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TITOLO TESI

Development of Organocatalytic Stereoselective S_N1 type reaction

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Glossary

(R)-TRIP	3,3-Bis(2,4,6-triisopropylphenyl)-1,1´-binaphthyl-2,2´-diylhydrogenphosphate
2,6-Cl_2pyr	2,6-chloropyridine
3,5-Me_2PhMgBr	(3,5-dimethylphenyl)magnesium bromide
4-FPhMgBr	(4-fluorophenyl) magnesium bromide
9 epi-QDA	9-epi- 9-amino- 9-deoxyepi-quinidine
acac	Acetylacetonato
$AgNO_3$	Silver nitrate
AgOTf	Silver trifluromethansulfonate
Au(I)	silve (I)
$AuCl_3$	silver (III) trichloride
BF_4	Tetrafluoroborate
$Bi(OTf)_3$	Bismuth (III) trifluoromethansulfonate
BINAP	2,2-bis(diphenylphosphino)-1,1´-binaphthyl
BINOL	1,1-Binaphthol
BnBr	Benzyl bromide
Boc	tert-Butoxycarbonyl
CAN	Cerium ammonium nitrate
$Ca(OTf)_2$	Calcium (II) trifluoromethansulfonate
CDC	Cross-dehydrogenative-coupling
$CDCl_3$	Chloroform deuterated
CH_3CN	Acetonitrile
CH_3NO_2	Nitromethane
$Cu(OAc)_2$	Copper (II) acetate
$Cu(OTf)_2$	Copper (II) trifluoromethansulfonate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DET	Diethyl tartrate
DiPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
DIPEA	N,N-diisopropylethylamine
DMF	Dimethylformamide

E	Electrophile
ECD	Electronic Circular Dichroism
Et_3SiH	Triethylsilane
Et_2O	Diethyl ether
Et_3B	Triethyl borane
EtI	Ethyl iodide
EtOAc	Ethyl acetate
F.C	Field Craft
$Fe(acac)_3$	Tris(acetylacetonato)iron(III)
H_20	water
HBF_4	Fluoroboric acid
HgO	Mercury (II) oxide
In	Indium
$In(OTf)_3$	Indium (III) trifluoromethansulfonate
$InBr_3$	Indium (III) tribromide
$InCl_3$	Indium (III) trichloride
K_2CO_3	Potassium Carbonate
$K_3Fe(CN)_6$	Potassium ferricyanide
KPF_6	Potassium hexafluorophosphate
$K_2S_2O_8$	Potassium persulfat
L-DOPA	L- 3,4-dihydroxyphenylalanine
L.A	Lewis acid
$LiBEt_3$	Lithium triethylborohydride or Superhydride
K	rate constant
LUMO	Lowest unoccupied molecular orbital
Me_3SiBr	Trimethylsilyl bromide
MeI	Methyl iodide
MeOH	Methanol
N	Nucleophile
$NaN(SiMe_3)_2$	Sodium bis (trimethylsilyl)amide
NaH	Sodium hydride
NaH_2PO_4	Sodium hydrogenphosphate
Na_2SO_4	Sodium sulfate
$NaBH_4$	Sodium tetrafluoroborate
$NaClO_2$	Sodium chlorite
NaOH	Sodium hydroxide

NH_3	ammonia
NH_4Cl	Ammonium chloride
N-Boc-Phe-OH	tert-Butoxycarbonyl-Phenylalinine
O_3	Ozone
p-Me_2PhCHO	Para-dimethylbenzaldehyde
p-NO_2PhCOOH	Para-nitrobenzoic acid
p-TSA	p-Toluenesulfonic acid
Pd	Palladium
$Pd(OPPh_3)_4$	
Pd/C	Palladium/carbon
$PdCl_2(PPh_3)_2$	Bis-(triphenylphosphine)palladium (II) chloride
Ph	Phenyl
PhCOOH	Benzoic acid
Ph_3PAuCl	Chloro triphenylphosphine gold (I)
Ru	Ruthenium
s	Constant of electrophilicity
SiO_2	Silice oxide
S_N1	Nucelophilic substitution
SOMO	highest occupied molecular orbital
TADDOL	α,α,α´,α´-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBSCl	tert-Buthyldimethylsilyl chloride
tBuOMe	Methyl t-butyl ether
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxyl
TD-DFT	Time-dependent Density Functional Theory
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
$TMSCHN_2$	trimethylsilyldiazomethane
$Zn(OTf)_2$	Zinc (II) trifluoromethansulfonate

Support information

General methods

General Methods. ^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ= 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ= 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: *m/z* (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Determination of enantiomeric excess were performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line), specific rotation was expressed as deg $cm^3g^{-1}dm^{-1}$ and concentration as gcm^{-3}. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected. Materials: All reactions were carried out under inert gas and under anhydrous conditions. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and used avoiding purification.

Abstract

The proposal in my thesis has been the study of Stereoselective α-alkylation through S_N1 type reaction. S_N1 type reaction involves a stabilized and reactive carbocation intermediate By taking advantages of stability of particular carbocations, the use of carbocations in selective reactions has been important. In this work has been necessary to know the stability and reactivity of carbocations. And the work of Mayr group has helped to rationalize the behaviour and reactivity between the carbocations and nucleophiles by the use of Mayr's scale of reactivity.

The use of alcohols to performed the stable and reactive carbocations have been the key in my thesis. The direct nucleophilic substitution of alcohols has been a crucial scope in the field of organic synthesis, because offer a wide range of intermediates for the synthesis of natural products and pharmaceutics synthesis. In particular the catalytic nucleophilic direct substitution of alcohols represents a novel methodology for the preparation of a variety of derivatives, and water only as the sub-product in the reaction.

The stereochemical control of the transformation C-H bond into stereogenic C-C bond adjacent to carbonyl functionalized has been studied for asymmetric catalysis. And the field of organocatalysis has introduced the use of small organic molecule as catalyst for stereoselective transformations.

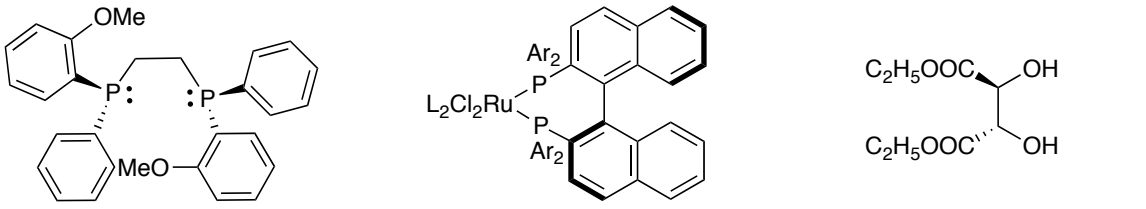
Merging these two concepts Organocatalysis and Mayr's scale, my thesis has developed a new approach for the α-alkylation of aldehydes and ketones through S_N1 type reaction.

Chapter 1. Introduction

1. Asymmetric catalysis

The development of synthetic methods for the preparation of optically active compounds is a challenged in Organic Chemistry. In 1980s the development of asymmetric catalytic methodologies has reached the maturity and a number of practical and innovative solution, both in academia and in industry, were presented. Several groups studied new strategies in the asymmetric synthesis field within the past decade. The pioneers were many groups, and in this area of research Sharpless, Noyori and Knowles were awarded by the novel prize in Chemistry 2001, which was divided, on half part for W.S.Knowles and R.Noyori ¨for their work on chiral catalysis hydrogenation reactions¨ and k.B.Sharpless ¨for his work on chirally catalysed oxidations reactions¨

W.S.Knowles and co-workers used the idea developed by Kagan towards a practical and highly stereoselective methodology, demonstrating that rhodium complex contain chiral phosphine ligand were able to catalyze the enantioselective hydrogenation. This process industrially developed by Knowles was the synthesis of anti-Parkinson-drug amino acid L-DOPA.[1] At the same time Noyori 1974 developed the synthesis of BINAP (2,2- bis(diphenylfoshine)-1,1-binaphtile) one of phosphine C_2-symmetric, a new catalyst system based on ruthenium, BINAP-Ru[2] was invented. Simultaneously, K. B. Sharpless and co-workers developed small, highly enantioselective catalysts for the asymmetric oxidation of alkynes.[3]



DiPAMP
(W.S.Knowles, 1968)

Ru-BINAP
(R.Noyori, 1974)

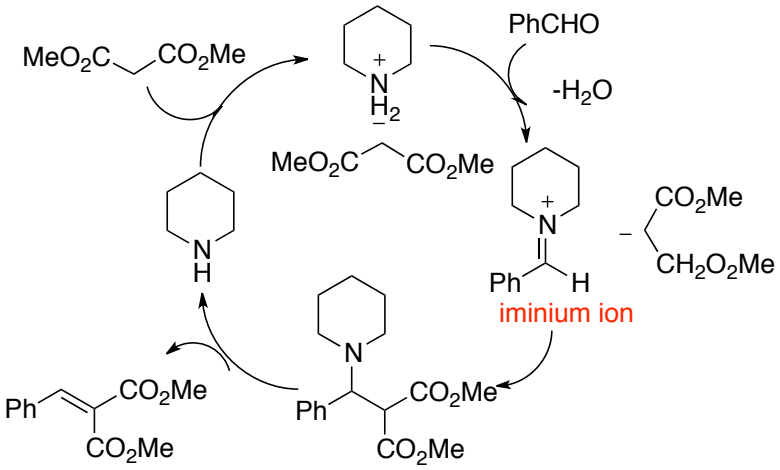
DET
(K.B.Sharpless, 1980)

Figure 1. The first catalysts introduce in asymmetric catalysis

Over the past four decades the capacity to induce asymmetric transformations with enantioselective catalysis has remained a focal point for extensive research efforts in both industrial and academic settings. The asymmetric catalytic reactions have been invented in accord with the increasing need for enantiopure medicinal agents and quickly advancement of the field of asymmetric synthesis. There are three pillars in the asymmetric catalysis, bio-and metal catalyst and the most new was the organocatalysis, which was not until the late 1990s born as organocatalysis.[4]

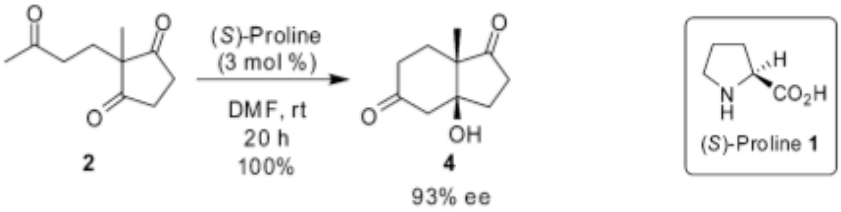
1.2 Origen of the organocatalysis [5]

The progress of organocatalysis over the last 10 years has brought a breathtaking growing in asymmetric catalysis. The origins of organocatalysis have been developed over the last century. Emil Knoevenagel found the primary and secondary amines, as salts, catalyzed the aldol condensation of β-ketoesters or malonates with aldehydes or ketones.[6] Twenty years later, Khun and Hoffer made the important observation that secondary amine catalyzed self-and cross aldol condensation of aldehydes.[7] Langebeck suggested the first studies about Khun-Knoevengel –type covalent catalyst mechanism.[8]



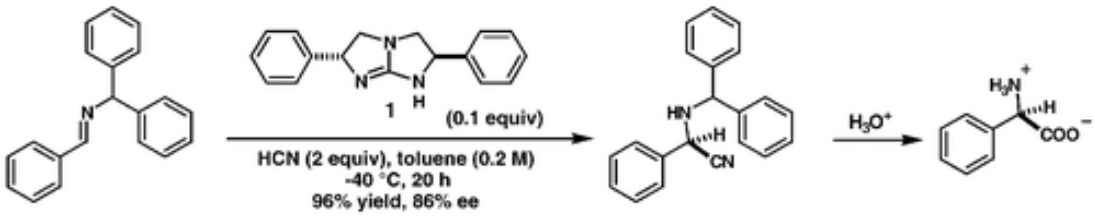
Scheme 1. The Knoevenagel reaction (1896)

This background set the stage for the discover of the first asymmetric amine catalyzed aldolization by two independent reports one by Hajos-Parrish and other for Weichert-Sauer-Eder of an enantioselective intramolecular aldol reaction, that was catalyzed by proline.[9a,b.]



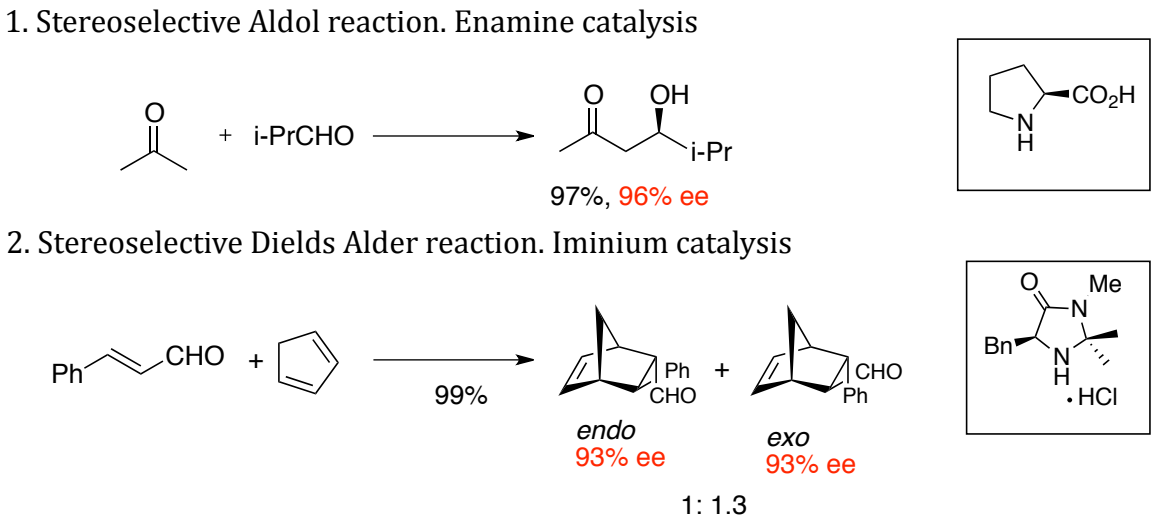
Scheme 2. Hajos-Parrish Reaction catalyzed by (S)-proline. (1974)

In the late 1990s, Yian Shi[10a] Schott Denmark[10b], and Dan Yang[10c] demostrated the enantiomerically pure ketones could have been used to catalyze the enantioselective epoxidation of simple alkenes. Jacobsen and Corey demonstrated the first example hydrogen-bonding-catalysis is asymmetric Strecker reaction.[11a,b] Scott Miller[12] introduced the concept of minimal peptides for the enantioselectivity kinetic resolution alcohols. These works demostrated the use of small organocatalyst could be used to solve problems in organic synthesis.



Scheme 3. Strecker Reaction using Chiral Bicyclic Guanidine as catalyst.(1999)

But the ¨explosion¨ in organocatalysis was not until 2000, with two independently publications, one by Barbas, Lernen and List[13] with the enamine catalysis, and the other by MacMillan and co-workers[14] with iminium catalysis.



Scheme 4

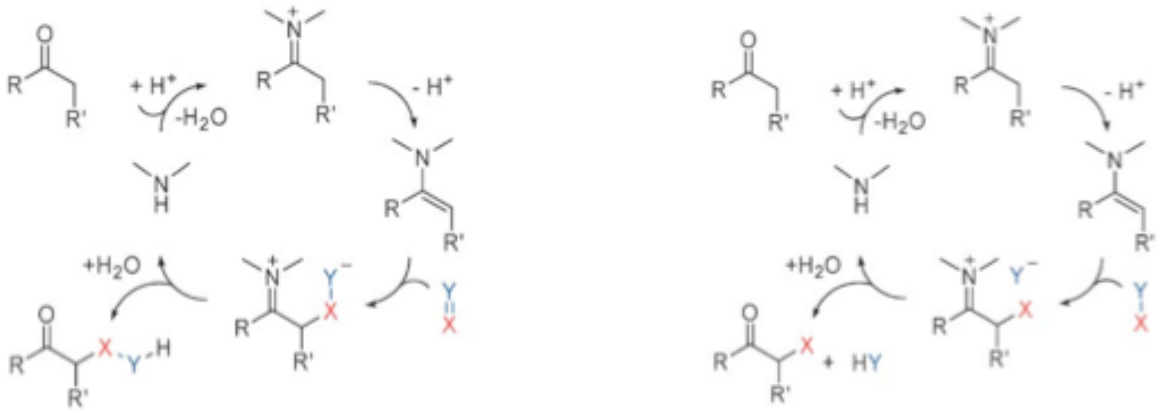
The exponential growth of studies and publications in the field of the organocatalysis can be explained by three factors, 1) organic molecules used as catalysts in organocatalytic reactions are insensitive to oxygen and moisture in the atmosphere. 2) a large range of compounds source of chiral organocatalysts are naturally available from biologic sources as a single enantiomers, 3) small organic molecules used as organocatalysts are typically non-toxic and environmentally friendly. The studies

and the new reactions discovered in the field of organocatalysis has helped to conceptualize the organocatalysis as a new field of research that demonstrated the use of small organic molecule to catalyze stereoselective organic transformations, and this phrase has been used as a definition of organocatalysis in the past decades until now.

1.2.1 The advent of generic mode of catalyst activation[15]

Enamine catalysis

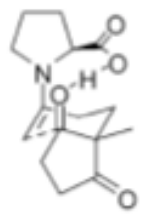
Recent years have been a growth in the field of asymmetric enamine catalysis.[16] The base of enamine catalysis is the reversible generation of enamine from a catalytic amount of an amine in the presence of stoichiometric amount of a carbonyl compound. The key factors that give rise to enamine formation is the LUMO lowering effect and resulting dramatic increase in C-H acidity in α upon initial conversion of carbonyl compound into iminium ion. There are two modes of enamine catalysis, depending on the class of electrophiles. Aldehydes, or iminium (Mannich acceptors) can react as electrophiles with enamines. While reaction with π-acceptors electrophiles with enamines is quite straightforward, the reaction of other electrophiles, such as alkyl halides, can be more problematic.[17]



Nucleophilic addition **Substitution reactions**

Scheme 5. Modes of activation in enamine catalysis

In the early 1970s, was discovered the first example of aminocatalysis asymmetric aldol reaction by Hajos-Parrish-Eder-Sauer-Weichert, the 6-enolendo aldolization reaction.[9a,b] The first amine-catalyzed asymmetric direct intramolecular aldol reaction was developed by Barbas-Lernen and List in 2000. [13,18]

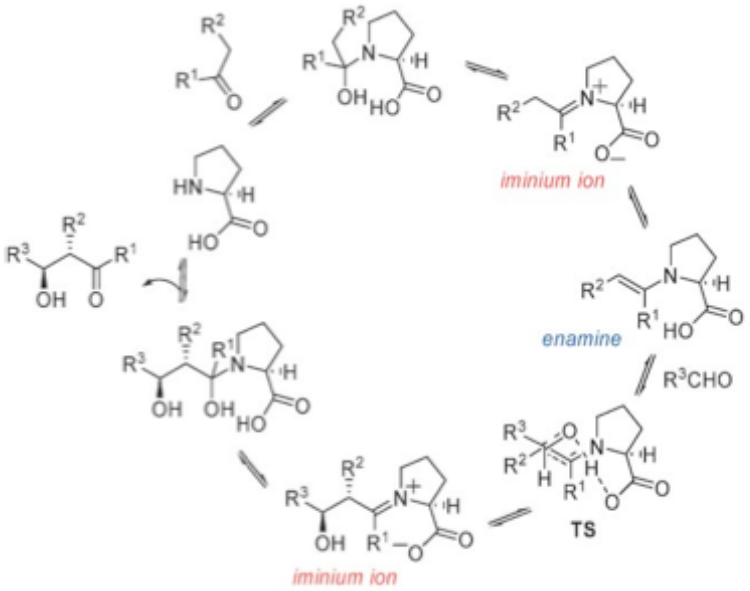


D

Houk Model

Extensive research about the enamine catalysis mechanism has been studied for several research groups, and the mechanistic proposal seemed quite similar to the class I aldolse mechanism. Mechanistically enamine catalysis could be describe as a

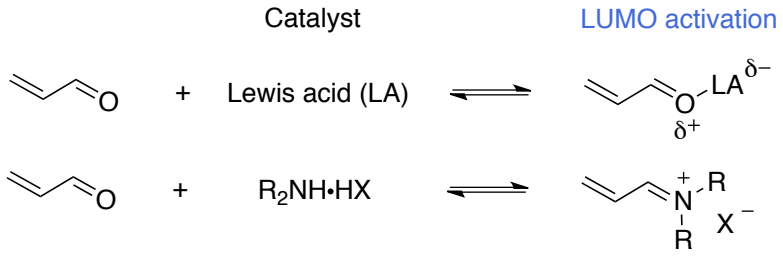
bifunctional catalyst because the amine catalyst (proline) interacts with the carbonyl compound to form enamine species and simultaneously is engaged with electrophile partner through hydrogen bond interaction mediated by the carboxylic acid moiety. Theoretical studies by Houk and co-workers supported one proline mechanism in which the sidechain enamine reacted with the acceptor carbony group under activation via hydrogen bonding to proline's carboxylic group.[17]



Scheme 6. The proposed Mechanism and transition state of proline-catalyzed aldolitzations

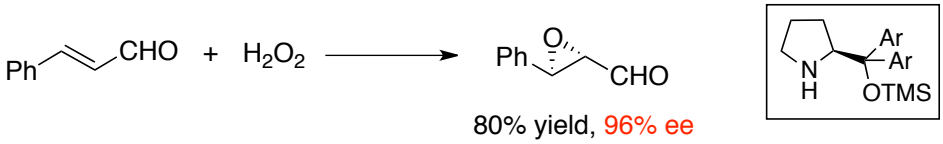
Iminium catalyst

In 1999, MacMillan group introduced a new mode of activation for asymmetric synthesis base on the capacity of chiral amine to function as enantioselective LUMO-lowering catalyst that was employed as a Lewis acid. This strategy was founded on the mechanistic postulate that (i) the LUMO-lowering activation and (ii) the kinetic liability toward ligand substitution that enables the turnover of Lewis acid catalyst. MacMillan group[19] investigated the first highly enantioselective amine catalyzed Diels Alder reaction between α,β-insaturate aldehydes and various dienes.



