Università degli Studi di Ferrara

DOTTORATO DI RICERCA IN
"Scienze Chimiche"

CICLO XXXI

COORDINATRICE/COORDINATORE Prof. Carlo Alberto Bignozzi

Organo- and bio-catalytic approaches to the synthesis of biologically relevant compounds by the Umpolung strategy

Settore Scientifico Disciplinare CHIM/06

Dottorando
Dott. Di Carmine Graziano
(firma)

Tutore
Prof.ssa Bortolini Olga
(firma)

Anni 2015/2018

CHAPTER I: Umpolung Catalysis promoted by NHCs (N-Heterocyclic Carbenes)..... 5

1. Introduction 5

1.1. Organocatalysis 5

1.1.1 The origin 5
1.1.2 Enamine catalysis 5
1.1.3 Iminium-ion catalysis 6
1.1.4 Brønsted acid catalysis 6
1.1.5 Hydrogen-bond donor catalysis 7
1.1.6 NHC catalysis 7

1.2 Umpolung reactivity. 8

1.2.1. A general feature 8
1.2.2. N-Heterocyclic carbene. Structure and reactivity 10
1.2.3. Benzoin reaction 11
1.2.3. Stetter reaction 17
1.2.4. Umpolung reactions with unconventional acceptors 20
1.2.5. Aza-Benzoin reaction 21
1.2.5. Homoenolate reactivity 24
1.2.6. Oxidative NHC-catalysis 27

1.3. References 38

2 Synthesis of functionalized imidazolidine-2-thiones via NHC/base-promoted aza-benzoin/ aza-acetalization domino reactions 42

2.1 introduction 42

2.2 results and discussion 43

2.3. References 53

2.4. Experimental section 56

3 Enantioselective Dearomatization of Alkylpyridiniums by N-Heterocyclic Carbene-Catalyzed Nucleophilic Acylation 70

3.1 introduction 70

2.2 Results and discussion 71

3.3. References 83

3.4. Experimental section 85

4 NHC-Catalyzed Oxidative Desymmetrization of Pharmaceutically Relevant 1,4-Dihydropyridines 94

4.1 Introduction 94

4.2 Results and discussion 95

4.3 References 102

4.4 Experimental section 105

CHAPTER II: Umpolung Catalysis promoted by Thiamine dependent Enzyme 118

1. Introduction 118

1.1. Enzyme in organic synthesis 118

1.2 Immobilization of enzymes 120

1.3 Promiscuity 123

1.4 Thiamine-Diphosphate-dependent Enzymes 123

1.4.1 General features 123
1.4.2 Benzoin reaction 125
1.4.3 Cross-benzoin reaction 127
1.4.4 Aliphatic Benzoin-type reactions 128
1.4.5 Aliphatic Cross-Benzoin-Type Reactions 130
1.4.6 Aliphatic-Aromatic vs Aromatic-Aliphatic Cross-Benzoin Type Reactions 134
1.4.7 Aldehyde-Ketone Cross-Benzoin-Type Reactions 136

1.5 References 137

2 (S)-Phenylacetyl Carbinol Synthesis employing Wild-Type Enzyme Acetoin:Dichlorophenolindophenol Oxidoreductase from Bacillus licheniformis 141

2.1 Introduction 141

2.2 Results and Discussion 143

2.3 References 148

2.4 Experimental Section 151

3 Enzymatic Cross-Benzoin-Type Condensation of Aliphatic Aldehydes: Enantioselective Synthesis of 1-Alkyl-1- hydroxypropan-2-ones and 1-Alkyl-1-hydroxybutan-2-ones 158

3.1 Introduction 158

3.2 Results and Discussion 159

3.3 References 165

3.4 Experimental Section 168

CHAPTER III: 1,3-dipolar cycloaddition of amide promoted by Vaska complex 174

1. Introduction 174

2. Stoichiometric reductive coupling of amide by formation of iminium triflate intermediate .. 175

3. Catalytic reductive coupling of amide 177

4. 1,3-Dipolar cycloaddition reactions 178

5. Results and discussion 180

6. References 187

NOTE

This thesis is structured in three chapters, which describe different topics.

The first and the second chapter is related to the scientific work carried out in the organic chemistry group at the University of Ferrara under the supervision of Prof.ssa Olga Bortolini. The two topics are the ***Umpolung Catalysis promoted by NHCs (N-Heterocyclic Carbenes) (Pag.5-114) and Umpolung Catalysis promoted by Thiamine dependent Enzyme (Pag. 115-165)***

The third chapter is related to the scientific work carried out during my research period abroad, at the University of Oxford in the Group of Prof. Darren J. Dixon. The main topic of this research is ***1,3-dipolar cycloaddition of amide promoted by Vaska complex (Pag. 167-185).***

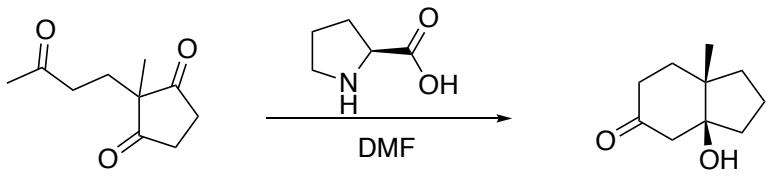
CHAPTER I: Umpolung Catalysis promoted by NHCs (N-Heterocyclic Carbenes)

1. Introduction

1.1. Organocatalysis

1.1.1 The origin

Nowadays the word organocatalysis refers to a specific area of catalysis in which a chemical transformation is promoted by small metal-free organic molecules. The term was used for the first time by David MacMillan at the beginning of the new millennium[1]. However, a chemical reaction that falls in this definition was already reported in 1971 by Hajos and Parrish (Hoffmann-La Roche) and by Weichert, Sauer and Eder (Schering-AG), who independently disclosed a proline-catalyzed intramolecular asymmetric aldol reaction (Scheme 1)[2].

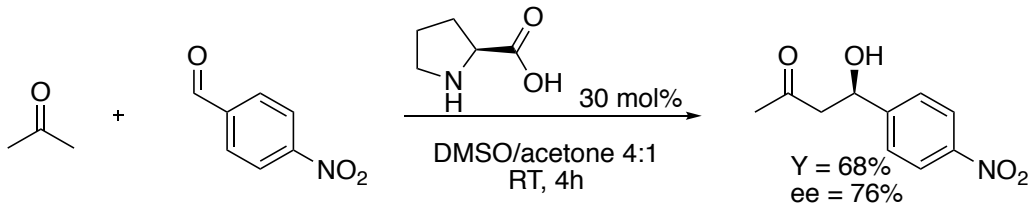


Scheme 1. Hajos–Parrish–Eder–Sauer–Wiechert reaction for the synthesis of the Wieland-Miescher ketone

This approach was ignored until 2000 when this field quickly began to grow thanks to the seminal works by List and Macmillan on the intermolecular aldol reaction and the asymmetric Diels-Alder reaction, respectively[3,1]. Today, the organocatalysts are involved in a large number of transformations, in which new carbon-carbon and carbon-heteroatoms bonds are formed; organocatalysts are classified in classes depending on the activation and the interaction with the substrate (see below)[4].

1.1.2 Enamine catalysis

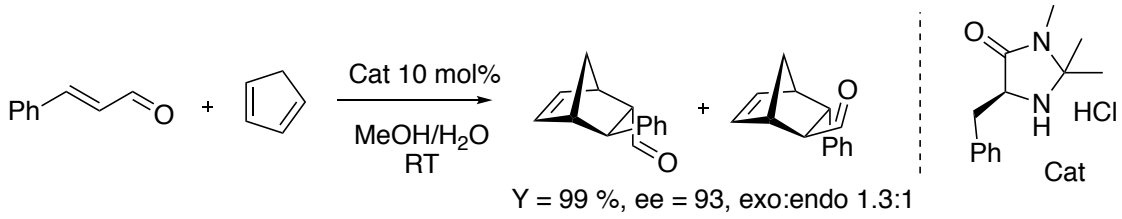
The first example of organocatalysis involving enamine activation was proposed by Weichert et al. for the synthesis of the Wieland-Miescher ketone[2]. Strangely, this extraordinary activation mode promoted by the simple proline was not exploited until more than 30 years later. Only in 2000, List et al. generalized the enamine catalysis concept to form carbon-carbon bonds in cross intermolecular aldol reactions (Scheme 2)[3]. This activation mode is typically promoted by secondary amines, which are involved in the formation of the enamine by condensation with ketones or aldehydes; then, the formation of this intermediate activates the α-carbon of the substrate for reactions with electrophiles.



Scheme 2. The proline-catalyzed aldol reaction disclosed by List

1.1.3 Iminium-ion catalysis

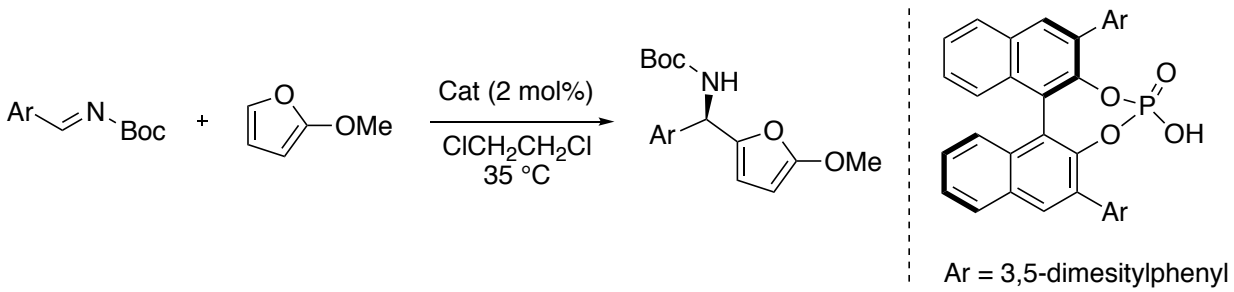
The mechanism of iminium activation was disclosed by MacMillan in 2000 and it was founded on the hypothesis that the reversible formation of iminium ions between α,β-unsaturated aldehydes and amines was able to emulate the dynamic LUMO-lowering iminium ion activation typical of Lewis acid catalysis (Scheme 3)[1].



Scheme 3. Organocatalyzed Diels-Alder reaction proposed by MacMillan

1.1.4 Brønsted acid catalysis

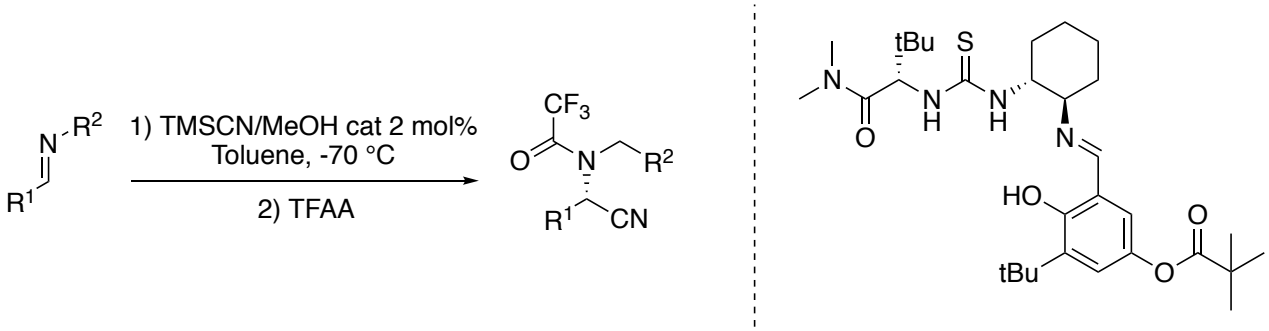
The most used Brønsted acids in organocatalysis are the Chiral Phosphoric Acids (CPAs). They are employed to activate an electrophilic substrate towards a nucleophilic addition in a simple fashion. The electrophile acts as a base taking the proton from the acid and generate an ion pair resulting in a LUMO-lowering activation of the electrophile. Furthermore, the bulky groups on the CPA counter anion generate a chiral environment around the reactive site making this kind of activation highly enantioselective[5].



Scheme 4. Activation of imine by CPA (Chiral Phosphoric acid) towards the addition of electron-rich furan

1.1.5 Hydrogen-bond donor catalysis

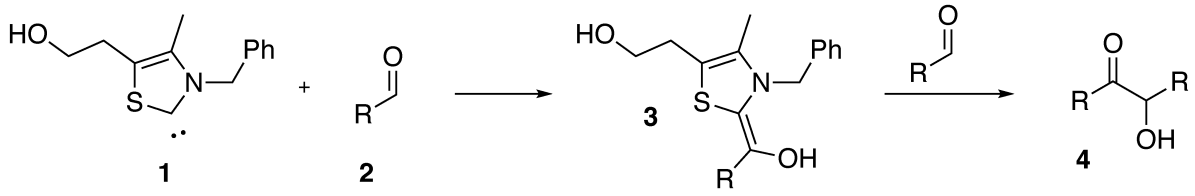
Two seminal works about hydrogen-bond activation mode were disclosed in 1998 and 1999 by Jacobsen (Scheme 5)[6] and Corey[7], respectively. Both researchers presented a Strecker reaction in which the catalyst activates the electrophilic partner of the reaction by multiple hydrogen-bond interactions. Nowadays the most used catalysts in this activation mode are thioureas. This type of catalysts has several advantages such as good stability and conformational rigidity. Furthermore, they are easily accessible through very simple synthetic procedures[8].



Scheme 5. Jacobsen's thiourea catalyzes Strecker reaction

1.1.6 NHC catalysis

In N-heterocyclic carbene (NHC) catalysis the carbene **1** reacts as a nucleophile with an aldehyde **2** to generate the so-called Breslow intermediate **3**. At this point the C1 of the aldehyde displays a nucleophilic reactivity instead of the usual electrophilic reactivity of the carbonyl group and it can intercept another free aldehyde **2** (in this case the reaction is called benzoin condensation and the product **4** benzoin) (Scheme 6).



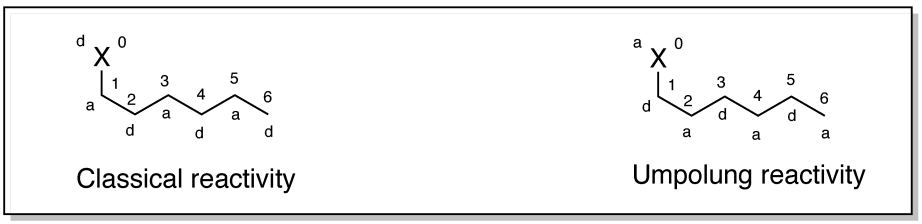
Scheme 6. In the benzoin condensation an aldehyde turns the reactivity in the C1 and acts as nucleophile

Overall, this strategy is named umpolung (polarity inversion)[9]. The NHC catalysis and the umpolung strategy are the main topics of this thesis and they will be discussed deeply in the next sections[9].

1.2 Umpolung reactivity.

1.2.1. A general feature

The Umpolung concept was introduced by Seebach and E.J. Corey[10] in a retrosynthetic analysis aimed at identifying the necessity of the polarity inversion in a the synthetic process. Seebach defined the umpolung as "any process by which the normal alternating donor and acceptor reactivity pattern of a chain, which is due to the presence of O or N heteroatoms, is interchanged"[11]. The concept was also graphically exposed by the author (Scheme 7). It is assumed that the alternate donor/acceptor reactivity in the carbon atoms along the skeleton is due to the presence of the heteroatom X. If this feature is inverted by a chemical modification of the molecule, an inversion of reactivity that propagates along the chain is observed.

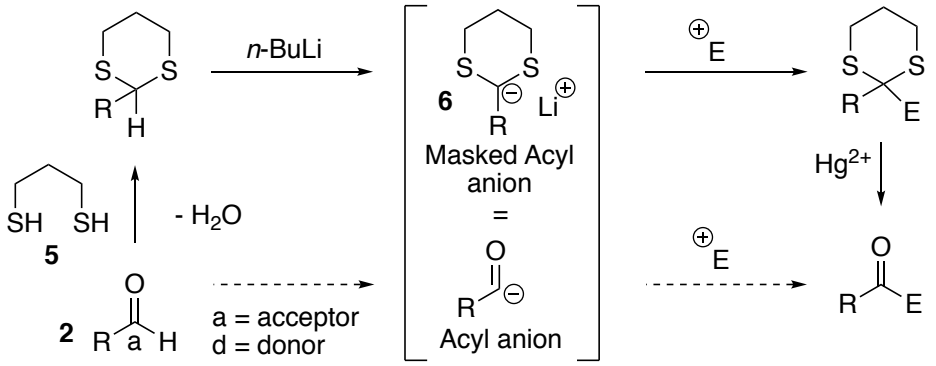


Scheme 7. Graphical Seebach's differentiation between classical and umpolung reactivity

Although the inversion of polarity is reported in imine chemistry, this approach is relegated to few examples[12]; instead, aldehydes are ubiquitous for traditional C-C bond-forming reactions by the umpolung strategy.

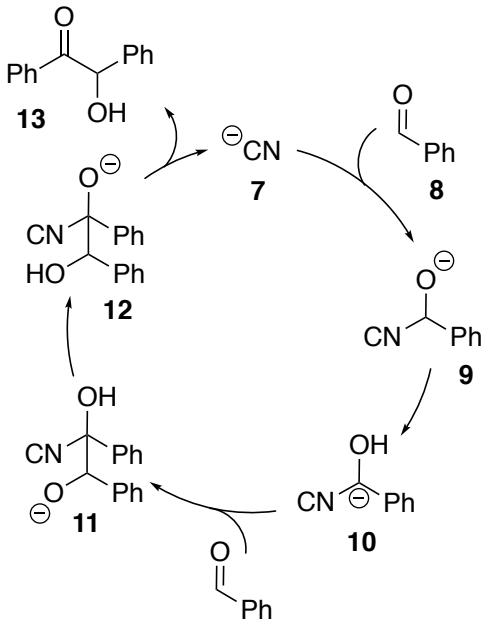
A chemical transformation is usually required in order to invert the polarity of the substrate; for example, in the Corey-Seebach reaction[10] the aldehyde **2** is protected as dithiane by treatment with 1,3-propandithiol **5** (Scheme 8). At this point, the hydrogen in C1 is acid enough to be taken from a strong base such as *n*-BuLi. The conjugate base **6** is a masked acyl anion, in fact it can be reacted

with a large number of electrophiles and subsequently deprotected with mercury salts. At the end of the process the carbon C1 on the aldehyde acted as nucleophile in an umpolung process.



Scheme 8. In the Seebach-Corey reaction 1,3-propandithiol is used to invert the polarity of aldehyde

Main issues related to this reaction are the required protection/deprotection steps and the use of toxic mercury salts. Another way to generate a reverse of polarity for synthetic scope is the catalytic umpolung process. In this case, a catalyst is used to impart a nucleophilic behavior to the C1 of aldehydes. The most famous example of this approach is the benzoin condensation in which the cyanide ion catalyzes the dimerization of two aldehydes. This reaction was discovered by Liebig and Wöhler in 1832[13]. The benzoin condensation is an important strategy to create new C-C bonds leading the formation of α-functionalized carbonyl compounds and its mechanism have been intensively studied (Scheme 9).



Scheme 9. The mechanism of the benzoin reaction promoted by cyanide ion

The reaction starts with the addition of the cyanide **7** ion on benzaldehyde **8** to form the intermediate **9**, which undergoes an intramolecular proton transfer to give the species **10**. This transient molecule

is intercepted by another benzaldehyde to generate the adduct **11**. After the final proton transfer to give **12**, the system releases the benzoin **13** along with the cyanide anion ready for another catalytic cycle.

1.2.2. N-Heterocyclic carbene. Structure and reactivity

A carbene is a molecule characterized by a neutral di-coordinated carbon with a sextet of electrons. Carbenes are generally unstable but in rare cases they could be isolated. There are two kinds of carbenes (Figure 1): singlet carbenes and triplet carbenes. If the carbene displays two unshared valence electrons respectively placed on the sp^2 and p orbital, the carbene is called a triplet carbene (Figure 1 a). If the two electrons are placed on the sp^2 orbital with the relative p orbital empty, the carbene is called singlet carbene (Figure 1 b)[14].

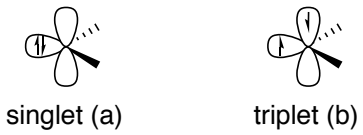


Figure 1. Electronic features of singlet (a) and triplet (b) carbenes

Generally, singlet carbenes are appreciated ligands for metal-based catalysis due their double effect to accept and release electron density and, in the past, they were largely used in metal catalysis especially in metathesis reactions. N-Heterocyclic Carbenes lie within the family of more general nucleophilic carbenes and they are characterized by a geminal nitrogen atom on the carbene. The electronic feature of this element is particularly suitable to stabilize the carbene. In fact, two effects have been identified: the lone-pair present on the nitrogen can stabilize the empty orbital by resonance, while the electron-withdrawing nature of the heteroatom can remove density from the occupied sp^2 orbital. This effect is well-known as "push-pull effect" (Figure 2)[15].

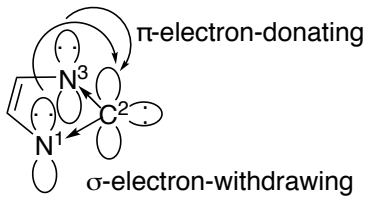


Figure 2. A graphical representation of the "push-pull effect" in NHCs

Generally, these species are generated *in situ* by deprotonation of the imidazolium, imidazolinium, triazolium or thiazolium salts (Figure 3).

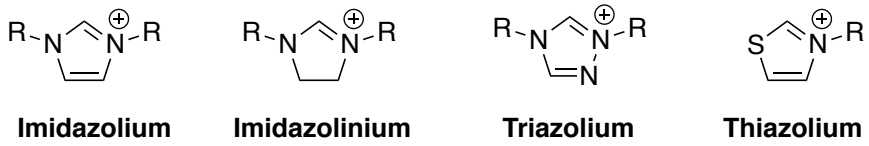


Figure 3. General precursors of NHCs

NHCs could be depicted by two possible structures of resonance (Figure 4). In one of these, the carbenic carbon bears a formal negative charge, while the heteroatom presents a positive charge due to the sharing of the lone pair on the empty p orbital of carbon. This structure of resonance shows very well the nucleophilic feature of the carbenic carbon.

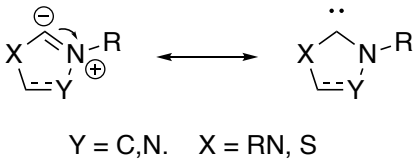


Figure 4. Resonance in NHCs

Historically, in 1991 Arduengo and co-worker could isolate and characterize, for the first time, an NHC (Figure 5). The structure was determined by X-Ray analysis and the bulky group placed on the nitrogen atoms are required to make the molecule stable enough to be handled[16].

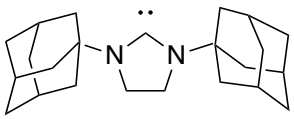
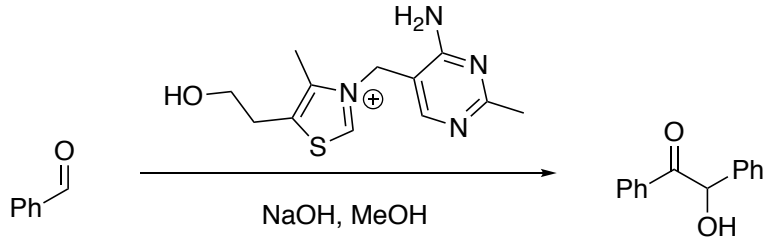


Figure 5. Stable NHC isolated by Arbuengo in 1991

After the seminal work by Arduengo, further experimental and theoretical work has been disclosed on the topic, and nowadays a plethora of new stable NHCs has been presented. It has been established that the kinetic stability of NHCs is due to steric features, which make more difficult the dimerization of carbenes. On the other hand, electronic features contribute to stabilize the NHCs via "push-pull effect"[17].

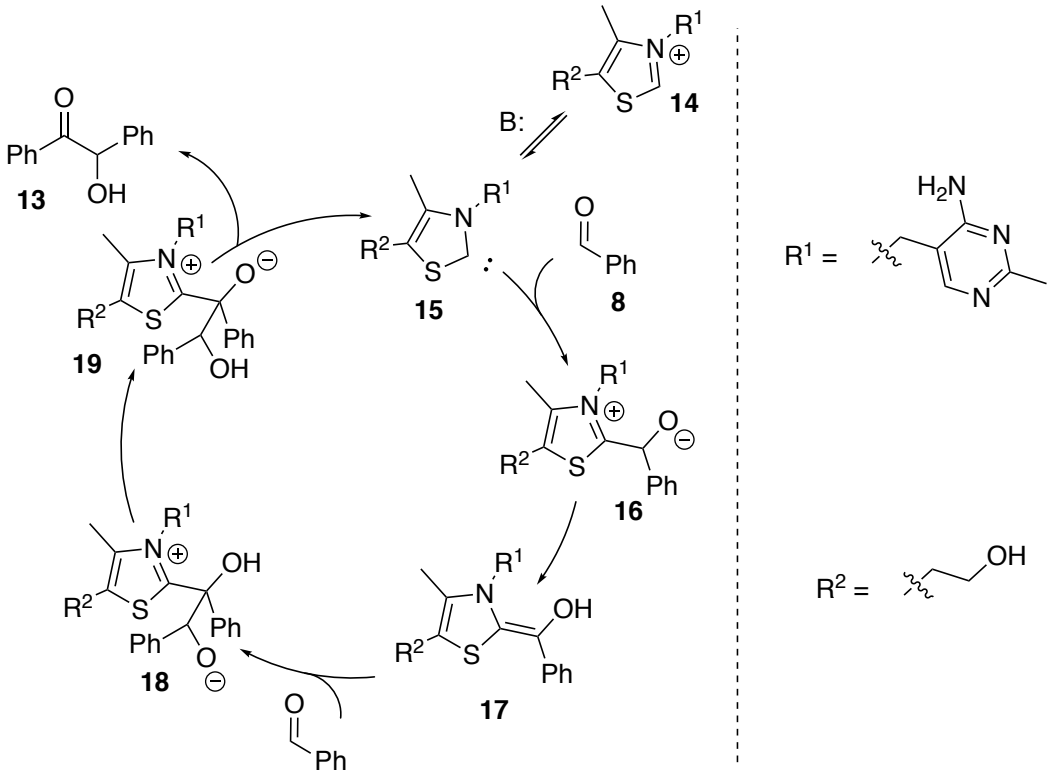
1.2.3. Benzoin reaction

NHCs are widely employed as organocatalysts in umpolung reactions. In this context, an NHC generated by deprotonation of a thiamine salt was used by Ugai and co-workers to mimic the cyanide ion in the benzoin condensation (Scheme 10)[18].



Scheme 10. The benzoin reaction promoted by Thiamine Hydrochloride salt disclosed by Ugai

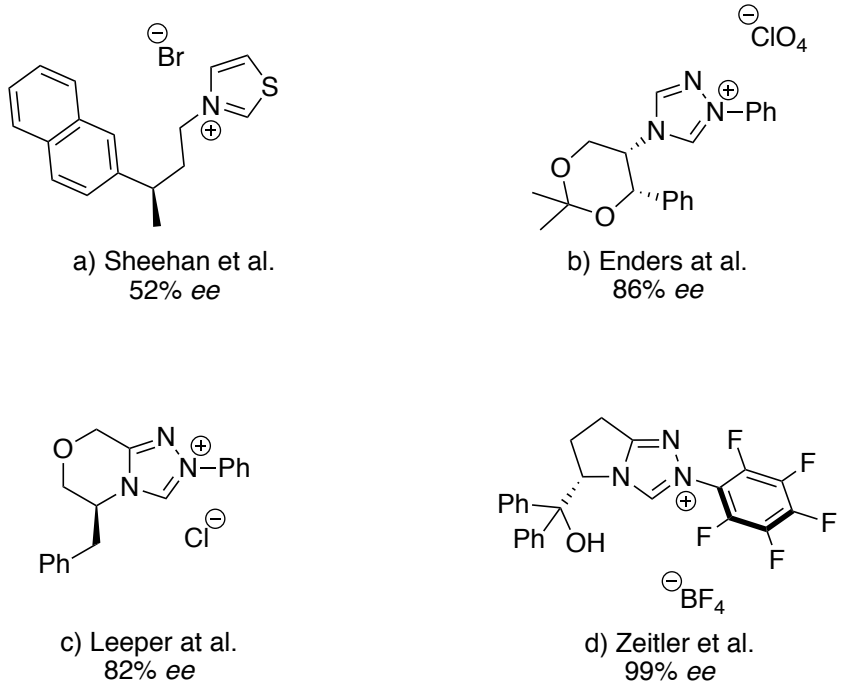
For this transformation a large number of mechanisms have been proposed but the most widely accepted is that one presented by Breslow in 1958 (Scheme 11)[19].



Scheme 11. Proposed mechanism for benzoin reaction catalyzed by thiazolium salts

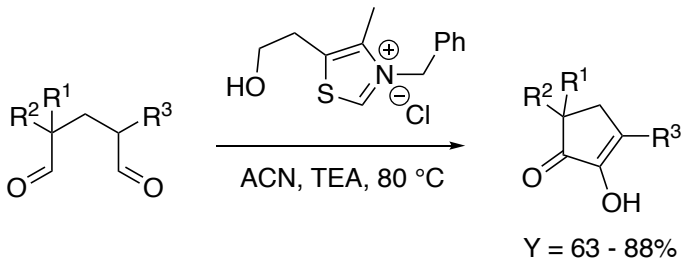
The thiamine chlorohydrate salt **14** is initially deprotonated by the base in order to generate the free carbene **15**. The carbene **15** acts as a Lewis base adding itself onto the electrophilic aldehyde carbon to form the adduct **16**, which rapidly undergoes an intramolecular proton transfer to give the Breslow intermediate **17**. This species acts as a nucleophile at C-1 intercepting a free molecule of aldehyde to generate **18** that, via a proton transfer, becomes the intermediate **19**. At this point, the release of catalyst **15** takes place along with the formation of benzoin adduct **13**. The mechanism proposed by Breslow has been recently corroborated by the seminal experiment performed by Berkessel and co-worker, who observed for the first time the elusive Breslow intermediate by NMR experiments[20]. The use of NHCs instead of the cyanide ion in the benzoin condensation resulted in a large number of advantages. For example, the use of NHCs avoids the risk of toxicity related to the cyanide ion.

Furthermore, it has been possible to perform the reaction in an enantioselective fashion by designing chiral NHCs[21]. In this regard, some research groups have successfully synthetized and used new kinds of NHCs in order to access benzoin adducts with high optical purity. Sheehan and co-workers disclosed an asymmetric version of the benzoin condensation employing a chiral derivate of a thiazolium salt, but the enantioselectivity was far to be satisfactory (Scheme 12 a). Subsequently, Enders and Leeper reported a similar methodology, in which a new class of chiral triazolium pre-catalysts were used with significantly improved enantioselectivities (Scheme 12 b and c). More recently, is has been demonstrated that NHCs with a hydrogen donor group allows to drastically increase the enantioselectivity in the process (Scheme 12 d)[22].



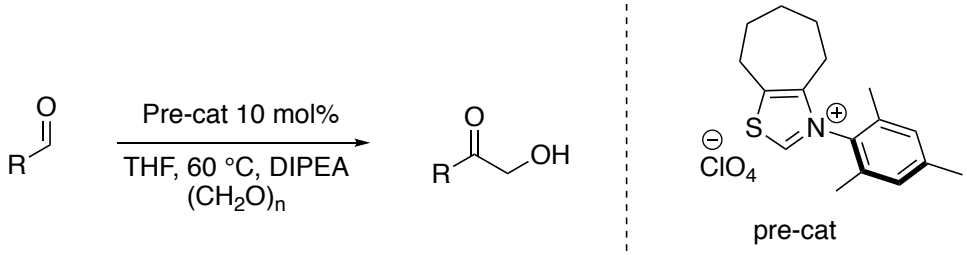
Scheme 12. Several chiral NHCs employed in asymmetric benzoin condensation

Similar to the aldol reaction, the *cross*-benzoin condensation is particularly challenging. In this case, the NHC must be added selectively onto the aldehyde that should act as nucleophile and the corresponding Breslow intermediate should be intercepted selectively by the second aldehyde, avoiding or minimizing the by-products s formed by the homo-coupling or the unwanted cross-coupling. In 1976 Cookson and Lane disclosed for the first time the intramolecular cross-coupling benzoin between two aldehydes (Scheme 13)[23].



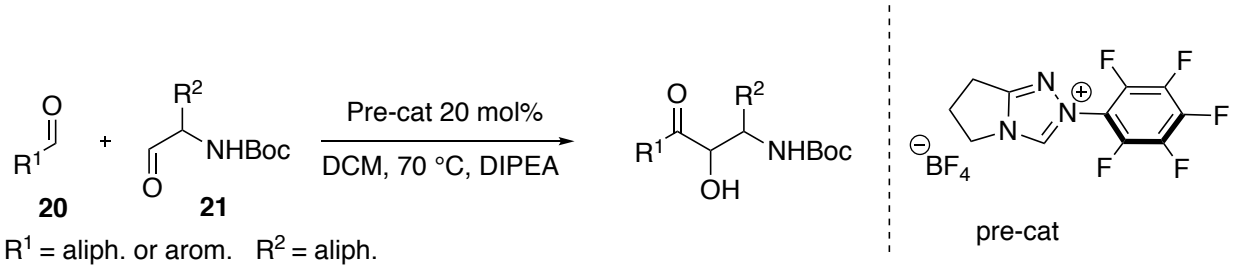
Scheme 13. Intramolecular cross-benzoin reaction presented by Cookson and Lane

In 2011 Glorius and co-workers employed formaldehyde as acceptor substrate in cross-benzoin reactions using a plethora of different aldehydes (Scheme 14)[24].



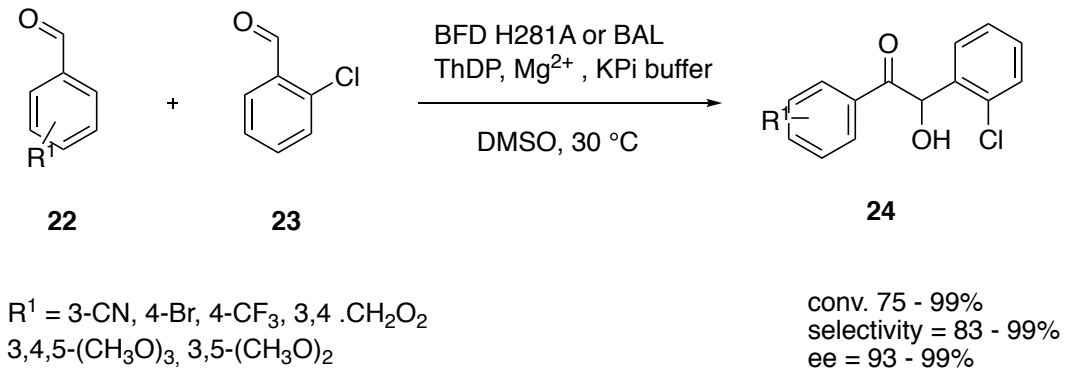
Scheme 14. Intermolecular cross-benzoin reaction disclosed by Glorius

Furthermore, Gravel and co-workers disclosed an interesting cross-benzoin reaction using Boc-protected α-amino aldehydes **21** as acceptors. Both the hindrance due the presence of the bulky group near the aldehyde functionality and the scarce electronic density on the aldehydic carbon made these substrates preferentially reactive as electrophiles towards the umpoled aliphatic or aromatic aldehyde **20** (Scheme 15)[25].



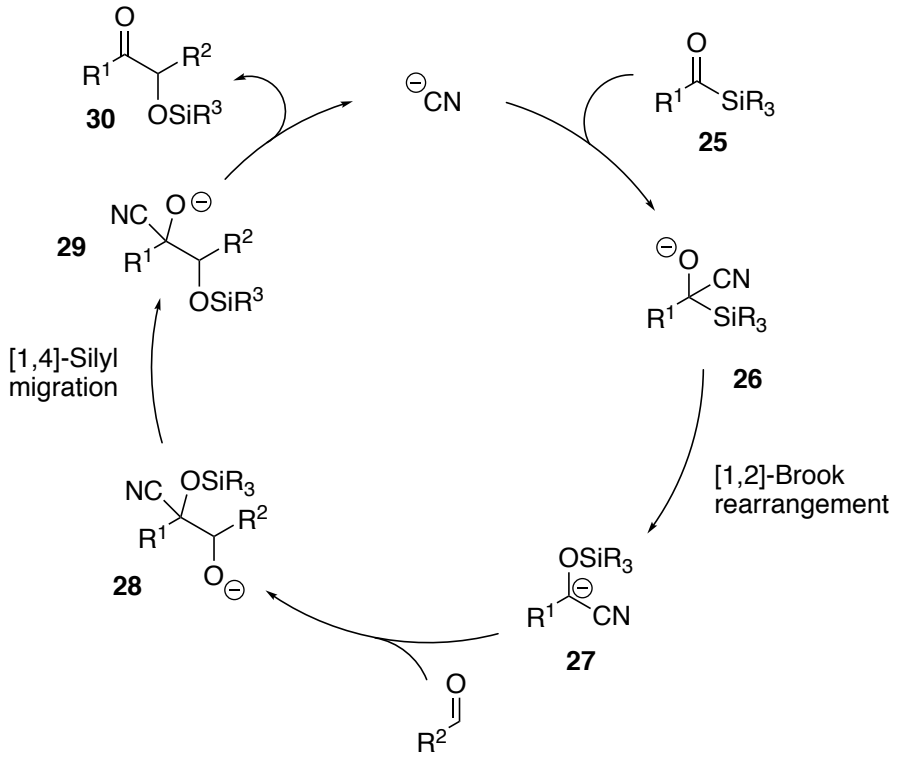
Scheme 15. cross-benzoin reaction reported by Gravel

However, except for few examples, the regiochemical control in the *cross*-benzoin condensation still remains a big challenge. In some cases, enzymatic catalysis can fill the lack on this heading. In this regard, in 2002 Müller and co-workers disclosed the first enzymatic *cross*-benzoin condensation obtaining benzoins **24** with high selectivity and enantiomeric excess utilizing the thiamine diphosphate (ThDP)-dependent enzyme benzaldehyde lyase (BAL) (Scheme 16)[26].



Scheme 16. Enzymatic cross-benzoin reaction reported by Müller

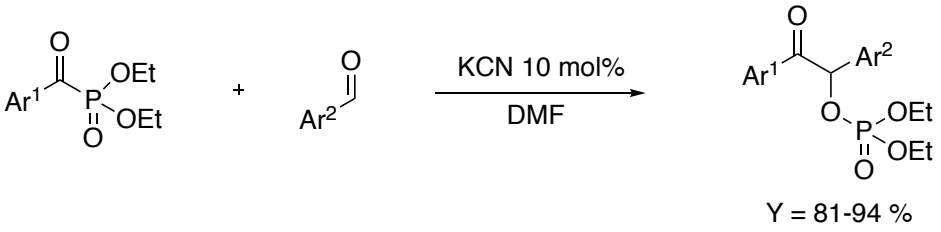
Another investigated strategy to access cross-benzoin products avoiding the formation of undesired by-products was disclosed by Jonson and co-workers, who reported the use of acyl silane derivates in the cyanide catalyzed benzoin reaction. The proposed mechanism for the reaction is similar to the classical benzoin reaction (Scheme 17)[26].



Scheme 17. Mechanism proposed for the silyl benzoin reaction disclosed by Jonson

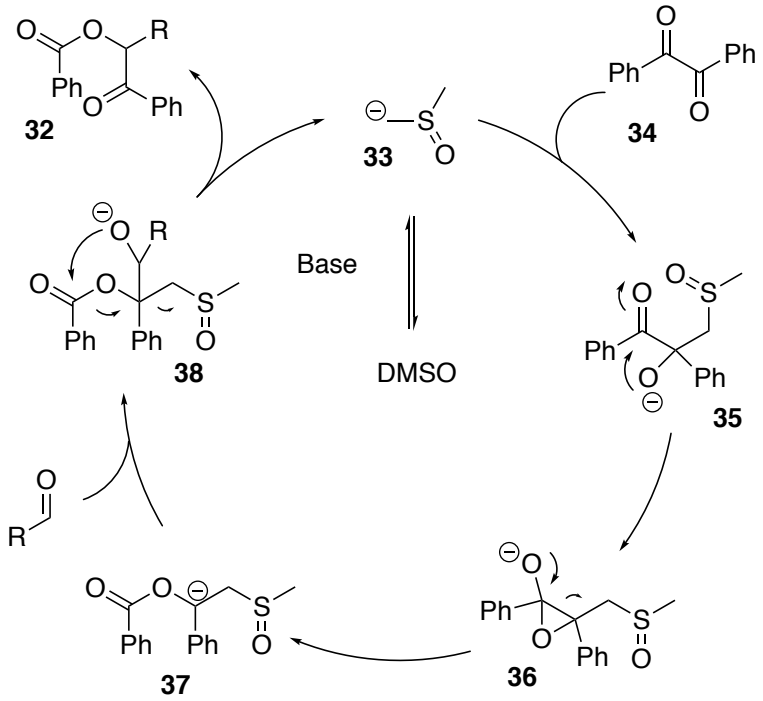
In this case, the acyl silane derivate **25** preferentially undergoes the addition by the cyanide ion in order to generate the intermediate **26**, which evolves in the active specie **27** through a [1,2]-Brook rearrangement. Then, **27** can attack the aldehyde to form the adduct **28**, which in turn is transformed in **29** by [1,4]-silyl migration. The target product **30** is finally obtained with the release of the catalyst. In the field of alternative acyl anion sources, remarkable works was disclosed by Demir and co-

workers, who reported a cross-benzoin reaction in which acyl phosphonates act in similar manner to that reported by Jonson (Scheme 18)[27].



Scheme 18. Cross-Benzoin reaction reported by Demir

Recently, our group discovered a new type of activation mode for α-diketones to generate acyl anions using the elusive dimsyl anion as catalyst. The reaction allowed to obtain benzoyl protected *cross*-benzoin adducts **32** in good yield using the in situ formed dimsyl anion **33** in place of the more toxic cyanide anion (Scheme 19)[28].

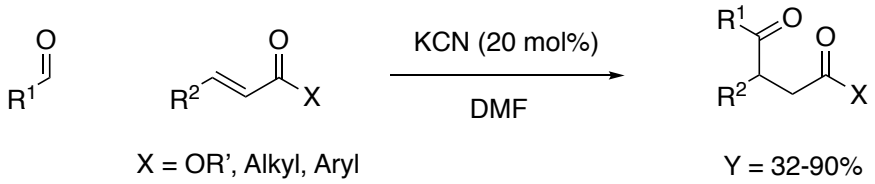


Scheme 19. Mechanism for cross-benzoin reaction of α-diketones

Theoretical calculations and MS experiments have shown that the addition of dimsyl **33** to benzil **34** forms the intermediate **35**, which then evolves to the epoxide **36**. This species undergoes a rearrangement to generate the nucleophilic masked acyl anion **37**. At this point, the intermediate **37** is rapidly sequestrated by the aldehyde to form the adduct **38** and then the *cross*-benzoin product **32** along with the release of catalyst **33**.

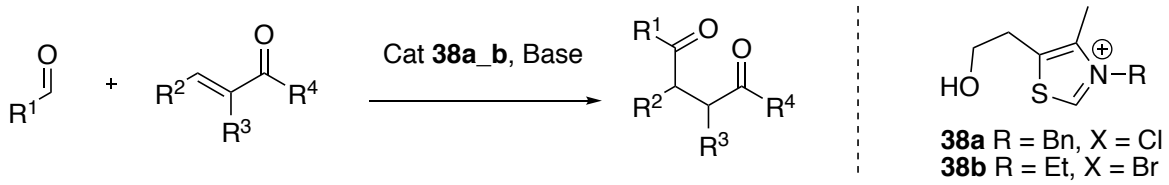
1.2.3. Stetter reaction

Organic chemists have always searched for new reaction partners when a new reactivity is disclosed in order to form C-C or C-X bonds in a more efficient manner. In this regard, beside the benzoin condensation, other reactions in which NHCs act as umpolung mediators are present in the literature. An important example was reported by Stetter in 1970; this author disclosed, for the first time, a reaction (today named Stetter reaction in his honor), which transfers the concept of umpolung catalysis to classical Michael acceptors (Scheme 20)[29].



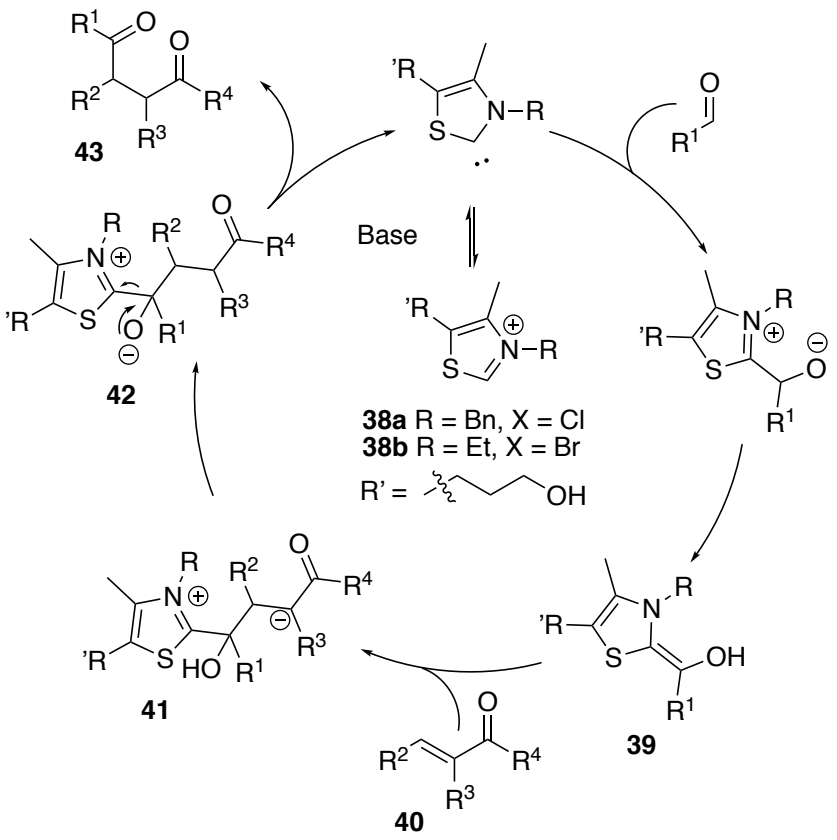
Scheme 20. Addition of Umpoled Aldehydes to Michael acceptor presented by Stetter

The Stetter reaction has opened the door to the synthesis of 1,4-difunctional molecules, such as 1,4-diketones and 1,4-ketoesters. Several thiazolium salts were employed and it has been found that the benzyl-substituted thiazolium salt **38a** is the best choice for the addition of aliphatic aldehydes, while the ethyl-substituted thiazolium salt **38b** works better for aromatic aldehydes (Scheme 21)[30].



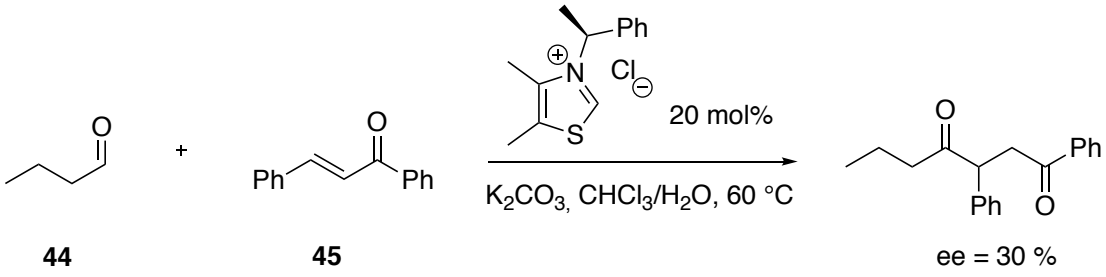
Scheme 21. Stetter reaction promoted by thiazolium salts

The first part of the mechanism is exactly the same of the benzoin condensation. The aldehyde undergoes the addition by the NHC **38a_b**, forming the Breslow intermediate **39** with the same pathway. At this point, the nucleophilic enaminol **39** attacks the Michael acceptor **40** in β-position leading to the formation of adduct **41,** which is converted into **42** via proton transfer. Finally, the release of NHC, ready for another catalytic cycle, occurs along with the formation of the 1,4-diketone **43** (Scheme 22).



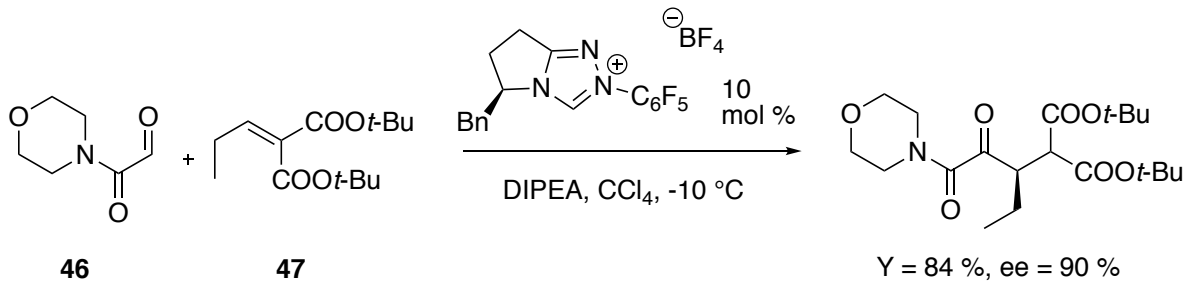
Scheme 22. Proposed mechanism for the Stetter reaction

The asymmetric version of this reaction has remained unexplored for many years until in 1989 Enders and co-workers presented the cross coupling of n-butanal **44** with chalcone **45** to access the corresponding 1,4-diketones with modest enantioselectivity (30 % *ee*) and low yield (Scheme 23) [31].



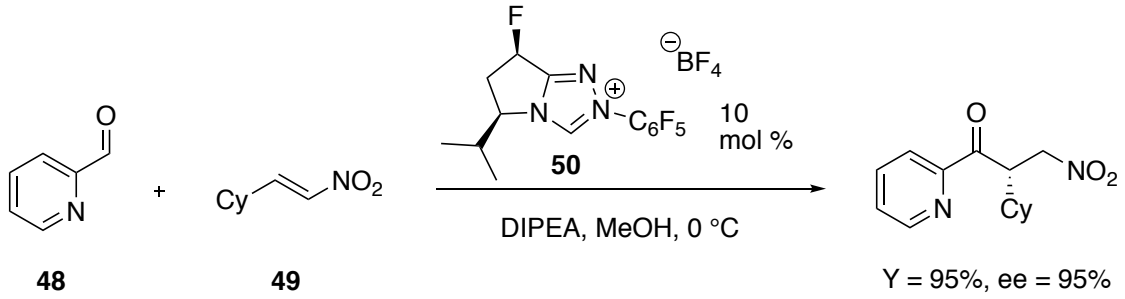
Scheme 23. Asymmetric Stetter reaction reported by Enders

Better results in terms of enantioselectivity were subsequently achieved by Rovis, who reported in 2008 the reaction between glyoxamides **46** and alkylidene malonates **47** in good yield and excellent enantioselectivity (Scheme 24)[32].



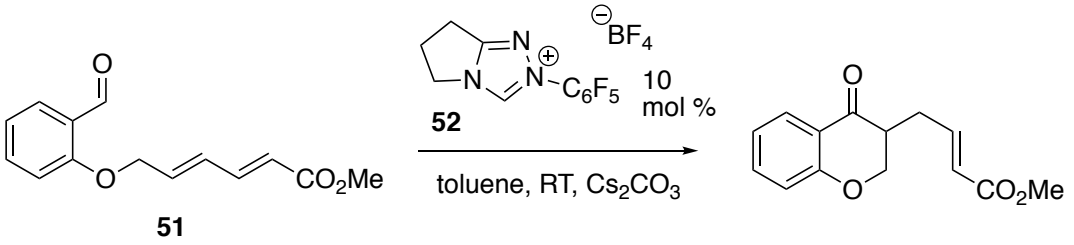
Scheme 24. Asymmetric Stetter reaction reported by Rovis

Beside 1,4-diketones and 1,4-ketoesters, new coupling partners were investigated in the Stetter reaction. For example, in 2009 Rovis and co-workers disclosed a new asymmetric Stetter reaction in which highly reactive heteroaromatic aldehydes **48** react with aliphatic nitroalkenes **49**. In this reaction the design of catalyst **50** plays an important role. In fact, the fluorine atom on the backbone determines both the level of reactivity and enantioselectivity. The authors tried to explain this result obtaining a crystal structure and speculating that the better reaction outcome was due to the preferential formation of the conformational isomer Cγ-*exo* in respect with the Cγ-*endo* isomer by a clear orbital alignment (Scheme 25)[33].



Scheme 25. Asymmetric Stetter reaction with nitroalkenes reported by Rovis

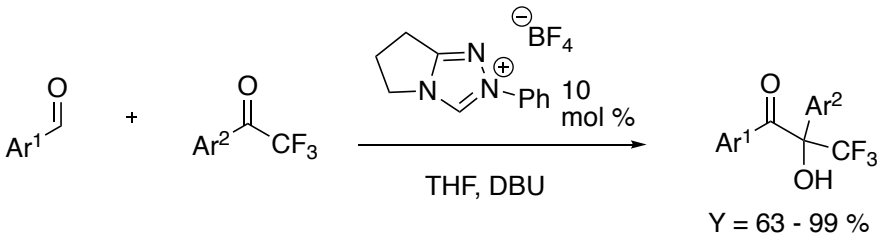
A vinylogous Stetter reaction has been disclosed as well. In 2013 McErlean and co-workers presented an NHC catalyzed reaction extended to 1,6-acceptors in an intramolecular fashion. They employed a class of vinylogous Michael acceptors **51** prepared by treating salicylaldehyde derivates with methyl bromosorbate and they found that triazolium pre-catalyst **52** was the most suitable promoter in this reaction. The authors also presented an enantioselective version in the same paper. However, only few examples were reported (Scheme 26)[34].



Scheme 26. Intramolecular Vinylogous Stetter reaction promoted by triazolium salt

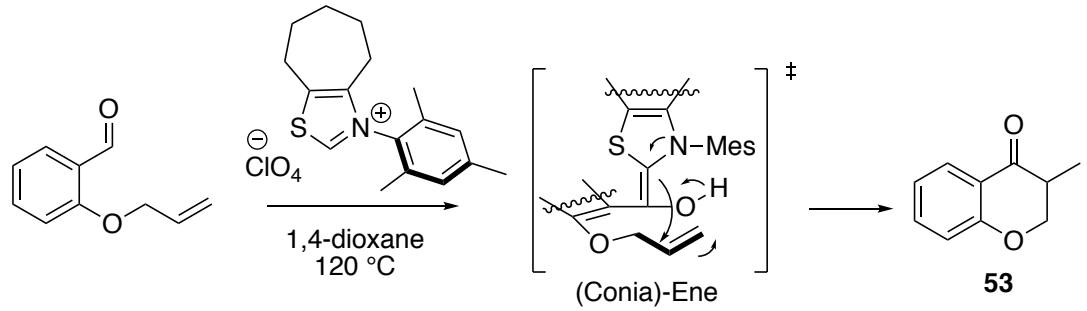
1.2.4. Umpolung reactions with unconventional acceptors

The Umpolung catalysis promoted by NHC has deeply attracted the attention of synthetic chemists and recently these catalysts have been successfully employed in reactions between aldehydes and unconventional electrophiles. Enders and Henseler have reported the use of activated ketones, employed as electrophiles, in cross-benzoin-like reactions. The authors assert that the high selectivity towards the tertiary alcohol is the result of the reversibility of the homo-benzoin reaction (Scheme 27)[35].



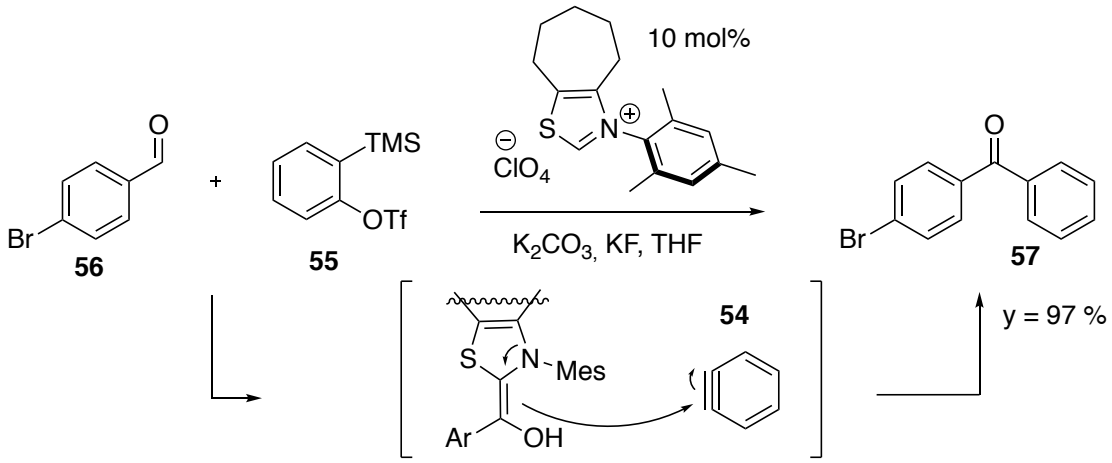
Scheme 27. Cross-benzoin reaction with activated ketones reported by Enders and Henseler

Surprisingly, NHCs are able to promote the intramolecular nucleophilic addition of an acyl anion to unactivated C-C double bonds. Glorius and co-workers have disclosed a novel reactivity, which brought towards the synthesis of substituted chromanones **53** via intramolecular C-C bond formation between umpoled aldehydes and the homo allyl ether functionality. The authors proposed a mechanism in which the C-C bond formation involves an asynchronous concerted Conia-Ene-like transition state (Scheme 28)[36].



Scheme 28. Hydroacylation of unactivated olefins reported by Glorius

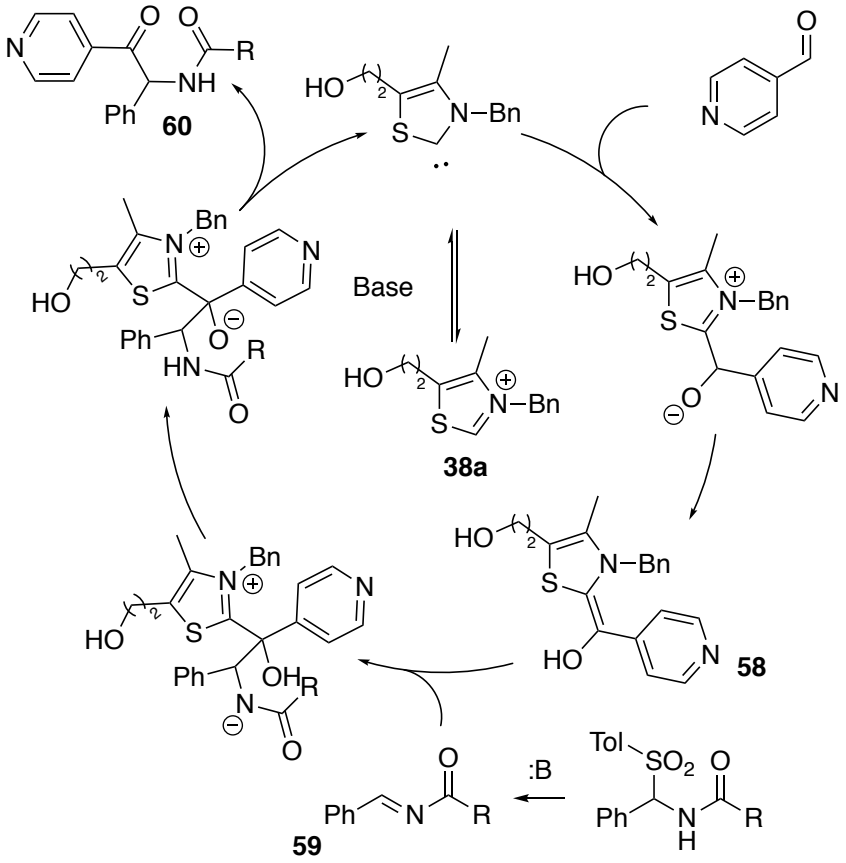
The same group in 2010 reported an elegant approach to the hydroacylation of arynes (Scheme 29) [37]. Although arynes are useful and highly reactive species, there are only few examples where these ephemeral intermediates are employed in Organocatalysis. The arynes **54** are generated in situ treating 2-trimethylsilysaryl triflates **55** with KF and reacted in the presence of aldehyde **56** and NHC. Diaryl ketones **57** were collected in excellent yield by this protocol.



Scheme 29. Hydroacylation of in situ generated arynes reported by Glorius

1.2.5. Aza-Benzoin reaction

The reaction between umpoled aldehydes and imines, known as aza-benzoin condensation, is proved to be an efficient single-step strategy to provide α-amino ketones[38]. The aza-benzoin reaction was first reported in 1988 employing activated imines and the mechanism proposed, in analogy with the benzoin condensation, envisages the formation of Breslow intermediate **58**. At this point, the enaminol **58** attacks the electrophilic imine **59** generated in situ and, after the proton transfer process, the elimination of catalyst provides the condensation adduct **60** (Scheme 30)[39].



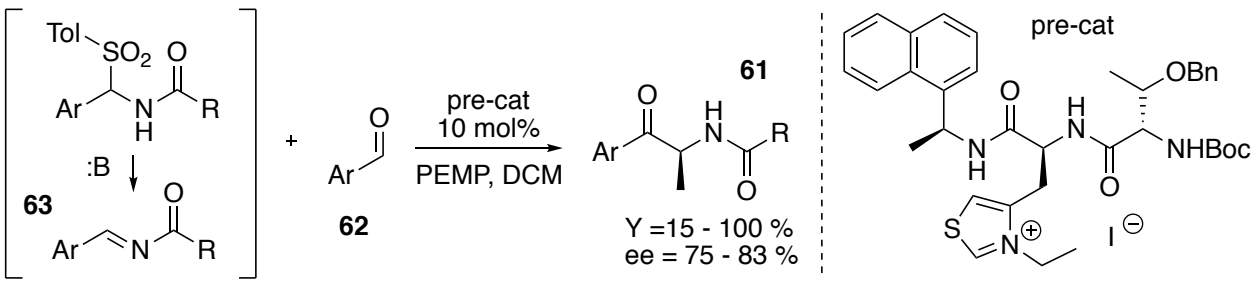
Scheme 30. Proposed mechanism for the aza-benzoin reaction presented by Murry

Generally, harsh conditions are required for unactivated imines. In 2007 You and co-workers have presented the first aza-benzoin reaction employing N-substituted aryl imine to access the corresponding aminoketones in good yield. The authors have remarked that high temperature is required to ensure that the reaction takes place (Scheme 31)[40].

Scheme 31. aza-benzoin reaction with unactivated imines

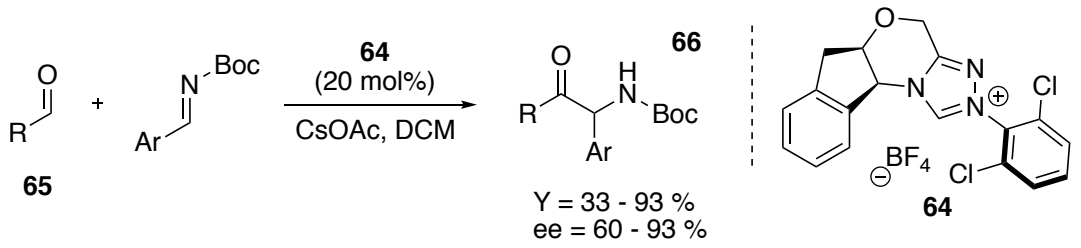
For these reasons, an enantioselective version for this kind of imines remains an open challenge. The first example of asymmetric aza-benzoin reaction was disclosed by Miller, who used chiral thiazolium salts derived from histidine. Optical pure α-amino ketones **61** were obtained in good yield and good enantioselectivity by the coupling between aromatic aldehydes **62** and in situ generated acylimines **63**. The products quickly undergo racemization under basic conditions via enolization equilibrium.

Thus, the authors needed to carefully control the reaction time and the amount of imine in order to avoid the erosion of enantiopurity (Scheme 32)[41].



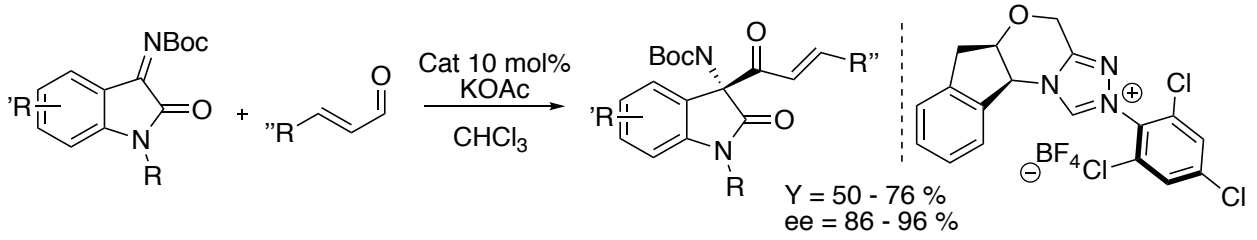
Scheme 32. Asymmetric aza-benzoin reaction reported by Miller

In this direction, Rovis and co-workers in 2012 contributed to improve the efficiency of this reaction. They assumed that less activated imines would have led to make more stable the newly formed stereocenter. Thus, replacing acyl imines with N-Boc substituted imines in presence of the chiral catalyst **64** along with aliphatic aldehydes **65** they were able to isolate the products **66** in high yields and excellent enantioselectivity (Scheme 33)[42].



Scheme 33. Asymmetric aza-benzoin reaction reported by Rovis

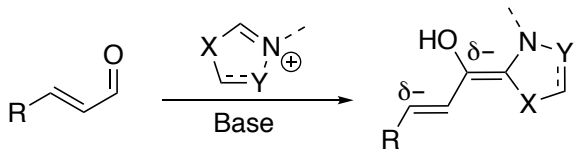
In the field of Aza-benzoin condensation, cyclic N-protected ketimines have attracted significant interest. This is due their efficient and stereodivergent preparation (both E and Z isomers are accessible). In particular, oxindole scaffolds are privileged motifs common in many natural products; the reaction between 2,3-dioxo-1,3-dihydroindole (isatin)-derived ketimines and umpoled unsaturated aldehydes has been deeply investigated by Chi, who obtained 3-disubtituted oxindoles with good yield and excellent enantioselectivity (Scheme 34)[43].



Scheme 34. Asymmetric aza-benzoin reaction with isatin-derived ketimines reported by Chi

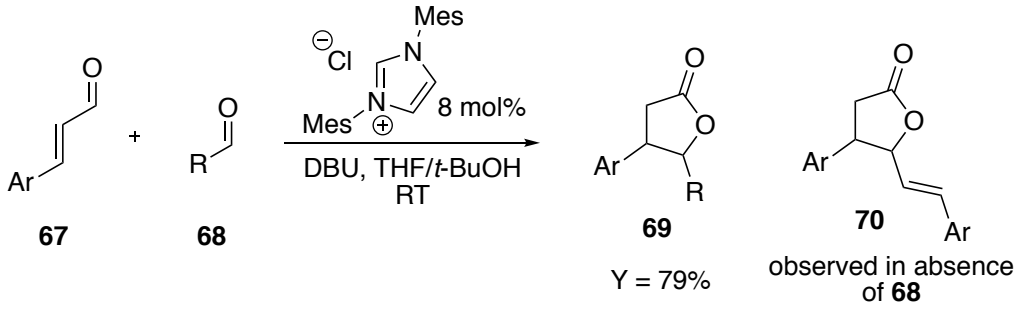
1.2.5. Homoenolate reactivity

Homoenolate reactivity via NHC catalysis was reported by Bode and Glorius independently in 2004 [44]. They discovered that the Breslow intermediate formed by addition of NHC onto α,β-unsaturated aldehydes exhibits nucleophilic character at the β-carbon by virtue of conjugation (Scheme 35).



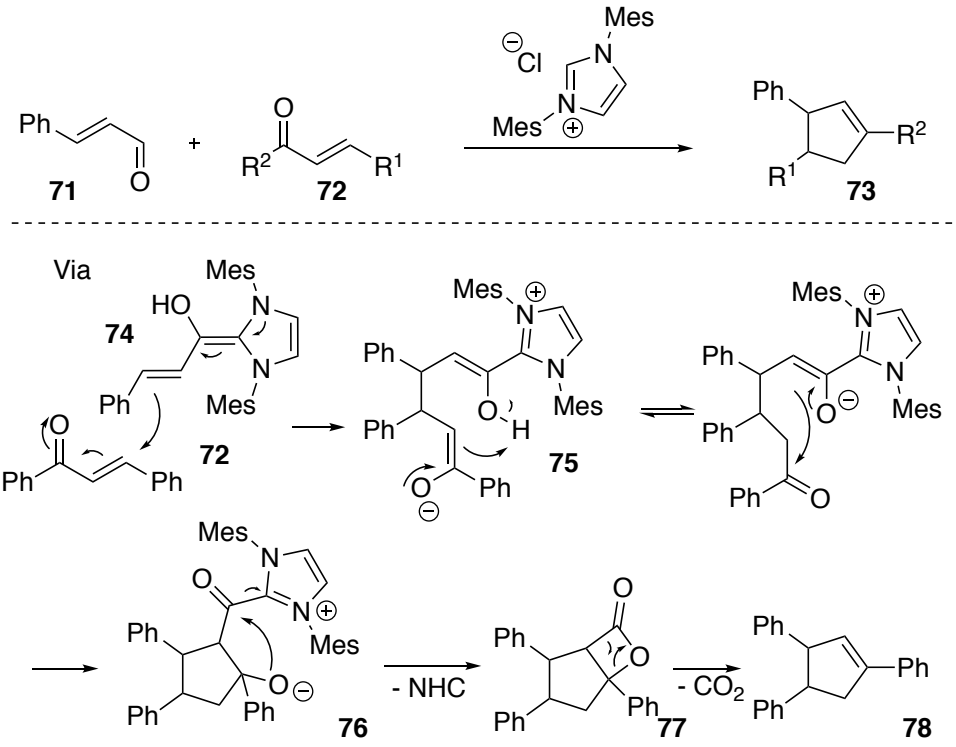
Scheme 35. Generation of homoenolate by NHC condensation onto α,β-unsaturated aldehydes

The umpoled intermediate generated from enals **67** could be intercepted by aldehyde **68** leading to γ-lactones **69**. In order to explain the formation of **69**, a homoenolate species must be invoked and, in the absence of an intercepting agent, the homo-dimerization product **70** was observed by the authors (Scheme 36).



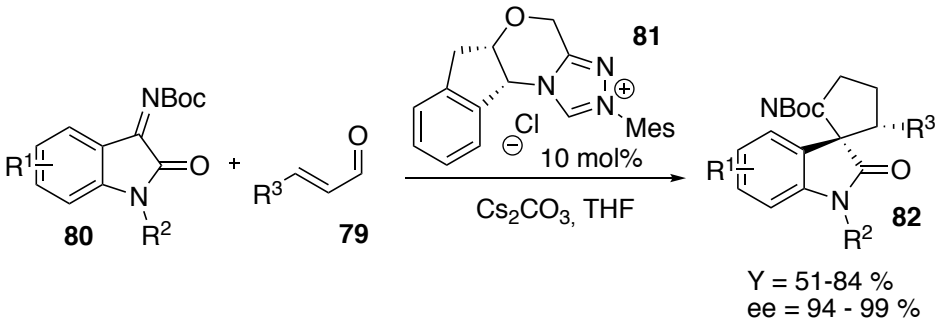
Scheme 36. Generation of homoenolate by NHC-promoted condensation onto α,β-unsaturated aldehydes

Another interesting reaction pathway was reported by Nair and co-workers in 2006. They observed that the reaction between **71** and enone **72** afforded a trisubstituted cyclopentene **73**. The mechanistic insight showed that the Michael addition of homoenolate **74** to enone **72** produces two different enolate groups on the same molecule **75**. The enolate functionality proximal to the azolium moiety attacks the carbonyl group forming the 5-member ring intermediate **76**, which undergoes an intermolecular esterification to generate **77**. The last intermediate rapidly evolves to **78** through decarboxylation (Scheme 37)[45].



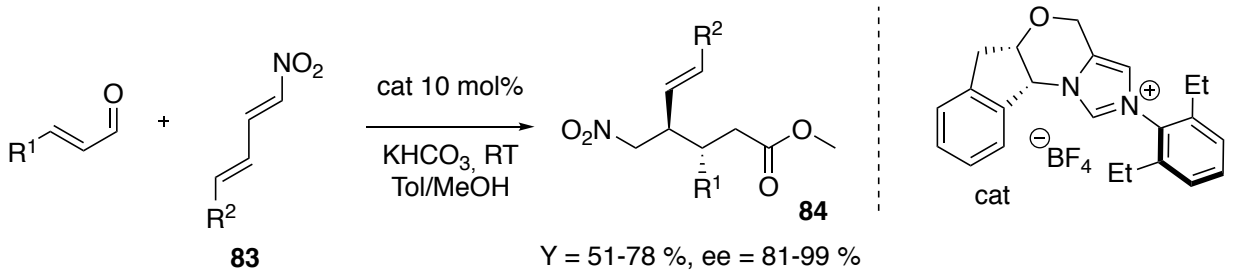
Scheme 37. Cyclopentene derivates synthesis by homoenolate approach

Homoenolate strategy turned out to be a powerful tool to access spirocyclic compounds with high optical purity. An enantioselective homoenolate annulation was reported to afford spirocyclic lactones **82**. The authors showed that enals **79** react with isatins **80** in presence of triazolium catalyst **81** under cooperative conditions affording the products **82** with high yield and almost complete enantioselectivity (Scheme 38)[46].



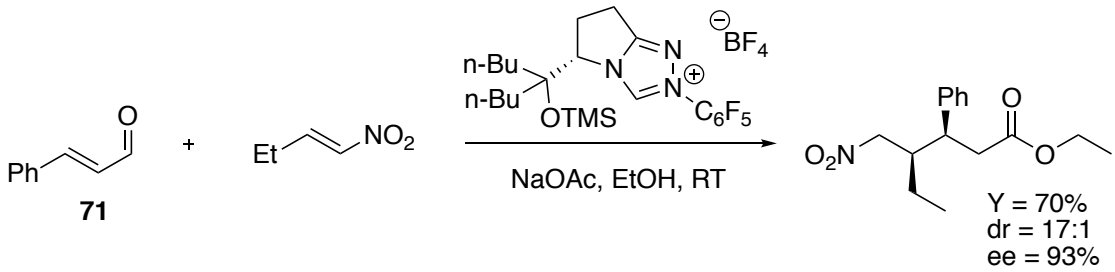
Scheme 38. Synthesis of spirocyclic isatin derivates reported by Chi

In general, Michael acceptors have been shown to be suitable substrates in NHC-catalyzed homoenolate chemistry. Liu and co-workers reported the enantioselective Michael addition of homoenolates to nitro-styrenes **83** to afford nitrocarboxylates **84**, which may be readily converted into γ-lactams by reductive lactamization[47]. The authors showed that the formation of the corresponding *anti* γ-nitro esters **84** was achieved with high enantioselectivity (Scheme 39).



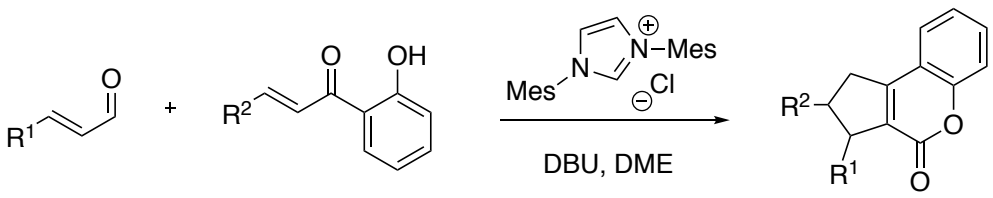
Scheme 39. Nitrocarboxylates synthesis reported by Liu

Furthermore, *syn* products can be obtained using a protocol reported by Rovis[48]. The Rovis procedure allows to use also aliphatic nitroolefins (as electrophiles), which are not compatible with the previous method disclosed by Liu (Scheme 40).



