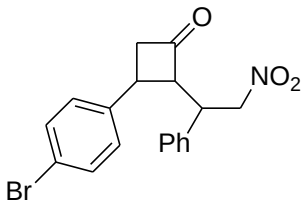
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51-1.65 (m, 2 H), 2.04-2.11 (m, 1H), 2.24-2.47 (m, 2H), 2.64-3.17 (m, 3H), 3.65-3.74 (m, 1H), 4.65-4.73 (m, 1H), 5.14 (dd, 1H J=12.9, 4.5Hz), 6,93 (d, 2 H, J= 3 Hz), 7.25-7.41 (m, 8 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 30.2, 33.6, 37.2, 44.5, 49.8, 66.1, 77.5, 125.9, 127.6, 128.0, 128.2, 128.3, 128.4, 129.1, 136.8, 206.9

MS: *m/z* (%) = 91 (100) [M^+ - 42], 281 (2), 234 (12), 219 (4), 143 (42), 129 (26), 115 (12).

The ee was determined to be 32% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 98:02, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 25.6 min; t_R(minor) = 34.2 min.

3-(4-bromophenyl)-2-(2-nitro-1-phenylethyl)cyclobutanone (157d)



157d

FW 373
$C_{18}H_{16}BrNO_3$

Yield 83%.

White solid.

IR (film): ν = 2256, 1798cm^{-1}.

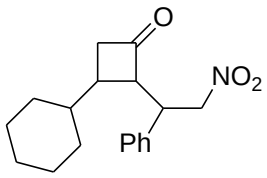
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19-3.28 (m, 2H), 3.36-3.41 (m, 1H), 3.51-3.54 (m, 1H), 3.80-3.84 (m, 1H), 4.63-4.67 (m, 1H), 5.08 (dd, 1H J=13, 5Hz), 6,66 (d, 2 H, J= 8.5 Hz), 7.07-7.08 (m, 2 H), 7.23-7.27 (m, 5H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 34.8, 44.6, 51.3, 69.6, 77.6, 120.6, 127.8, 127.9, 128.3, 129.1, 131.1, 135.9, 140.5, 141.2, 205.8

MS: *m/z* (%) = 205 (100) [M^+ - 40], 333 (11), 286 (33), 182 (45), 115 (31), 91 (40).

The ee was determined to be 64% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 19.3 min; t_R(minor) = 27.8 min.

3-cyclohexyl-2-(2-nitro-1-phenylethyl)cyclobutanone (157e)



157e

FW 301
$C_{18}H_{23}NO_3$

Yield 63%.

White solid.

IR (film): ν = 2926, 1772cm^{-1}.

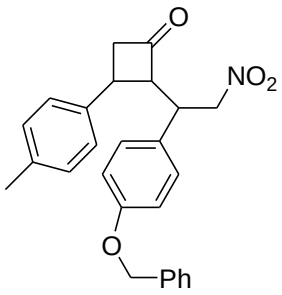
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.44-0.47 (m, 1H), 0.75-0.78 (m, 1H), 1.01-1.05 (m, 3H), 1.23 (d, 2H, J= 10), 1.50-1.67 (m, 4H), 1.86-1.92 (m, 1H), 2.7 (ddd, 1H, J= 18, 7.5, 3 Hz), 2.99 (ddd, 1H, J= 18, 9, 3 Hz), 3.13-3.18 (m, 1H), 3.65-3.70 (m, 1H), 4.67-4.72 (m, 1H), 5.06 (dd, 1H J=13, 5Hz), 7.21-7.34 (m, 5 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 25.7, 25.9, 29.8, 30.3, 35.9, 42.0, 44.8, 47.6, 64.2, 77.3, 127.9, 128.0, 128.6, 128.9, 137.4, 207.9

MS: *m/z* (%) = 212 (100) [M^+ - 42], 359 (1), 243 (2), 197 (16), 155 (18), 129 (31), 109 (36), 91 (50).