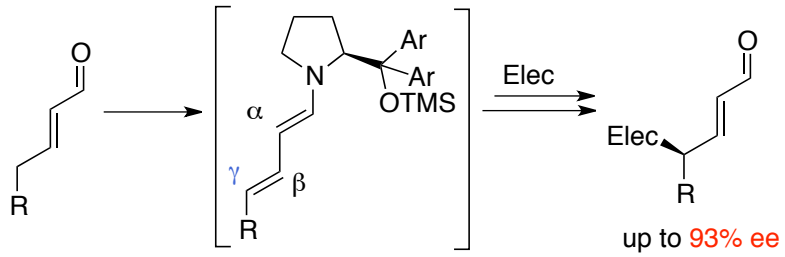
Scheme 7. Concept iminium activation

Another contribution in iminium catalyst was introduced by Jørgensen and co-workers, that demonstrated the epoxidation of substituted α,β-unsaturated aldehydes can be carried out in high level of enantioselectivity using proline derivative and stoichiometric amount of an oxidizing agent.[20]



Scheme 8. Asymmetric Organocatalytic Epoxidation of α,β-insaturated aldehydes

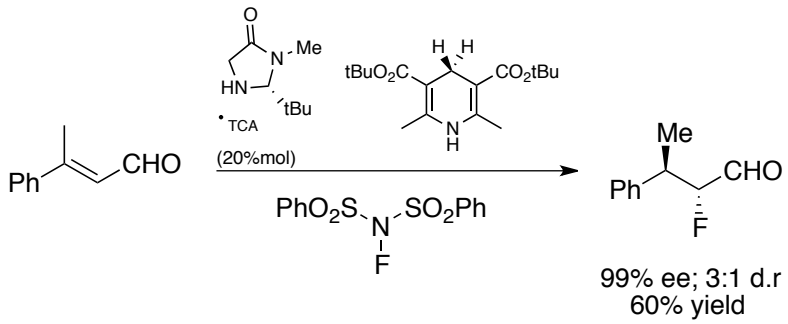
The β-functionalitzation of the α,β-unsaturated carbonyl compounds has become a new methodology for the stereoselective synthesis based on cycloadditon or 1,4-addition. The condensation of enamine between the secondary amine and α,β-unsaturated aldehyde forms an iminium ion, which reacts with a nucleophile to the β-carbon. Jørgensen and co-workers studied the mechanism of the organocatalytic β-functionalization of α,β-unsaturated aldehydes discovered a new mode of activation called the dienamine catalysis. The presence of this intermediate takes place from the transient iminium-ion being deprotonated in the γ-position leading to the electron-rich dienamine intermediate that reacts with electrophiles such as azadicarboxylate.[21]



Scheme 9. The Asymmetric amination. Dienamine catalysis

Tandem reactions

The enamine and iminium catalysis are two divergent reaction mode of activation in organocatalysis. Enamine catalysis proceeds via iminium ion formation, and the same for iminium catalysis. The two catalytic intermediates are opposites but complementary. Combing the two catalysis principles in tandem sequences is a new strategy for organic synthesis, and the generation of molecular complexity in a simple one pot reaction.[22]

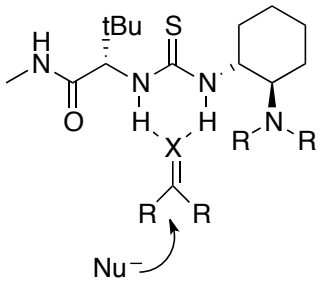


Scheme 10. Tandem iminium- enamine catalysis

In summary, the asymmetric amine catalysis has become a new source in the design of new catalyst, new mode of activation and new reactions are being discovered and applied in asymmetric synthesis.

Hydrogen-bonding catalyst[23]

In the early 1890s, studies of asymmetric catalysis by chiral organic small molecule implicated H-bonding between catalyst and electrophile as a mechanism of electrophile activation. Pioneers were two independently groups one of them was Jacobsen group and the other was Corey group.[11a,b] In 1998, Jacobsen group reported the thiourea Schiff base to promote highly enantioselective Strecker reaction of N-allyl imines. Other catalysts as TADDOL derivatives and chiral biphenol emerged as H-bond donator catalyst for enantioselective reactions and activation of aldehydes and ketones electrophiles toward nucleophilic attack.[24] One example of H-bonding catalysis was enantioselective aldol reactions with performed enolates with chiral diol catalyst.



Scheme 11. Mode of activation of hydrogen bonding catalyst

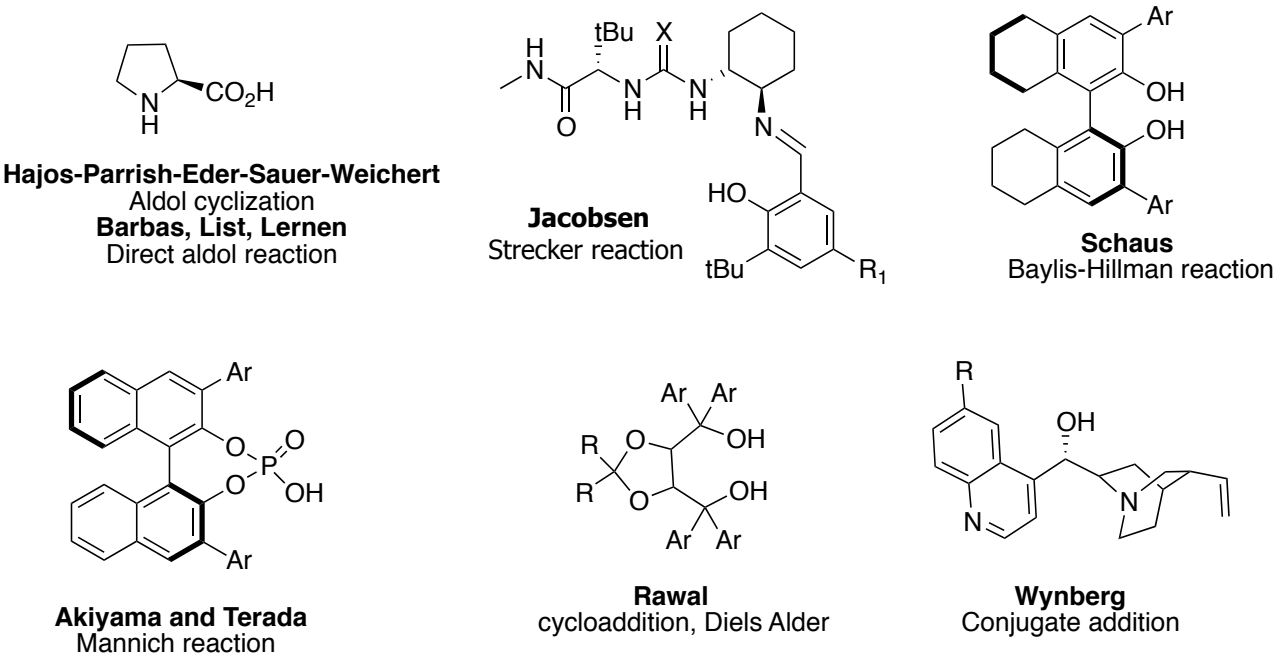
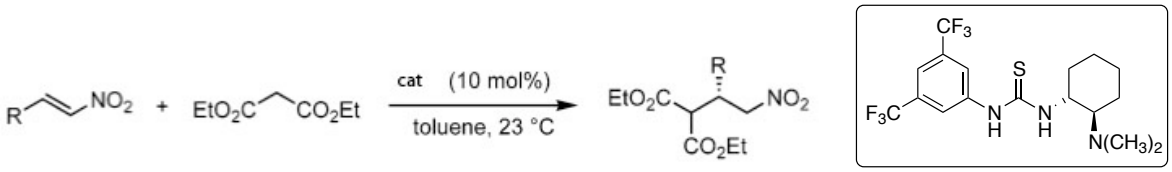


Figure 2. Representative catalysts for the H-bond donadors in asymmetric catalysis

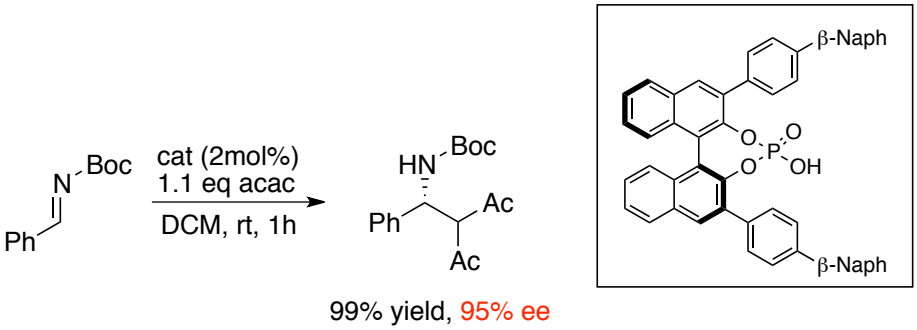
In 2003, Takemoto and co-workers reported the application of thiourea derivative to the enantioselective addition of malonate to β-nitrostyrene. In this reaction, theoretical investigations supported a chiral π-activation mechanism catalyst.[25]



up to 96% yield
up to 93% ee

Scheme 12. Enantioselective conjugate addition reaction

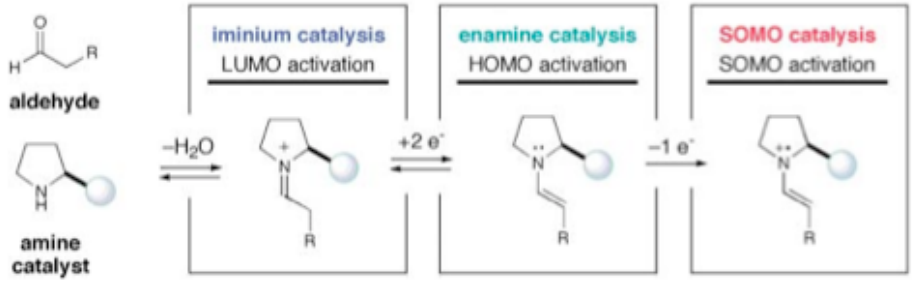
Imine electrophiles are strong and directional H-bond acceptor, therefore the majority of applications of asymmetric H-bonding catalysis have been in context with nucleophilic addition of nucleophile to imines. One example is the Mannich reaction –addition of enolates equivalent to imine- for β–amino carbonyl compounds.[26] Two independent groups Akiyama and other Terada group reported the chiral phosphoric acids as a chiral Brønsted acids catalyst in the context of Mannich reaction of N-aryl and N-Boc imines.[27]



Scheme 13. Direct Mannich reaction catalyzed by chiral phosphoric acids

SOMO catalysis

In 2006, MacMillan and co-workers demonstrated the concept of singly occupier molecular orbital SOMO-activation with a highly selective α-alkylation of aldehydes. The idea was the capacity of enamine and iminium ions to rapidly interconvert via a redox process whether it might be possible to interrupt this equilibrium chemically and thereby to access a mode of catalyst that intermediate between enamine and iminium formation. MacMillan group hypothesized that one electron oxidation of a transient enamine species should generate a three-π electron radical cation with a singly occupied molecular orbital (SOMO) using stoichiometric amount of oxidant.[28]

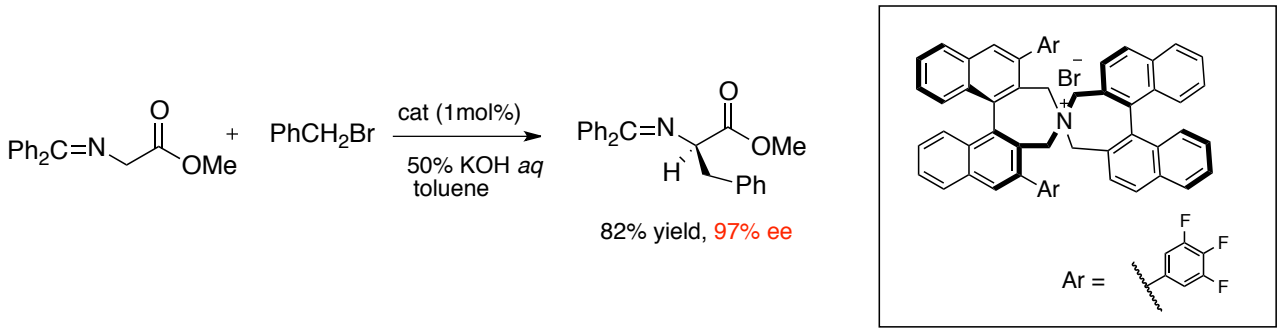


Scheme 14. Concept SOMO

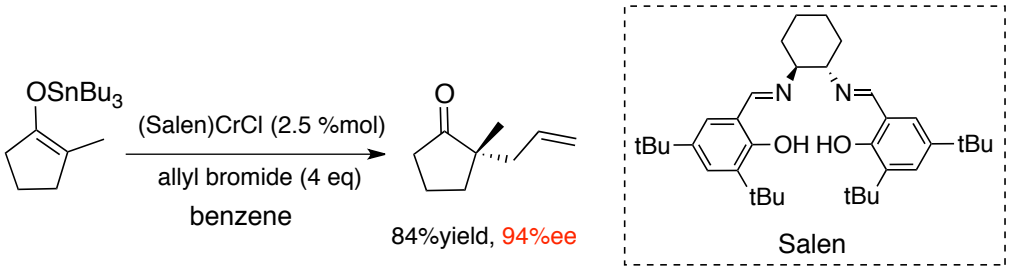
1.3 Asymmetric C-C bond forming bond

α-alkylation in organocatalysis

α-alkylation of carbonyl compounds is central C-C bond forming reaction in organic synthesis.[29] The use of chiral auxiliaries have been reported by asymmetric α-alkylation from different groups such as Evans, Seeback, etc…[30] Moreover, the development of a general catalytic α-alkylation has been studied for different groups. For example, Maruoka and co-workers reported one strategy limited in scope, using phase transfer catalysis applied in the synthesis of α-aminoacids.[31] Jacobsen group proposed the Cr(Salen) complex system for α-alkylation of carbonyl compounds with electrophiles as alkyl halides.[32]



Scheme 15. C_2-symmetric chiral phase-transfer catalyst in catalytic enantioselective alkylation



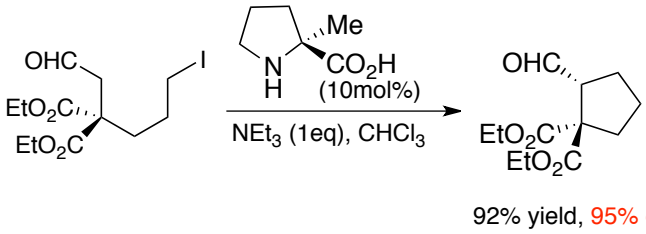
Scheme 16. Enantioselective alkylation catalyzed with Cr(Salen)Cl

The problem in α-alkylation of aldehydes is controlled to perform aldehyde enolates, because of several side reactions such as self-condensation, Canizzaro or Tischchenko reaction and N-or O-alkylation are competing process in the reaction of metal enolate and enamine catalysis.[33]

There are two problems in the α-alkylation reaction:

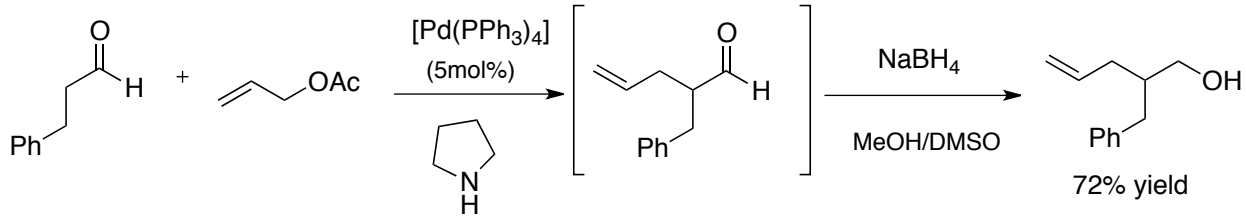
a) susceptibility of the nucleophilic Lewis- or Brønsted base catalyst toward an unproductive alkylation reaction with electrophile.
b) Racemization of product for the formation of acid in the reaction.

In 2004, List group reported the first intramolecular α-alkylation reaction, they hypothesized that the enamine intermediate should react with alkyl halide, while the potential N-alkylation of the amine catalyst itself to give catalytically inactive tertiary ammonium salt should not occur. And 1eq of acid HX forming in the reaction to be trapped by stoichiometric amount of added base affording the product of α-alkylation. Optimizing the reaction conditions, treating aldehyde with (S)-α-methylproline with 1 eq triethylamine furnished cyclopentane carbaldehyde in 92% yield, and enantioselectivity 95%ee.[34]



Scheme 17. Enantioselective intramolecular α-alkylation of aldehydes

In 2006, the direct catalytic intramolecular α-allylic alkylation of aldehydes and cyclic ketones was studied by Córdova and co-workers merging two concepts transition-metal with Pd (0) and organocatalysis. The combination of organocatalyst with transition-metal has explored new frontiers in the field of the organocatalysis, which will be explained in more detail below. (Chapter 2)



Scheme 18. Direct α-allylic alkylation

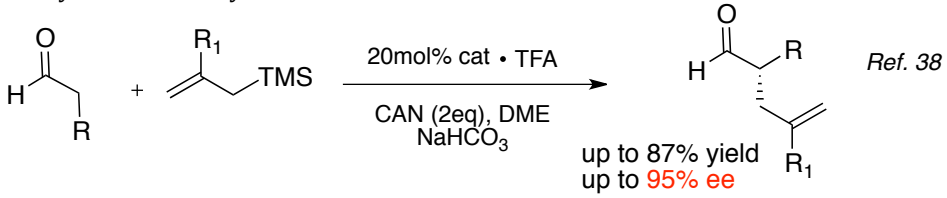
Merging both catalytic cycles would enable C-C bond formation by allowing enamine intermediate and electrophilic palladium π-allyl complexes. Reductive elimination and subsequent hydrolysis of the iminium intermediate would regenerate de Pd(0) and amine catalyst.[35].

MacMillan group in 2007 introduced a new mode of organocatalytic activation, termed singly occupied molecular orbital (SOMO) catalysis[28], which has been described in the paragraph 1.2.