Scheme 40. Nitrocarboxylates synthesis reported by Rovis

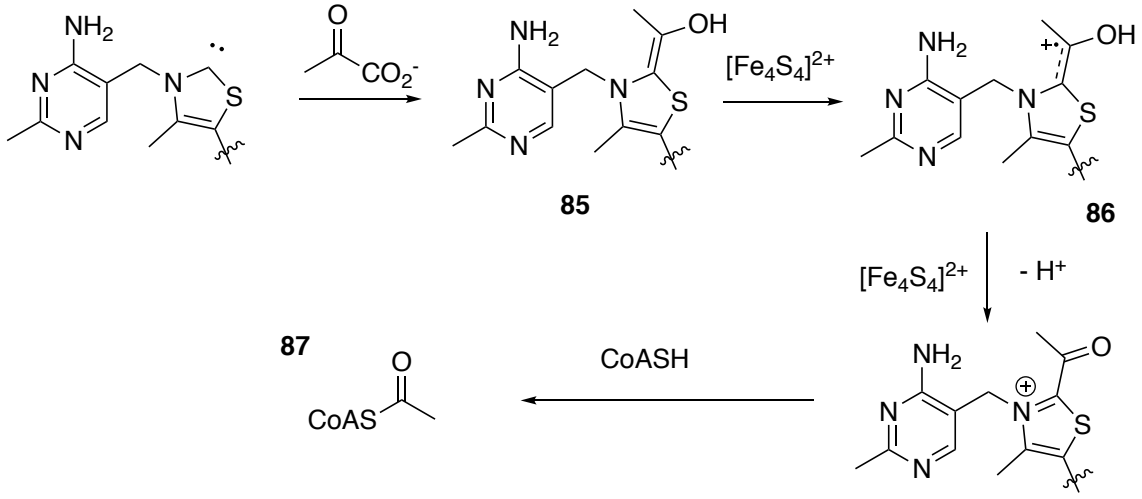
Cascade processes are powerful tools to increase the molecular complexity through sequential C-C or C-X bond forming reactions. Within this realm, homoenolate chemistry has gained more and more interest during the last years. For example, 2'-hydroxy chalcones were successfully employed in NHC-catalyzed homoenolate annulation reactions[49]. Cyclopentane fused coumarins were obtained with good yield and excellent diastereoselectivity. The authors proposed a mechanism similar to that described by Nair for the synthesis of substituted cyclopentenes (see above, Scheme 37). The main difference is that the acyl azolium is not involved in a β-lactone formation. Instead, the product is formed through the acylation of the phenolic oxygen by the acyl azolium species followed by dehydration (Scheme 41).



Scheme 41. Coumarins synthesis via homoenolate of enals

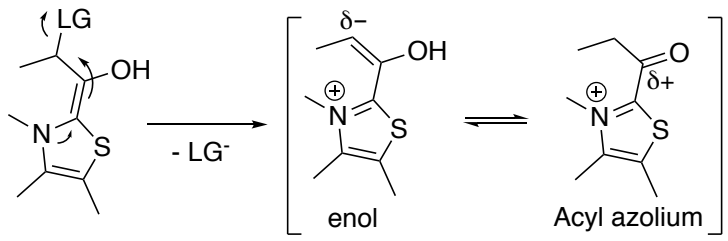
1.2.6. Oxidative NHC-catalysis

In biochemistry, the fate of the Breslow intermediate seldom follows a route different to that related to its nucleophilic behavior. For example, in the mechanism of pyruvate ferredoxin oxidoreductase, which uses thiamine pyrophosphate as carbene cofactor to generate the Breslow intermediate by decarboxylation, the enaminol **85** is oxidized by ferredoxin by an additional cofactor characterized by an [Fe_4S_4] cluster. An electron transfer from the electron-rich Breslow intermediate to the Iron cluster leads to a radical cation **86**; this ephemeral intermediate renews the electron transfer in the presence of CoASH to provide CoASAc **87** through the formation of a key acyl azolium intermediate [50] (Scheme 42).



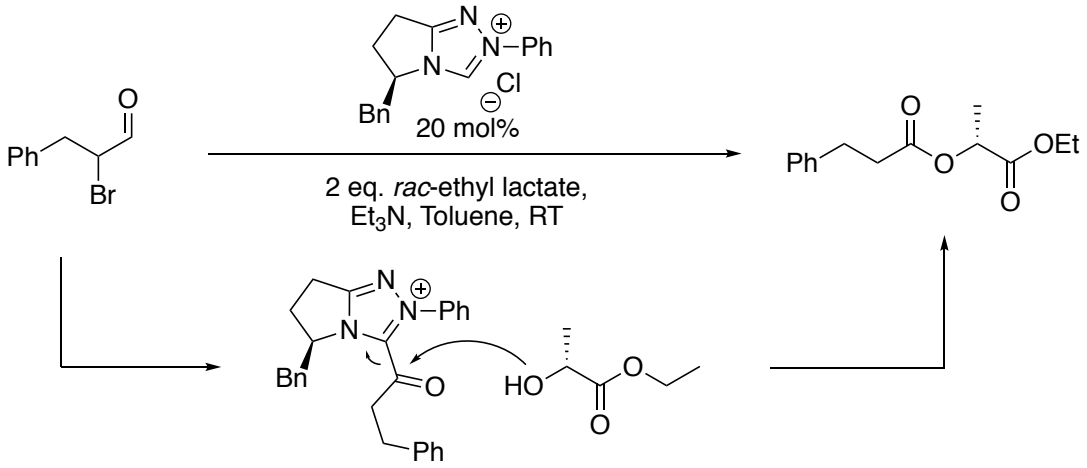
Scheme 42. Ferredoxin oxidoreductase mechanism

This well-known biological mechanism has prompted chemists to develop catalytical processes that proceed through the oxidation of the enaminol intermediate. Generally, the Breslow intermediate can be oxidized either placing a redox functionality into the substrate (internal oxidation) or using external oxidant reagents (external oxidation)[51]. In the internal oxidation, substrates that bear a leaving group or unsaturation adjacent to the carbonyl can be diverted to uncommon reaction pathways through two distinct catalytic intermediates: enol and acyl azolium (Scheme 43). During the last years, each of these activation mechanisms have been exploited in a plethora of new reactions to afford highly functionalized and enantiopure products starting from readily available aldehydes[52].



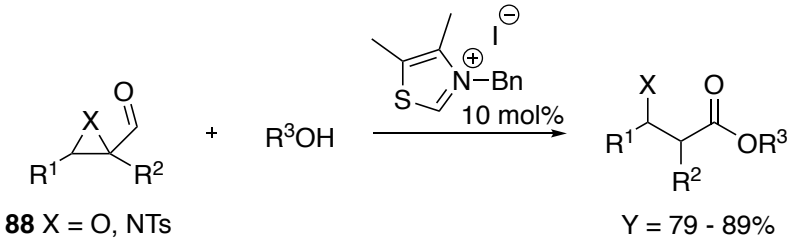
Scheme 43. Enol and acyl azolium intermediates involved in the internal oxidation strategy

In 2004 Rovis and co-workers presented a new methodology where α-halo aldehydes undergo halogen elimination after the formation of the Breslow intermediate to generate the enolate, which quickly turns into the acyl azolium species. The authors employed this strategy in the resolution of alcohols using a chiral NHC with a modest resolution efficiency (ee = 31 %) (Scheme 44)[53]. Furthermore, the authors found that elimination occurred more readily with Bromide instead of Chloride.



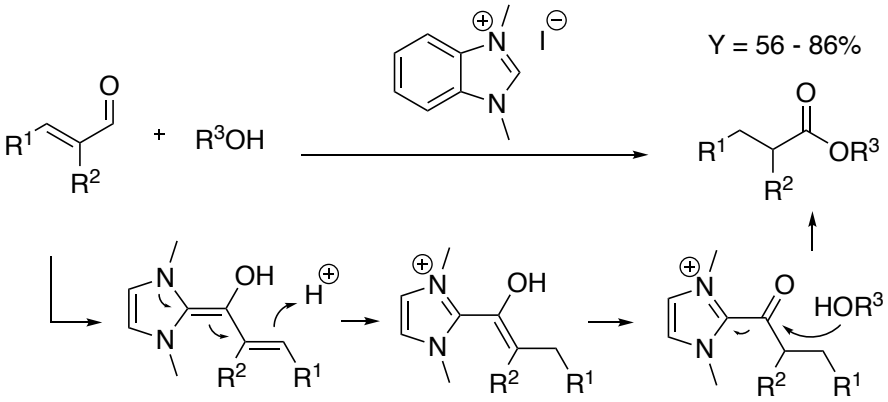
Scheme 44. Internal oxidation strategy for the resolution of alcohols presented by Rovis

In the same year, Bode and co-workers disclosed a similar strategy in which α,β-epoxy aldehydes and α,β-aziridinyl aldehydes **88** were employed to generate the acyl azolium intermediate using a thiazolium catalyst (Scheme 45)[54].



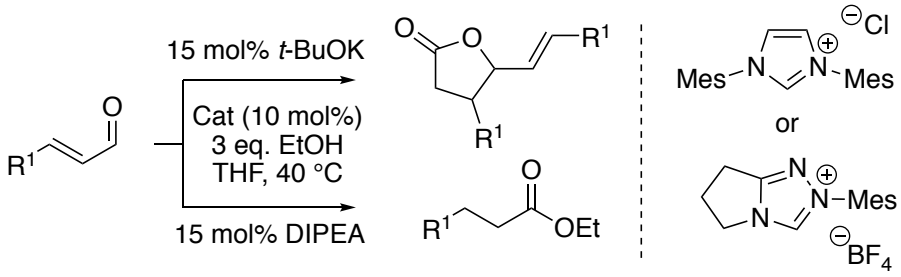
Scheme 45. Internal oxidation strategy with epoxy/aziridinyl aldehydes reported by Bode

In 2005 Bode and Scheidt independently disclosed that α,β-unsaturated aldehydes can turn into saturated esters in the presence of alcohols and NHCs. Scheidt and co-workers observed that treating enals with benzimidazolium pre-catalyst was an efficient method to acylate primary, secondary alcohols and phenols (Scheme 46)[55].



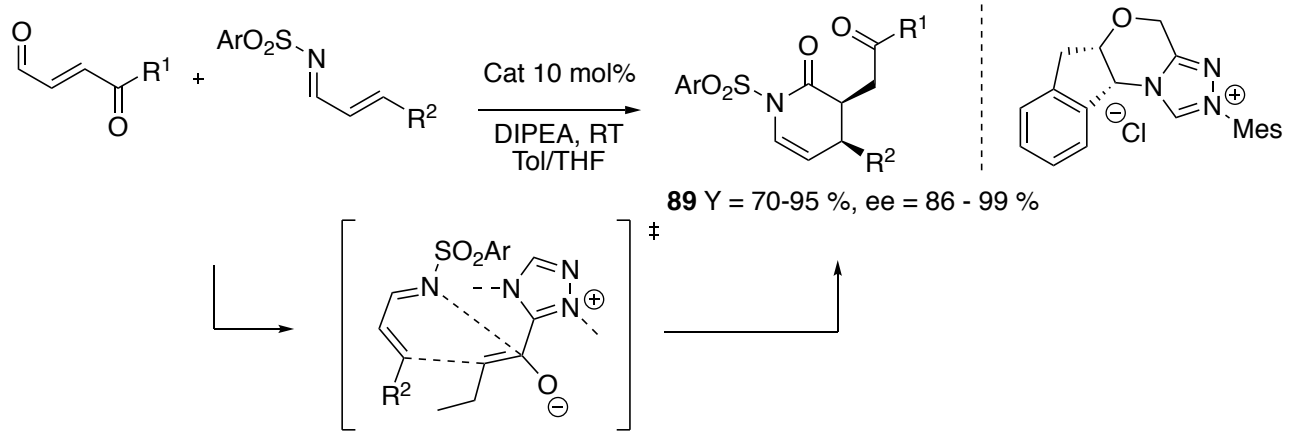
Scheme 46. Internal disproportionation reported by Scheidt

Bode demonstrated that the choice of the base plays an important role in the reaction outcome. In fact, a strong base, in this case potassium *tert*-butoxide, is necessary to generate a lactone dimer by the nucleophilic addition of homoenolate to another equivalent of free aldehyde. By contrast, a milder base such as DIPEA smoothly affords the corresponding acyclic saturated ester in presence of an alcohol (Scheme 47)[56].



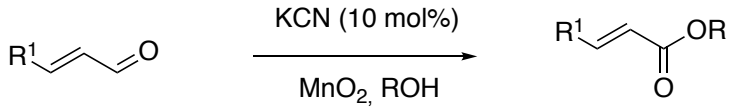
Scheme 47. Internal disproportionation reported by Bode

Since the process of acyl azolium generation involves the formation of a nucleophilic intermediate, trapping of this species is potentially possible. In fact, in 2006 Bode and co-workers presented a stereoselective NHC-catalyzed Diels-Alder (DA) reaction of α,β-unsaturated aldehyde with α,β-unsaturated imines to provide chiral dihydropyridinone products **89**. The scope of reaction proved to be quite broad for the nucleophilic partner. Noteworthy, the reaction also proceeded decreasing the catalytic loading to 0.5 mol% with good yields (70-95 %) and excellent stereoselectivity (86-9 9% *ee* and 3:1 to 20:1 *dr*). The preferential formation of the *cis* adduct is explainable with the generation of the (Z)-enolate during the NHC-promoted redox process (Scheme 48)[57].



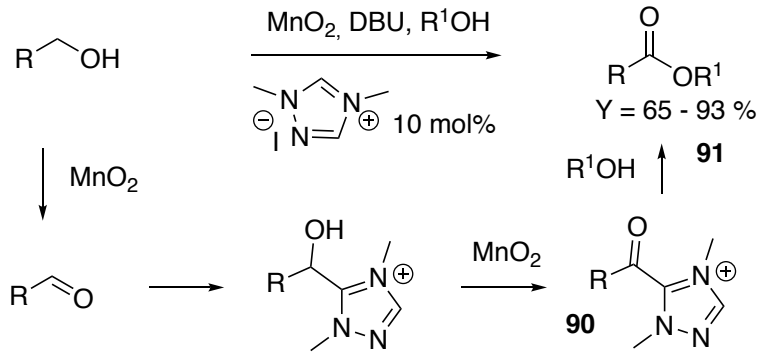
Scheme 48. DA promoted by NHC disclosed by Bode

Inspired by the mechanism of pyruvate ferredoxin oxidoreductase, chemists tried to employ external oxidant reagents to generate the acyl azolium intermediate without using α-reducible substrates. In this regard, a large number of oxidants was found to be consistent with NHC-catalyzed oxidative transformation of aldehydes. Inorganic oxidants have been among the first employed. The first reaction in which a Breslow-like intermediate was oxidized by an inorganic reactant was reported by Corey, who used MnO_2 in a cyanide-catalyzed oxidative esterification of aldehydes (Scheme 49) [58].



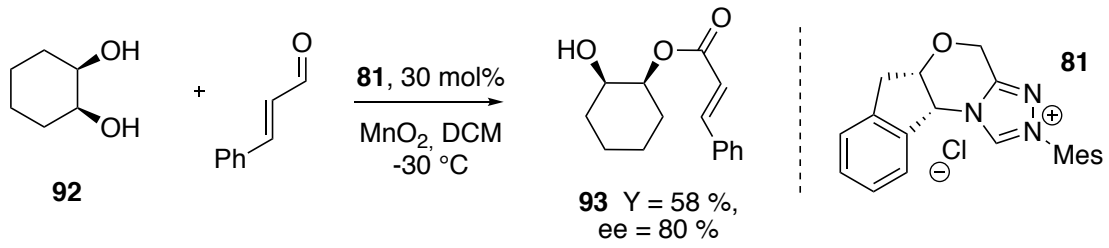
Scheme 49. Oxidation of aldehydes promoted by Cyanide anion and MnO_2 reported by Corey

Later, Scheidt recognized that this reaction could be more efficient using a triazolium catalyst instead of cyanide anion (Scheme 50). Two distinct oxidation steps are involved in the reaction: alcohol is first oxidized to aldehyde, which undergoes the addition of NHC in order to generate the Breslow intermediate. Then, the enaminol under oxidative conditions is quickly converted into the acyl azolium **90**, which is rapidly intercepted by a molecule of alcohol to access the corresponding ester **91**[59].



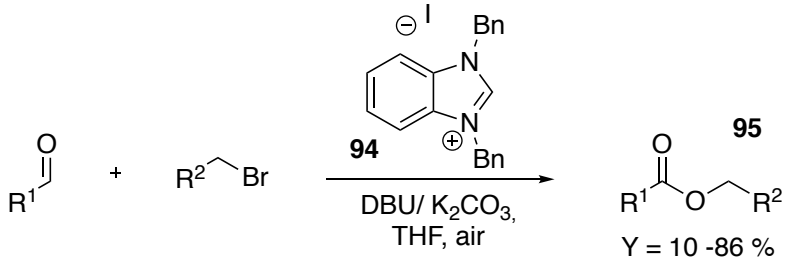
Scheme 50. Oxidation of aldehydes promoted by NHC and MnO_2 reported by Scheidt

Cis-1,2-cyclohexandiols **92** were successfully desymmetrized at low temperature using a chiral NHC under similar conditions to afford the corresponding esters **93** with good enantioselectivity (Scheme 51).



Scheme 51. NHC-catalyzed oxidative desymmetrization of *cis*-1,2-diols

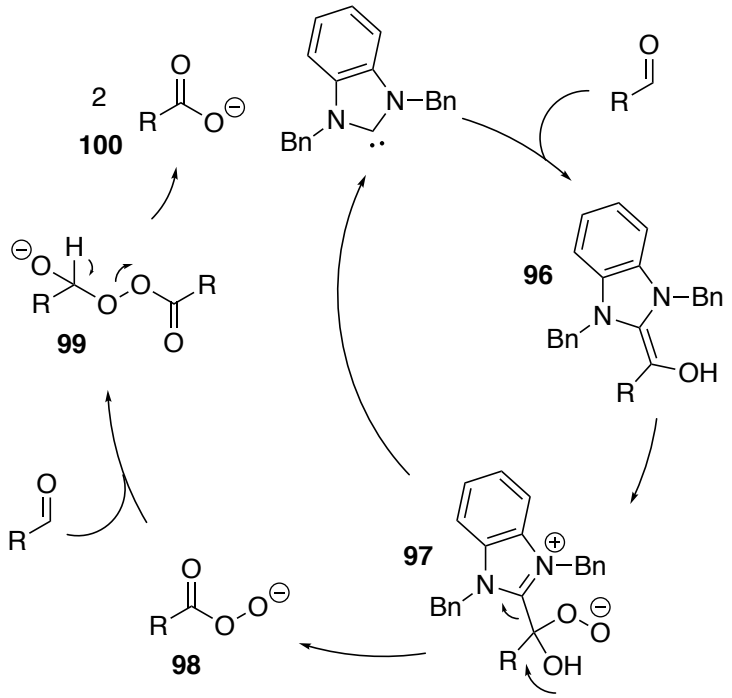
The use of dioxygen as final electron acceptor in NHC-mediated oxidations of aldehydes was successfully achieved by several groups. Liu and co-workers disclosed the oxidation of cinnamyl and aryl aldehydes into carboxylic esters mediated by benzimidazolium pre-catalyst **94** using air as the terminal oxidant (Scheme 52)[60].



Scheme 52. Aerobic oxidation promoted by NHCs reported by Liu

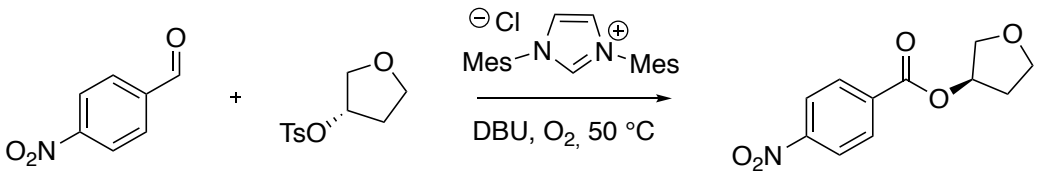
In this reaction the formation of ester **95** is possible via alkylation of the carboxylate generated by the NHC-catalyzed oxidation promoted by the atmospheric oxygen. Furthermore, the reactivity trend showed that electron-poor aldehydes are more prone to be oxidized. Several mechanistic studies were performed about the NHC-promoted aerobic oxidation of aldehydes. The first postulated pathway (Scheme 53) consists in the formation of Breslow intermediate **96** that, in the presence of oxygen, affords the zwitterionic peroxy-intermediate **97**. The subsequent fragmentation gives the carbene,

ready for another catalytic cycle, along with the corresponding deprotonated peracid **98**, which is intercepted by a molecule of aldehyde to form the intermediate **99**. At this point, cleavage of the O-O bond and deprotonation furnish two molecules of acid **100** (oxygenative pathway), which is accessible for the O-alkylation step to afford the ester **95**.



Scheme 53. Postulated mechanism for the aerobic oxidation promoted by NHCs

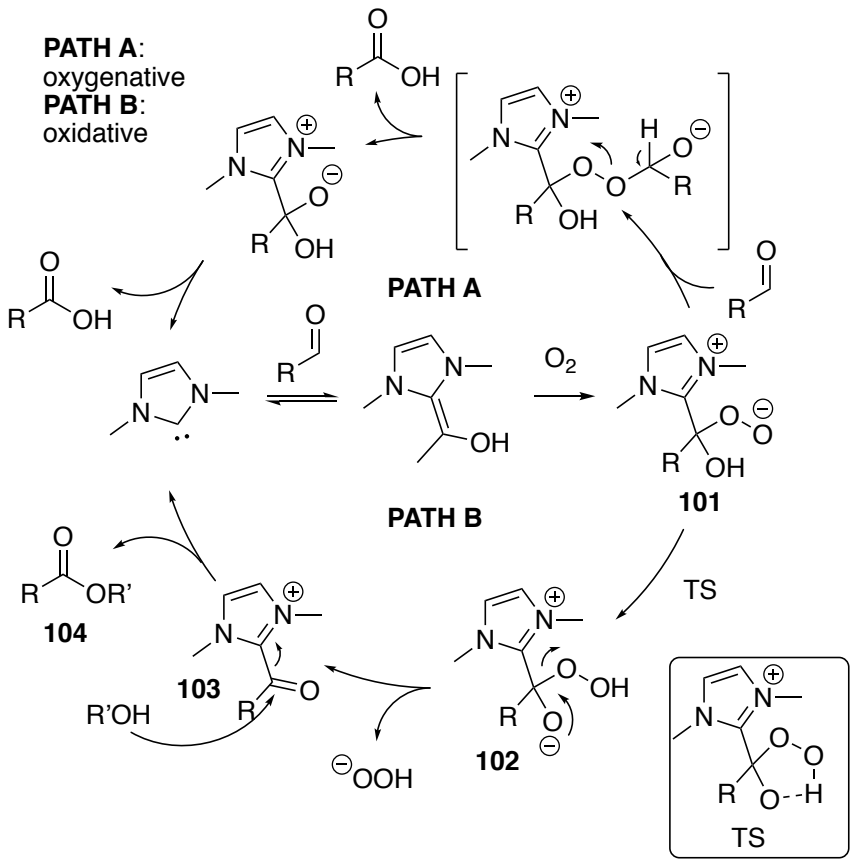
The O-alkylation of activated tetrahydrofuran performed by Hui under similar conditions seems to corroborate the last part of the mechanism proposed by Liu[61]. In fact, the observed inversion of configuration at the stereogenic center of tetrahydrofuran is in accordance with the S_N2 step explained by Liu (Scheme 54).



Scheme 54. Reaction reported by Hui to confirm the formation of the carboxylic acid

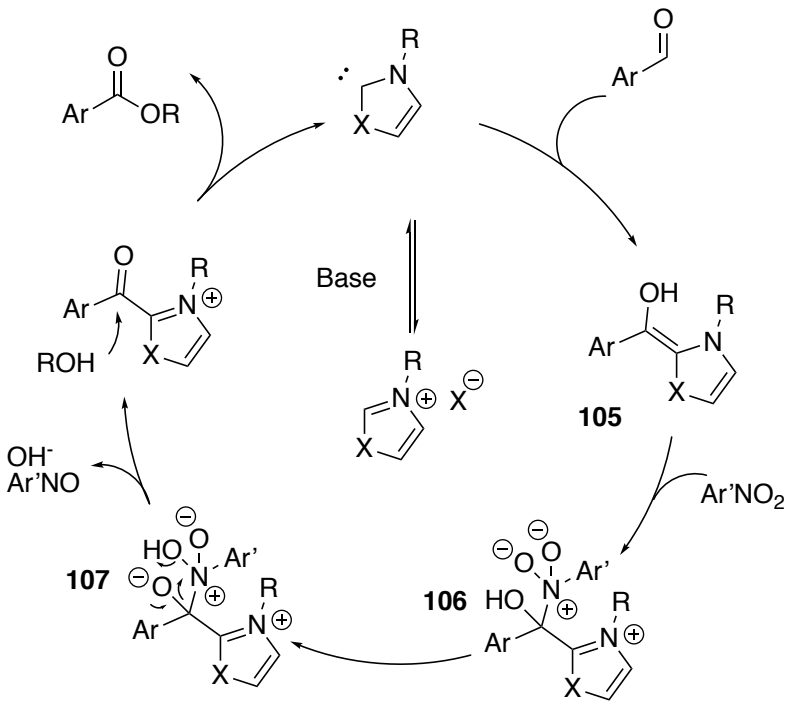
In the presence of alcohol, it has been demonstrated that the oxygenative pathway is in competition with the oxidative pathway and the favorite pathway is influenced by the stereoelectronic features of the aldehyde substrate. In 2014 Bortolini and co-workers detected several key intermediates involved in the two mechanisms through ESI-MS analysis, elucidating the dichotomy behind the oxidation reaction[62]. The zwitterionic peroxy-intermediate **101** is common to both the oxygenative (PATH A) and oxidative (PATH B) pathways. In the oxidative route, **101** evolves into the species **102** through

a proton transfer, which is followed by the elimination of hydrogen peroxide anion to give the acyl azolium **103** that reacts with the alcohol to afford the corresponding ester **104** (Scheme 55).



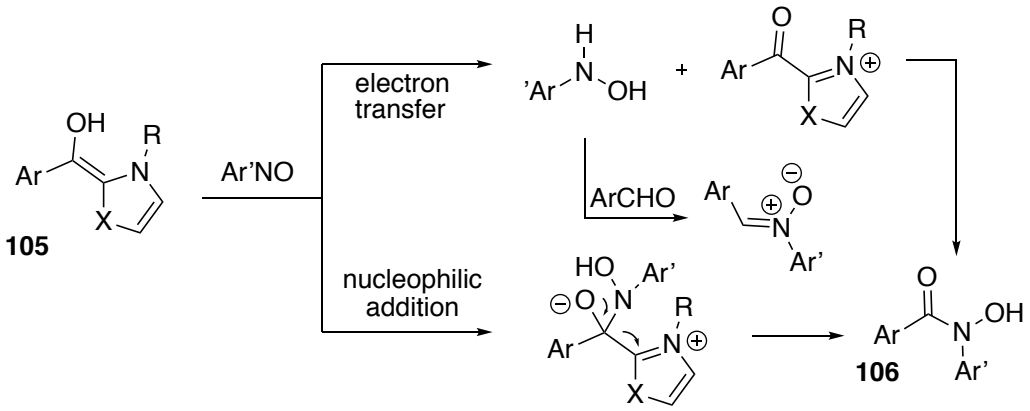
Scheme 55. Reaction reported by Hui to confirm the formation of the carboxylic acid

The authors have also demonstrated that more hindered aldehydes such as 2-Br-benzaldehyde prefer the oxygenative pathway[63]. Nowadays, organic oxidants are the most employed reactants in NHC-catalyzed oxidative transformations. The first organic oxidants used were the aromatic nitro and nitroso derivates[64]. For the reaction mediated by nitro derivates, the following mechanism is widely accepted. The nitrogen atom of the nitro compound undergoes a nucleophilic addition by the Breslow intermediate **105** to generate the intermediate **106**, which is converted into **107** by intramolecular proton transfer. Finally, fragmentation of **107** affords the acyl azolium intermediate, the corresponding nitroso derivate and the hydroxyl anion (Scheme 56).



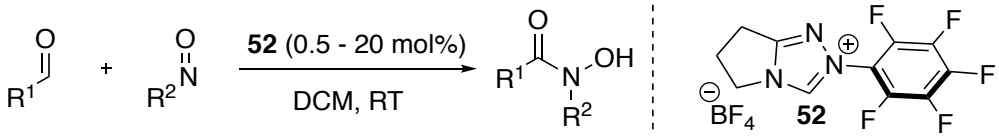
Scheme 56. Proposed mechanism for the NHC-catalyzed oxidation of aldehydes by nitro derivates

Nitroso compounds have also been employed as external oxidants and two reaction mechanisms have been postulated. The first one involves as the key step the consecutive double electrons transfer from the enaminol **105** to the nitroso functional group. In the second hypothesis, the Breslow intermediate acts as a nucleophile attacking the nitroso compound onto the nitrogen in order to form the hydroxy amide **106**[65]. In general, it has been demonstrated that both mechanisms are feasible depending on the substrate. In fact, in some cases, the hydroxylamine derivate was detected in large amount, suggesting that the reaction was dominated by the electron transfer mechanism. Vice versa, changing the features of the substrates resulted in the formation of the hydroxylamine just in traces (Scheme 57).



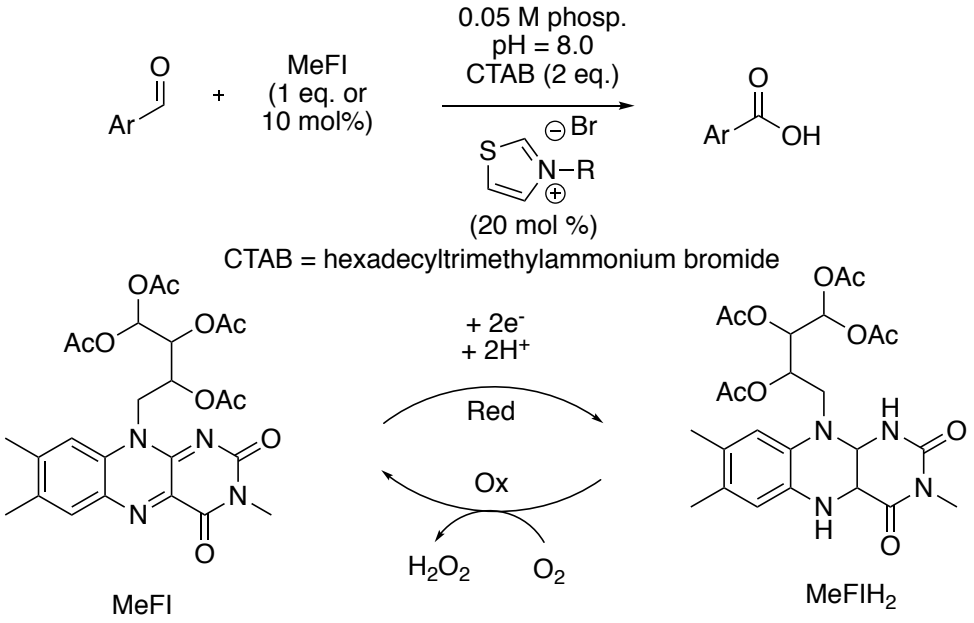
Scheme 57. Postulated mechanisms for the NHC-catalyzed oxidation by nitroso derivates

Seayad and co-workers reported an efficient conversion of aldehydes into the corresponding hydroxamic derivates promoted by a triazolium catalyst using nitrosoarenes as external oxidants (Scheme 58)[66].



Scheme 58. Direct Amidation of Aldehydes with Nitroso Compounds reported by Seayad

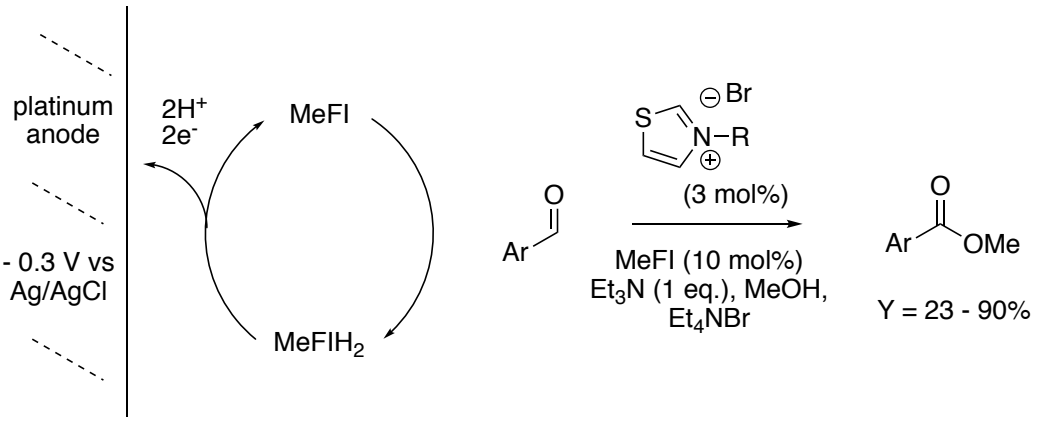
Furthermore, the authors demonstrated that the reaction could be used for the kinetic resolution of α-branched aldehydes, though with a moderated selectivity. Inspired by the mechanism of the pyruvate dehydrogenase, which uses thiamine pyrophosphate (TPP) and flavin adenine dinucleotide (FAD) to obtain acetic acid from pyruvic acid, Shinkai and Yano studied a non-enzymatic version using methyl tetra-O-acetyl riboflavin (MeFI) as electron reservoir for the oxidation of the Breslow intermediate [67]. Interestingly, the reaction was performed in water employing a micelle solution of thiazolium salt pre-catalyst. Water also acted as nucleophile to intercept the acyl azolium intermediate generated in the presence of catalytic amounts of MeFI and molecular oxygen as terminal oxidant (Scheme 59).



Scheme 59. Oxidation of Aldehydes using MeFI as oxidant

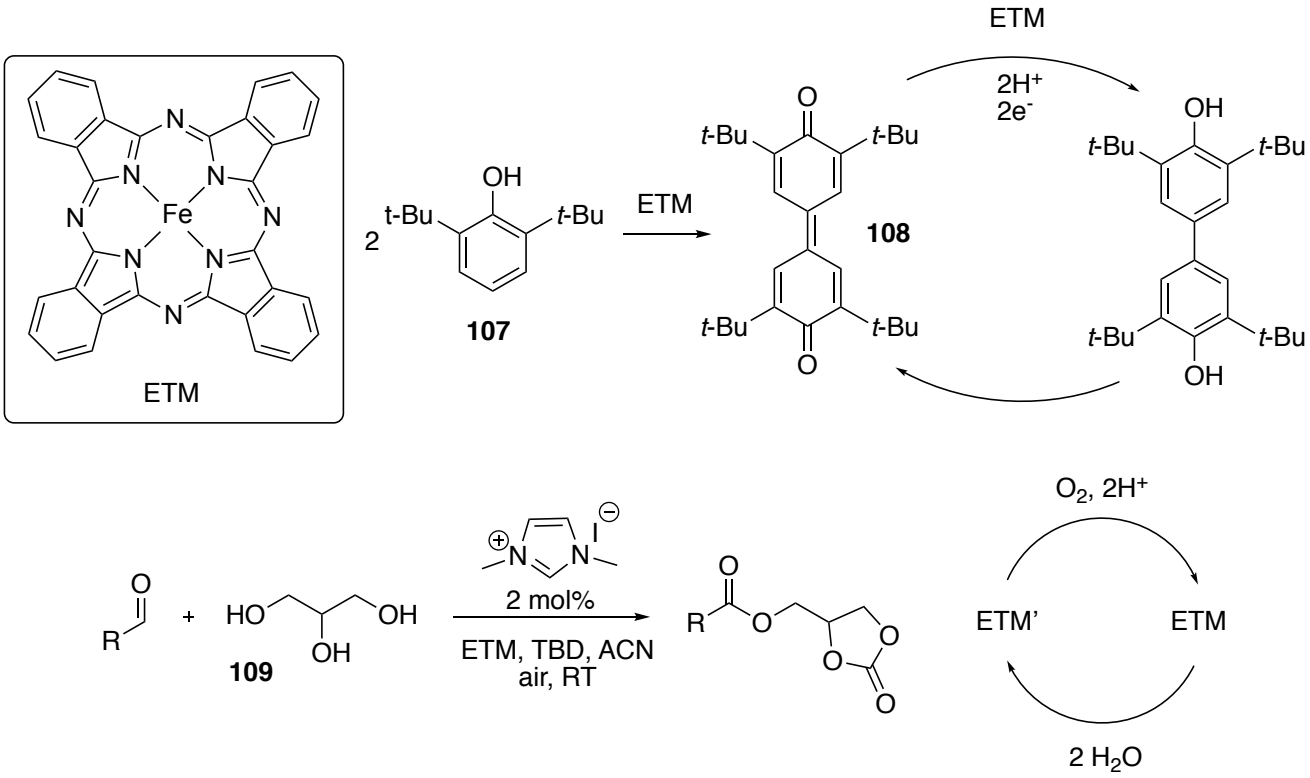
MeFI was found to be a versatile mediator in NHC-catalyzed oxidative reactions and other methods were disclosed to regenerate in situ the mediator. For example, Diederich and co-workers reported that MeFI could be regenerated electrochemically in an argon atmosphere at low voltage (-0.3 V) avoiding the destruction of the NHC. The authors presented a methodology in which was possible to

oxidize aromatic aldehydes to methyl ester employing a glassy carbon rod cathode and a platinum plate anode and the mediator in catalytic amount (Scheme 60)[68].



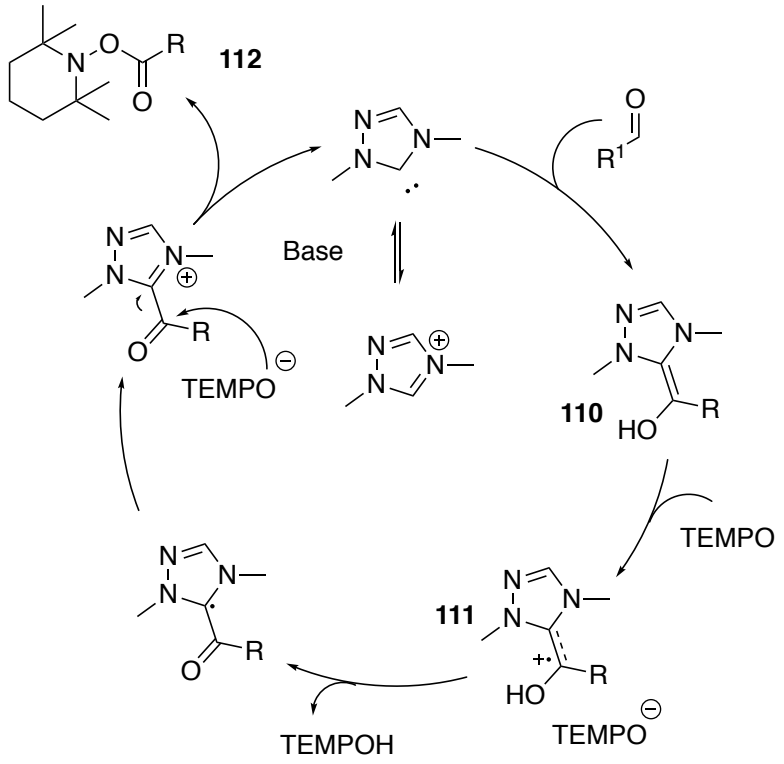
Scheme 60. Electrochemical oxidation of Aldehydes using MeFI

Recently, the use of mediators in the NHC-catalyzed oxidative reaction has gained a remarkable interest. Along this line, Sundèn and co-workers disclosed an efficient biomimetic protocol in which iron (II) phthalocyanine (FePc) is employed as electron transport mediator (ETM) and air as the final electron acceptor[69]. Indeed, the alcohol **107** is converted in situ into the Kharasch oxidant **108**, which is continuously regenerated by the ETM. The authors successfully applied this protocol to the esterification of glycerol **109** using cinnamyl and aromatic aldehydes as the acylating precursors (Scheme 61).



Scheme 61. Glycerol esterification by NHC-catalyzed oxidation of aldehydes

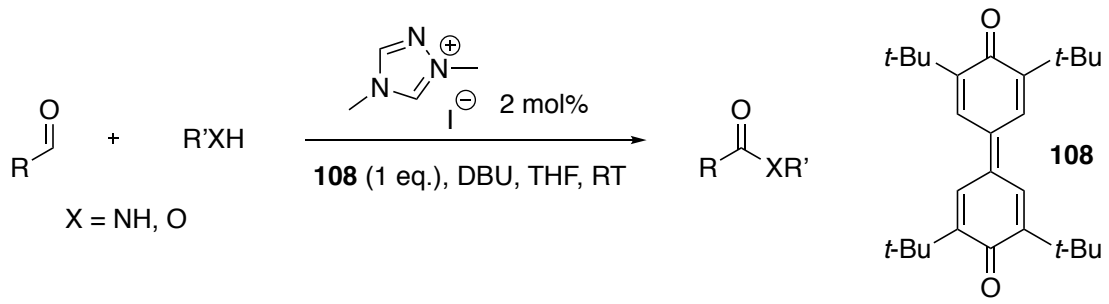
A bioinspired NHC-catalyzed oxidation of aldehydes promoted by the popular electron transfer oxidant 2,2,6,6-tetra-methyl piperidine N-oxyl radical (TEMPO) was reported in 2008 by Studer and co-workers[70]. Several aldehydes were converted into the corresponding TEMPO esters employing cheap triazolium precursors and 2 equivalents of oxidant. A very clean oxidation occurred for aromatic aldehydes while the reaction time needed to be prolonged for aliphatic aldehydes. The proposed mechanism starts with the formation of the Breslow intermediate **110**, which undergoes a first oxidation by TEMPO generating the radical cation **111**. At this point, a deprotonation by the reduced form of TEMPO occurs followed by a second electron transfer to form the acyl azolium, which is rapidly intercepted by the nucleophilic $TEMPO^-$ to generate the corresponding TEMPO ester **112**. The authors found that trapping of the acyl azolium intermediate with TEMPO was too fast to permit the utilization of other nucleophiles in the reaction. Nevertheless, they demonstrated that it was possible to easily convert the TEMPO esters into any generic esters under acidic conditions (Scheme 62).



Scheme 62. NHC-catalyzed oxidation of aldehydes promoted by TEMPO

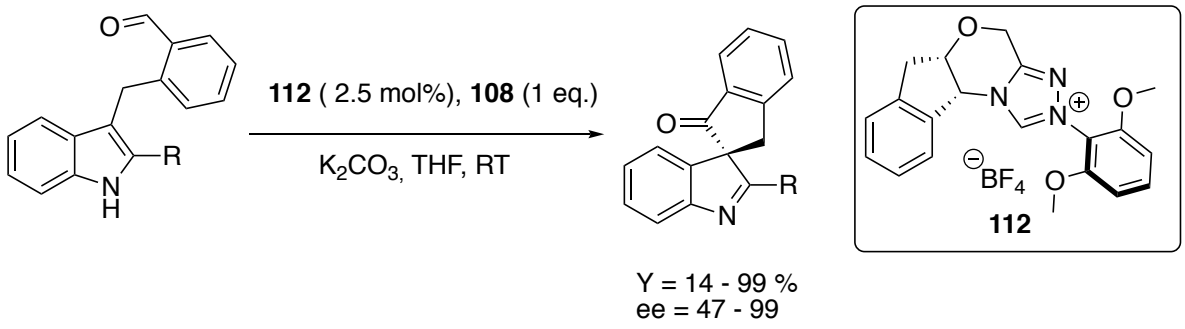
In order to avoid the insertion of the oxidant in the final product, Studer and co-worker searched for a reactant which could act as electron acceptor without showing nucleophilic features. Finally, in 2010 they found the right candidate in the readily available 3,3',5,5'-tetra-*tert*-butyldiphenoquinone **108**. Several aromatic aldehydes were efficiently converted into the corresponding esters with low catalytic loading employing the cheap triazolium salts. Indeed, the bisphenol formed from **108** by

consecutive double SET (single electron transfer) resulted too bulky for reacting with the acyl azolium intermediate (Scheme 63)[71].



Scheme 63. NHC-catalyzed oxidation of aldehydes promoted by Kharasch oxidant

In general, hard nucleophiles are required to intercept the acyl azolium intermediate, thus alcohols and amines are the most employed substrates. However, there are some examples in the literature where carbon nucleophiles are involved in the addition onto the acyl azolium intermediate. In this regard, Studer and co-workers in 2017 reported an elegant protocol for the dearomatization of indoles via an NHC-catalyzed oxidative approach[72]. The reaction is performed using the Kharasch oxidant **108** to generate the acyl azolium intermediate and a C-C bond is formed in intramolecular fashion. The amino indanol-derived triazolium **113** was found to be the best pre-catalyst for this transformation and the authors applied the optimized methodology to a large number of indoles with good yields and excellent enantioselectivities (Scheme 64).



Scheme 64. dearomatization of indole via NHC-catalyzed oxidation of aldehydes

1.3. References

[1] K. Ahrendt, C. J. Borths, D. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[2] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Eng.* **1971**, *10*, 496.

[3] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395.

[4] A. Dondoni, A. Massi, *Angew. Chem. Int. Ed*. **2008**, 47, 4638.

[5] T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, 348, 999.

[6] M. S. Sigman E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 4901.

[7] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, 1, 157.

[8] M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, 45, 1520.

[9] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev*. **2007**, 107, 5606.

[10] D. Seebach, E. J. Corey, *J. Org. Chem*. **1975**, 40, 231.

[11] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 239.

[12] a) A. Patra, S. Mukherjee, T. K. Das, S. Jain, R. G. Gonnade, A. T. Biju, *Angew. Chem. Int. Ed.* **2017**, 56, 2730; b) T. K. Das, S. Mondal, R. G. Gonnade, A. T. Biju, *Org. Lett.* **2017**, 19, 5597; c) A. Patra, F. Gelat, X. Pannecoucke, T. Poisson, T. Besset, A. T. Biju, Org. Lett. **2018**, 20, 1086.

[13] F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249.

[14] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.*, **2000**, 100, 39.

[15] M, N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature*, **2014**, 510, 485.

[16] A. J. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.*, **1991**, 113, 361.

[17] D. Tapu, D. A. Dixon, C. Roe, *Chem. Rev.*, **2009**, 109, 3385.

[18] T. Ugai, R. Tanaka, T. J. Dokawa, *Pharm. Soc. Jpn.*, **1943**, 6, 296.

[19] R. Breslow, *J. Am. Chem. Soc.*, **1958**, 80, 3719.

[20] A. Berkessel, S. Elfert, V. R. Yatham, J. Neudörfl, N. E. Schlörer, J. H. Teles, *Angew. Chem. Int. Ed.*, **2012**, 51, 12370.

[21] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, **2015**, 115, 9307.

[22] a) J. C. Sheehan, T. Hara, *J. Org. Chem.*, **1974**, 39, 1196; b) D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta*, **1996**, 79, 1217; c) R. L. Knight, F. J. Leeper, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 0, 1891; d) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.*, **2009**, 74, 9214.

[23] R. C. Cookson, R. M. Lane, *J. Chem. Soc., Chem. Commun.*, **1976**, 0, 804.

[24] N. Kuhl, F. Glorius, *Chem. Commun.*, **2011**, 47, 573.

[25] P. Haghshenas, M. Gravel, *Org. Lett.*, **2016**, 18, 4518.

[26] X. Linghu, J. R. Potnick, J. S. Johnson, *J. Am. Chem. Soc.*, **2004**, 126, 3070.

[27] A. S. Demir, Ö Reis, A. C. Igdir, I. Esiringű, S. Eymur, *J. Org. Chem.,* **2005**, 70, 10584.

[28] O. Bortolini, G. Fantin, V. Ferretti, M. Fogagnolo, P. P. Giovannini, A. Massi, S. Pacifico, D. Ragno, *Adv. Synth. Catal.*, **2013**, 355, 3244.

[29] H. Stetter, M. Schreckenberg, *Angew. Chem. Int. Ed.*, **1973**, 12, 81.

[30] H. Stetter, J. Krasselt, *J. Heterocycl. Chem.*, **1977**, 0, 573.

[31] J. Tiebes, *Diploma Thesis, RWTH Aachen, Aachen, Germany*, **1990**.

[32] Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.,* **2008**, 130, 14066.

[33] D. A. DiRocco, K. M. Oberg, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.*, **2009**, 131, 10872.

[34] K. R. Law, C. S. P. McErlean, *Chem. Eur. J.*, **2013**, 19, 15852.

[35] D. Enders, A. Henseler, *Adv. Synth. Catal.*, **2009**, 351, 1749.

[36] K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.*, **2009**, 131, 14190.

[37] A. T. Biju, F. Glorius, *Angew. Chem. Int. Ed.*, **2010**, 49, 9761.

[38] D. C. M. Albanese, N. Gaggero, *Catalysts*, **2018**, 8, 181.

[39] a) J. Castells, F. López-Calahorra, M. Bassedas, P. Urrios, *Synthesis*, **1988**, 4, 314; J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.*, **2001**, 123, 9696.

[40] G. Li, L. Dai, S. You, *Chem. Commun.*, **2007**, 0, 852.

[41] S.M. Mennen, J.D. Gipson, Y. Kim, J. S. Miller, *J. Am. Chem. Soc.*, **2005**, 127, 1654.

[42] D. A. DiRocco, T. Rovis, *Angew. Chem. Int. Ed*., **2012**, 51, 5904.

[43] J. Xu, C. Mou, T. Zhu, B. Song, Y. R. Chi, *Org. Lett.*, **2014**, 16, 3272.

[44] a) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.*, **2004**, 126, 14370, b) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.*, **2004**, 43, 6205.

[45] V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.*, **2006**, 128, 8736.

[46] H. Lv, B. Tiwari, J. Mo, C. Xing, Y. R. Chi, *Org. Lett.*, **2012**, 14, 5412.

[47] B. Maji, L. Ji, S. Wang, S. Vedachalam, R. Ganguly, X. Liu, *Angew. Chem. Int. Ed.*, **2012**, 51, 8276.

[48] N. A. White, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.*, **2013**, 135, 8504.

[49] A. Bhunia, A. Patra, V. G. Puranik, A. T. Biju, *Org. Lett.*, **2013**, 15, 1756.

[50] E. Chabrière, X. Vernède, B. Guigliarelli, M. Charon, E. C. Hatchikian, J. C. Fontecilla-Camps, *Science*, **2001**, 294, 2554.

[51] S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.*, **2013**, 19, 4664.

[52] H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.*, **2012**, 354, 1617.

[53] N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.*, **2004**, 126, 9518.

[54] K. Y. Chow, J. W. Bode, *J. Am. Chem. Soc.*, **2004**, 126, 8126.

[55] A. Chan, K. A. Scheidt, *Org. Lett.*, **2005**, 7, 905.

[56] S. S. Sohn, J. W. Bode, *Org. Lett.*, **2005**, 7, 3873.

[57] M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.*, **2006**, 128, 15088.

[58] E. J. Corey, N. W. Gilman, B. E. Ganem, *J. Am. Chem. Soc.*, **1968**, 90, 5616.

[59] B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.*, **2007**, 9, 371.

[60] B. Maji, S. Vedachalan, X. Ge, S. Cai, X. Liu, *J. Org. Chem.*, **2011**, 76, 3016.

[61] Y. Xin, S. Shi, D. Xie, X. Hui, P. Xu, *Eur. J. Org. Chem.*, **2011**, 0, 6527.

[62] O. Bortolini, C. Chiappe, M. Fogagnolo, P. P. Giovannini, A. Massi, C. S. Pomelli, D. Ragno, *Chem. Commun.*, **2014**, 50, 2008.

[63] O. Bortolini, C. Chiappe, M. Fogagnolo, A. Massi, C. S. Pomelli, *J. Org. Chem.*, **2017**, 82, 302.

[64] J. Castells, H. Llitjos, M. Moreno-Manas, *Tetrahedron Lett.*, **1977**, 0, 205.

[65] M. D. Corbett, *Bioorg. Chem.*, **1974**, 3, 361.

[66] F. T. Wong, P. K. Patra, J. Seayad, Y. Zhang, J. Y. Ying, *Org. Lett.*, **2008**, 10, 2333.

[67] S. Shinkai, T. Yamashita, Y. Kusano, O. Manabe, *Tetrahedron Lett.*, **1980**, 21, 2543.

[68] S. Tam, L. Jimenez, F. Diederich, *J. Am. Chem. Soc.*, **1992**, 114, 1503.

[69] A. Axelsson, A. Antoine-Michard, H. Sundén , *Green Chem.*, **2017**, 19, 2477.

[70] J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem. Int. Ed.*, **2008**, 47, 8727.

[71] S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.*, **2010**, 132, 1190.

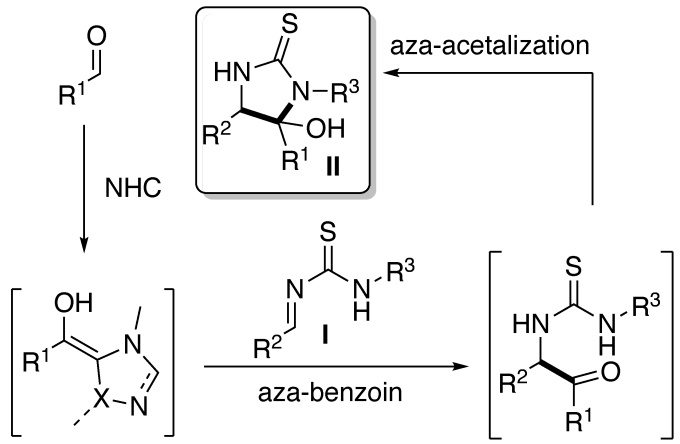
[72] S. Bera, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.*, **2017**, 56, 7402.

2 Synthesis of functionalized imidazolidine-2-thiones via NHC/base-promoted aza-benzoin/ aza-acetalization domino reactions

2.1 introduction

In recent years, Umpolung reactivity has become more and more important as an alternative strategy to conventional carbon–carbon and carbon–heteroatom bond-forming methods[1]. In this context, N-heterocyclic carbenes (NHCs) have been demonstrated to promote a plethora of transformations in both chiral and achiral fashion[2]. Furthermore, NHCs have shown a broad range of applications in the area of domino transformations, allowing to develop powerful protocols for the rapid construction of complex scaffolds[3]. For example, a large number of functionalized carbo- and hetero-cyclic systems have been synthesized by NHC-promoted oxidation/oxa-Michael addition[4], aza-Michael/aldol [5], Mannich/lactamization[6], and Michael/Michael/esterification[7] reaction sequences. Typically, NHCs are mainly employed in benzoin and Stetter reactions, where the umpoled aldehyde reacts with a carbonyl compound[8] or a Michael acceptor[9], respectively. Nevertheless, the use of unconventional reaction partners in umpolung processes has been capturing the attention of synthetic chemists in recent years[10]. For example, arynes, non-activated C–C double or triple bonds, and activated alkyl or aryl halides have been successfully employed in hydroacylation[11] and nucleophilic substitution reactions[12]. Very recently NHCs have been used in the polarity reversal of α,β-unsaturated esters[13], enones[14], and styrenes[15] as well as in the addition to alkyl halides[16], iminium salts[17], aldimines[18], and isocyanides[19]. Moreover, our group has recently demonstrated that α-diketones can be employed as alternative acyl anion donors in nucleophilic acylations by the umpolung strategy[20]. As a further extension of our interest in the field of NHC-catalyzed umpolung reactions, we have introduced a novel class of acyl anion acceptors, namely benzylidenethioureas **I**, and we have demonstrated their synthetic utility in domino processes for the synthesis of the 5-hydroxy-imidazolidine-2-thione scaffold **II** (Scheme 1)[21]. Imidazolidine-2-thiones and the corresponding imidazole-2-thione derivates are special classes of biologically relevant thiourea derivatives[22], which have shown antithyroid[23], antitumor[24], antimicrobial [25], and dopamine inhibition activities[26]. Even though the relevance of this class of compounds is out of the question, the synthesis of imidazole/imidazolidine-2-thiones is still an open challenge. Generally, either harsh reaction conditions are required or access to starting materials is somewhat difficult. Typical procedures for the preparation of imidazolidine-2-thiones are: i) the addition of phenylisothiocyanate to α-aminoketones[27], ii) the reaction with the diethyl acetal of aminoacetaldehyde and isothiocyanates[28], and iii) the cyclization of N,N′-disubstituted thioureas with carbonyl compounds[29]. Furthermore, the condensation of benzoin with either N-substituted or N,N′-disubstituted thioureas have been exploited to obtain imidazole-2-thione derivatives[30]. Recently, the base-promoted metal-free hydroamination of propargylamines with isothiocyanates has

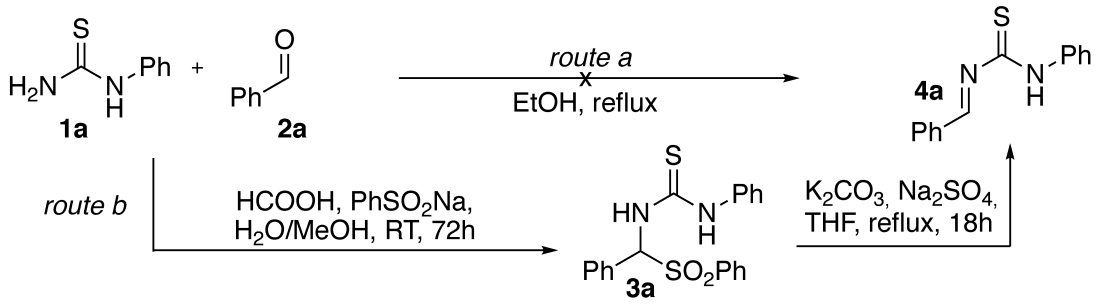
been reported to achieve imidazole-2-thiones and spirocyclic imidazolidine-2-thiones[31]. In our retro-synthetic analysis, we envisaged that the Breslow intermediate derived from the condensation of a simple aldehyde and an NHC, could promote an aza-benzoin reaction in the presence of the benzylidenethiourea acceptor **I** to access the adduct, which then takes part in a one-pot domino sequence via an aza-acetalization reaction in a fully atom economical manner (Scheme 1).



Scheme 1. Envisioned strategy for the synthesis of imidazolidine-2-thiones via domino process

2.2 results and discussion

At the outset of our project, we tried to prepare the benzylidenethiourea **4a** by condensation of N-phenylthiourea **1a** and benzaldehyde **2a** under literature conditions[32], but we were not able to obtain the desired product (Scheme 2, route a). Therefore, an optimization study was carried out. In this regard, the well-established protocol for the preparation of N-Boc imines was adopted[33]. Accordingly, coupling of **1a** and **2a** (2.0 equiv.) in the presence of sodium benzenesulfinate (2.5 equiv.) and formic acid (2.0 equiv.) in methanol/water (1:2 v/v) at room temperature for 72 h produced the desired α-sulfonylamine derivate **3a** in satisfactory 62% yield (Scheme 2, route b). Unfortunately, when **3a** was treated with K_2CO_3, in THF at reflux for 18 h to access the corresponding imine, the only isolable products were **1a** and **2a** produced by the hydrolysis of the ephemeral benzylidenethiourea **4a**.



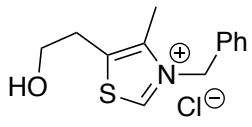
Scheme 2. Attempts to synthesize the benzylidenethiourea **4a**

Thus, in order to circumvent the problem relative to the isolation of **4a**, we envisaged the possibility to use the α-sulfonylamine precursor **3a** in the planned domino sequence, expecting that the base employed to form the NHC active species could also promote the formation of the actual imine acceptor **4a** directly in situ (Table 1).

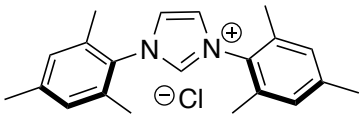
Table 1. Optimization of the model domino transformation to afford imidazolidine-2-thione **5a**[a]

Entry	NHC*HX (mol%)	Base	Yield[b]	d.r.[c]
1	**C1**(10)	TEA[d]	50	83/17
2	**C2**(10)	TEA[d]	Trace	-
3	**C3**(10)	TEA[d]	0	-
4	**C4**(10)	TEA[d]	0	-
5	**C5**(10)	TEA[d]	0	-
6	**C6**(10)	TEA[d]	11	81/19
7	**C1**(10)	Cs_2CO_3[d]	Trace[e]	-
8	**C1**(10)	DIPEA	22	80/20
9	**C1**(10)	DBU	39	83/17
10[f]	**C1**(10)	TEA	0	-
11[g]	**C1**(10)	TEA	0	-
12[h]	**C1**(10)	TEA	Trace[e]	-
13	**C1**(10)	TEA[i]	48	86/14
14	**C1**(10)	TEA[j]	51	86/14
15[k]	**C1**(10)	TEA[j]	42	85/15
16[l]	**C1**(10)	TEA[j]	60	86/14

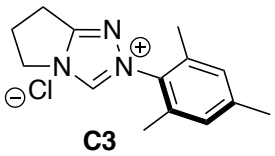
17[l]	**C1**(10)	TEA[j]	76	85/15



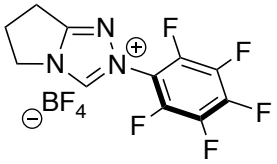
C1



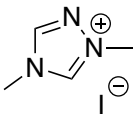
C2



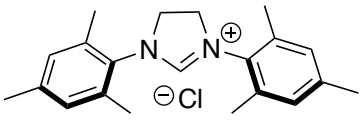
C3



C4



C5

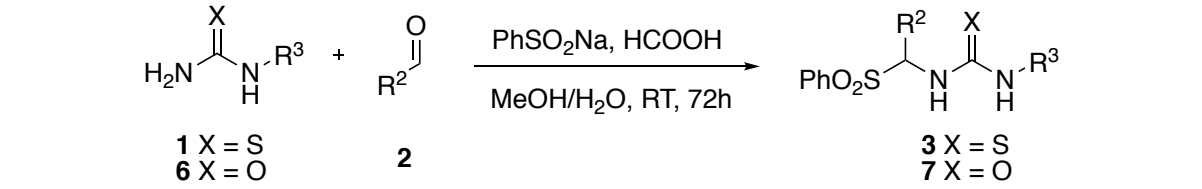


C6

[a]Reaction conditions: **3a** (0.5 mmol), **2b** (0.55 mmol), NHC*HX, base and 4 Å molecular sieves in DCM at 35 °C for 16 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]15 equiv. of base were used. [e]Detected by ^{1}H NMR analysis of the crude reaction mixture. [f]Reaction performed in toluene. [g]Reaction performed in DMSO. [h]Reaction performed in THF. [i]1.5 equiv. of TEA used. [j]3.0 equiv. of TEA used. [k]Reaction run at 25 °C. [l]Reaction run at 30 °C.

Therefore, the α-sulfonylamine **3a** and 4-chlorobenzaldehyde **1b** (1.1 equiv.) were led to react in DCM at 35 °C for 16 h in the presence of 4 Å molecular sieves utilizing the thiazolium chloride **C1** (10 mol%) as the pre-catalyst and an excess of TEA (15 equiv.) as the base[34]. Under these conditions, the target imidazolidine-2-thione **5a** was formed in 50% isolated yield as an inseparable mixture of diastereoisomers in 83:17 ratio (entry 1). Encouraged by this result, we started to test different pre-catalysts. **C2–6** were screened under the same conditions and the target **5a** was observed in only traces with the imidazolium salt **C2** (entry 2). The triazolium pre-catalysts **C3**, **C4**, and **C5** were completely ineffective (entries 3–5), while the imidazolinium salt **C6** gave access to **5a** in poor yield (11%, entry 6). At this point, we moved to screen the bases holding the pre-catalyst **C1** in DCM. The data collected revealed that the inorganic base Cs_2CO_3 caused a decreasing in terms of yield (entry 7); diisopropylethylamine and DBU shown less efficacy than triethylamine (entries 8 and 9). In particular, the stronger DBU base promoted the fast dehydration of **5a** to the corresponding imidazole-2-thione derivative. Different solvents were also tested (Toluene, DMSO, THF). However, DCM remained the optimal reaction medium (entries 10–12). The use of lower amounts of triethylamine (3.0 and 1.5 equiv.) did not significantly affect the yield but slightly increased the diastereoselectivity (entries 13 and 14). A study on the temperature effect was also performed. This showed that a partial loss of efficiency was achieved at 25 °C (entry 15), while the yield of **5a** raised to 60% when the domino sequence was performed at 30 °C (entry 16). A gratifying 76% yield was finally obtained at this temperature by increasing the catalyst loading to 20 mol% (entry 17). With the optimal conditions in hand, the generality of the reaction was next studied by first considering the scope of the synthesis of α-sulfonylamines **3** (Table 2).

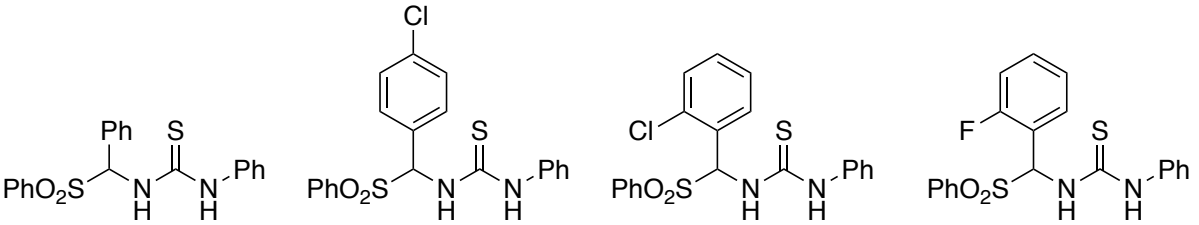
Table 2. Synthesis of α-sulfonylamines **3** and **7**[a]



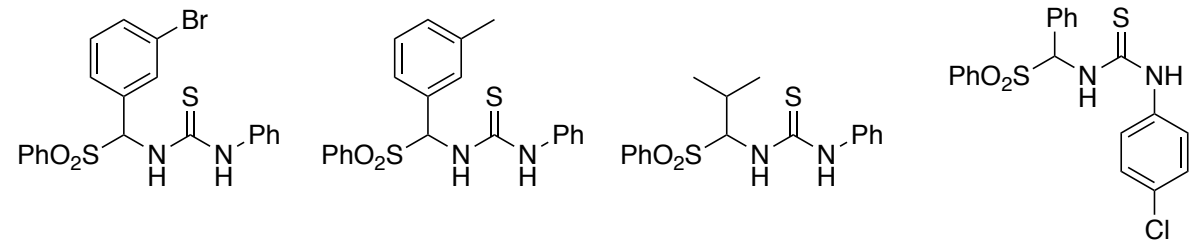
1 X = S
6 X = O

2

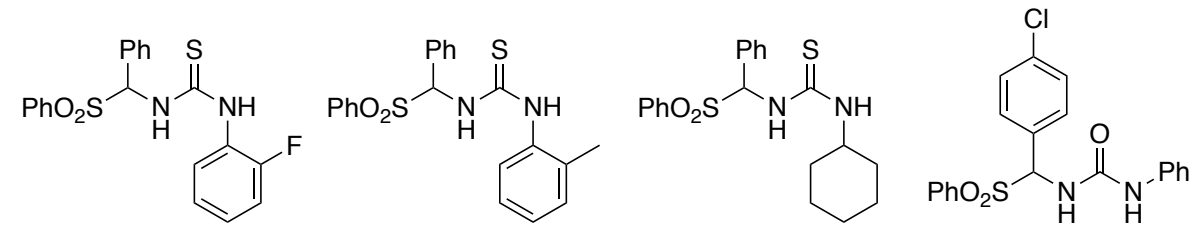
3 X = S
7 X = O



3a, 62% **3b**, 73% **3c**, 66% **3d**, 72%



3e, 53% **3f**, 64% **3g**, 50% **3h**, 50%



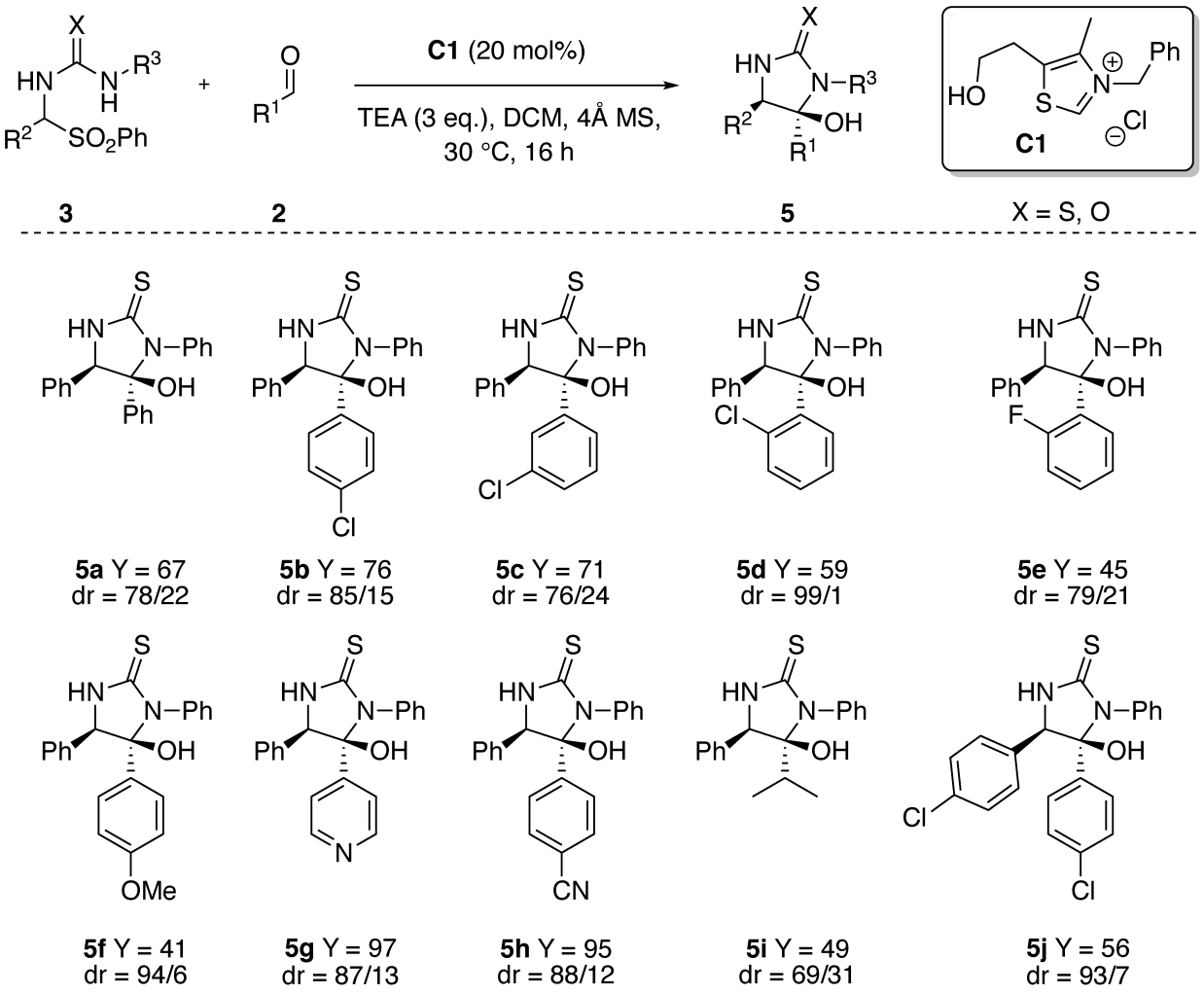
3a, 62% **3b**, 73% **3c**, 66% **3d**, 72%

[a]Typical reaction conditions: **2** (20 mmol), **1** or **6** (10 mmol), benzenesulfinic acid sodium salt (25 mmol) and formic acid (55% w/w in water, 0.76 mL, 20 mmol) in H_2O (20 mL) and MeOH (10mL) at RT for 72h.

The reactivity of substituted aromatic aldehydes **2b–f** (**b**: 4-ClPh; **c**: 2-ClPh; **d**: 2-FPh; **e**: 3-BrPh; **f**: 3-MePh) with N-phenylthiourea **1a** was found to be similar that of model substrate **2a**. An increasing of reactivity (Y = 66–73%) was observed for substrates bearing a halogen in the ortho-position (**3c**, **3d**) or the para-position (**3b**) compared with the meta-substituted analog (**3e**; 53%). Furthermore, reaction with m-tolualdehyde allowed to obtain the product with a good yield (64%) comparable to that of benzaldehyde (**3a**). Unfortunately, a partial decrease in reactivity was observed employing aliphatic aldehyde **2g** (**g**: i-Pr; **3g**: 50%). Moreover, α-sulfonylamines **3h**, **3i**, **3j**, and **3k** were prepared by reacting benzaldehyde **2a** with thioureas **1b**,**d**,**h**,**i** placing different N-substituents (**h**: 2-MePh; **i**: cyclohexyl). In all cases the reactivity was inferior irrespective of the electronic characteristic of the

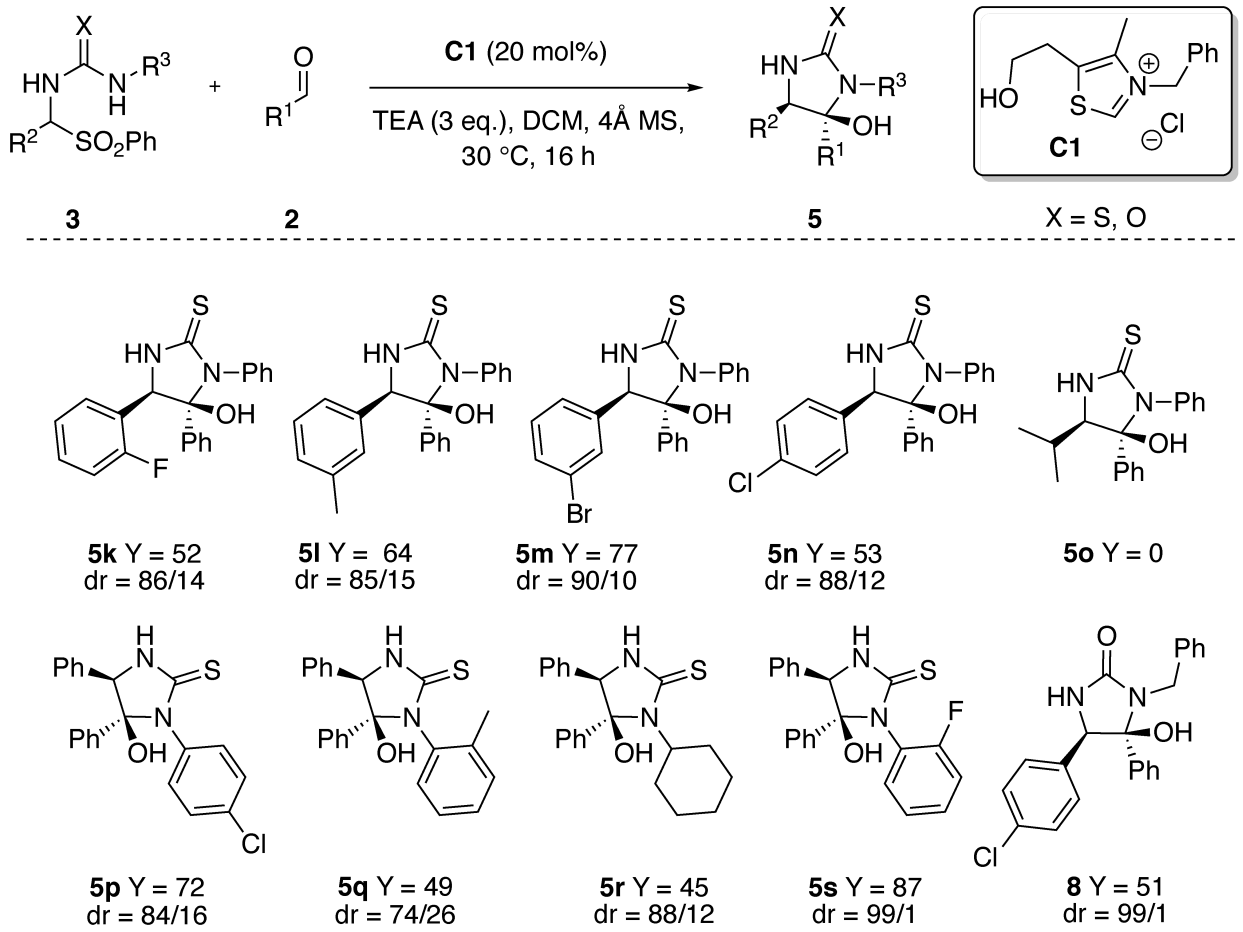
substituent on the nitrogen atom. Finally, envisaging the possibility to extend the domino sequence to benzylideneurea derivatives, we attempted the use of 3-benzylurea **6** (Bn) collecting the N-substituted urea **7** in a remarkable 81% yield. The optimal conditions of the domino sequence (Table 1, entry 17) were next applied to different combinations of substrates **2** and **3**/**7** (Table 3).

Table 3. Scope of the domino reaction, part a[a]



[a]Typical reaction conditions: **2** (1.2 mmol), **3** (1 mmol), **C1** (0.2 mmol), 4 Å MS, TEA (3.0 mmol) in DCM (5 mL) at 30 °C for 16 h. [b]Reaction run with 2.0 equiv. of 1. [c]See the Experimental section.

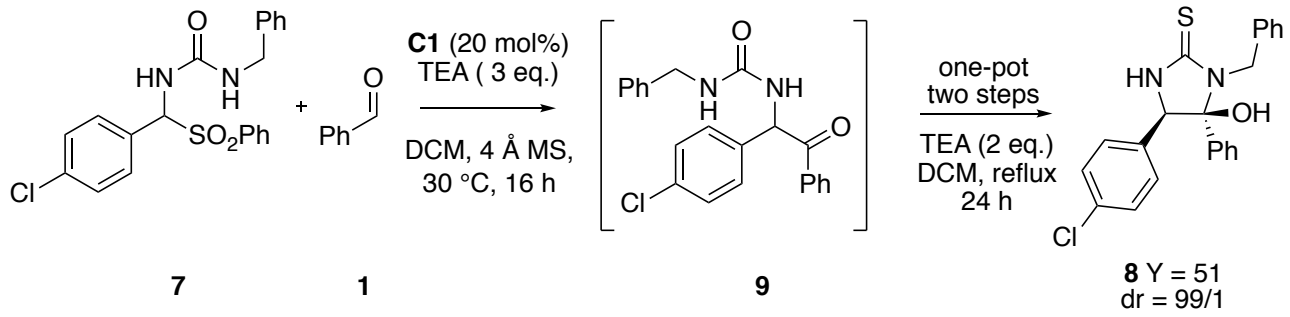
Table 3. Scope of the domino reaction, part b[a]



[a]Typical reaction conditions: **2** (1.2 mmol), **3** (1 mmol), **C1** (0.2 mmol), 4 Å MS, TEA (3.0 mmol) in DCM (5 mL) at 30 °C for 16 h. [b]Reaction run with 2.0 equiv. of 1. [c]See the Experimental section.