The ee was determined to be 59% ee by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane-*i*-PrOH = 98:02, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 11.9 min; t_R(minor) = 13.3 min.

2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl)-3-p-tolylcyclobutanone (157f)



157f

FW 415

$C_{26}H_{25}NO_4$

Yield 55%.

White solid.

IR (film): ν = 2240, 1777cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.23-3.37 (m, 3H), 3.53-3.56 (m, 1H), 3.78-3.84 (m, 1H), 4.59-4.64 (m, 1H), 4.89 (d, 1H, J= 7.5), 5.01-5.05 (m, 2H), 6.78 (d, 2H, J= 7.5 Hz), 6.86 (d, 2H, J= 8.5 Hz), 6.98-7.04 (m, 4H), 7.17-7.20 (m, 1 H), 7.39-7.44 (m, 4H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 20.8, 34.5, 43.8, 51.2, 69.0, 69.9, 77.9, 115.2, 126.1, 126.2, 127.2, 127.9, 128.4, 128.9, 129.1, 129.3, 129.5, 136.2, 136.7, 138.6, 158.4, 206.9.

MS: *m/z* (%) = 91 (100) [M^+ - 60], 355 (1), 276 (18), 220 (13), 187 (3), 148 (5), 118 (12).

The ee was determined to be 40% ee by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane-*i*-PrOH = 92:08, flow rate 1 mL/min, λ = 254 nm): t_R(major) = 49.0 min; t_R(minor) = 90.5 min.

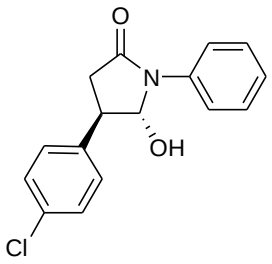
CHAPTER 5

General procedure for the synthesis of authentic racemic samples: To a solution of prochiral cyclobutanone (3 mmol) and nitrosobenzene (0.6 mmol) in $CHCl_3$ (2 mL) was added (±)-proline (0.18 mmol). The resulting mixture was stirred at room temperature for 96 h. The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, hexane-Et_2O).

General Procedure (Using Catalyst I). To a $CHCl_3$ (2.7 mL) solution of the prochiral cyclobutanone **100** (3 mmol) and *L*-proline (0.18 mmol) was added a $CHCl_3$ (0.9 mL) solution of nitrosobenzene (0.6 mmol) over 48 h at 0 ˚C via syringe pump, and the mixture was stirred for 96 h at that temperature. The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, hexane-Et_2O).

General Procedure (Using Catalyst IV). In a glass vial equipped with a magnetic stirring bar, to 0.375 mmol of the prochiral cyclobutanone **180**, catalyst **IV** (0.075 mmol, 20 mol%) was added, and the reaction mixture was stirred at ambient temperature for 10-15 min. To the reaction mixture nitrosobenzene (1.13 mmol) was added and stirred at 0 ˚C for the time indicated in Tables 10 and 11 . The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, mixture of hexane-Et_2O).

4-(4-Chlorophenyl)-5-hydroxy-1-phenylpyrrolidin-2-one (182a)



182a

FW 287
$C_{16}H_{14}ClNO_2$

Yield 60%;

Yellow oil.

IR (film): ν = 3400, 1650 cm^{-1}.

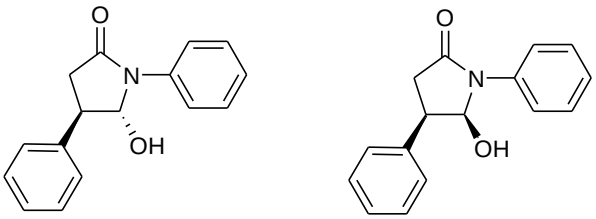
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (dd, 1 H, *J* = 4.5, 14.1 Hz), 2.93 (t, 1 H, *J* = 14.4 Hz), 3.26-3.33 (m, 1 H), 5.48 (d, 1 H, *J* = 5.4 Hz), 7.18-7.72 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9, 47.86, 103.2, 120.0, 125.6, 128.6, 128.7, 129.2, 133.6, 137.6, 139.3, 169.8.