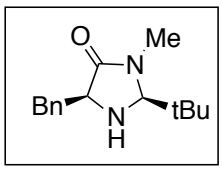
Enantioselective SOMO catalysis is a unique and versatile mode of organocatalytic activation that features the transient generation of a 3 π-radical cation specie, which can participate in asymmetric bond construction with a variety of π-rich nucleophiles or electron neutral SOMO-philes.[28] MacMillan group have successfully utilitzed this activation mode to describe different reactions in asymmetric catalysis such as α-allylic alkylations[28a], α-enolation[28b], α-vinylation[36], α-chlorination, α-allylation

ketones[37], intramolecular α- allylation aldehydes[38] and α-arylation of aldehydes and ketones,[39] provide a wide range of precursors in natural products and medicinal agents synthesis. In 2008, MacMillan group introduced the marriage of two concepts, photoredox catalyst and organo-catalyst in enantioselective catalytic α-alkylation of aldehydes.[40]

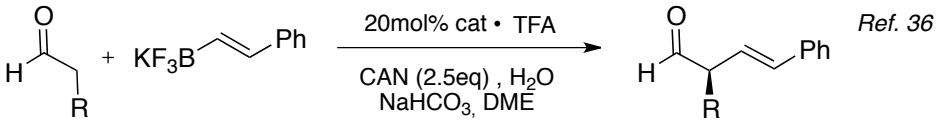
1. α-allylation of aldehydes



Ref. 38

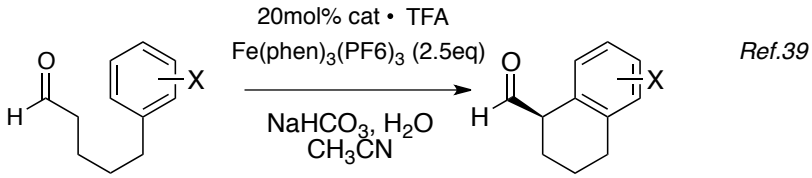


2. α-Vinylation of aldehydes



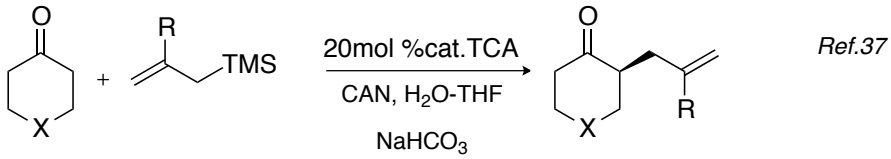
Ref. 36

3. α-Arylation of aldehydes



Ref.39

4. α-Allyltion of ketones



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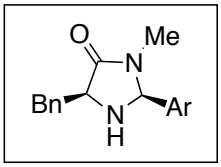
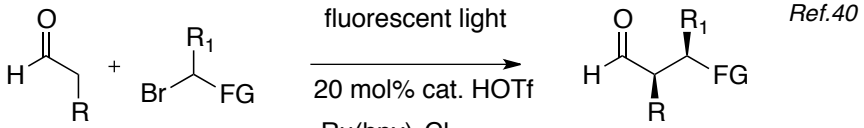
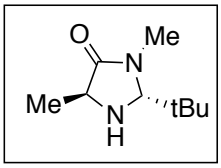


5. α-Alkylation of aldehydes. Photoredox/organocatalysis



Ref.40

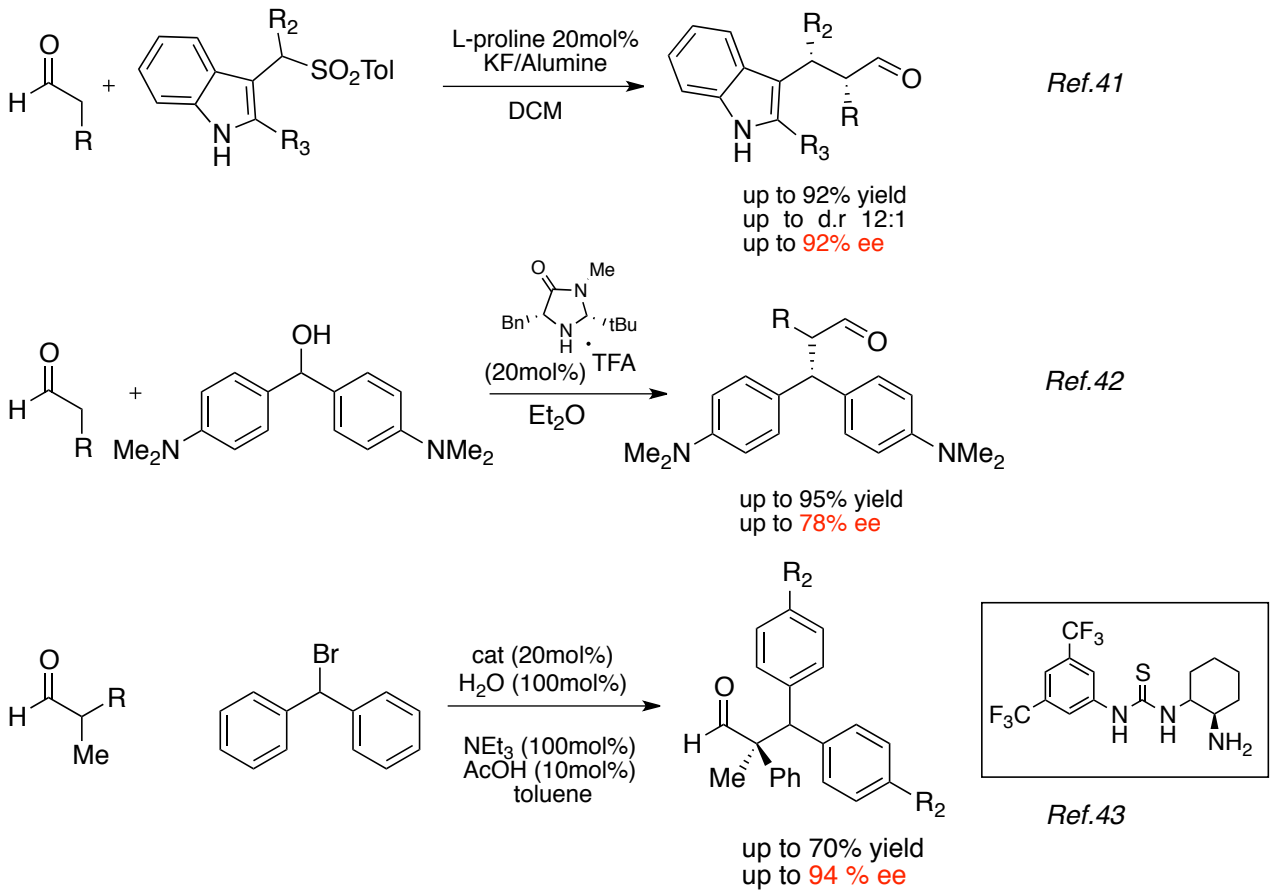


Scheme 19. Reactions of SOMO catalysis and photoredox by MacMillan group

This new asymmentric alkylation methodology proposed a dual-catalysis from alkylation of aldehydes. The proposed mechanism was the generation of π-electron-rich enamine from amine catalyst and

electron-deficient alkyl radical via reduction of an alkyl bromide with a Ru photoredox catalyst. (Scheme 20)

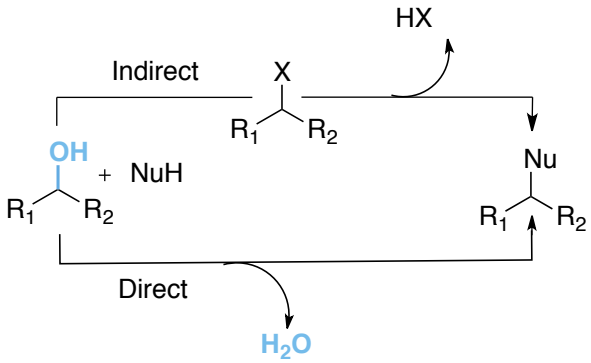
Other novel approach in the α-alkylation of aldehydes has been the generation of stabilized carbocations that can intercept the enamine intermediate to perform a new strategy for the stereoselective α-alkylation of aldehydes. Two publications appeared in the same time, one from Melchiorre group[41], that introduced sulfonylindoles as suitable electrophile precursors, that sulfonyl moiety was a good leaving group to generate electrophile species that is able to react with enamine specie to afford α-alkylation products with indolic core in good yields and stereoselectivity. And other work from my group, Cozzi group[42] that described the stereoselective α-alkylation of aldehydes by S_N1 type reactions of alcohols. In this study of the basis of the electrophilicity introduced by Mayr´s scale, stable carbocations, generated by alcohols were employed for exploring the direct nucleophilic enantioselective substitution. Cozzi group hypothesized the α-alkylation of aldehyde could be realized by using enamine catalysis coupled with the generation of stabilized carbocations from alcohols. Recently, Jacobsen and co-workers[43] reported the enantioselective α-alkylation of aldehydes via SN1 type reaction using primary thiourea derivatives as catalysts that was able to induce the alkylation pathways from simple carbocations via anion abstraction through the H-bond donator catalyst.



Scheme 20. α-alkylation of aldehydes via S_N1 type reaction

2. S_N1-type reaction

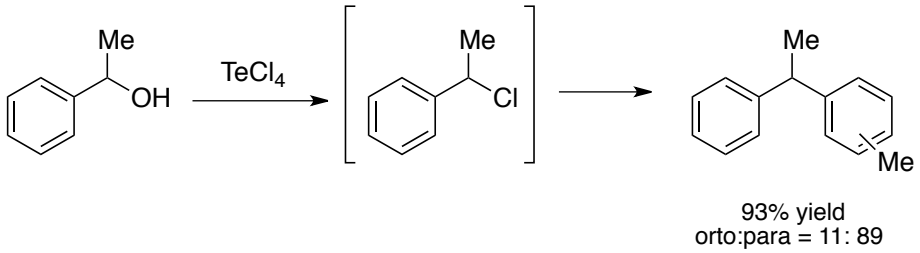
Nucleophilic substitution of alcohols is an important process used in the synthesis of organic compounds. Normally the alcohol is activated towards the substitution by formation of an alcohol derivative, bearing a better leaving group (i.e. tosylate, halides) In some cases, the alcohols are transformed into the corresponding halides (bromide or iodide). However the formation of the corresponding halide requires one additional step, and the process generates many waste or byproduct. In addition, bromide or iodide can be slightly toxic compounds. Less toxic alkylation reagents such as alcohols would improve the conditions in the reaction, which become more environmental friendly. Thus, the direct nucleophilic substitution of alcohols offers a potential solution to environmental issues, producing water as by-product of the reaction. However, hydroxide group is a poor leaving group and therefore the activation is usually necessary, through the substitution of hydroxide group for better leaving groups.



Scheme 21. Diagram Nucleophilic substitution

In this chapter is reported our studies in the recent development in direct substitution of alcohols. In particular alcohols able to form relatively stabilized carbenium ion were used. Benzylic, propargylic and allylic alcohols were investigated recently as suitable precursors through S_N1 type reaction using Lewis acid and Brønsted acids.[44]

In 1887, Charles Friedel and James Crafts introduced one of the first reaction using Lewis acid in organic synthesis, but also the first example of what is now considered the first Friedel-Crafts reaction.[45] In 1986, Uemura and co-workers investigated the chlorination of benzyl and alkyl alcohols mediated by $SeCl_4$ and $TeCl_4$. In the studies they discovered the formation C-C bond forming, thus their work was the first description of a catalytic F.C alkylation using benzyl alcohol.[46] (Scheme23)



Scheme 22. Friedel-Crafts reaction

Generally, the carbenium ions are believed to be unstable species and highly reactive; however there is a quantitative approach to classify the stability and reactivity of carbocations. A quantitative definition of activated alcohols can be derived from stability of carbocation generated by alcohols. If the carbocation is very electrophile and it reacts to diffusion limit, only a limited range of nucleophiles will be able to intercept the presence of carbocation. Mayr's group has investigated all these concepts of electrophilicity and nucleophilicity. Several can be rationally designed through the use of Mayr´s scale of reactivity [47]

In a recent review [44] were described many methodologies for the direct nucleophilic S_N1 type reaction using catalytic amount of Brønsted acid or Lewis acid.

Direct substitution of alcohols with catalytic amount of Brønsted acids

Only a few groups have presented the direct substitution of alcohols through Brønsted acids. Sanz described the nucleophilic direct substitution of secondary o propargylic alcohols by catalytic amount of Brønsted acids, in particular p-Toluensulfonic acid (pTSA, pKa -5). [48]

However, the major contribution in S_N1-type reactions has been described by the activation of alcohols through catalytic amount of Lewis acids.

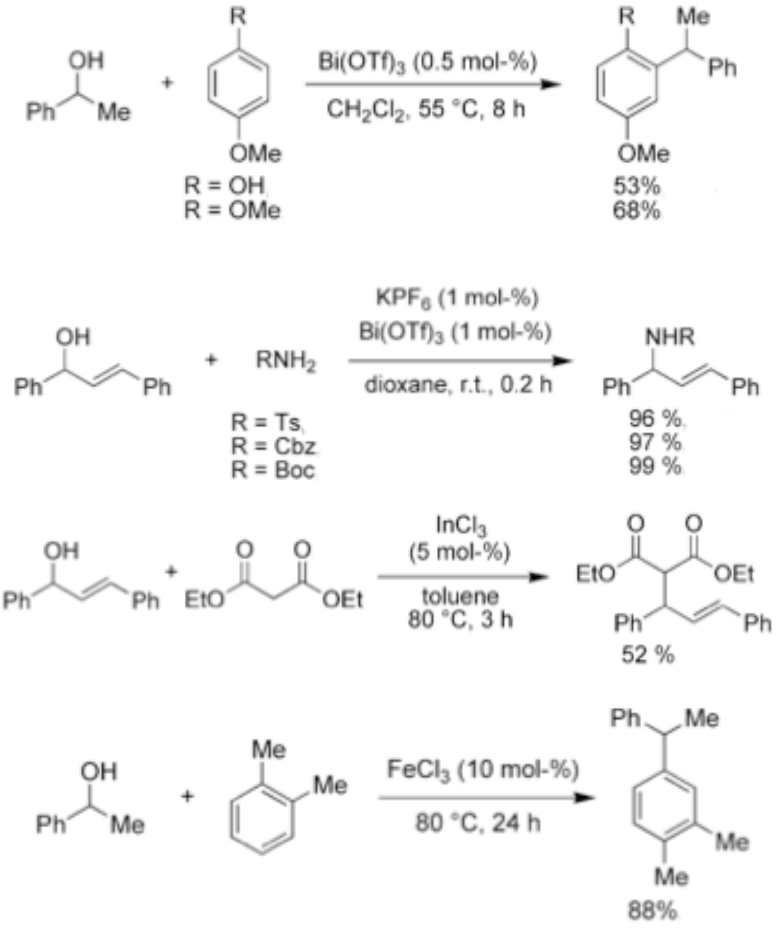
Direct substitution of alcohols with catalytic amount of Lewis acids

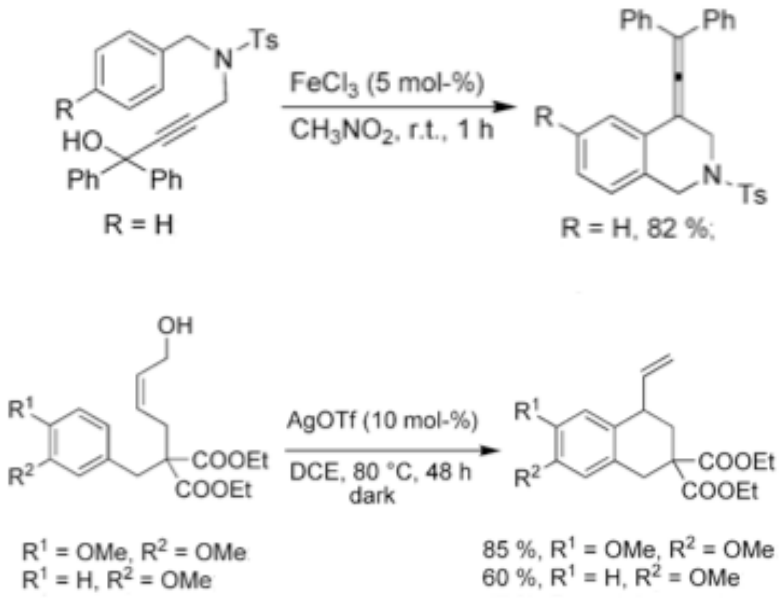
Bismuth(III) catalyzed benzylation of arenes with alcohols was described by Rueping group.[49] The use of $BiCl_3$ in catalytic amount was described by Zhan and co workers[50] in the substitution reaction of propargylic alcohols with carbon or heteroatom centred nucleophiles. Indium salts were reported by Shibasaki and Matsunaga in 2007. They described the reaction of propargylic alcohols with amines in the presence of $Bi(OTf)_3$ / KPF_6 .[51] Borane as Lewis acid, was reported by Li and co-workers[52] in a catalytic F.C intermolecular cyclization of iodinated allylic alcohols. Baba and co-workers[53] reported the use $InCl_3$ in the direct substitution of allylic alcohols with malonate.

Other S_N1 type reaction using In(III) as a catalysts was the catalytic amination of a Baylis-Hillamn adduct promoted by $In(OTf)_3$.[54]

Iron is a potential Lewis acid, poor toxic and cheap metal; other propriety is the tolerance of a wide variety of functional groups and to a different nucleophiles. Several groups studied the direct substitution of allylic and benzylic alcohols with $FeCl_3$ as catalyst.

Many other metals and complexes, apart those cited here were reported in the cited review.[44] Is worth to mention, for our discussion the studies presented by Olah and co-workers[55] about the structure resonances of propargylic cations and the introduction of a metal stabilized the propargylic carbocations have been employed in S_N1 type reactions. Nishibayashi and co-workers[56] studied the reactivity of Thiol-bridged diruthenium complex in propargylic alkylation in presence of different nucleophiles. Other metal complex as Au(I), or Pd(II) have been reported as effective way in S_N1 type reaction of activated alcohols.[44]





Scheme 23. Carbocations generated by Lewis acids.

In conclusion, the carbocations generated by the treatment of alcohols with Lewis acids o Brønsted acids can be considered new synthetic targets for nucleophiles. By taking the challenge that the employment of these species are imposing, new processes can be certainly realized. To include in the challenge, stereoselective transformations that are using carbenium ion are certainly the most difficult, as in many S_N1-type reaction the carbenium ion are attached by nucleophiles at the same manner to the top or to the bottom face.

As we will present in the next chapters, we have taken this challenge and thanks to the opportunity offered by organometallic and organocatalysis methodologies, we have discovered and studied novel stereoselective S_N1-type reactions.

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Chapter 2. Merging Organocatalysis with an Indium (III)- Mediated Process: A Stereoselective α-alkylation of Aldehydes with Allylic, Benzhylic and benzhydrylic alcohols.

I. Introduction general

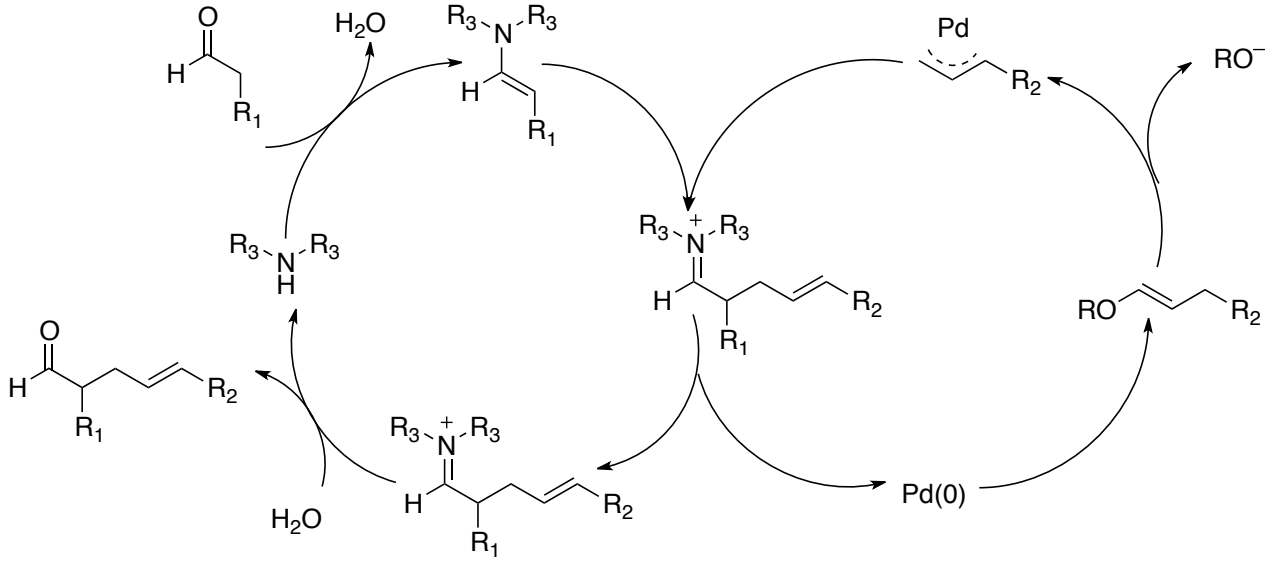
1. Combining Organocatalysis and metal catalysis

The asymmetric catalysis involves now both fields of the organometallic catalysis and organocatalysis.[1] The organic reactions promoted by transition metals catalysts have been established as a powerful tool in organic synthesis for the efficiency and versatility.[2] On the other hand, organocatalysis has grown up to become one of the most useful methodology in organic chemistry, the use of small organic molecule as catalyst in organic transformations.[3] One advantages in organocatalysis is which can promote various organic transformations through unique activation mode, as compared to transition metal. Therefore the combination between organocatalysis and organometallic catalysis can promote a new approach in the synthesis of intermediates for natural products or pharmacologic products. Thus in the recent years, the concept to combine transition metal catalyst and organocatalysis has appeared as a new strategy for developing new reactions and to solve problems not possible resolved by simply employing one of the two catalysts. [4]

The α-alkylation of carbonyl compounds is a fundamental carbon-carbon bond forming reaction in organic synthesis.[5] The direct α-alkylation of non activated aldehydes and ketones is challenging due to competing side reactions, such as aldol -condensation, Cannizzaro or Tischenko reactions, and N-or O-alkylations.[6] Therefore, there are a few methods for the catalytic intermolecular α-alkylation of non activated aldehydes and ketones using metal catalyzed reactions. In general these α-alkylation of carbonyl compounds are performed using stoichiometric amount of metals or additives. Tamaru and co-workers[7] reported an α-allylic alkylation of aldehydes possible in presence of catalytic amount of palladium and a slight excess of Et_3B.

In the field of organocatalysis, many groups have studied the α-alkylation of aldehydes and ketone using chiral primary or secondary amines as catalyst through different mode of activation. One pioneering group was List and co-workers[8] that reported the amino acid catalyzed intramolecular α-alkylation reaction. Cordova's group was the first to report the concept of combined transition metal and aminocatalysis with the direct catalytic intermolecular α-allylic alkylation of aldehydes and cyclic ketones in an achiral fashion.[9] This novel catalytic reaction the α-allylic alkylation of aldehydes and cyclic ketones with allyl acetates could be accomplished by combining enamine- and transition-metal catalysis in one pot. Thus, the merging of the two catalytic cycles would enable to activate electrophile

and nucleophile. (Scheme 1) Ding[10] proposed the first reaction combining π-activation by silver salt and enamine catalysis by proline to afford the product 1,2-dihydroisoquinoline derivatives. (Figure 1) Therefore, transition metal and amine catalysis can appear as a new methodology for the development of new reactions and expanding the concept of one pot combination of transition metal and enamine catalysis to other catalysts and electrophiles to render a reaction highly enantioselective.