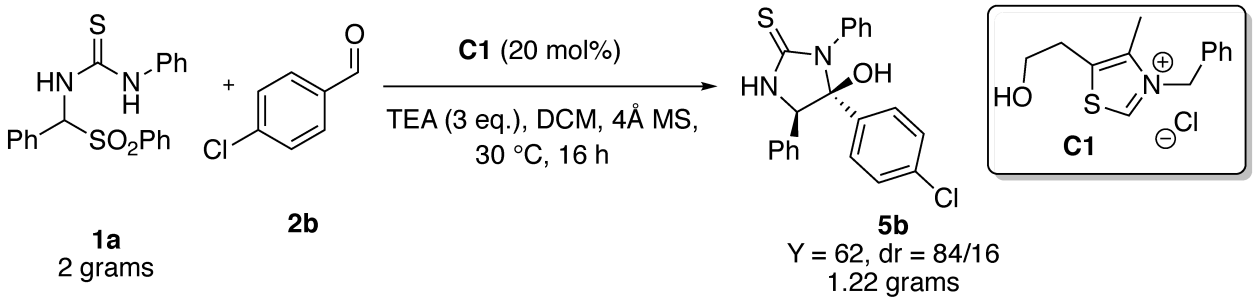
We started the study employing the α-sulfonylamine **3a** as the reacting partner of several aldehyde donors **2** bearing different steric and/or electronic features. Within the series of halogen-substituted benzaldehydes, we observed that both yields and diastereoselectivities were influenced by either the character or the position of the halogen atom. 2-Chlorobenzaldehyde **2c** and 2-fluorobenzaldehyde **2d** showed less reactivity than 4-Chlorobenzaldehyde **2b** and 3-Chlorobenzaldehyde **2k** likely because of steric effects (**5d** and **5e** vs. **5b** and **5c**). The best result in terms of diastereoselectivity was obtained for the compound **5d**, which bears a chlorine atom in ortho position. Probably, the steric hindrance made more selective the closing step towards a single diastereoisomer. However, in the case of the 2-fluoro-substituted analog **5e** this effect was not observed maybe because of the size of the fluorine atom, which is comparable to that of a hydrogen atom. Predictably, the electron-poor donors **2m** and **2n** (m: 4-pyridyl; n: 4-CNPh) leading to **5g** and **5h**, respectively, performed much better than the electron-neutral benzaldehyde **2a**, while the electron-rich donor **2l** (l: 4-OMePh) gave **5f** in poor yield with high diastereoselectivity. A substantial maintenance of reaction efficiency was

also observed for **5i** starting from isobutyraldehyde **2g**, which is usually a poor reactive in NHC-catalyzed umpolung transformations. At this point, we moved to explore the electronic and steric effects on the position R^2 and modest to good yields were obtained for products **5** bearing electron-rich and halogen-substituted aromatic moieties (**5j**, **5k**, **5l**, **5m**, **5n**). The desired product was not detected for the alkyl substituted derivative **5o**. Finally, we found that changing the substituents on the nitrogen there was not a suppression in terms of reactivity (**5p**, **5q**, **5r**, **5s**). However, better results were observed in the presence of halogen-substituted aromatic residues (**5p**, **5s**), which likely made the aniline proton more acidic facilitating the ring-closing step. As a general consideration, a higher excess (2.0 equiv.) of aldehyde was found to be required in some combinations (**5f**, **5i**, **5k**, **5m**, **5n**) to surmount the side competition of the more reactive aldehyde, formed in situ by hydrolysis of the benzylidene-thiourea acceptor. Interestingly, we observed that for the synthesis of imidazolidine-2-one **8** a slight adjustment in the procedure was required. The reaction of urea **7** with benzaldehyde **2a** (2.0 equiv.) proceeded in a one-pot, two-step mode and the second step was less favored than the ring-closing for thiourea derivates **3**. In fact, under the optimized reaction conditions, the aza-benzoin adduct **9** was predominantly detected by ^{1}H NMR analysis of the crude reaction mixture. However, addition of supplementary triethylamine base (2.0 equiv.) and heating at reflux for 24 h allowed to access the expected cyclization product **8** in 51% yield with very high diastereoselectivity (dr = 99/1). The electronic effect caused by the presence of the oxygen atom likely made the aza-acetalization process more energetically demanding (Scheme 3).



Scheme 3. Synthesis of Imidazolidine-2-one **8**

We also demonstrated that this domino protocol could be run under optimized conditions on gram scale without losing reactivity or diastereoselectivity and with improved practicality. Accordingly, the α-sulfonylamine **3a** (2 grams) was reacted with 4-chlorobenzaldehyde **2b** to obtain the expected compound **5b** in 62% yield and 84/16 diastereomeric ratio after purification by recrystallization (Scheme 4).



Scheme 4. Preparative gram scale of imidazolidine-2-thione **5b**

HMQC and ROESY experiments were performed to determine the relative configuration of diastereomeric imidazolidine-2-thiones **5** by using the pyridyl-substituted derivative **5g**. A correlation between δ 5.68 (H-4 imidazoline ring) and δ 7.80 (H-3′ pyridyl ring) for the major diastereoisomer was detected as shown in Figure 1, thus supporting a relative syn configuration of the phenyl and hydroxyl substituents at C4 and C5 of the imidazolidine-2-thione ring.

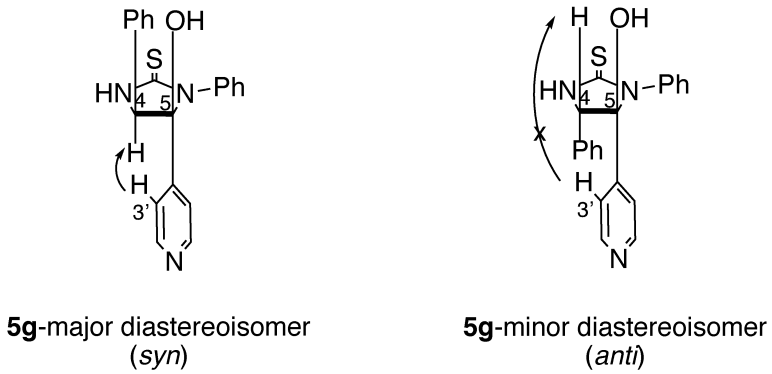
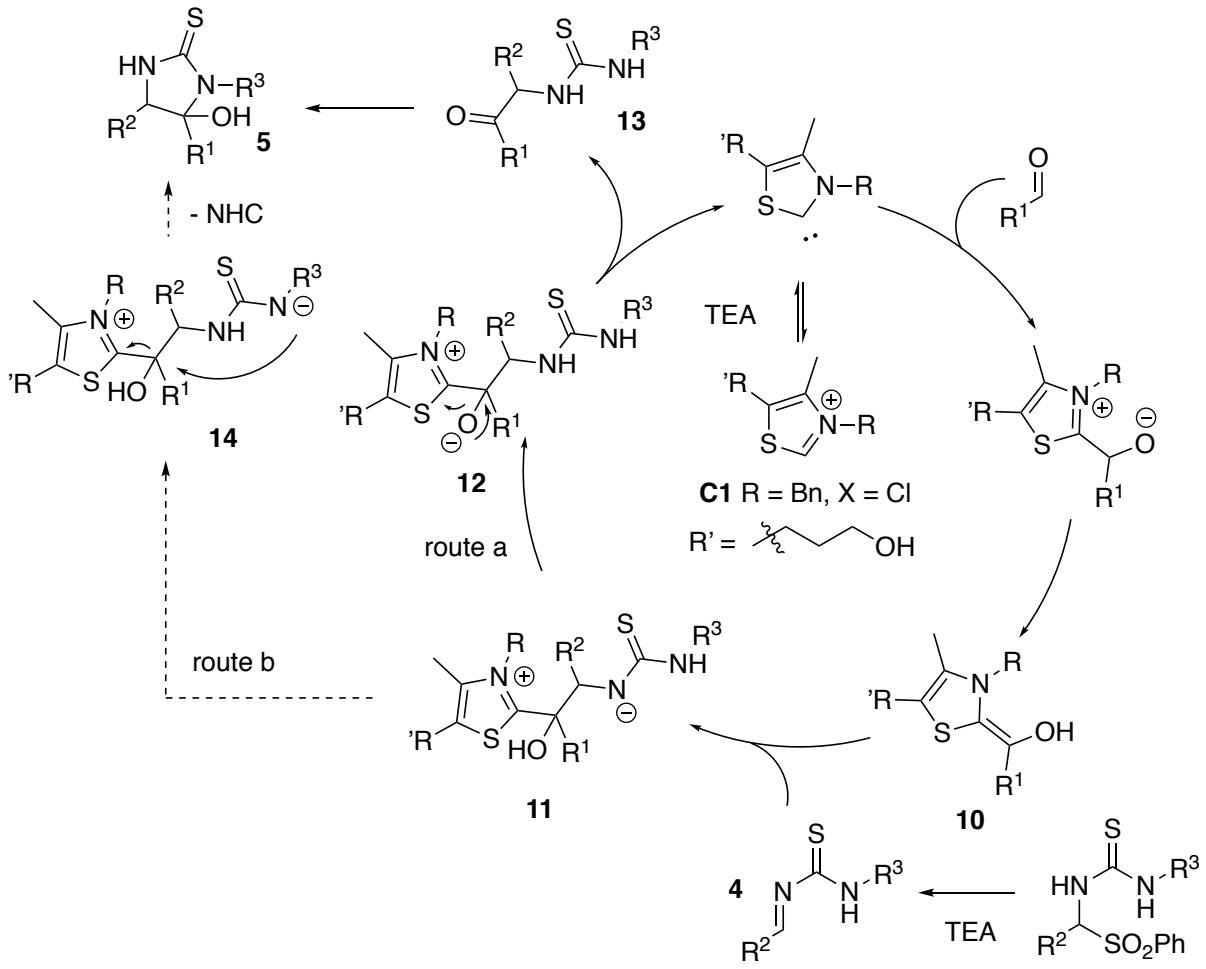


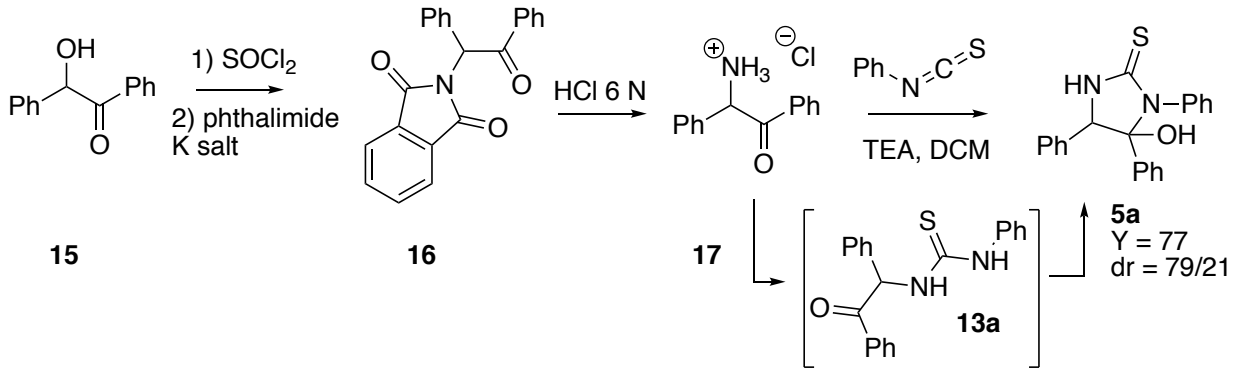
Figure 1. Stereochemical assignment of **5g**

The assignment was corroborated by the concomitant absence of correlation for the minor diastereoisomer of **5g** and was extended to all products **5** by analogy. Two plausible mechanisms were rationalized for the domino sequence (Scheme 5).



Scheme 5. Proposed mechanisms for the domino process

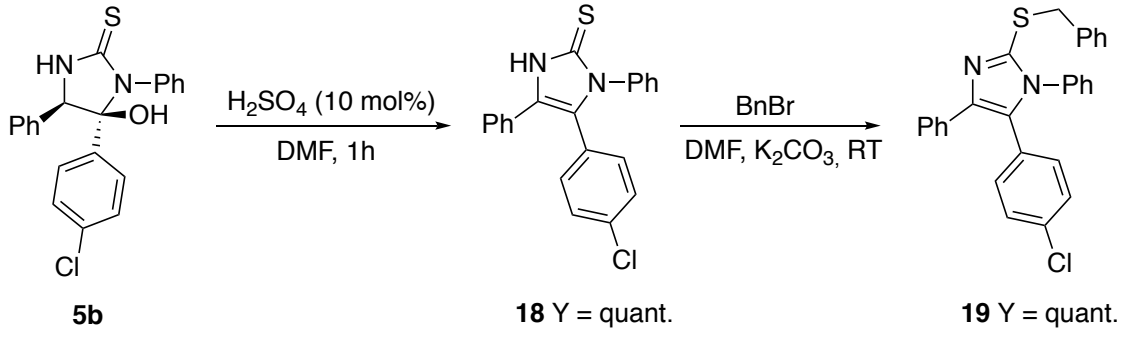
The attack of the enaminol intermediate **10** on the in situ generated imine **4** forms the alkoxide **12** through the intermediate **11** (route a). At this point, the NHC is released along with the aza-benzoin adduct **13**, which can take part in the aza-acetalization reaction to afford the imidazolidine-2-thione **5**. On the other side, the direct intramolecular S_N2 reaction of anion **14** originating from the common intermediate **11** is possible (route b). The first route of our mechanistic proposal was partially validated by the control experiment described in Scheme 6, which is characterized by the synthesis of key intermediates.



Scheme 6. Experiment for mechanism elucidation

First of all, the benzoin **15** was turned into the ammonium salt **17** via well-known synthetic methodologies; intermediate **17** was then treated with the Edman's reagent under the optimal conditions previously found for the domino sequence (TEA, DCM), affording the imidazolidine-2-thione **5a** in 77% yield. Since the reaction between phenylisothiocyanate and **17** is expected to form the adduct **13a**, one may conclude that the latter represents the actual precursor of the imidazolidine-2-thione **5a**. Thus, this result makes more probable that the ring-closing step takes place after the release of the NHC in the catalytic cycle (route a; Scheme 5) rather than through a S_N2 mechanism (route b). This conclusion is further supported by the analysis of the diastereoselectivity of compound **5a** that seems to be not affected by the structure of the NHC.

Finally, we presented a simple synthetic elaboration of **5b** towards imidazole-2-thione derivatives, keeping in mind the biological importance of these class of molecules (Scheme 7)[35]. Hence, dehydration of **5b** (H_2SO_4, DMF, reflux, 1 h), followed by an alkylation step (BnBr, K_2CO_3, DMF, RT) were performed to achieve compound **19**, which was collected in quantitative yield without purification of the intermediate **18**[36].



Scheme 7. Synthetic elaboration of **5b** to access biologically relevant S-alkyl-imidazole derivates

2.3. References

[1] a) E. J. Corey, *Pure Appl. Chem.*, **1967**, 14, 19; b) B.-T. Gröbel, D. Seebach, *Synthesis*, **1977**, 357; c) D. Seebach, Angew. *Chem., Int. Ed. Engl.*, **1979**, 18, 239.

[2] For selected recent reviews on NHC catalysis, see: a) Q. Ren, M. Li, L. Yuan, J. Wang, *Org. Biomol. Chem.*, **2017**, 15, 4731; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, **2015**, 115, 9307; c) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature*, **2014**, 510, 485; d) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem., Int. Ed.*, **2012**, 51, 11686; e) X. Bugaut, F. Glorius, *Chem. Soc. Rev.*, **2012**, 354, 3511; f) J. L. Moore, T. Rovis, *Top. Curr. Chem.*, **2010**, 291, 77; g) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta*, **2009**, 42, 55; h) D. Enders, A. A. Narine, *J. Org. Chem.*, **2008**, 73, 7857; i) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.*, **2007**, 107, 5606; j) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.*, **2007**, 46, 2988.

[3] For selected reviews on NHC-catalyzed domino processes, see: a) P. Chauhan, D. Enders, *Angew. Chem., Int. Ed.*, **2014**, 53, 1485; b) A. Grossmann, D. Enders, *Angew. Chem., Int. Ed.*, **2012**, 51, 314; c) M. Fleige, F. Glorius, *Chem. Eur. J.*, **2017**, 23, 10773.

[4] S. W. Youn, H. S. Song, J. H. Park, *Org. Biomol. Chem.*, **2014**, 12, 2388.

[5] Y. Zhu,C. Cai, *New J. Chem.*, **2015**, 39, 5104.

[6] Q. Ni, X. Song, J. Xiong, G. Raabe, D. Enders, *Chem. Commun.*, **2015**, 51, 1263.

[7] T. Shu, Q. Ni, X. Song, K. Zhao, T. Wu, R. Puttreddy, K. Rissanen, D. Enders, *Chem. Commun.*, **2016**, 52, 2609.

[8] R. S. Menon, A. T. Biju, V. Nair, *Beilstein J. Org. Chem.*, **2016**, 12, 444.

[9] S. R. Yetra, A. Patra, A. T. Biju, *Synthesis*, **2015**, 1357.

[10] A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.*, **2011**, 44, 1182.

[11] For examples of NHC-catalyzed hydroacylation reactions, see: a) D. Janssen-Müller, M. Fleige, D. Schlüns, M. Wollenburg, C. G. Daniliuc, J. Neugebauer, F. Glorius, *ACS Catal.*, **2016**, 6, 5735; b) J. Wu, C. Zhao, J. Wang, *J. Am. Chem. Soc.*, **2016**, 138, 4706; c) D. Janssen- Müller, M. Schedler, M. Fleige, C. G. Daniliuc, F. Glorius, *Angew. Chem., Int. Ed.*, **2015**, 54, 12492; d) M. Schedler, D.-S. Wang, F. Glorius, *Angew. Chem., Int. Ed.*, **2013**, 52, 2585; e) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.*, **2011**, 13, 5624; f) F. Liu, X. Bugaut, M. Schedler, R. Fröhlich, F. Glorius, *Angew. Chem., Int. Ed.*, **2011**, 50, 12626; g) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem., Int. Ed.*, **2011**, 50, 4983.

[12] For examples of NHC-catalyzed substitution reactions, see: a) M. Zhao, J. Chen, H. Yang, L. Zhou, *Chem. Eur. J.*, **2017**, 23, 2783; b) M. Zhao, H. Yang, M.-M. Li, J. Chen, L. Zhou, *Org. Lett.*, **2014**, 16, 2904; c) P. Singh, S. Singh, V. K. Rai, L. D. S. Yadav, *Synlett*, **2010**, 2649; d) V. P. Mehta, A. K. Sharma, S. G. Modha, S. Sharma, T. Meganathan, V. S. Parmar, E. Van der Eycken, *J. Org. Chem.*, **2011**, 76, 2920.

[13] a) C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.*, **2006**, 128, 1472; b) S. Matsuoka, Y. Ota, A. Washio, A. Katada, K. Ichioka, K. Takagi, M. Suzuki, *Org. Lett.*, **2011**, 13, 3722; (c) A. T. Biju, M. Padmanaban, N. E. Wurz, F. Glorius, *Angew. Chem., Int. Ed.*, **2011**, 50, 8412.

[14] Y. Nakano, D. W. Lupton, *Angew. Chem., Int. Ed.*, **2016**, 55, 3135.

[15] a) M. Schedler, D.-S. Wang, F. Glorius, *Angew. Chem. Int. Ed.*, **2013**, 52, 2585; b) M. Schedler, N. E. Wurz, C. G. Daniliuc, F. Glorius, *Org. Lett.*, **2014**, 16, 3134.

[16] (a) B. Maji, M. Horn, H. Mayr, *Angew. Chem., Int. Ed.*, **2012**, 51, 6231; (b) C. E. I. Knappke, A. J. Arduengo III, H. Jiao, J.-M. Neudörfl, A. J. von Wangelin, *Synthesis*, **2011**, 3784; (c) C. E. I. Knappke, J.-M. Neudörfl, A. J. von Wangelin, *Org. Biomol. Chem.*, **2010**, 8, 1695.

[17] D. A. DiRocco, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.*, **2012**, 134, 6143.

[18] a) A. Patra, S. Mukherjee, T. K. Das, S. Jain, R. G. Gonnade, A. T. Biju, *Angew. Chem. Int. Ed.*, **2017**, 56, 2730; b) Y. Wu, L. Hu, Z. Li and L. Deng, *Nature*, **2015**, 523, 445; c) M. Waser and J. Novacek, *Angew. Chem. Int. Ed.*, **2015**, 54, 14228.

[19] J. Kim and S. H. Hong, *Chem. Sci.*, **2017**, 8, 2401.

[20] a) O. Bortolini, G. Fantin, V. Ferretti, M. Fogagnolo, P. P. Giovannini, A. Massi, S. Pacifico, D. Ragno, *Adv. Synth. Catal.*, **2013**, 355, 3244, b) D. Ragno, O. Bortolini, P. P. Giovannini, A. Massi, S. Pacifico, A. Zaghi, *Org. Biomol. Chem.*, **2014**, 12, 5733; c) D. Ragno, O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Massi, *J. Org. Chem.*, **2015**, 17, 1937.

[21] a) L. Tian, Y.-C. Luo, X.-Q. Hu, P.-F. Xu, *Asian J. Org. Chem.*, **2016**, 5, 580; b) A. Bhaumik, R. S. Verma, B. Tiwari, *Org. Lett.*, **2017**, 19, 444; c) Q. Wu, C. Li, W. Wang, H. Wang, D. Pana, P. Zheng, *Org. Chem. Front.*, **2017**, 4, 2323.

[22] J. K. Savjani, A. K. Gajjar, Pak., *J. Biol. Sci.*, **2011**, 14, 1076.

[23] a) F. Isaia, M. C. Aragoni, M. Arca, F. Demartin, F. A. Devillanova, G. Floris, A. Garau, M. B. Hursthouse, V. Lippolis, R. Medda, F. Oppo, M. Pira, G. Verani, *J. Med. Chem.*, **2008**, 51, 4050.

[24] (a) Nisha, P. Singh, D. T. Hendricks, K. Bisetty, V. Kumar, *Synlett*, **2013**, 24, 1865; (b) S. Cesarini, A. Spallarossa, A. Ranise, S. Schenone, C. Rosano, P. La Colla, G. Sanna, B. Busonera, R. Loddo, *Eur. J. Med. Chem.*, **2009**, 44, 1106.

[25] M. A. Salama, L. A. Almotabacani, *Phosphorus, Sulfur Silicon Relat. Elem.*, **2004**, 174, 305.

[26] A. Beliaev, D. A. Learmonth, P. Soares-da-Silva, *J. Med. Chem.*, **2006**, 49, 1191.

[27] Y. Honma, H. Tamaki, T. Magaribuchi, M. Takido, *U.S. Patent* 4996217, 1991

[28] K. Matsuda, I. Yanagisawa, Y. Isomura, T. Mase and T. Shibanuma, *Synth. Commun.*, **1997**, 28, 3565.

[29] a) G. S. Yellol, C.-T. Chou, W.-J. Chang, B. Maiti, C.-M. Sun, *Adv. Synth. Catal.*, **2012**, 354, 187; b) R.-S. Zeng, J.-P. Zou, S.-J. Zhi, J. Chen, Q. Shen, *Org. Lett.*, **2003**, 5, 1657.

[30] M. Kidwai, S. Kukreja, S. Rastogi, K. Singhal, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **2007**, 1549.

[31] A. Ranjan, R. Yerande, P. B. Wakchaure, S. G. Yerande, D. H. Dethe, *Org. Lett.*, **2014**, 16, 5788.

[32] a) R. Kirithick, U. S. Lakshmipati, M. Ambarish, K. Vignesh Maharaaj, *Polym.-Plast. Technol. Eng.*, **2014**, 54, 497; b) A. P. Mishra, M. Khare, S. K. Gautam, *Synth. React. Inorg. Met.-Org. Chem.*, **2002**, 32, 1485.

[33] D. Wang, P. Cao, B. Wang, T. Jia, Y. Lou, M. Wang, J. Liao, *Org. Lett.*, **2015**, 17, 2420.

[34] J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.*, **2001**, 123, 9696.

[35] a) A. S. Salman, A. Abdel-Aziem, M. J. Alkubbat, *Am. J. Org. Chem.*, **2015**, 80, 57; b) G. Roy, D. Das, G. Mugesh, *Inorg. Chim. Acta*, **2007**, 360, 303.

[36] G. Di Carmine, D. Ragno, C. De Risi, O. Bortolini, P. P. Giovannini, G. Fantin, A. Massi, *Org. Biomol. Chem.*, **2017**, 15, 8788.

2.4. Experimental section

All commercially available reagents were used as received without further purification, unless otherwise stated. Catalysts **C1–6** were purchased from Sigma-Aldrich. Liquid aldehydes and bases were freshly distilled before their utilization. All solvents were dried over standard drying agents. 4 Å MS were activated before use. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ^{1}H (300/400 MHz), ^{13}C (76/101 MHz), and ^{19}F (376 MHz) NMR spectra were recorded in the stated deuterated solvent at room temperature. Peak assignments were aided by ^{1}H–^{1}H COSY and gradient-HMQC experiments. For accurate mass measurements, the compounds were detected in positive ion mode by HPLC-Chip Q/TOF-MS (nanospray) analysis using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. IR spectra were recorded on a PerkinElmer FT-IR Paragon 500 system.

To a vigorously stirred suspension of (thio)urea **2/6** (10.0 mmol), aldehyde **1** (20.0 mmol, 2.0 equiv.), benzenesulfi- nic acid sodium salt (25.0 mmol, 2.5 equiv.) in H_2O (20 mL) and MeOH (10 mL), an aqueous solution of formic acid (55% w/w, 0.760 mL, 20 mmol, 2.0 equiv.) was added in one portion. The suspension was stirred at room temperature for 72 h; then the white fluffy precipitate was filtered and washed with a large amount of Et_2O until the elimination of unreacted alde- hyde to afford the desired product **3** or **7** as a white amorphous solid.

General procedure for the synthesis of α-sulfonylamines

1-Phenyl-3-(phenyl(phenylsulfonyl)methyl)thiourea (3a)

White amorphous solid (2.37 g, 62%). ^{1}H NMR (300 MHz, acetone-d6) δ 9.69 (s, 1H, NH(1)), 8.69 (d, J = 10.4 Hz, 1H, NH (3)), 8.01–7.93 (m, 2H, Ar), 7.77–7.66 (m, 1H, Ar), 7.64–7.54 (m, 4H, Ar), 7.47–7.38 (m, 5H, Ar), 7.33–7.21 (m, 3H, Ar, CH), 7.16–7.07 (m, 1H, Ar); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d6) δ 181.3, 139.4, 137.3, 134.7, 130.8, 130.1, 130.0, 129.8, 129.7, 129.6, 129.0, 128.8, 128.7, 125.2, 124.7, 123.8, 76.2; HRMS (ESI) m/z calcd for $C_{20}H_{19}N_2O_2S_2$ [M + H]+ 383.0882, found 383.0865; IR (neat) νmax/cm^{-1} 3285, 3061, 2921, 1597, 1527, 1495, 1446, 1343, 1314, 1283, 1257, 1180, 1130, 1080, 1024, 971, 874, 848, 762.

1-((4-Chlorophenyl)(phenylsulfonyl)methyl)-3-phenylthiourea (3b)

White amorphous solid (3.04 g, 73%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.90 (s, 1H, NH(3)), 9.35 (d, J = 10.3 Hz, 1H, NH(1)), 7.95–7.87 (m, 2H, Ar), 7.78–7.70 (m, 1H, Ar), 7.66–7.57 (m, 3H, Ar), 7.56–7.51 (m, 4H, Ar), 7.35–7.20 (m, 3H, Ar), 7.17–7.03 (m, 2H, Ar, CH); $^{13}C\{1H\}$ NMR (76 MHz, DMSO- d6) δ 186.3, 144.3, 142.1, 139.9, 136.4, 135.5, 134.8, 133.8, 133.2, 130.2, 128.8, 80.5;

HRMS (ESI) m/z calcd for $C_{20}H_{18}ClN_2O_2S_2$ [M + H]+ 417.0493; found 417.0511; IR (neat) νmax/cm^{-1} 3337, 3068, 2926, 1594, 1520, 1489, 1447, 1410, 1348, 1310, 1294, 1226, 1196, 1149, 1092, 1078, 1015, 999, 972, 938, 845, 828, 776, 749.

1-((2-Chlorophenyl)(phenylsulfonyl)methyl)-3-phenylthiourea (3c)

White amorphous solid (2.75 g, 66%). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H, NH(3)), 9.36 (d, J = 10.2 Hz, 1H, NH(1)), 7.90–7.81 (m, 2H, Ar), 7.81–7.73 (m, 1H, Ar), 7.73–7.57 (m, 4H, Ar), 7.57–7.45 (m, 3H, Ar), 7.38–7.33 (m, 2H, Ar), 7.31–7.22 (m, 2H, Ar, CH), 7.14–7.04 (m, 1H, CH, Ar); ^{13}C {1H} NMR (101 MHz, DMSO-d6) δ 181.3, 139.3, 137.3, 135.1, 131.8, 130.6, 130.1, 129.9, 129.4, 128.9, 128.1, 125.3, 124.7, 123.7, 72.5; HRMS (ESI) m/z calcd For $C_{20}H_{18}ClN_2O_2S_2$ [M + H]+ 417.0493, found 417.0508; IR (neat) νmax/cm^{-1} 3290, 3103, 3042, 2931, 1592, 1521, 1490, 1449, 1410, 1349, 1311, 1294, 1225, 1199, 1089, 1071, 1015, 991, 973, 846, 829, 774, 742.

1-((2-Fluorophenyl)(phenylsulfonyl)methyl)-3-phenylthiourea (3d)

White amorphous solid (2.88 g, 72%). ^{1}H-NMR (300 MHz, DMSO-d6) δ 10.02 (s, 1H, NH(3)), 9.39 (d, J = 10.3 Hz, 1H, NH(1)), 7.88–7.81 (m, 2H, Ar), 7.79–7.71 (m, 1H, Ar), 7.67–7.58 (m, 3H, Ar), 7.57–7.44 (m, 2H, Ar), 7.39–7.35 (m, 1H, Ar), 7.33–7.26 (m, 3H, Ar, CH), 7.24–7.21 (m, 2H, Ar), 7.15–7.02 (m, 1H, Ar); ^{13}C{1H} NMR (76 MHz, DMSO-d6) δ 181.7, 162.6, 159.3, 139.6, 137.2, 135.2, 132.7, 132.6, 131.0, 130.0, 129.8, 129.3, 129.1, 128.8, 125.5, 124.9, 124.1, 123.7, 118.9, 118.7, 116.5, 116.2, 70.5; ^{19}F-NMR (376 MHz, DMSO-d6) δ −115.58, −118.07; HRMS (ESI) m/z calcd for $C_{20}H_{18}FN_2O_2S_2$ [M + H]+ 401.0788, found 401.0779; IR (neat) νmax/cm^{-1} 3284, 3102, 3043, 2934, 1615, 1585, 1558, 1525, 1495, 1446, 1344, 1315, 1283, 1240, 1132, 1080, 1025, 998, 975, 956, 912, 879, 812, 764, 753.

1-((3-Bromophenyl)(phenylsulfonyl)methyl)-3-phenylthiourea (3e)

White amorphous solid (2.44 g, 53%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.74 (s, 1H, NH(3)), 9.2 (d, J = 12.0 Hz, 1H, NH(1)), 7.98–7.86 (m, 2H, Ar), 7.80–7.72 (m, 2H, Ar), 7.69–7.60 (m, 3H, Ar), 7.59–7.51 (m, 1H, Ar), 7.48–7.41 (m, 1H, Ar), 7.34–7.22 (m, 4H, Ar), 7.17–7.01 (m, 2H, Ar, CH); ^{13}C{1H} NMR (101 MHz, DMSO-d6) δ 181.2, 139.3, 137.0, 135.0, 133.4, 132.9, 132.2, 131.1, 129.7, 129.0, 128.8, 125.3, 123.8, 122.1, 75.4; HRMS (ESI) m/z calcd for $C_{20}H_{18}BrN_2O_2S_2$ [M + H]+ 460.9988, found 461.0008; IR (neat) νmax/cm^{-1} 3297, 3143, 3040, 2908, 1596, 1573, 1523, 1496, 1474, 1446, 1344, 1318, 1279, 1243, 1192, 1181, 1142, 1080, 1025, 998, 973, 903, 865, 843, 772, 748.

1-Phenyl-3-((phenylsulfonyl)(m-tolyl)methyl)thiourea (3f)

White amorphous solid (2.53 g, 64%). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H, NH(1)), 9.22 (d, J = 10.4 Hz, 1H, NH (3)), 7.97–7.84 (m, 2H, Ar), 7.77–7.69 (m, 1H, Ar), 7.64–7.56 (m, 2H, Ar), 7.38–7.29 (m, 5H, Ar), 7.29–7.24 (m, 3H, Ar), 7.14–6.99 (m, 2H, Ar, CH), 2.34 (s, 3H); ^{13}C{1H} NMR (101 MHz, DMSO- d6) δ 181.2, 139.3, 138.2, 137.3, 134.7, 130.6, 130.2, 129.6, 128.9, 128.8, 126.9, 125.2, 123.7, 76.1, 21.4; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_2O_2S_2$ [M + H]+ 397.1039, found 397.1056; IR (neat) νmax/cm^{-1} 3295, 3075, 2916, 1584, 1515, 1447, 1343, 1284, 1255, 1179, 1136, 1080, 1025, 971, 854, 794, 760.

1-(2-Methyl-1-(phenylsulfonyl)propyl)-3-phenylthiourea (3g)

White amorphous solid (1.70 g, 50%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.81 (s, 1H, NH(3)), 8.38 (d, J = 10.5 Hz, 1H, NH (1)), 7.86–7.79 (m, 2H, Ar), 7.73–7.64 (m, 1H, Ar), 7.60–7.52 (m, 2H, Ar), 7.40–7.35 (m, 1H, Ar), 7.34–7.29 (m, 2H, Ar), 7.27–7.22 (m, 1H, Ar), 7.12–7.04 (m, 1H, Ar), 5.92 (d, J = 10.5 Hz, 1H, CH), 2.78–2.53 (ept, J = 6.8 Hz, 1H, CH_{ipr}), 1.09 (d, J = 6.8 Hz, 3H, CH_{3ipr}), 1.00 (d, J = 6.8 Hz, 3H, CH_{3ipr}); ^{13}C{1H} NMR (101 MHz, DMSO-d6) δ 182.4, 139.4, 138.4, 134.4, 129.5, 129.3, 129.1, 128.8, 125.1, 124.8, 123.6, 123.4, 76.4, 40.6, 40.4, 40.1, 39.9, 39.7, 39.5, 39.3, 27.7, 20.8, 17.9; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_2S_2$ [M + H]+ 349.1039, found 349.1055; IR (neat) νmax/cm^{-1} 3286, 3075, 2964, 2901, 1593, 1519, 1495, 1448, 1311, 1283, 1229, 1179, 1083, 1059, 1026, 867, 829, 791, 768, 749, 727, 716.

1-(4-Chlorophenyl)-3-(phenyl(phenylsulfonyl)methyl)thiourea (3h)

White amorphous solid (2.08 g, 50%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.93 (s, 1H, NH(1)), 9.37 (d, J = 10.3 Hz, 1H, NH(3)), 7.94–7.81 (m, 2H, Ar), 7.79–7.68 (m, 1H, Ar), 7.69–7.56 (m, 2H, Ar), 7.56–7.50 (m, 2H, Ar), 7.50–7.41 (m, 3H, Ar), 7.38–7.26 (m, 4H, Ar), 7.07 (d, J = 10.3 Hz, 1H, CH); ^{13}C {1H} NMR (76 MHz, DMSO-d6) δ 181.9, 181.6, 138.9, 138.6, 137.5, 135.0, 130.9, 130.3, 130.0, 129.9, 129.2, 128.9, 125.5, 125.2, 125.0, 76.4; HRMS (ESI) m/z calcd for $C_{20}H_{18}ClN_2O_2S_2$ [M + H]+ 417.0493, found 417.0512; IR (neat) νmax/cm^{-1} 3288, 2918, 1583, 1523, 1490, 1447, 1403, 1331, 1307, 1283, 1233, 1179, 1130, 1079, 1015, 971, 878, 850, 829, 762.

1-(2-Fluorophenyl)-3-(phenyl(phenylsulfonyl)methyl)thiourea (3i)

White amorphous solid (1.84 g, 46%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.62 (d, J = 10.3 Hz, 1H, NH(3)), 9.55 (s, 1H, NH(1)), 7.94–7.84 (m, 2H, Ar), 7.79–7.70 (m, 1H, Ar), 7.64–7.56 (m, 3H, Ar), 7.56–7.43 (m, 5H, Ar), 7.25–7.14 (m, 2H, Ar, CH), 7.13–7.02 (m, 2H, Ar); ^{13}C{1H} NMR (101 MHz, DMSO- d6) δ 182.4, 157.1, 154.6, 137.3, 134.8, 130.6, 130.5, 130.1, 130.0, 129.8, 129.7, 129.6, 129.0, 128.8, 127.9, 127.4 127.3, 127.1, 127.0, 124.7, 124.3 (2C), 116.0, 115.8, 76.5; ^{19}F NMR (376 MHz, DMSO-d6) δ −124.19 to −124.25 (m, 1F, Ar); HRMS (ESI) m/z calcd for $C_{20}H_{18}FN_2O_2S_2$ [M

+ H]+ 401.0788, found 401.0805; IR (neat) νmax/cm−1 3283, 3095, 2921, 1600, 1582, 1526, 1456, 1446, 1339, 1251, 1141, 1079, 1027, 886, 848, 812, 796, 753.

1-(Phenyl(phenylsulfonyl)methyl)-3-(o-tolyl)thiourea (3j)

White amorphous solid (1.94 g, 49%). ^{1}H NMR (300 MHz, DMSO-d6) δ 9.42 (d, J = 10.4 Hz, 1H, NH(1)), 9.30 (s, 1H, NH (3)), 7.98–7.89 (m, 2H, Ar), 7.78–7.68 (m, 1H, Ar), 7.66–7.53 (m, 4H, Ar), 7.51–7.43 (m, 3H, Ar), 7.20–7.11 (m, 2H, Ar), 7.07 (m, 3H, Ar, CH), 1.96 (s, 3H, CH_3); ^{13}C{1H} NMR (101 MHz, DMSO- d6) δ 182.5, 137.7, 137.5, 134.7, 134.6, 130.8, 130.5, 130.0, 129.8, 129.6, 129.0, 128.7, 128.1, 126.8, 126.3, 124.7, 76.4, 18.1; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_2O_2S_2$ [M + H]+ 397.1039, found 397.1020; IR (neat) νmax/cm^{-1} 3293, 3079, 2917, 1585, 1549, 1514, 1456, 1447, 1343, 1284, 1257, 1180, 1121, 1109, 1080, 1045, 1025, 998, 970, 882, 854, 795.

1-Cyclohexyl-3-(phenyl(phenylsulfonyl)methyl)thiourea (3k)

White amorphous solid (1.98 g, 51%). ^{1}H NMR (300 MHz, acetone-d6) δ 8.16 (d, J = 10.5 Hz, 1H, NH(3)), 7.97–7.86 (m, 2H, Ar, NH(1)), 7.75–7.65 (m, 1H, Ar), 7.62–7.57 (m, 1H, Ar), 7.55–7.49 (m, 3H, Ar), 7.46–7.38 (m, 4H, Ar), 7.26 (d, J = 10.5 Hz, 1H, CH), 4.12–3.81 (m, 1H), 1.91–1.70 (m, 2H), 1.70–1.59 (m, 2H) 1.49–1.40 (m, 1H), 1.38–1.03 (m, 5H); ^{13}C{1H} NMR (101 MHz, acetone-d6) δ 181.8, 138.0, 133.8, 131.2, 129.5, 129.3 (2C), 128.9, 128.4, 76.0, 52.7, 32.4, 32.1, 31.9, 25.3, 24.8, 24.4, 24.3; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_2S_2$ [M + H]+ 389.1352, found 389.1378; IR (neat) νmax/cm−1 3282, 3065, 2930, 2853, 1618, 1586, 1524, 1497, 1447, 1368, 1310, 1256, 1230, 1162, 1081, 1027, 998, 974, 891, 846, 805, 760.

1-Benzyl-3-((4-chlorophenyl)(phenylsulfonyl)methyl)urea (7)

White amorphous solid (3.35 g, 81%). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.89–7.80 (m, 3H), 7.80–7.69 (m, 1H), 7.65–7.54 (m, 2H), 7.53–7.47 (m, 4H), 7.31–7.12 (m, 4H), 7.02–6.93 (m, 1H), 6.47–6.39 (m, 1H), 6.32–6.23 (m, 1H), 4.09 (dd, J = 15.4, 6.2 Hz, 1H, CH_2), 4.00 (dd, J = 15.4, 6.2 Hz, 1H, CH_2); ^{13}C{1H} NMR (101 MHz, DMSO-d6) δ 156.0, 140.4, 137.6, 134.4, 131.7, 129.7, 129.6, 129.4, 128.7, 128.6, 127.2, 127.1, 73.6, 43.1; HRMS (ESI) m/z calcd for $C_{21}H_{20}ClN_2O_3S$ [M + H]+ 415.0878, found 415.0861; IR (neat) νmax/cm^{-1} 3380, 2979, 1715, 1589, 1493, 1367, 1165, 1054, 1027, 1015, 982, 971, 941, 849, 796, 747.

General procedure for the synthesis of 5-hydroxy-imidazolinine-2-thione

To a vigorously stirred suspension of **3** (1.00 mmol), pre-catalyst a (54 mg, 0.20 mmol), and 4 Å MS (25 mg) in anhydrous DCM (5 mL), aldehyde **2** (1.20 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (balloon) three times. At this point, TEA (417 μL, 3.00 mmol) was added in one portion and the suspension was stirred at 30 °C for 16

h, filtered over a pad of Celite, diluted with brine (10 mL), and extracted with EtOAc (2 × 40 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (cyclohexane/EtOAc/TEA) to afford the desired product **5**. The diastereoisomeric ratio was determined by 1H-NMR. Reactions for the preparation of compounds **5f**, **5i**, **5k**, **5m**, and **5n** were performed using 2.00 mmol of aldehyde **2**.

(±)-5-Hydroxy-1,4,5-triphenylimidazolidine-2-thione (5a)

Method A: General procedure. Column chromatography with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5a** as white amorphous solid (231 mg, 67%, dr 78/22). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.26 (s, 0.78H, NH_{maj}), 11.15 (s, 0.22H, NH_{min}), 10.28 (s, 0.22H, OH_{min}), 9.53 (s, 0.78H, OH_{maj}), 8.05–8.03 (m, 0.44H, Ar_{min}), 7.99–7.96 (m, 1.56H, Ar_{maj}), 7.89–7.87 (m, 2H, Ar), 7.57–7.54 (m, 0.44H, Armin), 7.46–7.44 (m, 1.56H, Ar), 7.42–7.33 (m, 5.44H, Ar), 7.37–7.10 (m, 1.56H, Ar_{maj}), 7.21–7.16 (m, 0.44H, Ar_{min}), 7.15–6.94 (m, 1.56H, Ar_{maj}), 5.75 (s, 0.22H, H-4_{min}), 5.68 (s, 0.78H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 184.5, 141.6, 139.6, 130.1, 129.9, 128.6, 128.5 (2C), 128.4, 128.2, 127.7, 126.9, 99.8 (C-4_{min}), 97.2 (C-5_{maj}), 73.5 (C-4_{min}), 72.5 (C-4_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2OS$ [M + H]+ 347.1213, found 347.1237; IR (neat) νmax/cm^{-1} 3349, 3178, 2243, 1700, 1596, 1494, 1450, 1395, 1360, 1254, 1229, 1174, 1132, 1103, 1076, 1047, 1022, 989, 916, 893, 852, 821, 792, 747, 693.

Method B: Mechanistic study. To a vigorously stirred suspension of crude **17** (247 mg, 1.00 mmol) in DCM (5 mL), TEA (417 µL, 3.00 mmol) was added in one portion. The mixture was stirred for 30 min at room temperature, then phenyl isothiocyanate (110 µL, 1.00 mmol) was added in one portion. The mixture was stirred for additional 16 h at room temperature, then concentrated, diluted with brine (10 mL), and extracted with EtOAc (2 × 40 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel with cyclohexane/EtOAc/TEA 7 : 3 : 0.5 to afford the desired products **5a** (265 mg, 77%, dr 79/21).

(±)-5-(4-Chlorophenyl)-5-hydroxy-1,4-diphenylimidazolidine- 2-thione (5b)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5b** as a white amorphous solid (290 mg, 76%, dr 85/15). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.31 (s, 0.85H, NH_{maj}), 11.21 (s, 0.15H, NH_{min}), 10.43 (s, 0.15H, OH_{min}), 9.70 (s, 0.85H, OH_{maj}), 8.05–8.00 (m, 0.30H, Ar_{min}), 7.98–7.93 (m, 1.70H, Ar_{maj}), 7.85–7.80 (m, 1.70H, Ar_{maj}), 7.54–7.51 (m, 0.30H, Ar_{min}), 7.48–7.23 (m, 8H, Ar), 7.21–7.04 (m, 2H, Ar), 5.73 (s, 0.15H, H-4_{min}), 5.65 (s, 0.85H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 185.2, 151.1, 151.0, 150.1, 141.0, 140.1, 139.9, 138.7, 138.5, 135.8, 134.9, 134.3, 130.9, 130.7, 130.6, 130.5, 130.4, 130.2, 130.0, 129.4 (2C), 129.3, 129.2 (2C), 129.1, 128.9, 128.4, 128.3, 127.7 (2C), 126.5, 124.8, 123.7, 99.9 (C-5_{min}), 97.4 (C-5_{maj}), 74.0(C-4min), 73.1 (C-4_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{18}ClN_2OS$ [M + H]+ 381.0823, found 381.0846;

IR (neat) νmax/cm^{-1} 3155, 3059, 1697, 1598, 1564, 1494, 1450, 1389, 1290, 1235, 1134, 1047, 1002, 917, 843, 814, 780, 751.

(±)-5-(3-Chlorophenyl)-5-hydroxy-1,4-diphenylimidazolidine- 2-thione (5c)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5c** as a white amorphous solid (270 mg, 71%, dr 76/24). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.38 (s, 0.76H, NH_{maj}), 11.28 (s, 0.24H, NH_{min}), 10.55 (s, 0.24H, OH_{min}), 9.80 (s, 0.76H, OH_{maj}), 8.07–8.03 (m, 0.76H, Ar_{maj}), 8.01–7.95 (m, 0.24H, Ar_{min}), 7.79–7.77 (m, 1.52H, Ar_{maj}), 7.59–7.58 (m, 0.24H, Ar_{min}), 7.46–7.41 (m, 0.76H, Ar_{min}), 7.44–7.30 (m, 7.6H, Ar), 7.29–7.25 (m, 2.28H, Ar), 7.24–7.09 (m, 0. 24H, Ar_{min}), 7.12–6.91 (m, 0.24H, Ar_{min}), 5.74 (s, 0.24H, H-4_{min}), 5.69 (s, 0.76H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 184.5, 150.3, 144.0, 141.4, 139.4, 138.0, 135.7, 135.5, 134.2, 130.1, 130.0, 129.9, 129.8, 129.1, 128.8, 128.7, 128.6 (2C), 128.5, 128.4, 128.2, 128.1, 127.5, 127.1 (2C), 126.9, 126.7, 99.0 (C-5_{min}), 96.6 (C-5_{maj}), 73.4 (C-4_{min}), 72.4 (C-4_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{18}ClN_2OS$ [M + H]+ 381.0823, found 381.0847; IR (neat) νmax/cm^{-1} 3198, 1689, 1597, 1576, 1495, 1451, 1399, 1354, 1227, 1199, 1189, 1044, 997, 892, 831, 794, 752.

(±)-5-(2-Chlorophenyl)-5-hydroxy-1,4-diphenylimidazolidine- 2-thione (5d)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5d** as a white amorphous solid (224 mg, 59%, dr 99/1). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.34 (s, 1H, NH), 9.85 (s, 1H, OH), 8.24–8.19 (m, 2H, Ar), 7.44–7.42 (m, 3H, Ar), 7.34–7.29 (m, 3H, Ar), 7.25–7.21 (m, 3H, Ar), 7.21–7.14 (m, 2H, Ar), 7.07–7.02 (m, 1H, Ar), 6.23 (s, 1H, H-4); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 183.9, 139.1, 137.9, 136.2, 135.5, 132.7, 131.9, 131.3 (2C), 130.6, 129.5, 128.7, 128.5, 128.2, 127.1, 126.8, 123.9, 123.6, 123.4, 95.5, 68.1. HRMS (ESI) m/z calcd for $C_{21}H_{18}ClN_2OS$ [M + H]+ 381.0823, found 381.0839; IR (neat) νmax/cm^{-1} 3156, 1704, 1597, 1554, 1540, 1495, 1450, 1393, 1292, 1233, 1209, 1035, 1002, 843, 812, 782, 753.

(±)-5-(2-Fluorophenyl)-5-hydroxy-1,4-diphenylimidazolidine- 2-thione (5e)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5e** as a white amorphous solid (164 mg, 45%, dr 79/21). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.30 (s, 0.79H, NH_{maj}), 11.19 (s, 0.21H, NH_{min}), 10.54 (s, 0.21H, OH_{min}), 9.83 (s, 0.79H, OH_{maj}), 8.16–8.14 (m, 0.42H, Ar_{min}), 8.07–8.05 (m, 1.79H, Ar), 7.98–7.93 (m, 1.21H, Ar), 7.59–7.56 (m, 1.79H, Ar), 7.48–7.46 (m, 2.79H, Ar), 7.34–7.31 (m, 3H, Ar), 7.26–7.14 (m, 2.58H, Ar) 7.03–7.01 (m, 0.42H, Ar_{min}), 5.98 (s, 0.79H, H-4_{maj}), 5.90 (s, 0.21, H-4_{min}); ^{13}C {1H} NMR (101 MHz, pyridine-d5) δ 182.3, 159.9, 157.5, 137.7, 129.9, 129.8, 129.1, 128.3, 127.8, 127.1 (2C), 126.9 (2C), 126.5, 126.0, 125.7, 122.8, 115.2, 115.0, 93.1, 71.8 (C-4_{min}), 68.3 (C-4_{maj}); ^{19}F NMR (376 MHz, pyridine-d5) δ −107.44 (s, br, 0.21 F, F_{min}), −111.61 to −111.68 (m, 0.79 F, F_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{18}FN_2OS$ [M +

H]+ 365.1118, found 365.1131; IR (neat) νmax/cm^{-1} 3147, 1617, 1587, 1551, 1538, 1492, 1453, 1406, 1360, 1307, 1255, 1232, 1128, 1108, 1044, 1021, 1002, 970, 826, 782, 758, 680.

(±)-5-Hydroxy-5-(4-methoxyphenyl)-1,4-diphenylimidazolidine- 2-thione (5f)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5f** as a white amorphous solid slightly contaminated by uncharacterized by-products (154 mg, 41%, dr 94/6). ^{1}H NMR (400 MHz, pyridine-d5, selected data) δ 11.21 (s, 0.94H, NH_{maj}), 11.10 (s, 0.06H, NH_{min}), 9.83 (s, 0.06H, OH_{min}), 9.43 (s, 0.94H, OH_{maj}), 8.08–8.04 (m, 0.12H, Ar_{min}), 8.02–7.98 (m, 1.88H, Armaj), 7.90–7.86 (m, 0.12H, Ar_{min}), 7.85–7.81 (m, 1.88H, Ar_{maj}), 7.52–7.48 (m, 2H, Ar), 7.39–7.22 (m, 6H), 7.09–7.03 (m, 1H, Ar), 7.00–6.96 (m, 1H, Ar), 5.70 (s, 0.94H, H-4_{maj}), 5.66 (s, 0.06H, H-4min), 3.62 (s, 0.18H, CH_{3min}), 3.57 (s, 2.82H, CH_{3maj}); ^{13}C {1H} NMR (101 MHz, pyridine-d5) δ 184.1, 159.5, 139.4, 135.4, 133.0, 129.7, 129.2, 128.4, 128.2, 128.1, 126.6, 113.5, 96.9, 72.2, 54.8; IR (neat) νmax/cm^{-1} 3155, 2837, 2250, 1669, 1611, 1596, 1538, 1514, 1492, 1450, 1396, 1362, 1304, 1229, 1206, 1173, 1135, 1107, 1034, 1016, 981, 968, 916, 893, 840, 817, 795, 784, 753, 728, 701.

(±)-5-Hydroxy-1,4-diphenyl-5-(pyridin-4-yl)imidazolidine-2- thione (5g)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 6 : 4 : 0.5 afforded **5g** as a white amorphous solid (337 mg, 97%, dr 87/13). 1H NMR (400 MHz, pyridine-d5) δ 11.44 (s, 0.87H, NH_{maj}), 11.39 (s, 0.13H, NH_{min}), 9.84 (s, 1H, OH), 8.79–8.74 (m, 1.74H, Ar_{maj}), 8.48–8.47 (m, 0.26H, Ar_{min}), 8.03–8.01 (m, 0.26H, Ar_{min}), 7.98–7.95 (m, 1.74H, Ar_{maj}), 7.81–7.79 (m, 1.74H, Ar_{maj}), 7.51–7.33 (m, 7.26H, Ar), 7.29–7.07 (m, 3H, Ar), 5.77 (s, 0.13H, H-4_{min}), 5.68 (s, 0.87H, H-4_{maj}); 13C{1H} NMR (101 MHz, pyridine-d5) δ 184.6, 150.4, 150.2, 150.0, 149.7, 149.6, 139.2, 135.9, 135.6, 135.4, 135.1, 130.0, 129.7, 129.5, 128.9, 128.8, 128.7 (2C), 128.6 (2C), 128.5, 127.6, 127.2, 125.9, 123.9, 123.6, 123.4, 123.0, 96.2, 72.1; HRMS (ESI) m/z calcd for C20H18N3OS [M + H]+ 348.1165, found 348.1144; IR (neat) νmax/cm^{-1} 3155, 3063, 1604, 1564, 1495, 1449, 1389, 1527, 1235, 1134, 1048, 1003, 917, 843, 812, 779, 751, 692.

(±)-4-(4-Hydroxy-3,5-diphenyl-2-thioxoimidazolidine-4-yl)benzonitrile (5h)

Column chromatography on silica gel with cyclo- hexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5h** as a white amorphous solid (352 mg, 95%, dr 88/12). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.45 (s, 0.88H, NH_{maj}), 11.34 (s, 0.12H, NH_{min}), 10.73 (s, br, 0.12H, OH_{min}), 9.99 (s, 0.88H, OH_{maj}), 8.06–8.00 (m, 0.24H, Ar_{min}), 7.99–7.93 (m, 3.76H, Ar), 7.71–7.66 (m, 2H, Ar), 7.47–7.40 (m, 2H, Ar), 7.39–7.30 (m, 2H, Ar), 7.29–7.24 (m, 2H, Ar), 7.19–7.07 (m, 2H, Ar), 5.75 (s, 0.12H, H-4_{min}), 5.66 (s, 0.88H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 184.6, 150.2, 150.1, 146.5, 139.3, 138.1, 137.8, 135.1, 132.4, 131.5, 130.0, 129.7, 129.5, 129.4, 129.1, 128.9, 128.8, 128.7 (2C), 128.6, 128.4, 127.5, 127.2, 125.9, 120.4, 119.2, 112.4, 110.0, 96.8 (C-5_{min}), 96.6 (C-5_{maj}), 73.4 (C-4_{min}), 72.3 (C-4_{maj});

HRMS (ESI) m/z calcd for $C_{22}H_{18}N_3OS$ [M + H]+ 372.1165, found 372.1150; IR (neat) νmax/cm^{-1} 3317, 3197, 2243, 1596, 1585, 1495, 1452, 1395, 1350, 1231, 1204, 1173, 1131, 1102, 1089, 1049, 990, 892, 852, 820, 748, 699.

(±)-5-Hydroxy-5-isopropyl-1,4-diphenylimidazolidine-2-thione (5i)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5i** as a white amorphous solid contaminated by uncharacterized by-products (153 mg, 49%, dr 69/31). ^{1}H NMR (400 MHz, pyridine-d5, selected data) δ 11.24 (s, 0.31H, NH_{min}), 10.78 (s, 0.69H, NH_{maj}), 10.24 (s, 0.31H, OH_{min}), 9.51 (s, 0.69H, OH_{maj}), 7.97–7.95 (m, 1.28H, Ar_{maj}), 7.91–7.87 (m, 0.69H, Ar_{maj}), 7.78–7.74 (m, 1.28H, Ar_{maj}), 7.44–7.40 (m, 1.69H, Ar), 7.37–7.31 (m, 3.94H, Ar), 7.08–7.03 (m, 1H, Ar), 5.68 (s, 0.31H, H-4_{min}), 5.40 (s, 0.69H, H-4_{maj}), 2.30 (ep, J = 6.9 Hz, 1H, CH_{ipr}), 1.23 (d, J = 6.9 Hz, 3H, CH_{3ipr}), 1.21 (d, J = 6.9 Hz, 3H, CH_{3ipr}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 181.8, 137.3, 137.1, 134.0, 129.9, 128.4, 128.2, 128.0, 127.6, 127.2, 126.9, 126.7, 126.6, 126.2, 125.4, 97.5 (C-5_{maj}), 95.7 (C-5_{min}), 71.0 (C-4_{min}), 61.6 (C-4_{maj}), 34.7 (CH_{ipr}), 16.1 (CH_{3ipr}), 15.2 (CH_{3ipr}); IR (neat) νmax/cm−1 3156, 2968, 1699, 1596, 1494, 1450, 1409, 1304, 1230, 1131, 1026, 968, 825, 752.

(±)-4,5-Bis(4-chlorophenyl)-5-hydroxy-1-phenylimidazolidine- 2-thione (5j)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5j** as a white amorphous solid (230 mg, 56%, dr 93/7). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.29 (s, 0.93H, NH_{maj}), 11.18 (s, 0.07H, NH_{min}), 10.41 (s, 0.07H, OH_{min}), 9.74 (s, 0.93H, OH_{maj}), 8.01–7.99 (m, 0.14H, Ar_{min}), 7.95–7.90 (m, 1.86H, Ar_{maj}), 7.86–7.80 (m, 1.86H, Ar_{maj}), 7.57–7.52 (m, 0.14H, Ar_{min}), 7.45–7.41 (m, 2H, Ar), 7.40–7.36 (m, 1H, Ar), 7.36–7.12 (m, 5H, Ar), 7.14–7.03 (m, 1H), 5.73 (s, 0.07H, H-4_{min}), 5.63 (s, 0.93H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 183.2, 138.6, 137.8, 132.9, 132.8, 132.7, 128.5, 128.4, 128.3, 127.3, 127.2, 127.1, 125.7, 95.1, 70.3; HRMS (ESI) m/z calcd for $C_{21}H_{16}Cl_2N_2OS$ [M + H]+ 414.0360, found 414.0378; IR (neat) νmax/cm^{-1} 3156, 2948, 1594, 1553, 1499, 1454, 1385, 1348, 1308, 1285, 1228, 1207, 1176, 1127, 1089, 1038, 1015, 998, 971, 897, 825, 801, 748, 695.

(±)-4-(2-Fluorophenyl)-5-hydroxy-1,5-diphenylimidazolidine- 2-thione (5k)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5k** as a white amorphous solid (189 mg, 52%, dr 86/14). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.15 (s, 0.86H, NH_{maj}), 11.12 (s, 0.14H, NH_{min}), 10.46 (s, br, 0.14H, OH_{min}), 9.53 (s, 0.86H, OH_{maj}), 8.11–8.07 (m, 0.28H, Ar_{min}), 8.03–7.98 (m, 0.86H, Ar_{maj}), 7.97–7.94 (m, 1.86H, Ar), 7.93–7.87 (m, 1.72, Ar_{maj}), 7.72–7.67 (m, 0.28H, Ar_{min}), 7.39–7.31 (m, 1.86H, Ar), 7.30–7.24 (m, 1.86H, Ar), 7.20–7.15 (m, 1.86H, Ar), 7.14–6.98 (m, 3.42H, Ar), 6.10 (s, 0.14H, H-4_{min}), 6.05 (s, 0.86H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 183.1 (C-2_{min}), 182.8 (C-2_{maj}), 161.3, 158.8, 140.7, 137.8, 137.6, 136.9,

128.8, 128.7 (2C), 128.6, 128.5, 128.0, 127.7, 127.2 (2C), 127.0, 126.9 (2C), 126.6, 126.0, 125.9, 125.8, 125.6, 125.4, 122.8 (2C), 114.2, 113.9, 113.7, 98.0 (C-5_{min}), 95.3 (C-5_{maj}), 65.8 (C-4_{min}), 64.9 (C-4_{maj}); ^{19}F NMR (376 MHz, pyridine-d5) δ −116.25 to −116.31 (m, 0.14 F, Ar_{min}), −116.41 to −116.47 (m, 0.86 F, Ar_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{18}FN_2OS$ [M + H]+ 365.1118, found 365.1102; IR (neat) νmax/cm^{-1} 3158, 2809, 1618, 1587, 1552, 1489, 1451, 1407, 1356, 1307, 1239, 1220, 1132, 1082, 1020, 998, 970, 951, 901, 834, 825, 817, 786, 740, 696.

(±)-5-Hydroxy-1,5-diphenyl-4-(m-tolyl)imidazolidine-2-thione (5l)

Column chromatography on silica gel with cyclohexane/ EtOAc/TEA = 7 : 3 : 0.5 afforded **5l** as a white amorphous solid (230 mg, 64%, dr 85/15). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.19 (s, 0.85H, NH_{maj}), 11.09 (s, 0.15H, NH_{min}), 10.19 (s, br, 0.15H, OH_{min}), 9.46 (s, 0.85H, OH_{maj}), 8.06–8.02 (m, 0.30H, Ar_{min}), 8.01–7.96 (m, 1.70H, Ar_{maj}), 7.93–7.87 (m, 1.70H, Ar_{maj}), 7.68–7.63 (m, 0.30H, Ar_{min}), 7.39–7.33 (m, 2H, Ar), 7.32–7.23 (m, 2H, Ar), 7.19–6.96 (m, 5.85, Ar), 8.06–8.02 (m, 0.30H, Ar_{min}), 6.95–6.90 (m, 0.15, Ar_{min}), 5.75 (s, 0.15H, H-4_{min}), 5.67 (s, 0.85H, H-4_{maj}), 2.23 (s, 0.45H, CH_{3min}), 2.08 (s, 2.55H, CH_{3maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 184.1 (C-2_{min}), 184.1 (C-2_{maj}), 141.5, 139.2, 138.9, 138.8, 137.6, 137.3, 135.6, 129.8, 129.6, 129.4, 129.3, 129.2 (2C), 129.1, 129.0, 128.9, 128.8, 128.4, 128.2, 127.9, 127.8, 127.5, 127.3, 126.8, 126.6 (2C), 125.5, 125.3, 125.2, 124.5, 123.9, 123.8, 123.6, 123.3, 123.1, 122.8, 99.6 (C-5_{min}), 96.9 (C-5_{maj}), 73.1 (C-4_{min}), 72.1 (C-4_{maj}), 21.0 (C–CH_{3min}), 20.9 (C–CH_{3maj}); HRMS (ESI) m/z calcd for $C_{22}H_{21}N_2OS$ [M + H]+ 361.1369, found 361.1342; IR (neat) νmax/cm^{-1} 3177, 3035, 1596, 1548, 1538, 1492, 1426, 1348, 1305, 1241, 1197, 1140, 1041, 1022, 969, 875, 823, 798, 753, 715, 698.

(±)-4-(3-Bromophenyl)-5-hydroxy-1,5-diphenylimidazolidine- 2-thione (5m)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5m** as a white amorphous solid (326 mg, 77%, dr 90/10). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.21 (s, 0.90H, NH_{maj}), 11.11 (s, 0.10H, NH_{min}), 9.69 (s, br, 1H, OH), 8.02–7. 92 (m, 2H, Ar), 7.91–7.86 (m, 2H, Ar) 7.83–7.79 (m, 1H, Ar), 7.54–7.46 (m, 1H, Ar), 7.39–7.33 (m, 1H, Ar), 7.29–7.22 (m, 1H, Ar), 7.20–7.10 (m, 4H, Ar), 7.09–7.02 (m, 2H, Ar), 5.75 (s, 0.10H, H-4_{min}), 5.68 (s, 0.90H, H-4_{maj}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 183.0, 139.8, 137.9, 136.8, 130.0, 129.8, 128.8, 128.4, 127.2, 127.0 (2C), 126.6, 125.8, 125.6, 121.1, 95.6, 70.4; HRMS (ESI) m/z calcd for $C_{21}H_{18}BrN_2OS$ [M + H]+ 425.0318, found 425.0336; IR (neat) νmax/cm^{-1} 3145, 2785, 1595, 1596, 1549, 1538, 1496, 1475, 1427, 1409, 1344, 1305, 1268, 1236, 1201, 1134, 1040, 996, 948, 849, 826, 773, 761, 733, 697.

(±)-4-(4-Chlorophenyl)-5-hydroxy-1,5-diphenylimidazolidine- 2-thione (5n)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5n** as a white amorphous solid (201 mg, 53%, dr 88/12). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.22 (s, 0.88H,

NH_{maj}), 11.18 (s, 0.12H, NH_{min}), 10.41 (s, br, 0.12H, OH_{min}), 9.55 (s, 0.88H, OH_{maj}), 8.04–7.98 (m, 0.24H, Ar_{min}) 7.97–7.92 (m, 1.76H, Ar_{maj}), 7.90–7.81 (m, 2H, Ar), 7.41–7.31 (m, 5H, Ar), 7.30–7.17 (m, 3.76H, Ar), 7.13–6.98 (m, 1.24H, Ar), 5.74 (s, 0.12H, H-4_{min}), 5.65 (s, 0.88H, H-4_{maj}); $^{13}C\{1H\}$ NMR (101 MHz, pyridine-d5) δ 183.1, 139.9, 137.9, 133.1, 132.6, 128.5, 128.4, 127.2, 127.0 (2C), 126.6, 125.5, 95.5, 70.4; HRMS (ESI) m/z calcd for $C_{21}H_{18}ClN_2OS$ [M + H]+ 381.0823, found 381.0805; IR (neat) νmax/cm^{-1} 3164, 1594, 1549, 1538, 1493, 1452, 1413, 1392, 1351, 1305, 1231, 1208, 1128, 1091, 1018, 998, 968, 941, 898, 849, 824, 811, 773, 760, 738, 701.

(±)-1-(4-Chlorophenyl)-5-hydroxy-4,5-diphenylimidazolidine- 2-thione (5o)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5o** as a white amorphous solid (274 mg, 72%, dr 84/16). ^{1}H-NMR (400 MHz, pyridine-d5) δ 11.41 (s, 0.84H, NH_{maj}), 10.95 (s, 0.16H, NH_{min}), 10.31 (s, br, 0.16H, OH_{min}), 9.56 (s, 0.84H, OH_{maj}), 8.01–7.98 (m, 0.32H, Ar_{min}), 7.95–7.90 (m, 1.84H, Ar), 7.89–7.83 (m, 1.68H, Ar_{maj}), 7.48–7.23 (m, 7.68H, Ar) 7.19–6.97 (m, 2.48H, Ar), 5.74 (s, 0.16H, H-4_{min}), 5.68 (s, 0.84, H-4_{min}); 13C{1H} NMR (101 MHz, pyridine-d5) δ 183.9, 141.0, 138.0, 131.9, 131.1, 130.8, 128.4 (2C), 128.2, 128.1, 127.8, 127.5, 127.3, 99.4 (C-5_{min}), 96.8 (C-5_{maj}), 73.1 (C-4_{min}), 72.2 (C-4_{maj}); HRMS (ESI) m/z calcd for $C_{21}H_{18}ClN_2OS$ [M + H]+ 381.0823, found 381.0841; IR (neat) νmax/cm^{-1} 3156, 2896, 1595, 1550, 1494, 1452, 1392, 1352, 1305, 1232, 1208, 1175, 1128, 1091, 1040, 1019, 1003, 969, 941, 898, 850, 811, 773, 761, 739, 699.

(±)-5-Hydroxy-4,5-diphenyl-1-(o-tolyl)imidazolidine-2-thione (5p)

Column chromatography on silica gel with cyclo- hexane/EtOAc/TEA = 8 : 2 : 0.5 afforded **5p** as a white amorphous solid (176 mg, 49%, dr 74/26). ^{1}H NMR (400 MHz, pyridine-d5) δ 11.12 (s, 0.74H, NH_{maj}), 10.95 (s, 0.26H, NH_{min}), 9.60 (s, br, 0.26H, OH_{min}), 9.33 (s, 0.74H, OH_{maj}), 8.14–8.09 (m, 0.52H, Ar_{min}), 7.91–7.95 (m, 1.48H, Ar_{maj}), 7.65–7.60 (m, 0.52H, Ar_{min}), 7.52–7.46 (m, 1.48H, Ar_{maj}), 7.35–7.22 (m, 6H, Ar), 7.15–6.92 (m, 3.74H, Ar), 6.89–6.73 (m, 0.26H, Ar_{min}), 6.10 (s, 0.74H, H-4_{maj}), 5.60 (s, 0.26H, H-4_{min}); $^{13}C\{1H\}$ NMR (101 MHz, pyridine-d5) δ 183.2, 144.9, 141.0, 139.7, 138.5, 137.8, 137.0, 135.4, 131.1, 131.0, 130.7, 129.3, 129.2, 129.0, 128.6 (2C), 128.5, 128.2, 128.1, 127.9 (2C), 127.6, 127.0, 125.9, 125.7, 125.5, 110.2, 97.7 (C-5_{min}), 96.8 (C-5_{maj}), 71.8 (C-4_{min}), 70.6 (C-4_{maj}), 19.7 (C–CH_{3min}), 19.6 (C–CH_{3maj}); HRMS (ESI) m/z calcd for $C_{22}H_{21}N_2OS$ [M + H]+ 361.1369, found 361.1384; IR (neat) νmax/cm−1 3154, 3061, 2250, 1682, 1602, 1538, 1494, 1449, 1397, 1300, 1235, 1203, 1136, 1072, 1052, 1027, 1002, 968, 940, 886, 824, 784, 746, 720, 698.

(±)-1-Cyclohexyl-5-hydroxy-4,5-diphenylimidazolidine-2-thione (5q)

Column chromatography on silica gel with cyclohexane/ EtOAc/TEA = 9 : 1 : 0.5 afforded **5q** as a white amorphous solid (158 mg, 45%, dr 88/12). ^{1}H-NMR (400 MHz, pyridine-d5) δ 10.45 (s, 0.88H,

NH_{maj}), 10.20 (s, 0.12H, NH_{min}), 9.40 (s, br, 0.12H, OH_{min}), 8.61 (s, 0.88H, OH_{maj}), 7.93–7.89 (m, 2H, Ar), 7.55–7.41 (m, 3H, Ar), 7.36–7.25 (m, 3H, Ar), 7.20–7.15 (m, 1H, Ar), 7.14–7.06 (m, 1H, Ar), 5.62 (s, 0.12H, H-4_{min}), 5.40 (s, 0.88H, H-4_{maj}), 4.28 (s, br, 0.12H, Ali_{min}), 4.01 (s, br, 0.88H, Ali_{maj}), 3.08 (s, br, 0.12H, Ali_{min}), 2.96 (s, br, 0.88H, Ali_{maj}), 2.74 (s, br, 1H, Ali), 2.18–2.06 (m, 1.76H, Ali_{maj}), 2.03–1.95 (m, 0.24H, Ali_{min}), 1.67–1.46 (m, 2H, Ali), 1.15–0.88 (m, 4H, Ali); $^{13}C\{1H\}$ NMR (101 MHz, pyridine-d5) δ 183.4, 142.7, 135.6, 128.5, 128.2, 128.0, 127.9 (2C), 127.8, 127.5, 127.3, 99.3 (C-5_{min}), 96.9 (C-5_{maj}), 72.4 (C-4_{min}), 71.4 (C-4_{maj}), 57.2, 56.7, 31.2, 30.7, 26.4, 25.4; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2OS$ [M + H]+ 353.1682, found 353.1699; IR (neat) νmax/cm^{-1} 3198, 2936, 2851, 1684, 1539, 1485, 1450, 1404, 1349, 1304, 1259, 1234, 1208, 1175, 1110, 1070, 1010, 968, 908, 894, 826, 790, 701.

(±)-1-(2-Fluorophenyl)-5-hydroxy-4,5-diphenylimidazolidine- 2-thione (5r)

Column chromatography on silica gel with cyclohexane/EtOAc/TEA = 7 : 3 : 0.5 afforded **5r** as a white amorphous solid (317 mg, 87%, dr 99/1). ^1H NMR (400 MHz, pyridine-d5) δ 11.41 (s, 1H, NH), 9.56 (s, br, 1H, OH), 8.05–7.95 (m, 2H, Ar), 7.48–7.22 (m, 8H, Ar), 7.20–6.99 (m, 3H, Ar), 6.98–6.84 (m, 1H, Ar), 5.81 (s, 1H, H-4); $^{13}C\{1H\}$ NMR (101 MHz, pyridine-d5) δ 184.1, 160.9, 158.4, 140.6, 137.8, 130.5, 129.4, 129.2, 128.5 (2C), 128.3, 128.2, 128.1 (2C), 127.9, 127.8, 127.7, 127.5, 127.4, 127.1, 125.6, 124.1, 123.8, 116.2, 116.0, 96.9, 72.5; ^{19}F NMR (376 MHz, pyridine-d5) δ −114.11 (s, 1F, Ar); HRMS (ESI) m/z calcd for $C_{21}H_{18}FN_2OS$ [M + H]+ 365.1118, found 365.1101; IR (neat) νmax/cm^{-1} 3146, 3064, 1682, 1587, 1538, 1504, 1450, 1396, 1359, 1304, 1238, 1108, 1041, 1024, 968, 942, 898, 824, 784, 747, 727, 699.

(±)-1-Benzyl-4-(4-chlorophenyl)-5-hydroxy-5-phenylimidazoli- dine-2-one (8)

Method A: To a vigorously stirred suspension of **7** (415 mg, 1.00 mmol), pre-catalyst **C1** (54 mg, 0.20 mmol) and 4 Å MS (25 mg) in anhydrous DCM (5 mL), benzaldehyde **2a** (203 µL, 2.00 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (balloon) three times. At this point, TEA (417 µL, 3.0 mmol) was added in one portion and the suspension was stirred at 30 °C for 16 h. After this time, another portion of TEA was added (278 µL, 2.00 mmol) and the mixture was refluxed for 1 day. The mixture was cooled to room temperature, filtered over a pad of Celite, diluted with brine (10 mL), and extracted with EtOAc (2 × 40 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel with cyclohexane/EtOAc/TEA 7 : 3 : 0.5 to afford the desired product **8** as a white amorphous solid (193 mg, 51%, dr 99/1). ^1H NMR (400 MHz, pyridine-d5) δ 8.64 (s, 1H, OH), 7.79–7.72 (m, 2H, Ar), 7.49–7.43 (m, 2H, Ar), 7.42–7.25 (m, 9H, Ar, NH), 7.21–7.16 (m, 2H, Ar), 5.31 (s, 1H, CH), 4.83 (d, J = 15.4 Hz, 1H, CH_2), 4.45 (d, J = 15.4 Hz, 1H, CH_2); $^{13}C\{1H\}$ NMR (101 MHz, pyridine-d5) δ 162.1, 141.7, 140.1, 136.0, 133.2, 131.0, 129.6, 128.9, 128.6, 128.2,

128.1, 128.0 (2C), 127.6, 126.6, 92.4, 67.5, 44.3; HRMS (ESI) m/z calcd for $C_{22}H_{20}ClN_2O_2$ [M + H]+ 379.1208, found 379.1224; IR (neat) νmax/cm^{-1} 3041, 2922, 2809, 1672, 1597, 1496, 1452, 1406, 1146, 1028, 768, 982, 969, 912, 894, 841, 820, 795, 783, 762, 729, 700, 696.

Method B: To a vigorously stirred suspension of **7** (415 mg, 1.00 mmol), pre-catalyst **C1** (54 mg, 0.20 mmol) and 4 Å MS (25 mg) in anhydrous DCM (5 mL), benzaldehyde **2a** (203 µL, 2.00 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (balloon) three times. At this point, TEA (417 µL, 3.0 mmol) was added in one portion and the suspension was stirred at 30 °C for 16 h, filtered over a pad of Celite, diluted with brine (10 mL), and extracted with EtOAc (2 × 40 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude mixture containing **9** and **8** as determined by ^{1}H-NMR. Selected data of **9**: ^{1}H NMR (300 MHz, pyridine-d5) δ8.30 (d, J = 6.6 Hz, 2H, Ar), 7.82 (d, J= 6.6 Hz, 2H, Ar), 6.55(s, 1H, CH), 5.06–5.01 (d, J = 15 Hz, 0.25H, CH_{min}), 4.79–4.53 (m, 1.5H, CH_{2maj}), 4.49–4.44 (d, J = 15 Hz, 0.25H, CH_{min}); ^{13}C{1H} NMR (101 MHz, pyridine-d5) δ 197.3, 158.2, 141.0, 136.0, 130.2, 130.0, 129.7, 129.4, 129.2, 128.6 (2C), 128.0, 127.7, 127.5, 126.9, 126.6, 59.2, 44.1.