MS: *m/z* (%)= 269 (100) [M^+ - 18], 240 (80), 206 (17), 136 (23), 104 (72).

The ee was determined to be 58% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane-*i*-PrOH = 80:20, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 12.1 min; t_R(minor) = 14.4 min.

5-Hydroxy-1,4-diphenylpyrrolidin-2-one (182b/182b')



182b **182'b**

FW 253
$C_{16}H_{15}NO_2$

Spectral data refer to a 95:5 inseparable mixture of two *trans*- and *cis*-diastereomers. Ù

Yield 40%;

Yellow oil.

IR (film): ν = 3400, 1650 cm^{-1}.

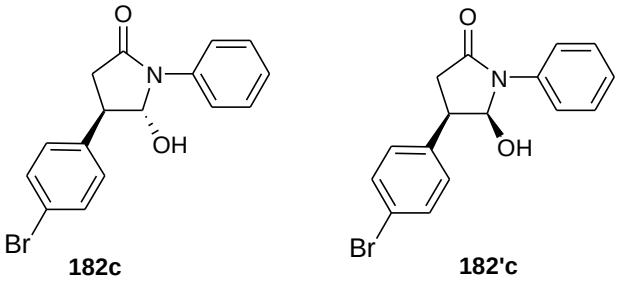
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58-2.66 (m, 1 H), 2.74-2.81 (m, 1 H), 2.90 (t, 1 H, *J* = 14.1 Hz), 3.05 (t, 1 H, *J* = 13.8 Hz), 3.14-3.20 (m, 1 H), 3.23-3.30 (m, 1 H), 4.58 (br s, 1 H), 4.92 (t, 1 H), 5.48 (d, 1 H, *J* = 5.4 Hz), 5.55 (dd, 1 H, *J* = 7.05, 9.6 Hz), 6.74-7.73 (m, 20 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1, 38.6, 48.5, 48.8, 92.4, 103.5, 114.6, 118.8, 120.1, 124.9, 125.5, 127.0, 127.2, 127.6, 127.8, 128.5, 128.6, 129.0, 129.1, 129.3, 139.3, 139.5, 170.3, 170.8.

MS: *m/z* (%, the same for the two diastereomers) = 235 (100) [M^+ - 18], 206 (100), 115 (20), 104 (48), 77 (57), 63 (7), 51 (16).

The ee was determined to be 20% ee for the *trans*-diastereomer by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane-*i*-PrOH = 90:10, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 30.8 min; t_R(minor) = 36.6 min.

4-(4-bromophenyl)-5-hydroxy-1-phenylpyrrolidin-2-one (182c/182c')



182c **182'c**

FW 331
$C_{16}H_{14}BrNO_2$

Spectral data refer to a 27:73 mixture of two *cis* and *trans* inseparable diastereoisomers. Yield: 57%.

Orange oil.

IR (film): 3400, 1650 ν/cm^{-1};

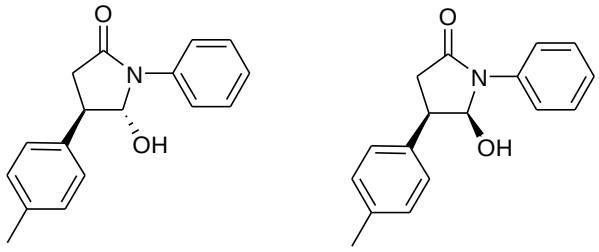
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54-2.62 (m, 1H), 2.70-2.88 (m, 2H), 2.95-3.03 (m, 1H), 3.13-3.25 (m, 2H), 5.35 (d, 1H, *J* = 5.4 Hz), 5.47 (dd, 1H, *J* = 9.6 Hz and *J* = 6.9 Hz), 7.05-7.71 (m, 18H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 38.2, 47.8, 48.1, 92.2, 103.2, 114.6, 118.8, 120.0, 120.1, 120.4, 121.4, 121.6, 125.0, 125.4, 128.5, 128.9, 129.2, 130.5, 131.9, 132.0, 134.5, 138.3, 139.4, 169.9, 170.0.