Scheme 1. Mechanism combining transition-metal and enamine catalysis

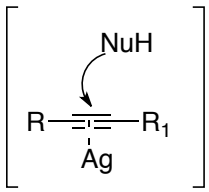
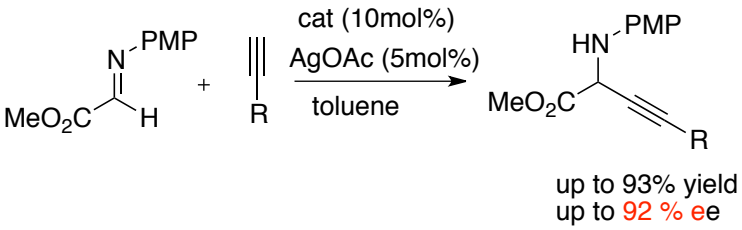
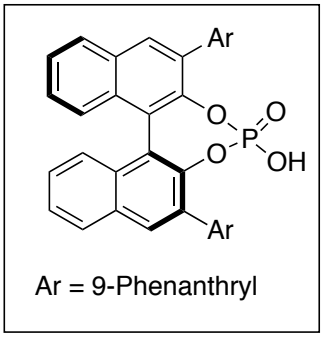


Figure 1. π-acid activation of C-C triple bond toward nucleophilic attack

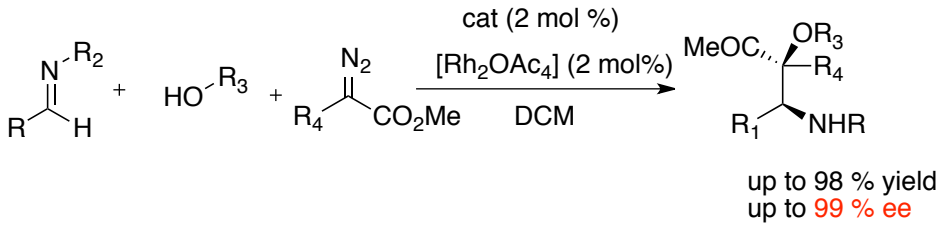
In organocatalysis this new concept developed new reactions combining metal catalysis with different mode of activation in organocatalysis. One of them has been has been by hydrogen bonding or ion pair complexes using Brønsted acid catalysis.[11,12] Combining Brønsted acids and transition metal catalyst to perform a dual catalysis enantioselective was reported by Rueping group,[13] which studied the asymmetric alkynylation of α-imine ester, combining chiral binaphtol-derived phosphoric acid catalyst and silver salt. Furthermore, Hu, Gong and co-workers [14] developed the asymmetric variant of three multicomponent reaction with the dual catalyst approach. Using $Rh(OAc)_4$ catalyst three components: diazo compound, alcohols and imines. Other work was the enantioselective construction of quaternary stereocenters through the enantioselective α-allylation of α-branched aldehydes using transition metal complex $Pd(OPPh_3)_4$ with (R)-TRIP as chiral Brønsted acid, that was studied by List and co-workers.[15] This new approach for the enantioselective construction of quaternary stereocenters has emerged as an important instrument in organic synthesis.

1. Activation a-imine ester by Rueping group

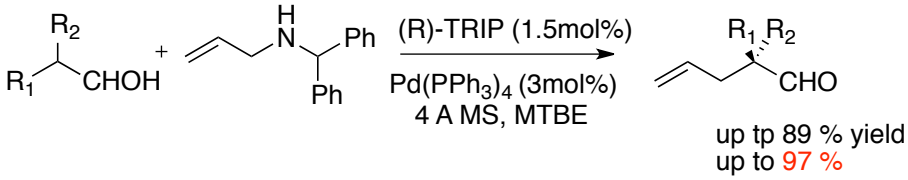




2. Multicomponent reaction by Gong and co-workers.



3. a-allylation of propionaldehydes by List group



Scheme 2. Transition metal and Brønsted acid catalyst

2. Stable carbocations Mayr's Scale

On the other hand, the generation of stable carbocations has been employed as alternative alkylation agent to perform enantioselective intermolecular α-alkylation of aldehydes. The pioneering groups have been Melchiorre and co-workers[16] and Cozzi group[17] that reported independently two works using stable carbocations with enamine catalysis. Recently Jacobsen group[18] reported the enantioselective α-alkylation using hydrogen bond catalyst through anion binding.

Mayr has developed a kinetic method for predicting the rates of reactivity between electrophiles and nucleophiles, which established that some carbocations and related electrophiles could be characterized by one electrophilic parameter (E), that is useful for predicting rates of reactions with nucleophiles.[19] The same from nucleophiles was assigned two parameters (N) and s. Eq[1][20]

$$\log k = s\,(E+N)$$

This rate equation established a table of reactivity between electrophiles and nucleophiles, showing in the Figure 2. A easy interpretation of the table should be: a nucleophile that react with the parent benzhydrylium ion on the top of Figure 2 within 1 min would require 20 billion years to react with the carbenium ion at the bottom. On the other hand, a comparable reactivity range is established by nucleophiles listed, which are arranged according the increasing nucleophilicity from the top to bottom. Thus the nucleophiles in the top do not react with the electrophiles at the bottom, while the nucleophiles at the bottom react with the electrophiles at the top with diffusion control. And the nucleophiles and electrophiles with similar range in Figure 2 can be combined with activation control.

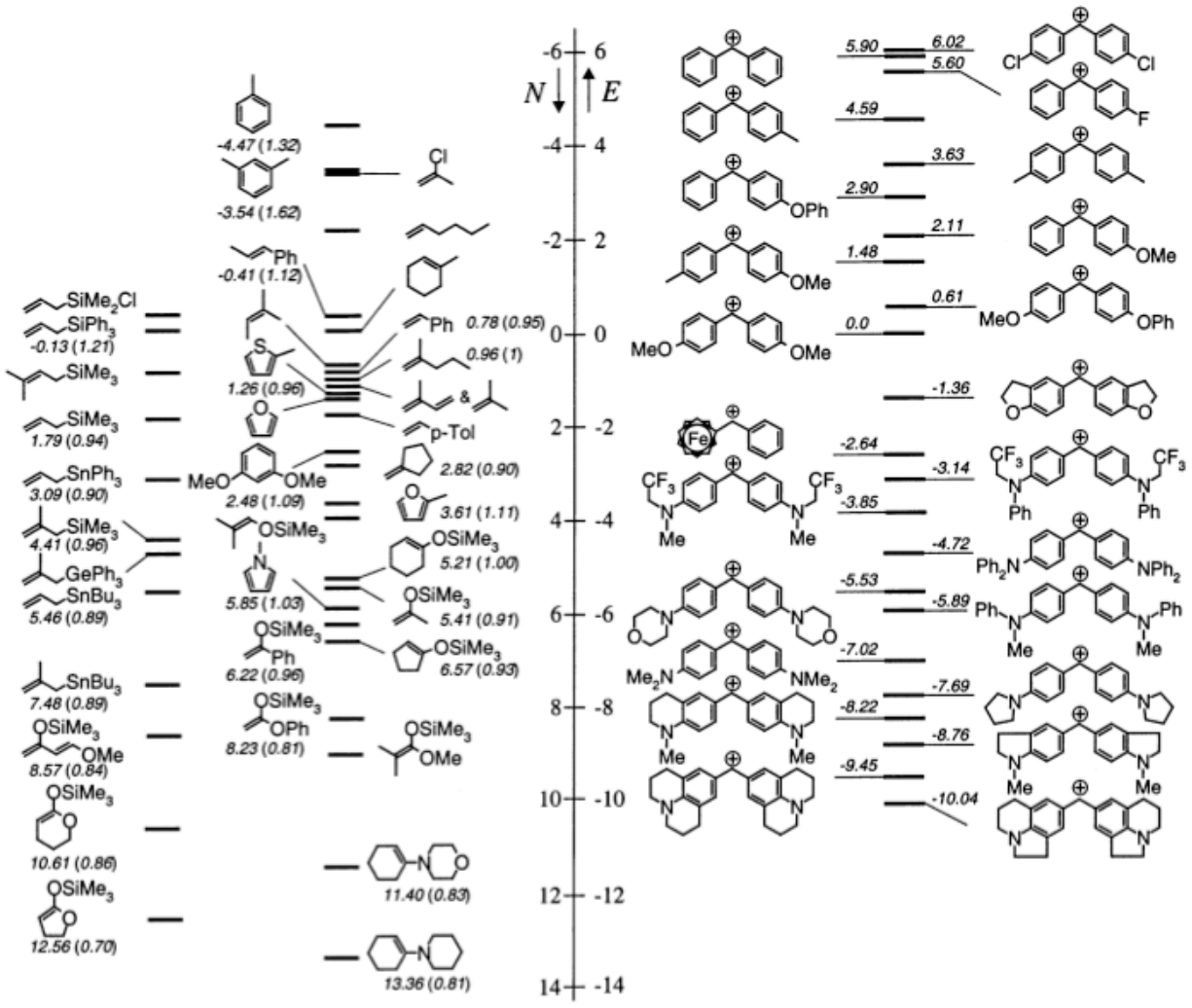


Figure 2. Scale of reactivity between Nucelophiles and electrophiles

The key of combination of nucleophiles and electrophiles that will take place in synthetic transformations, is related to reaction rate. For qualitative analysis from Mayr's group, can expect electrophiles-nucleophiles combination take place if **N+E > -5.** [19c] Since diffusion limit is reached at K = 10^5-10^{10} $M^{-1}s^{-1}$ when N+E > 10. To explain this equation is showing the Figure 3, where in the green part are found the most synthetic used reactions, in the red part, the nucleophile-electrophile combination take place through diffusion, not control in the reactivity.

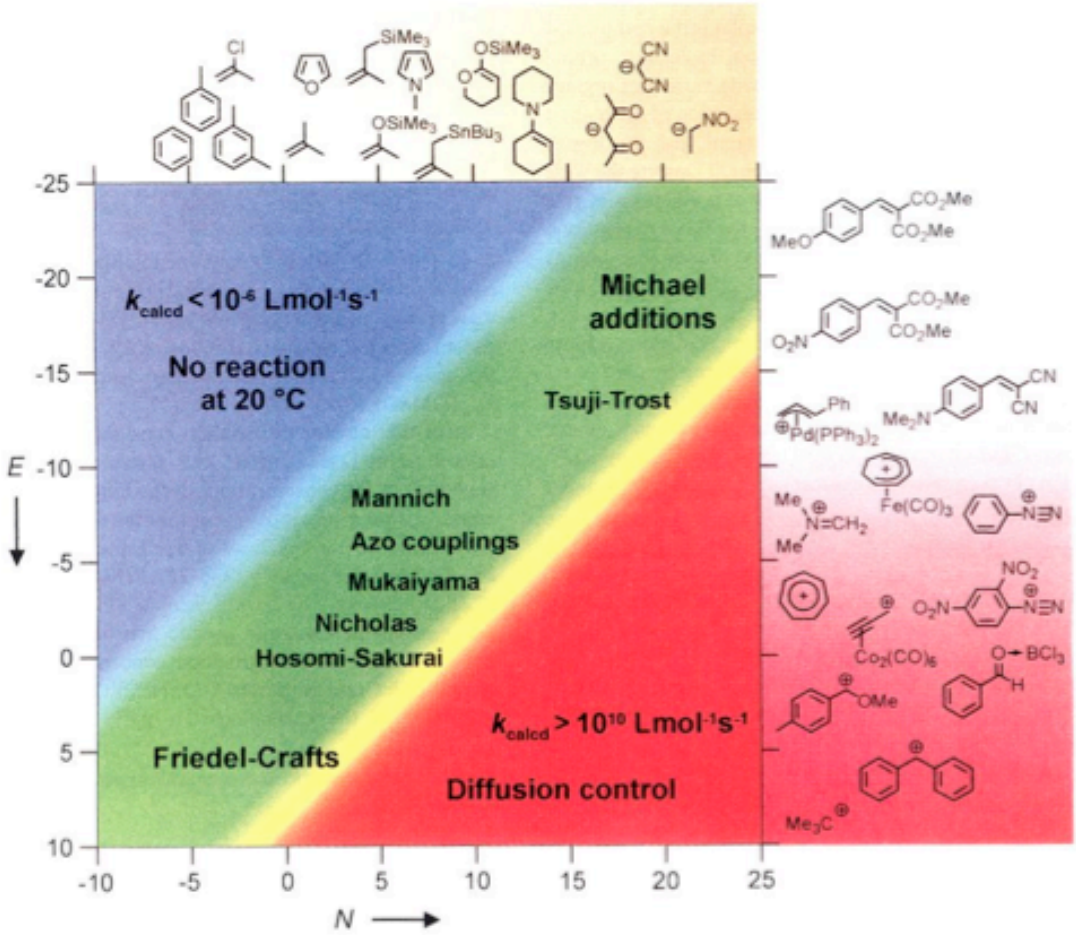


Figure 3. Table of reactivity between nucleophiles and electrophiles

From the reactivity parameters N, E and s that have been derived from reactivates toward of the reference compounds can be expected to provide new predictions for nucleophiles and electrophiles, without the need for reparametrization of the parameters.

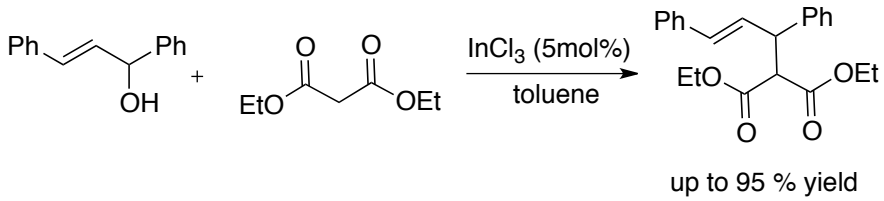
3. Stereoselective allylic alkylation

Allylic alkylation through metal catalyst. S_N1 reaction

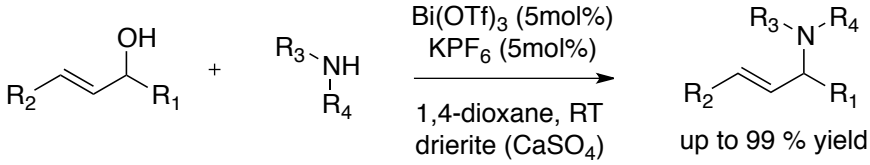
The reactions of allylic alkylations have been performed with activated nucleophiles or acylated allyl alcohols, the use of direct substitution of allylic alcohols could be considered as a clean process for the generation of water as only side product. The allylic alkylation represent an important transformation in organic chemistry and various metal processes have been describes for this reaction. Thus, the direct activation of allylic alcohols represented a powerful method in organic chemistry. Baba group[21] developed a direct process C-C bond formation from allylic alcohols and different activated nucleophiles in presence of Indium catalytic. Recently, two independently group reported the use of bismuth catalyst in direct substitution of alcohol with different nucleophiles. One work was from Rueping group [22] that reported the first Bismuth catalyzed direct allylic alkylation with different 1,3-

dicarboxylic compound using a free allylic alcohol as electrophile. Other work from Shibasaki and co-workers[23] presented bismuth catalyzed direct substitution of allylic, propargylic and benzylic alcohols with amides derivatives. Thus, the allylic alkylations presents an important transformation and various metals-catalyzed processes have been describe in the literature. (Scheme 3)

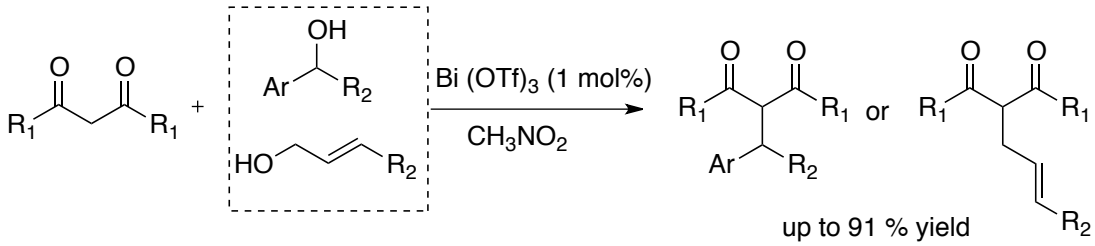
1. Direct allylic alkylation catalyzed by $InCl_3$. Baba group



2. Direct substitution of hydroxy group with sulfoamides, carbamates and carboxamides catalyzed by $Bi(OTf)_3$. Shibasaki group.

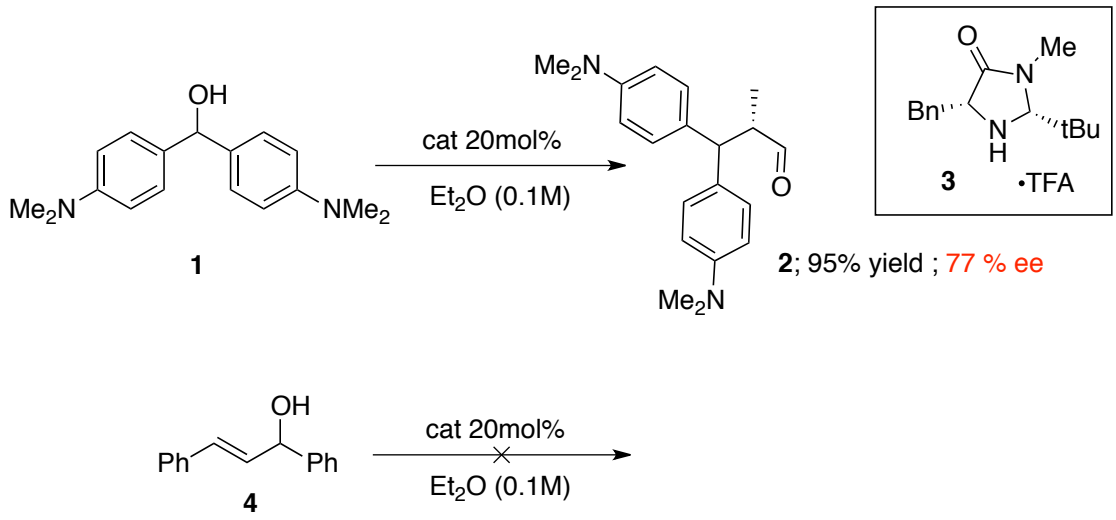


3. Direct allylic alkylation of 2,4-pentanediones. Rueping group



Scheme 3.

On the base of electrophilicity parameters introduced by Mayr's scale,[19] our group hypothesized the α-alkylation using less reactive carbocations generated from alcohols, which react with highly nucleophile in Mayr's scale as enamine that reported the enantioselective α-alkylation of aldehydes through S_N1 type reaction using stabilized carbocations and enamine catalysis.[17] The benzylic carbocations generated in situ in the α-alkylation of aldehydes from this work are positioned from -7 to -1 of the Mayr's scale, limiting the substrates used in the reaction. The alcohols positioned in the limits of reactivity under -7 on the Mayr's scale, such as 1,3-diphenyl-allyl alcohols **4**, were un-reactive in the conditions of reaction, and only self-condensation of aldehyde was observed. (Scheme 4)



Scheme 4. Model of reaction for stereoselective α-alkyaltion of aldehydes

The generation of allylic carbocations from corresponding alcohols and their reaction with aldehydes in presence of an organocatalyst could be considered a new strategy for enantioselective allylic alkylation. Thus to promoted the formation of stabilized allyl carbocations was proposed to use Lewis acid as co-catalyst. In this work has been reported a stereoselective α-alkylation of aldehydes with allylic alcohols, merging two concepts enamine catalysis and metal catalysis.

A Stereoselective α-alkylation of aldehydes with allylic alcohols

II. Results and Discussion

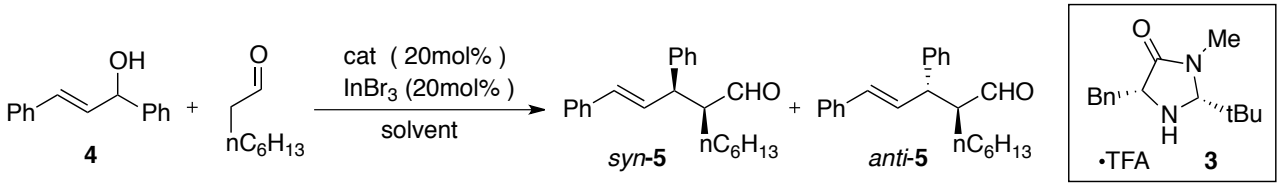
The direct substitution of allylic alcohols with enamine specie as nucleophiles is considered an ideal process for the C-C bond formation because the transformation of the starting material would not be required and the generation of water as the only side product. However, the main limitations of this strategy are the catalytic activation of alcohol is generally difficult because of the inefficiently ability of the hydroxide group as leaving group, and the range of possible nucleophiles is limited in this reaction.[23]

The first experiments were investigated with 1,3-diphenylallyl alcohol **4** as a model substrate with octanal and 20 mol% of MacMillan catalyst **3** TFA using various acids as co-catalyst.

Brønsted acids were insufficiently reactive to perform the stabilized carbocation from allylic alcohol. The screening of Lewis acid such as $Cu(OTf)_2$, $Zn(OTf)_2$, $La(OTf)_3$, $Bi(OTf)_3$, $AuCl_3$, Ph_3PAuCl gave either a complex mixture of products or not presence of product.