Multigram scale synthesis of (±)-5b

To a vigorously stirred suspension of **3a** (2.00 g, 5.24 mmol), pre-catalyst **C1** (0.27 g, 1.05 mmol) and 4 Å MS (125 mg) in anhydrous DCM (25 mL), 4-chlorobenzaldehyde **2b** (0.87 g, 6.20 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (balloon) three times. At this point, TEA (2.10 mL, 15.6 mmol) was added in one portion and the suspension was stirred at 30 °C for 16 h, filtered over a pad of Celite, concentrated, diluted with saturated solution of Na_2CO_3 (30 mL), and extracted with EtOAc (2 × 100 mL). The collected organic phases were dried (Na_2SO_4), concentrated, and crystallized from hot toluene to afford the desired product **5b** (1.22 g, 62%, dr 84 : 16) as a white amorphous solid.

2-Oxo-1,2-diphenylethanaminium chloride (17)

To a cooled (0 °C), stirred mixture of benzoin **15** (2.00 g, 9.43 mmol) in anhydrous DCM (25 mL), $SOCl_2$ (2.70 mL, 37.0 mmol) and 3 drops of DMF were added under a N_2 atmosphere. The mixture was stirred at 0 °C for 1 h, then warmed to room temperature, stirred for an additional 4 h, concentrated, diluted with EtOAc (25 mL), and washed with water (10 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford the desired 2-chloro-1,2-diphenylethanone product (1.60 g), which was used in the next step without further purifications. Selected data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.17 Hz, 2H, Ar), 7.53–7.31 (m, 8H, Ar), 6.32 (s, 1H, CH).

To a stirred mixture of the above crude 2-chloro-1,2-di- phenylethan-1-one (1.60 g, ~6.96 mmol) in anhydrous DCM (10 mL), phthalimide potassium salt (1.55 g, 8.32 mmol) was added in one portion.

The mixture was stirred at room temperature for 18 h, then concentrated, diluted with brine (20 mL), and extracted with Et2O (2 × 60 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford **16** as a white solid (2.2 g), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.78 (m, 4H, Ar), 7.72–7.67 (m, 2H, Ar), 7.52–7.45 (m, 4H, Ar), 7.39–7.30 (m, 4H, Ar), 6.78 (s, 1H, CH).

A stirred solution of crude **16** (2.20 g, ~6.45 mmol) in acetic acid (10 mL) and HCl 6 N (10 mL) was refluxed for 3 days, then cooled to room temperature, and filtered. The filtrate was concentrated to give **17** as a white amorphous solid (1.56 g, 67% overall yield). This compound was used in the coupling with Edman's reagent without further purification. ^{1}H NMR (300 MHz, D_2O) δ 7.81–7.75 (m, 2H, Ar), 7.62–7.56 (m, 1H, Ar), 7.55–7.36 (m, 2H, Ar), 7.33–7.21 (m, 5H, Ar), 6.09 (s, 1H, CH); ^{13}C{1H} NMR (101 MHz, D_2O) δ 194.3, 172.1, 134.9, 132.2, 131.6, 131.2, 130.3, 129.8, 129.0, 128.9, 128.5, 59.5.

5-(4-Chlorophenyl)-1,4-diphenyl-1,3-dihydro-2H-imidazole-2- thione (18)

To a stirred solution of **(±)-5b** (191 mg, 0.50 mmol) in DMF (5 mL), concentrated sulfuric acid (3 µl) was added in one portion. The solution was stirred under reflux for 1 hour, then cooled to room temperature, diluted with brine (10 mL), and extracted with Et2O (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give **18** (181 mg, >95%) at least 95% pure as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, br, 1H, SH), 7.42–7.33 (m, 4H, Ar), 7.30–7.20 (m, 6H, Ar), 7.18–7.13 (m, 2H, Ar), 6.98–6.93 (m, 2H, Ar); 13C{1H} NMR (101 MHz, $CDCl_3$) δ 161.9, 135.3, 134.2, 131.2, 128.6, 128.4 (2C), 128.2, 128.0, 127.0, 126.7, 126.2, 125.9; HRMS (ESI) m/z calcd for $C_{21}H_{16}ClN_2S$ [M + H]+ 363.0717, found 363.0737; IR (neat) νmax/cm−1 3036, 2902, 2730, 1667, 1597, 1489, 1447, 1374, 1263, 1342, 1089, 1017, 966, 915, 863, 781, 764, 736, 745, 702.

2-(Benzylthio)-5-(4-chlorophenyl)-1,4-diphenyl-1H-imidazole (19)

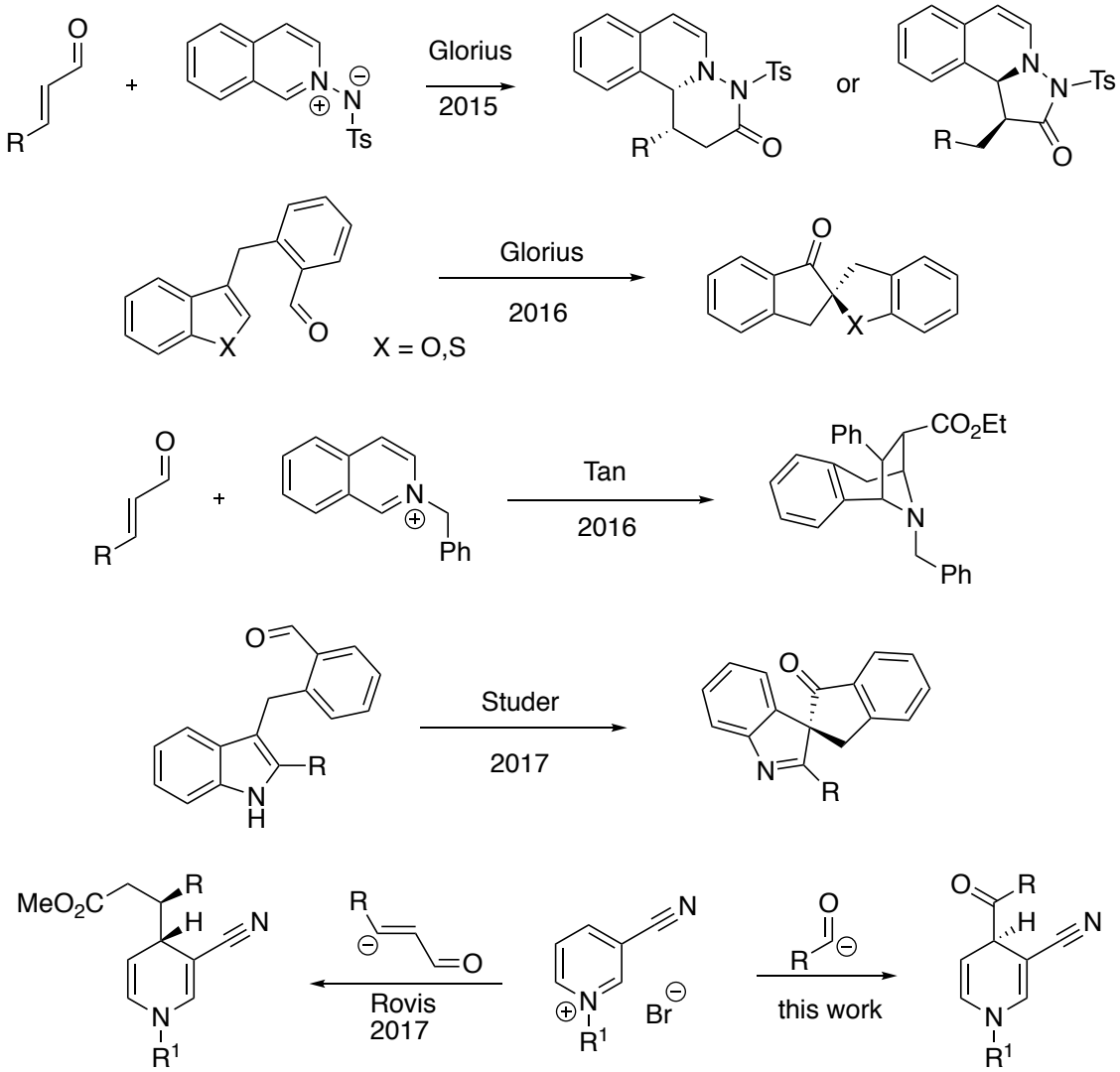
To a stirred solution of **17** (73 mg, 0.20 mmol) and benzyl bromide (25 µL, 0.21 mmol) in DMF (2 mL), cesium carbonate (78 mg, 0.24 mmol) was added in one portion. The suspension was stirred until the consumption of the starting 17 (24 h monitoring by TLC), then diluted with brine (5 mL), and extracted with Et2O (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), concentrated and purified by column chromatography on silica gel with cyclohexane/EtOAc 8 : 2 to afford **18** as a white amorphous solid (91 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.52 (m, 2H, Ar), 7.34–7.19 (m, 11H, Ar), 7.19–7.13 (m, 2H, Ar), 7.02–6.95 (m, 2H, Ar), 6.94–6.87 (m, 2H, Ar), 4.40 (s, 2H, CH_2); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 143.2, 139.1, 137.4, 135.6, 134.0, 133.8, 131.8, 129.7, 129.2, 129.0, 128.8, 128.7 (2C), 128.4, 128.3, 128.0, 127.4, 127.2, 126.9, 38.3; HRMS (ESI) m/z calcd for $C_{28}H_{22}ClN_2S$ [M + H]+ 453.1187; found 453.1206; IR (neat) νmax/cm^{-1} 3029,

2932, 2849, 1596, 1495, 1479, 1449, 1428, 1397, 1367, 1321, 1297, 1275, 1230, 1175, 1091, 1071, 1016, 960, 917, 832, 779, 769, 747, 692.

3 Enantioselective Dearomatization of Alkylpyridiniums by N-Heterocyclic Carbene-Catalyzed Nucleophilic Acylation

3.1 introduction

During the last 30 years, the development of catalytic stereoselective protocols to form C−C bonds has gained more and more attention within the organic synthetic community, maybe due to the possibility to access rapidly enantioenriched structural motifs, increasing in the same time the molecular complexity[1]. Catalytic asymmetric dearomatization reactions have attracted a great deal of attention over the recent years due to the ready availability of the substrates such as indoles, phenols, pyridines, pyrroles and (iso)quinolines[2]. Despite the huge synthetic versatility of this strategy, a main challenge is the poor reactivity of substrates toward nucleophilic additions due the resonance stability energy as well as the control of the regio- and stereoselectivity in the formation of the desired product. Transition-metal are ubiquitous in catalytic dearomatization reactions and they have been largely employed for the enantioselective dearomatization of (hetero)-aromatic compounds [3], whereas organocatalytic approaches are less common[4]. In 2005 Jørgensen, Jacobsen and their co-workers presented, for the first time, the dearomatization of isoquinolinium salts; later on, only few contributions were reported in the literature dealing with the dearomatization of (iso)quinolines, indoles and of the more demanding pyridines by organocatalytic strategies (amino, hydrogen-bonding, and anion-binding catalysis)[5]. The asymmetric dearomatization of (hetero)aromatic compounds via Umpolung catalysis by the use of N-heterocyclic carbenes (NHCs) as organocatalysts has also been presented but in a very limited number of recent examples, mainly involving α,β-unsaturated aldehydes (enals) as the nucleophiles (homoenolate chemistry) and/or intramolecular processes (Scheme 1)[6]. In 2015, Glorius and co-workers developed an elegant dearomatizing annulation reaction of N-imino(iso)quinolinium ylides using NHC-generated homoenolates or enolates with switchable reactivity[4i]. Later, Tan and co-workers demonstrated that simple N-alkyl isoquinolinium salts are suitable substrates for NHC-catalyzed dearomatizing double Mannich reactions leading to tropane derivates with excellent enantiocontrol[4j]. Furthermore, an intramolecular dearomatization of benzofurans/benzothiophenes by hydroacylation of indoles by external oxidative NHC catalysis was disclosed by the groups of Glorius[4k] and Studer[4l], respectively. Finally, Rovis and Flanigan have presented an enantioselective addition of umpoled enals to N-alkylpyridinium salts via NHC catalysis[4m] to access 1,4-dihydropyridines (DHPs) with good regioselectivity and enantioselectivity[8f]. Notably, 1,4-DHPs are privileged pharmaceutically structures employed in the treatment of a large number of diseases, such as hypertension, cancer, and infection[7]. In our study, we have presented a complementary enantioselective NHC-catalyzed approach for the dearomatization of pyridines through the addition of umpoled aliphatic aldehyde, leading to enantioenriched 1,4-DHPs with complete regiocontrol (Scheme 1)[8].

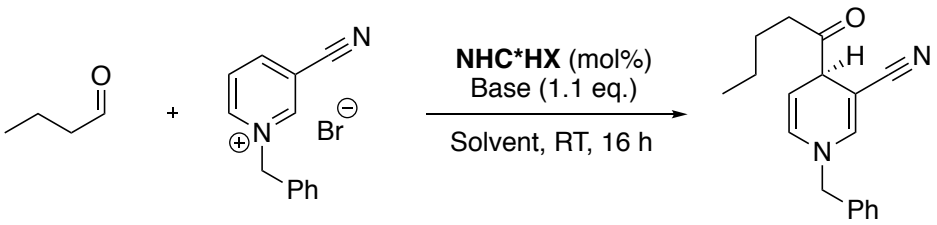


Scheme 1. Enantioselective dearomatizations mediated by NHC

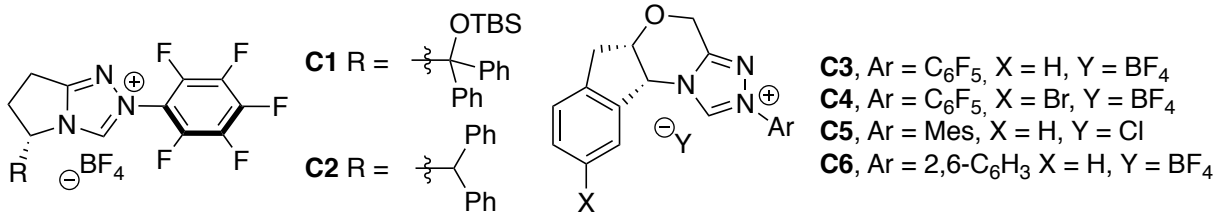
2.2 Results and discussion

We started our study reacting n-butanal **1a** and N-benzylpyridinium salt **2a**, bearing a cyano group at the 3-postion, with a catalytic amount (10 mol %) of triazolium salt **C1** and K_3PO_4 as the base in toluene (Table 1, entry 1).

Table 1. Optimization of the dearomatization of pyridinium **1a** part a[a]



2a **1a** **3a**

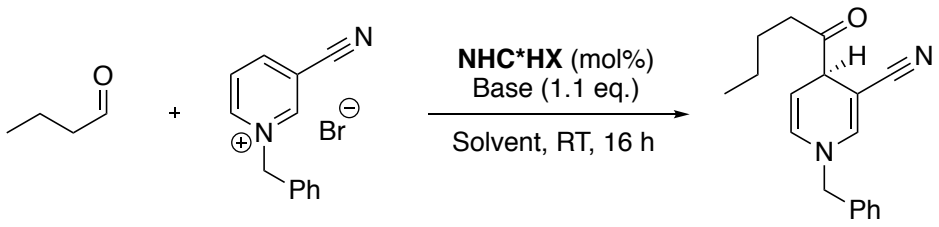


C3, Ar = C_6F_5, X = H, Y = BF_4
C4, Ar = C_6F_5, X = Br, Y = BF_4
C5, Ar = Mes, X = H, Y = Cl
C6, Ar = 2,6-C_6H_3 X = H, Y = BF_4

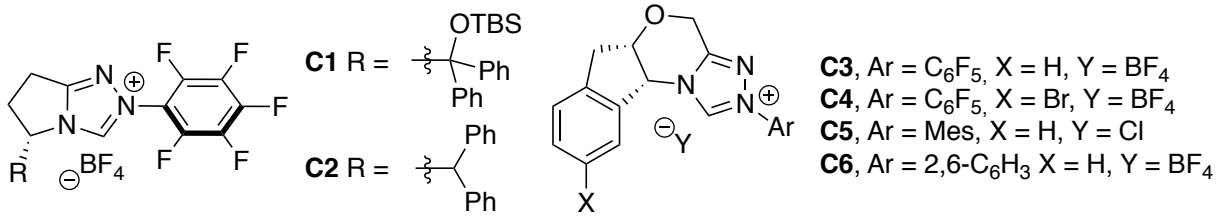
entry	NHC*HX	solvent	base	Yield (%)[b]	ee[c]
1	C1	toluene	K_3PO_4	-	-
2	C2	toluene	K_3PO_4	91	31
3	C3	toluene	K_3PO_4	90	53
4	C4	toluene	K_3PO_4	93	58
5	C5	toluene	K_3PO_4	9	78
6	C6	toluene	K_3PO_4	81	69
7	C6	C_6H_5Cl	K_3PO_4	80	68
8	C6	DCM	K_3PO_4	62	42
9	C6	THF	K_3PO_4	-	-
10	C6	CCl_4	K_3PO_4	25	74

[a]Reaction conditions: 1.5 equiv of **2a** (0.30 mmol), 1.0 equiv of **1a** and **Cn** (10 mol%) in the stated solvent (0.15 M). [b]Isolated yield. [c]Determined by chiral stationary phase HPLC. [d]Reaction run in the presence of LiCl (0.5 equiv). [e]Reaction run at 0 °C. [f]Reaction run at −30 °C. gReaction performed with 5 mol% of **C6** Reaction run with 2 mmol of **2a**.

Table 1. Optimization of the dearomatization of pyridinium **1a** part b[a]



2a **1a** **3a**



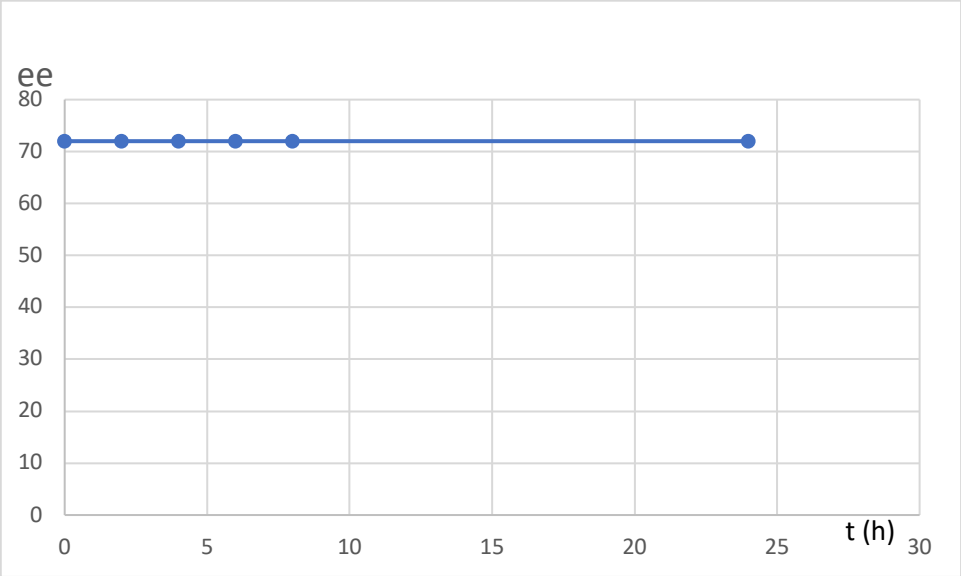
C3, Ar = C_6F_5, X = H, Y = BF_4
C4, Ar = C_6F_5, X = Br, Y = BF_4
C5, Ar = Mes, X = H, Y = Cl
C6, Ar = 2,6-C_6H_3 X = H, Y = BF_4

entry	NHC*HX	solvent	base	Yield (%)[b]	ee[c]
11	C6	toluene	DIPEA	-	-
12	C6	toluene	Na_2CO_3	80	70
13	C6	toluene	Cs_2CO_3	81	62
14	C6	toluene	Na_2CO_3	77	70
15	C6	toluene	K_3PO_4	74	70
16	C6	toluene	K_3PO_4	33	70
17	C6	toluene	K_3PO_4	29	78
18	C6	toluene	Na_2CO_3	84	70

[a]Reaction conditions: 1.5 equiv of **2a** (0.30 mmol), 1.0 equiv of **1a** and **Cn** (10 mol%) in the stated solvent (0.15 M). [b]Isolated yield. [c]Determined by chiral stationary phase HPLC. [d]Reaction run in the presence of LiCl (0.5 equiv). [e]Reaction run at 0 °C. [f]Reaction run at −30 °C. gReaction performed with 5 mol% of **C6** Reaction run with 2 mmol of **2a**.

Gratifyingly, the 1,4-DHP **3a** was collected in high yield (90%) as a single regioisomer, which resulted from the selective addition of the umpoled aldehyde onto the C-4 position of the pyridinium ring with an encouraging enantiomeric excess (53% ee). Hence, we moved to investigate the catalyst substituent effect, and we found a slightly improved reaction outcome using the newly synthesized triazolium **C4** (entry 4). The Bode's triazolium **C5** showed a remarkable increase of enantioselectivity (78% ee) accompanied, unfortunately, by a critical drop of reactivity (entry 5). Pleasantly, the amino-indanol-derived triazolium salt **C6** provided **3a** in 81% yield and 69% ee (entry 6). The pyrrole-derived triazolium salt **C2** gave a decrease in terms of enantioselectivity (entry 2), while the pre-

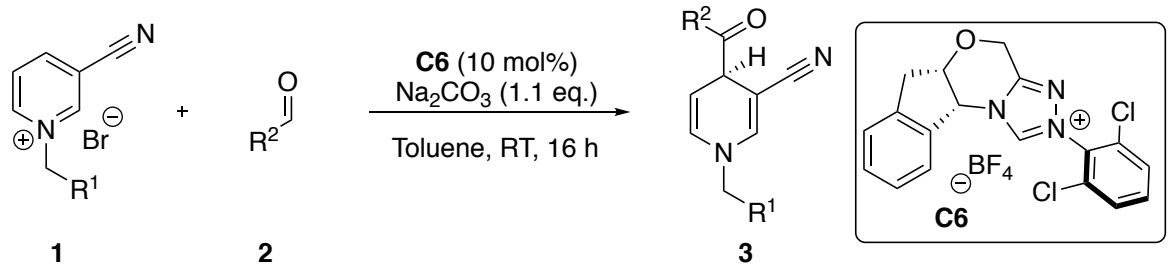
catalyst **C1** proved to be completely inactive (entry 1). The solvent screening with **C6** revealed that increasing the medium polarity caused a reduction of reaction efficiency (entries 7−9) along with the drop of the enantiocontrol; however, CCl_4 restored the enantiocontrol by the catalyst (74% ee), albeit at the expense of a diminished reactivity, likely due to the low solubility of the pyridinium salt **1a** (entry 10). We next replaced K_3PO_4 observing that nitrogen bases were unable to promote the transformation (entry 11). Among the inorganic bases, Na_2CO_3 performed better than Cs_2CO_3 in terms of enantioselectivity (entries 12 and 13), indicating a sort of influence of the hard/soft character of the metal in the stereochemical outcome. We also tried LiCl (50 mol %) as a cooperative Lewis acid additive and a lower reaction temperature without any significantly improvement in stereoselectivity (entries 14−16)[9]. Decreasing the catalyst loading to 5 mol % afforded **3a** with a lower yield but significantly higher ee (78%, entry 17). This result led us to suppose that the transformation could be reversible and/or a partial racemization of the product **3a** could occur under basic conditions. These hypotheses were excluded by a control experiment (Graphic 1), which showed no erosion of the ee in an authentic sample of **3a** under the optimized reaction conditions of entry 12.

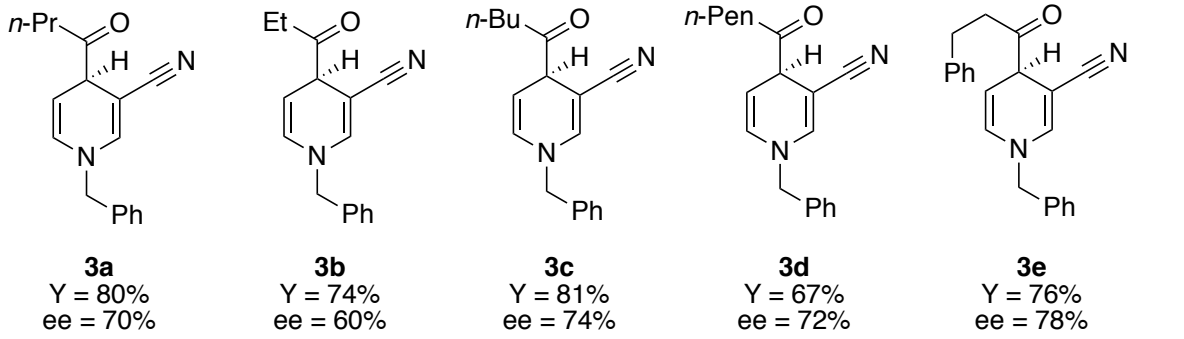


Graphic 1. Control experiment to detect possible racemization. **3a** (0.20 mmol, ee = 70%), pre-catalyst **C6** (0.02 mmol, 0.1 equiv.), anhydrous sodium carbonate (0.22 mmol, 1.1 equiv.), and anhydrous Toluene (1 mL) was vigorously stirred at room temperature under Argon. The eventual racemization was controlled by chiral HPLC analysis of aliquots (50 µL) of the reaction mixture.

We also scaled up the reaction to 2 mmol of **2a** without affecting the yield and enantioselectivity of **3a**, which could be conveniently recovered by simple filtration (entry 18). The optimal conditions were next applied to investigate the scope of the reaction (Table 2)

Table 2. Reaction scope[a]





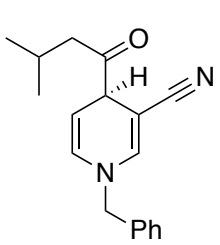
3a
Y = 80%
ee = 70%

3b
Y = 74%
ee = 60%

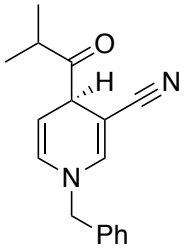
3c
Y = 81%
ee = 74%

3d
Y = 67%
ee = 72%

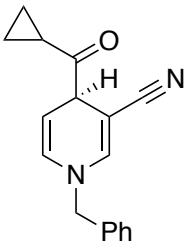
3e
Y = 76%
ee = 78%



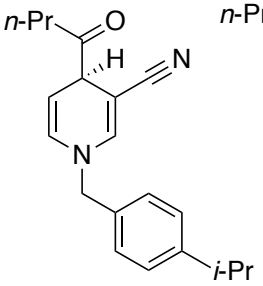
3g
Y = 37%
ee = 74%



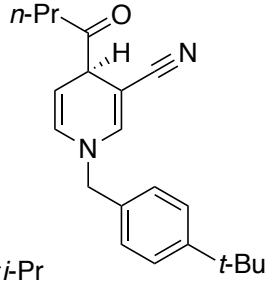
3h
Y < 5%



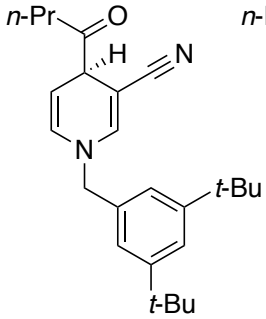
3i
Y = 47%
ee = 52%



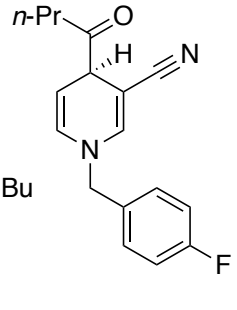
3j
Y = 37%
ee = 72%



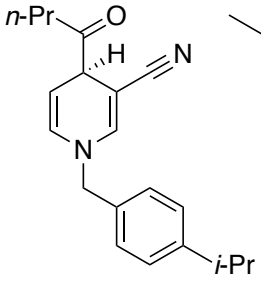
3k
Y = 80%
ee = 72%



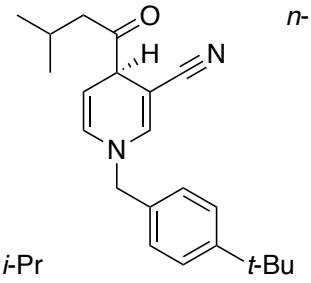
3l
Y = 53%
ee = 68%



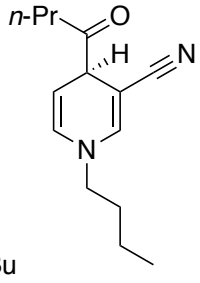
3m
Y = 81%
ee = 64%



3n
Y = 60%
ee = 72%



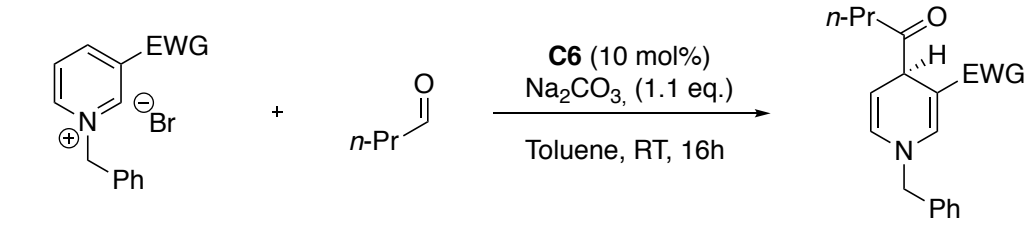
3o
Y = 60%
ee = 72%



3p
Y = 36%
ee = 74%

[a]Reaction conditions: 0.40 mmol of **1**, 1.5 equiv of **2**, 1.1. equiv of anhydrous sodium carbonate, and 10 mol % of **C6** in anhydrous toluene (2 mL).

revealing that short-chained aliphatic aldehydes **2a−c** (n-propanal **1b** and n-pentanal **1c**) reacted with **1a** to afford the corresponding 1,4-DPHs with good reactivity and enantioselectivity (from 60 to 74% ee), in agreement with the increase of steric hindrance of the linear alkyl substituent. This trend reversed with the medium-chained n-hexanal **2d** (72% ee), likely due a restricted conformational freedom of the n-pentyl moiety in the enantio-inductive transition state. Aldehydes **2e** and **2f** with substituents placed at the β-position reacted efficiently with an improvement of enantioselectivity compared to linear aldehydes. Unfortunately, the α-branched isobutyraldehyde **2g** showed no reactivity under the optimal conditions, while cyclopropanecarboxaldehyde **2h** furnished the 1,4-DHP **3i** in a good yield and a modest enantioselectivity. The effect of the N-substituent on reactivity of the N-alkyl-3-cyanopyridinium core was also explored with substrates **1b−f**. It seems there is no correlation between the stereoselectivity and steric hindrance on the pyridinium nitrogen group comparing the enantiomeric excess within the series **3a**, **3j**, **3k**, and **3l**. The limitation of the presented protocol was also investigated considering either pyridinium salts with different C3 Electron-withdrawing substituents (Scheme 2) or a model aromatic aldehyde (Table 3).



4a, EWG = Br
4b, EWG = NO_2
4c, EWG = CO_2Me
4d, EWG = $CONH_2$

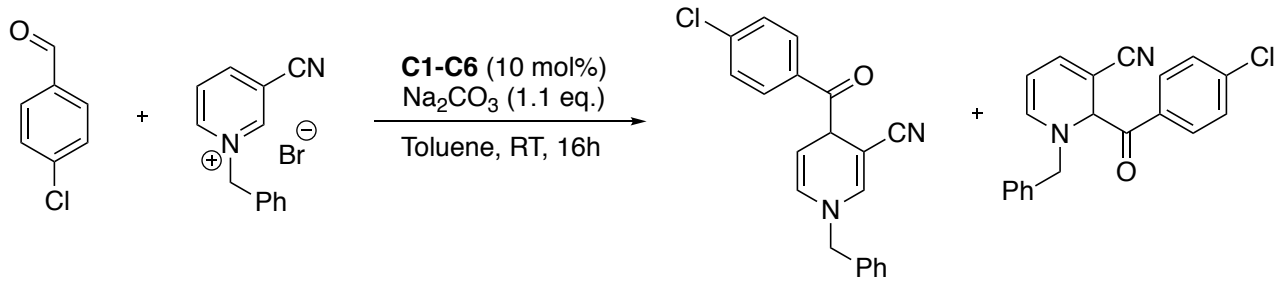
1a

5a, EWG = Br, Y < 5
5b, EWG = NO_2, Y < 5
5c, EWG = CO_2Me, Y < 5
5d, EWG = $CONH_2$, Y < 5

Scheme 2. Enantioselective dearomatization of pyridinium salts **4** bearing different C3 substituents

Unfortunately, replacing the cyano group with other electron-withdrawing groups (EWG) (compounds **4a−d**; EWG = Br, NO_2, CO_2Me, $CONH_2$) resulted in a complete absence of reactivity towards the formation of the corresponding DHPs **5** (Scheme 2). Additionally, p-chlorobenzaldehyde **6** was tested in the dearomatization of pyridinium salt **1a** to access the corresponding 1,4-DHP **7a** with low enantiocontrol (up to 50% ee) using the pre-catalysts **C1−C6** and Na_2CO_3 as the base (Toluene, rt; Table 3).

Table 3. Dearomatization of pyridinium **1a** with *p*-Chlorobenzaldehyde[a]



6 **1a** **7a** **8a**

entry	NHC*HX	Yield (%)[b]	7a/8a[c]	7a ee (%)[d]
1	C1	-	-	-
2	C2	88	94:6	29
3	C3	87	95:5	46
4	C4	88	95:5	50
5	C5	-	-	-
6	C6	-	-	-

[a]Reaction conditions: 0.20 mmol of **1a** and 1.5 equiv of **6** in anhydrous toluene (1 mL). [b]Combined yield of **7a** and **8a**. [d]Determined by ^{1}H NMR of the unpurified reaction mixture. [c]Determined by chiral stationary phase HPLC.

Interestingly, the formation of a small portion (ca. 5%) of the other regioisomer **8a** (1,2-addition) was observed. Furthermore, the dearomatization of **1a** with electron-rich benzaldehydes as *p*-anisaldehyde under the same conditions proved to be impractical due the poor conversion efficiency (<10%; not shown). Overall, these results confirmed the lower efficacy of aromatic aldehydes in the disclosed dearomatization method. Every attempt to obtain good crystals of the DHP derivates **3** was unsuccessful. Thus, the absolute configuration was determined by matching theoretical simulations of chiro-optical spectra and conformational analysis. Accordingly, the (4R) stereochemistry of two representative compounds (**3b** and **3p**) was determined by means of the time-dependent density functional theory (TD-DFT). A full conformational search was performed on a model of **3ba** (**model-3ba**), where the ethyl group was replaced by a methyl group using molecular mechanics (MMFF force field). After DFT optimization, only four conformations were found in a 2.0 kcal/mol range. The difference in the four conformations (Figure 1) is given by the disposition of the COMe and benzyl moieties. The preferred conformation of the benzyl moiety is almost perpendicular to the dihydropyridine ring.

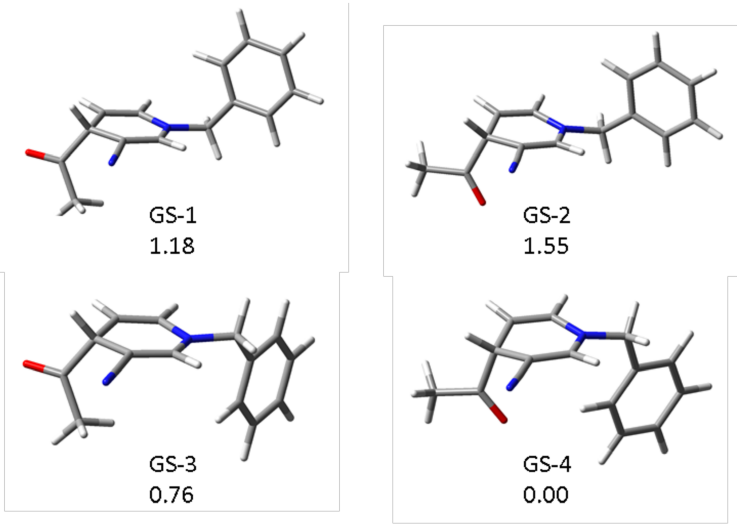


Figure 1. The four more stable conformations of **model-3ba**. The reported relative energies (in kcal/mol) are ZPE-corrected enthalpies.

For the compound **3af**, the conformational search was performed on a model where the propyl and N-butyl groups were replaced by two methyl groups (**model-3af**) in order to decrease the conformational freedom of the molecule giving two conformations (Figure 2).

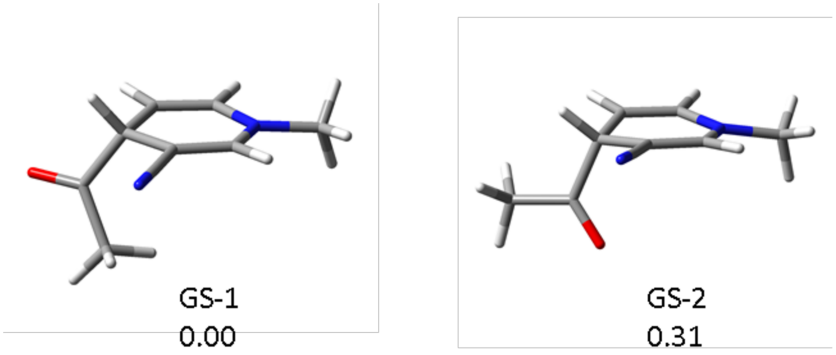


Figure 2. The two more stable conformations of the model of **model-3af**. The reported relative energies (in kcal/mol) are ZPE-corrected enthalpies.

The ECD spectra of compounds **3ba** and **3af** were acquired in acetonitrile solution ($1 \cdot 10^{-4}$ M) in the 190-400 nm region (Figure 3).

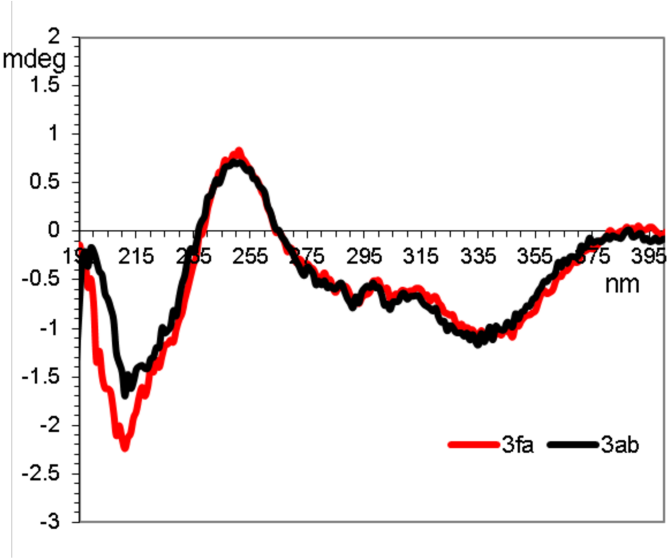


Figure 3. ECD spectrum of the two compounds **3ba** and **3af** in acetonitrile.

The two spectra are very similar, with two negative bands between 375 and 275 nm, a positive one at 250 and a negative band at 215 nm. Finally, the TD-DFT simulations of the ECD spectra were performed using the geometries of the four conformations of **model-3ba** and of the two conformations of the **model-3af**. In both cases, the TD-DFT calculations were run on the R absolute configuration. The simulations obtained for the four conformations of **model-3ba** and for the two conformations of the **model-3af** resulted rather similar in the low-energy region with the experimental ECD spectra, in agreement with the assignment of the R absolute configuration as shown in Figures 4 and 5[10].

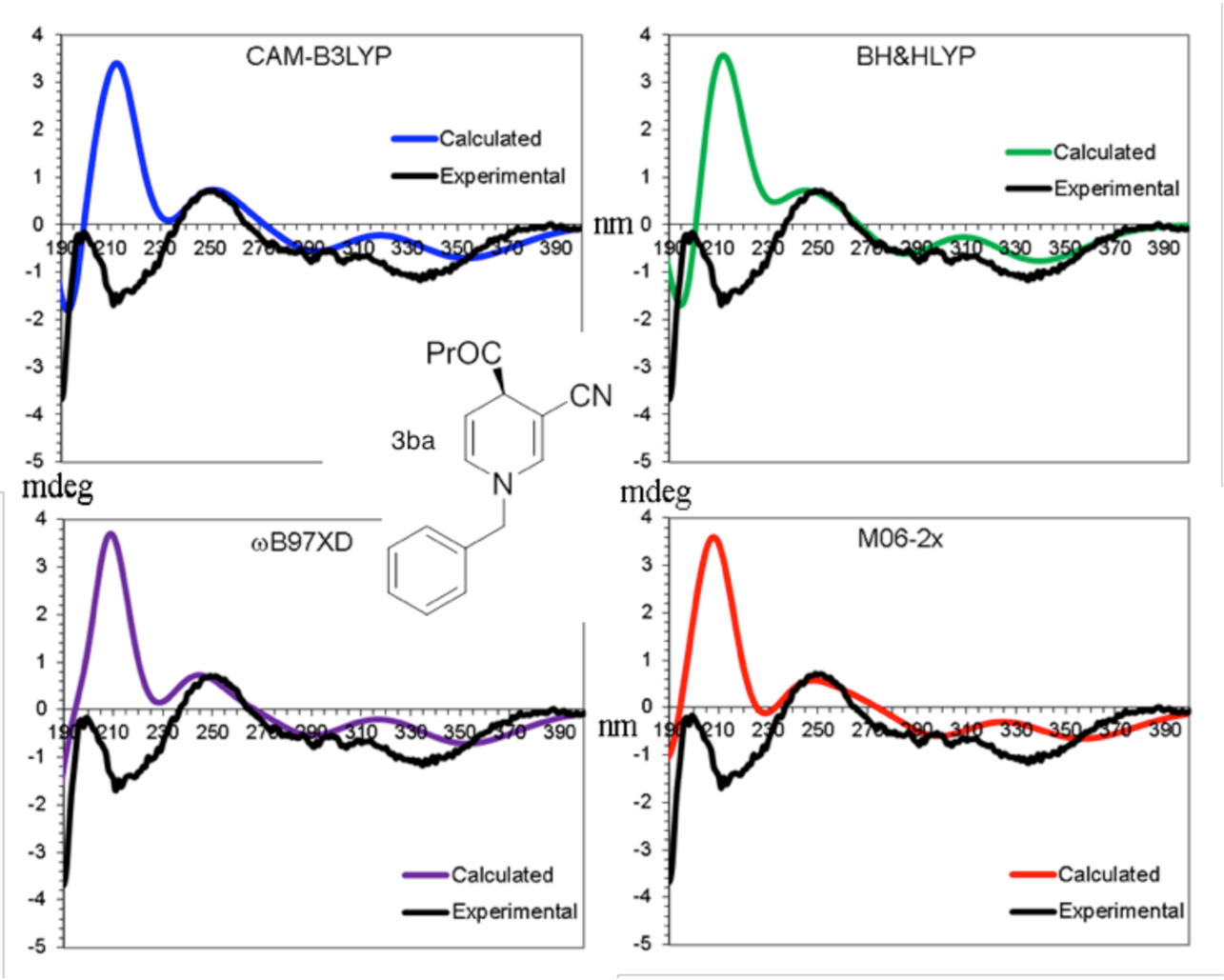


Figure 4. Simulations of the experimental ECD spectrum of **3ba**. For each quadrant, the black line corresponds to the experimental spectrum. The colored lines correspond to the simulations obtained on **model-3ba** (CO-Me instead of CO-Pr).

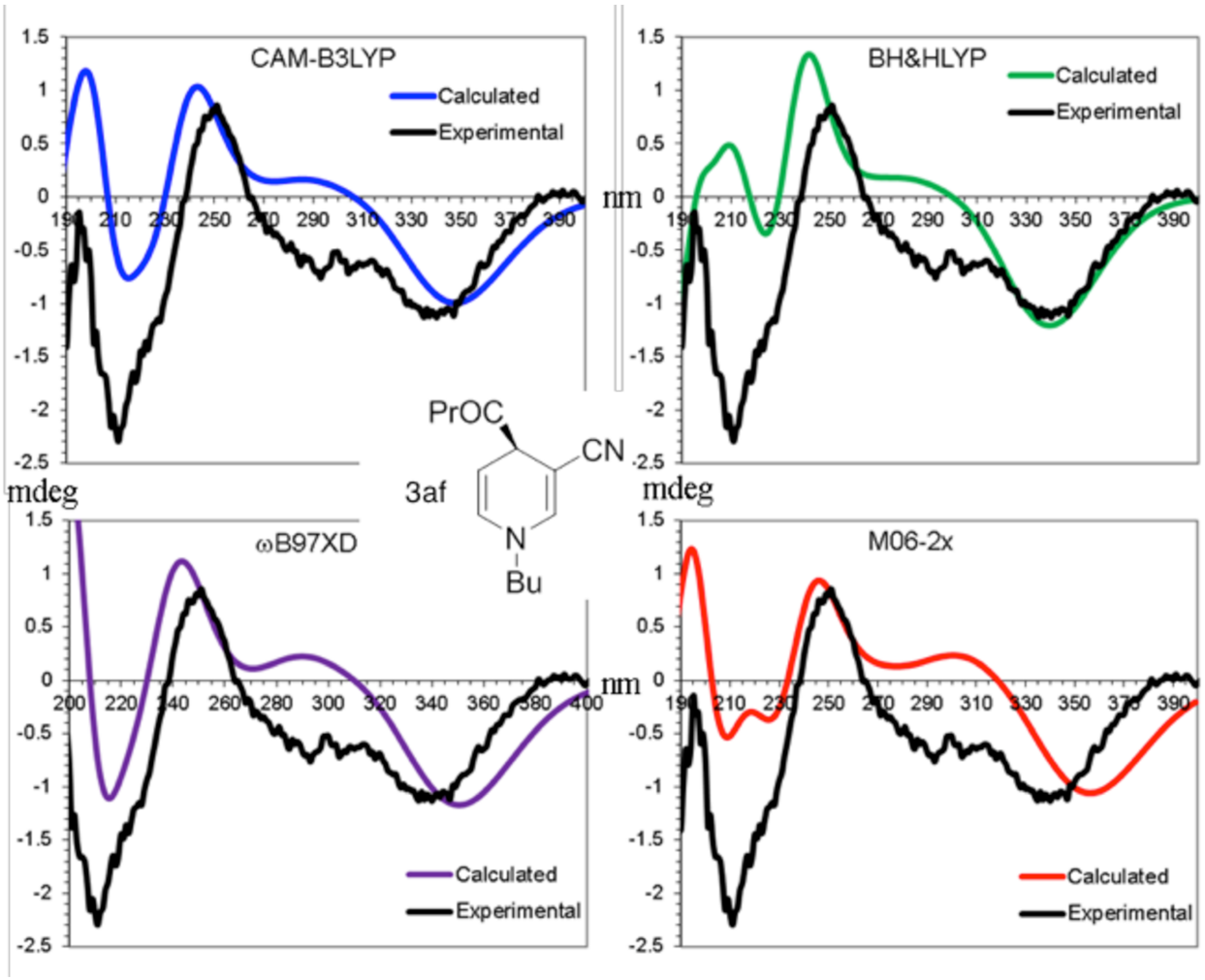
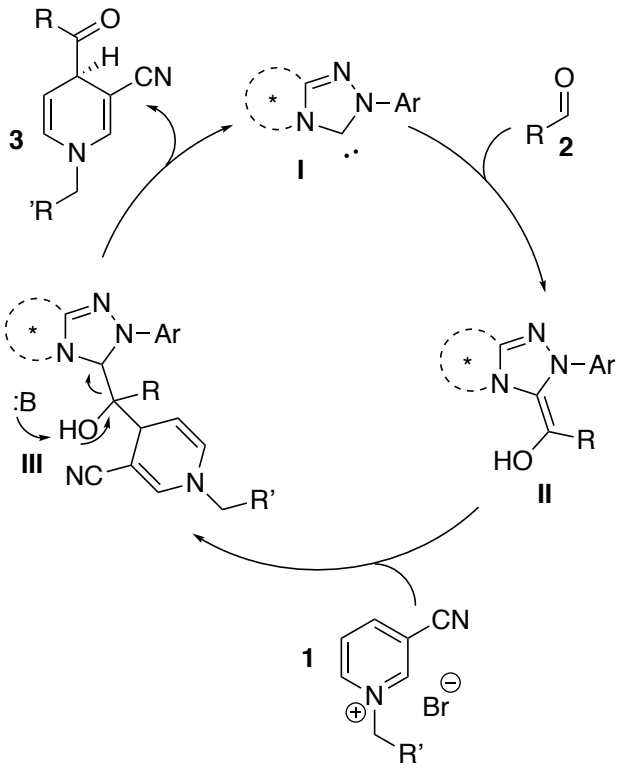


Figure 5. Simulations of the experimental ECD spectrum of **3af**. For each quadrant, the black line corresponds to the experimental spectrum. The colored lines correspond to the simulations obtained on **model-3af** (CO-Me instead of CO-Pr and N-Me instead of N-Bu.

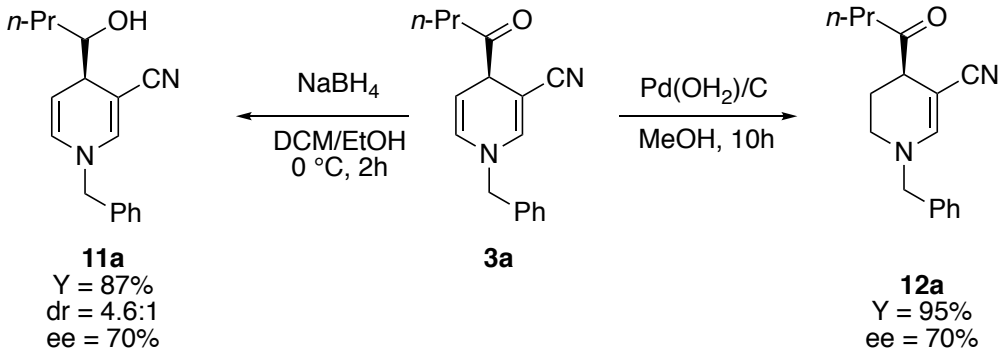
The mechanism for the reported dearomatization reaction has been postulated as shown in Scheme 3.



Scheme 3. Postulated Mechanism for the enantioselective dearomatization of pyridinium salts **1**

The carbene **I** is generated by deprotonation of triazolium salt **C4** and, after the condensation onto the aldehyde **2**, gives the corresponding enaminol intermediate **II**, which is quickly intercepted by the pyridinium salt **1** to afford the adduct **III**. The proton abstraction mediated by the inorganic base leads to the product **3** along with the release of the catalyst.

Finally, we have presented a short elaboration of the product **3a** (Scheme 4), which consisted in the chemoselective reduction to the 1,4-DHP **11a** with $NaBH_4$ or to the tetrahydropyridine derivate **12a** by hydrogenation (H_2, $Pd(OH)_2$).



Scheme 4. Elaboration of 1,4-DHP **3a**

In conclusion, an organocatalyzed nucleophilic dearomatization of activated N-alkylpyridinium salts via NHC catalysis has been disclosed. The process is characterized by a complete regioselectivity towards the addition onto the C-4 of the pyridinium and by a good level of enantioselectivity[11].

3.3. References

[1] E. J. Corey, L. Kürti, *Enantioselective Chemical Synthesis. Methods, Logic and Practice; Direct Book*: Dallas, TX, **2010**.

[2] a) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.*, **2014**, 12, 4807. b) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.*, **2012**, 112, 2642. c) W.-T. Wu, L. Zhang, S.-L. You, *Chem. Soc. Rev.*, **2016**, 45, 1570.

[3] a) C. Zheng, S.-L. You, *Chem.*, **2016**, 1, 830; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem., Int. Ed.*, **2012**, 51, 12662; c) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.*, **2014**, 47, 2558.

[4] a) Y.-C. Zhang, J.-J. Zhao, F. Jiang, S.-B. Sun, F. Shi, *Angew. Chem., Int. Ed.*, **2014**, 53, 13912; b) B. D. Horning, D. W. C. J. MacMillan, *J. Am. Chem. Soc.*, **2013**, 135, 6442; (c) O. G. Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem., Int. Ed.*, **2015**, 54, 8823; (d) G. Bertuzzi, A. Sinisi, L. Caruana, A. Mazzanti, M. Fochi, L. Bernardi, *ACS Catal.*, **2016**, 6, 6473; (e) G. Bertuzzi, A. Sinisi, D. Pecorari, L. Caruana, A. Mazzanti, L. Bernardi, M. Fochi, *Org. Lett.*, **2017**, 19, 834; (f) S.-G. Wang, Q. Yin, C.-X. Zhuo, S.-L. You, *Angew. Chem., Int. Ed.*, **2015**, 54, 647; (g) S.-G. Wang, X.-J. Liu, Q.-C. Zhao, C. Zheng, S.-B. Wang, S.-L. You, *Angew. Chem., Int. Ed.*, **2015**, 54, 14929. (h) T. Fischer, J. Bamberger, O. G. Mancheño, *Org. Biomol. Chem.*, **2016**, 14, 5794; i) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *Nat. Chem.*, **2015**, 7, 842; j) J.-H. Xu, S.-C. Zheng, J.-W. Zhang, X.-Y. Liu, B. Tan, *Angew. Chem., Int. Ed.*, **2016**, 55, 11834; k) D. Janssen-Müller, M. Fleige, D. Schlüns, M. Wollenburg, C. G. Daniliuc, J. Neugebauer, F. Glorius, *ACS Catal.*, **2016**, 6, 5735; l) S. Bera, C. G. Daniliuc, A. Studer, *Angew. Chem., Int. Ed.*, **2017**, 56, 7402. (m) D. M. Flanigan, T. Rovis, *Chem. Sci.*, **2017**, 8, 6566.

[5] a) S. P. Brown, N. C. Goodwin, D. W. C. J. MacMillan, *J. Am. Chem. Soc.*, **2003**, 125, 1192; b) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, **2005**, 44, 6700; c) K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem., Int. Ed.*, **2005**, 44, 6058; d) M. Zhang, W. Sun, G. Zhu, G. Bao, B. Zhang, L. Hong, M. Li, R. Wang, *ACS Catal.*, **2016**, 6, 5290.

[6] For selected recent reviews on NHC catalysis, see: a) Q. Ren, M. Li, L. Yuan, J. Wang, *Org. Biomol. Chem.*, **2017**, 15, 4731; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, 2015, 115, 9307; c) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem., Int. Ed.*, **2012**, 19, 11686.

[7] a) S. Goldmann, J. Stoltefuss, *Angew. Chem., Int. Ed.*, **1991**, 12, 1559; b) M. F. Gordeev, D. V. Patel, B. P. England, S. Jonnalagadda, J. D. Combs, E. M. Gordon, *Bioorg. Med. Chem.*, **1998**, 6, 883.

[8] E. J. Corey, D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **1965**, 4, 1075.

[9] For selected in which Lewis acid are used as additive in NHC catalyzed reactions, see: (a) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.*, **2010**, 6, 766; b) D. T. Cohen, K. A. Scheidt, *Chem. Sci.*, **2012**, 3, 53; c) J. Mo, X. Chen, Y. R. J. Chi, *J. Am. Chem. Soc.*, **2012**, 134, 8810; d) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem., Int. Ed.*, **2012**, 51, 4963; e) Y. Zhang, Y. Lu, W. Tang, T. Lu, D. Du, *Org. Biomol. Chem.*, **2014**, 12, 3009; f) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem., Int. Ed.*, **2014**, 53, 9622.

[10] a) A. Mazzanti, D. Casarini, *WIRES Comput; Mol. Sci.*, **2012**, 2, 613; b) G. Pescitelli, L. Di Bari, N. Berova, *Chem. Soc. Rev.*, **2011**, 40, 4603; c) G. Bringmann, T. Bruhn, K. Maksimenka, Y. Hemberger, *Eur. J. Org. Chem.*, **2009**, 17, 2717; d) T. D. Crawford, M. C. Tam, M. L. J. Abrams, *J. Phys. Chem. A*, **2007**, 111, 12057.

[11] G. Di Carmine, D. Ragno, O. Bortolini, P. P. Giovannini, A. Mazzanti, A. Massi, M. Fogagnolo, *J. Org. Chem.*, **2018**, 83, 2050.

3.4. Experimental section

General Experimental Methods. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers in $CDCl_3$ and acetone-d6 at room temperature. ^{13}C NMR spectra were acquired with the ^{1}H broad-band decoupled mode, and chemical shifts (δ) are reported in ppm relative to residual solvents signals. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230−400 mesh). IR spectra were recorded on a PerkinElmer FT-IR Paragon 500 unit. High-resolution mass spectra (HRMS) were recorded in positive ion mode by an Agilent 6520 HPLC-Chip Q/TF-MS nanospray using a time-of-flight, a quadrupole, or a hexapole unit to produce spectra. Optical rotations were measured at 20 ± 2 °C in the stated solvent; [α]D are given in 10^{-1} deg cm^2 g^{-1}. The enantiomeric ratios were determined by chiral stationary phase HPLC (Phenomenex Lux Amylose 2, 250 mm × 4.6 mm, particle size 5 μm), using an UV detector operating at 254 nm. All commercially available reagents were used as received without further purification, unless otherwise stated. Solvents were distilled from appropriate drying agents. Liquid aldehydes **2a−h** and bases (DBU, TEA, DIPEA) were freshly distilled before their utilization. Inorganic bases were dried (100−120 °C, 5 mmHg, 6 h) and stored in a chamber with phosphorus pentoxide (P_2O_5). Pyridinium salts **1a−f** were synthesized as reported in literature from 3-cyanopyridines and the respective benzyl and alkyl bromides.

(5a*S*,10b*R*)-9-Bromo-2-(perfluorophenyl)-5a,10b-dihydro-4H,6H-indeno[2,1b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium Tetrafluoroborate (C4)

To a flame-dried round-bottom flask with (4a*R*,9a*S*)-6- bromo-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2H)-one (1.00 g, 3.7 mmol, 1.0 equiv) in dichloromethane (25 mL) was added in one portion trimethyloxonium tetrafluoroborate (0.55 g, 3.7 mmol, 1.0 equiv). The suspension was stirred until a homogeneous mixture was achieved (5−6 h). Then (perfluorophenyl)hydrazine (0.73 g, 3.7 mmol, 1.0 equiv) was added, and the reaction was allowed to stir an additional 16 h at which point the reaction was concentrated. After a reflux condenser was installed, triethyl orthoformate (2.00 mL, 18.5 mmol, 5.0 equiv) and chlorobenzene (25 mL) were added and the mixture was heated to reflux in an oil bath for 48 h. The solution was concentrated, triturated with DCM/Et_2O for 4 h, and filtrated to afford the desired triazolium salt **C4** (1.00 g, 49%) as a tan solid: [α]D = −44.4 (c 1.0, acetone); mp (°C) 191−193; ^{1}H NMR (400 MHz, acetone-d6) δ 11.27 (s, br, 1H), 7.76 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.43(d, J=8.1Hz, 1H),6.40(d ,J=4.1Hz, 1H), 5.44(d, J=16.5Hz, 1H), 5.28 (d, J = 16.5 Hz, 1H), 5.22−5.18 (m, 1H), 3.52 (dd, J = 17.3, 4.1 Hz, 1H), 3.27 (d, J = 17.3 Hz, 1H); $^{13}C\{1H\}$ NMR

(101 MHz, acetone-d6) δ 151.6, 146.3, 140.4, 139.6, 137.7, 132.6, 129.4, 127.7, 127.5, 120.1, 77.5, 62.2, 60.1, 36.7; ^{19}F NMR (376 MHz, acetone-d6) δ −146.42 to −146.88 (m, 2F), −149.58 (tt, J =

18.0, 2.5 Hz, 1F), −151.94 (s, 4F), −161.63 (ddd, J = 20.9, 18.0, 2.5 Hz, 2F); FT-IR (neat, cm^{-1}) νmax 3126, 1664, 1595, 1518, 1479, 1326, 1241; HRMS (ESI) m/z [M − BF4]+ calcd for $C_{18}H_{10}BrF_5N_3O$ 457.9922; found 457.9939.

(5a*S*,10b*R*)-2-(2,6-Dichlorophenyl)-4,5a,6,10b-tetrahydroindeno-[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium Tetrafluoroborate (C6)

[α]D = −68.4 (c 1.0, acetone); mp (°C) 197−201; 1H NMR (400 MHz, acetone-d6) δ 11.20 (s, br, 1H), 7.94−7.88 (m, 3H), 7.67 (d, J = 7.6 Hz, 1H), 7.53−7.37 (m, 3H), 6.41 (d, J = 4.1 Hz, 1H), 5.41 (d, J = 16.3 Hz, 1H), 5.30 (d, J = 16.3 Hz, 1H), 5.26−5.24 (m, 1H), 3.58 (dd, J = 17.2, 4.9 Hz, 1H), 3.30 (d, J = 17.2 Hz, 1H); 13C{1H} NMR (101 MHz, acetone-d6) δ 152.4, 146.6, 141.9, 136.7, 135.6, 134.1, 131.2, 130.7, 130.6, 128.4, 126.7, 124.6, 78.4, 63.6, 61.0, 38.2; 19F NMR (376 MHz, acetone-d6) δ −151.5 (s, 4F); FT-IR (neat, cm−1) νmax 3127, 3090, 1595, 1571, 1431, 1352, 1230; HRMS (ESI) m/z [M − BF4]+ calcd for $C_{18}H_{14}Cl_2N_3O$ 358.0508, found 358.0527.

(*S*)-5-(((tert-Butyldimethylsilyl)oxy)diphenylmethyl)-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium Tetrafluoroborate (C1)

[α]D = −93.5 (c 0.40, acetone); mp (°C) 214− 216; ^{1}H NMR (400 MHz, acetone-d6) δ 10.00 (s, br, 1H), 7.66−7.58 (m, 2H), 7.52−7.45 (m, 6H), 7.39−7.34 (m, 2H), 6.38 (d, J = 9.0, 2.5 Hz, 1H), 3.45−3.30 (m, 1H), 3.13−3.04 (m, 1H), 2.01−1.87 (m, 1H), 0.96 (s, 9H), −0.22 (s, 3H), −0.29 (s, 3H); ^{13}C{1H} NMR (101 MHz, acetone-d6) δ 165.0, 143.7, 139.9, 129.5, 129.1, 129.0, 128.6, 128.5, 82.5, 67.6, 25.6, 20.7, 18.5, −4.0; ^{19}F NMR (376 MHz, acetone-d6) δ −146.68 to −146.73 (m, 2F), −149.33 (m, 1F), −151.97 (s, 4F), −161.90 (m, 2F); FT-IR (neat, cm−1) νmax 2950, 2936, 1538, 1520, 1100; HRMS (ESI) m/z [M − BF4]+ calcd for $C_{30}H_{31}F_5N_3OSi$ 572.2151, found 572.2127.

(*S*)-5-Benzhydryl-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium Tetrafluoroborate (C2)

To a flame-dried round-bottom flask with (*S*)-5-benzhydrylpyrrolidin-2-one (0.5 g, 2.00 mmol, 1 equiv) in dichloromethane (20 mL) was added trimethyloxonium tetrafluoroborate (0.33 g, 2.20 mmol, 1.1 equiv), and the reaction mixture was stirred overnight at room temperature. Then, (perfluorophenyl)hydrazine (0.44 g, 2.20 mmol, 1.1 equiv) was added to the mixture, which was stirred overnight and then concentrated. After a reflux condenser was installed, triethyl orthoformate (1.1 mL, 10 mmol, 5.0 equiv) and acetonitrile (15 mL) were added and the reaction mixture was heated at reflux and stirred at this temperature overnight. The solvent was removed in vacuo, and the product was precipitated from EtOAc/hexane to give **C2** (0.63 g, 57%) as an off-white powder: [α]D = +52.1 (c 1.1, acetone); mp (°C) 232−234; ^{1}H NMR (300 MHz, acetone-d6) δ 9.01 (s, br, 1H), 7.69−7.53 (m, 4H), 7.47−7.37 (m, 4H), 7.36−7.24 (m, 2H), 6.18 (ddd, J = 11.1, 7.8, 5.4 Hz, 1H), 4.74

(d, J = 11.1 Hz, 1H), 3.59−3.33 (m, 2H), 3.23−3.02 (m, 1H), 2.83−2.66 (m, 1H); $^{13}C\{1H\}$ NMR (101 MHz, acetone-d6) δ 164.6, 142.4, 140.2, 139.9, 129.6, 129.1, 128.2 (2C), 128.1, 127.6, 65.2, 54.8, 32.7, 21.3; ^{19}F NMR (376 MHz, acetone-d6) δ −146.69 to −147.21 (m, 2F), −149.93 (tt, J = 15.0, 3.0 Hz, 1F), −151.93 (s, 4F), −161.87 to −162.42 (m, 2F); FT- IR (neat, cm−1) νmax 3126, 1598, 1526, 1509, 1456, 1365, 1286, 1175, 999; HRMS (ESI) m/z [M − BF4]+ calcd for $C_{24}H_{17}F_5N_3$ 442.1337, found 442.1363.

General Procedure for the Dearomatization of Pyridinium Salts 1 with Aldehydes 2

General Procedure A (Asymmetric). To a stirred suspension of pyridinium salt **1** (0.40 mmol, 1 equiv) and precatalyst **C6** (0.04 mmol, 0.1 equiv) in anhydrous toluene (2 mL) was added freshly distilled aldehyde **2** (0.60 mmol, 1.5 equiv) under argon followed by the addition of anhydrous sodium carbonate (0.44 mmol, 1.1 equiv) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture) to afford the DHP **3**.

General Procedure B (Racemic). To a stirred suspension of pyridinium salt **1** (0.40 mmol, 1 equiv) and commercially available (Sigma-Aldrich) 6,7-dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate precatalyst (0.04 mmol, 0.1 equiv) in anhydrous toluene (2 mL) was added freshly distilled aldehyde **2** (0.60 mmol, 1.5 equiv) under argon followed by the addition of anhydrous sodium carbonate (0.44 mmol, 1.1 equiv) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture) to afford the racemic DHP **3** with a comparable yield to that of the enantiopure counterpart.

(*R*)-1-Benzyl-4-butyryl-1,4-dihydropyridine-3-carbonitrile (3a)

By following General Procedure A, **3a** (85 mg, 80%) was obtained as a yellow oil after column chromatography on silica gel (cyclo- hexane/EtOAc = 7:3): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 19.5, t_{min} = 26.2, e.r. 85:15; [α]D = −23.0 (c 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.30 (m, 3H), 7.23−7.12 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.1 Hz, 1H), 4.77 (dd, J = 8.1, 4.8 Hz, 1H), 4.36 (s, 2H), 3.96 (d, J = 4.8 Hz 1H), 2.57 (t, J = 8.0, 2H), 1.63 (tq, J = 8.0, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (76 MHz, $CDCl_3$) δ 207.6, 143.6, 136.0, 129.7, 129.4, 128.6, 127.4, 120.7, 101.2, 78.5, 57.9, 47.3, 41.5, 17.1, 14.0; FT-IR (neat, cm^{-1}) νmax 2928, 2857, 2196, 1708, 1662, 1585, 1459, 1399, 1371, 1184; HRMS (ESI) m/z [M + Na]+ calcd for $C_{17}H_{18}N_2NaO$ 289.1317, found 289.1325.

(*R*)-1-Benzyl-4-propionyl-1,4-dihydropyridine-3-carbonitrile (3b)

By following General Procedure A, **3b** (75 mg, 74%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 7.4 min, t_{min} = 8.4 min, e.r. 80:20; [α]D = −20.0 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.28 (m, 3H), 7.22−7.13 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.35 (s, 2H), 3.97 (d, J=4.8Hz, 1H),2.61(q, J=7.2Hz, 2H),1.08(t, J=7.2Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 208.1, 143.4, 135.7, 129.4, 129.1, 128.4, 127.2, 120.5, 101.0, 78.2, 57.6, 46.8, 32.6, 7.6; FT-IR (neat, cm^{-1}) νmax 2924, 2863, 2195, 1721, 1643, 1583, 1465, 1414, 1353, 1172; HRMS (ESI) m/z [M + Na]+ calcd for $C_{16}H_{16}N_2NaO$ 275.1160, found 275.1147.

(*R*)-1-Benzyl-4-pentanoyl-1,4-dihydropyridine-3-carbonitrile (3c)

By following General Procedure A, **3c** (91 mg, 81%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 16.6 min, t_{min} = 18.3 min, e.r. 87:13; [α]D = −18.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.28 (m, 3H), 7.22−7.15 (m, 2H), 6.78 (s, 1H), 5.98 (d, J = 8.0 Hz 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.58 (t, J = 7.0 Hz, 2H), 1.64−1.55 (m, 2H), 1.42−1.23 (m, 2H), 0.90 (t, J = 7.2, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 207.6, 143.5, 135.8, 129.5, 129.2, 128.4, 127.2, 120.5, 101.0, 78.3, 57.7, 47.2, 39.2, 25.6, 22.4, 14.0; FT-IR (neat, cm^{-1}) νmax 2922, 2857, 2196, 1718, 1646, 1590, 1461, 1401, 1362, 1196; HRMS (ESI) m/z [M + Na]+ calcd for $C_{18}H_{20}N_2NaO$ 303.1473, found 303.1481.

(*R*)-1-Benzyl-4-hexanoyl-1,4-dihydropyridine-3-carbonitrile (3d)

By following General Procedure A, **3d** (79 mg, 67%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 16.2 min, t_{min} = 19.4 min, e.r. 86:14; [α]D= −21.6 (c 1.0, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 3H), 7.22−7.13 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.77 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.96 (d, J = 4.8 Hz, 1H), 2.57 (t, J = 7.8, 2H), 1.65−1.54 (m, 2H), 1.37−1.22 (m, 4H), 0.88 (t, J = 7.4, 3H); ^{13}C{1H} NMR (76 MHz, $CDCl_3$) δ 207.7, 143.6, 136.0, 129.6, 129.3, 128.6, 127.4, 120.7, 101.2, 78.5, 57.9, 47.3, 39.6, 31.6, 23.4, 22.7, 14.2; FT-IR (neat, cm−1) νmax 2929, 2859, 2196, 1710, 1651, 1590, 1455, 1411, 1360, 1180; HRMS (ESI) m/z [M + Na]+ calcd for $C_{19}H_{22}N_2NaO$ 317.1630, found 317.1615.

(*R*)-1-Benzyl-4-(3-phenylpropanoyl)-1,4-dihydropyridine-3-carbonitrile (3e)

By following General Procedure A, **3e** (100 mg, 76%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5): HPLC (Phenomenex Lux Amylose 2)

n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 28.5 min, t_{min} = 34.5 min, e.r. 89:11; [α]D = −21.3 (c 1.2, CHCl3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.29 (m, 3H), 7.28−7.24 (m, 2H), 7.22−7.12 (m, 5H), 6.76 (s, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.71 (dd, J = 8.0, 4.8 Hz, 1H), 4.34 (s, 2H), 3.95 (d, J = 4.8 Hz, 1H), 2.92 (s, 4H); ^{13}C{1H} NMR (76 MHz, $CDCl_3$) δ 206.3, 143.5, 140.9, 135.7, 129.6, 129.1, 128.5, 128.4, 128.4, 128.4, 127.1, 126.1, 100.6, 78.1, 57.7, 47.3, 41.1, 29.6; FT-IR (neat, cm^{-1}) νmax 2962, 2934, 2197, 1717, 1674, 1455, 1261; HRMS (ESI) m/z [M + Na]+ calcd for $C_{22}H_{20}N_2NaO$ 351.1473, found 351.1480.

(*R*)-1-Benzyl-4-(3-methylbutanoyl)-1,4-dihydropyridine-3-carbonitrile (3f)

By following General Procedure A, **3f** (41 mg, 37%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 14.8 min, t_{min} = 18.8 min, e.r. 87:13; [α]D = −34.7 (c 1.1, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.27 (m, 3H), 7.22−7.14 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.75 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.94 (d, J = 4.8 Hz, 1H), 2.45 (d, J = 6.8 Hz, 2H), 2.26−2.10 (m, 1H), 0.92 (d, J = 6.5 Hz, 6H); ^{13}C{1H} NMR (101 MHz, CDCl3) δ 206.8, 143.4, 135.8, 129.5, 129.1, 128.4, 127.1, 120.4, 100.7, 78.2, 57.6, 48.3, 47.4, 24.2, 22.6, 22.6; FT-IR (neat, cm^{-1}) νmax 2959, 2871, 2196, 1710, 1673, 1590, 1465, 1408, 1363, 1179; HRMS (ESI) m/z [M + Na]+ calcd for $C_{18}H_{20}N_2NaO$ 303.1473, found 303.1487.

(*R*)-1-Benzyl-4-(cyclopropanecarbonyl)-1,4-dihydropyridine-3-carbonitrile (3g)

By following General Procedure A, **3g** (50 mg, 47%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 21.6 min, t_{min} = 33.5 min, e.r. 76:24; [α]D = −18.7 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.30 (m, 3H), 7.23−7.12 (m, 2H), 6.77 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.86 (dd, J = 8.0, 4.6 Hz, 1H), 4.36 (s, 2H), 4.17 (d, J = 4.6 Hz, 1H), 2.14 (tt, J = 7.0, 6.5 Hz, 1H), 1.14−1.05 (m, 2H), 1.02−0.92 (m, 2H); ^{13}C{1H} NMR (101 MHz, CDCl3) δ 207.1, 143.4, 135.8, 129.4, 129.1, 128.3, 127.1, 120.5, 100.9, 78.3, 57.6, 47.6, 29.7, 18.1, 12.1, 11.8; FT-IR (neat, cm−1) νmax 2923, 2854, 2197, 1715, 1674, 1591, 1412, 1387; HRMS (ESI) m/z [M + Na]+ calcd for $C_{17}H_{16}N_2NaO$ 287.1160, found 287.11579.

(*R*)-4-Butyryl-1-(4-isopropylbenzyl)-1,4-dihydropyridine-3-carbonitrile (3i)

By following General Procedure A, **3i** (46 mg, 37%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 13.3 min, t_{min} = 15. 5 min, e.r. 84:16; [α]D = −13.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 6.5 Hz, 2H), 7.10 (d, J = 6.5 Hz, 2H), 6.76 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.96 (d, J =

4.8 Hz, 1H), 2.97−2.84 (m, 1H), 2.56 (d, J = 7.4 Hz, 2H), 1.70−1.61 (m, 2H), 1.24 (d, J = 4.6 Hz, 6H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.4, 149.1, 143.4, 133.0, 129.5, 127.2, 127.1, 120.5, 100.7, 78.0, 57.4, 47.1, 41.2, 33.8, 23.9, 16.9, 13.7; FT-IR (neat, cm−1) νmax 2961, 2873, 2196, 1712, 1672, 1589, 1409, 1179, 1120; HRMS (ESI) m/z [M + Na]+ calcd for $C_{20}H_{24}N_2NaO$ 331.1786, found 331.1811.

(*R*)-1-(4-(tert-Butyl)benzyl)-4-butyryl-1,4-dihydropyridine-3-carbonitrile (3j)

By following General Procedure A, **3j** (103 mg, 80%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 6.3 min, t_{min} = 6.9 min, e.r. 86:14; [α]D = −20.2 (c 0.9, CHCl3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 6.5 Hz, 2H), 7.11 (d, J = 6.5 Hz, 2H), 6.76 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.96(d, J=4.8Hz, 1H), 2.55(d, J=7.5Hz, 2H), 1.64(tq, J= 7.5, 7.4 Hz, 2H), 1.31 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.4, 151.5, 143.4, 132.7, 129.6, 126.9, 126.0, 126.0, 120.6, 100.8, 78.0, 57.3, 47.1, 41.3, 34.6, 31.3, 31.3, 16.9, 13.7, 13.6; FT-IR (neat, cm−1) νmax 2964, 2870, 2196, 1719, 1674, 1592, 1415, 1180, 1115; HRMS (ESI) m/z [M + Na]+ calcd for $C_{21}H_{26}N_2NaO$ 345.1943, found 345.1961.

(*R*)-4-Butyryl-1-(3,5-di-tert-butylbenzyl)-1,4-dihydropyridine-3- carbonitrile (3k)

By following General Procedure A, **3k** (82 mg, 53%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8.5:1.5): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 6.3 min, t_{min} = 6.8 min, e.r. 84:16; [α]D = −39.0 (c 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.98 (s, 2H), 6.78 (s, 1H), 6.00 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.35 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.58 (t, J = 7.2 Hz, 2H), 1.62 (qt, J = 7.4, 7.2 Hz, 2H), 1.31 (s, 18H), 0.92 (t, J = 7.4 Hz, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.3, 151.8, 143.6, 134.9, 129.6, 122.3, 121.1, 120.6, 100.7, 77.9, 58.2, 47.2, 41.1, 34.9, 31.4, 16.9, 13.7; FT-IR (neat, cm−1) νmax 2959, 2873, 2191, 1731, 1664, 1591, 1406, 1182, 1131; HRMS (ESI) m/z [M + Na]+ calcd for $C_{25}H_{34}N_2NaO$ 401.2569, found 401.2553.