MS m/z: the same for the two diastereoisomers: 314 (M^+-18 (100)), 286 (67), 206 (25), 180 (13), 104 (77), 77 (77), 51 (21).

The ee of diastereoisomer *trans* was determined to be 27% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane/*i*-PrOH = 90:10, flow rate 1.2 mL/min, λ = 254 nm) t_R = 36.3 min (major), t_R = 44.2 min (minor).

5-hydroxy-1-phenyl-4-p-tolylpyrrolidin-2-one (182 d/182'd)



182d **182'd**

FW 267
$C_{17}H_{17}NO_2$

Spectral data refer to a 23:77 mixture of two *cis* and *trans* inseparable diastereoisomers. Yield: 30%.

Orange oil, IR (film): 3400, 1650 ν/cm^{-1};

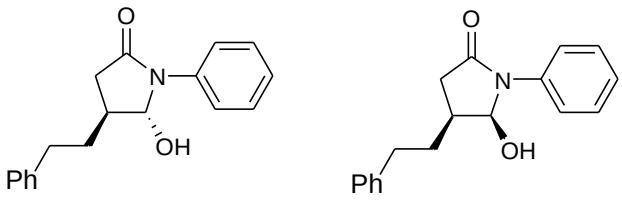
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54-2.62 (m, 1H), 2.70-2.88 (m, 2H), 2.95-3.03 (m, 1H), 3.13-3.25 (m, 2H), 5.35 (d, 1H, *J* = 5.4 Hz), 5.47 (dd, 1H, *J* = 9.6 Hz and *J* = 6.9 Hz), 7.05-7.71 (m, 18H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 38.2, 47.8, 48.1, 92.2, 103.2, 114.6, 118.8, 120.0, 120.1, 120.4, 121.4, 121.6, 125.0, 125.4, 128.5, 128.9, 129.2, 130.5, 131.9, 132.0, 134.5, 138.3, 139.4, 169.9, 170.0.

MS m/z: the same for the two diastereoisomers: 314 (M^+-18 (100)), 286 (67), 206 (25), 180 (13), 104 (77), 77 (77), 51 (21).

The ee of diastereoisomer *trans* was determined to be 28% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane/*i*-PrOH = 90:10, flow rate 1.2 mL/min, λ = 254 nm) t_R = 36.3 min (major), t_R = 44.2 min (minor).

5-Hydroxy-4-phenethyl-1-phenylpyrrolidin-2-one (182e)



182e **182'e**

FW 281
$C_{18}H_{19}NO_2$

Spectral data worked out from the 94:6 inseparable mixture of two *trans*- and *cis*-diastereomers **182e**/**182e'**.

Yield 65%;

Orange oil.

IR (film): ν = 3350, 1660 cm^{-1}.

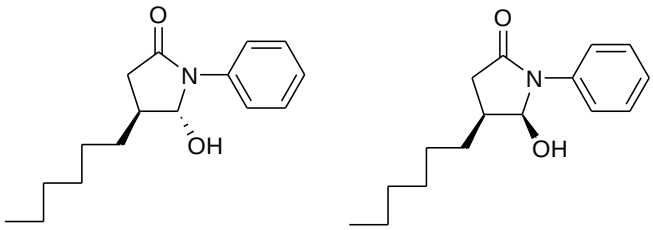
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77-2.14 (m, 3 H), 2.36-2.57 (m, 2 H), 2.71 (t, 2 H, *J* = 7.5 Hz), 3.41 (br s, 1 H), 5.29 (d, 1 H, *J* = 5.1 Hz), 7.13-7.69 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9, 36.0, 42.2, 52.3, 102.7, 119.9, 126.1, 128.2, 128.4, 128.5, 128.6, 139.6, 140.9, 170.4.