Recent advances in activation of allylic alcohols have been based in the use of $InCl_3$ as emerged as a powerful direct nucleophilic substitution of alcohols.[21] We were attracted to the use of indium (III) by

the compatibility of indium salts with water and basic amines. The model reaction was tested with different indiums salts and indium complex. On the base of these results, $InBr_3$ was found to act as the best co-catalyst affording the desired product **5** in 50% yield (table 1, entry 5). Other indiums salts gave lower yield or poor enantioselectivity or not product was observed. The screening the solvents showed that only DCM gave the desired product in 50% ee (table 1, entry 5), other solvents were ineffective in the reaction.

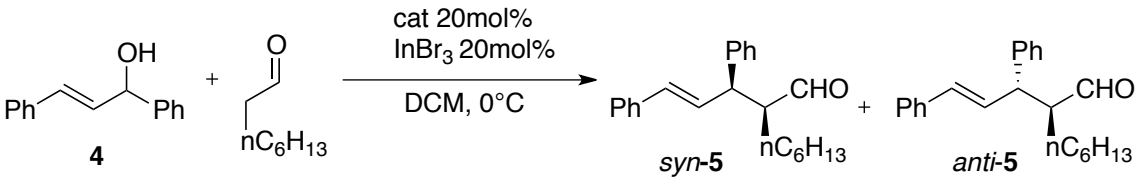


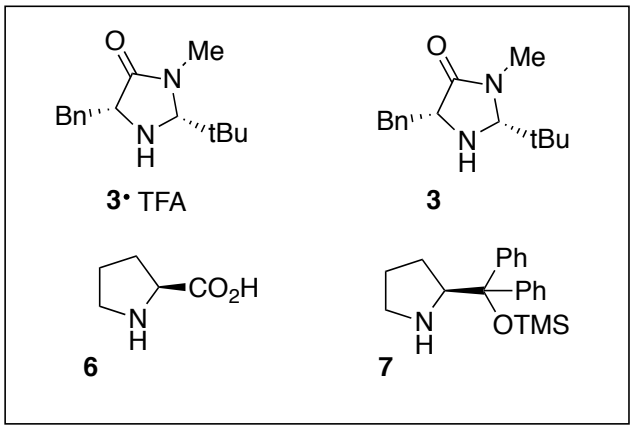
entry[a]	Time (h)	solvent	d.r[b]	ee (%)[c]
1	60	toluene	---	---
2	60	tBuOMe	---	---
3	60	CH_3CN	---	---
4	60	CH_3NO_2	---	---
5	12	DCM	1:1	50

The reactions were performed at r.t with 1 eq of alcohol **4**, 3eq of octanal in presence of 20 mol% of $InBr_3$ (0.33M solution in CH_3CN) was added and the reaction was running until complet conversion, controlled by TLC.[b] for all the reactions the d.r ratio measured by ^{1}NMR spectroscopy. [c] Determined by HPLC analysis. The syn and anti had the same enantiomeric excess.

Table 1. Model reaction screening of solvents

Next step to optimize the reaction was examined combination of different catalysts and $InBr_3$ at low temperature. The most active catalyst was imidazolidinone derivative **3** without TFA, which afforded the allyl alkylation product **3** in good yield and highly enantioselectivity 82% ee at O°C. (table 2, entry 4). Unfortunately, employing L-proline or proline derivative catalyst such as **6**-**7** were ineffective to promote the reaction. (table 2, entry 2-3) In decrease the temperature at -20°C, the reaction was so slowly and poor conversion into product was obtained.





entry[a]	catalyst	time (h)	Yield (%)[b]	d.r[c]	ee (%)[d]
1	3 TFA	12	71	1:1	71
2	3	24	---	---	---
3	7	24	---	---	---
4	5	12	70	1:1	82

[a] the reactions were performed at 0°C with alcohol **4** (1eq), aldehyde (3eq) in presence of 20mol% catalyst and $InBr_3$ (20mol%, 0.33M solution in CH_3CN).[b] Yield after chromatography purification. [c] For all the reactions the d.r ratio was determined by ^{1}HNMR spectroscopic analysis. [d] Determined by chiral HPLC analysis of the isolated products or of the corresponding alcohol. The syn and anti diasterisomers had the same excess enantiomeric.

Table2. Organocatalytic α-alkylation of octanal with allylic alcohol in presence of $InBr_3$ and different catalysts

To improve the efficiency of the reaction was used only 5 mol% of $InBr_3$ without any change in enantioselective and yield than using 20mol% $InBr_3$ (70% yield, 80%ee), but the time of reaction increase 72 hours. Using a complex $InBr_3$-BINOL the reaction took place in 5 hours with 80% enantioselectivity.

The limitation in this reaction was the moderate enantioselectivity and poor diastereselectivity (1:1) to obtained in the reaction using 1,3-diphenyl allylic alcohol **4** and different linear aldehydes. According to the addition of aldehydes to benzhydrols the sterical hindrance of benzhydrilic carbocations is controlling the d.r of the reaction[17], then to improve the stereoselectivity was planned to increase the hindrance of carbocation generated in the reaction.

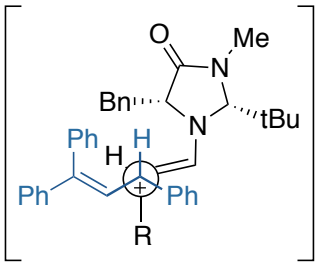
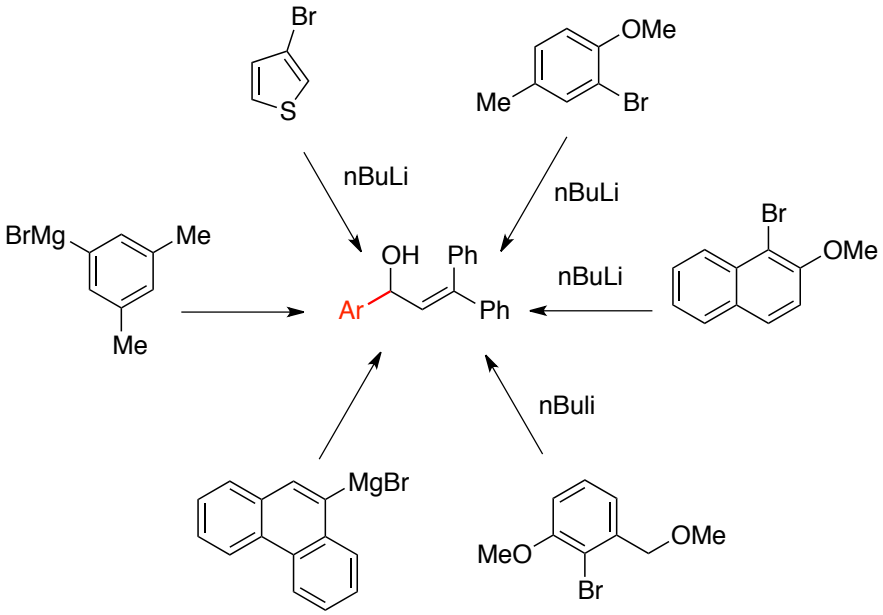


Figure 4 Hypothesis about approach carbenium ion versus enamine

The hypothesis was increasing the steric hindrance of allyl compounds would give improved selectivity in the reaction. Thus, the introduction of phenyl substituents in β-position could increase the diasteroselectivity in favour of the *syn* diasterisomer. (Figure 4)

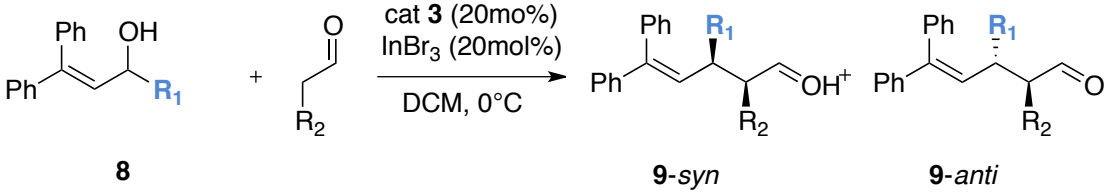
1,1,3-triphenylallyl carbocations were easy generated, in Mayr's scale were positioned at E = + 1.25.[25] Moreover the nucleophiles were shown to attack the less hindered position of allylic cation (Figure 4). Thus, a series of allyl substrates were synthetized by addition of lithium or magnesium aryl compounds to β-phenylcinnamaldehyde. (Scheme 5)

The reactivity of the alcohols was dependent on the stability of the corresponding allyl cation, for example 4, 4-dimethyl-1,1-diphenyl-pent-1-en-3-ol and 1,4,4-triphenyl-but-3-en-2-ol was unreactive as substrates under the reaction conditions.



Scheme 5. Starting materials from the synthesis of different allylic alcohols

After optimizing the reaction conditions, which included solvent, temperature, catalysts and co-catalyst, good yields and stereoselectivity were achieved, and the preliminary scope of the reaction was studied. (Table 3)



8 **9**-*syn* **9**-*anti*

entry[a]	R_1	R_2	Y(%)[b]	d.r[c]	ee (%) *syn*[d]	ee (%) *anti*[d]
1	Ph	nC_6H_{13}	**9a**; 70	2:1	90	75
2	Ph	CH_3	**9b**;63	2:1	88 (*2S,3R*)	80 (*2S,3S*)
3	Ph	Bn	**9c**; 90	2:1	89	64
4	Ph	nC_3H_7	**9d**;50	2:1	91	77
5	3-Thiophenyl	nC_6H_{13}	**9e**; 56	2:1	87	56
6	3,5-Me_2Ph	nC_6H_{13}	**9f**; 53	2:1	85	69
7	3,5-Me_2Ph	CH_3	**9g**; 69	2:1	85	73
8	9-Phenanthrenyl	nC_6H_{13}	**9h**; 66	4:1	86	67
9	9-Phenanthrenyl	CH_3	**9i**; 57	4:1	88	75
10	(2-MeO-6-Me)Ph	nC_6H_{13}	**9j**; 65	2:1	88	79
11	(2-MeO-6-Me)Ph	CH_3	**9k**; 50	2:1	93	84
12	2-MeO-1-Naphthyl	nC_6H_{13}	**9l**; 71	3:1	91	68
13	2-MeO-1-Naphthyl	CH_3	**9m**; 75	5:1	94	87
14	2-MeO-1-Naphthyl	Bn	**9n**; 77	5:1	98	65
15	(2-MeO-6-CH_2OMe)Ph	CH_3	**9o**; 65	4:1	95	81

[a] The reactions were performed at 0°C with alcohols **8** (1eq), aldehyde (3eq) in presence of 20mol% catalyst **3** and $InBr_3$ (20mol%, 0.33M solution in CH_3CN).[b] Yield after chromatography purification. [c] For all the reactions the d.r ratio was determined by ^{1}HNMR spectroscopic analysis. [d] Determined by chiral HPLC analysis of the isolated products or of the corresponding alcohol.

Table 3. α-alkylation of allylic alcohols with aldehydes

Introduction of phenyl substituent in β-position increased the d.r in the reaction up to 2:1 *syn* stereoselectivity. (Table 3, entry 1)

Different heteroaromatic and aromatic groups were tested in the optimal conditions using linear aldehydes. For the simple aryl substituent in allylic alcohols good yields and enantioselectivity was obtained in 50-90% yield, 87-91% ee. In all case, irrespective of the aldehydes employed, a d.r radio 2:1 was obtained. (Table 3, entry 1-4). Thus, the increased hindrance of the β-position enhances the steric interaction with the tert-butyl group of the MacMillan catalyst in the transition state (figure 4).

Furthermore introducing differently aryl substituent in position orto as well as 9-Phenanthrenyl, (2-MeO-6-Me)Ph, 2-MeO-1-Naphtyl or (2-MeO-6-CH_2OMe)Ph afforded the allyl alkylation with a d.r to up 5:1 in favour of the syn-diasterisomer. (Table 3, entry 8-16)

The carbocations as **8** (R_1= 2-OMe-1-Naphthyl) with OMe substituent (electron donating group) into orto position from aryl were more stabilized that the carbocation without electron donating group. For example, replacement of the benzhydryl hydrogen in benzhydrylium ions by a styryl group reduces the electrophilicity by 2 to 5 orders the magnitude. Thus, with catalytic amount of Brønsted acid was possible generated the stabilized carbocation that reacted with enamine specie to obtain the allyl alkylation product with a d.r up to 20:1 with enantiomeric excess of 99%ee. (Table 4)

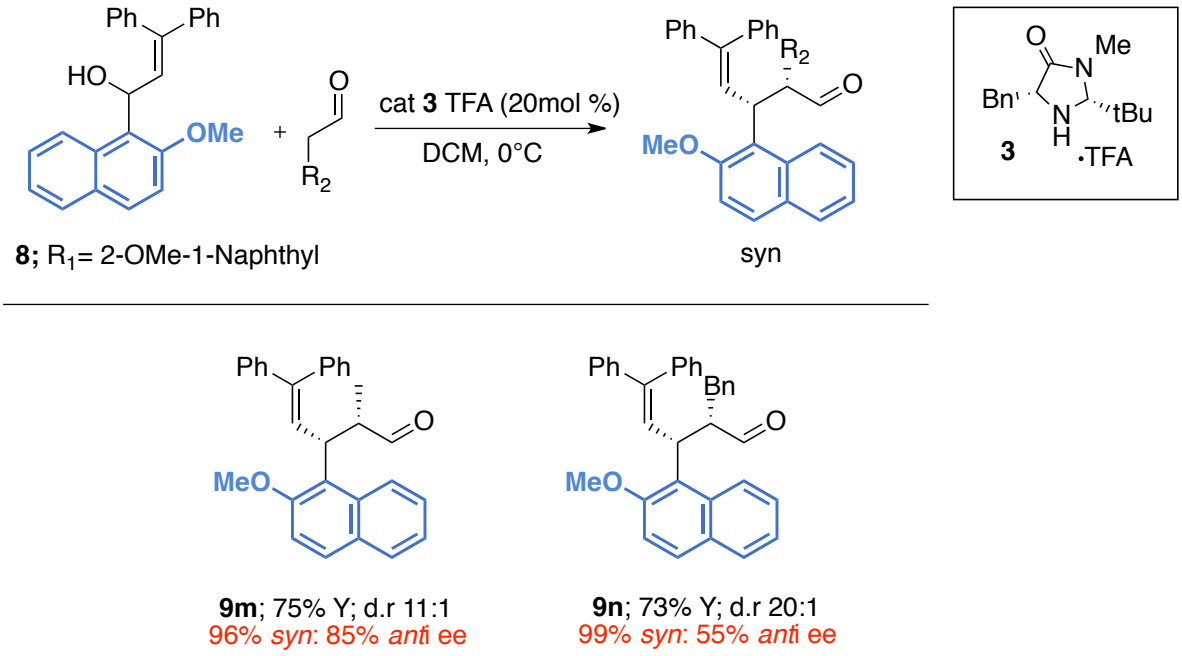
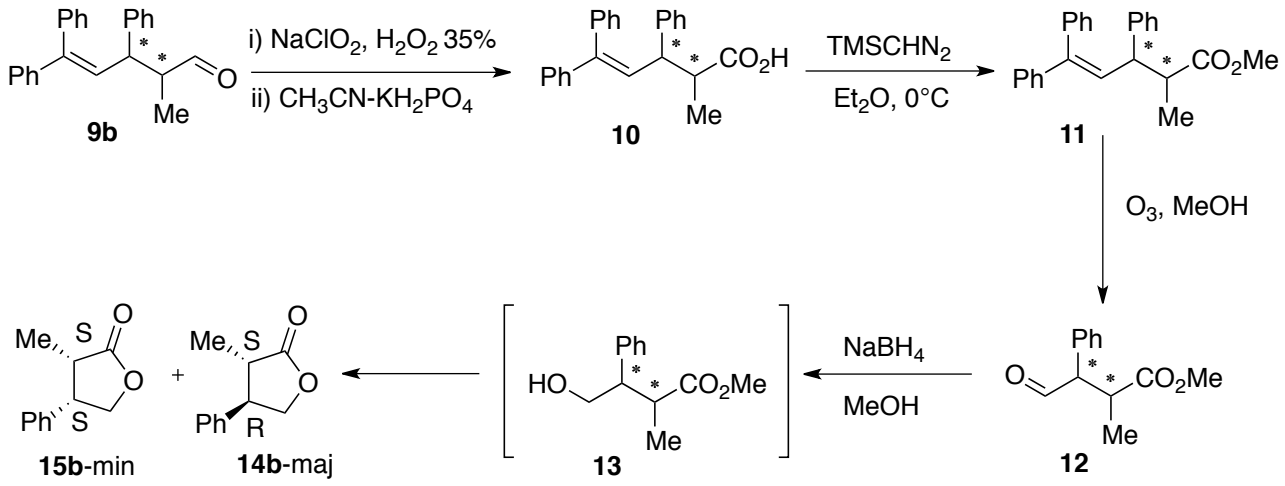


Table 4. Using Brønsted acid as co-catalyst

Determination of absolute configuration

The relative configuration of *syn –anti* adduct were assigned by chemical transformations of compounds **9b** to corresponding lactone. The lactonization gave the product **14b** and **15b**, separated by flash chromatography. (Scheme 6) The chemical shifts and the ^{3}J coupling constant of the separated products were compared to those reported in literature for assigning the *syn/anti* relative configuration.[26] The absolute configuration of the lactones derivatives was assigned on the basis of the time –dependent density functional theory (TD-DFT) calculation of the electronic circular dichroism (ECD) spectra.



Scheme 6. Several reactions were carried out to obtain compounds **14b** and **15b** in 45% yield

In summary, in this work has been reported the use of $InBr_3$ as co –catalyst in the α-alkylation of aldehydes with allylic alcohols. With the successful realization of this previously results using $InBr_3$ was hypothesized that In(III) co-catalyst would also be suitable for the activation of benzhylic alcohols and benzyhydrylic alcohols.

Indium (III) promoted Organocatalytic enantioselective α-alkylation of aldehydes with Benzhylic and benzhydrylic alcohols.

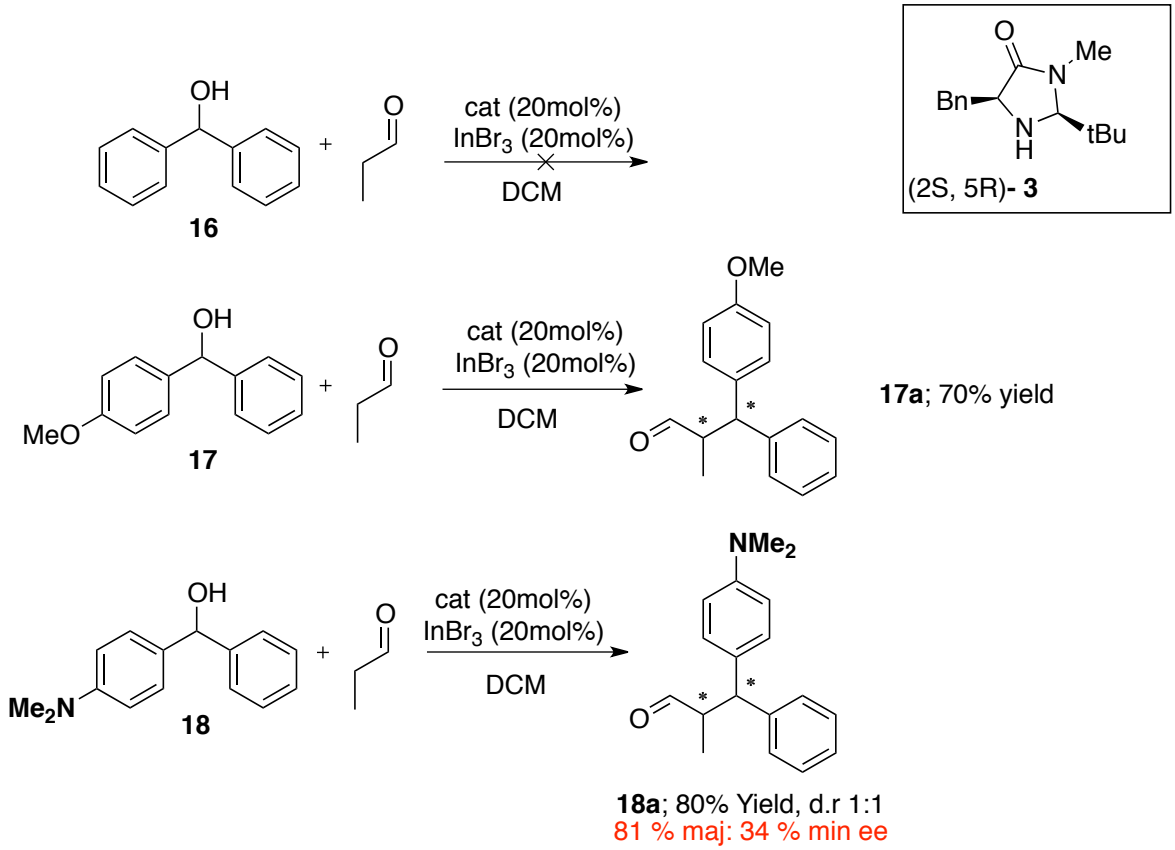
The benzylic and benzhydrylic carbocations have the same behaviour that allylic carbocations, furthermore are positioned in the limits of reactivity over -7 on Mayr's Scale.[19]

The compatibility of indium (III) Lewis acid with enamine catalysis has open a new approach to generate stable carbocation from un-reactive alcohols that are not possible generated through Brønsted acids catalyst. In the work of stereoselective allylic alkylation has been employed the InB_3 as co-catalyst without using palladium or iridium salts to activated the allylic alcohol.[27] Here, to open the scope of this new methodology towards benzylic and benzhydrylic alcohols, substrates that could give access to useful intermediates for the synthesis of biologically active enatioenriched diarylethane products or structure with biologic proprieties. Moreover the development of direct substitution of alcohol is an important task in efficient, economic and ecology valuables transformations.