(*R*)-4-Butyryl-1-(4-fluorobenzyl)-1,4-dihydropyridine-3-carbonitrile (3l)

By following General Procedure A, **3l** (92 mg, 81%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 18.5 min, t_{min} = 20.9 min, e.r. 82:18; [α]D = −19.0 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.13 (m, 2H), 7.13−7.00 (m, 2H), 6.77 (s, 1H), 5.93 (d, J = 8.0 Hz, 1H), 4.79 (dd, J = 8.0, 4.8 Hz, 1H), 4.34 (s, 2H), 3.97(d, J=4.8Hz, 1H), 2.56(d, J=7.2Hz, 2H), 1.66(qt, J=7.4, 7.2 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz,

$CDCl_3$) δ 207.3, 163.9, 161.4, 143.3, 131.6, 129.3, 129.0, 120.4, 116.3, 116.1, 101.1, 78.5, 57.0, 47.1, 41.4, 17.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.37 to −113.44 (m, 1F); FT-IR (neat, cm−1) νmax 2965, 2934, 2197, 1670, 1650, 1604, 1509, 1223, 1159; HRMS (ESI) m/z [M + Na]+ calcd for C17H17FN2NaO 307.1223, found 307.1235.

(*R*)-1-(4-Isopropylbenzyl)-4-(3-phenylpropanoyl)-1,4-dihydropyridine-3-carbonitrile (3m)

By following General Procedure A, **3m** (89 mg, 60%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5): HPLC (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 20.5 min, t_{min} = 26.3 min, e.r. 86:14; [α]D = −33.9 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.16 (m, 5H), 7.13− 7.01 (m, 4H), 6.74 (s, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.70 (dd, J = 8.0, 4.8 Hz, 1H), 4.30 (s, 2H), 3.95 (d, J = 4.8 Hz, 1H), 2.87−2.75 (m, 5H), 1.24 (d, J = 5.0, 6H); $^{13}C\{1H\}$ NMR (101 MHz, CDCl3) δ 206.4, 149.2, 143.5, 132.9, 129.7, 128.5, 128.5, 128.4, 127.2, 127.2, 126.1, 120.5, 100.5, 77.2, 57.5, 47.4, 41.1, 33.8, 29.6, 23.9; FT-IR (neat, cm^{-1}) νmax 2959, 2926, 2196, 1716, 1672, 1589, 1409, 1179, 1120; HRMS (ESI) m/z [M + Na]+ calcd for $C_{25}H_{26}N_2NaO$ 393.1943, found 393.1958.

(*R*)-1-(4-(tert-Butyl)benzyl)-4-(3-methylbutanoyl)-1,4-dihydropyridine-3-carbonitrile (3n)

By following General Procedure A, **3n** (60 mg, 45%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2): HPLC (Phenomenex LuxAmylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 9.4 min, t_{min} = 12.8 min, e.r. 88:12; [α]D = −27.9 (c 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.35 (m, 2H), 7.16−7.07 (m, 2H), 6.76 (s, 1H), 5.96 (d, J = 8.0 Hz, 1H), 4.75 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.94 (d, J = 4.8 Hz, 1H), 2.46 (d, J = 6.8 Hz, 2H), 2.13−2.21 (m, 1H), 1.31 (s, 9H), 0.92 (d, J = 6.6 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.9, 151.4, 143.4, 132.7, 129.6, 126.9, 126.0, 120.5, 100.6, 77.3, 57.4, 48.3 47.5, 34.6, 31.3, 24.2, 22.6; FT-IR (neat, cm−1) νmax 2959, 2871, 2197, 1711, 1672, 1589, 1408, 1362, 1179, 1117; HRMS (ESI) m/z [M + Na]+ calcd for $C_{22}H_{28}N_2NaO$ 359.2099, found 359.2107.

(*R*)-1-Butyl-4-butyryl-1,4-dihydropyridine-3-carbonitrile (3o)

By following General Procedure A, **3o** (33 mg, 36%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/ EtOAc = 8:2): HPLC (Phenomenex Lux Amylose 2) n-hexane/i- PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 12.3 min, t_{min} = 13.6 min, e.r. 87:13; [α]D = −19.1 (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1H), 5.90 (d, J = 7.9 Hz, 1H), 4.73 (dd, J = 8.0, 4.8 Hz, 1H), 3.94 (d, J = 4.8 Hz, 1H), 3.16 (t, J = 7.1 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.69−1.48 (m, 4H), 1.38−1.25 (m, 2H), 0.98−0.88 (m, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.6, 1433, 129.2, 120.8, 100.5, 77.3, 54.2, 47.0, 41.2, 31.9, 29.7, 19.4, 16.9, 13.7, 13.6; FT-IR

(neat, cm−1) νmax 2961, 2929, 2194, 1712, 1676, 1588, 1415, 1217, 1137; HRMS (ESI) m/z [M + Na]+ calcd for $C_{14}H_{20}N_2NaO$ 255.1473, found 255.1454.

(*R*)-1-Benzyl-4-(4-chlorobenzoyl)-1,4-dihydropyridine-3-carbonitrile (7a)

To a stirred suspension of pyridinium salt **1a** (0.20 mmol, 1 equiv) and pre-catalyst **C1−C6** (0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was added p-chlorobenzaldehyde **6** (42 mg, 0.30 mmol, 1.5 equiv) under argon followed by the addition of anhydrous sodium carbonate (23 mg, 0.22 mmol, 1.1 equiv) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc = 8:2) to afford the 1,4-DHP **7a** contaminated by the 1,2-DHP **8a**. (See Table 4 for yields and ratios.) For **7a** of entry 2: HPLC (Phenomenex Lux Cellulose 4) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 20.5 min, t_{min} = 30.6 min, e.r. 75:25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93−7.89 (m, 2H), 7.48−7.44 (m, 2H), 7.41−7.33 (m, 3H), 7.22−7.19 (m, 2H), 6.88 (s, 1H), 5.96 (d, J = 8.0 Hz, 1H), 4.91 (d, J = 4.6 Hz, 1H), 4.74 (dd, J = 8.0, 4.6 Hz, 1H), 4.39 (s, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 194.6, 143.8, 140.4, 135.9, 133.3, 130.6, 130.0, 129.4, 129.4, 128.6, 127.4, 120.5, 100.4, 78.2, 57.9, 42.9; FT-IR (neat, cm−1) νmax 2925, 2854, 2229, 1670, 1587,1264, 1091; HRMS (ESI) m/z [M + Na]+ calcd for $C_{20}H_{15}ClN_2NaO$ 357.0771, found 357.0793; **8a** ^{1}H NMR (300 MHz, $CDCl_3$; selected data) δ 7.83−7.80 (m, 2H), 5.87 (d, J = 8.0 Hz, 1H).

(*R*)-1-Benzyl-4-(1-hydroxybutyl)-1,4-dihydropyridine-3-carbonitrile (11a)

To a cooled (0 °C) and stirred solution of DHP **3a** (53 mg, 0.20 mmol, 1 equiv) in DCM/EtOH 3:1 (2 mL) was added $NaBH_4$ (9 mg, 0.24 mmol, 1.2 equiv) in one portion. The resulting mixture was vigorously stirred at 0 °C for 2 h; then a saturated NH_4Cl solution was added drop by drop until the release of gas stopped. After this point, the solution was extracted with DCM (3 × 5 mL). The combined organic phases were collected, dried (anhydrous Na_2SO_4), and purified by flash column chromatography on silica gel (cyclo-hexane/EtOAc mixture 7.5:2.5) to afford **11a** (45 mg, 87%, d.r. 82:18) as a yellow oil: HPLC for the major diastereoisomer (Phenomenex Lux Amylose 2) n-hexane/i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 12.17 min, t_{min} = 13.06 min, e.r. 83:17); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5H), 6.80−6.71 (m, 1H), 6.02−5.92 (m, 1H), 4.73 (dd, J = 8.1, 4.4 Hz, 0.15H_{min}), 4.65 (dd, J = 8.1, 4.4 Hz, 0.85H_{maj}), 4.32 (s, 2H), 3.62−3.53 (m, 0.85H_{maj}), 3.52− 3.49 (m, 0.15H_{min}), 3.33−3.30 (m, 0.15H_{min}), 3.29−3.23 (m, 0.85H_{maj}), 1.59−1.29 (m, 4H), 0.99−0.90 (m, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 144.3, 144.1, 136.1, 130.6, 129.6, 129.0, 128.2, 127.1, 121.0, 103.0, 100.8, 80.5, 76.8, 75.5, 74.0, 57.5, 39.9, 34.8, 34.6, 20.4, 19.3, 14.1; FT-IR (neat, cm^{-1}) νmax 3461, 2961, 2958, 2930, 2871, 2191, 1673, 1591, 1455, 1414, 1181; HRMS (ESI) m/z [M +Na] calcd for $C_{17}H_{20}N_2NaO$ 291.1473, found 291.1459.

(*R*)-1-Benzyl-4-butyryl-1,4,5,6-tetrahydropyridine-3-carbonitrile (12a)

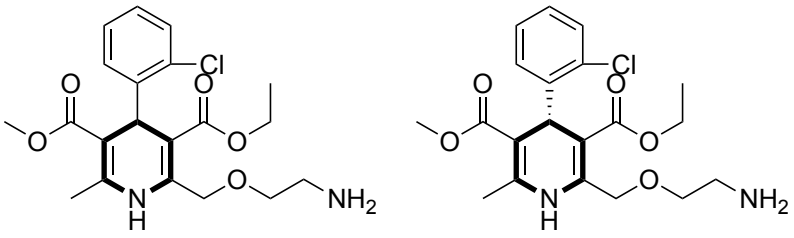
A vigorously stirred mixture of DHP **3a** (53 mg, 0.20 mmol, 1 equiv), $Pd(OH)_2/C$ (20% w/w, 20 mg), and MeOH (3 mL) was degassed under a vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The mixture was vigorously stirred at room temperature for 10 h, then filtered on Celite, and concentrated; the resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture 8:2) to afford **12a** (50 mg, 95%) as a yellow oil: HPLC (Phenomenex Lux Amylose 2) n-hexane/ i-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 15.5 min, t_{min} = 17.3 min, e.r. 85:15; [α]D = −39.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (m, 2H), 7.20−7.12 (m, 2H), 7.03 (s, 1H), 4.28 (s, 2H), 3.24−3.18 (m, 1H), 3.13 (dd, J = 12.2, 3.8 Hz, 1H), 3.06− 2.95 (m, 1H), 2.78−2.51 (m, 2H), 2.16 (ddt, J = 13.4, 3.8, 2.8 Hz, 1H), 1.71−1.50 (m, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 209.9, 148.0, 135.7, 129.0, 128.2, 127.4, 123.2, 69.7, 59.7, 43.7, 43.3, 42.5, 21.6, 17.1, 13.7; FT-IR (neat, cm^{-1}) νmax 2961, 2874, 2182, 1709, 1617, 1423, 1360, 1124; HRMS (ESI) m/z [M + Na]+ calcd for $C_{17}H_{20}N_2NaO$ 291.1473, found 291.1487.

4 NHC-Catalyzed Oxidative Desymmetrization of Pharmaceutically Relevant 1,4-Dihydropyridines

4.1 Introduction

1,4-Dihydropyridine (1,4-DHP) derivates are privileged pharmaceutically structures that are widely used in the treatment of cardiac diseases. They showed high vascular selectivity due to which these drugs are primarily employed to control the arterial pressure and circulatory disorders[1]. Moreover, they were found to exhibit a wide range of pharmacological activities such as analgesic, morphine agonist, antispasmodic and anticancer activities[2]. Beside their biological actions they are also useful intermediates to prepare other substituted heterocyclic frameworks[3] and they are broadly employed in reductive reaction as hydride source[4].

The first synthesis of 1,4-DHPs was disclosed by Hantzsch in 1881 and this procedure has remained the most common method for the preparation of this class of compounds[5]. However, the approach proposed by Hantzsch allows to efficiently obtain only symmetrical 3,5-disubstituted 1,4-DHPs from a β-dicarbonyl compound, an aldehyde, and a β-enamino ester. Furthermore, the control of the enantioselectivity in these pharmaceutically active molecules has proven to be crucial for the correct biological activity[6]. For example, adverse events such as peripheral edema, dizziness, headache, flushing and abdominal pain are associate to the use of Amlodipine (commercial name for the racemic mixture), while clinical trials have shown that Levamlodipine (*S*-enantiomer of Amlodipine) is rarely associated with these side effects (Scheme 1)[7]. Thus, synthetic chemists have assumed the challenge of preparing enantiomerically enriched 1,4-DHPs using chiral auxiliary or by resolution of racemates (Scheme 2)[8].



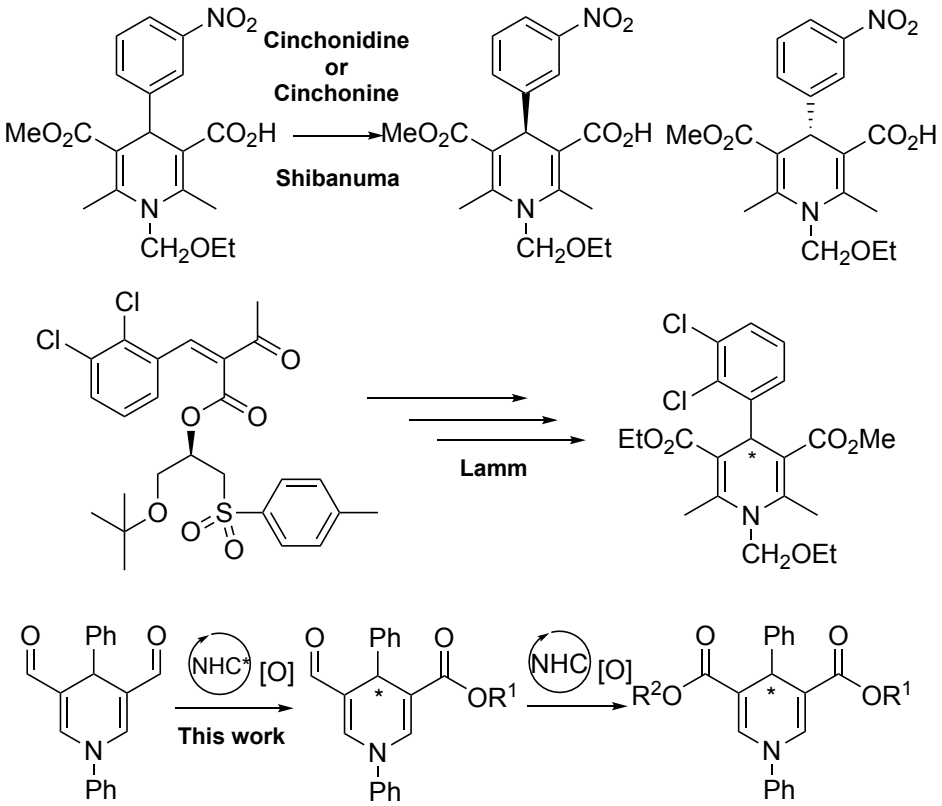
Amlodipine
Norvasc®, others

Levamlodipine
EsCordi Cor®, others

Scheme 1. Amlodipine was placed on the market in 1990 as racemic mixture. At the moment Levamlodipine, its (S)-enantiomer, is replacing Amlodipine.

Metal-catalyzed methods to obtain this class of compounds are missing in literature, whereas only few examples of organocatalytic enantioselective synthesis have been developed; importantly, there are no reported catalytic reactions to directly prepare enantioenriched 3,5-diesters, which are typically

bioactive molecules[9]. Recently, NHC (N-Heterocyclic Carbene) catalysis has emerged as a powerful tool in desymmetrization and resolution of alcohols via external and internal oxidation of Breslow intermediate[10]. In 2004, Rovis and co-workers disclosed the conversion of α-haloaldehydes into the corresponding acylazoliums promoted by a NHC-catalyzed internal oxidative process and applied this in desymmetrization of meso-diols[11]. Nowadays, the use of an external oxidant is preferable and after the seminal work reported by Studer and co-worker in 2010, the Kharasch oxidant is ubiquitous in works where NHC organocatalysts are applied in oxidative mode[12]. In our knowledge, dialdehydes are not covered in NHC-catalyzed oxidative desymmetrizations[13]. Thus, we envisioned the opportunity to investigate this approach, for the first time, on 1,4-dihydropyridine-3,5-dicarbaldehydes in order to access pharmacologically relevant enantioenriched 3,5-dicarboxyl-1,4-DHPs. Although the activation of β-aza-unsaturated aldehydes by NHC is challenging, due the poor attitude of the carbonyl to undergo nucleophilic addition, and 1,4-DHPs tend to aromatize into pyridines in the presence of an oxidant, we were able to obtain good results in terms of reactivity and enantioselectivity (Scheme 2).



Scheme 2. Preparation of optically pure asymmetric 3,5-dicarboxylic-1,4-dihydropyridines.

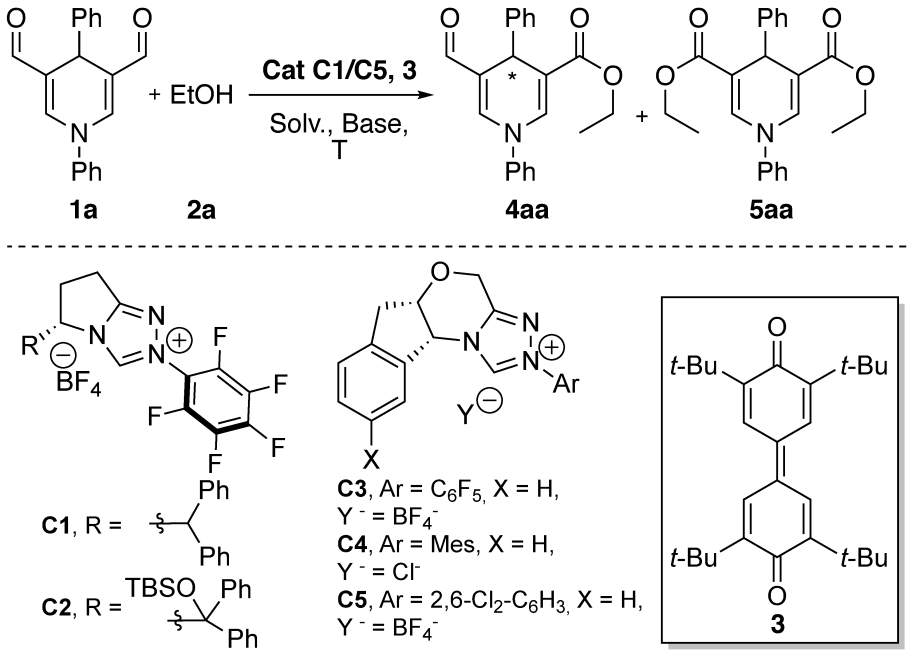
4.2 Results and discussion

At the outset of our study, we searched for a valid procedure to synthetize 1,4-dihydropyridine 3,5-dicarbaldehydes. After several attempts we modified a known three-component procedure using

microwave (MW) heating as thermal energy source (see Experimental Section)[14]. Even though the yields of DHPs are modest (35-56 %) by this procedure, the starting materials employed are cheap and readily available, and the purification is easy to perform by column chromatography. Hence, we started our investigation using DHP **1a** as the model dialdehyde, ethanol **2a** as the nucleophile and quinone **3** (Kharasch oxidant) as the external oxidant. Main results are summarized in Table 1 (see the Experimental Section for more details on the optimization step).

When the reaction was performed at room temperature in DCM with 20 mol% of **C1** and 25 mol% of DIPEA as base, **4aa** was formed smoothly in 48% yield with modest enantioselectivity (50% ee). The diester **5aa**, which was produced by consecutive NHC-catalyzed oxidation of the monoester **3aa**, was recovered in 12% yield (entry 1). This preliminary result encouraged us to screen different chiral NHCs in order to improve reactivity and enantioselectivity. Pyrrolidinone-derivates **C1** and **C2** gave good results in terms of reactivity but poor enantioselectivity (entries 1 and 2). Pentafluorophenyl- and mesityl-substituted aminoindanol-derived catalysts **C3** and **C4** showed no reactivity towards the substrates (entries 3 and 4), likely for bulky reasons in case of **C4**. Finally, we found that the 2,6-dichlorophenyl- substituted aminoindanol-derived catalyst **C5** afforded the best result in term of enantioselectivity (82% ee, entry 5) and for this reason we selected it as the catalyst for further screening. We observed a slightly increase of reactivity using an equimolar amount of base (entry 6) and a higher yield of **4aa** (51%) working at a higher concentration (0.16 M, entry 7). Then, we moved to screen different solvents and we realized that $CHCl_3$ was the most suitable medium for the reaction (entry 11). By contrast, THF, ACN and DCE showed no significant improvement (entries 8-10). Furthermore, we observed that in ACN the starting DHP **1a** was not completely soluble, and a greater amount of diester **5aa** (84%) was collected in this case (entry 9). We thought this result was due to the different solubility between **1a** and the product **4aa** that made this latter more accessible for a subsequence oxidation in the medium. We also tried the use of 4Å MS but no appreciable improvement was observed (entry 12). Different bases were screened as well. Unfortunately, replacement of DIPEA with other organic or inorganic bases did not improve the process (entries 13-15). Noteworthy, KHMDS and K_3PO_4 raised up the reaction rate but unfortunately the stereoselectivity dropped down, even though the reaction was performed at low temperature (for more details, see the Experimental Section). Finally, a further increase of concentration (0.40 M) and reaction temperature (40 °C) led to good reactivity along with excellent enantioselectivity (entry 17). Unfortunately, we tried to decrease the catalytic loading to 10 mol% but a significant loss of reactivity was observed (entry 18).

Table 1. Screening of reaction conditions[a].

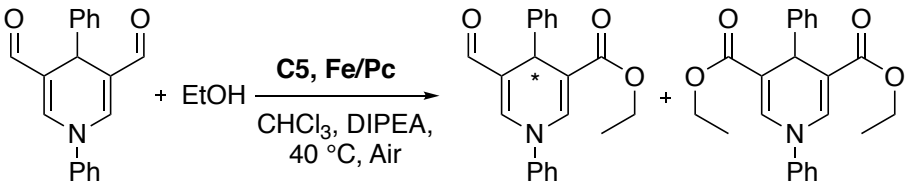


entry	NHC	Solvent (M)	Base (mol%)	4aa (%)[b]	5aa (%)[b]	ee (%)[c]
1	**C1**	DCM (0.04)	DIPEA (25)	43	12	50
2	**C2**	DCM (0.04)	DIPEA (25)	20	-	40
3	**C3**	DCM (0.04)	DIPEA (25)	-	-	nd
4	**C4**	DCM (0.04)	DIPEA (25)	-	-	nd
5	**C5**	DCM (0.04)	DIPEA (25)	29	-	82
6	**C5**	DCM (0.04)	DIPEA (100)	36	-	82
7	**C5**	DCM (0.16)	DIPEA (100)	51	8	82
8	**C5**	THF (0.16)	DIPEA (100)	31	12	3
9	**C5**	ACN (0.16)	DIPEA (100)	49	18	84
10	**C5**	DCE (0.08)	DIPEA (100)	67	10	84
11	**C5**	$CHCl_3$ (0.16)	DIPEA (100)	70	13	90
12[d]	**C5**	$CHCl_3$ (0.16)	DIPEA (100)	69	12	88
13	**C5**	$CHCl_3$ (0.16)	DBU (100)	-	-	-
14[e]	**C5**	$CHCl_3$ (0.16)	KHMDS[f] (25)	53	13	71
15[e,g]	**C5**	$CHCl_3$ (0.16)	K_3PO_4 (25)	74	11	82
17[h,i]	**C5**	$CHCl_3$ (0.40)	DIPEA (100)	70	7	91
18[i,j]	**C5**	$CHCl_3$ (0.40)	DIPEA (100)	25	2	91

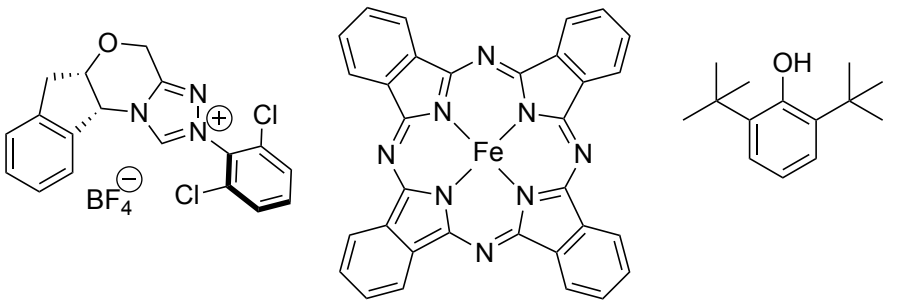
[a]Reactions performed with 0.04 mmol of **1a** at RT for 72 h, 20 mol% of NHC, **3** 0.04 mmol and **2a** 0.2 mmol. [b]Isolated yield. [c]Determined by CSP HPLC. [d]Reaction performed with 4Å MS. [e]7h. [f]1M in Toluene. [g]Reaction performed at 0 °C. [h]16h. [i]Reaction performed at 40°C. [j]Reaction performed using 10 mol% of NHC.

An aerobic oxidation version with a catalytic amount of iron (II) phthalocyanine (**6** Fe/PC), which acts as an electron-transfer mediator (ETM), was also investigated[15]. This catalytic system allows to obtain and regenerate in situ the oxidant **3** employing catalytic 2,6-di-*tert*-butylphenol **7** as the precursor and O_2 as the terminal oxidant. With the conditions optimized before (Table1, entry 17), a poorer result was observed with the new catalytic system at room temperature in terms of yield (46%) and stereoselectivity (86% ee; Table 2, entry 1). Increasing the loading of **6** and **7** (10 mol% and 40 mol%, respectively) led to an improve of yield (53%) and enantioselectivity as well (90% ee, entry 2). Performing the reaction at 40 °C accelerated the catalytic process at the expense, however, of enantioselectivity (entries 3 and 4). Therefore, we decided to move back to the method in which the Kharasch oxidant **3** is employed in stoichiometric amount, supported by the fact that the reduced product of **3** (not shown) is readily recovered by chromatography of the reaction mixture and re-oxidized to **3** (see the Experimental Section).

Table 2. Screening of reaction conditions using Fe/Pc mediator system[a].



1a **2a** **4aa** **5aa**



C5 **6 Fe/Pc** **7**

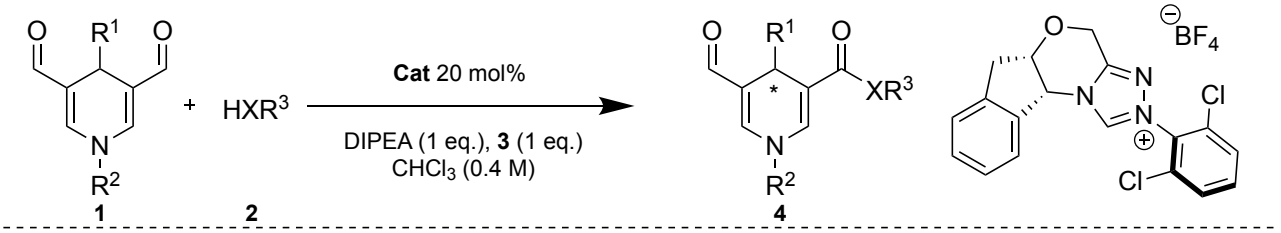
entry	**7** (eq.)	Fe/Pc (eq.)	Temp. (°C)	Time (h)	**4aa** (%)[b]	**5aa** (%)[b]	ee (%)[c]
1	0.2	0.05	25	24	46	5	86
2	0.4	0.1	25	24	53	7	90
3	0.4	0.1	40	24	52	7	86
4	0.4	0.1	40	5	44	4	86

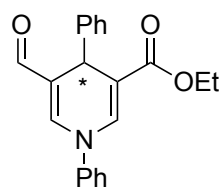
[a]Reaction conditions: **1a** (0.04 mmol, 1 eq.), **2a** (0.2 mmol, 5 eq.), **DIPEA** (0.004 mmol, 1eq.), **C5** (0.008 mmol, 0.2 eq.), $CHCl_3$ (250 μL), balloon with air. [b]Isolated yield. [c]Determined by CSP HPLC.

With the optimized conditions in hand (Table 1, entry 17) we explored the scope of the reaction as summarized in Table 3. We observed an interesting trend replacing ethanol **2a** with other alcohols. Indeed, an increase in the hindrance of nucleophile produced an improvement in terms of enantioselectivity (**4aa**, **4ab**, **4ac**, **4ae**), which could be explained by a synergist effect during the addition of the catalyst onto the dialdehyde. Likely, a hydrogen bonding network with the nucleophile is involved in the transition state. This hypothesis is corroborated by the strong erosion of enantiomeric excess when ethanethiol was used instead of ethanol (**4ad**: 79% ee; **4aa**: 91% ee). Unfortunately, the reactivity dropped down in case of the bulky isopropyl alcohol as the nucleophile (**4ac**, 25% yield). The presence of electron withdrawing and electron donating groups on the aromatic ring in position 4 of the 1,4-DHP did not significantly affect the reactivity and enantioselectivity of the oxidation process (**4ba**, **4ca**, **4da**, **4ea**, **4fa**, **4ga**, **4ha**). Noteworthy, groups in the *ortho* position

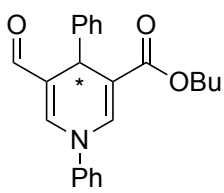
of the C4 aryl substituent make the enantioselectivity more efficient (**4da**, **4ea**). Best results in terms of reactivity were observed with aliphatic substituents in position 4 of the DHP (**4ia**, **4if**, **4ja**) with maintenance of good levels of enantioselectivity. Even when electron withdrawing and electron donating groups were placed on the N1 aniline moiety no appreciable variation of the reaction efficiency was observed (**4ka**, **4ia**). On the contrary, an aliphatic substituent on N1 led to a significant drop of reactivity (**4ma**).

Table 3. Reaction scope[a].

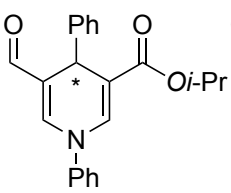




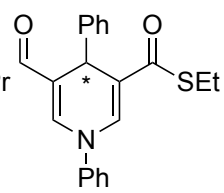
4aa Y =70%
ee = 91%



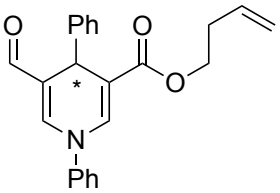
4ab Y =62%
ee = 95%



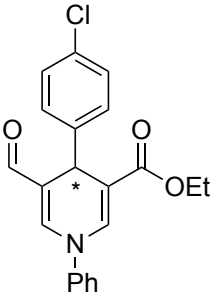
4ac Y =25%
ee = 98%



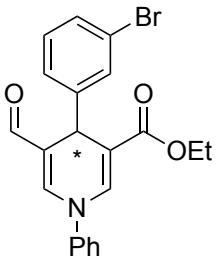
4ad Y =64%
ee = 79%



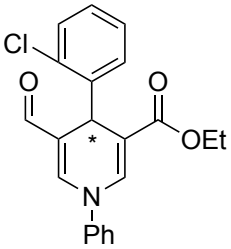
4ae Y =67%
ee = 96%



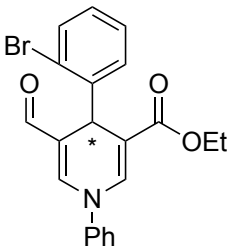
4ba Y =55%
ee = 93%



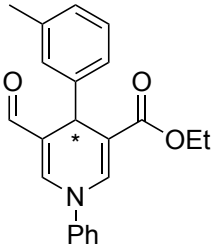
4ca Y =48%,
ee = 94%



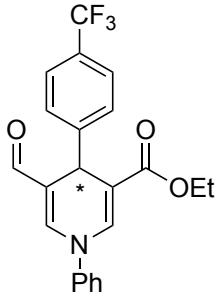
4da Y =70%
ee = 98%



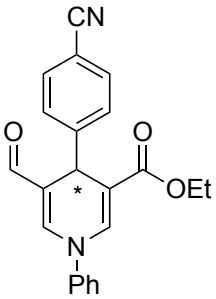
4ea Y =61%
ee = 96%



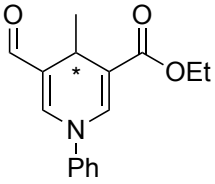
4fa Y =68%
ee = 92%



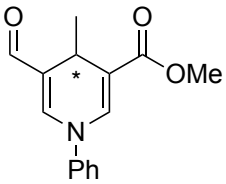
4ga Y =64%
ee = 92%



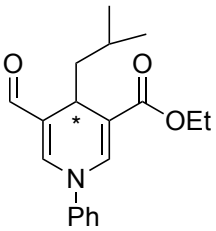
4ha Y =64%
ee = 93%



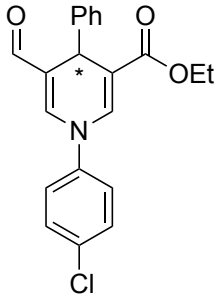
4ia Y =70%
ee = 97%



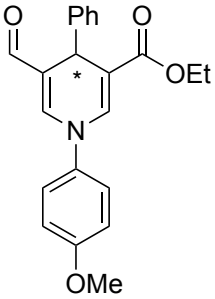
4if Y =70%
ee = 89%



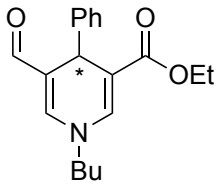
4ja Y =75%
ee = 94%



4ka Y =55%
ee = 94%



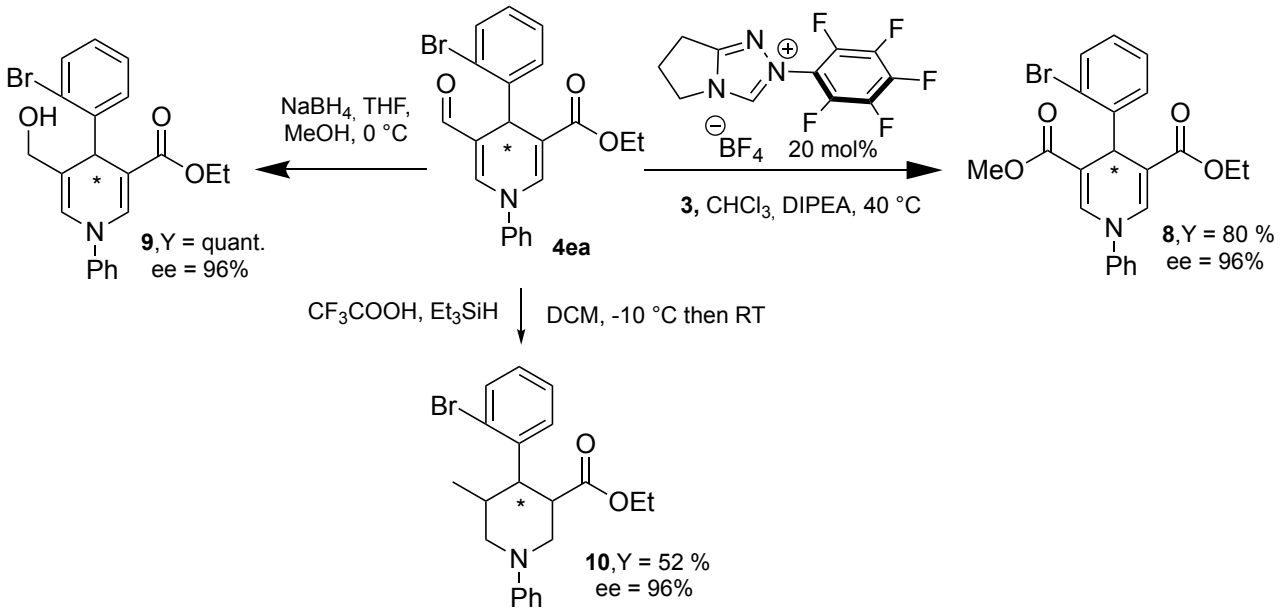
4la Y =56%
ee = 90%



4ma Y =20%
ee = 98%

[a]Reactions performed with 0.08 mmol of **1** with 20 mol% of **C5**, 0.08 mmol of oxidant **3** 0.08 mmol of **DIPEA** and 0.4 mmol of nucleophile **2** in $CHCl_3$ (0.4 M) at 40 °C for 16 h. The ee was determined by CSP HPLC.

As a proof of concept, the optically pure 1,4 dihydropyridine **4ea** was easily converted into the asymmetric disubstituted 3,5-diester **8** applying the optimized oxidative process with methanol and the achiral pre-catalyst. Furthermore, the same substrate was reduced by $NaBH_4$ to access alcohol **9**, which belongs to the class of molecules used as chiral reactants in the hydride addition to α-ketoesters[16]. We also found that treating **4ea** in presence of a strongly excess of Et_3SiH and trifluoroacetic acid the over-reduced piperidine product **10** was formed in prevalence as a single diastereoisomer without erosion of enantiomeric excess, demonstrating the utility of optically active 1,4-DHPs as intermediates to obtain new chiral heterocyclic scaffolds. (Scheme 4).



Scheme 4. Synthetic elaboration of **4ea**.

In summary, we have developed a novel approach to desymmetrize 1,4-dihydropyridine-3,5-dicarbaldehydes via NHC external oxidative catalysis to access pharmaceutically relevant 1,4-DHPs. Various optically pure 1,4-DHPs were obtained with good yield and excellent enantioselectivity and the elaboration of these molecules has been briefly explored.

4.3 References

[1] (a) M. F. Gordeev, D. V. Patel, B. P. England, S. Jonnalagadda, J. D. Combs and E. M. Gordon, *Bioorg. Med. Chem.*, **1998**, 6, 883; (b) V. A. Burgess, S. G. Davies and R. T. Skerlj, *Tetrahedron: Asymmetry*, **1991**, 2, 299; (c) E. Carosati, P. Ioan, M. Micucci, F. Broccatelli, G. Cruciani, B.S. Zhorov, A. Chiarini, R. Budriesi, *Current Medicinal Chemistry*, **2012**, 19, 4306.

[2] S. A. Khedkar, P. B. Auti, *Mini-Reviews in Medicinal Chemistry*, **2014**, 14, 282.

[3] (a) M. L. Bennasar, C. Juana, J. Boscha, *Chem. Commun.*, **2000**, 24, 2459; (b) M. G. P. Buffat, *Tetrahedron*, **2004**, 60, 1701; (c) T. Shamim, M. Gupta, S. Paul, *Journal of Molecular Catalysis A:*

Chemical, **2009**, 302, 15; (d) X. Wang, A. M. Kauppi, R. Olsson, F. Almqvist, *Eur. J. Org. Chem.* **2003**, 4586.

[4] (a) F. Gu, W. Huang, X. Liu, W. Chen, X. Cheng, *Adv. Synth. Catal.* **2018**, 360, 925; (b) J. Chen, Z. Zhang, Z. Bao, Y. Su, H. Xing, Q. Yang, Q. Ren, *ACS Appl. Mater. Interfaces*, **2017**, 9, 9772.

[5] A. Hantzsch, *Chemische Berichte*, **1881**, 14, 1637.

[6] S. Mane, *Anal. Methods*, **2016**, 8, 7567.

[7] J. Dalal, J. C. Mohan, S. S. Iyengar, J. Hiremath, I. Sathyamurthy, S. Bansal, D. Kahali, A. Dasbiswas, *International Journal of Hypertension*, **2018**, 1-14.

[8] (a) V. K. Sharmaa, S. K. Singh, RSC Adv., 2017, 7, 2682; (b) T. Shibanuma, M. Iwanani, K. Okuda, T. Takenaka, M. Murakami, *Chem. Pharm. Bull.*, **1980**, 28, 2809; (c) D. M. Gotrane, R. D. Deshmukh, P. V. Ranade, S. P. Sonawane, B. M. Bhawal, M. M. Gharpure, M. K. Gurjar, *Org. Process Res. Dev.*, **2010**, 14, 640; (d) B. Lamm, R. Simonsson, S. Sundell, *Tetrahedron Lett.*, **1989**, 30, 6423.

[9] (a) F. Auria-Luna, E. Marqués-López, R. P. Herrera, Adv. Synth. Catal. 2017, 359, 2161. (b) M. L. Tîntas¸, R. Azzouz, L. Peauger, V. Gembus, E. Petit, L. Bailly, C. Papamicaeľ, V. Levacher, *J. Org. Chem.*, **2018**, 83, 10231; (c) F. Auria-Luna, E. Marqueś-Lopez, M. Concepcioń Gimeno, R. Heiran, S. Mohammadi, Raquel P. Herrera, *J. Org. Chem.*, **2017**, 82, 5516; (d) G. Di Carmine, D. Ragno, O. Bortolini, P. P. Giovannini, A. Mazzanti, A. Massi, Marco Fogagnolo, *J. Org. Chem.*, **2018**, 83, 2050.

[10] for review on NHC employs in desymmetrization and resolution see: Z. Wang, D. Pan, T. Li, Z. Jin, *Chem Asian J.*, **2018**, 17, 2149; for review on NHC in general see: D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, **2015**, 115, 9307; for review on organocatalytic desymmetrization see: A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson, D. J. Dixon, *Chem. Soc. Rev.*, **2016**, 45, 5474.

[11] N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.*, **2004**, 126, 9518.

[12] (a) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.*, **2010**, 49, 9266. (b), S. Bera, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.*, **2017**, 56, 7402; (c) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.*, **2014**, 47, 696; (d) D. Ragno, A. Brandolese, D. Urbani, G. Di Carmine, C. De Risi, O. Bortolini, P. P. Giovannini, A. Massi, *Reaction Chemistry & Engineering*, **2018**, DOI: 10.1039/C8RE00143J.

[13] (a) Z. Wu, Jian Wang, *ACS Catal.*, **2017**, 7, 7647; (b) B. Li, Y- Wang, R. S. J. Proctor, Z. Jina, Y. Robin Chi, *Chem.Commun.*, **2016**, 52, 8313; (c) Q. Lin, Y. Li, D. Kumar Das, G. Zhang, Z. Zhao, S. Yang, X. Fang, *Chem.Commun.*, **2016**, 52, 6459; (d) Z. Huang, X. Huang, B. Li, C. Mou, S. Yang, B. Song, Y. Robin Chi, *J. Am. Chem. Soc.*, **2016**, 138, 7524; (e) Y. Li, S. Yang, G. Wen, Q. Lin, G.

Zhang, L. Qiu, X. Zhang, G. Du, X. Fang, J. Org. Chem. 2016, 81, 2763; (f) S. Li, B. Liu, L. Chen, X. Li, J. Cheng, *Org. Chem. Front.*, ***2018***, 5, 1101.

[14] S. Sueki, R. Takei, Y. Zaitsu, J. Abe, A. Fukuda, K. Seto, Y. Furukawa, I. Shimizu, *Eur. J. Org. Chem.*, **2014**, 5281.

[15] (a) A. Axelsson, A. A. Micharda, H. Sundén, *Green Chem.*, **2017**, 19, 2477; (b) J. E. Backvall, A. K. Awasthi, Z. D. Renko, *J. Am. Chem. Soc.*, **1987**, 109, 4750; (c) J. E. Backvall, R. B. Hopkins, H. Grennberg, M. M. Mader, A. K. Awasth, *J. Am. Chem. Soc.*, **1990**, 112, 5160; (d) A. B. Sorokin, *Chem. Rev.*, **2013**, 113, 8152; (e) J. Piera, J. E. Bäckvall, *Angew. Chem. Int. Ed.*, **2008**, 47, 3506.

[16] A. I. Meyers, T. Oppenlaender, *J. Am. Chem. Soc.*, **1986**, 108, 1989.

4.4 Experimental section

General Experimental Methods. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers in $CDCl_3$ at room temperature. ^{13}C NMR spectra were acquired with the ^{1}H broad-band decoupled mode, and chemical shifts (δ) are reported in ppm relative to residual solvents signals. Reactions were monitored by TLC on silica gel 60 F254 with detection by UV lamp operating at 254 nm and 365 nm. Flash column chromatography was performed on silica gel 60 (230−400 mesh). High-resolution mass spectra (HRMS) were recorded in positive ion mode by an Agilent 6520 HPLC-Chip Q/TF-MS nanospray using a time-of-flight, a quadrupole, or a hexapole unit to produce spectra. Optical rotations were measured at 20 ± 2 °C in the stated solvent; [α]D are given in 10^{-1} deg cm^2 g^{-1}. The enantiomeric ratios were determined by chiral stationary phase HPLC (Phenomenex Lux Cellulose 1 or Daicel Chiralpak IA), using an UV detector operating at 254 nm. Microwave-assisted reactions were carried out using a single-mode cavity dedicated reactor (Biotage Initiator™). Reactions were performed with temperature-controlled pro-grams in glass vials (0.5–2 or 2–5 mL depending on the scale) sealed with a Teflon septum. Temperatures were measured externally by an IR sensor. The reaction time was counted when the reaction mixture reached the stated temperature. Pressure was measured by a non-invasive sensor integrated into the cavity lid. All commercially available reagents were used as received without further purification, unless otherwise stated. Solvents were distilled from appropriate drying agents. Liquid aldehydes and bases (DBU, TEA, DIPEA) were freshly distilled before their utilization. Inorganic bases were dried (100−120 °C, 5 mmHg, 6 h) and stored in a chamber with phosphorus pentoxide (P_2O_5).

Synthesis of substituted 1,4-dihydropyridine-3,5-dicarbaldehydes

In a MW vial equipped with a magnetic stirring bar, the corresponding aminium chloride (1 mmol) was dissolved in DMSO (1.5 mL). At this point aldehyde (1.1 mmol, 1.1 eq.) and 1,1,3,3-tetramethoxypropane (2.5 mmol, 2.5 eq.) were added and the resulting mixture was heated using a MW for 3h. Hereafter, the black solution was cooled to RT, DCM (15 mL) was added and the resulting organic moiety was washed with a saturated solution of $NaHCO_3$ (5 mL x 3 times). The organic layer was collected and dried with Na_2SO_3 and concentrated. The crude was purified by Silica gel Chromatography to afford the resulting 1,4-dihydropyridine-3,5-dicarbaldehyde.

1,4-diphenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1a)

Obtained as a yellow powder in 41% yield (119 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 2H, CHO), 7.58 – 7.50 (m, 2H, Ar), 7.45 – 7.34 (m, 6H, Ar), 7.30 – 7.22 (m, 3H, Ar, H-2), 7.19 – 7.13 (m, 1H, Ar), 5.09 (s, 1H, H-4); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 188.9, 143.8, 130.7, 128.7, 128.4, 128.0, 127.3, 123.9, 121.7, 77.8, 77.6, 77.3, 76.9, 34.3; HRMS(ESI): calcd. for $C_{19}H_{16}NO_2$+ (M + H+): 290.1181; found: 290.1189.

4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1b)

Obtained as a yellow powder in 53% yield (172 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 2H, CHO), 7.59 – 7.51 (m, 2H, Ar), 7.46 – 7.36 (m, 3H, Ar), 7.34 – 7.31 (m, 3H, Ar), 7.29 (s, 1H, Ar), 7.27 – 7.21 (m, 2H, H-2), 5.06 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 144.1, 142.9, 142.8, 133.0, 130.8, 129.9, 128.8, 128.2, 123.5, 121.7, 77.8, 77.4, 77.0, 33.9; HRMS(ESI): calcd. for $C_{19}H_{15}ClNO_2$+ (M + H+): 324.0791; found: 324.0792.

4-(3-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1c)

Obtained as a yellow powder in 49% yield (180 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 2H, CHO), 7.56 (t, J = 8 Hz, 2H, Ar), 7.47 – 7.36 (m, 5H, Ar), 7.33 – 7.24 (m, 3H, Ar, H-2), 7.20 – 7.11 (m, 1H, Ar), 5.07 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 144.2, 131.3, 130.8, 130.4, 130.2, 128.2, 127.6, 123.2, 121.8, 77.8, 77.4, 76.9, 34.2; HRMS(ESI): calcd. for $C_{19}H_{15}BrNO_2$+ (M + H+): 368.0286; found: 368.0293.

4-(2-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1d)

Obtained as a yellow powder in 36% yield (117 mg) after column chromatography on silica gel (DCM/Acetone = 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 2H, CHO), 7.58 – 7.46 (m, 3H, Ar), 7.45 – 7.35 (m, 3H, Ar), 7.31 – 7.27 (m, 3H, Ar, H-2), 7.21 (td, J = 7.5, 1.5 Hz, 1H, Ar), 7.12 (td, J = 7.5, 1.5 Hz, 1H, Ar), 5.40 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 144.9, 142.9, 140.7, 134.2, 132.8, 130.7, 130.5, 128.6, 128.1, 127.1, 122.3, 121.8, 77.8, 77.4, 77.0, 34.5; HRMS(ESI): calcd. for $C_{19}H_{15}ClNO_2$+ (M + H+): 324.0791; found: 324.0797.

4-(2-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1e)

Obtained as a yellow powder in 40% yield (147 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 2H, CHO), 7.59 – 7.34 (m, 8H, Ar, H-2), 7.30 – 7.21 (m, 2H, Ar), 7.03 (t, J = 7.3 Hz, 1H, Ar), 5.43 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 144.5, 133.9, 132.8, 130.7, 128.8, 128.0, 127.7, 122.7, 121.7, 77.8, 77.3, 76.9, 36.5; HRMS(ESI): calcd. for $C_{19}H_{15}BrNO_2$+ (M + H+): 368.0286; found: 368.0291.

1-phenyl-4-(m-tolyl)-1,4-dihydropyridine-3,5-dicarbaldehyde (1f)

Obtained as a yellow powder in 43% yield (131 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 2H, CHO), 7.54 (t, J = 8 Hz, 2H, Ar), 7.44 – 7.36 (m, 3H, Ar), 7.31 (s, 2H, H-2), 7.20 – 7.12 (m, 3H, Ar), 7.02 – 6.92 (m, 1H, Ar), 5.05 (s, 1H, H-4), 2.30 (s, 3H, CH_3); 13C NMR (75 MHz, $CDCl_3$) δ 188.9, 144.3, 143.8, 143.0, 138.2, 130.7, 129.2, 128.6, 128.1, 128.0, 125.4, 123.9, 121.7, 77.8, 77.4, 76.9, 34.2, 21.8; HRMS(ESI): calcd. for $C_{20}H_{18}NO_2$+ (M + H+): 304.1338; found: 304.1342.

1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde (1g)

Obtained as a yellow powder in 60% yield (214 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 2H, CHO), 7.60 – 7.49 (m, 6H, Ar), 7.48 – 7.38 (m, 3H, Ar), 7.35 (s, 2H, H-2), 5.17 (s, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5, 147.6, 144.1, 142.3, 130.4, 128.5, 127.9, 125.4, 125.3, 125.2, 122.7, 121.4, 77.4, 77.0, 76.7, 34.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4; HRMS(ESI): calcd. for $C_{20}H_{15}F_3NO_2$+ (M + H+): 358.1055; found: 358.1063.

4-(3,5-diformyl-1-phenyl-1,4-dihydropyridin-4-yl)benzonitrile (1h)

Obtained as a yellow powder in 56% yield (176 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 2H, CHO), 7.61 – 7.53 (m, 4H, Ar), 7.53 – 7.43 (m, 3H, Ar), 7.41 – 7.35 (m, 4H, Ar, H-2), 5.14 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 149.3, 144.6, 142.6, 132.5, 130.8, 129.4, 128.4, 122.7, 121.8, 119.2, 111.0, 77.9, 77.4, 77.0, 34.8; HRMS(ESI): calcd. for $C_{20}H_{15}N_2O_2$+ (M + H+): 315.1134; found: 315.1139.

4-methyl-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1i)

Obtained as a yellow powder in 51% yield (116 mg) after column chromatography on silica gel (DCM/Acetone = 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 2H, CHO), 7.54 – 7.46 (m, 2H, Ar), 7.37 (t, J = 6.8 Hz, 1H, Ar), 7.30 (d, J = 7.6 Hz, 2H, Ar), 7.13 (s, 2H, H-2), 4.01 (q, J = 6.6 Hz, 1H, H-4), 1.22 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 144.7, 130.6, 127.8, 125.6, 121.5, 77.8, 77.3, 76.9, 23.8, 22.5; HRMS(ESI): calcd. for $C_{14}H_{14}NO_2$+ (M + H+): 228.1025; found: 228.1032.

4-isobutyl-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1j)

Obtained as a yellow powder in 42% yield (113 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 2H, CHO), 7.54 – 7.46 (m, 2H, Ar), 7.41 – 7.34 (t, J = 7.6 Hz, 1H, Ar), 7.34 – 7.29 (d, J = 7.6 Hz, 2H, Ar), 7.20 (s, 2H, H-2), 4.05 (t, J = 6.5 Hz, 1H, H-4), 1.55 (m, 1H, CH_{isobut}), 1.34 (t, J = 6.5 Hz, 2H, $CH_{2isobut}$), 0.94 (d, J = 6.5 Hz, 6H, $CH_{3isobut}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 145.2, 142.9, 130.6, 127.8, 124.8, 121.5, 77.8, 77.4, 77.0, 47.2, 26.2, 24.9, 23.4; HRMS(ESI): calcd. for $C_{17}H_{20}NO_2$+ (M + H+): 270.1494; found: 270.1493.

1-(4-chlorophenyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1k)

Obtained as a yellow powder in 53% yield (172 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 2H, CHO), 7.50 (d, J = 8.9 Hz, 2H, Ar), 7.37 – 7.30 (m, 4H, Ar), 7.29 – 7.23 (m, 4H, Ar, H-2), 7.14 (t, J = 6.4 Hz, 1H, Ar), 5.06 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 144.1, 143.4, 141.4, 133.7, 130.8, 128.8, 128.4, 127.4, 124.0, 123.0, 77.8, 77.4, 77.0, 34.3; HRMS(ESI): calcd. for $C_{19}H_{15}ClNO_2$+ (M + H+): 324.0791; found: 324.0797.

1-(4-methoxyphenyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1l)

Obtained as a yellow powder in 48% yield (153 mg) after column chromatography on silica gel (DCM/Acetone = 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 2H, CHO), 7.41 – 7.34 (m, 2H, Ar), 7.32 – 7.24 (m, 5H, Ar), 7.21 (s, 2H, H-2), 7.02 (d, J = 9.1 Hz, 2H, Ar), 5.09 (s, 1H, H-4), 3.87 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.6, 159.1, 144.4, 144.2, 135.8, 128.4, 128.1, 126.9, 123.4, 123.0, 115.4, 77.4, 77.1, 76.8, 55.8, 33.8; HRMS(ESI): calcd. for C20H18NO3+ (M + H+): 320.1287; found: 320.1291.

1-butyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (1m)

Obtained as a yellow powder in 39% yield (105 mg) after column chromatography on silica gel (DCM/Acetone = 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 2H,CHO), 7.31 – 7.21 (m, 4H, Ar), 7.18 – 7.09 (m, 1H, Ar), 6.86 (s, 2H, H-2), 5.03 (s, 1H, H-4), 3.56 (t, J = 7.2 Hz, 2H, CH_2), 1.87 – 1.71 (m, 2H, CH_2), 1.53 – 1.40 (m, 2H, CH_2), 1.03 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 145.8, 145.0, 128.6, 128.3, 127.0, 122.3, 77.9, 77.4, 77.0, 55.5, 34.0, 32.5, 19.9, 14.0; HRMS(ESI): calcd. for $C_{17}H_{20}NO_2$+ (M + H+): 270.1494; found: 270.1499.

NHC catalyzed reaction for the synthesis of monoester 1,4-dihydropyridines

General procedure (asymmetric). In a GC test tube (1 mL) equipped with a magnetic stirring bar, charged with 1,4-dihydropyridine-3,5-dicarbaldehydes **1** (0.08 mmol, 1 equiv.), pre-catalyst **C5** (0.016 mmol, 0.2 eq.) and the oxidant **3** (0.08 mmol, 1 equiv.) anhydrous $CHCl_3$ was added (0.2 mL) followed by the nucleophile 2 (0.4 mmol, 5 eq.) and DIPEA (0.08 mmol, 1 equiv.). The resulting solution was stirred at 40 °C for 16 hours. At this point the crude was directly charged on silica gel and purified by column chromatography to afford the desired product **4**.
General procedure (Racemic). In a GC test tube (1 mL) equipped with a magnetic stirring bar, charged with 1,4-dihydropyridine-3,5-dicarbaldehydes **1** (0.04 mmol, 1 equiv.), pre-catalyst 6,7-Dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate (0.008 mmol, 0.2 eq.) and the oxidant **3** (0.04 mmol, 1 equiv.) anhydrous $CHCl_3$ was added (0.1 mL) followed by the nucleophile 2 (0.2 mmol, 5 eq.) and DIPEA (0.04 mmol, 1 equiv.). The resulting solution was stirred at 40 °C for 16 hours. At this point the crude was directly charged on silica gel and purified by column chromatography to afford the desired product **4**.

Ethyl 5-formyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4aa)

Following the general procedure, product **4aa** was obtained as a yellow powder in 70% yield (19 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of **4aa** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 7.2 min, t_{min} = 8.8 min, 91% ee); [α]D25 °C = - 2.8 (c = 1.0, CHCl3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.71 (d, J = 1.6 Hz, 1H, H-2), 7.55 – 7.46 (m, 2H, Ar), 7.40 – 7.32 (m, 5H, Ar, H-6), 7.28 – 7.23 (m, 3H, Ar), 7.17 (tt, J = 6.4, 1.6 Hz, 1H, Ar), 5.04 (s, 1H, H-4), 4.19 – 4.03 (m, 2H, CH_2), 1.19 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 166.6, 145.4, 144.0, 143.2, 136.0, 130.5, 128.5, 127.4, 127.1, 122.9, 121.4, 113.1, 77.8, 77.4, 76.9, 60.8, 36.2, 14.5; HRMS(ESI): calcd. for $C_{21}H_{20}NO_3$+ (M + H+): 334.1443; found: 334.1450.

Butyl 5-formyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4ab)

Following the general procedure, product **4ab** was obtained as a yellow powder in 62% yield (18 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of **4ab** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 19.3 min, t_{min} = 24.5 min, 95% ee); [α]D25 °C = -2.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.72 (d, J = 1.5 Hz, 1H, H-2), 7.56 – 7.44 (m, 2H, Ar), 7.41 – 7.32 (m, 5H, Ar, H-6), 7.32 – 7.23 (m, 3H, Ar), 7.16 (t, J = 7.0 Hz, 1H, Ar), 5.03 (s, 1H, H-4), 4.14 – 3.96 (m, 2H,

CH_2), 1.57 – 1.47 (m, 2H, CH_2), 1.31 – 1.17 (m, 2H, CH_2), 0.86 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 166.8, 145.4, 144.1, 136.1, 130.5, 128.6, 128.5, 127.4, 127.1, 122.9, 121.4, 113.1, 77.8, 77.4, 76.9, 64.8, 36.2, 31.0, 19.4, 14.0; HRMS(ESI): calcd. for $C_{23}H_{24}NO_3$+ (M + H+): 362.1756; found: 362.1764.

Isopropyl 5-formyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4ac)

Following the general procedure, product **4ac** was obtained as a yellow powder in 25% yield (7 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ac** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 16.7 min, t_{min} = 22.4 min, 98% ee); [α]D25 °C = - 2.1 (c = 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.69 (d, J = 1.6 Hz, 1H, H-2), 7.50 (t, J = 8.0 Hz, 2H, Ar), 7.40 – 7.32 (m, 5H, Ar), 7.28 – 7.24 (m, 3H, Ar, H-6), 7.16 (t, J = 7.2, 1H, H-6), 5.03 (s, 1H, H-4), 4.97 (ept, J = 6.2 Hz, 1H, $CH_{isoprop}$), 1.22 (d, J = 6.2 Hz, 3H, $CH_{3isopropA}$), 1.06 (d, J = 6.2 Hz, 3H, $CH_{3isopropB}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 166.2, 145.5, 144.1, 143.2, 135.8, 130.5, 128.6, 128.5, 127.4, 127.0, 122.9, 121.4, 113.6, 77.8, 77.6, 77.4, 76.9, 68.3, 36.3, 22.3, 21.9; HRMS(ESI): calcd. for $C_{22}H_{22}NO_3$+ (M + H+): 348.1600; found: 348.1609.

S-ethyl 5-formyl-1,4-diphenyl-1,4-dihydropyridine-3-carbothioate (4ad)

Following the general procedure, product **4ad** was obtained as a yellow powder in 64% yield (18 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of **4ad** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 8.0 min, t_{min} = 8.9 min, 79% ee); [α]D25 °C = -227 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H, CHO), 7.78 (d, J = 1.2 Hz, 1H, H-2), 7.51 (t, J = 7.5 Hz, 2H, Ar), 7.41 – 7.32 (m, 5H, Ar, H-6), 7.28 (t, J = 7.4 Hz, 2H, Ar), 7.23 – 7.14 (m, 2H, Ar), 5.18 (s, 1H, H-4), 2.88 (q, J = 7.4 Hz, 2H, CH_2), 1.20 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 188.9, 144.6, 143.6, 143.1, 134.7, 130.6, 128.7, 128.5, 127.6, 127.2, 123.3, 121.6, 120.5, 77.8, 77.4, 77.0, 36.2, 23.5, 15.0; HRMS(ESI): calcd. for $C_{21}H_{20}NO_2S$ (M + H+): 350.1215; found: 350.1219.

but-3-en-1-yl 5-formyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4ae)

Following the general procedure, product **4ae** was obtained as a yellow powder in 67% yield (19 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ae** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 6.7 min, t_{min} = 8.3 min, 96% ee); [α]D25 °C = -5.4 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.34

(s, 1H, CHO), 7.73 (d, J = 1.6 Hz, 1H, H-2), 7.57 – 7.43 (m, 2H, Ar), 7.39 – 7.33 (m, 4H, Ar), 7.31 – 7.22 (m, 4H, Ar, H-6), 7.17 (t, J = 7.1 Hz, 1H, Ar), 5.67 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H, $CH_{olefinic}$), 5.10 – 4.93 (m, 3H, H-4, $CH_{2olefinic}$), 4.20 – 4.02 (m, 2H, OCH_2), 2.31 (ddd, J = 8.1, 6.7, 5.2 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 166.6, 145.3, 143.9, 143.2, 136.2, 134.3, 130.5, 128.6, 128.5, 127.4, 127.1, 123.0, 121.4, 117.4, 112.9, 77.8, 77.3, 76.9, 64.0, 36.2, 33.4; HRMS(ESI): calcd. for $C_{23}H_{22}NO_3$+ (M + H+): 360.1600; found: 360.1606.

Ethyl 4-(4-chlorophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ba)

Following the general procedure, product **4ba** was obtained as a yellow powder in 55% yield (16 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of **4ba** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 8.0 min, t_{min} = 8.8 min, 93% ee); [α]D25 °C = -2.0 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H, CHO), 7.70 (d, J = 1.6 Hz, 1H, H-2), 7.55 – 7.47 (m, 2H, Ar), 7.40 – 7.34 (m, 2H, Ar), 7.33 – 7.28 (m, 3H, Ar), 7.27 – 7.21 (m, 3H, Ar, H-6), 5.02 (s, 1H, H-4), 4.18 – 4.05 (m, 2H, CH_2), 1.19 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 166.4, 144.1, 143.9, 143.1, 136.2, 132.8, 130.5, 129.9, 128.7, 127.5, 122.5, 121.4, 112.7, 77.8, 77.3, 76.9, 60.9, 35.8, 14.5; HRMS(ESI): calcd. for $C_{21}H_{19}ClNO_3$+ (M + H+): 368.1053; found: 368.1064.

ethyl 4-(3-bromophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ca)

Following the general procedure, product **4ca** was obtained as a yellow powder in 48% yield (7 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ca** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 6.8 min, t_{min} = 8.3 min, 94% ee); [α]D25 °C = -1.2 (c = 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.70 (d, J = 1.5 Hz, 1H, H-2), 7.52 (t, J = 7.8 Hz, 2H, Ar), 7.46 (t, J = 1.8 Hz, 1H, Ar), 7.41 – 7.29 (m, 5H, Ar), 7.27 (d, J = 1.6 Hz, 1H, H-6), 7.14 (t, J = 7.8 Hz, 1H, Ar), 5.02 (s, 1H, H-4), 4.20 – 4.04 (m, 2H, CH_2), 1.21 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 166.4, 144.3, 136.3, 131.6, 130.6, 130.2, 130.0, 127.6, 127.5, 122.2, 121.5, 112.5, 77.8, 77.4, 76.9, 61.0, 36.1, 14.5. HRMS(ESI): calcd. for $C_{21}H_{19}BrNO_3$+ (M + H+): 412.0548; found: 412.0547.

ethyl 4-(2-chlorophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4da)

Following the general procedure, product **4da** was obtained as a yellow powder in 70% yield (21 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4da** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 90:10, 1.0 mL/min, t_{maj} = 11.7

min, t_{min} = 14.7 min, 98% ee); [α]D25 °C = - 31 (c = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H, CHO), 7.69 (d, J = 1.6 Hz, 1H, H-2), 7.50 (t, J = 7.5 Hz, 2H, Ar), 7.43 – 7.25 (m, 6H, Ar, H-6), 7.19 (td, J = 7.5, 1.5 Hz, 1H, Ar), 7.11 (td, J = 7.5, 1.5 Hz, 1H, Ar), 5.43 (s, 1H, H-4), 4.17 – 4.01 (m, 2H, CH_2), 1.17 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 166.6, 144.6, 143.2, 142.3, 136.9, 134.0, 132.2, 130.5, 130.2, 128.3, 127.4, 127.0, 121.5, 111.9, 77.8, 77.4, 76.9, 60.9, 35.2, 14.4; HRMS(ESI): calcd. for $C_{21}H_{19}ClNO_3$+ (M + H+): 368.1053; found: 368.1059.

ethyl 4-(2-bromophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ea)

Following the general procedure, product **4ea** was obtained as a yellow powder in 61% yield (20 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ea** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 6.4 min, t_{min} = 7.8 min, 96% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H, CHO), 7.70 (s, 1H, H-2), 7.56 – 7.44 (m, 3H, Ar), 7.40 – 7.32 (m, 4H, Ar, H-6), 7.32 – 7.18 (m, 2H, Ar), 7.02 (t, J = 7.8 Hz, 1H, Ar), 5.44 (s, 1H, H-4), 4.17 – 4.04 (m, 2H, CH_2), 1.18 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 166.6, 144.3, 143.2, 136.8, 133.5, 132.2, 130.5, 128.5, 127.7, 127.4, 124.1, 122.2, 121.4, 112.4, 77.8, 77.4, 76.9, 60.9, 37.2, 14.5; HRMS(ESI): calcd. for $C_{21}H_{19}BrNO_3$+ (M + H+): 412.0548; found: 412.0551.

ethyl 5-formyl-1-phenyl-4-(m-tolyl)-1,4-dihydropyridine-3-carboxylate (4fa)

Following the general procedure, product **4fa** was obtained as a yellow powder in 68% yield (19 mg) after column chromatography on silica gel (DCM/Toluene = 6.5:3.5). The enantiomeric excess of **4fa** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 5.8 min, t_{min} = 7.1 min, 92% ee); [α]D25 °C = +4.4 (c = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.70 (d, J = 1.6 Hz, 1H, H-2), 7.51 (t, J = 8.1 Hz, 2H, Ar), 7.40 – 7.30 (m, 3H, Ar), 7.25 (d, J = 1.6 Hz, 1H, H-6), 7.21 – 7.11 (m, 3H, Ar), 7.03 – 6.94 (m, 1H, Ar), 5.00 (s, 1H, H-4), 4.19 – 4.04 (m, 2H, CH_2), 2.31 (s, 3H, CH_{3Ar}), 1.20 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 166.6, 145.3, 144.0, 143.3, 138.0, 135.9, 130.5, 129.3, 128.4, 127.9, 127.3, 125.6, 122.9, 121.4, 113.2, 77.8, 77.3, 76.9, 60.8, 36.1, 21.8, 14.5; HRMS(ESI): calcd. for $C_{22}H_{22}NO_3$+ (M + H+): 348.1600; found: 348.1605.

Ethyl 5-formyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3-carboxylate (4ga)

Following the general procedure, product **4ga** was obtained as a yellow powder in 64% yield (21 mg) after column chromatography on silica gel (DCM/Toluene = 6.5:3.5). The enantiomeric excess of **4ga** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 5.9 min, t_{min} = 6.6 min, 92% ee); [α]D25 °C = -11.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H, CHO), 7.73 (d, J = 1.6 Hz, 1H, H-2), 7.57 – 7.45 (m, 6H, Ar), 7.42 – 7.32 (m, 3H, Ar), 7.28 (d, J = 1.6 Hz, 1H, H-6), 5.12 (s, 1H, H-4), 4.18 – 4.05 (m, 2H, CH_2), 1.19 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 166.2, 149.1, 144.4, 143.0, 136.5, 130.6, 128.9, 127.7, 125.6, 125.5, 122.2, 121.5, 112.4, 77.8, 77.3, 76.9, 61.0, 36.3, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4; HRMS(ESI): calcd. for $C_{22}H_{19}F_3NO_3$+ (M + H+): 402.1317; found: 402.1325.

ethyl 4-(4-cyanophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ha)

Following the general procedure, product **4ha** was obtained as a yellow powder in 64% yield (18 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ha** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 8.9 min, t_{min} = 9.9 min, 93% ee); [α]D25 °C = -7.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H, CHO), 7.73 (d, J = 1.6 Hz, 1H, H-2), 7.61 – 7.46 (m, 6H, Ar), 7.43 – 7.32 (m, 3H, Ar), 7.28 (d, J = 1.6 Hz, 1H, H-6), 5.10 (s, 1H, H-4), 4.17 – 4.05 (m, 2H, CH_2), 1.18 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 166.1, 150.3, 144.5, 142.9, 136.7, 132.5, 130.6, 129.4, 127.8, 121.8, 121.5, 119.3, 111.9, 110.9, 77.8, 77.4, 76.9, 61.1, 36.7, 14.5; HRMS(ESI): calcd. for $C_{22}H_{19}N_2O_3$+ (M + H+): 359.1396; found: 359.1399.

ethyl 5-formyl-4-methyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ia)

Following the general procedure, product **4ia** was obtained as a yellow powder in 70% yield (15 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of 4ia was determined by chiral stationary phase HPLC (Cellulose 1, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 15.1 min, t_{min} = 19.6 min, 97% ee); [α]D25 °C = +579 (c = 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H, CHO), 7.50 (d, J = 1.6 Hz, 1H, H-2), 7.49 – 7.42 (m, 2H, Ar), 7.32 (d, J = 7.3 Hz, 1H, Ar), 7.29 – 7.27 (m, 1H, Ar), 7.26 – 7.24 (m, 1H, Ar), 7.12 (d, J = 1.6 Hz, 1H, H-6), 4.35 – 4.13 (m, 2H, CH_2), 3.94 (q, J = 6.5 Hz, 1H, H-4), 1.30 (t, J = 7.1 Hz, 3H, CH_{3Et}), 1.21 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 164.1, 142.4, 140.4, 133.3, 127.5, 124.3, 121.2, 118.3,

111.6, 74.9, 74.5, 74.1, 57.9, 22.5, 20.5, 11.8; HRMS(ESI): calcd. for $C_{16}H_{18}NO_3$+ (M + H+): 272.1287; found: 272.1294.

methyl 5-formyl-4-methyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4if)

Following the general procedure, product **4if** was obtained as a yellow powder in 70% yield (14 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4if** was determined by chiral stationary phase HPLC (Cellulose 1, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 22.0 min, t_{min} = 31.1 min, 89% ee); [α]D25 °C = + 46.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H, CHO), 7.51 (d, J = 1.5 Hz, 1H, H-2), 7.49 – 7.41 (m, 2H, Ar), 7.32 (d, J = 7.4 Hz, 1H, Ar), 7.29 – 7.23 (m, 2H, Ar), 7.12 (d, J = 1.5 Hz, 1H, H-6), 3.93 (q, J = 6.5 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 1.20 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 167.4, 145.1, 143.2, 136.4, 130.4, 127.2, 124.1, 121.2, 114.1, 77.8, 77.4, 76.9, 51.9, 25.3, 23.3; HRMS(ESI): calcd. for $C_{15}H_{16}NO_3$+ (M + H+): 258.1130; found: 258.1132.

ethyl 5-formyl-4-isobutyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (4ja)

Following the general procedure, product 4ja was obtained as a yellow powder in 75% yield (19 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8:2). The enantiomeric excess of **4ja** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 5.6 min, t_{min} = 6.5 min, 94% ee); [α]D25 °C = +107 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H, CHO), 7.58 (d, J = 1.5 Hz, 1H, H-2), 7.50 – 7.42 (m, 2H, Ar), 7.35 – 7.26 (m, 3H, Ar), 7.19 (d, J = 1.5 Hz, 1H, H-6), 4.33 – 4.14 (m, 2H, CH_2), 3.99 (t, J = 6.2 Hz, 1H, H-4), 1.62 – 1.51 (m, 1H, CH_{isobut}), 1.36 – 1.27 (m, 5H, CH_3, $CH_{2isobut}$), 0.95 (d, J = 6.5 Hz, 3H, $CH_{3isobutA}$), 0.91 (d, J = 6.5 Hz, 3H, $CH_{3isobutB}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 167.2, 145.5, 143.2, 136.5, 130.4, 127.1, 123.5, 121.2, 113.9, 77.8, 77.3, 76.9, 60.8, 48.0, 27.8, 24.7, 23.7, 23.2, 14.6; HRMS(ESI): calcd. for $C_{19}H_{24}NO_3$+ (M + H+): 314.1756; found: 314.1757.

ethyl 1-(4-chlorophenyl)-5-formyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4ka)

Following the general procedure, product **4ka** was obtained as a yellow powder in 55% yield (16 mg) after column chromatography on silica gel (cyclohexane/EtOAc = 8.5:1.5). The enantiomeric excess of **4ka** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 8.7 min, t_{min} = 10.8 min, 94% ee); [α]D25 °C = -2.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H, CHO), 7.65 (d, J = 1.6 Hz, 1H, H-2), 7.47 (d, J = 9.0 Hz, 2H, Ar), 7.35 (d, J = 7.1 Hz, 2H, Ar), 7.31 – 7.23 (m, 4H, Ar, H-6), 7.21 – 7.13 (m, 2H, Ar), 5.03 (s, 1H, H-4), 4.17 – 4.05 (m,

2H, CH_2), 1.19 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 161.7, 140.4, 138.7, 137.0, 130.8, 128.3, 125.8, 123.8, 123.8, 122.4, 118.4, 117.9, 108.7, 73.0, 72.8, 72.6, 72.2, 56.2, 31.4, 9.7; HRMS(ESI): calcd. for $C_{21}H_{19}ClNO_3$+ (M + H+): 368.1053; found: 368.1059.

ethyl 5-formyl-1-(4-methoxyphenyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate (4la)

Following the general procedure, product **4la** was obtained as a yellow powder in 56% yield (16 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4la** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 8.6 min, t_{min} = 11.5 min, 90% ee); [α]D25 °C = +4.5 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H, CHO), 7.60 (d, J = 1.5 Hz, 1H, H-2), 7.37 (d, J = 7.3 Hz, 2H, Ar), 7.30 – 7.24 (m, 4H, Ar), 7.20 – 7.15 (m, 1H, Ar), 7.14 (d, J = 1.5 Hz, 1H, H-6), 6.99 (d, J = 7.3 Hz, 2H, Ar), 5.03 (s, 1H, H-4), 4.16 – 4.03 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 1.18 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 166.7, 159.0, 145.6, 144.7, 136.7, 129.0, 128.5, 128.4, 127.0, 123.5, 122.3, 115.5, 112.5, 77.8, 77.3, 76.9, 60.7, 56.0, 36.1, 14.5; HRMS(ESI): calcd. for $C_{22}H_{22}NO_4$+ (M + H+): 364.1549; found: 364.1557.

ethyl 1-butyl-5-formyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4ma)

Following the general procedure, product **4ma** was obtained as a yellow powder in 20% yield (5 mg) after column chromatography on silica gel (DCM/Toluene = 7:3). The enantiomeric excess of **4ma** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 80:20, 1.0 mL/min, t_{maj} = 7.9 min, t_{min} = 14.5 min, 98% ee); [α]D25 °C = + 36.1 (c = 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H, CHO), 7.31 – 7.21 (m, 5H, Ar, H-2), 7.14 (t, J = 6.5 Hz, 1H, Ar), 6.78 (d, J = 1.4 Hz, 1H, H-6), 4.97 (s, 1H, H-4), 4.13 – 4.01 (m, 2H, CH_2), 3.48 (t, J = 7.2 Hz, 2H, CH_{2but}), 1.81 – 1.66 (m, 2H, CH_{2but}), 1.51 – 1.36 (m, 2H, CH_{2but}), 1.17 (t, J = 7.1 Hz, 3H, CH_3), 0.99 (t, J = 7.4 Hz, 3H, CH_{3but}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 166.8, 146.0, 137.5, 128.4, 128.4, 126.8, 121.0, 111.2, 77.8, 77.3, 76.9, 60.6, 55.3, 35.9, 32.6, 19.9, 14.5, 14.0; HRMS(ESI): calcd. for $C_{19}H_{24}NO_3$+ (M + H+): 314.1756; found: 314.1757.

diethyl 1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (5aa)

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H, H-2), 7.50 – 7.43 (m, 2H, Ar), 7.40 – 7.34 (m, 3H, Ar), 7.33 – 7.28 (m, 4H, Ar), 7.17 (t, J = 7.2 Hz, 1H, Ar), 4.96 (s, 1H, H-4), 4.18 – 4.01 (m, 4H, CH_2), 1.20 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 135.5, 129.9, 128.4, 128.0, 126.6,

126.3, 120.7, 111.0, 77.3, 77.0, 76.7, 60.3, 37.7, 29.6, 14.2. HRMS(ESI): calcd. for $C_{23}H_{24}NO_4$+ (M + H+): 378.1705; found: 378.1713.