MS: *m/z* (%, the same for the two diastereomers) = 263 (31) [M^+ - 18], 172 (100), 106 (14), 91 (60), 77 (27), 65 (10), 51 (8).

The ee of the *trans*-diastereomer was determined to be 51% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane-*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm): t_R(major) = 26.1 min; t_R(minor) = 33.6 min.

4-Hexyl-5-hydroxy-1-phenylpyrrolidin-2-one (182f/182f')



182f **182'f**

FW 261
$C_{16}H_{23}NO_2$

Spectral data refer to a 67:33 inseparable mixture of two *trans*- and *cis*-diastereomers.

Yield 60%; Orange oil.

IR (film): ν = 3400, 1660 cm^{-1}.

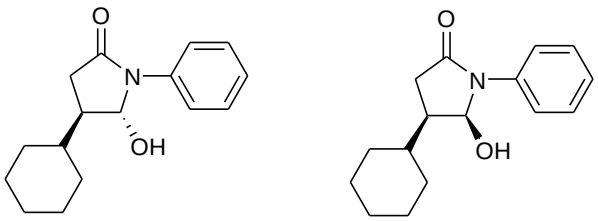
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84-1.59 (m, 26 H), 1.92-2.06 (m, 2 H), 2.27-2.63 (m, 4 H), 4.73 (d, 1 H, *J* = 9.3 Hz), 5.17 (d, 1 H, *J* = 4.8 Hz), 5.22 (dd, 1 H, *J* = 6.9, 9.3 Hz), 6.76-7.72 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.6, 26.8, 29.1, 31.6, 33.0, 33.8, 36.1, 37.3, 42.7, 43.3, 91.4, 102.8, 114.5, 118.6, 119.9, 125.2, 128.5, 129.3, 139.7, 144.1, 170.7, 171.0.

MS: *m/z* (%, the same for the two diastereomers) = 243 (77) [M^+ - 18], 172 (100), 158 (26), 130 (14), 104 (24), 77 (33).

The ee was determined to be 38% ee for the *trans*-diastereomer and 44% ee for the *cis*-diastereomer by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane-*i*-PrOH = 95:5, flow rate 0.8 mL/min, λ = 254 nm): *trans*-diastereomer: t_R(minor) = 14.3 min(minor); t_R(major) = 17.4 min; *cis*-diastereomer: t_R(major) = 22.2 min; t_R(minor) = 26.9 min.

4-cyclohexyl-5-hydroxy-1-phenylpyrrolidin-2-one (182g and 182g')



182g **182'g**

FW 259
$C_{16}H_{21}NO_2$

Spectral data refer to a 15:85 mixture of two *cis* and *trans* inseparable diastereoisomers.

Yield: 48%.

Yellow oil

IR (film): 3400, 1650 ν/cm^{-1};

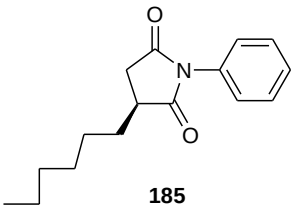
^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92-1.91 (m, 24H), 2.38-2.63 (m, 4H), 5.39 (t, 1H, *J* = 5.4 Hz and *J* = 5.4), 5.49 (dd, 1H, *J* = 8.1 Hz and *J* = 6.6 Hz), 6.9-7.86 (m, 10H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 25.8, 25.9, 29.4, 30.1, 33.5, 34.6, 39.2, 46.1, 47.6, 89.5, 100.9, 118.7, 124.3, 128.3, 128.4, 129.0, 140.1, 145.3, 170.4, 170.9.

MS m/z: the same for the two diastereoisomers: 241 (M^+-18 (100)), 198 (50), 175 (35), 159 (60). 130 (25), 104 (25), 77 (55), 55 (20).