III. Results and discussion

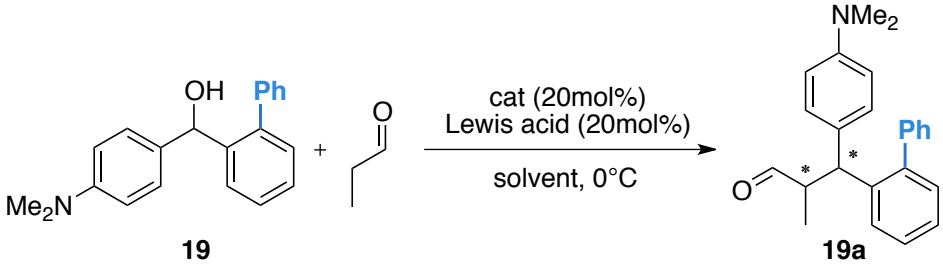
The studies from allylic alcohols with $InBr_3$ have demonstrated that the formation of carbenium ion located at -1 or above the Mayr's scale[19] was possible, and that the formation of carbenium ion throught indium (III) salt can be intercepted by enamine formed in situ with the MacMillan catalyst.

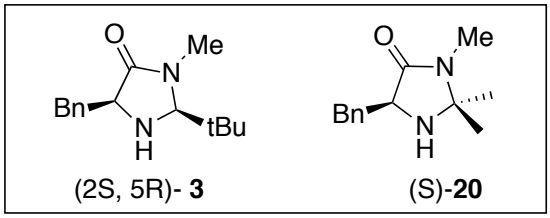
The alcohols **16**-**18** were choose as substrates in the model reaction, using 3 eq of aldehyde, 20 mol % imidazolidinone catalyst (2S, 5R)-**3** , 20 mol % $InBr_3$ in DCM, no reaction was observed without the presence of indium salt. The substrate diphenylmethanol **16** was unreactive, thus in para-position from one aryl group was introduced an electron donating group that stabilized the carbocation generated in situ from reactive alcohol. The p-OMe derivative **17** was rather un-reactive, the conversion in product at r.t took place after 2 days with 70% yield. Other benzhydrylic bearing the methoxy substituent derivatives were considered but in all case the reaction gave poor results. The substrate p-NMe_2 derivative **18** at 0°C gave the desired product in 80% yield, but poor stereo control in the reaction (Scheme 7, d.r 1:1, 81:34% ee)



Scheme 7. Preliminary results with benzhydrylic alcohols

In the work of allylic alcohols was established that the hindrance of the incoming carbenium ion was controlling the stereoselectivity of the reaction. Therefore in order to increase the stereoselectivity with benzhydrylic alcohols was introduced one substituent in position orto. The alcohol **19** was selected as model reaction and the reaction was performed with different indium (III) salts with imidazolidinone derivatives as catalysts in dichloromethane at 0°C. (Table 5)



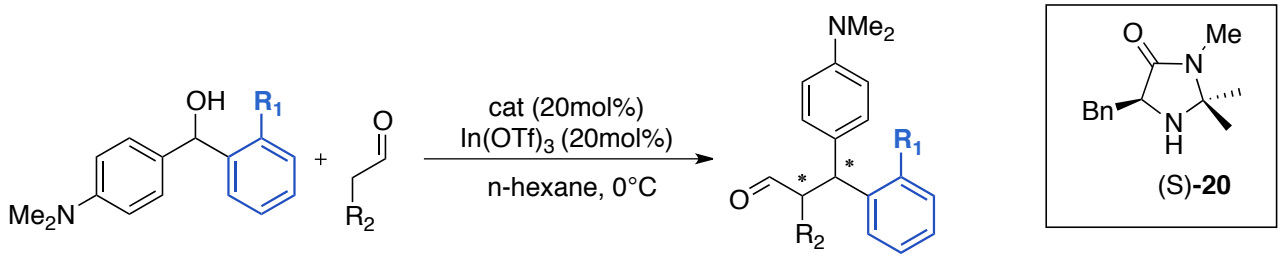


Entry[a]	L.A	cat	solvent	Yield (%)[b]	d.r[c]	ee maj %[d]	ee min%[d]
1	$InBr_3$	3 (2S,5R)	DCM	73	3:1	78	35
2	$In(OTf)_3$	3 (2S,5R)	DCM	80	5:1	79	36
3	$Bi(OTf)_3$	3 (2S,5R)	DCM	75	4:1	70	26
4	$InCl_3$	3 (2S,5R)	DCM	75	3:1	79	40
5[e]	---	3 (2S,5R)	DCM	60	4:1	50	50
6	$In(OTf)_3$	20	DCM	80	7:1	98	56
7	$In(OTf)_3$	20	CH_3CN	50	3:1	97	42
8	$In(OTf)_3$	20	n-hexane	80	5:1	99	85

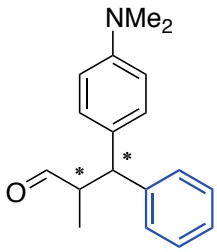
[a] All the reactions were performed at 0°C with 1 eq. of alcohol, 3eq. of aldehyde, 20 mol % cat and 20 mol% co – catalyst at 0°C. Time of reaction 6 hours. [b] Isolate yield after chromatographic purification. [C] d.r ratio was measured on the crude of reaction mixture by ^1H NMR.[d] Enantiomeric excesses were measured by Chiral HPLC [e] the reaction was carried out with 20 mol% TFA.

Table 5. α-alkylation of aldehydes with benzhydrylic alcohols with different Lewis acids and MacMillan catalysts

As revealed in the table 5, using imidazolidinone derivatives (2S, 5R)- **3**as catalyst with $InBr_3$ or $InCl_3$ providing the α-alkylation in good yield to obtain the desired product **19a** 73-75% yield and moderated stereoselectivity d.r 3:1, 79% maj: 35-40 % ee min. (Table 5, entry 1,4) Using $M(OTf)_3$ such as $Bi(OTf)_3$ or $Bi(OTf)_3$ was observed an increase in d.r to up 5:1, but maintaining the reaction efficiency and enantioselectivity.(Table5, entry 2-3) Therefore, $In(OTf)_3$ was chosen as the Lewis acid in the reaction. To study the efficiently of the catalyst, several experiments were performed. The catalyst **20**, first generation MacMillan catalyst, gave excellent results in d.r 7:1 and 98% ee maj: 56 % ee min. (Table 5, entry 6) By varying the solvents, and using catalyst **20** in the reaction good results in terms of enantioselectivity were obtained in 98% yield up to 99% maj ee, the most efficient solvents were apolar solvents such as dichloromethane and *n*-hexane. (Table 5, entry 6-8) Optimized the conditions of reaction and heartened by the previously results, the reaction was tested with different benzhydrylic alcohols to prove the scope of this new methodology for stereoselective α-alkylation of aldehydes. (Table 6)



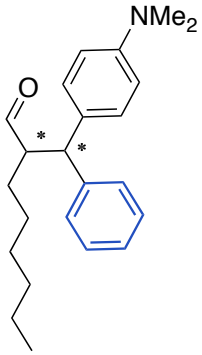
1



80%

98% anti; 96%syn ee

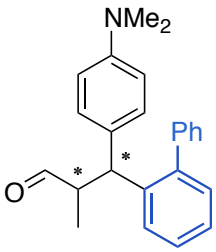
2



85%

89% anti: 81% syn ee

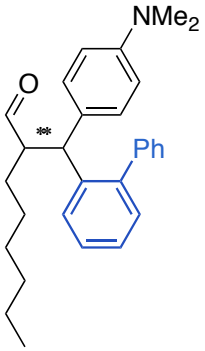
3



90%, d.r 5:1

99% anti: 83%syn ee

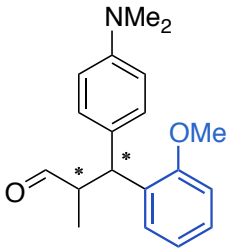
4



66%, d.r 3:1

93% anti: 71% syn ee

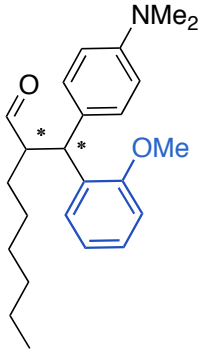
5



70%, d.r 2:1

98%anti: 91% syn ee

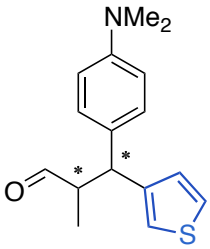
6



86%, d.r 1:1

90% anti: 88% syn ee

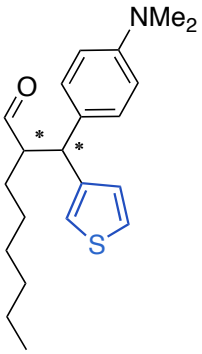
7



84%; d.r 2:1

93% anti: 90% syn ee

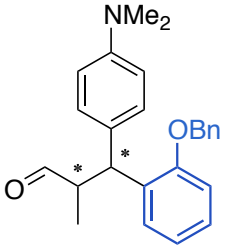
8



70%; d.r 1.5:1

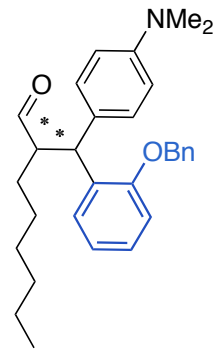
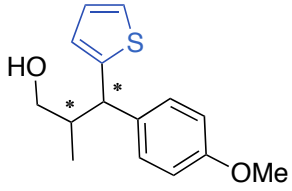
88% anti: 80% syn ee

9



60%, d.r 1:1

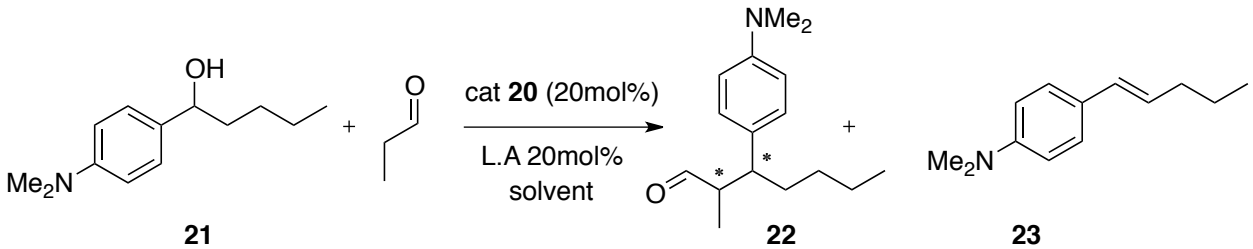
94% anti: 95% syn ee

10			
	79%, d.r 1:1	88% , d.r 1.1:1	
	90% anti: 81% syn ee	88anti: 86%syn ee	

All the reactions were performed at 0°C using 1 eq of alcohol, 3 eq. of aldehyde, 20mol% catalyst **20** and 20mol% $In(OTf)_3$, and were conducted until completation (by TLC) for 6 hours. Isolated yields after chromatographic purification. The d.r ratio determined by ^{1}HNMR. Enantiomeric excess were measured by chiral HPLC

Table 6. Stereoselective α-alkylation of aldehydes with benzhydrylic alcohols

The introduction of the NMe_2 group was essential to stabilized the carbenium ion, so the study of benzhylic alcohols was investigated with p-NMe_2 group in order to be enough to stabilized the carbenium ion. The α-alkylation with benzylic alcohols was evaluated using propanal, 1-(4-dimethylamino)phenyl)pentan-1-ol **21**, catalyst **20** and a series of Lewis acids. As was showed in table 7. Initial investigations revealed one secondary reaction that was elimination reaction generating alkene as side product. As revealed in table 7, using DCM or acetonitrile as solvent the majority product was alkene **23**. Use of apolar solvents such as *n*-hexane or toluene significantly improved the conversion at product **22**. Water as solvent did not afford any product (table7, entry 8). The addition of Me_3SiBr did not increase the yield. Finally, the use of $In(OTf)_3$ was important in order to minimized the formation of the alkene **23** and performing the reaction, at 0°C gave the total conversion at product **22** without any elimination reaction. (Table 7, entry 9,10).



21 **22** **23**

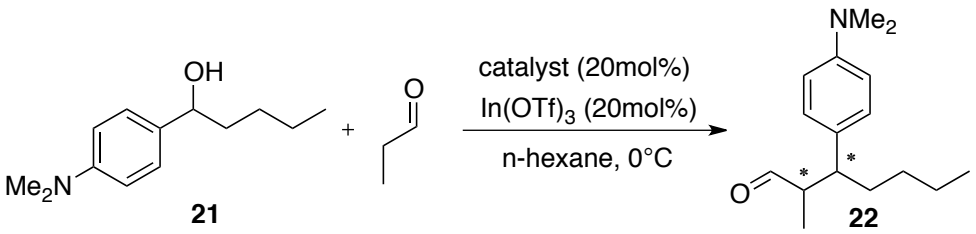
entry[a]	L.A	solvent	Yproduct(%)[c]	Alkene (%)[c]
1	$Yb(OTf)_3$	DCM	12	88
2	$InBr_3$	DCM	20	80

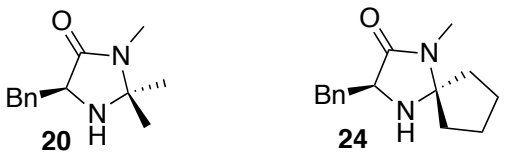
3	$InBr_3$	toluene	41	59
4	$InCl_3/Me_3SiBr$	DCM	15	85
5	$InCl_3/Me_3SiBr$	n-hexane	61	39
6	$InCl_3/Me_3SiBr$	MeCN	30	70
7	$In(OTf)_3$	DCM	30	70
8	$In(OTf)_3$	H_2O	---	n.d
9	$In(OTf)_3$	n-hexane	80	20
10[b]	$In(OTf)_3$	n-hexane	94	0

[a]All the reactions were performed at r.t with 20mol% catalyst, 20 mol % L.A , 3 eq of aldehyde and 1 eq alcohol. [b] the reaction were conducted at 0°C until completion by TLC. [C]. The yields after chromatography purification.

Table 7. α-alkylation with benzhylic alcohols. Screening of solvent and Lewis acids

The efficiency of the catalyst was studied changing the temperature of the reaction and several experiments were performed. At r.t with 20mol% of catalyst **20** was promoted the product **22** in 80% yield, d.r 1.5:1 and 76maj: 59min % ee. The same reaction with catalyst **20** at 0°C promoted the product **22** in 94% yield, d.r 2:1 and 98maj:94%min %ee. The employment of catalyst **24** the enantioselectivity remained the same, but the d.r jumped to 4.5:1 (table 8, 94% yield, d.r 4.5:1, 98maj: 90min % ee)





Y = 94%, d.r 2:1
98:94 % ee

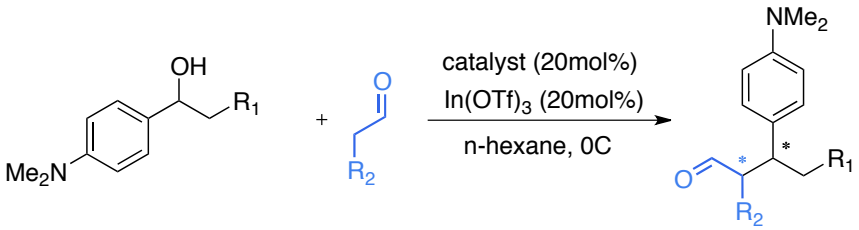
Y = 94%, d.r 4.5:1
98:90 % ee

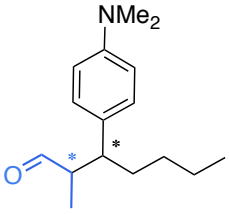
All the reactions were performed at 0°C with 20mol% catalyst, 20 mol % $In(OTf)_3$, 3 eq of aldehyde and 1 eq alcohol. The reaction were conducted at 0°C until completion by TLC. The yields after chromatography purification. The d.r ratio determined by ^{1}HNMR. Enantiomeric excess were measured by chiral HPLC

Table 8. Screening different imidazolidinone derivatives as catalysts

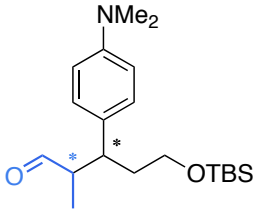
Then for varying the benzylic alcohol and aldehyde was explored the generality of the $In(OTf)_3$ catalyzed with enamine catalyst reaction. The benzylic alcohols were synthesized by the reaction of p-$Me_2NPhCHO$ with the corresponding alkynes lithiated alkynes or through a Grignard reaction. After the alcohols were treated with hydrogen Pd/C catalyst to promote the desired functionalized benzylic alcohols in good yields. The different substituent benzylic alcohols were reacted with aldehydes in the presence of the MacMillan catalysts. (Table 9)

The employment of catalyst **24** was able to give a better d.r. ratio than catalyst **20** in the case of the propanal aldehyde. On the other hand, when the more hindered aldehyde was employed such as octanal, with different functionalized substrates, better terms of d.r. ratio were obtained by the employment of catalyst **20**. (Table 9)

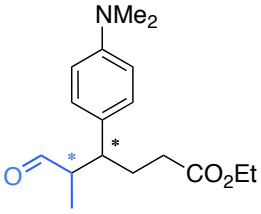




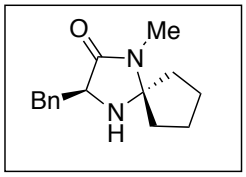
Y= 94%, d.r 4.5:1
98%*anti* : 90%*syn* ee

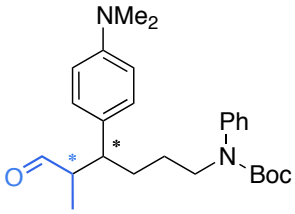


Y= 85%, d.r 6:1
99%*anti* : 86%*syn* ee

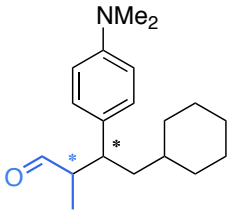


Y=45%, d.r 6:1
97%*anti* : 82%*syn* ee

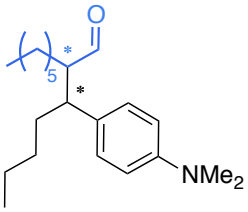




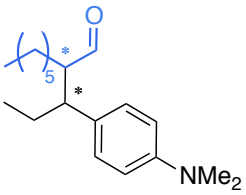
Y=92%, d.r 4.5:1
95%*anti* : 97%*syn* ee



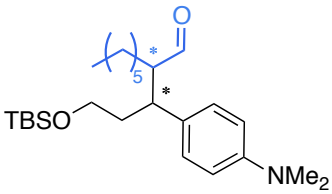
Y=88%, d.r 5:1
92%*anti* :86%*syn* ee



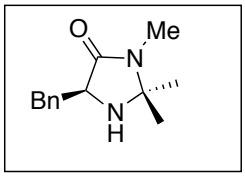
Y=94%, d.r 2:1
92%*anti* : 86%*syn* ee

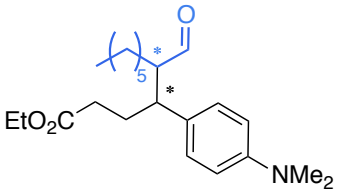


Y=90%, d.r 3:1
76%*anti* : 94%*syn* ee

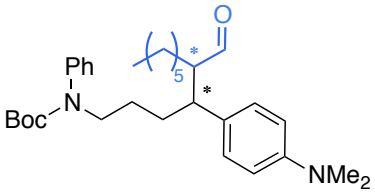


Y=60%, d.r 2:1
96%*anti* : 92%*syn* ee





Y=60%, d.r 2.5:1
96%*anti* : 91%*syn* ee



Y=75%, d.r 2.5:1
96%*anti* : 91%*syn* ee

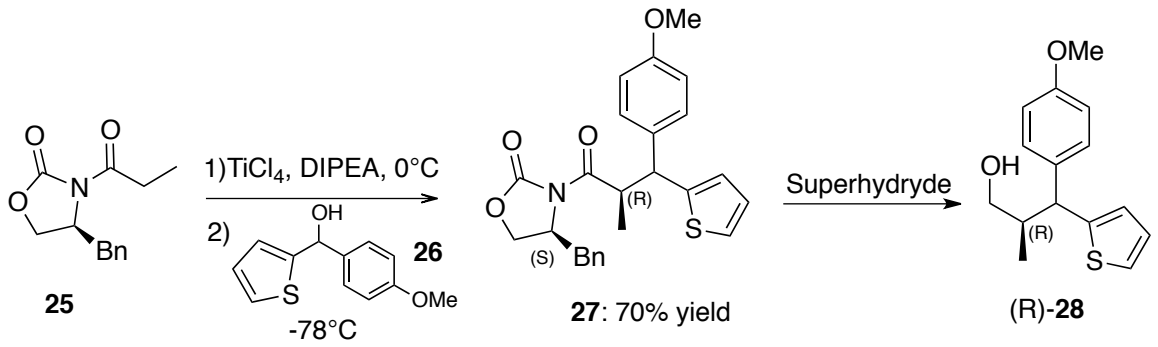
Yield after chromatographic purification. For all reactions the d.r (anti vs.syn) was measured by using ^{1}H NMR and HPLC analysis. Determined by chiral HPLC analysis of the isolated products or of corresponding alcohols.