3-ethyl 5-methyl 4-(2-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8)

In a GC test tube (1 mL) equipped with a magnetic stirring bar, charged with ethyl 4-(2-bromophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (0.04 mmol, 1 equiv.), 6,7-Dihydro-2-pentafluorophenyl-5H-pyrrolo[2,1-c]-1,2,4-triazolium tetrafluoroborate (pre-catalyst) (0.008 mmol, 0.2 eq.) and the oxidant (0.04 mmol, 1 equiv.) anhydrous $CHCl_3$ was added (0.1 mL) followed by methanol (0.2 mmol, 5 eq.) and DIPEA (0.04 mmol, 1 equiv.). The resulting solution was stirred at 40 °C for 16 hours. At this point the crude was directly charged on silica gel and purified by column chromatography (cyclohexane/EtOAc 9:1) to afford the desired product **8** as white powder (Y = 80 %, 14 mg). The enantiomeric excess of **8** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 93:7, 1.0 mL/min, t_{maj} = 10.8 min, t_{min} = 11.3 min, 96% ee); [α]D25 °C = -7.0 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 1.5 Hz, 1H, H-2) 7.67 (d, J = 1.5 Hz, 1H, H-6), 7.52 – 7.43 (m, 3H, Ar), 7.40 – 7.27 (m, 5H), 7.07 – 6.95 (m, 1H), 5.41 (s, 1H, H-4), 4.23 – 4.00 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 1.19 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 167.0, 145.9, 143.4, 136.6, 133.2, 131.9, 130.3, 128.3, 127.9, 126.8, 124.0, 121.0, 111.3, 110.9, 77.8, 77.4, 76.9, 60.7, 51.8, 37.9, 14.6; HRMS(ESI): calcd. for $C_{22}H_{21}BrNO_4$+ (M + H+): 442.0654; found: 442.0662.

ethyl 4-(2-bromophenyl)-5-(hydroxymethyl)-1-phenyl-1,4-dihydropyridine-3-carboxylate (9)

To a cooled (0 °C) and stirred solution of ethyl 4-(2-bromophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (0.04 mmol, 1 equiv.), in THF/EtOH 2:1 (2 mL) was added $NaBH_4$ (0.044 mmol, 1.1 equiv) in one portion. The resulting mixture was vigorously stirred at 0 °C for 3 h; then a saturated NH_4Cl solution was added drop by drop until the release of gas stopped. After this point, the solution was extracted with DCM (3 × 5 mL). The combined organic phases were collected, dried (anhydrous Na_2SO_4), and purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture 7:3) to afford the desired product **9** as yellow powder (Y = quant., 17 mg). The enantiomeric excess of **9** was determined by chiral stationary phase HPLC (IA, n-hexane/IPA 70:30, 1.0 mL/min, t_{maj} = 5.0 min, t_{min} = 5.7 min, 96% ee); [α]D25 °C = -41.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 1.7 Hz, 1H, H-2), 7.49 (dd, J = 8.0, 1.3 Hz, 1H, Ar), 7.47 – 7.37 (m, 3H, Ar), 7.31 – 7.22 (m, 5H, Ar), 7.04 (td, J = 7.3, 1.8 Hz, 1H, Ar), 6.57 (s, 1H, H-6), 5.23 (s, 1H, H-4), 4.13 – 3.88 (m, 5H, CH_2, CH_2O, OH), 1.13 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 146.0, 144.0, 137.8, 132.5, 131.2, 130.1, 128.6, 128.4, 125.6, 123.7,

123.3, 121.4, 120.2, 106.4, 77.8, 77.4, 76.9, 63.3, 60.3, 39.5, 14.6; HRMS(ESI): calcd. for $C_{21}H_{21}BrNO_3$+ (M + H+): 414.0705; found: 414.0709.

ethyl 4-(2-bromophenyl)-5-methyl-1-phenylpiperidine-3-carboxylate (10)

A solution of ethyl 4-(2-bromophenyl)-5-formyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (0.04 mmol, 1 equiv.) in DCM (1 mL) was cooled to -10 °C, and triethylsilane (122 µL, 20 eq.) was added along with trifluoracetic acid (90 µL, 25 eq.). This mixture was then allowed to stir while warming to room temperature. After 24 h, volatiles were removed under reduced pressure. The resulting crude oil was purified by column chromatography (DCM/MeOH) to give **10** as single diastereoisomer (Y =52 %, 8 mg). The enantiomeric excess of **10** was determined by chiral stationary phase HPLC (Cellulose 1, n-hexane/IPA 98:2, 1.0 mL/min, t_{maj} = 7.3 min, t_{min} = 8.7 min, 96% ee); [α]D25 °C = -8.0 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.0, 1.3 Hz, 1H, Ar), 7.33 – 7.25 (m, 4H), 7.16 (dd, J = 7.9, 1.8 Hz, 1H, Ar), 7.07 (td, J = 7.6, 1.8 Hz, 1H, Ar), 7.00 – 6.93 (m, 1H, Ar), 6.87 (t, J = 7.3 Hz, 1H, Ar), 7.04 - 3.91 (m, 3H, CH2, CH_{piper}), 3.73 (dd, J = 12.2, 4.2 Hz, 1H, CH_{piper}), 3.63 (d, J = 12.3 Hz, 1H, CH_{piper}), 3.43 (t, J = 10.7 Hz, 1H, CH_{piper}), 3.22 – 3.11 (m, 1H, CH_{piper}), 2.97 (t, J = 11.3 Hz, 1H, CH_{piper}), 2.42 – 2.28 (m, 1H, CH_{piper}), 1.02 (t, J = 7.1 Hz, 3H, CH_3), 0.89 (d, J = 7.0 Hz, 3H, CH3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 133.6, 129.5, 129.0, 128.2, 127.2, 120.1, 117.3, 77.8, 77.4, 76.9, 60.8, 57.6, 53.4, 47.0, 42.4, 31.8, 14.3, 13.3. HRMS(ESI): calcd. for $C_{21}H_{25}BrNO_2$+ (M + H+): 402.1069; found: 402.1079.

CHAPTER II: Umpolung Catalysis promoted by Thiamine dependent Enzyme

1. Introduction

1.1. Enzyme in organic synthesis

An Enzyme is a biological catalyst which, as every other catalyst, accelerates the reaction by lowering the activation energy (E_a)[1]. This capability, named "the rate acceleration" was generally attributed to transition-state stabilization of the reaction by the enzyme[2]. Furthermore, the chiral environment of the active site in the enzyme makes diastereomeric the enzyme-substrate complexes. In principle two of these are possible (EnzA and EnzB), which are characterized by different values of free energy (ΔG) for the transition states $[EnzA]^{\neq}$ and $[EnzB]^{\neq}$ respectively. The difference between these two transition states $\Delta\Delta G^{\neq}$ determines the "chiral recognition" or the direct measure of the selectivity, which has as consequence that one enantiomer will be converted faster the than other one, this is the origin of "Stereospecifity" of the enzyme[3]. Furthermore, since the chirality is a quality of space, and the active site of the enzyme has a specific three-dimensional architecture, the substrate is positioned firmly in the catalytic site to ensure spatial recognition and driving the transformation towards a high degree of enantioselection. Thus, the enzyme is also "enantioselective"[4]. Among the advantages that belong to the enzyme catalysis in organic synthesis there is the "regioselectivity" which allows the enzyme to distinguish between functional groups which are chemically identical but placed in different positions within the same molecule. Finally, enzymes also show "chemoselectivity" due to their ability to act on a single type of functional group avoiding to touch other functional groups which would not survive under chemical catalysis[5]. There are also some disadvantages to take into account: often, Nature provides enzyme in only one enantiomeric form. In fact, the enzymes are made up by L-aminoacids, the only enantiomeric form of natural aminoacids. However, in some cases, it is possible to modify the catalytic site of an enzyme via protein engineering in order to access the opposite enantiomer[6]. Furthermore, many enzymes display inhibition phenomena caused by the substrate or by the product of reaction, which may generate a drop of the reaction rate working at high substrate concentration[7]. About the enzyme catalysis advantage of working under mild reaction condition, it can sometimes turn into a drawback. In fact, if the reaction is too slow under given parameters of temperature or pH, drastic changing are not permitted, because of elevated temperatures and extreme pH may cause the degradation of the enzyme leading to a complete deactivation[8]. Water is the natural medium in which enzymes generally works and they display their highest activity in water but this solvent is usually the least suitable solvent for the most organic reaction[9]. Another important point to stress is that many enzymes needs specific cofactors and even though they are extremely flexible for accepting non natural substrates, they are strictly selective for their own natural cofactors (heme, NAD(P)H, flavin, ATP etc.) which are fundamental for the catalytic transformation. These cofactors are often unstable

molecules and too expensive to be used in stochiometric amounts. Even though the recycling of cofactor works very well in some case this is still not a trivial task[10].

Biocatalysts used for biotransformations can be very diverse and they could be employed in different forms. It is possible to use pure enzymes, crude enzymes or whole microorganisms cells all under free or immobilized form. The final decision depends on several factors, such as: the type of reaction, if the cofactors have to be recycled, and the scale in which the biotransformation has to be performed[11].

The three-dimensional structure of the enzyme is determined by its primary structure (amino acidic sequence). Because of the enzyme works naturally in water, the hydrophilic polar groups (such as: -OH, $-NH_3^+$, -SH, $CONH_2$, COO^-) are mainly located on the surface of the enzyme and they are hydrated. Whereas the hydrophobic substituents (such as: aryl and alkyl chains) are placed inside[12]. The thin layer made up of water particles is a distinctive part of the enzyme and is fundamental to maintain its three-dimensional structure and its catalytic activity. This layer of water is called structural water and it cannot be removed by lyophilization[13]. If an exhaustive drying of the enzyme is performed a conformational change of the enzyme occurs resulting in a loss of activity. About the general mechanism of action of enzymes, numerous studies were performed. In 1894 E. Fischer, for the first time, tried to propose a general mechanism, involved in the enzymatic transformation. He proposed a lock-and-key approach in which the substrate is accepted in the catalytic site as a key is accepted by a lock (figure 1)[14].

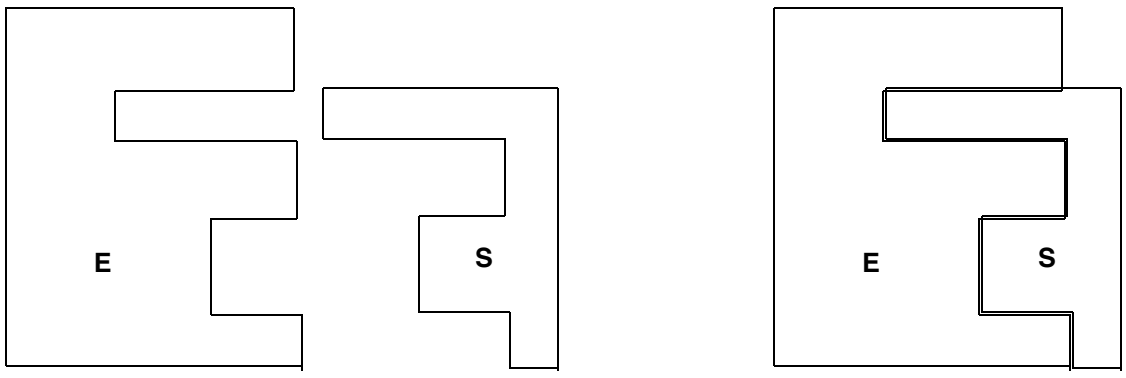


Figure 1. Schematic representation of the 'lock-and-key' mechanism. E is the Enzyme and S the substrate

The problem of this proposed mechanism is that assumes a completely rigid enzyme structure which cannot explain why many enzymes act on bulkier substrates, whereas, they are completely inactive on the smaller ones. Furthermore, it is not explicable why many enzymes can convert not only their natural substrates but also a plethora of non-natural compounds. A hypothesis which takes into account that enzymes are not rigid was presented by Koshland in 1960[15]. He said that while the substrate approaches to the enzyme, this change its conformation under the influence of the substrate

structure in order to accept it better. This mechanism is named “induced fit” and it could be illustrated by the interaction of a hand and the glove. While the hand is wearing the glove, the glove change is form to fit better with the hand. This model can explain why the enzyme can accept non-natural substrates and why in many cases several functional group must be located at quite distance in addition to the reactive functional group (figure 2).

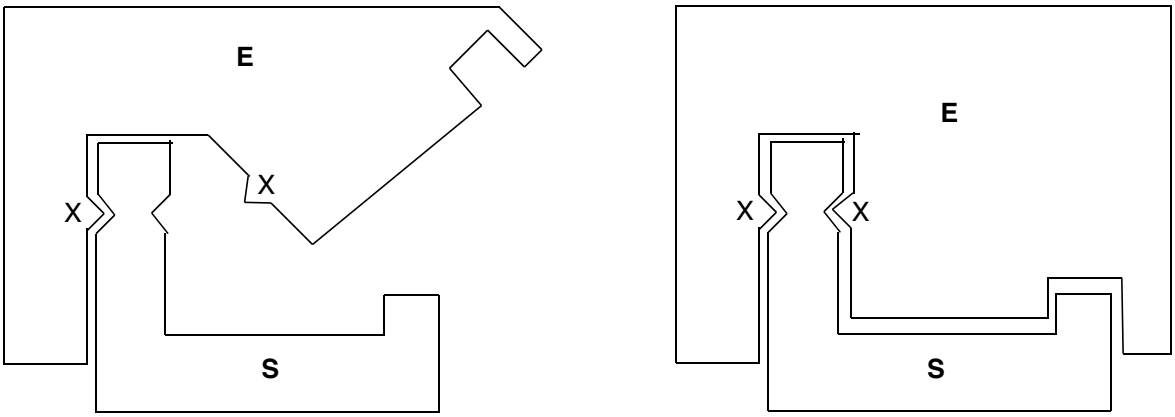


Figure 2. Schematic representation of the ‘induced-fit’ mechanism. E is the Enzyme and S the substrate

The International Union of Biochemistry and Molecular Biology (IUBMB) has recognized about 4000 enzymes and it is believed that 25000 enzymes are present in nature. In general, enzymes were classified into six categories according to the type of reaction which they can promote[16]. Among the most employed: oxidoreductases are able to reduce or oxidize a large number of functional group (Such as: C-H, C-C, C=C, etc.), transferases are employed to transfer functional groups from a molecule to another one. Hydrolases can promote the hydrolysis-formation of esters, amides, anhydrides and etc. and Ligases are useful enzyme engaged in the formation-cleavage of C-O, C-S, C-N and C-C bonds. From an industrial point of view, it is preferable to use enzymes in a crude form because they are relatively inexpensive. Furthermore, the crude preparation, which contains inactive proteins, stabilizer, buffer salts and carbohydrates, is often more stable than the purified enzyme.

1.2 Immobilization of enzymes

Several enzymes, and specially purified enzymes, are not sufficiently stable under the reaction conditions employed for synthetic applications. The immobilization of enzymes is a strategy that can overcome this problems[17].

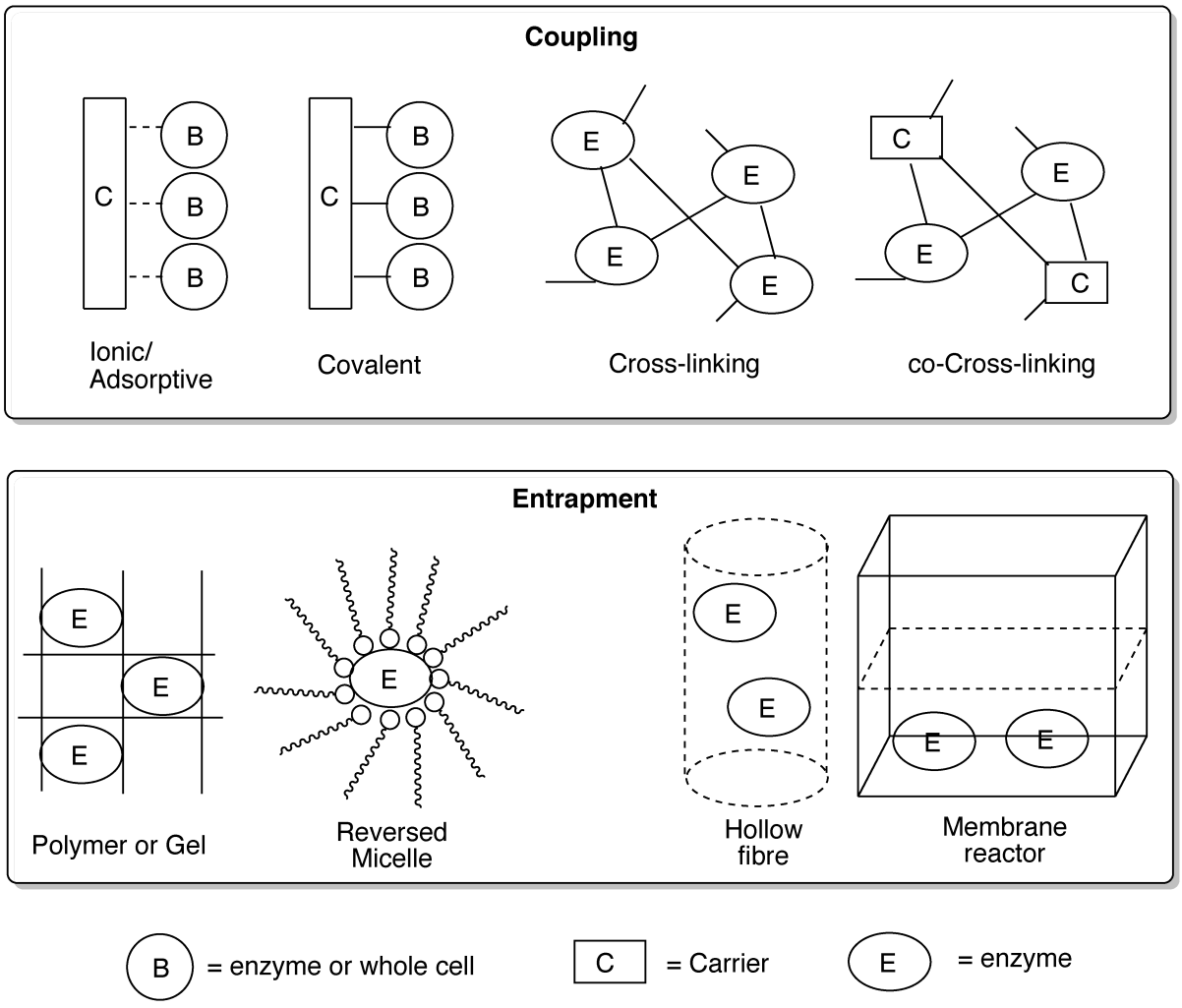
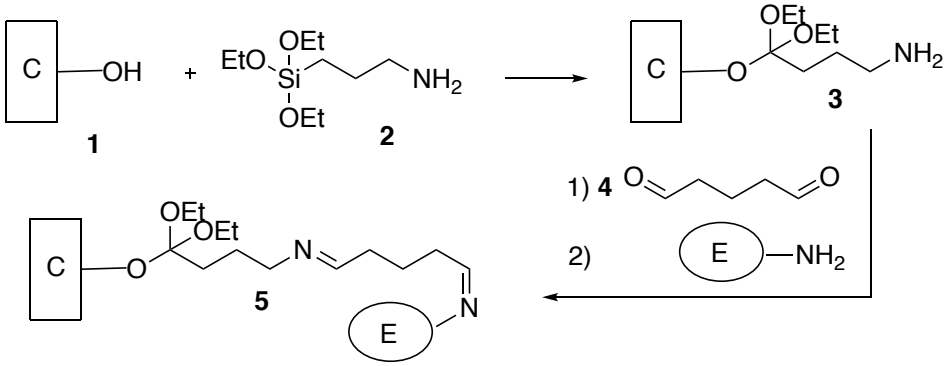


Figure 3. Several methods to immobilize enzymes or whole cells

Generally, immobilization occurs via the attachment of the enzyme onto a solid support by means of a chemical coupling. However, there are other way to immobilize an enzyme. When an enzyme is immobilized some properties such as selectivity, stability, kinetic (k_{cat} and K_m) may be altered because of some conformational changes of the native form.

The oldest method to immobilize an enzyme is the adsorption onto an insoluble macroscopic carrier. The adsorption occurs via weak interaction forces such as London forces, ionic interactions and hydrogen bonds. The major drawback is the leaching of the enzyme which can happen when some changes in the reaction parameters are applied (Temperature, pH, concentration etc.). During the years, numerous carriers have been tried both inorganic and organic (silica, alumina, cellulose etc.)[18]. The affinity towards the support depend on the class of the enzyme; for example, lipases prefer hydrophobic support, whereas the other classes are more prone to interact with hydrophilic carriers[19]. Because of the interaction on the surface is very weak, losses in the enzyme activity are usually low. Another way to immobilize the enzymes is via ionic binding. In this case ion exchange resins are employed to adsorb the enzyme in a manner similar to the above described absorption

through weak bonding. The major advantage in this case is a lower risk of leaching. Finally, covalent binding of enzymes to solid support have been deeply investigated as well. The binding through the formation of irreversible and stable chemical bonds makes the heterogeneous enzyme more resistant to the leaching. However, harsher conditions are required to immobilize the enzyme through covalent bonds and, consequently, some loss of activity is sometimes observed[20]. Generally, this kind of immobilization is performed in two steps namely the activation of the carrier with a reactive spacer followed by the enzyme attachment. A classic example of chemical immobilization is shown in scheme 1.



Scheme 1. Covalent immobilization of enzymes

A generic support with an oxydrilic function **1** is treated with an aminoalkyl triethoxysilane **2** to obtain the support with a spacer and a terminal amino group **3**. At this point dialdehyde (linker) **4** is led to react with the support **3** followed by the enzyme in order to attach the protein onto the support **5.** Furthermore, the imine functionality can be reduced in order to make stronger the linking with the support[21]. A decrease in catalytic activity is inevitably when a supported enzyme is employed, due to an introduction of a large portion of inactive ballast. It is possible to avoid partially this drawback attaching enzymes onto each other via "cross-linking" to covalent bonds. In general, α,ω-glutardialdehyde, dimethyl adipimidate or isocyanate are the most common linker. The major drawback in this technique is that the soft aggregates which comes from the cross-linking, are similar to gelatin and this prevents their use in packed-bed reactors[22]. Furthermore, diffusional problems may cause limitation in the enzyme activity. When the enzyme does not tolerate direct binding it may be possible encaging it in a macroscopic matrix. It is necessary in this case that the substrates and the products can freely pass through the macroscopic structure. Biological matrixes are the most used cages, such as: alginate gels, agar gels and carrageenan and the gel formation is usually initiated either by changing the ionotropic environment of the system or by variation of the temperature.

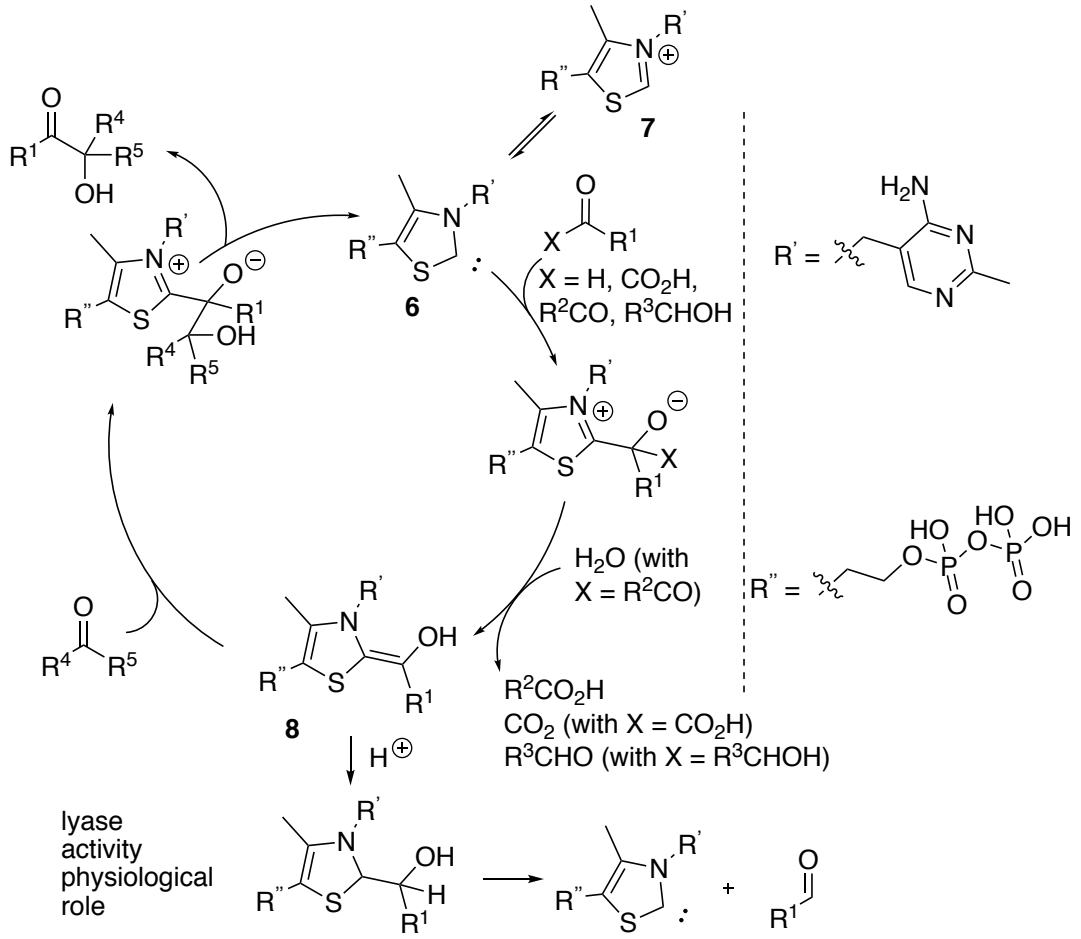
1.3 Promiscuity

An ability that makes the enzymes attractive for organic chemists is the “promiscuity”. Although an enzyme is a specific catalyst beside of its native activity it can sometimes promote fortuitous side reactions[23]. In Nature the utility of this ability is reasonable. In fact, under new external pressures this side activity may confer a benefit promoting quickly the evolution of the promiscuous activity as the new main activity. A promiscuous reaction is in general catalyzed with lower efficiency with respect to the main one and the difference depends on the specificity of the enzyme. An enzyme is “specialist” if the affinity for a particular substrate (natural or physiological substrate) is high, as well as the rate of transformation of such substrate and, on the contrary, very low reaction rates are exhibited for non-natural substrates[24]. Vice versa an enzyme is “generalist” if it shows a broad substrate range, but low main activity. Three different kinds of promiscuity are known: substrate promiscuity, when the enzyme catalyze the conversion of nonnatural substrate; if a nonnatural reaction is catalyzed the enzyme shows catalytic promiscuity; finally, if the catalysis occurs in a nonnatural environment is observed a condition promiscuity.

1.4 Thiamine-Diphosphate-dependent Enzymes

1.4.1 General features

As mentioned above, many enzymes need cofactors to work. Generally, cofactors can be divided into two major group; organic (such as Flavin, heme, etc.) or inorganic cofactor (Mg^{2+}, Cu^{+}, iron-sulfur clusters, etc.). Within this realm, thiamine-diphosphate plays a central role among the enzymes employed to form or break C-C bonds[25]. For example, a schematic representation of the mechanism of enzymatic carboligation by ThDP-dependent enzymes is depicted in Scheme 2.



Scheme 2. benzoin and benzoin-type reactions catalyzed by ThDP-dependent enzyme.

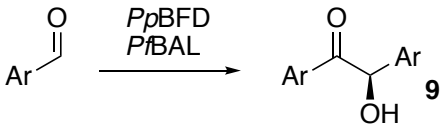
The nucleophilic attack of the ylide or carbene **6**, formed by the deprotonation of the ThDP (**7**), onto the carbonyl group of the substrate followed by intramolecular transfer of the former aldehydic proton or by protonation of the oxyanion and simultaneous cleavage of the C-X bond for non-aldehydic substrates, leads to an enaminol intermediate known as a Breslow intermediate **8**. In this specie, the electrophilic feature of the carbonyl substrate is inverted. Transformations of this type are called umpolung reactions (inversion of polarity) and the Breslow intermediate is, for all intents, an acyl anion equivalent[26]. A plethora of ThDP-dependent enzyme-catalyzed reactions have been described in literature in the last century, but from the end of the 1990s it is possible to see an exponential increase in synthetic applications of such enzymes, thanks to the progress achieved in molecular biology which made available remarkable amounts of them in pure form[27]. Noteworthy, the synthetic value of α-hydroxyketones has forced organic chemist to emulate Nature by developing and designing organic catalysts, like the NHCs described in Chapter I, able to perform umpolung transformation. Unfortunately, despite of the high efficiency of NHCs in promoting umpolung reactions, these organocatalytic methodologies rarely are chemoselective[28] This selectivity limitation, makes biocatalytic approaches based on Thiamina-dependent enzymes, very attractive from a synthetic point of view. It is important to stress that in the physiological pathways the same

acyl anion equivalent **8** can also come from different donor such as: α-diketones, α-hydroxy ketones and α-ketoacids as shown in scheme 2. Generally, the catalytic mechanism exploited for synthetic applications is based on side reactivity. For examples a large number of enzymes employed in Umpolung C-C form reaction are lyases, which have the physiological role of breaking a bond[29].

1.4.2 Benzoin reaction

Among the enzymes which can promote the synthesis of benzoin adducts, benzoyl formate decarboxylase from *Pseudomonas putida* (*Pp*BFD) has been successfully employed in the synthesis of optical pure benzoins on preparative scale[30]. This enzyme catalyzes the non-oxidative decarboxylation of benzoylformate in the mandelate catabolism. It is also able to promote the benzoin condensation of various aromatic aldehyde substrates. In this case the Breslow intermediate formed by the attack of the thiamine ylide on an aromatic aldehyde (donor) is intercepted by another free aldehyde giving access to the enantioenriched benzoin adducts **9** with *R* absolute configuration. The protocol fails when *ortho*-substituted benzaldehydes, with the exception of the 2-fluoro derivative, are employed as substrate (table 1). In this case, another ThDP-dependent enzyme, namely the Benzaldehyde lyase from *Pseudomonas fluorescens* (*Pf*BAL) can be employed which efficiently promotes the enantioselective formation of the expected *ortho*-substituted (*R*)-benzoins[31].

Table 1. Enzymatic benzoin synthesis promoted by *Pp*BFD and *Pf*BAL



entry	Aryl	*Pp*BFD (Y)	*Pp*BFD (*ee*)	*Pf*BAL (Y)	*Pf*BAL (*ee*)
1	C_6H_5	70	>99 (R)	96	>99 (R)
2	2-FC_6H_4	68	>99 (R)	68	96 (R)
3	2-ClC_6H_4	-	-	80	97 (R)
4	2-BrC_6H_4	<2	n.d.	90	>99 (R)
5	2-MeC_6H_4	<2	n.d.	87	>99 (R)
6	3-FC_6H_4	-	-	80	97 (R)
7	3-ClC_6H_4	-	-	94	>99 (R)
8	3-BrC_6H_4	-	-	94	>99 (R)

9	3-IC_6H_4	-	-	-	
10	3-$MeOC_6H_4$	18	>99 (R)	93	>99 (R)
11	3-$(OH)C_6H_4$	-		84	n.d.
12	4-FC_6H_4	25	>99 (R)	89	>99 (R)
13	4-ClC_6H_4	17	>99 (R)	95	>99 (R)
14	4-BrC_6H_4	13	>99 (R)	83	>99 (R)
15	4-$MeOC_6H_4$	12	>99 (R)	95	>99 (R)
16	4-MeC_6H_4	69	>99 (R)	94	>99 (R)
17	2-furyl	62	94 (R)	88	92 (R)
18	5-Me-2-furyl	50	96 (R)	-	-
19	2-thiophenyl	65	95 (R)	-	-
20	2-pyridyl	70	94 (R)	-	-
21	2,4-$F_2C_6H_3$	-	-	87	>99 (R)
22	2-naphthalenyl	-	-	98	>99 (R)

n.d.: not detected.

Furthermore, the (*R*)-benzoin synthesis was also performed under heterogeneous conditions in a batch reactor with the enzyme immobilized[32]. Generally, Enzymes found in Nature are selective towards (R)-Benzoin. Thus, a biocatalytic strategy to achieve the S counterpart, has been based on the kinetic resolution of racemic benzoins promoted by *Pf*BAL[33]. Only recently protein engineering based on rational design mutagenesis has afforded an(*S*)-specific variant of the pyruvate decarboxylase from *Acetotobacter pasteurianus* (*Ap*PDC) capable to catalyzing S-specific benzoin-type reactions reactions. The inversion of stereoselectivity in the engineered enzymes has been demonstrated for the chemoselective condensation between acetaldehyde (donor) and benzaldehyde (acceptor) which afford the valuable synthetic intermediate (*S*)-1-hydroxy-1-phenylpropan-2-one, better known as phenylacetylcarbinol (PAC) **10**. This result has been addressed through in the expansion of the acceptor binding site (the so-called *S* pocket) obtained by replacing Glu469 with Gly. This variation allows a mutual antiparallel orientation of the acceptor and the donor during the nucleophilic attack. Unfortunately, because of the hindered donor binding site, benzaldehyde is not a suitable donor for the *Ap*PDC-Glu469Gly variant. Thus, a further mutation has been introduced, identifying Thr384 as

the main residue responsible for the constriction of the donor binding site. Indeed, the replacement of this residue with glycine, afforded the *Ap*PDC-Glu469Gly/Thr384Gly variant, which showed good activity and a moderate (*S*)-enantioselectivity (conversion = 52% and ee = 59%) (figure 4).

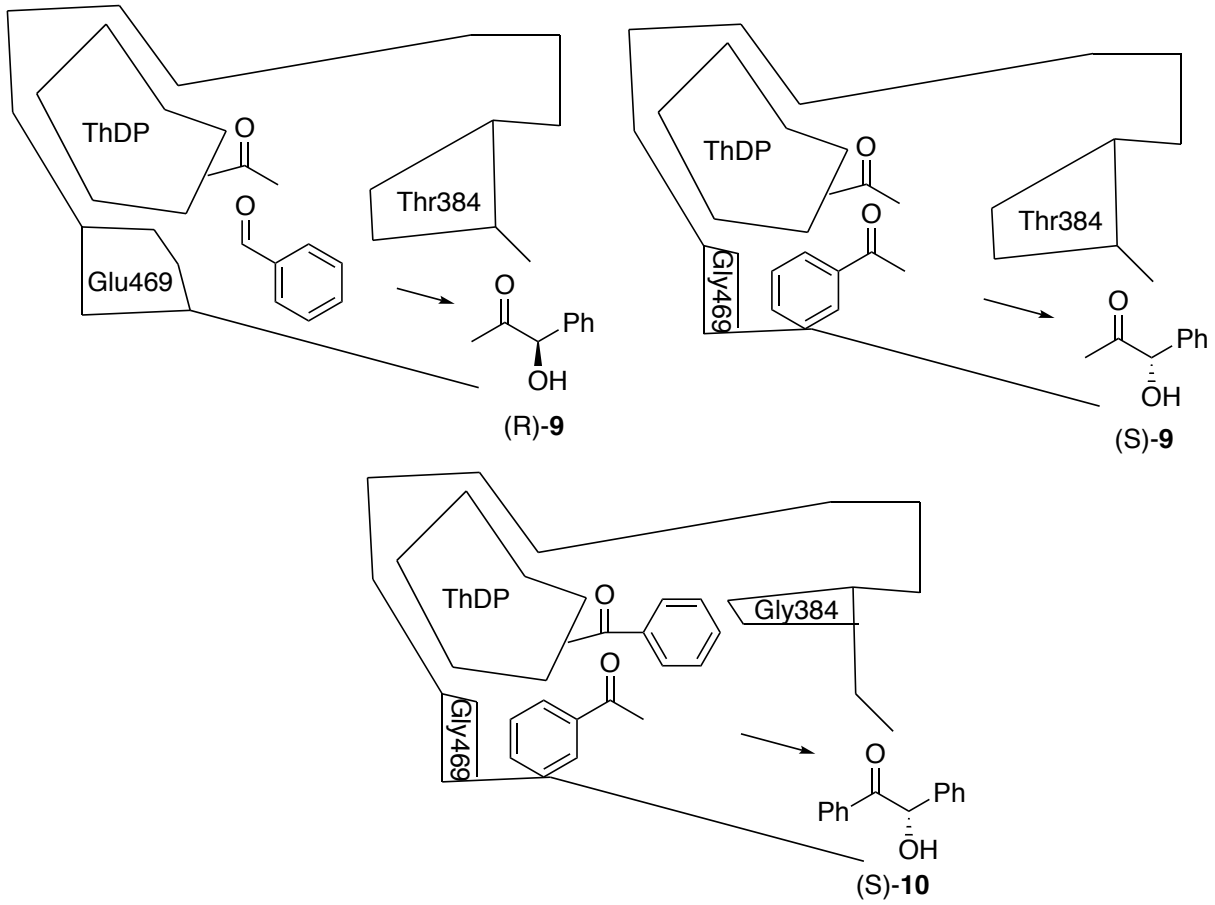


Figure 4. Interaction with substrates in the catalytic pocket of ThDP-dependent enzymes

In order to improve the enantioselectivity a further mutations have been introduced by replacing Ile468 and Trp534, the residues that contribute to favor the parallel orientation of the aromatic acceptor, with Ala and Phe respectively. The new mutated enzyme has shown an excellent enantioselectivity towards the synthesis of (*S*)-benzoin (Conversion = 66% and ee = 98%)[34].

1.4.3 Cross-benzoin reaction

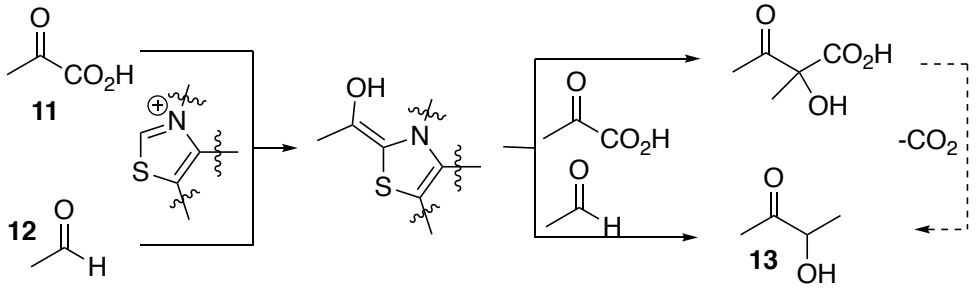
The chemoselective feature, which characterize enzymes catalysis, has inspired synthetic chemist to employ these biocatalysts in order to overcome the selectity issue encountered in cross-benzoin reactions promoted by classical chemical catalysis. For instance, in the *Pp*BFD-catalyzed synthesis of substitute benzoins, it has been envisaged that the low reactivity shown by 2-methoxy-, 2-chloro-, and 2-methylbenzaldehydes, as donors, could be an opportunity to use these compounds as selective acceptors in cross-benzoin reactions with benzaldehyde as donor. In these experiments, a variant of

*Pp*BFD-His281Ala has been successfully employed as catalyst, and the expected cross-benzoin adducts have been obtained with very high selectivity (Scheme 3)[35].

Scheme 3. benzoin and benzoin-type reactions catalyze by ThDP-dependent enzyme.

1.4.4 Aliphatic Benzoin-type reactions

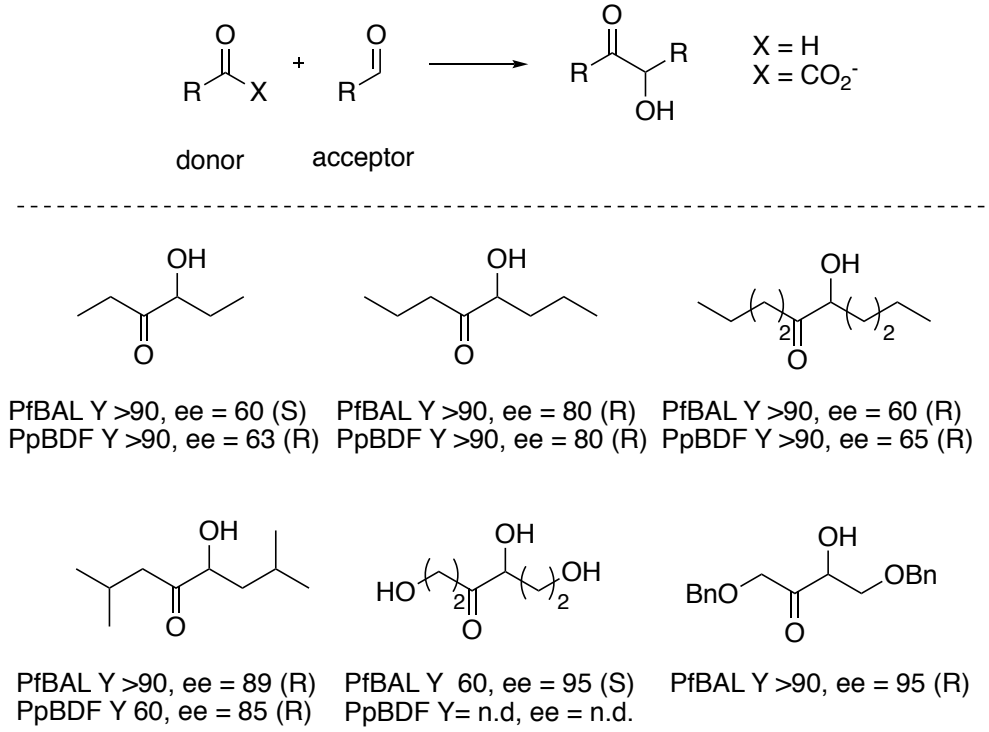
Many ThDP-dependent enzymes are able to catalyze the homocoupling of aliphatic aldehydes to afford the corresponding symmetrically substituted acyloins. The enzymatic formation of Acetoin (3-hydroxybutan-2-one,) **13**, the simplest product obtainable through this approach, has been extensively studied and deeply used as a test reaction to investigate the catalytic mechanisms of various ThDP-dependent enzymes. Enzymatic preparation of acetoin can be performed involving different donor/acceptor combinations. For example, PDCs from *Zymomonas mobilis* and *Saccharomyces cerevisiae* (*Zm*PDC, *Sc*PDC), and the cyclohexane-1,2-dione hydrolase from *Azoarcus sp.* (CDH) catalyze the synthesis of acetoin through three possible routes (Scheme 4)[36].



Scheme 4. Acetaldehyde and pyruvate homocoupling/cross-coupling.

Pyruvate **11** and acetaldehyde **12** can be employed either as acceptor or donor by these enzymes. Interestingly, the enantioselectivity of the reaction does not depend on the synthetic pathway followed. This in contrast with the transformation promoted by SucA, the E1 component of the α-keto glutarate dehydrogenase complex from *Escherichia coli K12*. In this case acetoin **13** is achieved with low (ee = 8 %) or high (ee = 90 %) enantioselectivity when pyruvate or acetaldehyde are employed as acceptor respectively. The drop of enantioselectivity observed in the reaction with pyruvate was explained by the demonstration that acetoin arise from the non-enzymatic decarboxylation of the coupling product acetolactate. In order to increase carboligation activity,

*Zm*PDC-Glu473Gln variant was designed on the basis of the proven role of Glu473 in the protonation of the enamine intermediate[37]. Interestingly, the expected increase in reactivity has been observed along with reverse in enantioselectivity. This result has allowed to identify Glu473 as a hotspot for a rational engineering approach for the fine-tuning and switching of the *Zm*PDC enantioselectivity. In fact, replacing Glu473 with Ala has given a highly *S*-selective variant (ee 98 % starting from pyruvate). More complex symmetrically acyloins have been prepared by utilizing several ThDP-dependent enzymes and donor/acceptor combinations. Enzymatic self-condensations of C3–C5 linear aliphatic aldehydes in the presence of *Pp*BFD and *Pf*BAL have been successfully performed. Both enzymes have given similar results in terms of either conversion and enantioselectivity. Noteworthy, all the substrates were turned into the corresponding products with *R* configuration (ee values ranging from 60 to 89 %) except from propanal, which afford the (S)-enantiomer when the reaction is catalyzed by *Pf*BAL (ee = 60 %). Furthermore, when propan-2-ol is employed as co-solvent (20 %, v/v) the enantioselectivity of *Pf*BAL in the reactions with butanal (ee values from 60 % to 80 %) and pentanal (ee values from 30 % to 60 %) as substrates (Scheme 5) increases.

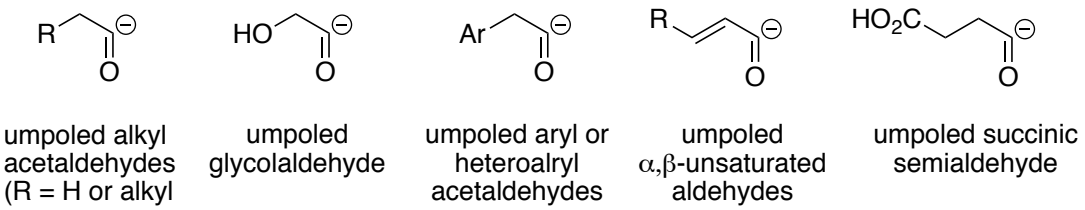


Scheme 5. Enzymatic aliphatic benzoin-type reactions.

Although isovaleraldehyde has been efficiently converted in the presence of *Pf*BAL and *Pp*BFD, neither of these enzymes are suitable to promote the self-condensation of α-branched aldehydes such as isobutyraldehyde and pivaldehyde[38].

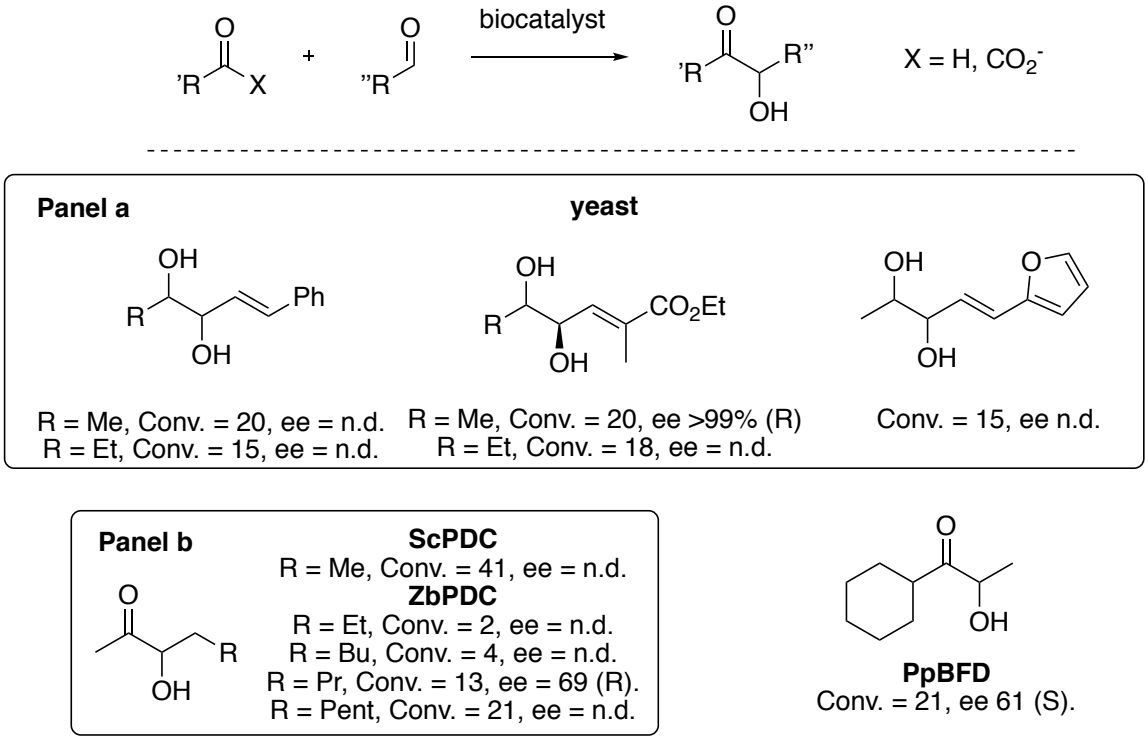
1.4.5 Aliphatic Cross-Benzoin-Type Reactions

Asymmetric synthesis of aliphatic acyloins with different substituents on the carbinol and carbonyl centers based on the use of ThDP-dependent enzymes are widespread in literature. Due the huge amount of reaction disclosed in this area, a rational classification should be carefully set. These benzoin-type reactions have been recently classified on the basis of the kind of acyl anion transferred as shown in scheme 6[39].



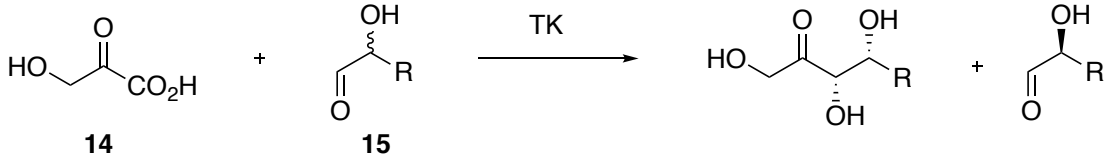
Scheme 6. Main types of acyl anions transferred in cross-benzoin-type reactions.

Alkyl acyl anion donors are the simplest umpoled aldehydes employed in cross-acyloins reaction. In this regard, several studies baed on the use of ThDP-dependent enzymes have been presented in literature. The 2-oxobutanoate and pyruvate have been successfully reacted with different α,β-unsaturated aldehydes employing yeast whole cells (Scheme 7a). Condensation of pyruvate with small linear aliphatic aldehydes (C3-C7) in the presence of purified PDCs from *Zigosaccharomices bisporus* and *S. cerevisiae* has been reported as well. However, the scope of reaction in these studies is narrow and the enantioselectivity is often not acceptable for synthetic purposes (Scheme 7b)[40].



Scheme 7. ThDP-dependent enzyme-catalyzed synthesis of aliphatic acyloins (reduction for the reaction preformed with whole is due to the presence of the enzyme oxydoreductase).

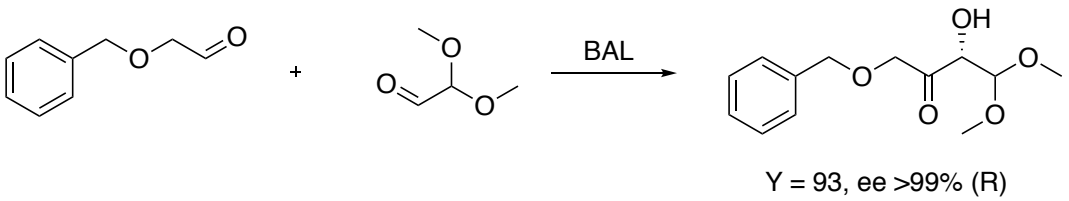
Reaction of umpoled glycolaldehyde with aliphatic aldehyde acceptors for the preparation of aliphatic mixed acyloins has been intensively investigated. The most employed biocatalysts for this transformation are Transketolases (Tks). The eligibility comes from its natural catalytic activity, which involves the transfer of a C2-ketol unit from D-xylulose-5-phosphate to either D-ribose-5-phosphate or D-erythrose-4-phosphate in the pentose phosphate pathway[41]. Generally, natural ketose donor is replaced by hydroxypyruvate **14** in order to make TK-promoted carboligation irreversible. The coupling between acceptor-type **15** and activated glycolaldehyde intermediate formed by **14**, along with the release of carbon dioxide, is the general protocol adopted (Scheme 8).



Scheme 8. Transketolase-catalyzed carboligations with natural ketose and hydroxypyruvate donors

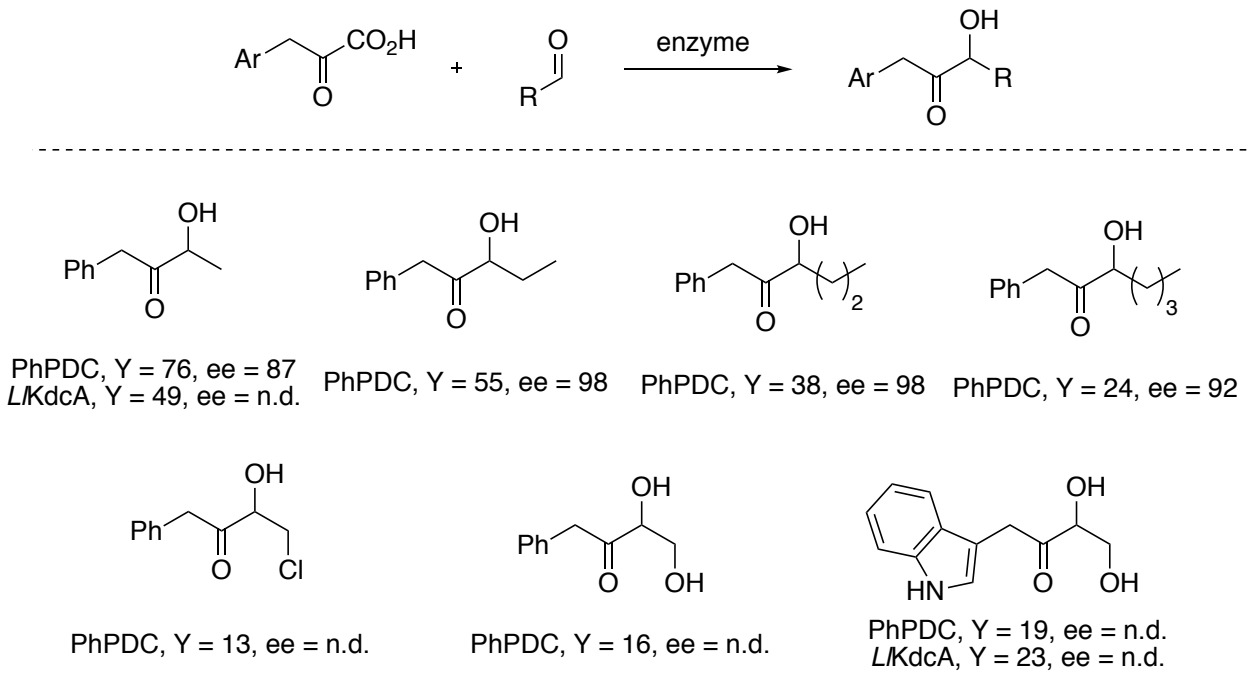
Homologation of α-hydroxylated acceptors have been among the first synthetic uses of TKs[42]. It has been demonstrated that TKs derived from both spinach and yeast are highly stereospecific for (*R*)-aldehyde acceptors, affording the new stereogenic center with *S* configuration. Interestingly, these enzymes, as well as TK from *E. coli*[43] have been successfully employed as catalyst also for the condensation of α-hydroxypyruvate with non-hydroxylated aldehydes. Beside of transketolases,

it has been found that BAL is able to catalyze the addition of umpoled benzylated glycoaldehydes to several aliphatic aldehydes (Scheme 9).



Scheme 9. BAL-catalyzed cross-coupling of benzylated glycolaldehyde 16 and 2,2-dimethoxyacetaldehyde

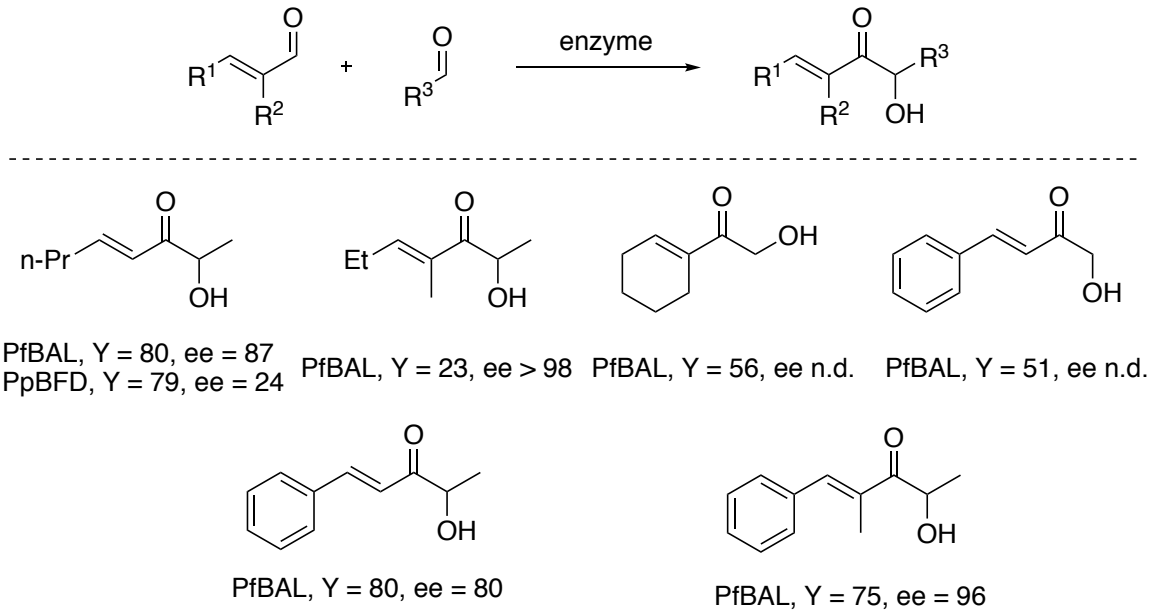
Phenylpyruvate and its analogue indole-3-pyruvate have proved to be versatile donors in enzymatic benzoin-like reaction. Good results in terms of reactivity and enantioselectivity have been achieved in carboligation of these donors with C2-C5 linear aliphatic aldehydes, chloroacetaldehyde and glycolaldehyde, employing phenylpyruvate decarboxylate (PhPDC) from *Achromobacter Eurydice* as catalyst (Scheme 10).



Scheme 10. Enzymatic cross-couplings between arylpyruvates and aliphatic aldehydes

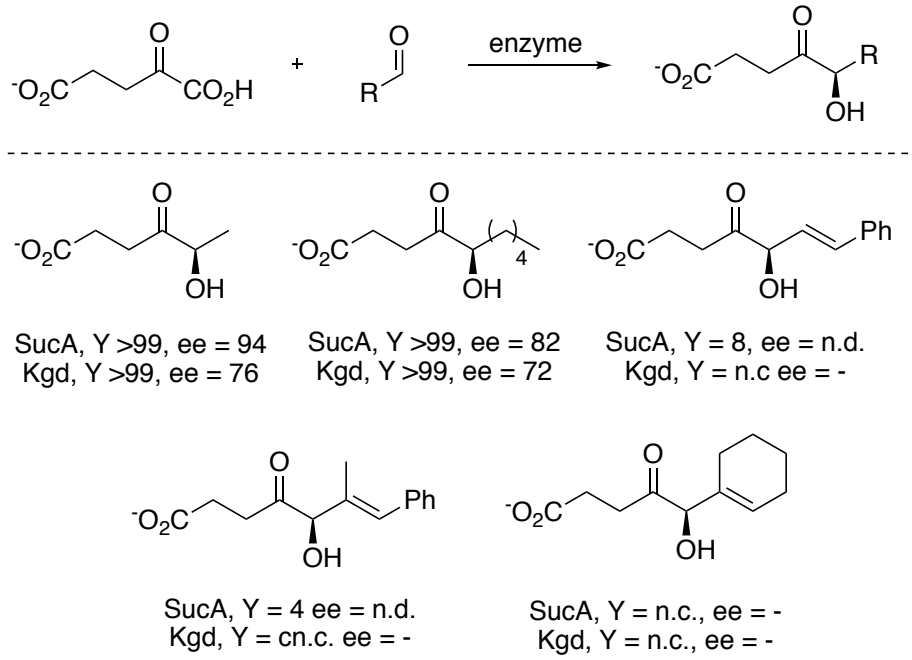
Unfortunately, the acceptor substrate scope has proved to be quite narrow. Especially, for longer-chain aldehydes, aromatic aldehydes, α,β-unsaturated aldehydes and α-methylated aldehydes, which are unreactive or less reactive in this transformation.

Also α,β-unsaturated aldehydes are suitable donor for cross-benzoin-like reactions with acetaldehyde and formaldehyde as acceptors under *Pf*BAL catalysis. This enzyme has shown excellent chemoselectivity and the products have been achieved with good to excellent enantioselectivity (ee = 50 to 98%) (Scheme 11)[44].



Scheme 11. Selected examples of Enzymatic Aliphatic cross-benzoin-type reactions with α,β-unsaturated aldehyde donors

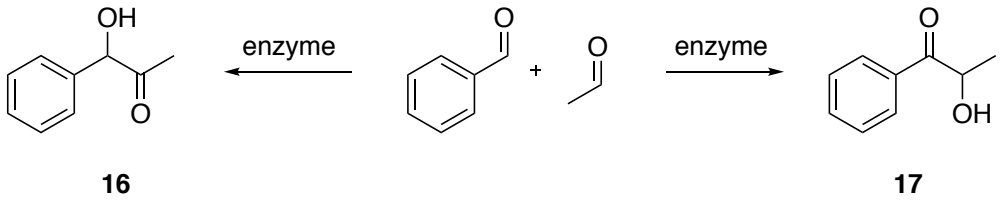
Umpoled succinic semialdehyde has been also generated by different enzymes from α-keto glutaric acid and intercepted by several aliphatic aldehydes. The enzymes SucA and Kgd, engaged in Keto glutarate dehydrogenase enzyme system (KGD) found in *E. coli* K12 and *Mycobacterium tuberculosis*, respectively, have shown to be suitable for this kind of transformation [45]. A comparative study of the carboligation activity of these two enzymes has been conducted with their physiological donor employing various aliphatic and aromatic aldehydes. All these enzymes catalyze the complete conversion of C2-C6 linear aliphatic aldehydes to achieve the corresponding (*R*)-acyloins. In terms of stereoselectivity SucA has shown best results (ee = 82 to 94%), whereas, only moderate enantioselectivity has been observed for Kgd catalyzed reactions (ee = 70 to 82%). Unfortunately, α,β-unsaturated aldehydes have proved to be poor aldehyde acceptors and unsatisfactory results were obtained with SucA, whereas Kgd has been completely inactive (Scheme 12)[46].



Scheme 12. Selected examples of Aliphatic cross-benzoin-type reactions catalyzed by SucA, Kgd

1.4.6 Aliphatic-Aromatic vs Aromatic-Aliphatic Cross-Benzoin Type Reactions

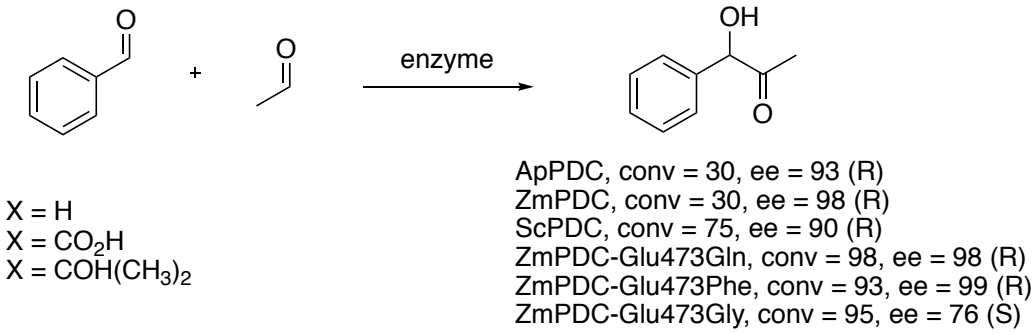
It is important to divide into two categorizes each benzoin-type reaction involving an aromatic and an aliphatic reagent, depending on which role the two partners play. If the aliphatic species act as donors and the aromatic as acceptors the products are α-oxo alkyl aryl carbinols **16** (scheme 13) and the reaction is classified as aliphatic-aromatic cross-benzoin-type reaction. Vice versa the combination of aromatic donors with aliphatic acceptors accesses α-hydroxy alkyl aryl ketones **17** (Scheme 12) and the reaction falls under the category of aromatic-aliphatic cross-benzoin-type reactions.



Scheme 13. Enzymatic couplings of benzaldehyde and acetaldehyde to access phenylacetylcarbinol (PAC) **16** and 2-hydroxypropiophenone (2-HPP) **17**

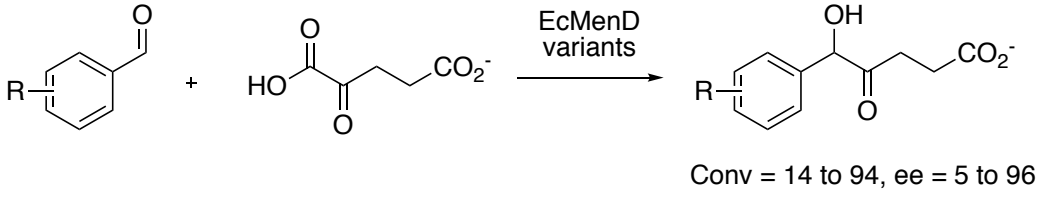
These two enzymatic transformations have been deeply investigated also due to the incredible interesting of the synthetic chemists community on the preparation of the pharmacologically relevant phenyl acetyl carbinol (PAC). Noteworthy, the first enzymatic synthesis has been reported in 1921 employing yeast to access phenyl acetyl carbinol with *R* absolute configuration and exploited for large scale production of (-)-ephedrine[47]. The *in vivo* production of PAC was performed employing

several microorganism, while the most commonly isolated PDCs are from *S. cerevisiae*, *A. pasteurianus* and *Z. Mobilis*[48]. Furthermore, several PDC variants with improved carboligation activity have been obtained by protein engineering through site-directed mutagenesis. *Zm*PDC-Glu473Gln variant catalyzes PAC formation with a yield that is three-times higher than the wild-type enzyme (from 30 to 98%). A reasonable explanation is that the enaminol intermediate undergoes the protonation more slowly in the variant than in the wild-type enzyme due the replacing of the acid Glu473 residue with Gln. Recently, several other enzymes have been added to the biocatalytic toolbox for the synthesis of PAC (Scheme 14).



Scheme 14. Enzymatic synthesis of phenylacetylcarbinol (PAC)

The ThDP-dependent enzyme cyclohexane-1,2-dione hydrolase (CDH), which has the biological role of anaerobic degradation of alicyclic alcohol, was successfully employed to promote the synthesis of PAC. Even though the natural substrate for this enzyme is cyclohexane-1,2-dione, the non-physiological carboligation of this enzyme towards the formation of (R)-PAC, starting from pyruvate and benzaldehyde, occurs smoothly[49]. Furthermore, a plethora of monosubstituted benzaldehydes have proved to be suitable acceptors with CDH, affording the corresponding PAC analogous with excellent *R*-enantioselectivity (92-99% ee). A diversification, in the synthesis of PAC derivates, could also be achieved increasing the complexity of the aliphatic moiety. In this regard, several aliphatic donors have been tested using benzaldehyde as acceptor. For example, synthesis of many 5-hydroxy-4-oxo-5-phenylpentanoate derivates was performed using the ThDP-dependent enzyme *Ec*MenD as promoter and α-ketoglutarate as donor substrate (Scheme 15)[50].



Scheme 15. 5-Hydroxy-4-oxo-5-phenylpentanoate derivatives obtained by use of *Ec*MenD

The (*R*) enantiomer has been obtained in quantitative yield and excellent enantioselectivity (ee from 93 to >99 %) utilizing the wild-type enzyme from *E. coli*. Noteworthy, the (*S*) enantiomer has been

obtained employing the doubly mutated MenD-Ile474Ala/Phe475Gly variant, which is featured by a less hindered active site according to the "S pocket concept". The same approach was followed to obtain several *S*-selective engineered variants of the Bacillus subtilis MenD (BsMenD) by mutation of the residues Ile476 and Phe477 with Ala or Gly[51]. Interestingly, few examples about the synthesis of (*S*)-phenyl acetyl carbinol have been presented in literature and in each case protein engineering of the enzyme has been necessary to achieve the product with this absolute configuration.

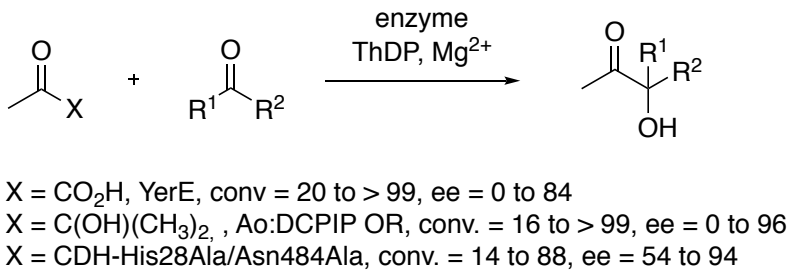
The enzymatic preparation of 2-hydroxy-1-phenylpropan-1-one (2-HPP) **17** (scheme 13), the simplest of the aromatic-aliphatic cross-benzoin type reaction, is principally performed with *Pf*BAL and *Pp*BFD, which show complementary stereoselectivity, affording (*R*)-2-HPP and (*S*)-2-HPP, respectively. *Pp*BFD has been the first purified enzyme employed in this transformation. The physiological role of this enzyme in the decarboxylation of benzoylformate was reported in 1992. When the reaction is carried out in presence of acetaldehyde, the formation of (*S*)-2-HPP is observed in addition to the expected benzaldehyde[52]. The optimal condition, found employing a large excess of acetaldehyde (16 eq.), allows to access the target (*S*)-2-HPP with 62 % of yield in very good enantioselectivity (ee = 92%). Interestingly, due to the reversibility of the benzoylformate decarboxylation, benzaldehyde can be employed as donor in the carboligation reaction. However, both reactivity and enantioselectivity drastically drop in presence of too high concentration of benzaldehyde[53]. Regard to the acceptor substrate scope, *Pp*BFD has shown a narrow capability to accept different aliphatic aldehydes. Either low or no reactivity have been observed for glycolaldehyde, acrolein, 2-chloroacetaldehyde and propanal[54]. This drawback was overcome by *Pp*BFD engineering. A random mutagenesis has identified the Leu476 residue as the hotspot and its mutation afforded BFD variants with an increased carboligation activity. Furthermore, it has been observed that one of these mutated enzymes (*Pp*BFD-Leu476Gln) presents an improvement in terms of enantioselectivity, compared with the wild type counterpart. In addition, *Pp*BFD-Leu476Gln is also able to promote the reaction with ortho-substituted benzaldehydes to achieve the corresponding 2-HPP analogues in quantitative yield and excellent enantiopurity (ee = 96.5 to >99%)[55]. In order to explain the reasons of the complementary stereoselectivity, shown by *Pf*BAL and *Pp*BFD, a comparative molecular modeling study of their catalytic sites has been performed. The results showed that a small donor pocket is present in the *Pp*BFD in contrast to the less hindered one present in the *Pf*BAL.

1.4.7 Aldehyde-Ketone Cross-Benzoin-Type Reactions

As a consequence of the attack of the acyl anion to an aldehyde a secondary alcohol is formed (primary only when the acceptor is the formaldehyde). Benzoin-type reactions can also give access to tertiary alcohol products by using ketones as acceptors. Despite of the high synthetic value of this class of compounds, the preparation via umpolung catalysis has been only limited. YerE and MenD

have proved to catalyze the formation of tertiary carbinol products through pyruvate and α-keto glutarate homo-coupling. Unfortunately, the α-hydroxy-β-ketoacid products of these reactions easily undergo spontaneous decarboxylation, giving the corresponding racemic secondary α-hydroxy ketones and limiting the synthetic value of these reactions[56]. Few examples of enzymatic cross-benzoin-type reactions affording stable tertiary alcohols are present in literature. The first one has been published in 2010 and demonstrate that YerE catalyzes the cross-coupling of pyruvate with a broad set of ketone acceptors. The substrate scope study has shown a very broad tolerance of this biocatalyst, which allowed the enantioselective conversion of cyclic and open-chain ketones, as well as diketones and α- and β-keto esters, into the corresponding tertiary carbinols.

In 2010 our group has disclosed an enzymatic aldehyde-ketone cross-benzoin-type reactions in which the same α-diketone served as acyl donor and acceptor substrate. The reactions were promoted by an enzyme present in cell-free extracts of *B. licheniformis*[57]. The ThDP-dependent enzyme catalyzes the cleavage of different α-diketones, resulting in the formation of reactive umpoled aldehyde intermediates (acetyl and propionyl anion equivalents only) along with the release of the corresponding carboxylic acids. The acyl anion equivalent is quickly intercepted by the α-diketone generating either an achiral product or a mixture composed by an achiral product and a chiral product, depending on the structure of the substrate (Scheme 16).



Scheme 16. Scope of aldehyde-ketone cross-benzoin-type reactions mediated by YerE, Ao:DCPIP OR, and CDH His28Ala/Asn484Ala

1.5 References

[1] H. Eyring, *J. Chem. Phys.*, **1935**, 3, 107.

[2] J. Kraut, *Science*, **1988**, 242, 533.

[3] a) C.H. Wong, *Science*, **1989**, 1145, b) R. Wolfenden, *Bioorg. Med. Chem.*, **1999**, 647.

[4] P. Kielbasinski, P. Goralczyk, M. Mikolajczyk, N. W. Wieczorek, W. R. Majzner, *Tetrahedron: Asymmetry*, **1998**, 9, 2641.

[5] H. M. Sweers, C. H. Wong, *J. Am. Chem. Soc.*, **1986**, 108, 6421.

[6] P. Mugford, U. Wagner, Y. Jiang, K. Faber, R. Kazlauskas, *Angew. Chem. Int. Ed.*, **2008**, 47, 8782.

[7] P. D'Arrigo, C. Fuganti, G. Pedrocchi-Fantoni, S. Servi, *Tetrahedron*, **1998**, 54, 15017.

[8] R. S. Phillips, *Trends Biotechnol.*, **1996**, 14, 13.

[9] A. M. Klibanov, *Acc. Chem. Res.*, **1990**, 23, 114.

[10] D. Nelson, *Lehninger's Principles of Biochemistry.*, New York: W.H. Freeman and Company, **2008**, p. 184.

[11] L. Y. Jayasinghe, A. J. Smallridge,M. A. Trewhella, *Tetrahedron Letters*, **1993**, 35, 3949.

[12] C. B. Anfinsen, *Science*, **1973**, 181, 223.

[13] R. Cooke, I. D. Kuntz, *Ann. Rev. Biophys. Bioeng.*, **1974**, 3, 95.

[14] E. Fischer, *Ber. dtsch. chem. Ges.*, **1894**, 2985.

[15] D. E. Koshland, K. E. Neet, *Ann. Rev. Biochem.*, **1968**, 359.

[16] S. Kindel, *Technology*, **1981**, 10, 62.

[17] U. T. Bornscheuer, *Angew. Chem. Int. Ed.*, **2003**, 42, 3336.

[18] a) O. Miyawaki, L. B. Wingard, *Biotechnol. Bioeng.*, **1984**, 26, 1364; b) W. Krakowiak, M. Jach, J. Korona, H. Sugier, *Starch*, **1984**, 396; c) A. Petri, P. Marconcini, P. Salvadori, *J. Mol. Catal. B*, **2005**, 32, 219; d) H. Takahashi, B. Li, T. Sasaki, C. Myazaki, T. Kajino, S. Inagaki, *Micropor. Mesopor. Mater.*, **2001**, 44, 755; e) A. X. Yan, X. W.Li, Y. H. Ye, *Appl. Biochem. Biotechnol.*, **2002**, 113; f) J. Wiegel, M. Dykstra, *Appl. Microbiol. Biotechnol.*, **1984**, 59; g) T. Kato, K. Horikoshi, *Biotechnol. Bioeng.*, **1984**, 595.

[19] a) M. Sugiura, M. Isobe, *Chem. Pharm. Bull.*, **1976**, 58, 72; b) H. Akita, Biocatalysis, **1996**, 104, 141; c) V. M. Balcao, A. L. Paiva, F. X. Malcanta, *Enzyme Microb. Technol.*, **1996**, 18, 392; d) J. Lavayre, J. Baratti, *Biotechnol. Bioeng.*, **1982**, 24, 1007.

[20] J. Bryjak, B. N. Kolarz, *Biochemistry*, **1998**, 102, 409.

[21] H. H. Weetall, R. D. Mason, *Biotechnol. Bioeng.*, **1973**, 15, 455.

[22] S. S. Wong, L. J. C. Wong, *Enzyme Microb. Technol.*, **1992**, 14, 866.

[23] B. Srinivasan, H. R. Marks, S. Mitra, D. Smalley, J. Skolnick, *Biochemical Journal.*, **2016**, 473, 2165.

[24] N. Tokuriki, D. S. Tawfik, *Current Opinion in Structural Biology*, **2009**, 19, 596.

[25] R. Kluger, K. Tittmann, *Chem. Rev.*, **2008**, 108, 1797.

[26] R. Breslow, *J. Am. Chem. Soc.*, **1958**, 80, 3719.

[27] M. Müller, G. A. Sprenger, M. Pohl, *Curr. Opin. Chem. Biol.*, **2013**, 17, 261.

[28] S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.*, **2011**, 76, 347.

[29] J. J. Bloomfield, D. C. Owsley, J. M. Nelke, *Org. React.*, **1976**, 23, 259.

[30] A. S. Demir, T. Dünnwald, H. Iding, M. Pohl, M. Müller, *Tetrahedron: Asymmetry*, **1999**, 10, 4769.

[31] a) A. S. Demir, M. Pohl, E. Janzen, M. Müller, *J. Chem. Soc. Perkin Trans. 1*, **2001**, 0, 633; b) A. S. Demir, Ö. Şeşenoglu, E. Eren, B. Hosrik, M. Pohl, E. Janzen, D. Kolter, R. Feldmann, P. Dünkelmann, M. Müller, *Adv. Synth. Catal.*, **2002**, 344, 96.