The ee of diastereoisomer *trans* was determined to be 37% ee by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 95:5, flow rate 1.2 mL/min, λ = 254 nm) t_R = 9.71 min (minor), t_R = 12.39 min (major).

Procedure for the Synthesis of 3-Hexyl-1-phenyl-pyrrolidine-2,5-dione (185)



185

FW 259

$C_{16}H_{21}NO_2$

PCC (85.1 mg, 0.395 mmol) was added to a solution of compounds **182f/182f'** (dr = 67:33; 70 mg, 0.270 mmol) in CH_2Cl_2 (8 mL), the mixture was then stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad, concentrated to give the crude mixture, which was then purified by flash column chromatography (hexane-Et_2O = 3:1) on silica gel to give the pure pyrrolidine-2,5-dione **185**.

Yield 60%;

Yellow oil.

IR (film): ν = 1774,1701, 1443, 1376 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83-1.45 (m, 10 H), 1.58-1.68 (m, 2 H), 1.95-2.03 (m, 1 H), 2.50-2.61 (m, 1 H), 2.91-3.05 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.6, 28.9, 29.6, 31.51, 31.54, 34.5, 40.0, 126.4, 128.5, 129.1, 131.9, 175.6, 178.9.

MS: *m/z* (%) = 259 (10) [M^+], 188 (35), 175 (100), 147 (10), 119 (30), 93 (16), 77 (7), 55 (14).

The ee was determined to be 40% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane-*i*-PrOH = 95:5, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 41.8 min; t_R(minor) = 44.8 min.

ABSTRACT

The main topic of the first chapter is the organocatalysis, applications of the most common organocatalysts are discussed. The vast majority of organocatalytic reactions use chiral amine as catalysis (asymmetric aminocatalysis). Different types of organocatalysis involve the use of Brønsted acids and bases, Lewis acids, hydrogen bond-mediated catalysis, phase transfer and N-heterocyclic carbene catalysis.

The second chapter deals with the reactivity of cyclobutanones. High electrophilicity and ring strain make the cyclobutanone and its derivatives a good substrate for ring transformation reactions. Characteristic reactions of functionalized cyclobutanones involve the ring opening, ring contraction and ring expansion reactions.

In the third chapter the synthesis of 2,2-disubstituted cyclobutanones via direct aldol reaction of 2-hydroxycyclobutanone with several aldehydes catalyzed by primary amines is presented. The results show that the 2-hydroxycyclobutanone is particularly amenable to solvent-free L-threonine-catalyzed direct aldol reactions with reasonable stereocontrol.

In the fourth chapter we describe the synthesis of 2,3-disubstituted cyclobutanones through direct aldol reactions of 3-substituted cyclobutanones and aryl aldehydes, catalyzed by N-phenylsulfonyl (S)-proline and through asymmetric nitro-Michael reaction of 3-substituted cyclobutanones and several nitrostyrenes, catalyzed by derivatives of thiourea. In the first case the relative aldol products were obtained with an unprecedented control of all three contiguous stereocenters while in the latter the relatives γ-nitro cyclobutanones were obtained in good yield but in modest enantioselectivity.

In this last chapter an organocatalyzed enantioselective desymmetrization reaction of 3-substituted cyclobutanones is presented using nitrosobenzene as an electrophile and proline derivatives as catalysts. This reaction involves a ring-expanding O-nitroso aldol-cyclization domino sequence to give 5-hydroxy-γ-lactams in good yield and with the generation of two new stereogenic centers. This results were unexpected as in the literature it is reported that the enantioselective nitroso aldol reaction of nitroso benzene and simple aldehyde end ketones, using proline based catalysts, give the α-aminooxy carbonyl compound as the only product.

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Al termine di questo lavoro i miei ringraziamenti vanno in particolare ad alcune persone tra cui il Prof. Pier Paolo Piras, il Dott. Jean Ollivier e il Dott. Angelo Frongia, per avermi impartito insegnamenti preziosi per la mia crescita professionale.

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