Table 9. Representative stereoselective α-alkylation of aldehydes with benzhylic alcohols.

Determination of absolute configuration

The absolute and relative configuration from alkylation of benzhydrylic alcohols

The relative configuration of *anti-syn* adduct was established by the reaction of benzyhdrylic alcohol **26** with the titanium enolate of the chiral oxazolidinone **25**, to obtain the desired product **27** in 70 % yield and d.r 1:1, then the **27** was reduced with Super Hydride in THF affording the (R)-**28**.

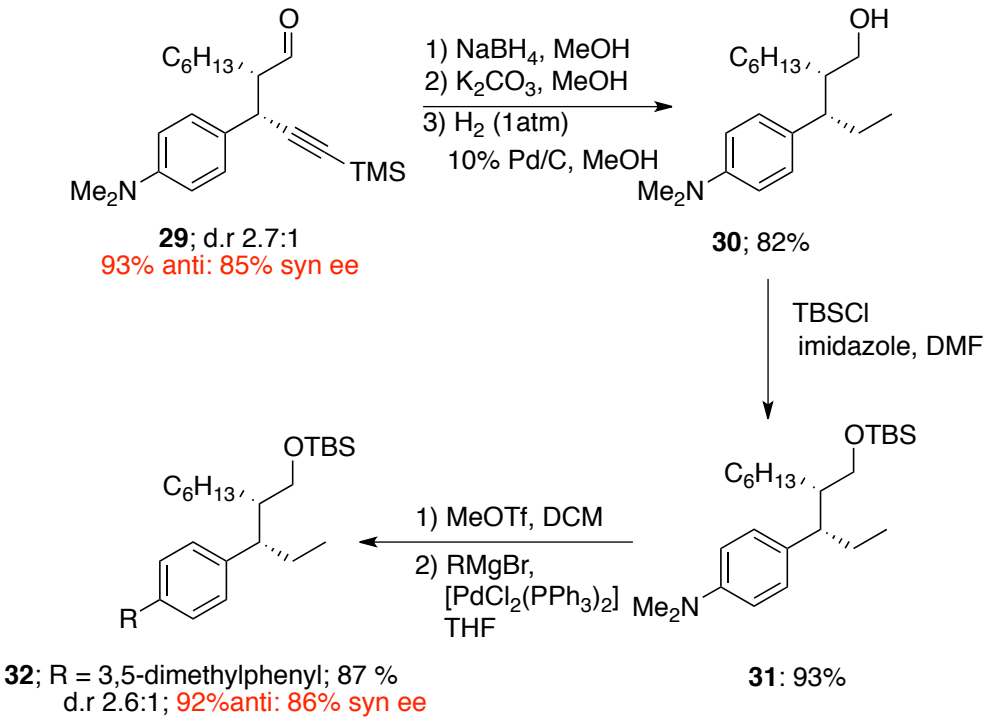


Scheme 8. Determination configuration

From this synthesis of Evans only was possible determined one stereocenter at the 2 C position. The determination of the other stereocenter was stablished by comparison of the HPLC trace of the product **28** obtained in the organocatalysis reaction after reduction to corresponding alcohol. The stereisomer obtained in the reaction was in agreement with our previously suggest model. The diasterisomeric ration of the major diastereoisomer was assigned as anti on the basis of the results obtained with he benzylic substrates.

The absolute and relative configuration from alkylation of benzylic alcohols

The absolute and relative configuration from the reaction with benzylic alcohols was determined from the previous work with organocatalytic propargylation of aldehydes.[28] The absolute and relative configuration of the benzylic substrates was obtained by comparison of the HPLC traces with the product **32** which was previously assigned.



Scheme 9. Functionalization of the products obtained by the organocatalytic alkylation through a Pd-catalyzed arylation of the trimethyl ammonium triflate

The substrate **30** obtained from the reduction $NaBH_4$, removal of the silyl group, catalytic hydrogenation of the triple bond was protected with TBSCl to obtain the product **31** that was transformed into the corresponding ammonium triflate and successive treatment of ammonium salt with 3,5-Me_2PhMgBr and 4-FPhMgBr and catalytic amount of complex of palladium to obtain the desired product **32**. (Scheme 9)

IV. Conclusion

In summary, in this chapter were described two stereoselective processes: one from allylic alcohols and other from benzhydrilic and benzylic alcohols, both with the same concept using In(III) as co-catalyst to generated stabilized cations that react with enamine catalysis, merging the enamine catalysis with metal-catalysis process. However, in this work has described the first catalytic stereoselective addition of aldehydes to allylic, benzhydrilic and benzylic alcohols promoted by the combination of organocatalysis and metal-catalyzed process. Furthermore in this work is presented the tolerance of In (III) salts with enamine base catalyst and water generate during the reaction. And the possibility to generated stable carbocation with unreactive alcohols in the stereoselective S_N1 type reactions.

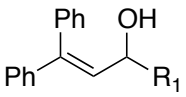
A wide range of applications for pharmaceutically or compounds intermediates in the synthesis of natural products can be applied this new methodology in the stereoselective construction of C-C bonds, by marriage the organocatalysis and organometallic catalysis.

V. Experimental section

A Stereoselective α-alkylation of aldehydes with allylic alcohols

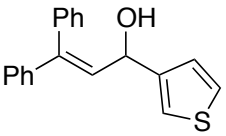
Procedure for the starting materials

1,1,3-triphenylallylalcohol



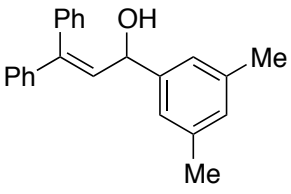
Compound **8** R_1= Ph was prepared by the addition of phenylmagnesium chloride to β-phenylcinnamaldehyde to obtain the desired product (ref. 29 of the Communication). **^{1}NMR (200MHz, $CDCl_3$)** δ 7.39-7.27 (15H, m); 6.31 (1H, d, J = 9.2Hz); 5.28 (1H, d, J = 9.2Hz); 1.92 (OH, s).

1-(3-thiophene)-3,3-diphenylprop-2-en-1-ol



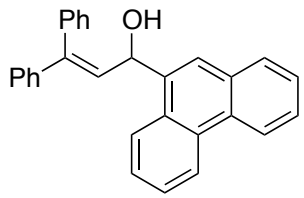
To a solution of 3-bromo-thiophene (162mg, 1.0mmol) in anhydrous Et_2O (1mL) under inert atmosphere was added n-BuLi (1.2mmol, 480μL, 2.5M in hexane) at -78°C. The mixture was stirred for 15 min at the same temperature. The mixture was warmed at 0°C and stirred for 1 hour, and then β-phenylcinnamaldehyde (208mg, 1.0mmol) was added at 0°C. The resulting mixture was warmed at room temperature until no further conversion took place (controlled by TLC). Then the reaction was quenched with saturated NH_4Cl aq. and the organic layer was separated. The aqueous layer was extracted twice with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give orange oil. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O = 7:3) to afford the product in (200mg, 0.70mmol, 70% yield) as a yellow solid. **^{1}H NMR (200MHz, $CDCl_3$)** δ 7.42-7.20 (11H, m); 7.07-6.91 (2H, m); 6.33 (1H, d, J = 10.6Hz); 5.59 (1H,d, J = 10.6Hz); 2.21 (OH,s).

1-(3,5-dimethylphenyl)-3,3-diphenylprop-2-en-1-ol



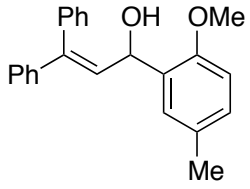
To a solution of 3,5-dimethyphenylmagnesium bromide (1.4mL, 0.65M in THF) was added β-phenylcinnamaldehyde (100mg,0.48mmol) under inert atmosphere at 0°C. The mixture was allowed to warm at room temperature until no further conversion took place (monitored by TLC), and then the solution was quenched with water, and the organic layer was separated. The aqueous layer was separated and extracted twice with Et_2O. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to afford the product in (150mg, 0.48mmol, 99% yield). **^{1}H NMR (200MHz, $CDCl_3$) δ** 7.43-7.22 (10H, m); 6.99 (2H, s); 6.92 (1H, s); 6.32 (1H, d, J = 9.2Hz); 5.20 (1H, d, J = 9.2Hz); 2.32 (6H, m); 1.93 (OH,s).

1-(phenanthren-9-yl)-3, 3 - diphenylallylalcohol



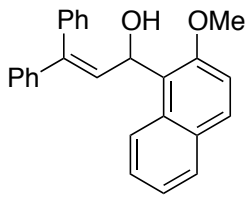
To a solution of 9-bromophenanthrene (257mg, 1mmol) in anhydrous Et_2O: benzene (2mL; 1:1) under inert atmosphere were added Mg (24mg, 1mmol) and I_2 (2mg, 0.76mol%). The resulting mixture was stirred at reflux for 1 hour. The Grignard solution of phenanthren-9-ylmagnesium bromide (1mmol, 0.5M in Et_2O: benzene) obtained was cooled to 0°C, then was added β-phenylcinnamaldehyde (187mg, 0.9mmol) in anhydrous Et_2O (0.5mL). The mixture was gradually warmed to room temperature, and stirred for 2 hours. The reaction was quenched with water, and the organic layer was separated. The organic layer was washed with brine and water, dried over Na_2SO_4, and concentrated to give yellow orange oil. The residue was purified by flash chromatography ($Si0_2$; cyclohexane/Et_2O = 7:3) to afford the product in (312 mg, 0.81mmol, 90% yield) as a yellow solid. **^{1}H NMR (200MHz, $CDCl_3$) δ** 8.76-8.66 (2H, m); 8.00 (1H, s); 7.93-7.84 (2H, m); 7.70-7.25 (14H); 6.48 (1H ,d, J = 9.2Hz); 5.96 (1H,d,J = 9.2Hz); 2.00 (OH, s).

1-(2-methoxy-5-methylphenyl) -3,3-diphenylallylalcohol



To a solution of 2-bromo-4-methylphenol (242µL, 2mmol) in dry DMF (2mL) were added K_2CO_3 (414mg, 3mmol) and MeI (246µL, 4mmol) and the resulting mixture was stirred at reflux for 24 hours (monitored by TLC). The reaction was quenched with water. The organic layer was separated, and the aqueous layer further extracted with Et_2O. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated to give quantitatively the product 2-bromo-4-methoxyanisol. The purified product 2-bromo-4-methoxyanisol (200mg, 1mmol) was dissolved in anhydrous Et_2O (1mL) under inert atmosphere and n-BuLi was added (400µL, 1mmol, 2.5M in hexane) at -78°C. The mixture was stirred for 15 min at the same temperature. The mixture was warmed at 0°C for 1 hour, and then β-phenylcinnamaldehyde (208mg, 1mmol) was added at 0°C. The mixture was allowed to warm from 0°C to room temperature in 2 hours. The reaction was quenched with saturated NH_4Cl aq. and the organic layer was separated. The aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O = 7:3) to afford the product in (297mg, 0.9mmol, 90%yield) as a white oil. **^{1}H NMR (200MHz, $CDCl_3$) δ** 7.41-7.18 (10H,m); 7.05 (1H,s); 6.83-6.77 (2H,m); 6.48 (1H, d, J = 9.2Hz); 5.36 (1H, bd, J = 9.2 Hz); 3.83 (3H, s); 3.14 (OH,s); 2.30 (3H, s).

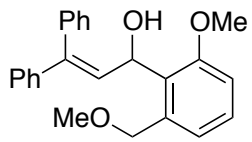
1-(2-methoxynaphtalen-1-yl) -3,3- diphenylallylalcohol



Following the same procedure described for **1-(3-thiophene)-3,3-diphenylprop-2-en-1-ol**, the compound was obtained in (90% yield) as a yellow oil starting from 1-bromo-2-methoxynaphtalene and β-

phenylcinnamaldehyde. **^{1}H NMR (200MHz, $CDCl_3$) δ** 7.83-7.74 (2H, m); 7.4-7.2 (14H, m); 6.70 (1H,d,J = 9.4Hz); 6.08 (1H, bd); 4.05 (3H, s); 1.59 (OH, s).

1-(2-methoxy-6-(methoxymethyl)phenyl)- 3,3- diphenylallylalcohol



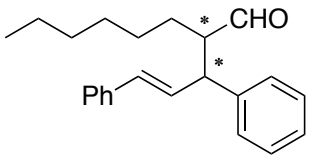
To a solution of NaH (106mg, 2.6mmol), in anhydrous THF (1.0mL) under inert atmosphere were added (3-methoxyphenyl)methanol (184mg, 1.3 mol) and MeI (124µL, 2mmol) at 0°C. The mixture was warmed at room temperature and stirred until no further conversion took place (monitored by TLC). The reaction was quenched with water and the organic layer was separated. The aqueous layer was extracted twice with EtO_2. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated to give 1-methoxy-3-(methoxymethyl)benzene (176mg, 1.15mmol), which was dissolved in anhydrous hexane (3mL) under inert atmosphere at 0°C. Then n-BuLi (555µL, 1.4mmol, 2.5M in n-hexane) was added and the mixture was stirred for 5 days at 0°C. Then β-phenylcinnamaldehyde (187mg, 1,03mmol) was added slowly at the same temperature. The mixture was warmed at room temperature, then it was stirred for 24 hours, quenched with saturate NH_4Cl aq. and the organic phase was separated. The aqueous layer was extracted twice with EtO_2. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2; cyclohexane: Et_2O = 7:3) to afford the product in (200mg, 0.5 mmol, 62% yield) as an orange solid. **^{1}H NMR (400MHz, $CDCl_3$) δ** 7.4-7.18 (11H, m); 6.90 (2H, d, J = 8Hz); 6.57 (1H,d, J = 13.6Hz); 5.5 (1H, bs); 4.01 (1H, d, J = 11.6); 3.92 (1H, d, J = 11.6); 3.89 (3H, s); 3.04 (3H, s) 1.5 (OH, s).

Organocatalytic allylic alkylations of aldehydes with alcohols

General procedure

To a solution of the allylic alcohols (0.1mmol, 1eq) in DCM (1mL) were added MacMillan catalyst **3** (0.02mmol, 20mol%) and aldehyde (0.3mmol, 3eq) at 0°C. The mixture was stirred for 5 min at the same temperature and then the solution of $InBr_3$ (20mol%, 0.33M in acetonitrile) was added slowly. The mixture was stirred until no further conversion took place (monitored by TLC) at the same temperature. Then the reaction was quenched with water. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O= 7:3).

2- (1,3-diphenylallyl)octanal (5-syn; 5-anti)

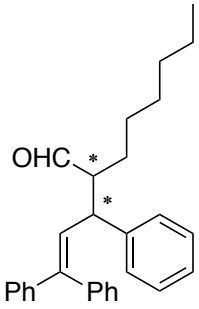


Compound **5** was obtained as white oil (90% yield; d.r: 1:1; 82%syn: 82%anti ee). **^{1}H NMR (400MHz,$CDCl_3$) δ=** 9.64 (1H, d, J = 4Hz); 9.48 (1H, d, J = 3.6Hz); 7.36-7.19 (20H, m); 6.47 (1H, d, J = 20.4Hz); 6.43 (1H, d, J = 20.4Hz); 6.34-6-27 (2H, m); 3.71 (2H, m); 2.8-2.75 (2H, m); 1.7-1.65 (4H, m); 1.29-1.16 (16H, m); 0.83 (6H, t, J = 7.2Hz). **HPLC-MS**: t_r: 15.97 min; t_r : 16.34 min; m/z: 338 (M+H_2O); 343 (M+Na) .

2- (1,3-diphenylallyl)octanol

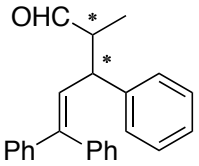
The compound from **5** (1eq, 0.1mmol) was reduced in the crude reaction mixture with with DIBAL (2 eq.) at -78°C. The solution was stirred during 15 min at the same temperature, and quenched with water. The mixture was concentrated and extracted with ethyl acetate. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O = 7:3), to obtain compound **5 alcohol** as a yellow oil (72%yield, d.r 1:1; 80%syn, 80% anti ee). **^{1}H NMR (400MHz, $CDCl_3$) δ** 7.37-7.19 (20H,m); 6.47-6.41 (4H,m); 3.76-3.65 (2H,m); 3.59-3.43 (4H,m); 1.98-1.85 (2H,m); 1.41-1.59 (4H,m); 1.18-1.05 (16H,m); 0.89-0.83 (6H,m). **^{13}C NMR (100MHz, $CDCl_3$) δ** 143.6 (2C); 143.3 (C); 137.3 (C); 132.7 (CH); 132.1 (CH); 131.0 (CH); 130.3 (CH); 128.7 (2CH); 128.6 (2CH); 128.5 (CH); 128.4 (2CH); 128.3 (CH); 128.0 (2CH); 127.8 (2CH); 127.2 (CH); 127.1 (CH); 126.3 (CH); 126.3 (CH); 126.2 (4CH); 63.0 (CH_2OH); 62.8 (CH_2OH); 51.8 (CH); 51.1 (CH); 45.6 (CH); 45.4 (CH); 31.8 (2CH_2); 29.7 (CH_2); 29.6 (CH_2); 29.4 (CH_2); 28.5 (CH_2); 28.2 (CH_2); 27.2 (CH_2); 26.9 (CH_2); 22.6 (CH_2); 14.0 (2CH_3). **HPLC analysis** IC, gradient from 99:1 (*n*-hexane: i-PrOH) to 9:1 in 30', flow 0.5mL/min; TM(maj): 26.0min; tm(maj): 21.0min; TM(min): 31.3min; tm(min): 38.4min.

2- (1,3,3-triphenylallyl)octanal (9a)



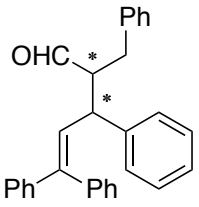
Compound **9a** was obtained as a yellow oil (70% yield, d.r 2:1; 90%syn, 75%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** 9.43 (1Hanti, d, J = 4.8Hz); 9.34 (1Hsyn, d, J = 4Hz); 7.46-7.1 (30H, m); 6.14 (1Hsyn, d, J = 10.6Hz); 6.26 (1Hanti, d, J = 11Hz); 3.75(1Hsyn, t, J = 9.6Hz); 3.64 (1Hanti, t, J = 9.6Hz); 2.74 (2Hsyn+anti, m); 1.65-1,62 (4H, m); 1.26-1.13 (16H, m); 0.89 (6H, t, J = 6.2Hz). **^{13}C NMR (50MHz, $CDCl_3$) δ** 204.5 (CHOanti); 204.2 (CHOsyn); 141.9 (2C); 141.8 (4C); 139.5 (2C); 129.7 (4CH); 129.3 (CH); 129.0 (CH); 128.8 (4CH); 128.3 (4CH); 128.2 (3CH); 128.1 (CH); 127.9 (2CH); 127.8 (2CH); 127.4 (5CH); 127.2 (3CH); 126.7 (2CH); 58. 5 (CHanti); 57.8 (CHsyn); 46.1 (CHanti); 45.9 (CHsyn); 31.6 (CH_2); 31.4 (CH_2); 29.3 (CH_2); 28.9 (CH_2); 27.5 (CH_2); 27.4 (CH_2); 27.1 (CH_2); 26.9(CH_2); 22.5 (2CH_2); 14.0 (2CH_3). **HRMS** Calcd for $C_{29}H_{32}O$: 396.245315 $[M]^+$, found: 396.24588. **HPLC analysis** IC (reduction to alcohol), 99:1 (n-hexane: i-PrOH), flow 0.5mL/min. TM(maj): 23.6min; tm(maj): 17.2min; TM(min): 19.2min; tm(min): 20.6min.

2-methyl-2,5,5-triphenylpent-4-enal (9b)



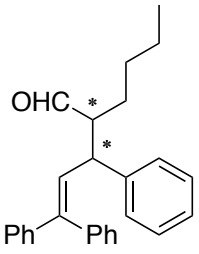
Compound **9b** was obtained as a yellow oil (63% yield, d.r 2:1, 88%syn; 80%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** 9.56 (1Hanti, d, J = 3.4Hz); 9.39 (1Hsyn, d, J =2.2Hz); 7.40-7.10 (30Haromatic, m); 6.31 (1Hanti, d, J = 10.6Hz); 6.27 (1Hsyn, d, J = 11Hz); 3.78(1Hsyn, t, J = 8.8Hz); 3.58 (1Hanti, t, J = 10.2Hz); 2.89-2.78 (2H, m); 1.13 (3Hsyn, d, J = 6.4Hz); 0.85 (3Hanti, d, J = 7Hz). **^{13}C NMR (50MHz, $CDCl_3$) δ** 204.4 (CHOanti); 204.0 (CHOsyn); 143.5 (C); 143.0 (C); 142.0 (2C); 141.9 (C); 141.6 (C); 139.5 (C); 130.6 (C)**;** 129.7 (3C); 129.2 (C); 128.8 (4C); 128.4 (4C); 128.3 (2C); 128.2 (3C); 128.1 (2C); 127.9 (2C); 127.8 (3C); 127.5 (2C); 127.4 (2C); 127.3 (2C); 126.8 (2C); 52.6 (CHanti); 52.1 (CHsyn); 47.2 (CHanti); 46.4 (CHsyn); 12.4 (CH_3anti); 11.6 (CH_3syn). **HRMS** Calcd for $C_{24}H_{22}O$: 326.16707 $[M]^+$, found: 396.24588. **HPLC analysis** OD-H, 99.5:0.5 (*n*-hexane: i-PrOH), flow 0.6mL/min. TM(maj): 13.7 min; tm(maj): 20.5min; TM(min): 19.4min; tm (min): 12.9 min.