[32] a) S. Tural, B. Tural, A. S. Demir, *Chirality*, **2015**, 27, 635; b) R. Mikolajek, A. C. Spiess, J. Büchs, *J. Biotechnol.*, **2007**, 2, 723.

[33] P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, *J. Am. Chem. Soc.*, **2002**, 124, 12084.

[34] R. Westphal, C. Vogel, C. Schmitz, J. Pleiss, M. Müller, M. Pohl, D. Rother, *Angew. Chem. Int. Ed.*, **2014**, 53, 9376.

[35] E. S. Polovnikova, M. J. McLeish, E. A. Sergienko, J. T. Burgner, N. L. Ander- son, A. K. Bera, F. Jordan, G. L. Kenyon, M. S. Hasson, *Biochemistry*, **2003**, 42, 1820.

[36] a) S. Bornemann, D. H. G. Crout, H. Dalton, D. W. Hutchinson, G. Dean, N. Thomson, M. M. Turner, *J. Chem. Soc. Perkin Trans. 1*, **1993**, 309; b) D. Meyer, L. Walter, G. Kolter, M. Pohl, M. Müller, K. Tittmann, *J. Am. Chem. Soc.*, **2011**, 133, 3609; c) S. Loschonsky, S. Waltzer, V. Brecht, M. Müller, *ChemCatChem*, **2014**, 6, 969.

[37] C. Wechsler, D. Meyer, S. Loschonsky, L.-M. Funk, P. Neumann, R. Ficner, F. Brodhun, M. Müller, K. Tittmann, *ChemBioChem*, **2015**, 16, 2580.

[38] P. D. de María, M. Pohl, D. Gocke, H. Gröger, H. Trauthwein, T. Stillger, L. Walter, M. Müller, *Eur. J. Org. Chem.*, **2007**, 18, 2940.

[39] P. P. Giovannini, O. Bortolini, A. Massi, *Eur. J. Org. Chem.*, **2016**, 26, 4441.

[40] F. Neuser, H. Zorn, R. G. Berger, Z. Naturforsch. *C*, **2000**, 560.

[41] P. Srere, J. R. Cooper, M. Tabachnick, E. Racker, *Arch. Biochem. Biophys.*, **1958**, 74, 295.

[42] a) Y. Kobori, D. C. Myles, G. Whitesides, *J. Org. Chem.*, **1992**, 57, 5899; b) L. Hecquet, J. Bolte, C. Demuynck, *Tetrahedron*, **1994**, 50, 8677.

[43] Z. Guo, A. Goswami, V. B. Nanduri, R. N. Patel, *Tetrahedron: Asymmetry*, **2001**, 12, 571.

[44] A. Cosp, C. Dresen, M. Pohl, L. Walter, C. Röhr, M. Müller, *Adv. Synth. Catal.*, **2008**, 755.

[45] a) R. A. W. Frank, A. J. Price, F. D. Northrop, R. N. Perham, B. F. Luisi, *J. Mol. Biol.*, **2007**, 368, 639; b) T. Wagner, M. Bellinzoni, A. Wehenkel, H. M. O'Hare, P. M. Alzari, *Chem. Biol.*, **2011**, 18, 1011.

[46] M. Beigi, S. Waltzer, A. Fries, L. Eggeling, G. A. Sprenger, M. Müller, *Org. Lett.*, **2013**, 15, 452.

[47] G. Hildebrandt, W. Klavehn, *Deutsches Reichspatent*, Nr. 548549, **1932**.

[48] D. Gocke, T. Graf, H. Brosi, I. Frindi-Wosch, L. Walter, M. Müller, M. Pohl, *J.*

Mol. Catal. B, **2009**, 23, 30.

[49] S. Fraas, A. K. Steinbach, A. Tabbert, J. Harder, U. Ermler, K. Tittmannd, A. Meyer, P. M. H. Kroneck, *J. Mol. Catal. B*, **2009**, 47.

[50] R. Westphal, S. Waltzer, U. Mackfeld, M. Widmann, J. Pleiss, M. Beigi, M. Müller, D. Rother, M. Pohl, *Chem. Commun.*, **2013**, 49, 2061.

[51] À. Gómez Baraibar, E. von Lieres, W. Wiechert, M. Pohl, D. Rother, *Top. Catal.*, **2014**, 401.

[52] R. Wilcocks, O. P. Ward, S. Collins, N. J. Dewdney, Y. Hong, E. Prosen, *Appl. Environ. Microbiol.*, **1992**, 58, 1699.

[53] R. Wilcocks, O. P. Ward, *Biotechnol. Bioeng.*, **1992**, 39, 1058.

[54] B. Lingen, J. Grötzinger, D. Kolter, M. R. Kula, M. Pohl, *Protein Eng.*, **2002**, 15, 585.

[55] B. Lingen, D. Kolter-Jung, P. Dünkelmann, R. Feldmann, J. Grötzinger, M. Pohl, M. Müller, *ChemBioChem*, **2003**, 4, 721.

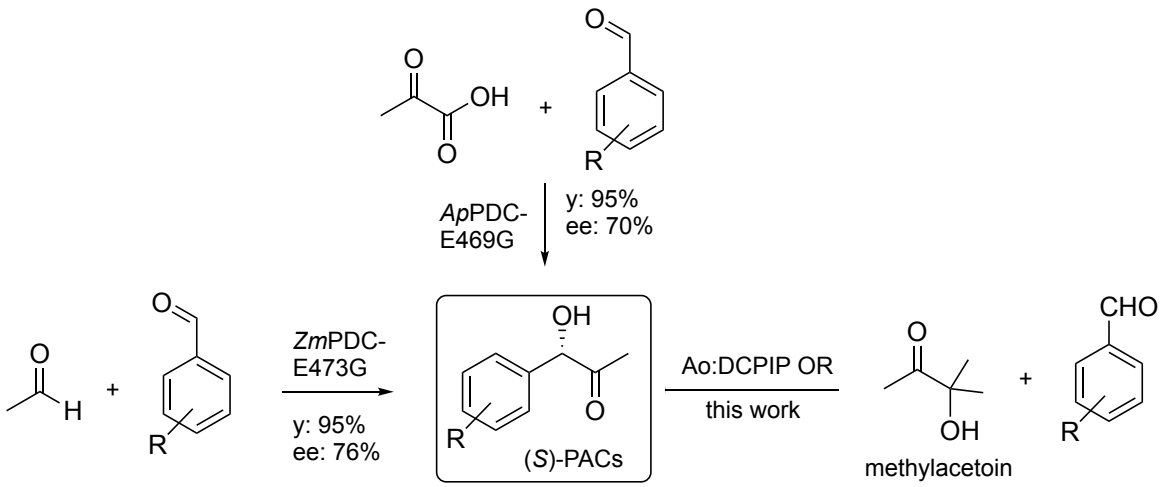
[56] P. Lehwald, M. Richter, C. Röhr, H.-W. Liu, M. Müller, *Angew. Chem. Int. Ed.*, **2010**, 49, 2389.

[57] P. P. Giovannini, P. Pedrini, V. Venturi, G. Fantin, A. Medici, *J. Mol. Catal. B*, **2010**, 66, 113.

2 (*S*)-Phenylacetyl Carbinol Synthesis employing Wild-Type Enzyme Acetoin:Dichlorophenolindophenol Oxidoreductase from *Bacillus licheniformis*

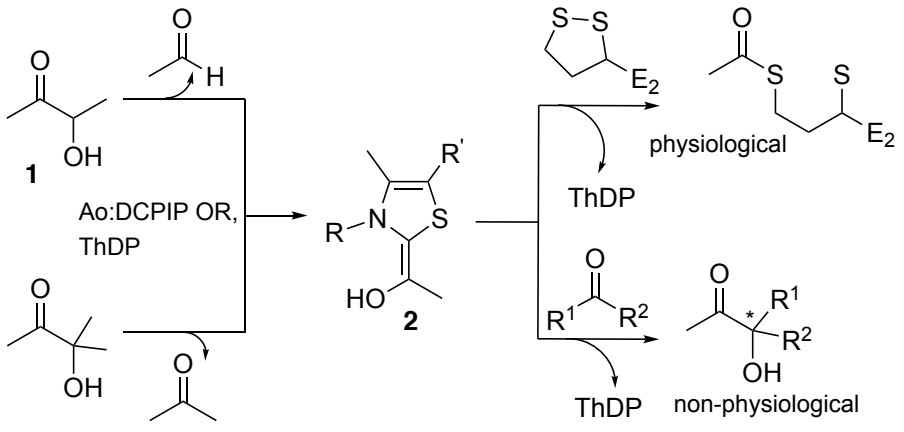
2.1 Introduction

α-Hydroxy ketones are privileged synthons in organic synthesis, especially for the preparation of chiral amino alcohols and diols[1]. They are also structural subunits of many active pharmaceutical ingredients (APIs) including antifungal, antidepressants agents, antitumor and antibiotics[2]. Due to their biological and synthetic importance, a large number of chemical approaches have been disclosed for their preparation. A plethora of metal and organocatalytic protocol has been reported in literature such as: the ketohydroxylation of olefins[3], the α-hydroxylation of ketones with chiral oxidants[4], the asymmetric dihydroxylation of silyl enol ethers[5], the mono-oxidation of 1,2- diols[6], the α-oxygenation of ketones,[7] and the direct asymmetric condensation of two aldehydic molecules by umpolung (polarity reversal) benzoin reaction. Regard to the organocatalytic benzoin reaction, this approach suffers from both chemoselectivity and enantioselectivity issues[8]. Even though some organocatalytic strategies for the cross-benzoin-like condensation have been investigated[9], the reaction is strongly reliant on the nature of the substrates. Thus, thiamine diphosphate (ThDP)-dependent enzymes represent an attractive way to overcome these limitations, allowing to access chiral α-hydroxy ketones with high optical purity and complete chemoselectivity under environmentally benign conditions[10]. For example, (*R*)-phenylacetyl carbinol [(*R*)-PAC], the key intermediate in the L-ephedrine syntheses, is prepared from pyruvic acid and benzaldehyde employing pyruvate decarboxylase (PDC) as biocatalyst[11]. A toolbox of different wild-type (wt) ThDP-dependent lyases, including several PDCs, branched-chain keto acid decarboxylase (KdcA), benzoylformate decarboxylase (BFD), and benzaldehyde lyase (BAL), is available for the chemoselective cross-benzoin-type condensation of several aliphatic and aromatic aldehydes. Unfortunately, the majority of the enzymes found in Nature is able to synthetize only of the (*R*)-enantiomer of the products[12]. The (*S*)-isomers are accessible, employing wt enzyme, only for what concerns several benzoyns, through *Pf*BAL-catalyzed kinetic resolution[13]. However, mutagenesis studies have allowed the design of (*S*)-selective variants of several ThDP-dependent enzymes, increasing the substrate tolerance as well, for the synthesis of (S)-5-hydroxy-4-oxo-5-phenylpentanoate derivatives (from α-ketoglutarate donor and benzaldehydes as acceptors)[14], and for the production of (*S*)-benzoins[15]. Since the preparation of pharmaceutically relevant *S*-PACs is challenging, a variant of PDC from *Acetobacter pasteurianus* was generated in a breakthrough study to produce PAC derivatives with (*S*)-selectivity for the first time[16]. While the mutant enzyme promoted the carboligation between benzaldehyde and acetaldehyde with modest efficiency, (*S*)-PAC was successfully obtained employing the same enzyme and pyruvate as donor (ee = 70%, Y = 95%) (Scheme 1)[17].



Scheme 1. Enzymatic carboligations for the asymmetric preparation of (S)-phenylacetyl carbinols (PACs).

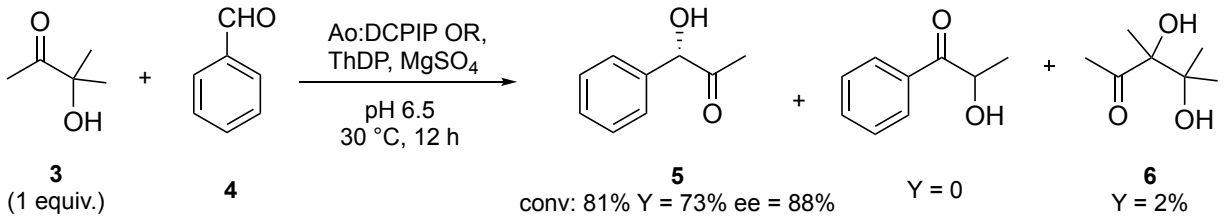
Noteworthy, a variant of PDC from *Zymomonas mobilis* has been recently introduced for the chemoselective formation of (*S*)-PAC (76% ee, 95% yield; Scheme 1)[18]. It seems clear that efficiently protocol to access valuable (*S*)-PAC derivates with extended reaction scope and using readily available enzymes would be highly desirable. Herein, we disclose the unprecedented (*S*)-selective synthesis of phenylacetyl carbinols mediated by the wt ThDP-dependent enzyme acetoin :dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR; EC 2.3.1.190) via carboligation of methylacetoin (acetyl anion precursor) with several substituted benzaldehydes displaying different stereo and electronic features. The final results clearly elect Ao:DCPIP OR as a suitable candidate to fill the gap in the stereoselective synthesis of (*S*)-PAC derivatives exploiting ThDP-dependent enzymes catalysis. Ao:DCPIP OR belongs to the complex of acetoin dehydrogenase enzyme system (AoDH ES)which is expressed in many bacteria[19,20]. Its physiological role is the oxidative cleavage of acetoin **1** releasing acetaldehyde and transfering the (hydroxyethyl)thiamine diphosphate intermediate **2** (acetyl anion equivalent) to the lipoamide cofactor of the consecutive enzyme of the system (Scheme 2, physiological).



Scheme 2. Physiological and non-physiological activities of Ao:DCPIP OR.

2.2 Results and Discussion

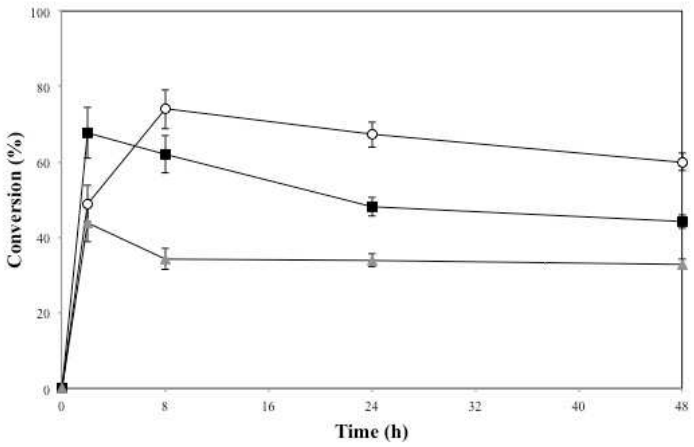
Our group has recently demonstrated that Ao:DCPIP OR from *Bacillus licheniformis*, cloned and overexpressed in *E. coli*, can mediate the non-physiological 1,2-addition of methylacetoin (donor) to activated ketones (acceptors) to afford chiral tertiary α-hydroxy ketones with high efficiency (Scheme 2, non physiological)[21]. Complete control of the chemoselectivity could be achieved in this transformation due to the use of methylacetoin, which forms the Breslow intermediate (Acyl anion) along with elimination of unreactive acetone. Interestingly, some of the products obtained have been formed with opposite stereochemistry compared to those obtained employing other ThDP-dependent enzymes[21]. Thus, as natural extension of that study, we have envisaged the possibility to examine the efficiency of the Ao:DCPIP OR-methylacetoin enzyme-substrate pair in the cross-benzoin-like reaction with aromatic aldehydes to access phenylacetyl carbinols, eventually with unusual (*S*)-configuration. Gratifyingly, condensation of methylacetoin **3** with benzaldehyde **4** under reaction conditions similar to those previously reported in the preparation of optically pure tertiary alcohols [21] [**3** (20 mM), **4** (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% v/v), ThDP (0.4 mM), $MgSO_4$ (0.9 mM), purified and lyophilized Ao:DCPIP OR 0.5 $mgmL^{-1}$, 30 °C, 12 h], afforded the enantioenriched (*S*)-1-hydroxy-1-phenylpropan-2-one [**5**, (*S*)-PAC] with 81% conversion (Y = 73%) and 88% enantiomeric excess (ee), as determined by chiral-phase GC analyses (Scheme 3).



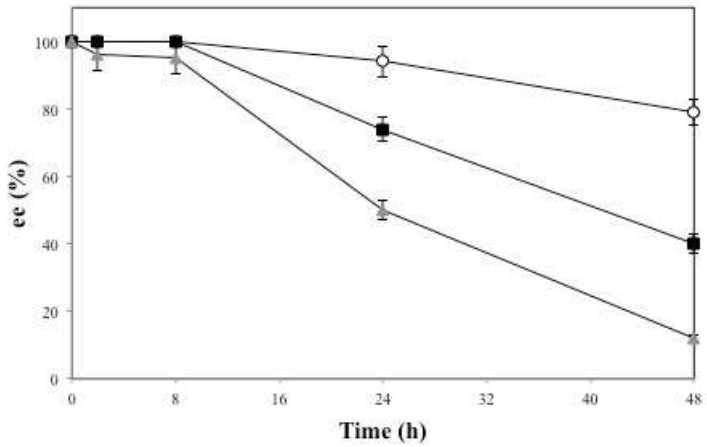
Scheme 3. Explorative study of the cross-benzoin-like reaction of methylacetoin and benzaldehyde catalyzed by Ao:DCPIP OR.

The (*S*)-configuration of **5** has been confirmed matching the obtained PAC with an authentic sample of (*R*)-PAC prepared employing the (*R*)-selective cyclohexane-1,2-dione hydrolase (CDH).[22] Hence, the first important result of this explorative study has been the confirmation of the Ao:DCPIP OR peculiarity to promote carboligation reactions with opposite stereochemical outcome compared to other wt ThDP-dependent enzymes. Moreover, the previously observed high level of chemoselectivity induced by Ao:DCPIP OR catalysis was confirmed in the (*S*)-PAC synthesis as well; indeed, the methylacetoin homocoupling product **6** was detected in very small amounts (2%) and in a racemic form, whereas benzoin and 2-HPP by-products were not observed in the crude reaction mixture (Scheme 3). Thus, we moved to investigate the effect of variation of the substrate molar ratio, reaction time, and enzyme amount on the efficiency of the model cross-benzoin-type

condensation. Using equimolar concentrations of **3** and **4**, a loss of reactivity has been observed for reaction times of approximately 8–10 h, furthermore, this effect was found to be more pronounced increasing the enzyme concentration (from 0.5 to 4.0 mg mL^{-1}, Graphic 1). Interestingly, the graphic 2 reporting the enantiomeric excess values vs time at different enzyme concentrations shows a similar trend with erosion of enantioselectivity at long reaction times and with high concentrations of enzyme.

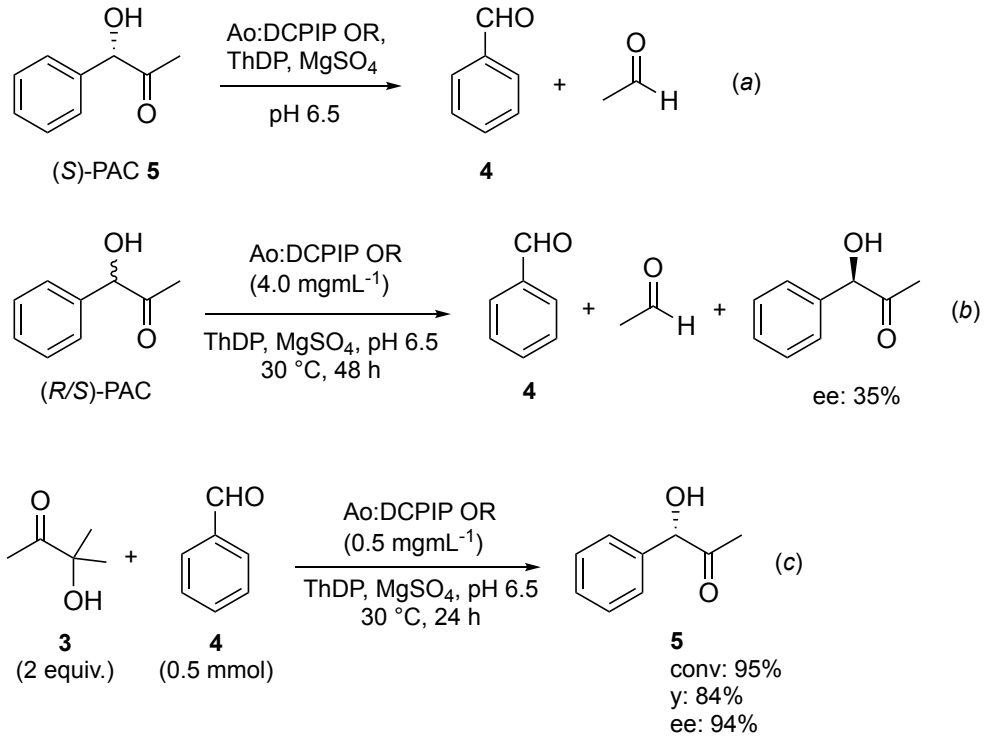


Graphic 1. Conversion of benzaldehyde as a function of time at different enzyme concentrations (Circle: 0.5 mg mL^{-1}; square: 2.0 mg mL^{-1}; triangle: 4.0 mg mL^{-1}).



Graphic 2. Enantiomeric effect as a function of time at different enzyme concentrations (Circle: 0.5 mg mL^{-1}; square: 2.0 mg mL^{-1}; triangle: 4.0 mg mL^{-1}).

These results were rationalized assuming that Ao:DCPIP OR could also catalyze the cleavage of (*S*)-PAC **5** to yield benzaldehyde **4** and acetaldehyde [Scheme 4, Eq. (a)].

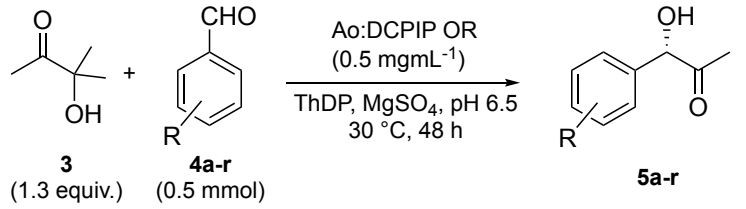


Scheme 4. Cleavage of (S)-PAC (eq. (a)), (R/S)-PAC (eq. (b)) and optimized conditions for the synthesis of (S)-PAC (eq. (c)).

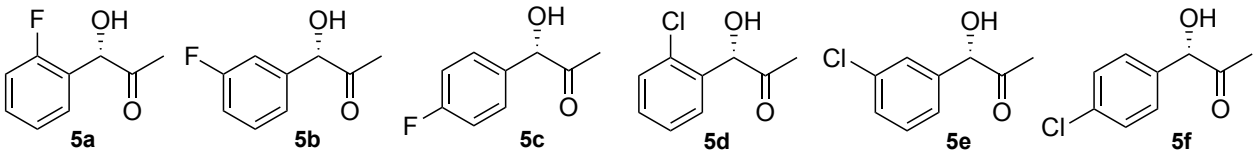
This hypothesis has been also corroborated by ^{1}H NMR analysis of the crude reaction mixture (Ao:DCPIP OR: 4 mgmL^{-1}; reaction time: 48 h) that showed, after extraction with $CDCl_3$, the presence of acetaldehyde. In addition, two control experiments has been performed where racemic PAC was led to react for 48 h under standard conditions with or without Ao:DCPIP OR. Indeed, benzaldehyde was formed only in the presence of the enzyme, which preferentially consumed the (*S*)-enantiomer of PAC, as determined by chiral GC analysis [Scheme 4, Eq. (b)]. Thus, to avoid the detrimental cleavage of Ao:DCPIP OR, the model cross-benzoin-type condensation has been optimized employing a low amount of enzyme (0.5 mg mL^{-1}), an excess of methylacetoin (**3**, 2 equiv.), and monitoring the reaction time (24 h). Under these conditions, (*S*)-PAC **5** was obtained in 84% yield (95% conversion) and 94% *ee* on a semipreparative scale [0.5 mmol; Scheme 3, Eq. (c)]. A brief solvent screen was also investigated and DMSO was found to be the best performing co-solvent, increasing slightly the conversion efficiency. At this point we moved to investigate the substrate scope of the Ao:DCPIP OR-mediated cross-benzoin reaction by testing the behavior of the *ortho*-, *meta*-, and *para*-substituted benzaldehydes (Table 1). Preliminary experiments (on analytical scale, enzyme concentration: 0.5 mgmL^{-1}; equimolar donor/acceptor) showed no decrease of conversion efficiency and enantioselectivity in the formation of the corresponding PACs **5a-r** within 8–48 h. This result was in contrast with the trend observed for **5**, suggesting that the cleavage of PAC derivatives with substituted aromatic moieties is slower compared with the PAC. Therefore, the

reaction time was set at 48 h for the subsequent screening study on a semi-preparative scale (0.5 mmol) using a slight excess (1.3 equiv.) of methylacetoin **3**.

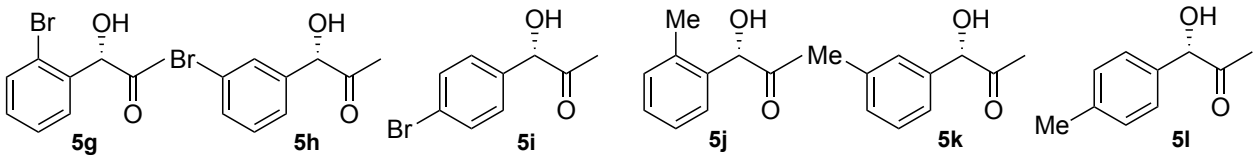
Table 1. Synthesis of PAC derivatives **5a-r** catalyzed by Ao:DCPIP OR



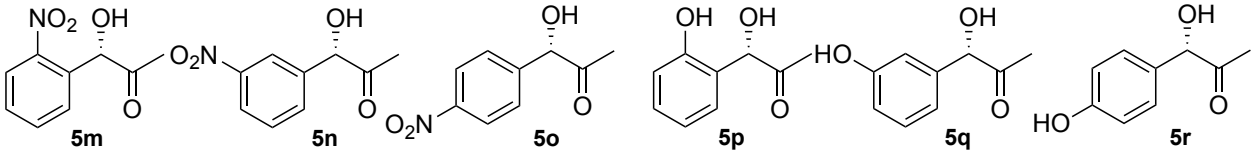
3 (1.3 equiv.) **4a-r** (0.5 mmol) **5a-r**



5a	**5b**	**5c**	**5d**	**5e**	**5f**
conv: 99% y: 90% ee: 83%	conv: 94% y: 85% ee: 80%	conv: 99% y: 88% ee: 92%	conv: 89% y: 81% ee: 68%	conv: 97% y: 87% ee: 78%	conv: 61% y: 55% ee: 89%



5g	**5h**	**5i**	**5j**	**5k**	**5l**
conv: 80% y: 72% ee: 89%	conv: 80% y: 71% ee: 78%	conv: 98% y: 88% ee: 68%	conv: 99% y: 90% ee: 97%	conv: 97% y: 88% ee: 91%	conv: 98% y: 90% ee: 99%

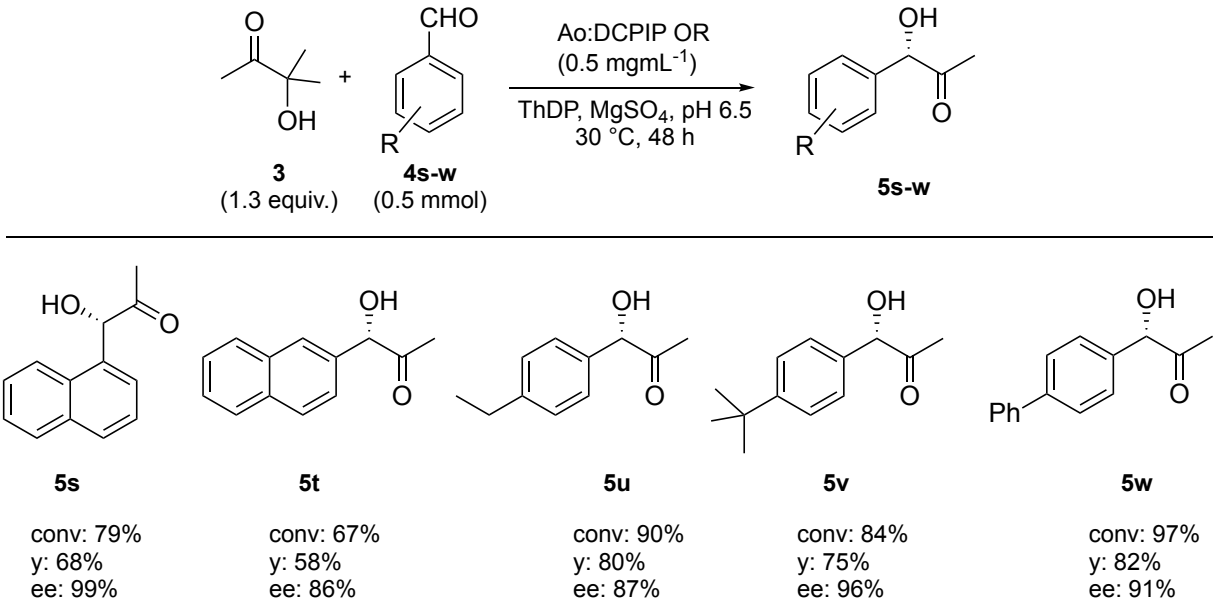


5m	**5n**	**5o**	**5p**	**5q**	**5r**
conv: 86% y: 79% ee: n.d.	conv: 91% y: 85% ee: n.d.	conv: 95% y: 0% ee: -	conv: 94% y: 86% ee: 99%	conv: 99% y: 89% ee: 85%	conv: 52% y: 44% ee: 99%

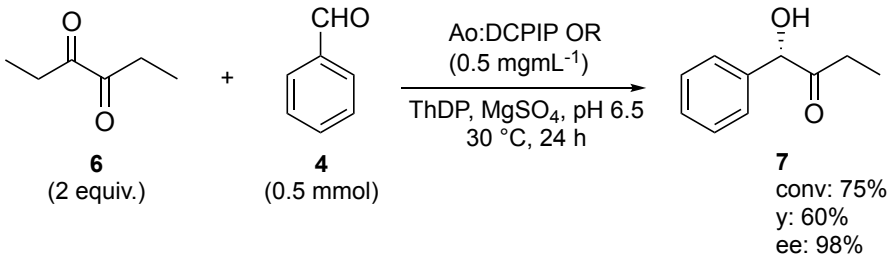
The absolute configuration of all the synthesized PAC analogue products (Table 1) was assigned to be (*S*) on the basis of circular dichroism analysis[25] and confirmed for products **5a-f**, **5j**, **5l** and **5t** by comparison of their optical rotations with literature values[27]. No racemization was observed for compounds under the reaction conditions; this has been checked in a control experiment with isolated **5c** (92% ee), which does not show *ee* erosion over a period of 48h [14c (20mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% v/v), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), 30 °C]. Overall, it was found that the electronic properties and position of the substituent on the aromatic ring have little effect on the conversion (52–99%) and enantioselectivity (68–99% ee) of the cross-benzoin processes, with the exceptions of *o*-chloro-and *p*-bromobenzaldehydes, which gave the corresponding PAC derivatives **5f** and **5i** with modest enantioselectivity (68% ee for both), and *p*-nitrobenzaldehyde. In this latter case, the full consumption of substrates occurred with formation of a quite complex reaction mixture not containing the expected PAC derivative **5o** (^{1}H NMR and MS analyses). It is worth

emphasizing, however, that Ao:DCPIP OR accepted nitro- and hydroxybenzaldehydes, which are suitable substrates only for a very limited number of ThDP-dependent enzymes.[23] Ao:DCPIP OR proved also to be an effective biocatalyst in the condensation of methylacetoin **3** with the sterically demanding aromatic aldehydes **4s-w**, furnishing the PAC analogues **5s-w** with good conversions (67–97%) and enantioselectivities (86–99% ee; Table 2).

Table 2. Synthesis of PAC derivatives **5s-w** catalyzed by Ao:DCPIP OR



Interestingly, hindered aryl aldehyde as 1-naphthaldehyde and 4-(tert-butyl)benzaldehyde were found to be suitable substrate in the cross-benzoin reaction. Noteworthy, these substrates are notoriously poor substrates in enzymatic transformations for steric and solubility reasons[24]. The donor substrate range of the Ao:DCPIP OR- catalyzed cross-benzoin reaction was briefly investigated in an explorative study on the carboligation of benzaldehyde **4** with 3,4-hexanedione **6** for the challenging synthesis of 1-hydroxy-1-phenylbutan-2-one (phenylpropionyl carbinol, PPC) **7** with (*S*)-selectivity (Scheme 5). It is important to remember that alkyl α-diketones are highly reactive donors in Ao:DCPIP OR catalysis[25]; however, their utilization in mixed condensations with carbonyl acceptors is complicated by the occurrence of the α-diketone homocoupling side-reaction, which reduces the chemoselectivity of the coupling process. Nevertheless, the cross-benzoin-type reaction of **6** and **4** was attempted to gain information about the Ao:DCPIP OR capability to promote the (*S*)-selective synthesis of PPC derivatives. Satisfyingly, under standard conditions [30 (40 mM), 5 (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% v/v), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}); 30 °C, 24 h] the target (*S*)-1-hydroxy-1-phenylbutan-2-one **7** was prepared in 60% isolated yield and 98% ee (Scheme 5)[26].



Scheme 5. Synthesis of (S)-phenylpropionyl carbinol (PPC) by Ao:DCPIP OR catalysis.

2.3 References

[1] a) C. Palomo, M. Oiarbidea, J. M. García, *Chem. Soc. Rev*., **2012**, 41, 4150; b) J. Streuff, *Synlett*, **2013**, 24, 276.

[2] a) Q. K. Fang, Z. Han, P. Grover, D. Kessler, C. H. Senanayake, S. A. Wald, *Tetrahedron: Asymmetry*, **2000**, 11, 3659; b) T. Tanaka, M. Kawase, S. Tani, *Bioorg. Med. Chem.*, **2004**, 12, 501; c) O. B. Wallace, D. W. Smith, M. S. Deshpande, C. Polson, K. M. Felsenstein, *Bioorg. Med. Chem. Lett.*, **2003**, 13, 1203.

[3] B. Plietker, *Eur. J. Org. Chem.*, **2005**, 1919.

[4] a) B. Plietker, *Tetrahedron: Asymmetry*, **2005**, 3453; For an enzymatic approach: b) R. Agudo, G.-D. Roiban, R. Lonsdale, A. Ilie, M. T. Reetz, *J. Org. Chem.*, **2015**, 80, 950.

[5] W. Adam, R. T. Fell, V. R. Stegmann, C. R. Saha-Mçller, *J. Am. Chem. Soc.*, **1998**, 708.

[6] O. Onomura, H. Arimoto, Y. Matsumura, Y. Demizu, *Tetrahedron Lett.*, **2007**, 48, 8668.

[7] a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.*, **2004**, 43, 1109; b) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.*, **2004**, 43, 1112.

[8] a) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci.*, **2012**, 3, 735; b) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.*, **2011**, 76, 347.

[9] a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.*, **2007**, 107, 5606; a) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, **2015**, 115, 9307.

[10] a) P. Hoyos, J. V. Sinisterra, F. Molinari, A. R. Alcàntara, P. Domínguez De María, *Acc. Chem. Res.*, **2010**, 43, 288; b) M. Müller, G. A. Sprenger, M. Pohl, *Curr. Opin. Chem. Biol.*, **2013**, 2, 261; c) M. Brovetto, D. Gamenara, P. S. Méndez, G. A. Seoane, *Chem. Rev.*, **2011**, 111, 4346.

[11] A. J. Smallridge, M. A. Trewhella, K. A. Willkinson, U.S. Patent 7,063,969 B2, **2006**

[12] a) M. Müller, D. Gocke, M. Pohl, *FEBS J.*, **2009**, 276, 2894; b) H. C. Hailes, D. Rother, M. Müller, R. Westphal, J. M. Ward, J. Pleiss, C. Vogel, M. Pohl, *FEBS J.*, **2013**, 280, 6374.

[13] a) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, J. Am. Chem. Soc., **2002**, 12084; b) A. S. Demir, M. Pohl, E. Janzen, M. Müller, *J. Chem. Soc. Perkin Trans. 1*, **2001**, 633.

[14] R. Westphal, S. Waltzer, U. Mackfeld, M. Widmann, J. Pleiss, M. Beigi, M. Müller, D. Rother, M. Pohl, *Chem. Commun.*, **2013**, 49, 2061.

[15] R. Westphal, C. Vogel, C. Schmitz, J. Pleiss, M. Müller, M. Pohl, D. Rother, *Angew. Chem. Int. Ed.*, **2014**, 53, 9376.

[16] a) T. Gerhards, U. Mackfeld, M. Bocola, E. von Lieres, W. Wiechert, M. Pohl, D. Rother, *Adv. Synth. Catal.*, **2012**, 354, 2805; b) D. Rother, G. Kolter, T. Gerhards, C. L. Berthold, E. Gauchenova, M. Knoll, J. Pleiss, M. Müller, G. Schneider, M. Pohl, *ChemCatChem*, **2011**, 3, 1587.

[17] T. Sehl, H. C. Hailes, J. M. Ward, U. Menyes, M. Pohl, D. Rother, *Green Chem.*, **2014**, 16, 3341.

[18] C. Wechsler, D. Meyer, S. Loschonsky, L.-M. Funk, P. Neumann, R. Ficner, F. Brodhun, M. Müller, K. Tittmann, *ChemBioChem*, **2015**, 16, 2580.

[19] a) F. B. Opperman, B. Schmidt, A. Steinbüchel, *J. Bacteriol.*, **1991**, 173, 757; b) Z. Xiao, *Crit. Rev. Microbiol.*, **2007**, 33, 127.

[20] a) H. Priefert, S. Hein, N. Krüger, K. Zeh, B. Schmidt, A. Steinbüchel, *J. Bacteriol.*, **1991**, 173, 4056; b) K. A. P. Payne, D. W. Hough, M. J. Danson, *FEBS Lett.*, **2010**, 584, 1231. c) N. Krüger, F. B. Opperman, H. Lorenzl, A. Steinbüchel, *J. Bacteriol.*, **1994**, 176, 3614.

[21] G. Bernacchia, O. Bortolini, M. De Bastiani, L. A. Lerin, S. Loschonsky, A. Massi, M. Müller, P. P. Giovannini, *Angew. Chem. Int. Ed.*, **2015**, 54, 7171.

[22] S. Loschonsky, S. Waltzer, S. Fraas, T. Wacker, S. L. A. Andrade, P. M. H. Kroneck, M. Müller, *ChemBioChem*, **2014**, 15, 389.

[23] a) M. Pohl, B. Lingen, M. Müller, *Chem. Eur. J.*, **2002**, 8, 5288; b) M. Pohl, C. Dresen, M. Beigi, M. Müller, *Enzyme Catalysis in Organic Synthesis*, 3rd edn., (Eds.: K. Drauz, H. Grçger, O. May), Wiley-VCH, Weinheim, **2012**, pp 919–946.

[24] P. Bisel, L. Al-Momani, M. Müller, *Org. Biomol. Chem.*, **2008**, 6, 2655.

[25] P. P. Giovannini, P. Pedrini, V. Venturi, G. Fantin, A. Medici, *J. Mol. Catal. B*, **2010**, 64, 113; b) P. P. Giovannini, O. Bortolini, A. Cavazzini, R. Greco, G. Fantin, A. Massi, *Green Chem.*, **2014**, 16, 3904.

[26] P. P. Giovannini, L. A. Lerin, M. Müller, G. Bernacchia, M. De Bastiani, M. Catani, G. Di Carmine, A. Massi, *Adv. Synth. Catal.*, **2016**, 358, 2767.

2.4 Experimental Section

General Methods. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 °C in the stated solvent; [a]D values are given in 10^{-1} deg cm^2 g^{-1}. ^1H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature. Peak assignments were aided by ^1H-^1H COSY and gradient-HMQC experiments. For HR-MS measure- ments, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to pro- duce spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L min^{-1}, respectively. The MS analyzer was externally calibrated with ESI-L low concentration tuning mix from m/z= 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H2O/ACN 0.1% TFA into the system at a flow rate of 0.4 mL min^{-1}. Chiral phase HPLC analyses were carried out on an HP 1100 chromatography system (Agilent) using a Chiralpak ID column (250 mm, particle size: 5mm) for compounds **5d-i**, **5s**, a Phenomenex Lux Cellulose-1 column (250 mm, particle size: 5 mm) for compounds **5p-q**, and a Phenomenex Amylose-2 lux (250 mm, particle size: 5 mm) for compounds **5r**, **5t** and **5w**. Analyses were performed using a detection wave-length of 254 nm and hexane/2-propanol (90:10) as eluent (flow rate : 1 mL min^{-1}), apart from compound **5r** (eluent : hexane/2-propanol/acetic acid 185 :14 :1). GC analyses were performed on a Carlo Erba 6000, equipped with an FID detector and a Megadex 5 column (25 m · 0.25 mm) with the temperature programs below specified. CD spectra of the products dissolved in acetonitrile were recorded on a Jasco J-810 spectrometer.

Effect of Enzyme Concentration and Reaction Time on the Synthesis of (*S*)-1-Hydroxy-1-phenylpropane- 2-one (5) [(*S*)-PAC]

Three reactions were performed by adding 0.75, 3 and 6 mg of lyophilized Ao:DCPIPOR, respectively, to a solution of benzaldehyde **4** (3.0 mL, 30 mmol), methylacetoin **3** (3.2 mL, 30 mmol), ThDP (0,4 mg, 0.6 mmol) and $MgSO_4$ (0.16 mg, 1.3 mmol) in 50 mM phosphate buffer at pH 6.5 (1.5 mL) containing DMSO (10% v/v). The reactions were gently shaken at 30 °C and after 2, 8, 24 and 48h samples (0.5mL) were withdrawn and extracted with $CDCl_3$ (1.0 mL). The organic extracts were dried with anhydrous Na_2SO_4 and analyzed by ^1H NMR and chiral-phase GC to determine conversion and ee, respectively.

Optimized Synthesis of (S)-1-Hydroxy-1-phenyl- propane-2-one (5) [(*S*)-PAC]

Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of benzaldehyde **4** (51 mL, 0.50 mmol), methylacetoin **3** (105 mL, 1.00 mmol), ThDP (4.5 mg, 10 mmol) and $MgSO_4$ (2.7 mg, 20 mmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 24 h and then extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (4:1) as eluent to afford pure **(*S*)- 6** (ee 94%) as a yellow pale oil; yield: 63mg (84%); [a]D: + 313 (c 0.3, $CHCl_3$), lit. :[32a] + 413 (c 0.82, $CHCl_3$) ; GC (temperature program from 100 to 200 °C rate 18C min^{-1}): Rt 28.6 min (*R*), 30.2 min (*S*) ; ^1H NMR : δ = 7.46–7.28 (m, 5H, Ar), 5.09 (d, J=4.2 Hz, 1H, H-1), 4.30 (d, J=4.2 Hz, 1H, OH), 2.07 (s, 3H, CH_3); ^{13}C NMR: δ = 207.1, 137.9, 129.0 (2 C), 128.7 (2 C), 127.3, 80.1, 25.3 ; HR-MS (ESI/Q- TOF): m/z = 173.0605, calcd. for $C_9H_{10}O_2Na$ [M + Na]+: 173.0578.

3,4-Dihydroxy-3,4-dimethylpentan-2-one: Obtained as described before from the reaction of equimolar amounts of **3** and **5** (0.50 mmol). ^1H NMR: d=2.24 [s, 3H, $C(O)CH_3$], 1.38 [s, 3H, $C(OH)CH_3$], 1.24 (s, 6H, $2CH_3$).

General Procedure for the Synthesis of the PAC Analogues 5a-w on Semipreparative Scale

Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of the substituted benzaldehyde **4a-w** (0.50 mmol), methylacetoin **3** (63 mL, 0.60 mmol), ThDP (4.5 mg, 10 mmol) and $MgSO_4$ (2.7 mg, 20 mmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 48h and then extracted with ethyl acetate (3 x 10mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel with the suitable elution system.

(*S*)-1-(2-Fluorophenyl)-1-hydroxypropan-2-one (5a):

Colorless oil ; yield : 90%; [a]D : + 176 (c 1.0, MeOH); GC (temperature program from 100 to 200 °C, rate 1 °C min^{-1}): Rt 22.3 min (*R*), 23.2 min (*S*); ee 83% (*S*); ^1H NMR: δ = 7.34–7.25 (m, 2H, Ar), 7.19–7.07 (m, 2H, Ar), 5.41 (s, 1H, H-1), 4.26 (bs, 1H, OH), 2.13 (s, 3H, CH_3); ^{13}C NMR: δ= 206.2, 160.5 (d, J = 246 Hz), 130.5, 128.8, 125.1, 124.9, 116.0, 73.6, 25.0 ; ^{19}F NMR: d=-118.3 (m); HR-MS (ESI/Q-TOF): m/z= 168.0531, calcd. for $C_9H_9FO_2$ [M]+: 168.0587.

(*S*)-1-(3-Fluorophenyl)-1-hydroxypropan-2-one (5b):

Colorless oil ; yields : 85%; [a]D : + 242.2 (c 0.93, $CHCl_3$; GC (temperature program from 100 to 200 °C, rate 5 °C min^{-1}): Rt 13.1 min (*R*), 13.2 min (*S*); ee 80% (*S*); ^1H NMR: δ = 7.40– 7.33 (m, 1H, Ar), 7.14 (dd, J=7.9, 0.8Hz, 1H, Ar), 7.07– 7.01 (m, 2H), 5.09 (s, 1H, H-1), 4.33 (s, 1H, OH), 2.10 (s, 3H, CH_3); ^{13}C NMR: δ = 206.4, 163.2 (d, J=248 Hz), 140.4, 130.7, 123.1, 115.9, 114.3, 79.6, 25.3; ^{19}F NMR: δ = -111.83 (m) ; HR-MS (ESI/Q-TOF): m/z = 168.0611, calcd. for $C_9H_9FO_2$ [M]+: 168.0587.

(*S*)-1-(4-Fluorophenyl)-1-hydroxypropan-2-one (5c):

Colorless oil ; yield : 88%; [a]D : + 330.3 (c 0.35, $CHCl_3$); GC (temperature program from 100 to 200 °C, rate 1 °C min^{-1}): Rt 33.6 min (*R*), 36.1 min (*S*); ee 92% (*S*); 1H NMR: δ = 7.38–7.18 (m, 2H, Ar), 7.15–6.99 (m, 2H, Ar), 5.07 (s, 1H, H-1), 4.28 (bs, 1H, OH), 2.07 (s, 3H, CH_3); ^{13}C NMR: δ 206.98, 163.0 (d, J = 247 Hz), 133.87, 129.2 (2 C), 116.1 (2 C), 79.5; ^{19}F NMR: δ = - 112.91 (m); HR-MS (ESI/Q-TOF) 168.0524, calcd. for $C_9H_9FO_2$ [M]+: 168.0587.

(*S*)-1-(2-Chlorophenyl)-1-hydroxypropan-2-one (5d)

Colorless oil; yield: 81%; [a]D: +179.5 (c 0.22, MeOH); HPLC : Rt 11.7 min (*S*), 12.7 min (*R*); ee 68% (*S*); ^1H NMR: δ = 7.50– 7.35 (m, 1 H, Ar), 7.35–7.18 (m, 3 H, Ar), 5.58 (s, 1 H, H-1), 4.35 (bs, 1H, OH), 2.13 (s, 3H, CH_3); ^{13}C NMR: δ = 206.3, 135.6, 133.4, 130.1, 129.9, 128.9, 127.5, 76.4, 25.3; HR-MS (ESI/Q-TOF): m/z = 207.0150, calcd. for $C_9H_9ClO_2Na$ [M + Na]+: 207.0189.

(*S*)-1-(3-Chlorophenyl)-1-hydroxypropan-2-one (5e):

Colorless oil ; yield : 87%; [a]D : + 218.8 (c 0.70, $CHCl_3$); HPLC: Rt 9.7 min (*S*), 12.3 min (*R*); ee 78% (S); ^1H NMR: δ = 7.34–7.31 (m, 3 H, Ar), 7.25–7.19 (m, 1 H, Ar), 5.06 (s, 1H, H-1), 4.31 (bs, 1H, OH), 2.11 (s, 3H, CH_3); ^{13}C NMR: δ = 206.3, 139.9, 135.1, 130.4, 129.1, 127.6, 125.6, 79.6, 25.4 ; HR-MS (ESI/Q-TOF): m/z = 207.0212, calcd. for $C_9H_9ClO_2Na$ [M+Na]+: 207.0189.

(*S*)-1-(4-Chlorophenyl)-1-hydroxypropan-2-one (5f):

Colorless oil ; yield : 55%; [a]D : + 222.5 (c 0.16, $CHCl_3$); HPLC : Rt 10.7 min (*R*), 11.6 min (*S*); ee 89% (S); ^1H NMR: d=7.42– 7.32 (m, 2 H, Ar), 7.29‑7.25 (m, 2 H, Ar), 5.06 (s, 1 H, H-1), 4.29 (s, 1H, OH), 2.08 (s, 3H, CH_3); ^{13}C NMR: δ = 206.6, 136.5, 134.8, 129.3 (2 C), 128.7 (2 C), 79.5, 25.3 ; HR-MS (ESI/Q-TOF): m/z = 207.0158, calcd. for $C_9H_9ClO_2Na$ [M + Na]+: 207.0189.

(*S*)-1-(2-Bromophenyl)-1-hydroxypropan-2-one (5g):

Colorless oil ; yield : 72%; [a]D : + 157.8 (c 0.32, $CHCl_3$) ; HPLC: Rt 12.4 min (*S*), 13.3 min (*R*); ee 89% (S); ^{1}H NMR: δ = 7.71–7.48 (m, 1 H, Ar), 7.45–7.26 (m, 1 H, Ar), 7.25–7.14 (m, 2H, Ar), 5.60 (d, J=3.5Hz, 1H, H-1), 4.38 (d, J= 3.50 Hz, 1H, OH), 2.14 (s, 3H, CH_3); ^{13}C NMR: δ = 206.3, 137.3, 133.4, 130.2, 128.9, 128.2, 123.7, 78.6, 25.5; HR-MS (ESI/Q-TOF): m/z = 227.9762, calcd. for $C_9H_9BrO_2$ [M]+: 227.9786.

(*S*)-1-(3-Bromophenyl)-1-hydroxypropan-2-one (5h):

Yellow pale oil ; yield : 71%; [a]D : + 223.5 (c 0.90, $CHCl_3$) ; HPLC: Rt 10.1 min (*S*), 12.3 min (*R*); ee 78% (*S*); ^{1}H NMR: δ = 7.58–7.36 (m, 2 H, Ar), 7.34–7.10 (m, 2 H, Ar), 5.05 (s, 1H, H-1), 4.31 (s, 1H, OH), 2.10 (s, 3H, CH_3); ^{13}C NMR: δ = 206.2, 140.1, 131.9, 130.5, 130.3, 125.9, 123.1, 79.4, 25.3 ; HR-MS (ESI/Q-TOF): m/z = 227.9806, calcd. for $C_9H_9BrO_2$ [M]+: 227.9786.

(*S*)-1-(4-Bromophenyl)-1-hydroxypropan-2-one (5i):

Colorless oil ; yield : 88%; [a]D : + 170.5 (c 1.19, $CHCl_3$) ; HPLC: Rt 11.1 min (*R*), 11.7 min (*S*); ee 68% (*S*); ^{1}H NMR: δ = 7.52 (d, J=8.4 Hz, 2H, Ar), 7.21 (d, J=8.4 Hz, 2H, Ar), 5.05 (s, 1H, H-1), 4.28 (bs, 1H, OH), 2.08 (s, 3H, CH_3); ^{13}C NMR : δ = 206.5, 137.0, 132.3 (2 C), 129.1 (2 C), 122.9, 79.6, 25.3 ; HR-MS (ESI/Q-TOF): m/z = 227.9711, calcd. for $C_9H_9BrO_2$ [M]+: 227.9786.

(*S*)-1-Hydroxy-1-(o-tolyl)propan-2-one (5j):

Colorless oil ; yield : 90% yield ; [a]D : + 173.0 (c 0.30, $CHCl_3$); GC (temperature program from 100 to 200 °C rate 5 °C min^{-1}): Rt 14.1 min (*S*), 14.2 min (*R*); ee 97% (*S*); ^{1}H NMR: δ = 7.24–7.08 (m, 4H, Ar), 5.26 (d, J=3.8 Hz, 1H, H-1), 4.16 (d, J=3.8 Hz, 1H, OH), 2.40 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C NMR: δ = 207.6, 136.4, 135.9, 131.3, 128.7, 128.3, 126.6, 78.1, 25.4, 19.3 ; HR-MS (ESI/Q-TOF): m/z = 164.0912, calcd. for $C_{10}H_{12}O_2$ [M]+: 164.0837.

(*S*)-1-Hydroxy-1-(m-tolyl)propan-2-one (5k):

Yellow pale oil ; yield : 88%; [a]D : + 351.1 (c 0.88, $CHCl_3$) ; GC (temperature program from 100 to 200 °C rate 1 °C min^{-1}): Rt 34.3 min (*R*), 35.5 min (*S*); ee 91% (*S*); ^{1}H NMR: δ = 7.33– 7.20 (m, 1 H, Ar), 7.20–7.03 (m, 3 H, Ar), 5.05 (s, 1 H, H-1), 4.26 (bs, 1H, OH), 2.35 (s, 3H, CH_3), 2.08 (s, 3H, CH_3); ^{13}C NMR : δ = 207.3, 138.9, 137.9, 129.6, 128.9, 127.9, 124.7, 80.2, 25.4, 21.5 ; HR-MS (ESI/Q-TOF): m/z = 164.0927 calcd. for $C_{10}H_{12}O_2$ [M]+: 164.0837.

(*S*)-1-Hydroxy-1-(p-tolyl)propan-2-one (5l):

Yellow pale oil ; yield : 90%; [a]D : + 394.0 (c 0.55, $CHCl_3$); GC (temperature program from 100 to 200 °C rate 1 °C min^{-1}): Rt 37.5 min (*R*), 39.6 (*S*); ee 99% (*S*); ^1H NMR: δ = 7.22– 7.17 (m, 4H, Ar), 5.06 (d, J=4.2 Hz, 1H, H-1), 4.25 (d, J= 4.2Hz, 1H, OH), 2.35 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR : δ = 207.4, 138.7, 135.1, 129.8 (2 C), 127.4 (2 C), 80.0, 25.4, 21.3. HR-MS (ESI/Q-TOF): m/z = 164.0711, calcd. for $C_{10}H_{12}O_2$ [M]+: 164.0837.

(*S*)-1-Hydroxy-1-(2-nitrophenyl)propan-2-one (5m):

Yellow amorphous solid; yield: 79%; [a]D: +183.0 (c 1.40, $CHCl_3$); ^1H NMR: δ = 8.00 (d, J=8.1 Hz, 1H, Ar), 7.76–7.57 (m, 1 H, Ar), 7.59–7.39 (m, 2 H, Ar), 5.61 (s, 1 H, H-1), 4.38 (s, 1H, OH), 2.21 (s, 3H, CH_3); ^{13}C NMR: δ = 205.3, 133.7, 133.3, 130.6, 130.5, 129.6, 125.1, 76.0, 25.6; HR-MS (ESI/Q- TOF): m/z = 196.0697, calcd. for $C_9H_{10}NO_4$ [M + H]+: 196.0610.

(*S*)-1-Hydroxy-1-(3-nitrophenyl)propan-2-one (5n):

Yellow amorphous solid ; yield : 85%; [a]D : + 59.0 (c 0.80, $CHCl_3$); ^1H NMR : δ = 8.30–8.24 (m, 2 H, Ar), 7.70–7.66 (m, 1 H, Ar), 7.60–7.55 (m, 1 H, Ar), 5.21 (s, 1 H, H-1), 4.39 (bs, 1H, OH), 2.14 (s, 3H, CH_3); ^{13}C NMR: δ= 205.5, 140.0, 133.1, 130.1, 125.0, 123.7, 122.3, 79.2, 77.3, 25.2; HR-MS (ESI/Q-TOF): m/z = 196.0671, calcd. for $C_9H_{10}NO_4$ [M + H]+: 196.0610.

(*S*)-1-Hydroxy-1-(2-hydroxyphenyl)propan-2-one (5p):

Colorless oil ; yield : 86%; [a]D : + 275.6 (c 0.64, MeOH) ; HPLC: Rt 20.0 min (*R*), 27.2 min (*S*); ee 99% (*S*); ^1H NMR: δ = 7.34–7.13 (m, 2 H, Ar), 6.98–6.90 (m. 1 H, Ar), 6.88–6.75 (m, 1H, Ar), 5.22 (s, 1H, H-1), 2.11 (s, 3H, CH_3). ^{13}C NMR: δ = 207.4, 154.9, 130.3, 129.4, 122.1, 120.9, 117.2, 78.7, 25.1. HR-MS (ESI/Q-TOF): m/z = 189.0601, calcd. for $C_9H_{10}O_3Na$ [M + Na]+: 189.0528.

(*S*)-1-Hydroxy-1-(3-hydroxyphenyl)propan-2-one (5q):

White amorphous solid ; yield : 89%; [a]D : + 101.2 (c 0.68, MeOH); HPLC: Rt 42.7 min (*S*), 45.0 min (*R*); ee 85% (*S*); ^1H NMR : δ = 7.28–7.06 (m, 1 H, Ar), 6.92–6.79 (m, 2 H, Ar), 6.74 (dd, J = 8.1, 1.0 Hz, 1 H, Ar), 5.07 (s, 1 H, H-1), 2.04 (s, 3 H, CH_3); ^{13}C NMR : δ = 209.4, 158.9, 141.4, 130.8, 119.3, 116.3, 114.8, 81.1, 25.3 ; HR-MS (ESI/Q-TOF): m/z = 189.0433, calcd. for $C_9H_{10}O_3Na$ [M + Na]+: 189.0528.

(*S*)-1-Hydroxy-1-(4-hydroxyphenyl)propan-2-one (5r)

White amorphous solid ; yield : 44%; [a]D : + 131.2 (c 0.42, MeOH); HPLC: Rt 27.4 min (*R*), 31.9 min (*S*); ee 99% (*S*); ^{1}H NMR (CD_3OD): δ = 7.19 (d, J=8.6 Hz, 2H, Ar), 6.78 (d, J=8.6 Hz, 2H, Ar), 5.07 (s, 1H, H.1), 3.31 (s, 1H, OH), 2.01 (s, 3 H, CH_3) ; ^{13}C NMR (CD_3OD): δ = 209.7, 158.9, 130.6, 129.6 (2 C), 116.6 (2 C), 80.7, 25.4 ; HR-MS (ESI/Q-TOF): m/ z = 189.0645, calcd. for $C_9H_{10}O_3Na$ [M + Na]+: 189.0528.

(*S*)-1-Hydroxy-1-(naphthalen-1-yl)propan-2-one (5s):

Yellow amorphous solid; yield: 68%; [a]D: +284.3 (c 1.30, $CHCl_3$); HPLC: Rt 10.1 min (S), 10.8 min (R); ee 99% (S); 1H NMR : δ = 8.10–7.95 (m, 1 H, Ar), 7.90–7.80 (m, 2 H, Ar), 7.60–7.40 (m, 4 H, Ar), 5.61 (s, 1 H, H-1), 2.05 (s, 3 H, CH_3); ^{13}C NMR : δ = 208.3, 134.3, 133.3, 131.1, 129.7, 129.0, 127.7, 126.9, 126.1, 125.4, 123.4, 79.3, 25.5; HR-MS (ESI/Q-TOF): m/z=223.0829, calcd. for $C_{13}H_{12}O_2Na$ [M+Na]+: 223.0735.

(*S*)-1-Hydroxy-1-(naphthalen-2-yl)propan-2-one (5t):

White solid; yield: 58%; [a]D: +308.5 (c 1.00, $CHCl_3$); HPLC: Rt 19.5 min (*S*), 22.7 min (*R*); ee 92% (*S*). ^{1}H NMR: δ = 8.01– 7.72 (m, 4H, Ar), 7.61–7.43 (m, 2H, Ar), 7.37 (dd, J= 8.5Hz, J=1.8, 1H, Ar), 5.26 (s, 1H, H-1), 4.42 (bs, 1H, OH), 2.11 (s, 3H, CH_3); ^{13}C NMR: δ = 207.1, 135.2, 133.3, 133.2, 128.9, 127.9, 127.7, 127.10, 126.5, 126.4, 124.1, 80.2, 25.3 ; HR-MS (ESI/Q-TOF): m/z = 223.0612, calcd. for $C_{13}H_{12}O_2Na$ [M+Na]+: 223.0735.

(*S*)-1-(4-Ethylphenyl)-1-hydroxypropan-2-one (5u):

Colorless oil; yield: 80%; [a]D: +326.0 (c 1.00, $CHCl_3$); GC (temperature program from 100 to 200 °C rate 1 °C min^{-1}): Rt 45.4 min (*R*), 47.5 min (*S*); ee 87% (*S*); ^{1}H NMR: δ = 7.26– 7.19 (m, 4H, Ar), 5.07 (s, 1H, H-1), 4.25 (bs, 1H, OH), 2.64 (q, J=7.6Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 1.23 (t, J= 7.6 Hz, 3 H, CH_2CH_3) ; ^{13}C NMR : δ = 207.3, 144.9, 135.1, 128.5 (2 C), 127.3 (2 C), 79.9, 28.5, 25.3, 15.5 ; HR-MS (ESI/ Q-TOF): m/z = 223.0628, calcd. for $C_{11}H_{14}O_2Na$ [M + Na]+: 223.0735.

(*S*)-1-(4-(tert-Butyl)phenyl)-1-hydroxypropan-2-one (5v):

Colorless oil ; yield : 75%; [a]D : + 195.8 (c 1.70, $CHCl_3$) ; GC (temperature program from 100 to 200 °C, rate 1 °C min^{-1}): Rt 56.4 min (*R*), 57.9 min (*S*); ee 96% (*S*); ^{1}H NMR δ = 7.54–7.30 (m, 2 H, Ar), 7.34–7.07 (m, 2 H, Ar), 5.07 (s, 1 H, H-1), 4.23 (bs, 1 H, OH), 2.09 (s, 3 H, CH_3), 1.31 (s, 9 H, $C(CH_3)_3$) ; ^{13}C NMR : δ = 207.3, 151.8, 134.9, 127.0 (2 C), 125.9 (2 C), 79.8, 34.6, 31.3, 25.4 ; HR-MS (ESI/Q-TOF): m/z=229.1098, calcd. for $C_{13}H_{18}O_2Na$ [M+Na]+: 229.1204.

(*S*)-1-([1,1'-Biphenyl]-4-yl)-1-hydroxypropan-2-one (5w):

Yellow amorphous solid; yield: 82%; [a]D: +267.1 (c 2.10, $CHCl_3$); HPLC: Rt 29.7 min (*S*), 34.7 min (*R*); ee 91% (*S*); ^{1}H NMR : δ = 7.71–7.50 (m, 4 H, Ar), 7.54–7.28 (m, 5 H, Ar), 5.15 (s, 1H, H-1), 4.32 (bs, 1H, OH), 2.14 (s, 3H, CH_3); ^{13}C NMR : δ = 207.0, 141.7, 140.4, 136.9, 128.8 (2 C), 127.8 (2C), 127.7 (2C), 127.6, 127.1 (2C), 79.9, 25.4; HR-MS [M]+: (ESI/Q-TOF): m/z = 226.0994, calcd. For $C_{15}H_{14}O_2$ [M]+: = 226.0727.

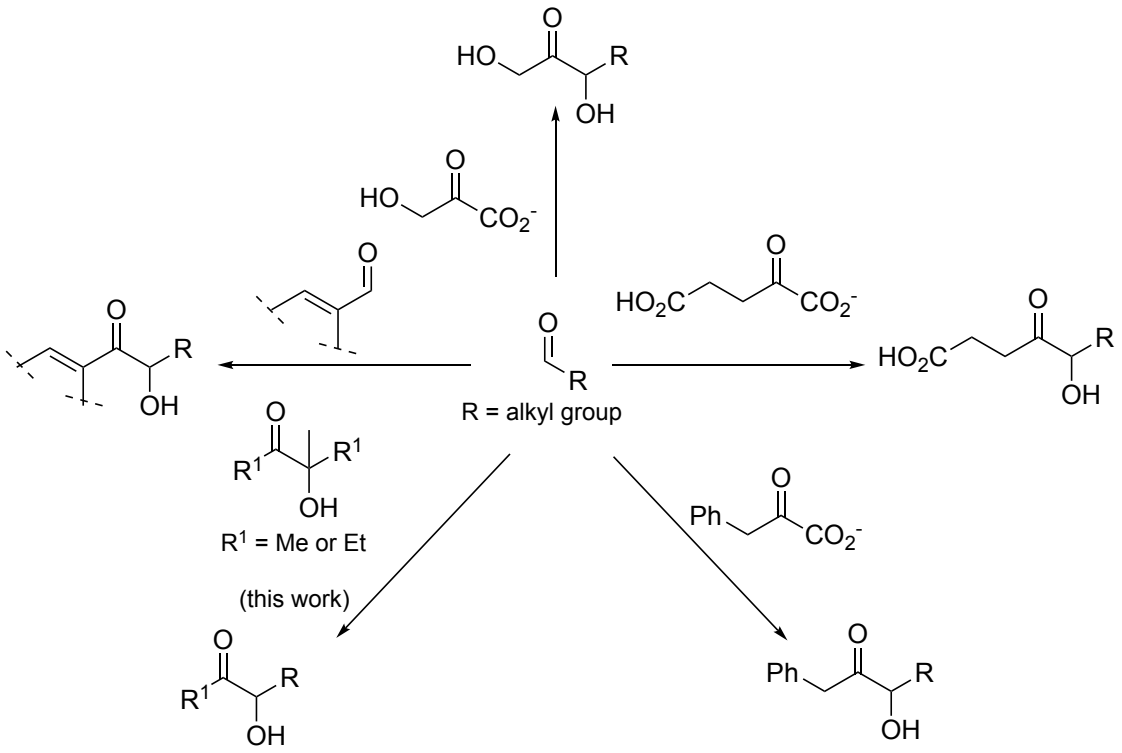
(*S*)-1-Hydroxy-1-phenylbutan-2-one (7)

Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of benzaldehyde **4** (0.50 mmol) and 3,4-hexandione **6** (121 mL, 1.0 mmol), ThDP (4.5 mg, 10 mmol) and $MgSO_4$ (2.7 mg, 20 mmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 48 h and then extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. After chromatography on silica gel with cyclohexane- ethyl acetate (4:1) as eluent, the product **7** was obtained as a colorless oil ; yield : 60%; [a]D : + 254 (c 0.3, $CHCl_3$); GC (temperature program from 100 to 200 °C rate 2 °C min^{-1}): Rt 19.0 min (*R*), 19.1 min (*S*); ee 98% (*S*); ^{1}H NMR: δ = 7.45–7.25 (m, 5H, Ar), 5.10 (s, 1 H, H-1), 4.35 (bs, 1 H, OH), 2.40–2.15 (m, 2 H, CH_2), 1.01 (t, 3H, J=7.0 Hz, CH_3); ^{13}C NMR: δ = 210.1, 138.2, 129.1 (2 C), 128.7, 127.4 (2 C), 79.5, 31.2, 7.7; HR-MS (ESI/Q-TOF): *m/z* = 164.0801, calcd. For $C_{10}H_{12}O_2$ [M]+ 164.0837.

3 Enzymatic Cross-Benzoin-Type Condensation of Aliphatic Aldehydes: Enantioselective Synthesis of 1-Alkyl-1- hydroxypropan-2-ones and 1-Alkyl-1-hydroxybutan-2-ones

3.1 Introduction

The constant demand of new chiral bioactive compounds has made the development of more and more efficient asymmetric synthetic methodologies of fundamental importance[1]. In this regard, the production of enantiopure building blocks has gained increasingly importance. In fact,the easy availability of such starting materials allows for the directed control of the stereochemical course of complex synthetic pathways[2]. Within this realm, molecules containing an α-hydroxy ketone motif, in which the configuration of the carbinolic center is often critical for the biological activity, are of fundamental importance[3]. Thus, the design of new catalytic protocol for the asymmetric synthesis of α-hydroxy ketones is of concern[4]. In this area relevant successes were achieved via α-oxidation of ketones[5] or of their enolate and enol ether derivatives[6]. In addition ketohydroxylation of olefins[7], and the mono-oxidation of diols are suitable methods[8], Furthermore, chiral *N*-heterocyclic carbene (NHC) catalysts have been successfully applied in the umpolung coupling of aldehydes (benzoin-type condensation)[9]. Consequently, a plethora of biocatalytic methodologies were developed. Enantioenriched α-hydroxy ketones can be obtained through the kinetic resolution by enantioselective acylation promoted by lipases[10], as well as via the monoreduction of α-diketones and the mono-oxidation of vicinal diols catalyzed in a stereoselective manner by NAD(P)-dependent dehydrogenases[11]. In addition, an elegant enantioselective α-oxidation of ketones promoted by a cytochrome P450 enzyme has been recently reported[12]. An alternative, straightforward biocatalytic approach is offered by the catalysis of thiamine diphosphate (ThDP) dependent lyases. Thanks to their tightly bound cofactor ThDP, the enzymes of this family catalyze benzoin-type condensations with the same umpolung mechanism as the above-noted NHC catalysts, often with a high level of enantioselectivity[13]. Furthermore, while the NHC catalysts need at least one aromatic aldehyde in order to direct the chemo- and regioselectivity of the cross-benzoin condensation, various ThDP-dependent lyases are known to efficiently catalyze the chemo- and stereoselective formation of fully aliphatic acyloins[14]. Scheme 1 shows generic structures of the more significant products achieved via these enzymatic approaches.

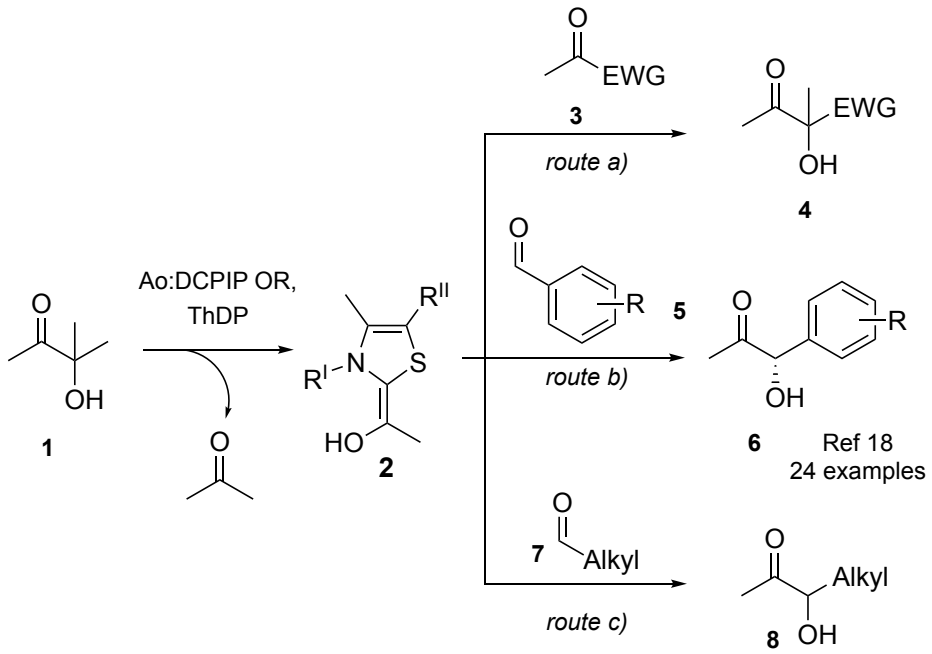


Scheme 1. Generic synthesis of aliphatic acyloins via ThDP-dependent enzyme catalysis.

Although the efficiency of acetaldehyde and propionaldehyde as both donor and acceptor has been demonstrated in ThDP-dependent enzyme-catalyzed homo-benzoin-type reactions[15]. only few examples of aliphatic cross-benzoin-type reactions, in which these aldehydes or their α-keto acids precursors (pyruvate and 2-oxobutyrate, respectively) are employed as donors, are present in literature and the resulting products were seldom characterized[16].

3.2 Results and Discussion

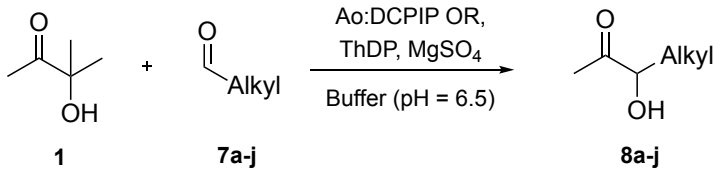
In this regard, we have reported the results obtained in benzoin-type condensations of 3-hydroxy-3-methylbutan-2-one (Scheme 1, R^1 = Me) and 4-hydroxy-4-methylhexan-3- one (Scheme 1, R^1 = Et), which act as precursors of activated acetaldehyde and propionaldehyde, respectively, with several aliphatic aldehydes as acceptors catalyzed by the ThDP-dependent enzyme acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR). We have recently demonstrated the synthetic value of methylacetoin (**1**, Scheme 2) as masked acetyl anion in presence of Ao:DCPIP OR from *Bacillus licheniformis* to access optical pure tertiary acyloins **4** (Scheme 2, route a)[17] and phenylacetylcarbinol (PAC) analogues **6** (Scheme 2, route b)[18].

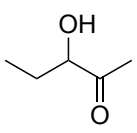


Scheme 2. Ao:DCPIP OR mediated benzoin-type reaction of methylacetoin **1** with activated ketones (route 1), aromatic aldehydes (route b) and aliphatic aldehydes (route c).

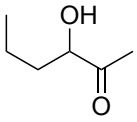
Most of the products have been obtained in highly enantioenriched form. Furthermore, reactions performed with aromatic aldehydes afforded the (*S*)-enantiomers of the PAC analogues, a rare behavior not observed with other wild-type ThDP-dependent enzymes[19]. Thus, we have envisaged the possibility to use Ao:DCPIP OR in benzoin-type reactions between donor **1** and aliphatic aldehydes **7** (Scheme 2, route c). In fact, apart from acetoin, which represents a particular case, few other α-hydroxy ketones of type **8** (Scheme 2, route c) were prepared employing the ThDP-dependent enzyme pyruvate decarboxylase (PDC). Additionally, in these few cases, the conversion were often low and, for most products, the enantiomeric excess (*ee*) was not determined[16]. The activity of the Ao:DCPIP OR enzyme has been tested on analytical scale reactions (1.5 mL reaction volume), using the linear aliphatic aldehydes propanal and butanal (**8a** and **8b**, Table 1).

Table 1. Ao:DCPIP OR mediated synthesis of 1-alkyl-1-hydroxypropan-2-ones **8a-j** employing methylacetoin **1** as donor

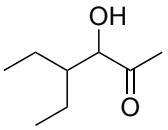




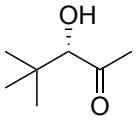
8a, conv = 99
Y = n.d., ee = 43



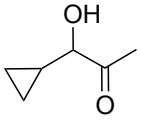
8b, conv = 57
Y = n.d., ee = 29



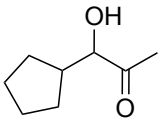
8c, conv = 99
Y = 49, ee = 99



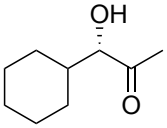
8d, conv = 99
Y = 42, ee = 99 (*S*)



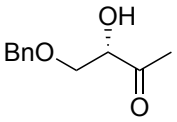
8e, conv = 99
Y = 81, ee = 72



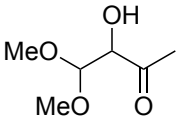
8f, conv = 89
Y = 82, ee = 86



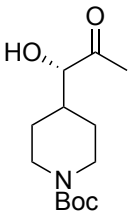
8g, conv = 99
Y= 89, ee = 92 (*S*)



8h, conv = 99
Y = 92, ee= 72(*S*)



8i, conv = 99
Y = 61, ee = n.d.

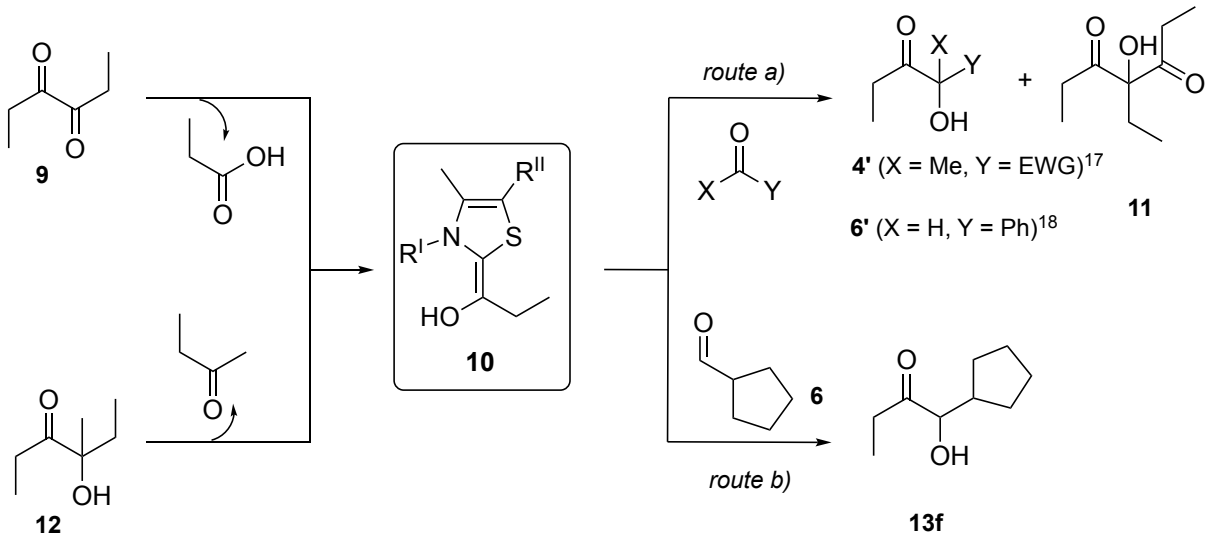


8j, conv = 99
Y = 93, ee = 84 (

By employing reaction conditions similar to those adopted for the synthesis of the PAC analogues **6** [18] [methylacetoin (1; 30 mM), **8a** or **8b** (20 mM), phosphate buffer pH 6.5 (50 mM), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1})], after 48 hours at 30 °C we have observed the formation of the expected products **8a** and **8b** with complete and 57% conversion, respectively. NMR analyses of the crude reaction have not revealed the presence of products deriving from the homo-coupling of aldehydes **7a** or **7b**. The absence of this reactivity has been also confirmed by experiments carried out without donor **1**. It seems that although aldehydes are good acceptors, they cannot act as acyl-anion donors since this enzyme needs α-hydroxy ketones or α-diketones for this role. Chiral-phase GC analyses of crude **8a** and **8b** indicated low *ee* for both products (43% and 29%, respectively). Previous studies on the synthesis of these products, performed with PDC as biocatalyst in the presence of pyruvate, have shown low conversions for **8a** and **8b** (41% and 2%, respectively) and informations about the optical purity of the products are missing. Encouraged by the results achieved with the short-chain linear aldehydes **7a** and **7b** we started our investigation on the activity of Ao:DCPIP OR in the condensation of methylacetoin **1** with more hindered acceptors, such as the α-branched aliphatic and alicyclic aldehydes **7 c–g** (Table 1). Gratifyingly, in a preliminary study performed on an analytical scale (1.5 mL reaction volume) with different acceptor to donor molar ratios, all the aldehydes **7c–g** were found to be suitable as substrates by Ao:DCPIP OR. A slight excess of the donor (1.5 equivalents) is necessary to obtain complete

conversion for the major part of the acceptors. Noteworthy, products **8c–g** have never been obtained previously via ThDP dependent enzyme-catalyzed benzoin-type reactions (aldehydes **7e–g** have been employed as acceptors in benzoin-like reaction with hydroxypyruvate mediated by engineered transketolases)[16]. Reactions performed on a preparative scale (Table 1, **8c–g**) confirmed the high reactivity (89–99%) observed on the analytical scale. After purification by column chromatography, products **8e–g** were obtained in high yields (81–89%), whereas part of products **8c** and **8d** has been lost during the purification procedure, probably because of their high volatility (49% and 42% isolated yield for **8c** and **8d**, respectively). Volatile solvents such as: diethyl ether, pentane, dichloromethane or chloroform have been also tested in the purification step, unfortunately, without significant improvement.

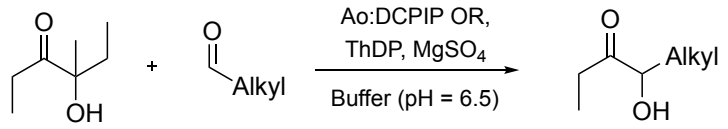
The high enantioselectivity observed in these reactions suggests that the alpha-branched structure impose a strong orientation of the acceptor within the active site. The use of α-oxygenated aldehydes **7h** and **7i** - as acceptor substrates afforded good results as well. By virtue of their protected alcoholic and aldehydic functionalities, the products **8h** and **8i** are interesting building blocks for asymmetric synthesis. Noteworthy, **7h** and **7i** were used as donor and acceptor respectivelly in a cross-benzoin-type reaction mediated by benzaldehyde lyase[20]. However, neither has been used as an acceptor of the activated acetaldehyde **2**. Gratifyingly, the reactions conducted with donor **1** and Ao:DCPIP OR as catalyst afforded the corresponding products **8h** and **8i** with almost complete conversion and a satisfactory 72% ee for **8h**. Finally, the tolerance of the procedure for bulky substrates has been tested utilizing 1-Boc-substituted piperidine-4-carboxaldehyde **7j** as acceptor. In this case, the desired product **8j** has been isolated in high yield (93%) and good *ee* (84). Furthermore, as we have demonstrated previously, Ao:DCPIP OR can also catalyze the cleavage of hexane-3,4-dione **9** and the addition of the resulting activated propionaldehyde **10** to various activated ketones[17] and benzaldehydes[18] (Scheme 3, route a).

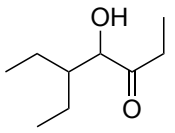


Scheme 3. Exploitation of 4-hydroxy-4-methyl-hexan-3-one **12** as propargyl anion donor (route b).

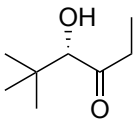
The synthetic efficiency of **9** as a donor, however, is negatively affected by the formation of the homo-coupling byproduct **11**, that imposes using an excess of the donor with the consequent complication of product purification. Thus, we have envisaged the possibility to convert diketone **9** into 4-hydroxy-4-methylhexan-3-one **12**, which shows a similar structure with respect to the methylacetoin, but with a propionyl function. This compound, obtained by addition of methyl Grignard reagent to the diketone **9**, can be used as propionyl anion donor through umpolung reactivity. by. The so-obtained acyloin **12** was tested as donor (1.5 equivalents) in the model reaction with acceptor **7f** (Scheme 3, route b). Gratifyingly, this afforded a 90% conversion and the expected product **13f** in good enantioselectivity (78% ee) (Table 2, entry 4). Noteworthy, in forming the activated aldehyde **10**, Ao:DCPIP OR catalyzes the cleavage of **12** with comparable rates for both enantiomers, as demonstrated by chiral-phase GC analysis of the residual donor in the reaction mixture. Additionally, ^{1}H NMR analysis of the same mixture excluded the presence of byproducts derived from donor homo-coupling. These conditions have been applied in all reactions performed on a preparative scale (25 mL) with donor **12** and acceptor substrates **7c–j**, the results of which are summarized in Table 2.

Table 2. Ao:DCPIP OR mediated synthesis of 1-alkyl-1-hydroxybutan-2-ones **13c-j** employing the new donor **12** as donor

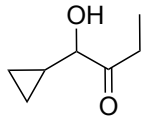




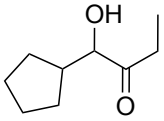
13c, conv = 99
Y = 52, ee = 90



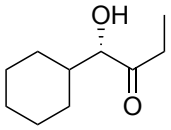
13d, conv = 95
Y = 45, ee = 99 (*S*)



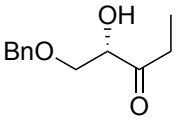
13e, conv = 83
Y = 70, ee = n.d.



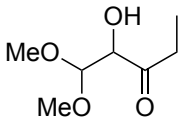
13f, conv = 90
Y = 82, ee = 78



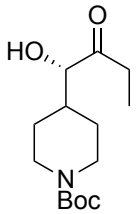
13g, conv = 85
Y= 78, ee = 59 (*S*)



13h, conv = 75
Y = 68, ee= 92(*S*)



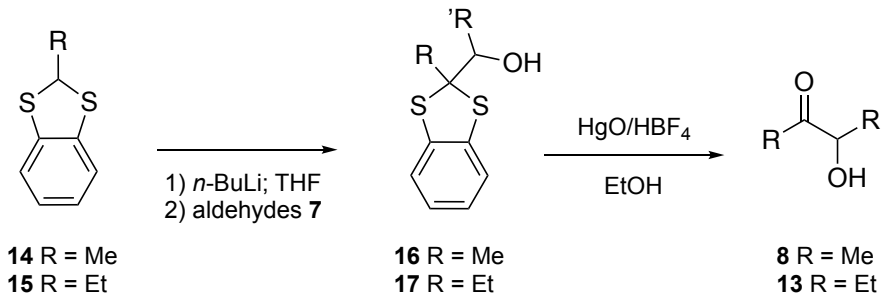
13i, conv = 99
Y = 62, ee = n.d.



13j, conv = 99
Y = 91, ee = 76 (*S*)

The conversions, yields and *ee* values of products **13c–j** are comparable with the results obtained for the lower homologues **8c–j**; therefore, **12** is a suitable propionyl anion donor in reactions catalyzed by Ao:DCPIP OR. The absolute configuration of products **8d**[21], **8g**[22], **8h**, **13d**[23], **13g**[24] and **13h** shows that, with acceptors **7d**, **7g** or **7h**, the enzyme is (*S*)-stereoselective independently from the use of **1** or **12** as donor. These results are congruent with those we previously reported using aromatic aldehydes as acceptors[18].

Finally, preparation of racemic samples to assess the optical purity of the enzymatic products by chiral-phase chromatographic analysis was required. Initial attempts to racemize the optically active products by acidic or basic treatment afforded the expected samples only for products **8e** and **8f**, albeit with very low conversions. Therefore, most of the acyloins were synthesized in their racemic form by addition of the carbanions generated from 2-methyl-1,3-benzodithiole **14** and 2-ethyl-1,3-benzodithiole **15**[25] to the aldehyde acceptors **7**, followed by hydrolysis of the resulting adducts[26] **16** and **17**, as depicted in Scheme 4[27].



14 R = Me
15 R = Et

16 R = Me
17 R = Et

8 R = Me
13 R = Et

Scheme 4. Synthesis of racemic samples of products

3.3 References

[1] G.-Q. Lin, Y.-M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, John Wiley & Sons, Inc., New York, **2001**, 47–65.

[2] W. A. Szabo, H. T. Lee, *Aldrichimica Acta*, **1980**, 13, 13.

[3] a) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.*, **2012**, 41, 4150; b) P. Hoyos, J. V. Sinisterra, F. Molinari, A. R. Alcantara, P. Domínguez de María, *Acc. Chem. Res.*, **2010**, 43, 288.

[4] J. Streuff, *Synlett*, **2013**, 24, 276.

[5] a) P. Merino, T. Tejero, *Angew. Chem. Int. Ed.*, **2004**, 43, 2995; b) O. A. Hame, A. El-Qisairi, H. Qaseer, E. M. Hamed, P. M. Henry, D. P. Becker, *Tetrahedron Lett.*, **2012**, 53, 2699.

[6] a) F. A. Davis, B.-C. Chen, *Chem. Rev.*, **1992**, 92, 919; b) N. Momiyama, H. Yamamoto, *Angew. Chem. Int. Ed.*, **2002**, 41, 2986; c) A. Yanagisawa, S. Takeshita, Y. Izumi, K. Yoshida, *J. Am. Chem. Soc.*, **2010**, 132, 5328.

[7] B. Plietker, *Eur. J. Org. Chem.*, **2005**, 2005, 1919.

[8] a) O. Onomura, H. Arimoto, Y. Matsumura, Y. Demizu, *Tetrahedron Lett.*, **2007**, 48, 8668; b) D. Minato, H. Arimoto, Y. Nagasue, Y. Demizu, O. Onomura, *Tetrahedron*, **2008**, 64, 6675.

[9] a) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.*, **2015**, 115, 9307; b) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci.*, **2012**, 3, 735; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.*, **2007**, 107, 5606; c) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.*, **2011**, 76, 347.

[10] a) P. Hoyos, M. Fernandez, J. V. Sinisterra, A. R. Alcantara, *J. Org. Chem.*, **2006**, 71, 7632; b) W. Adam, M. T. Diaz, R. T. Fell, C. R. Saha-Möller, *Tetrahedron: Asymmetry*, **1996**, 7, 2207; c) C. Tanyeli, I. Akhmedov, C. Iyigun, *Tetrahedron: Asymmetry*, **2006**, 17, 1125; d) G. Scheid, E. Ruijter, M. Konarzycka-Bessler, U. T. Bornscheuer, L. A. Wessjohann, *Tetrahedron: Asymmetry*, **2004**, 15,

2861; e) P. Ödman, L. A. Wessjohann, U. T. Bornscheuer, *J. Org. Chem.*, **2005**, 70, 9551; f) A. Petrenz, P. Domínguez de María, A. Ramanathan, U. Hanefeld, M. B. Ansorge-Schumacher, S. Kara, *J. Mol. Catal. B*, **2015**, 114, 42.

[11] a) K. Edegger, W. Stampfer, B. Seisser, K. Faber, S. F. Mayer, R. Oehrlein, A. Hafner, W. Kroutil, *Eur. J. Org. Chem.*, **2006**, 18, 1904; b) R. Médici, H. Stammes, S. Kwakernaak, L. G. Otten, U. Hanefeld, *Catal. Sci. Technol.*, **2017**, 7, 1831; c) J. Zhang, T. Xu, Z. Li, *Adv. Synth. Catal.*, **2013**, 355, 3147; d) P. P. Giovannini, G. Fantin, A. Massi, V. Venturi, P. Pedrini, *Org. Biomol. Chem.*, **2011**, 9, 8038.

[12] R. Agudo, G. D. Roiban, R. Lonsdale, A. Ilie, M. T. Reetz, *J. Org. Chem.*, **2015**, 80, 950.

[13] a) P. P. Giovannini, O. Bortolini, A. Massi, *Eur. J. Org. Chem.*, **2016**, 26, 4441; b) N. G. Schmidt, E. Eger, W. Kroutil, *ACS Catal.*, **2016**, 6, 4286; c) S. Schmidt, T. Pedroso de Almeida, D. Rother, F. Hollmann, *Green Chem.*, **2017**, 19, 1226; d) M. Beigi, E. Gauchenova, L. Walter, S. Waltzer, F. Bonina, T. Stillger, D. Rother, M. Pohl, M. Müller, *Chem. Eur. J.*, **2016**, 22, 13999.

[14] a) A. Ranoux, U. Hanefeld, *Top. Catal.*, **2013**, 56, 750; b) A. Càzares, J. L. Galman, L. G. Crago, M. E. B. Smith, J. Strafford, L. Ríos-Solís, G. J. Lye, P. A. Dalby, H. C. Hailes, *Org. Biomol. Chem.*, **2010**, 8, 1301; c) H. C. Hailes, D. Rother, M. Müller, R. Westphal, J. M. Ward, J. Pleiss, C. Vogel, M. Pohl, *FEBS J.*, **2013**, 280, 6374; d) A. Cosp, C. Dresen, M. Pohl, L. Walter, C. Röhr, M. Müller, *Adv. Synth. Catal.*, **2008**, 350, 759; e) M. Beigi, S. Waltzer, A. Fries, L. Eggeling, G. A. Sprenger, M. Müller, *Org. Lett.*, **2013**, 15, 452; f) A. Kurutsch, M. Richter, V. Brecht, G. A. Sprenger, M. Müller, *J. Mol. Catal. B*, **2009**, 61, 56; g) Z. Guo, A. Goswami, V. B. Nanduri, R. N. Patel, *Tetrahedron: Asymmetry*, **2001**, 12, 571.

[15] P. Domínguez de María, M. Pohl, D. Gocke, H. Gröger, H. Trauthwein, T. Stillger, L. Walter, M. Müller, *Eur. J. Org. Chem.*, **2007**, 2007, 2940.

[16] a) F. Neuser, H. Zorn, R. G. Berger, Z. Naturforsch., *C*, **2000**, 560; b) D. H. G. Crout, H. Dalton, D. W. Hutchinson, M. Miyagoshi, *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1329.

[17] G. Bernacchia, O. Bortolini, M. De Bastiani, L. A. Lerin, S. Loschonsky, A. Massi, M. Müller, P. P. Giovannini, *Angew. Chem. Int. Ed.*, **2015**, 54, 7171.

[18] P. P. Giovannini, L. A. Lerin, M. Müller, G. Bernacchia, M. De Bastiani, M. Catani, G. Di Carmine, A. Massi, *Adv. Synth. Catal.*, **2016**, 358, 2767.

[19] T. Sehl, S. Bock, L. Marx, Z. Maugeri, L. Walter, R. Westphal, C. Vogel, U. Menyes, M. Erhardt, M. Müller, M. Pohl, D. Rother, *Green Chem.*, **2017**, 19, 380.

[20] a) A. S. Demir, Ö. S¸Sesenoglu, P. Dünkelmann, M. Müller, *Org. Lett.*, **2003**, 5, 2047.

[21] W.-Y. Zhang, D. J. Jakiela, A. Maul, C. Knors, J. W. Lauher, P. Helquist, D. Enders, *J. Am. Chem. Soc.*, **1988**, 110, 4652.

[22] M. Hatano, T. Mizuno, K. Ishihara, *Chem. Commun.*, **2010**, 46, 5443.

[23] N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *J. Org. Chem.*, **1991**, 56, 2499.

[24] K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.*, **2003**, 125, 3442.

[25] a) S. Ncube, A. Pelter, K. Smith, P. Blatcher, S. Warren, *Tetrahedron Lett.*, **1978**, 8, 2345; b) D. R. Boyd, N. D Sharma, J. H. Dorman, R. Dunlop, J. F. Malone, R. A. S. McMordie, A. F. Drakeb, *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1105.

[26] D. Cheng, J. Zhou, E. Saiah, G. Beaton, *Org. Lett.*, **2002**, 4, 4411.

[27] G. Di Carmine, O. Bortolini, A. Massi, M. Müller, G. Bernacchia, G. Fantin, D. Ragno, P.P. Giovannini, *Adv. Synth. Catal.,* **2018**, 360, 4132.

3.4 Experimental Section

General Methods. All commercially available reagents were used as received without further purification, unless otherwise stated. Liquid aldehydes were freshly distilled before use. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh) or on Florisil (60–100 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers at room temperature using $CDCl_3$ as solvent. Chemical shifts (d) are reported in ppm relative to residual solvent signals. High-resolution mass spectra (HRMS) were recorded in positive ion mode with an Agilent 6520 HPLC-Chip Q/TOF-MS nanospray system using a time-of-flight, quadrupole or hexapole unit to produce spectra. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]D$ values are given in 10^{-1} deg cm^2 g^{-1}. The enantiomeric excess (ee) of products was determined by chiral-phase HPLC or GC analysis. For the HPLC analyses, a Phenomenex Amylose-2 Lux (250 × 4.6 mm, 5 mm particle size) or a Phenomenex Lux Cellulose-1 (250 × 4.6 mm, 5 mm particle size) column was used, together with a UV detector operating at 254 nm. GC analyses were performed using a flame ionization detector and a Megadex 5 column (25 m × 0.25 mm), with the temperature programs as specified.

General Procedure for the Synthesis of Products 8a–j on an Analytical Scale

Lyophilized Ao:DCPIP OR (0.75 mg) was added to a solution of aldehyde **7a–j** (30 μmol), methylacetoin (1; 4.7 μL, 45 μmol), ThDP (0.4 mg, 0.9 μmol) and $MgSO_4$ (0.16 mg, 1.3 μmol) in 50 mM phosphate buffer at pH 6.5 (1.5 mL). The reaction mixture was gently shaken at 30 °C and, after 8, 24 and 48 h, samples (0.5 mL) were withdrawn and extracted with $CDCl_3$ (1.0 mL). The organic extracts were dried with anhydrous Na_2SO_4 and analyzed by ^{1}H NMR spectroscopy and chiral-phase GC to determine the conversion and the ee, respectively.

General Procedure for the Synthesis of Products 8c–j on a Semipreparative Scale

Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of aldehyde **7c–j** (0.50 mmol), methylacetoin (1; 79 μL, 0.75 mmol), ThDP (4.5 mg, 10 μmol) and $MgSO_4$ (2.7 mg, 20 μmol) in 50 mM phosphate buffer at pH 6.5 (25 mL). The reaction mixture was gently shaken at 30 °C for 48 h and then extracted with Et_2O (3 × 5 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with the noted elution system.

4-Ethyl-3-hydroxyhexan-2-one (8c)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8c** as a colorless oil, 49% yield. [α]D +117 (c 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): tR (min) = 23.8 (minor), 25.1 (major); 99% ee; ^1H NMR (300 MHz): δ = 4.24 (s, 1H, H-3), 3.38 (bs, 1H, OH), 2.19 (s, 3H, CH_3), 1.69–1.36 (m, 3H), 1.30–1.06 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H, CH_3), 0.89–0.79 (m, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 210.9, 78.3, 44.7, 25.4, 23.3, 21.4, 12.2, 12.0; HRMS (ESI/Q-TOF): m/z = 167.1048, calcd for $C_8H_{16}NaO_2$ [M+Na]+: 167.1060.

(*S*)-3-Hydroxy-4,4-dimethylpentan-2-one [(S)-8d]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8d** as a colorless oil, 42% yield. [α]D +93 (c 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): tR (min) = 16.7 (*R*), 17.8 (*S*); 99% ee; ^1H NMR (300 MHz): δ = 3.88 (d, J = 6.3 Hz, 1H, H-3), 3.25 (d, J = 6.3 Hz, 1H, OH), 2.24 (s, 3H, CH_3), 0.99 (s, 9H); ^{13}C NMR (101 MHz): δ = 211.0, 84.5, 35.5, 29.4, 26.3; HRMS (ESI/Q-TOF): m/z = 153.0891, calcd for $C_7H_{14}NaO_2$ [M+Na]+: 153.0879.

1-Cyclopropyl-1-hydroxypropan-2-one (8e)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **8e** as a colorless oil, 81% yield. [α]D +112 (c 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): tR (min) = 6.3 (minor), 6.7 (major); 72% ee; ^1H NMR (300 MHz): d = 3.64 (dd, J = 7.7, 4.3 Hz, 1H, H-1), 3.50 (d, J = 4.3 Hz, 1H, OH), 2.31 (s, 3H, CH_3), 1.05–0.88 (m, 1H, CH_{cprop}), 0.73–0.35 (m, 4H); 13C NMR (101 MHz): d = 209.1, 79.1, 25.6, 14.2, 2.9, 2.0; HRMS (ESI/Q-TOF): m/z = 137.0578, calcd for $C_6H_{10}NaO_2$ [M+Na]+: 137.0590.

1-Cyclopentyl-1-hydroxypropan-2-one (8f)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8f** as a colorless oil, 82% yield. [α]D +47 (c 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): tR (min) = 17.7 (minor), 19.0 (major); 86% ee; ^1H NMR (300 MHz): d = 4.23 (dd, J = 4.8, 3.4 Hz, 1H, H-1), 3.42 (d, J = 4.8 Hz, 1H, OH), 2.38–2.23 (m, 1H, CH_{Cpent}), 2.20 (s, 3H, CH_3), 1.72–1.49 (m, 5H), 1.40–1.16 (m, 3H); ^{13}C NMR (101 MHz): d = 209.8, 78.5, 42.0, 29.5, 27.0, 26.0, 25.5, 24.7; HRMS (ESI/Q-TOF): m/z = 165.0891, calcd for $C_8H_{14}NaO_2$ [M+Na]+: 165.0878.

(*S*)-1-Cyclohexyl-1-hydroxypropan-2-one [(S)-8g]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8g** as a colorless oil, 89% yield. [α]D +146 (c 1.0, $CHCl_3$); 92% ee (determined by chiral-phase HPLC analysis after conversion into **16g**); ^{1}H NMR (300 MHz): d = 4.04 (d, J = 2.4 Hz, 1H, H-1), 3.36 (bs, 1H, OH), 2.19 (s, 3H, CH_3), 1.88–1.58 (m, 5H), 1.55–1.39 (m, 1H), 1.37–1.09 (m, 5H); ^{13}C NMR (101 MHz): d = 209.9, 81.1, 41.1, 30.1, 26.5, 26.0, 25.8, 25.5, 25.0; HRMS (ESI/Q-TOF): m/z = 179.1048, calcd for $C_9H_{16}NaO_2$ [M+Na]+: 179.1058.

4-(Benzyloxy)-3-hydroxybutan-2-one (8h)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **8h** as a colorless oil, 92% yield. [α]D +17 (c 1.0, $CHCl_3$); GC (temperature program: 120 to 210 °C, rate 2 °C min^{-1}): tR (min) = 33.0 (minor), 34.0 (major); 72% ee; ^{1}H NMR (300 MHz): d = 7.43–7.27 (m, 5H), 4.61 (d, J = 12.0 Hz, 1H, H_{aBn}), 4.49 (d, J = 12.0 Hz, 1H, H_{bBn}), 4.26 (m, 1H, H-3), 3.83 (dd, J = 10.4, 3.7 Hz, 1H, OCH_a), 3.72 (dd, J = 10.4, 3.7 Hz, 1H, OCH_b), 3.63 (d, J = 5.1 Hz, 1H, OH), 2.22 (s, 3H, CH_3); ^{13}C NMR (101 MHz): d = 207.8, 137.4, 128.5, 127.9, 127.8, 77.2, 76.9, 73.7, 70.8, 25.7; HRMS (ESI/Q-TOF): m/z = 217.0841, calcd for $C_{11}H_{14}NaO_3$ [M+Na]+: 217.0856.

3-Hydroxy-4,4-dimethoxybutan-2-one (8i)

Column chromatography on florisil gel with cyclohexane/EtOAc 10:3 afforded **8i** as a colorless oil, 61% yield. [α]D +76 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz): d = 4.40 (d, J = 3.2 Hz, 1H, H-4), 4.21 (m, 1H, H-3), 3.64 (bs, 1H, OH), 3.49 (s, 3H, CH_3O), 3.46 (s, 3H, CH_3O), 2.29 (s, 3H, CH_3); ^{13}C NMR (101 MHz): d = 207.2, 106.2, 77.7, 57.3, 55.8, 27.3; HRMS (ESI/Q-TOF): m/z = 171.0633, calcd for $C_6H_{12}NaO_4$ [M+Na]+: 171.0647.

tert-Butyl 4-(1-Hydroxy-2-oxopropyl)piperidine-1-carboxylate (8j)

Column chromatography with cyclohexane/EtOAc 6:4 afforded **8j** as a white waxy solid, 93% yield. [α]D +91 (c 1.0, $CHCl_3$); 84% ee (determined by chiral-phase HPLC analysis after conversion into **16j**); ^{1}H NMR (300 MHz): d = 4.25–4.10 (m, 2H, CH_2), 4.10–4.06 (m, 1H, H-1), 3.39 (bs, 1H, OH), 2.79–2.50 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.01–1.81 (m, 1H, H-4), 1.65 (m, 4H, 2 × CH_2), 1.43 (s, 9H, 3 × CH_3); ^{13}C NMR (101 MHz): d = 209.1, 154.6, 80.0, 79.5, 43.7, 39.4, 28.9, 28.4, 25.7, 24.4; HRMS (ESI/Q-TOF): m/z = 258.1705, calcd for $C_{13}H_{24}NO_4$ [M+H]+: 258.1721.

Synthesis of 4-Hydroxy-4-methylhexan-3-one (12)

To a stirred solution of hexane-3,4-dione (9; 9.4 g, 82.4 mmol) in anhydrous THF (30 mL), a 3.0 M MeMgBr solution in Et_2O (33 mL, 99 mmol) was added dropwise, at room temperature. The resulting mixture was refluxed for 2 h and then a saturated aqueous solution of NH_4Cl (50 mL) was slowly added. The organic layer was separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue (6.3 g, 6.6 mL) was purified by vacuum distillation (70 °C/10 mmHg) to obtain the expected product **12** as a yellow oil, 5.2 g (40 mmol, 48% yield). ^{1}H NMR (400 MHz): d = 3.89 (bs, 1H, OH), 2.60–2.41 (m, 2H, CH_2), 1.79–1.66 (m, 2H, CH_2), 1.34 (s, 3H, CH_3), 1.10 (t, J = 7.3 Hz, 3H, CH_3), 0.78 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): d = 215.1, 78.9, 32.5, 28.9, 25.3, 7.8, 7.7; HRMS (ESI/Q-TOF): m/z = 153.0891, calcd for $C_7H_{14}NaO_2$ [M+Na]+: 153.0905.

General Procedure for the Synthesis of Products 13c–j on an Analytical Scale

The reactions were performed and analyzed as described for the synthesis of products **8a–j** on an analytical scale, using 4-hydroxy-4-methylhexan-3-one (12; 6.2 µL, 45 µmol) instead of methylacetoin.

General Procedure for the Synthesis of Products 13c–j on a Semipreparative Scale

The reactions were performed and worked up as described for the synthesis products **8c–j** on a semipreparative scale, using 4-hydroxy-4-methylhexan-3-one (12; 103 µL, 0.75 mmol) instead of methylacetoin.

5-Ethyl-4-hydroxyheptan-3-one (13c)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13c** as a colorless oil, 52% yield. [α]D +60.8 (c 0.5, $CHCl_3$); 90% ee (determined by chiral-phase HPLC analysis after conversion into **17c**); ^{1}H NMR (300 MHz): d = 4.28–4.22 (m, 1H, H-4), 3.41 (d, J = 4.5 Hz, 1H, OH), 2.60–2.33 (m, 2H, CH_2), 1.67–1.37 (m, 4H), 1.29–1.15 (m, 1H), 1.12 (t, J = 7.3 Hz, 3H, CH_3), 1.01 (t, J = 7.2 Hz, 3H, CH_3), 0.83 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): d = 213.9, 77.8, 45.3, 31.4, 23.6, 21.6, 12.4, 12.3, 8.0; HRMS (ESI/Q-TOF): m/z = 181.1204, calcd for $C_9H_{18}NaO_2$ [M+Na]+: 181.1217.

(*S*)-4-Hydroxy-5,5-dimethylhexan-3-one [(S)-13d]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13d** as a colorless oil, 45% yield. [α]D +135 (c 0.6, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): tR (min) = 25.0 (*R*), 26.0 (*S*); 99% ee; ^{1}H NMR (300 MHz): d = 3.87 (s, 1H, H-4), 2.66–2.37 (m, 2H, CH_2), 1.10 (t, J = 7.2 Hz, 3H, CH_3), 0.98 (s, 9H, 3 × CH_3); ^{13}C NMR (76 MHz): d = 214.2, 84.0, 35.6, 27.1, 26.5, 8.0; HRMS (ESI/Q-TOF): m/z = 167.1048, calcd for $C_8H_{16}NaO_2$ [M+Na]+: 167.1062.

1-Cyclopropyl-1-hydroxybutan-2-one (13e)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **13e** as a colorless oil, slightly contaminated with unknown compounds, 70% yield. ^{1}H NMR (300 MHz): d = 3.64 (d, J = 7.7 Hz, 1H), 3.55 (bs, 1H, OH), 2.89–2.70 (m, 1H, $HaCH_2$), 2.60–2.40 (m, 1H, $HbCH_2$), 2.06–1.89 (m, 1H, CH_{cprop}), 1.16 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): d = 201.8, 78.8, 37.1; HRMS (ESI/Q-TOF): m/z = 151.0735, calcd for $C_7H_{12}NaO_2$ [M+Na]+: 151.0723.

1-Cyclopentyl-1-hydroxybutan-2-one (13f)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13f** as a colorless oil, 82% yield. [α]D +60.0 (c 0.5, $CHCl_3$); 78% ee (determined by chiral-phase HPLC analysis after conversion into 17f); ^{1}H NMR (300 MHz): d = 4.24 (d, J = 3.2 Hz, 1H, H-1), 3.46 (bs, 1H, OH), 2.63–2.38 (m, 2H, CH_2), 2.37–2.21 (m, 1H, CH), 1.85–1.42 (m, 6H), 1.39–1.19 (m, 2H), 1.15–1.09 (m, 3H, CH_3); ^{13}C NMR (76 MHz): d = 212.8, 78.0, 42.4, 31.6, 29.7, 26.2, 26.1, 25.0, 7.9; HRMS (ESI/Q-TOF): m/z = 179.1048, calcd for $C_9H_{16}NaO_2$ [M+Na]+: 179.1039.

(*S*)-1-Cyclohexyl-1-hydroxybutan-2-one [(S)-13g]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13g** as a colorless oil, 78% yield. [α]D +73.6 (c 1.0, $CHCl_3$); 59% ee; ^{1}H NMR (300 MHz): d = 4.24 (d, J = 1.7 Hz, 1H, H-1), 2.56–2.39 (m, 2H, CH_2), 1.89–1.56 (m, 10H), 1.55–1.41 (m, 1H), 1.11 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): d = 212.8, 80.5, 41.4, 31.4, 30.1, 29.7, 26.6, 26.0, 25.8, 25.1, 7.6; HRMS (ESI/Q-TOF): m/z = 193.1204, calcd for $C_{10}H_{18}NaO_2$ [M+Na]+: 193.1219.

1-(Benzyloxy)-2-hydroxypentan-3-one (13h)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **13h** as a colorless oil, 68% yield. [α]D +48.1 (c 1.0, $CHCl_3$); chiral-phase HPLC (Phenomenex Amylose-2 Lux column, n-hexane/propan-2-ol 9:1, flow 1.0 mL min^{-1}): tR (min) = 14.9 (major), 34.0 (minor); 92% ee; ^1H NMR (300 MHz): d = 7.38–7.23 (m, 5H), 4.60 (d, J = 12.1 Hz, 1H, H_{aBn}), 4.49 (d, J = 12.1 Hz, 1H, H_{bBn}), 4.30–4.22 (m, 1H, H-2), 3.81 (dd, J = 10.4, 3.7 Hz, 1H, OCH_a), 3.71 (dd, J = 10.4, 3.7 Hz, 1H, OCH_b), 2.69–2.34 (m, 2H, CH_2), 1.10 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): d = 210.8, 137.7, 128.7, 128.1, 128.0, 76.5, 73.9, 71.3, 71.2, 31.8, 7.6; HRMS (ESI/Q-TOF): m/z = 231.0997, calcd for $C_{12}H_{16}NaO_3$ [M+Na]+: 231.0985.

2-Hydroxy-1,1-dimethoxypentan-3-one (13i)

Column chromatography on florisil gel with cyclohexane/EtOAc 12:3 afforded **13i** as a colorless oil, 62% yield. [d]D +72.7 (c 0.8, $CHCl_3$); ^1H NMR (300 MHz): d = 4.37 (d, J = 3.2 Hz, 1H, H-1), 4.19 (dd, J = 5.3, 3.2 Hz, 1H, H-2), 3.62 (d, J = 5.3 Hz, 1H, OH), 3.45 (s, 3H, CH_3O), 3.42 (s, 3H, CH_3O), 2.82–2.65 (m, 1H, $HaCH_2$), 2.55–2.37 (m, 1H, $HbCH_2$), 1.05 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (76 MHz, $CDCl_3$): d = 210.2, 106.4, 76.8, 57.4, 55.9, 33.4, 7.5; HRMS (ESI/Q-TOF): m/z = 185.0790, calcd for $C_7H_{14}NaO_4$ [M+Na]+: 185.0803.

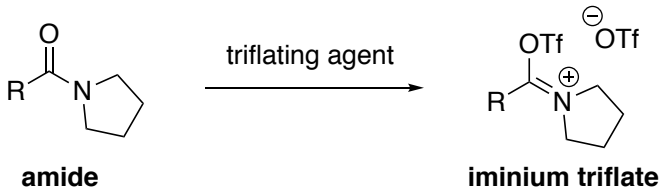
tert-Butyl 4-(1-Hydroxy-2-oxobutyl)piperidine-1-carboxylate (13j)

Column chromatography with cyclohexane/EtOAc 6:4 afforded **13j** as a white waxy solid, 91% yield. [α]D +34.6 (c 1.0, $CHCl_3$); 76% ee (determined by chiral-phase HPLC analysis after conversion into 17j); ^1H NMR (300 MHz): d = 4.16 (bs, 2H), 4.09 (bs, 1H, H-1), 3.40 (bs, 1H, OH), 2.82–2.38 (m, 5H), 1.97–1.80 (m, 1H), 1.71–1.57 (m, 3H), 1.43 (s, 9H, 3 × CH_3), 1.12 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): d = 212.0, 154.6, 79.5, 79.4, 43.6, 39.7, 31.6, 29.7, 28.9, 28.4, 24.4, 7.6; HRMS (ESI/Q-TOF): m/z = 272.1862, calcd for $C_{14}H_{26}NO_4$ [M+H]+: 272.1879.

CHAPTER III: 1,3-dipolar cycloaddition of amide promoted by Vaska complex

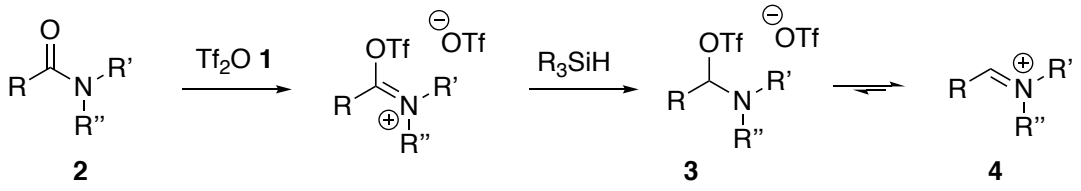
1. Introduction

Notoriously, the carboxamide is considered the least activated functional group among the carboxylic acid series, due to its high resonance stabilization[1]. However, during the past 140 years many procedures for the activation and functionalization of amides have been disclosed. Classical examples of amide activation, such as the Hofmann rearrangement[2], Vilsmeier−Haack[3], and the Bischler−Napieralski reactions are well-established organic transformations[4]. In addition to the above-mentioned protocols, several other methods of activation have been reported, including activation towards nucleophilic addition utilizing strong electrophiles[5], metal insertion into the C−N bond and transient formation of a formamidinyl group[6]. In this regard, treatment with trifluoromethanesulfonic anhydride (triflic anhydride) has led to the development of a large number of new synthetic methodologies. In all these transformations, the O-trifluoromethanesulfonyloxyiminium trifluoromethanesulfonate (iminium triflate) intermediate, formed by trapping the amide with the anhydride, is involved. This intermediate is practically an amide equivalent with an increased electrophilicity (Scheme 1)[7].



Scheme 1. Increasing Reactivity by Amide Activation using triflating agents

One of the most investigated type of transformation, in which the iminium triflate intermediate is involved, is the reductive coupling of amides to amines. The activation by addition of the triflic anhydride **1** onto the amide **2** makes the amide enough electrophilic towards the attack of poorly reactive hydride sources such as the hydrosilanes (Scheme 1)[8]. The new formed intermediate **3** quickly evolves to the iminium **4**, which is a strong electrophile that can be employed to explore a plethora of new carbon-carbon bond forming reactions (Scheme 2).

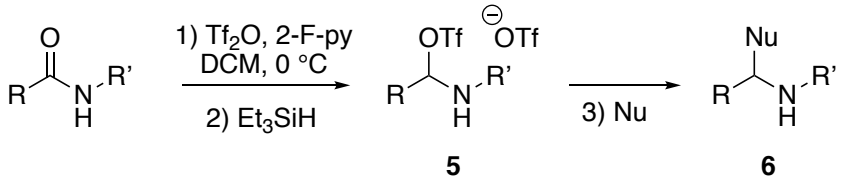


Scheme 2. Reductive activation of amide by Triflic anhydride and silane.

In this regard, several protocols have been presented during the last decade[9], and recently catalytic activation has been replacing the stoichiometric approach. In this short introduction the most relevant methods about the reductive coupling of amides will be covered.

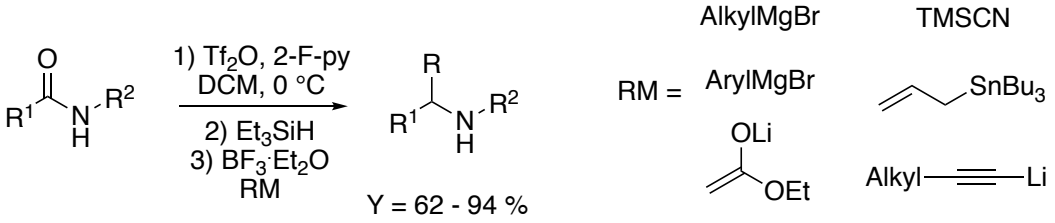
2. Stoichiometric reductive coupling of amide by formation of iminium triflate intermediate

In 2014 Xia and co-workers reported a general reductive functionalization of secondary amides employing triflic anhydride as activator[10]. In this protocol secondary amides were first reduced by Et_3SiH in order to form the N,O-acetal **5**, which in the presence of several nucleophile evolved towards the α-functionalized secondary amine **6** (Scheme 3).



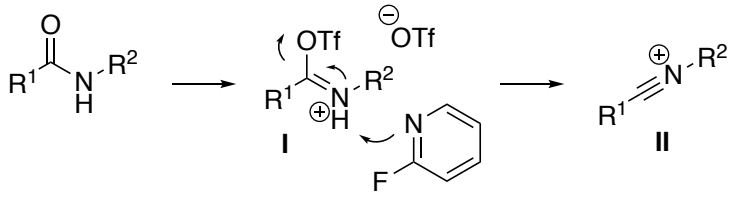
Scheme 3. Strategy based on Reductive coupling of amide for the preparation of α-functionalized amines.

After the treatment with triflic anhydride, 2-fluoropyridine and Et_3SiH, the addition of Grignard reagent smoothly proceeded towards the desired product in good to excellent yield (Scheme 4). Furthermore, other nucleophiles such as: organolithium compounds, enolates, stannanes, and trimethylsilyl cyanide were tested in order to make the procedure more general (Scheme 4).



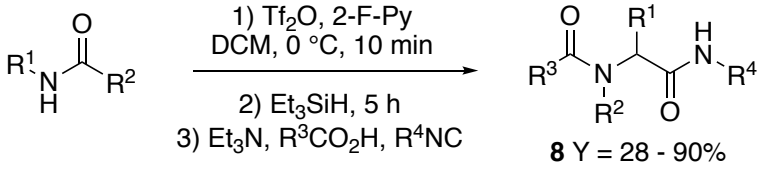
Scheme 4. Reductive coupling of amide with different nucleophiles.

Interestingly, the authors demonstrated that $BF_3{\cdot}Et_2O$ is necessary to activate the imine formed in situ towards the addition of the nucleophile. In fact, performing the reaction without this additive resulted in a drastic drop of reactivity (from 90 to 20%). Furthermore, the IR evidence in the formation of the intermediate **II** suggestes that the role of 2-fluoropyridine is central to deprotonate the intermediate **I** and make the species more prone to accept the hydride (Scheme 5).



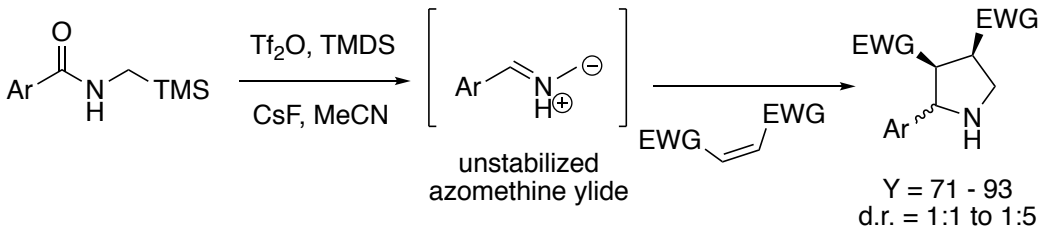
Scheme 5. Proposed action of the 2-F-Py in the acceleration of reaction.

Another important contribution on this topic was presented by Huang in 2015[11]. He disclosed an interesting Ugi-type three-component reaction, generating in situ the imine via mono-reduction of amide. The formation of the imine occurred smoothly by treating the amide **7** with triflic anhydride, 2-fluoropyridine in DCM followed by the addition of Et_3SiH. After replacing the DCM with TFE, triethylamine along with the acid and the isocyanide were added and the reaction afforded the corresponding Ugi adduct **8** in good yields (Scheme 6).



Scheme 6. one-pot reductive Ugi-type reaction of secondary amides.

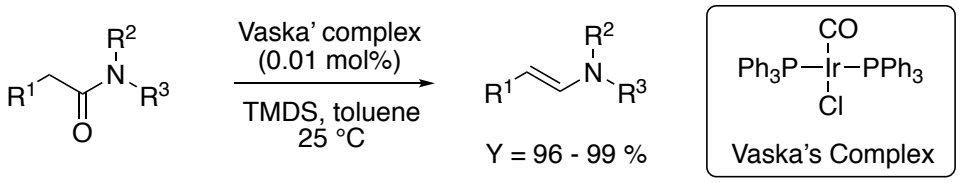
In 2016 the same group reported a 1,3-dipolar cycloaddition of secondary amides by trapping in situ formed nonstabilized azomethine ylides with several dipolarophiles[12]. In this case, a suitably designed amide bearing a methyl-TMS on the nitrogen atom, was employed to generate the nonstabilized ylide, which was quickly trapped by an electron poor olefin. In this case the most suitable hydride source was found to be the TMDS (tetramethyldisiloxane). Noteworthy, the use of a fluoride source was fundamental to cleavage the silicon-carbon bond and generate the ylide. The scope of reaction was investigated and both electron-poor and electron-rich amides were tested showing good reactivity. Furthermore, the reaction conditions were proved to tolerate many functional groups including those sensitive to reductive conditions (Scheme 7).



Scheme 7. Reductive 1,3-Dipolar Cycloaddition of N-(Silylmethyl)amides with Different Dipolarophiles.

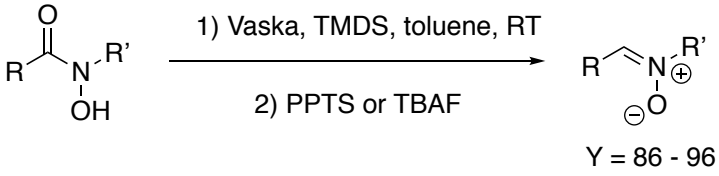
3. Catalytic reductive coupling of amide

In 2009 Nagashima and co-workers presented a novel chemoselective reduction of amides to enamines employing the Vaska complex[13]. The iridium catalyst showed a surprising tolerance towards the common high oxidation state carbon functional group and the authors were able to reduce amide with 0.01 mol% of catalyst using TMDS (tetramethyldisiloxane) as hydride source (Scheme 8). From this point forwards, this method has been deeply taken into account to replace the harsher protocol which requires triflic agents, and several reports have been presented in this regard.



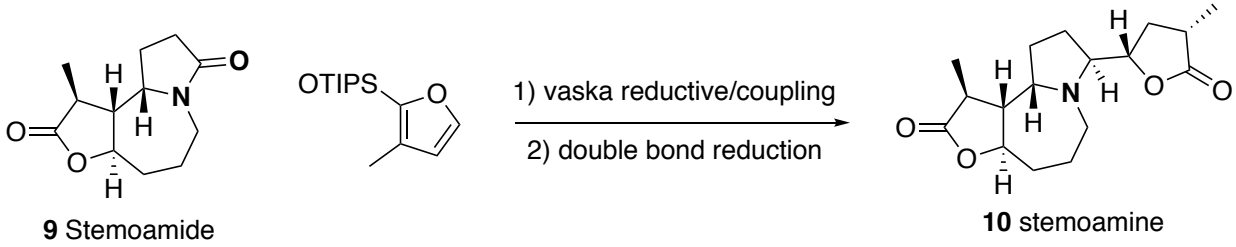
Scheme 8. Reduction of amide to enamine promoted by Vaska's Complex in presence of TMDS.

In 2016 Chida and co-workers used this approach in the synthesis of high synthetic valuable nitrones by selective mono-reduction of N-hydroxyamides (Scheme 9)[14]. Noteworthy, an excess of the hydride source (TMDS) is required and counter-intuitively the over-reductive product was not observed.



Scheme 9. Chida's reduction of N-hydroxyamides to nitrones.

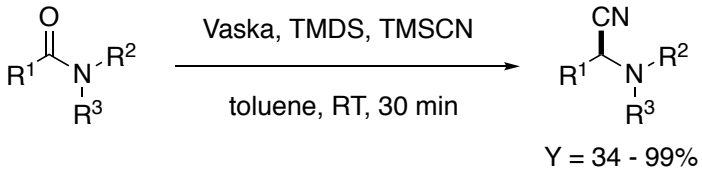
The same group also reported a reductive coupling promoted by the Vaska complex in the key step of the Stemona-type alkaloids total synthesis[15]. In this case the lactone moiety in the intermediate **9** was selectively reduced to the corresponding enamine, which in presence of a relative strong acid was trapped by an electron-rich furan to give Steoamine **10** (Scheme 10).



Scheme 10. Chida's total synthesis of Stemona-type alkaloids.

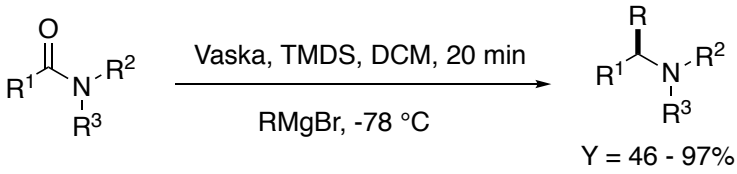
A huge contribution in this regard was provided by the Dixon group. In 2017 Dixon and co-workers reported an elegant variant of the Strecker reaction in which the iminium, generated via the general

protocol described above, was reacted with trimethylsilyl cyanide (Scheme 11)[16]. Interestingly, the reaction proved to be tolerant towards many functional groups and it was also applied to complex molecules as late step functionalization.



Scheme 11. Dixon's Strecker reaction by reductive coupling of amide.

The same group in 2018 reported a very robust protocol to access tertiary amines by addition of Grignard reagent to the in situ formed iminium, treating amides with the Vaska complex and TMDS in DCM[17]. In this case, the additive was not necessary differently from the previous protocol adopted by Xia (see above). Indeed, in the Dixon protocol, the most reactive iminium is quickly trapped by the organomagnesium compound (Scheme 12).

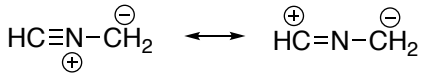
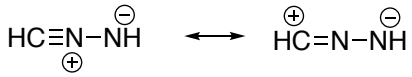
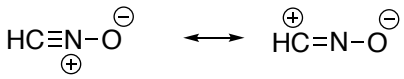
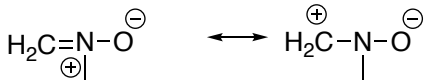
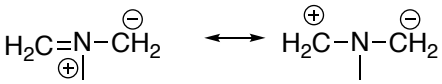


Scheme 12. Grignard addition to iminium formed in situ by amide reduction promoted by Vaska's Complex.

4. 1,3-Dipolar cycloaddition reactions

Dipolar cycloaddition reactions are intensively used for the synthesis of heterocyclic compounds and for carbon-carbon bond formation. Table 1 lists some of the typical molecules and intermediates that are capable to undergo dipolar cycloadditions[18]. These species, called 1,3-dipoles, have π electron systems, isoelectronic with allyl or propargyl anions, which consist of two filled and one empty p orbital. The presence of one charge-separated resonance structure with opposite charge in a 1,3-relationship is a sine qua non condition to ensure that these species can react in a dipolar cycloaddition fashion. The other reactant in a dipolar cycloaddition, usually an alkene or alkyne, is referred to as the dipolarophile. However, other multiply bonded functional groups such as imine, azo and nitroso functionalities can also act as dipolarophiles.

Table 1. List of some dipolarophiles

	Nitrile Ylides
	Nitrile imines
	Nitrile Oxide
	Nitrones
	Azomethine ylides

In 1,3-dipolar cycloadditions (1,3-DCAs) four π electrons from the dipole and two from the dipolarophile are involved and, as in the Diels-Alder reaction, the reactants approach each other in parallel planes to allow the interaction between the π and π* orbitals (Figure 1). Mechanistic studies have shown that the TSs for 1,3-DCAs are not very polar. In fact, the rate of reaction is not strongly related to the solvent polarity, and in most cases the reaction is a concerted ([2πs+4πs] cycloaddition)[19].

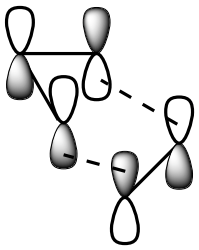


Figure 1. Interaction between π and π* orbitals in 1,3 dipolar cycloaddition reactions

Generally, each 1,3-dipole shows a characteristic regioselectivity towards different types of dipolarophiles, which can exhibit different orientation depending upon whether they have ERG or EWG substituents. The regioselectivity can be interpreted through the frontier orbital theory. Depending on the relative orbital energies in the 1,3-dipole and dipolarophile, the strongest interaction may be between the HOMO of the dipole and the LUMO of the dipolarophile or vice versa. Usually, for dipolarophiles with EWGs, the dipole- HOMO/dipolarophile-LUMO interaction is dominant (Figure 1.2). The reverse is true for dipolarophiles with ERG substituents. This, however, is not generalizable; in fact, the LUMO of azomethine ylide has an energy extremely high that makes impossible the interaction with the HOMO of electron-rich dipolarophile. Furthermore, the

diastereoselectivity is often unpredictable due the equilibrium of the 1,3-dipole between the E/Z form and the endo effect, that different to the Diels-alder reaction, is comparable in terms of energy with steric features[20].

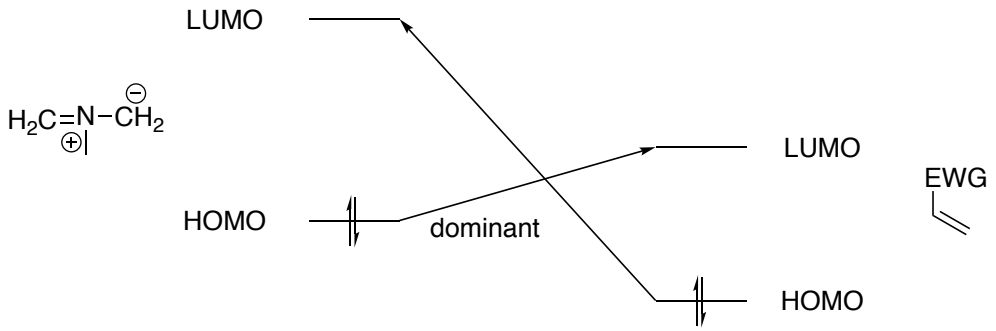
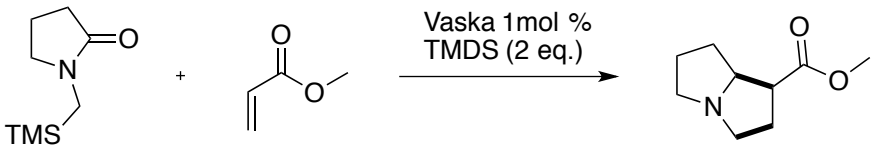


Figure 2. Cycloadduct energetic explanation by frontier molecular orbital theory

5. Results and discussion

We have started our investigation employing a pyrrolidinone-like amide as 1,3-dipole precursor and methyl acrylate as dipolarophile. The model amide was synthesized by a procedure reported in literature by treating N-methylpyrrolidinone with Iodo-methyltrimethylsilane in presence of sodium hydride in DMSO. The results of this preliminary exploration are summarized in Table 2.

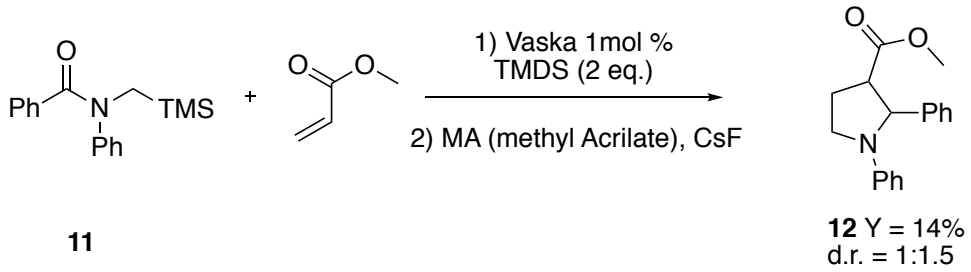
Table 2. Preliminary screening with aliphatic amide



entry	additive	T	Solvent	Yield	d.r
1	TFA (10 mol%)	RT	DCM (0.1M)	0	-
2	CsF (2 eq.)	RT	DCM (0.1M)	0	-
3	TFA(1.1 eq) TBAF (1.1 eq.)	RT	DCM (0.1M)	0	-
4	TFA(1.1 eq) Et_3N (1.1 eq.)	80	DCM/ACN (0.05M)	0	-
5	CsF (2 eq.)	RT	Tol/ACN (2/1) (0.1M)	0	-
6	CsF (2 eq.)	80	Tol/ACN (2/1) (0.1M)	0	-

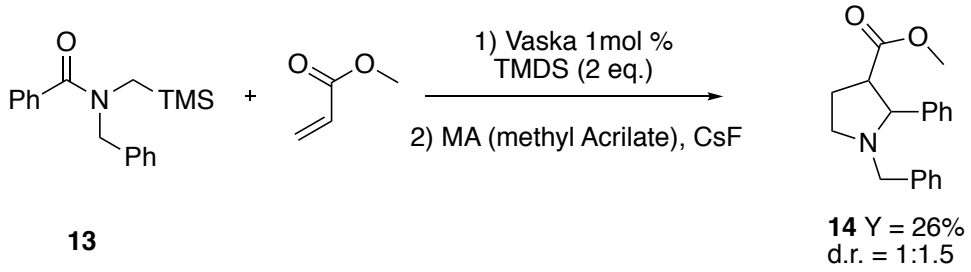
Unfortunately, in all the cases tested, we did not observe the desired product. We envisaged that the iminium formed by the system Vaska/TMDS could quickly and irreversibly evolve in an enamine. Thus, we moved to replace the pyrrolidinone-like amide with the aromatic amide **11**, which does not

display an α-enolizable proton. Gratifyingly, the cycloaddition product **12** was obtained in 14% yield employing CsF as additive in toluene (Scheme 13).



Scheme 13. 1,3-dipolar cycloaddition of amide **11** promoted by Vaska's complex.

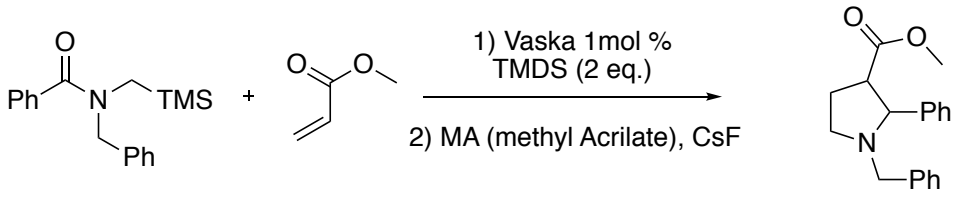
The low yield was partially due to the poor reactivity of the N-aryl substituted amide, which exhibits less Lewis basicity during the coordination of Iridium complex in the reductive step. Thus, we moved to use the amide **13** overcoming this drawback in the optimization step. Under the same conditions, the reaction was performed with the amide **13** and the target product **14** was collected in 26% yield (Scheme 14).



Scheme 14. 1,3-dipolar cycloaddition of amide **13** promoted by Vaska's complex

Encouraged by these results, we decided to screen different conditions utilizing this amide as model substrate in order to improve the efficiency of the reductive/cycloaddition sequence (Table 3). Absence of reactivity was observed replacing toluene with DCM (entry 2) and utilizing the TBAT instead of CsF as fluoride source (entry 3). A slightly better yield was obtained using TFA (trifluoroacetic acid) to promote the formation of the ylide in situ (entry 4). Hence, we decided to continue the screening keeping this additive and changing the other parameters. The reactivity increased when the amount of the dipolarophile was changed from 4 to 8 (entry 6). However, a more significant gain in terms of yield was achieved at higher concentration (entry 5). Noteworthy, the reduction step occurred very fast. In fact, the amide was consumed in 20 minutes, while the dipolar cycloaddition step proceeded slower (generally 12 h). Furthermore, the rate of the first step was not influenced by concentration; this suggested that the decrease of solvent was necessary to boost the cycloaddition step. Thus, it was performed a fine tuning of conditions by changing the concentration and the ratio of the two solvents, and finally we were able to obtain the product in 83% yield.

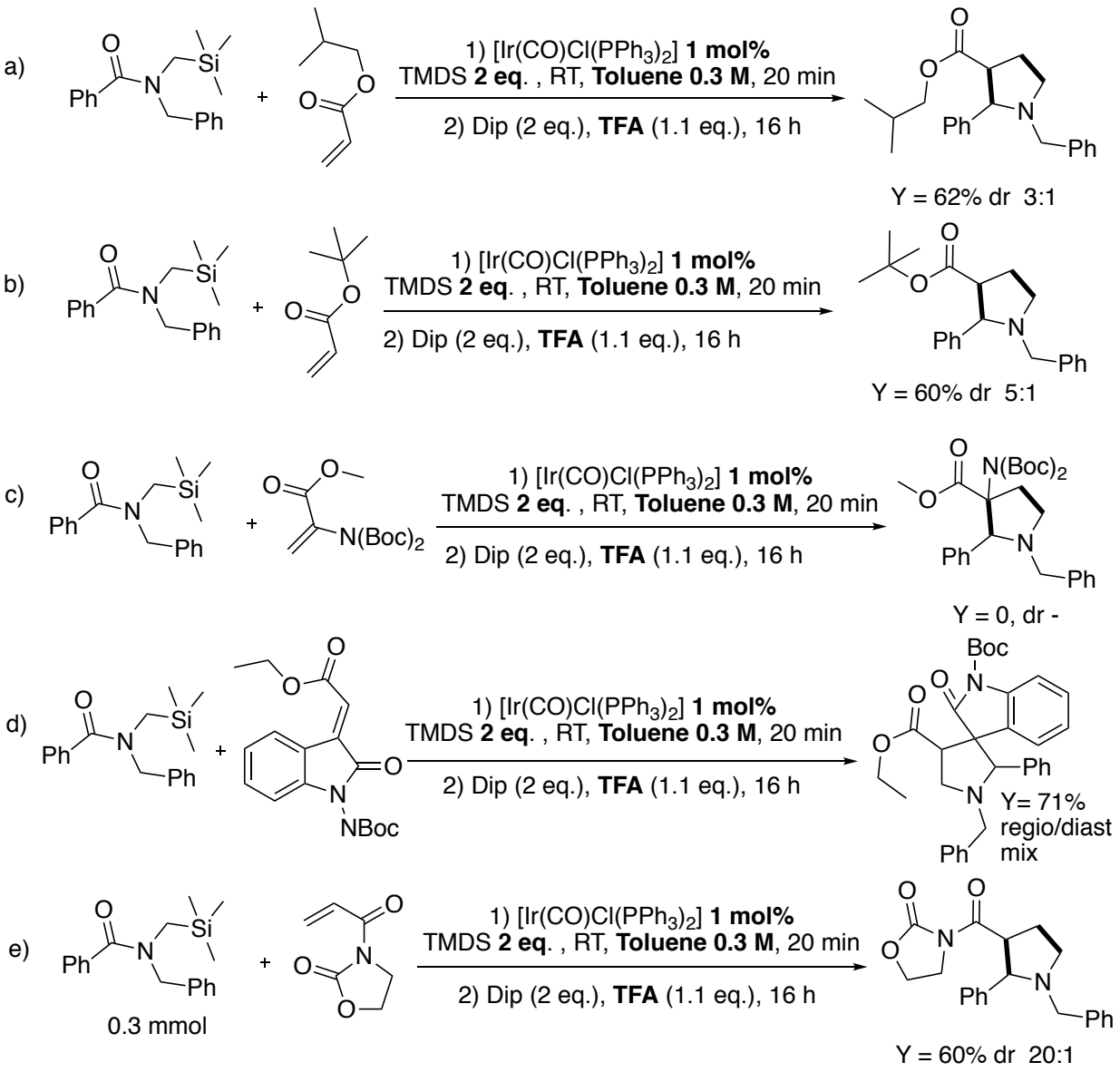
Table 3. Preliminary screening with aromatic amide



13 **14**

Entry	additive	MA eq.	M (tol)	ACN (µL)	Y/d.r.
1	CsF (2 eq.)	4	0.15	500	26/1.5:1
2	CsF (2 eq.)	2	0.15(DCM)	-	0
3	TBAT (2 eq.)	4	0.15	500	0
4	TFA (1.1 eq.)	4	0.15	500	37/1.5:1
5	TFA (1.1 eq.)	4	0.3	250	64/1.5:1
6	TFA (1.1 eq.)	8	0.15	500	48/1.5:1
7	TFA (0.2 eq.)	4	0.3	250	46/1.5:1
8	TFA (1.1 eq.)	4	0.3	500	47/1.5:1
9	TFA (1.1 eq.)	4	0.3	150	82/1.5:1
10	TFA (1.1 eq.)	4	0.3	0	**83/1.5:1**

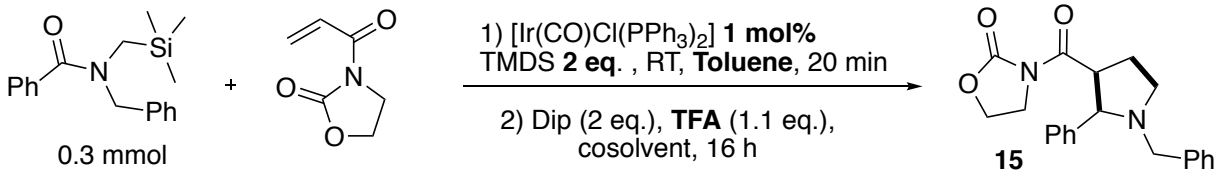
Unfortunately, the diastereoselectivity of the process seems to be not influenced by external parameters. It is well-known that for this type of reactions the preferential formation of one diastereoisomer is strongly related to the substrate nature. Hence, we decided to try different dipolarophiles applying the previously optimized conditions and focusing on the diastereoselectivity (Scheme 15).



Scheme 15. Dipolarophiles screening for the 1,3-dipolar cycloaddition of amide **13** promoted by Vaska's complex

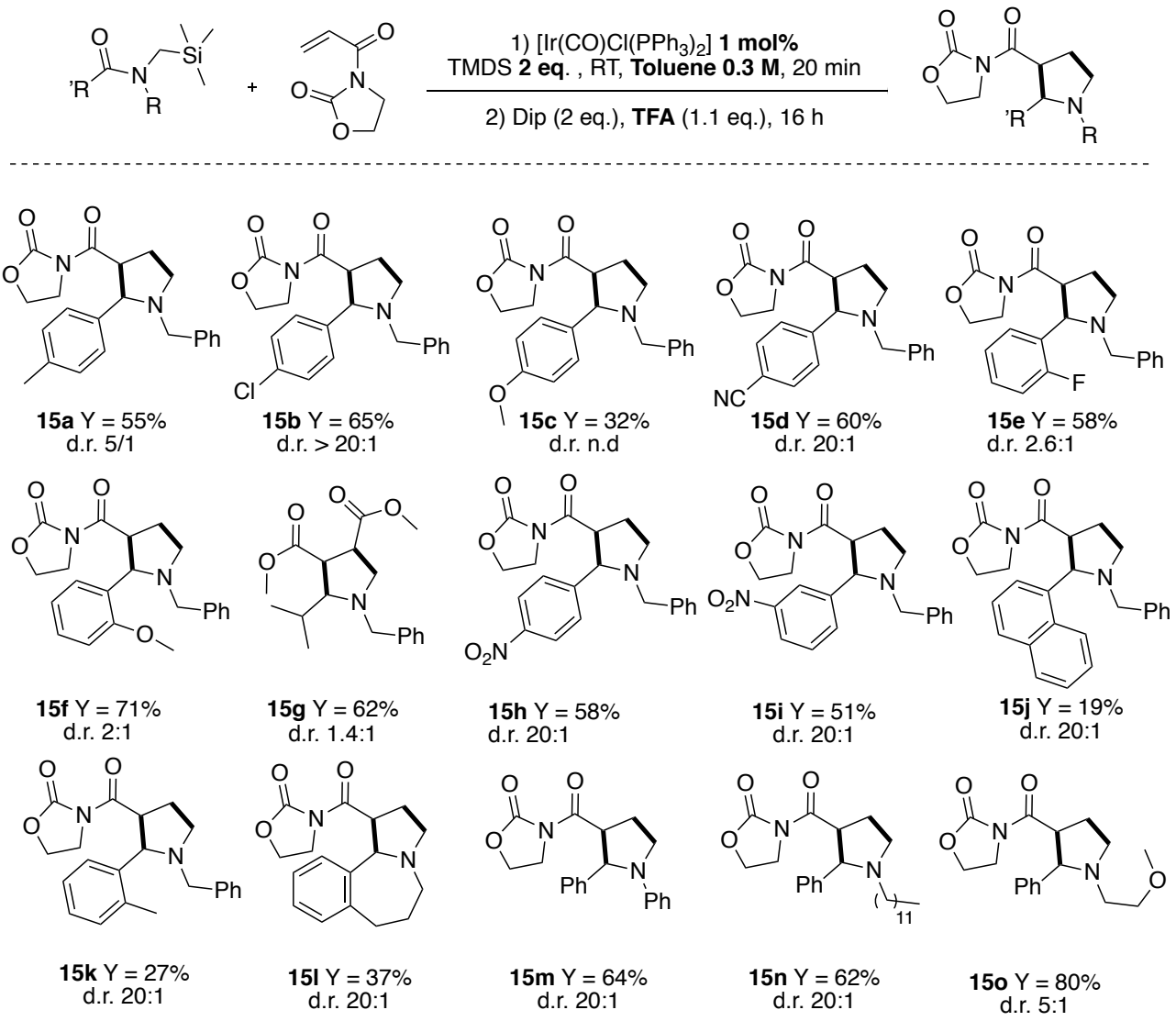
An improvement in diastereoselectivity was observed replacing the alkyl group on the oxygen of the acrylate (Scheme 15 a and b); this suggested that playing with the hindrance of the electrophile was the right way to reach an acceptable diastereomeric ratio. Unfortunately, di-protected nitrogen α-substituted methyl acrylate proved to be unreactive under the optimal conditions (Scheme 15 c), while the oxindole derivative reacted giving a complex mixture of regio/diastereoisomers (Scheme 15 d). Finally, the reaction with the Evans acrylate gave the expected cycloaddition adduct in excellent diastereoselectivity and good yield (Scheme 15e). At this point, we moved to reoptimize the conditions using this new dipolarophile (Table 4) and focusing our attention on the choice of the co-solvent because of the not complete solubility of this dipolarophile in toluene.

Table 4. Reaction screening with aromatic amide and Evans' acrylate



entry	Toluene	Cosolvent	Y	d.r.
1	900 µL (for 0.3 mmol starting)	-	60	20:1
2	900 µL (for 0.3 mmol starting)	ACN (200 µL)	66	20:1
3	800 µL (for 0.3 mmol starting)	Chloroform (200 µL)	69	20:1
4	800 µL (for 0.3 mmol starting)	Chloroform (300 µL)	68	20:1
5	800 µL (for 0.3 mmol starting)	THF (200 µL)	56	20:1
6	**900 µL (for 0.3 mmol starting)**	**Chloroform (100 µL)**	**73**	**20:1**
7	1 mL (for 0.3 mmol starting)	Chloroform (50 µL)	70	20:1

The best conditions for the model reaction were found using Chloroform as co-solvent (0.3 M) and subsequently they were applied to investigate the scope of reaction (Scheme 16).



Scheme 15. Scope of 1,3-dipolar cycloaddition of amide promoted by Vaska's complex

We first explored the electronic effect on the aromatic moiety on the amide. The reaction proceeded smoothly for aromatic amides bearing poor electro-donating group as methyl (**15a**) and electron-withdraw groups as chloride and nitrile (**15b** and **15d**). By contrast, more electro-rich aromatic rings as anisol substituent (**15c**) showed poor reactivity and in this case a diastereomeric ratio could not be determined due the complexity of the crude. Strangely, for the p-anisol substituent, the reaction proceeded towards the desired product in good yield, even though with poor stereoselectivity, suggesting that the reaction is strongly influenced by stereoelectronic effects. In this regard, replacing the hydrogen with a fluoride atom in ortho position drastically changed the diastereoselectivity (**15e**), although fluoride is comparable in size with the hydrogen. The good results in terms of diastereoselectivity obtained for the ortho-tolyl amide (**15k**), which bears a bulkier group in ortho-position, partially corroborate this speculation. The nitro series, composed by para and meta nitro-substituted benzamides (**15h** and **15i**) produced good results in terms of both reactivity and diastereoselectivity. We also tried to transpose the methodology to aliphatic amides but we were able

to observe reactivity in the only one case, when the amide does not bear enolizable protons and it was found to be reactive only with more electron-poor dipolarophiles (**15g**). Naphthylamide seemed to have a hindrance which limits its use in this transformation (**15j**). Furthermore, a much slower reactivity towards the reduction was observed with this particular amide. The effect on the substituent on the nitrogen atom was studied as well. For cyclic amide the reaction proceeded slower and only the 37% of yield was registered for **15l**, may be due conformational issues related to the approach of the dipolarophile onto the ylide. Vice versa for others aliphatic moieties drastic changes in reactivity were not observed (**15n** and **15o)**.

6. References

[1] a) A. J. Bennet, Q.-P. Wang, H. Slebocka-Tilk, V. Somayaji, R. S. Brown, *J. Am. Chem. Soc.*, **1990**, 112, 6383; (b) H. Slebocka-Tilk, R. S. Brown, *J. Org. Chem.*, **1987**, 52, 805.

[2] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, **1881**, 2725.

[3] A. Vilsmeier, A. Haack, *Ber. Dtsch. Chem. Ges. B*, **1927**, 119.

[4] A. Bischler, A. Napieralski, *Ber. Dtsch. Chem. Ges.*, **1893**, 1903.

[5] a) A. J. Speziale, L. R. Smith, *J. Org. Chem.*, **1963**, 28, 1805. b) B. Ravinder, R. S. Rajeswar, A. Panasa Reddy, R. Bandichor, *Tetrahedron Lett.*, **2013**, 54, 4908.

[6] a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature*, **2015**, 524, 79; (b) M. Kono, S. Harada, Y. Hamada, T. Nemoto, *Tetrahedron*, **2016**, 72, 1395.

[7] a) B. B. Snider, *Chem. Rev.*, **1988**, 88, 793; b) I. L. Baraznenok, V. G. Nenajdenko, E. S. Balenkova, *Tetrahedron*, **2000**, 56, 3077. b) C. Madelaine, V. Valerio, N. Maulide, *Chem.-Asian J.*, **2011**, 6, 2224.

[8] A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev.*, **2016**, 45, 6685.

[9] a) Y. Oda, T. Sato, N. Chida, *Org. Lett.*, **2012**, 14, 950; b) K. Shirokane, T. Wada, M. Yoriate, R. Minamikawa, N. Takayama, T. Sato, N. Chida, *Angew. Chem., Int. Ed.*, **2014**, 53, 512; c) Y. Nakayama, Y. Maeda, M. Kotatsu, R. Sekiya, M. Ichiki, T. Sato, N. Chida, *Chem.–Eur. J.*, **2016**, 22, 3300; d) H. Kobayashi, Y. Sasano, N. Kanoh, E. Kwon, Y. Iwabuchi, *Eur. J. Org. Chem.*, **2016**, 2016, 270.

[10] P.-Q. Huang, Y.-H. Huang, K.-J. Xiao, Y. Wang, X.-E. Xia, *J. Org. Chem.*, **2015**, 80, 2861.

[11] J.-F. Zheng, X.-Y. Qian, P.-Q. Huang, *Org. Chem. Front.*, **2015**, 2, 927.

[12] P.-Q. Huang, Q.-W. Lang, X.-N. Hu, *J. Org. Chem.*, **2016**, 81, 10227.

[13] Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto, H. Nagashima, *Chem. Commun.*, **2009**, 1574.

[14] S. Katahara, S. Kobayashi, K. Fujita, T. Matsumoto, T. Sato, N. Chida, *J. Am. Chem. Soc.*, **2016**, 138, 5246.

[15] M. Yoritate, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato, N. Chida, *J. Am. Chem. Soc.*, **2017**, 139, 18386.

[16] A. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery, D. J. Dixon, *Angew. Chem. Int. Ed.*, **2017**, 56, 3655.

[17] L.-G. Xie, D. J. Dixon, *Chem. Sci.*, **2017**, 8, 7492.

[18] a) R. Huisgen, R. Grashey, J. Sauer, *The Chemistry of Alkenes*, S. Patai, ed., interscience London, **1965**, 806.

[19] P. K. Kadaba, *Tetrahedron*, **1969**, 25, 3053.

[20] R. Huisgen, G. Szeimes, L. Moebius, *Chem. Ber.*, **1967**, 100, 2494.

Ringraziamenti

Ringrazio con tutto cuore la professoressa Olga Bortolini che mi ha dato la possibilità di far parte del suo team di ricerca. Ringrazio i professori Massi, Giovannini e De Risi che mi hanno insegnato come ci si approccia alla ricerca in maniera critica e produttiva senza abbattersi mai, anche se i primi risultati non sono sempre quelli sperati; i professori Fantin e Fogagnolo che con la loro esperienza e disponibilità hanno sempre cercato di aiutarmi quando incappavo in qualche problema di natura pratica. Ringrazio anche i tecnici di laboratorio Tatiana Bernardi, Paolo Formaglio ed Ercolina Bianchini per il prezioso supporto dato nella produzione dei dati che hanno portato alla stesura di questa tesi.

Ringrazio anche il professor Darren J. Dixon e tutti i ragazzi del suo gruppo per la splendida esperienza che mi hanno permesso di vivere a Oxford durante il mio periodo all'estero.

Un ringraziamento speciale va a tutti i compagni di laboratorio, persone con cui ho lavorato fianco a fianco condividendo un percorso che non è stato sempre semplice. Grazie a Daniele Ragno, Nicola Chinaglia, Anna Zaghi, Dario Cristofaro, Arianna Brandolese, Serena Baraldi, Daniel Pecorari, Alessandro Testi, Stefano Mancuso, Daniele Urbani, Irene Milan e Francesco Presini. Senza di voi non sarebbe stato lo stesso.