2-benzyl-3,5,5-triphenylpent-4-enal (9c)



Compound **9c** was obtained as a yellow oil (90% yield, d.r 2:1, 89%syn; 64%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** 9.5 (CHOanti, d, J = 2.8Hz); 9.42 (CHOsyn, d, J = 2.8Hz); 7.43-7.08 (40H aromatic); 6.38(1Hsyn, d, J = 10.6Hz); 6.33 (1Hanti, d, J = 10.6Hz); 3.87 (1H, t, J = 10.6Hz); 3.7 (1H, t, J = 10,6Hz); 3.20-3.04 (2H, m); 2.96 (4H, 1d, J = 7 Hz). **^{13}C NMR (50MHz, $CDCl_3$) δ** 203.6 (CHOanti); 203.4 (CHOsyn); 143.7 (C); 143.4 (C); 141.9 (C); 141.7 (C); 141.3 (2C); 139.4 (C); 139.1 (2C); 138.7 (C); 129.7 (2CH); 129.6 (2CH); 129.1 (2CH); 129.0 (2CH); 128.9 (2CH); 128.7 (2CH); 128.6 (CH); 128.5 (3CH); 128.4 (4CH); 128.4 (2CH); 128.3 (CH); 128.2 (3CH); 128.1 (CH); 127.9 (2CH); 127.5 (2CH); 127.5 (2CH); 127.4 (2CH); 127.3 (3CH); 126.9 (2CH); 126.3 (2CH); 60.1 (CHanti); 59.6 (CHsyn); 46.3 (CHsyn); 46.2 (CHanti); 33.7 (CH_2anti); 33.4 (CH_2syn). **HPLC-MS** t_r (syn): 13.4min; t_r (anti) 13.9min; *m/z*: 425 (M+Na). **HPLC analysis** OD-H, 99.5:0.5 (n-hexane: i-PrOH), flow 0.6mL/min. TM(maj): 23.4min; tm(maj): 22.5min; TM(min): 25.8min; tm(min): 17.5min.

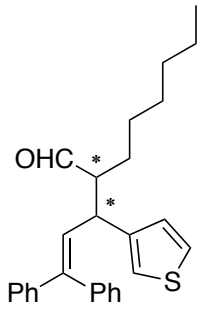
3,5,5-triphenyl-2-propylpent-4-enal (9d)



Compound **9d** was obtained as a yellow oil (50% yield, d.r 2:1, 91%syn; 77%anti ee).**^{1}HNMR (200MHz, CDCl3) δ** 9.42 (CHOanti, d, J = 4.6Hz); 9.33 (CHOsyn, d, J = 4Hz); 7.45-7.109 (30H, m); 6.26 (1Hsyn, d, J = 10.6Hz); 6.25 (1Hanti, d, J = 10.6Hz); 3.73 (1H, t, J = 10.6Hz); 3.6 (1H, t, J = 10.6 Hz); 2.81-2.68 (2H, m); 1.6-1.5 (4H, m); 1.33 -1.09 (4H, m); 0.905 (3H, t, J = 7Hz); 0.75 (3H, t, J= 7Hz). **^{13}C NMR (50MHz, $CDCl_3$)** δ 204.5 (CHOanti); 204.2 (CHOsyn); 143.2 (C); 142.8(C); 141.9(2C); 141.8(2C); 139.5(2C); 129.7 (4CH); 129.3 (CH); 128.9 (2CH); 128.9 (4CH); 128.3 (4CH); 128.2 (2CH);

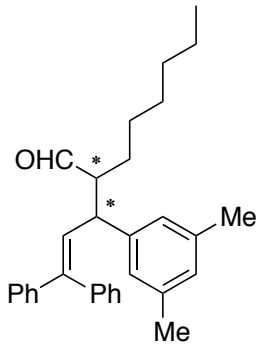
128.1 (2CH); 128.0 (CH); 127.9 (CH); 127.8 (3CH); 127.4 (4CH); 127.2 (2CH); 127.0 (CH); 126.8 (CH); 58.3 (CHanti); 57.6 (CHsyn); 46.1 (CHanti); 45.9 (CH syn); 29.6 ($2CH_2$); 20.4 (CH_2); 20.2 (CH_2); 14.1 (CH_3syn); 13.8 (CH_3anti). **HPLC-MS**: t_r (syn): 13.1min; t_r (anti): 13.7; *m/z*: 377 (M+Na). **HPLC analysis** IC, 99.5:0.5 (*n*-hexane: i-PrOH), flow 0.6 mL/min, T=40ºC. TM(maj): 13.2min; tm(maj): 13.8min; TM(min): 20.8min; tm(min): 16.9 min.

2-(3,3-diphenyl-1-(thiophen-3-yl)allyl)octanal (9e)



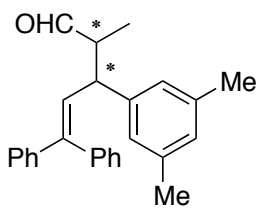
Compound **9e** was obtained as a yellow oil (56% yield, d.r 2:1, 87%syn; 56%anti ee).**^{1}H NMR (200MHz, $CDCl_3$) δ** 9.45 (CHOanti, d, J = 4Hz); 9.42 (CHOsyn, d, J = 3.6Hz); 7.40-7.09 (24H, m); 6.94 (1Hanti, d, J = 5.6Hz); 6.89 (1Hsyn, d, J = 5.4Hz); 6.20 (1Hsyn,d, J = 10.6Hz); 6.19 (1Hanti, d, J = 10.6Hz); 4.20-4.37 (2H, m); 2.68-2.64 (2H syn+anti, m); 1.6-1.5 (4H, m); 1.26 -1.14 (16H, m); 0.87 (6H, t, J = 6.6Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ** 203.5 (CHOanti); 203.1 (CHOsyn); 144.6 (C); 141.6 (C); 139.9 (2C); 138.8 (2C); 132.4 (CH); 130.0 (CH); 129.9 (CH); 129.8 (CH); 129.7 (4CH); 128.5 (3CH); 128.3 (3CH); 128.2 (CH); 127.7(2CH); 127.6 (3CH); 127.4 (4CH); 127.3 (CH); 127.2 (2CH); 124.8 (CH); 109.9 (C); 108.2 (C); 58.9 (CHanti); 58.8 (CHsyn); 40.6 (CHanti); 40.5 (CHsyn); 31.5 ($2CH_2$); 29.7 ($2CH_2$); 29.2 ($2CH_2$); 26.9 ($2CH_2$); 22.5 ($2CH_2$); 14.0 ($2CH_3$ syn+anti). **HPLC-MS:** t_r: (syn) 17.4min; t_r: (anti) 17.9min; m/z: 425 (M+Na). **HRMS** Calcd for $C_{27}H_{30}OS$: 402.201734 $[M]^+$, found: 402.20211. **HPLC analysis** OD-H, 99:1 (*n*-hexane: i-PrOH), flow 0.5 mL/min. TM(maj): 12.0min; tm(maj): 13.9min; TM(min): 13.0min; tm(min): 11.1min.

2-(1-(3,5-dimethylphenyl)-3,3-diphenyallyl)octanal (9f)



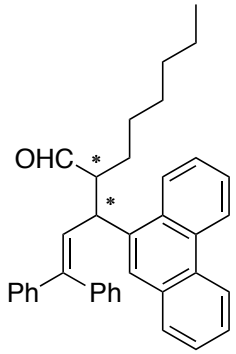
Compound **9f** was obtained as a yellow oil (53% yield, d.r 2:1, 85%syn; 69%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** 9.40 (CHOanti, d, J = 4.6Hz); 9.31 (CHOsyn, d, J= 4.2Hz); 7.4-7.12 (20H, m); 7.10-6.7 (6H, m) ; 6.25 (1Hsyn, d, J = 10.6Hz); 6.23 (1Hanti,d, J=11Hz); 3.7-3.60 (2Hsyn+anti,m); 2.69 (2Hsyn+anti,m); 2.33(6H,*s*); 2.29 (6H,*s*); 1.59 (4H,m); 1.28-1.13 (16H, m); 0.89 (6H,t, J=3.8Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ** 204.8 (CHanti); 204.5 (CHOsyn); 142.8 (2C); 141.6 (2C); 139,6 (2C); 138.3 (6C); 130 (CH); 129.8 (2CH); 129.5 (CH); 129.4 (CH); 129.2 (CH); 129.0 (CH); 128.4 (2CH); 128.3 (CH); 128.2 (3CH); 128.1 (2CH); 128.0 (CH); 127.9 (CH); 127.6 (CH): 127.4 (CH); 127.3 (3CH); 127.3 (2CH); 125.7 (CH); 125.6 (2CH); 125.0 (CH); 58.5 (CHanti); 57.7 (CHsyn); 45.9 (CHanti); 45.8 (CHsyn); 31.6 (CH_2); 29.3 ($2CH_2$); 27.6 ($2CH_2$); 27.4 (CH_2); 27.1($2CH_2$); 26.9 (CH_2); 22.5 (CH_2); 21.4 ($4CH_3$); 14.0 ($2CH_3$). **HRMS** Calcd for $C_{31}H_{36}O$: 424.27662 $[M]^+$, found: 396.24588. **HPLC analysis IC:** gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30min, flow 0.5 mL/min. TM(maj): 9.1min; tm(maj): 9.4min; TM(min): 12.7 min; tm(min): 8.8min.

3-(3,5-dimethylphenyl)-2-methyl-5,5-diphenylpent-4-enal (9g)



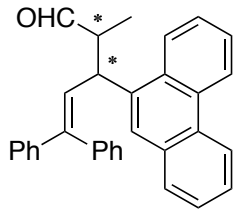
Compound **9g** was obtained as a yellow oil (69% yield, d.r 2:1, 85%syn; 73%anti ee).**^{1}H NMR (400MHz, $CDCl_3$) δ** 9.53 (1Hanti, d, J= 3.6Hz); 9.37 (1Hsyn, d, J=0.8Hz); 7.40-7.35 (6H, m); 7.28 -7.17 (10H, m); 7.1-7.09 (4H, m); 6.87 (1Hanti, s); 6.85 (1Hsyn, s); 6.79 (2Hsyn, s); 6.77(2Hanti, s); 6.28(1Hsyn, d, J = 10.8Hz); 6.26 (1Hanti, d, J = 10.8Hz); 3.68(1Hsyn, t, J = 9.6Hz); 3.49 (1Hanti, t, J = 9.6Hz); 2.82-2.7 (2Hsyn+anti, m); 2.30 (6Hanti, s); 2.29 (6Hsyn, s); 1.10 (3Hsyn, d, J = 6.8Hz); 0.84 (3Hanti, d, J = 6.8Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ** 204.3 (2CHO syn + anti); 143.1 (2C); 141.8 (4C); 139.6 (2C); 138.3 (4C); 130.0 (CH); 129.8 (2CH); 129.7 (CH); 129.5 (CH); 128.6 (2CH); 128.4 (3CH); 128.3(3CH); 128.2 (2CH); 128.1 (CH); 127.4 (3CH); 127.36 (2CH); 127.3 (4CH); 125.7 (CH); 125.5 (2CH); 52.6 (CHanti); 52.1 (CHsyn); 47.1 (CHanti); 46.3 (CHsyn); 21.4 (4CH); 12.4 (CH_3anti); 11.6 (CH_3syn). **HPLC-MS:** t_r: (syn) 13.5min; t_r: (anti) 13.9min; m/z: 377 (M+Na). **HRMS** Calcd for $C_{26}H_{26}O$: 354.19836 $[M]^+$, found: 354.19815. **HPLC analysis** IC, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30 min, flow 0.5mL/min. TM(maj): 11.5 min; tm(maj): 12.6 min; TM(min): 14.9min; tm(min): 11.0min.

2-(1-(phenanthrene-9-yl)-3,3-diphenylallyl)octanal (9h)



Compound **9h** was obtained as a yellow oil (66% yield, d.r 4:1, 86%syn; 67%anti ee). **^{1}H NMR (200MHz, $CDCl^3$) δ** 9.67 (CHOanti, d, J=3.6Hz); 9.49 (CHOsyn,d, J = 3Hz); 8.84-8.67 (4H, m); 7.91-7.01 (34H, m); 6.60 (2Hsyn+anti, d, J = 10.6Hz); 4.75 (1Hsyn, dd, J = 7.4Hz, J=10.6Hz); 4.64 (1H, t, J=8Hz); 2.96 (2Hsyn+anti, m); 1.84-1.6 (4H, m); 1.40-1.02 (16H, m); 0.84 (6Hsyn+anti, t, J = 6.6Hz). **^{13}C NMR (50MHz, $CDCl_3$) δ** 204.9 (CHOanti); 203.9 (CHOsyn);143.8 (2C); 142.2 (2C); 139.3 (2C); 136.6 (2C); 131.4 (2C); 131.0 (2C); 130.1 (2C); 129.8 (6C); 129.6 (2C); 128.5 (3C); 128.3 (6C); 128.2 (6C); 128 (2C); 127.6 (6C); 126.7 (2C); 126.6 (2C); 126.4 (2C); 123.6 (C); 123.5 (C); 123.4 (C); 122.4 (2C); 57.9 (CHanti); 57.8 (CHsyn); 40.2 (2CHsyn+anti); 31.5 (CH_2); 29.7 (CH_2); 29.2 (CH_2); 29.1 (CH_2); 27.6 (CH_2); 27.1 (CH_2); 26.9 (CH_2); 26.7 (CH_2); 22.5 ($2CH_2$); 14.0 ($2CH_3$syn+anti). **HRMS** Calcd for $C_{37}H_{36}O$: 496.27662 $[M]^+$, found: 354.19815. **HPLC analysis** IC, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:1 in 30 min, flow 0.6mL/min. TM(maj): 19.9min; tm(maj): 15.8min; TM(min): 14.3min; tm(min): 13.9min.

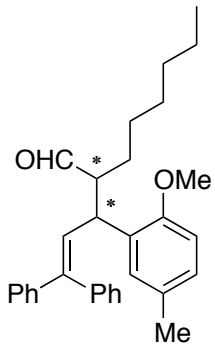
2-methyl-3-(phenanthren-9-yl)-5,5-diphenylpent-4-enal (9i)



Compound **9i** was obtained as a yellow oil (57% yield, d.r 4:1, 88%syn; 75%anti ee).**^{1}H NMR (400MHz, $CDCl_3$):** δ 9.77 (CHOanti, d, J= 2.8Hz); 9.55 (CHOsyn, d, J = 1.6Hz); 8.79-8.78 (2H, m); 8.70-8.68 (2H, m); 7.87 (2H, m); 7.802 (2H, s); 7.76

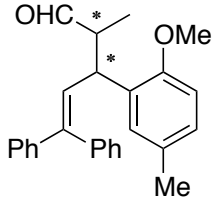
(2H, d, J = 8.4Hz); 7.7-7.58 (6H, m); 7.58-7.51 (2H, m); 7.35-7.25 (16H,m); 7.04 (2Hsyn, d, J = 8.4Hz); 7.01 (2Hanti, d, J = 8Hz); 6.6 (1Hanti, d, J = 10.4Hz); 6.61 (1Hsyn, d, J = 10.4 Hz); 4.84 (1Hsyn, dd, J = 6.4Hz, J = 10Hz); 4.53 (1Hanti, dd, J=8.4Hz, J = 10.4Hz); 3.09-3.05 (2Hsyn+anti, m); 1.2 (3H, d, J=7.2Hz); 0.90 (3H, d, J = 6.8Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ** 203.6 (CHOanti); 203.6 (CHOsyn); 144.2 (2C); 142.3 (2C); 139.4 (2C); 136.6 (2C); 131.4 (2C); 131.0 (2C); 129.8 (6C); 129.7 (2C); 129.6 (2C); 128.5 (CH); 128.5 (CH); 128.3 (4CH); 128.2 (4CH); 127.6 (3CH); 127.6 (3CH); 127.5 (CH); 127.5 (2CH); 127.07 (CH); 126.8 (2CH); 126.8 (CH); 126.7 (CH); 126.6 (CH); 126.6 (2CH); 126.4 (CH); 126.3 (CH); 123.8 (CH); 123.5 (CH); 123.4 (2CH); 122.4 (CH); 52.5 (CHanti); 51.6 (CHsyn); 40.4 (2CHsyn+anti); 10.5 ($2CH_3$syn+anti). **HPLC-MS:** t_r: (syn) 15.0min; t_r: (anti) 15.4min; m/z: 449 (M+Na). **HPLC analysis** IC, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30 min, flow 0.5mL/min. TM(maj): 18.6min; tm(maj): 17.9min; TM(min): 15.5min; tm(min): 13.9min.

2-(2-methoxy-5-methylphenyl)-3,3-diphenylallyl)octanal (9j)



Compound **9j** was obtained as a yellow oil (65 % yield, d.r 2:1, 88%syn ee; 79%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** 9.43 (1Hanti, d, J=4.4Hz); 9.29 (1Hsyn, d, J = 4Hz); 7.39-6.94 (24H, m); 6.78 (2H, pseudo-t, J = 8.8Hz); 6.42 (1Hsyn, d, J = 10.6Hz); 6.40 (1Hanti, d, J = 10.6Hz); 4.13-4.10 (2H, m); 3.78 (3Hanti, s); 3.75 (3Hsyn, s); 2.82-2.75 (2Hsyn+anti, m); 2.30 (3Hanti, s); 2.27 (3Hsyn, s); 1.6 (4H, m); 1.31-1.13 (16H, m); 0.92-0.80 (6H, m). **^{13}C NMR (50MHz,CDCl3) δ** 205.6 (CHOanti); 204.8 (CHOsyn); 155.0 (C); 154.4 (C); 143.1 (2C); 142.9 (C) ; 142.6 (C); 142.5 (C); 139.8 (2C); 130.1 (5CH); 130.0 (CH); 129.7 (2C); 129.7 (C); 129.3 (2CH); 128.2 (5CH); 128.1 (5CH); 127.6 (2CH); 127.5 (2CH); 127.3 (2CH); 127.2 (2CH); 110.9 (CH); 111.0 (CH); 57.1 ($2CH_3$); 55.4 (2CH); 40.51 (2CH); 31.7 (CH_2); 31.6 (CH_2); 29.5 (CH_2); 29.1 (CH_2); 27.8 ($2CH_2$); 27.3 (CH_2); 27.0 (CH_2); 22.7 (CH_2); 22.6 (CH_2); 20.7 ($2CH_3$); 14.2 (CH_3); 14.1 (CH_3). **HRMS** Calcd for $C_{31}H_{36}O_2$: 440.27153 $[M]^+$, found: 440.27135. **HPLC analysis** IC, (reduction to alcohol) gradient from 99:1 (*n*-hexane: i-PrOH) to 90:10 in 30min, flow 0.5mL/min. TM(maj): 13.9min; tm(maj): 15.0min; TM(min): 15.6min; tm(min): 16.0min.

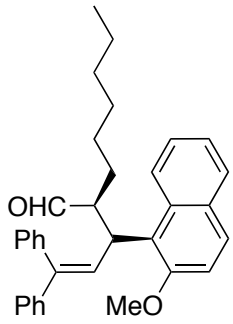
3-(2-methoxy-5-methylphenyl)-2-methyl-5,5-diphenylpent-4-enal (9k)



Compound **9k** was obtained as a yellow oil (50% yield; d.r: 2:1, 93%syn ee; 84%anti ee).**^{1}H NMR (400MHz, $CDCl_3$)** δ 9.45 (CHOanti, d, J = 3.2Hz); 9.27 (CHOsyn, d, J = 2Hz); 7.28-7.12 (20H, m); 6.99-6.92 (2H, m); 6.86 (1H, s); 6.82 (1H, s); 6.68 (2H, m); 6.36 (1Hanti, d, J = 10.4Hz); 6.33 (1Hsyn, d, J= 11.2Hz); 4.01-3.96 (1Hsyn, m); 3.8 (1Hanti, m); 3.67 (3Hanti, s); 3.62 (3Hsyn, s); 2.9-2.80 (2Hsyn+anti); 2.19 (3Hanti, s); 2.18 (3Hsyn, s); 1.00 (3Hsyn, d, J = 6.8Hz); 0.74 (3Hanti, d, J=7.2Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ** 205.2 (CHOanti); 204.8 (CHOsyn); 154.9 (2C); 154.3 (2C); 142.4 (2C); 139.7 (2C); 130 (2CH); 129.9 (2CH); 129.6 (2CH); 129.3 (4C); 128.6 (2CH); 128.4 (2CH); 128.1 (2CH);128.0

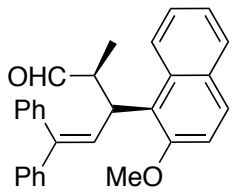
(2CH); 128.01 (2CH); 127.5 (2CH); 127.4 (2CH); 127.2 (CH); 127.15 (2CH); 127.1 (2CH); 126.6 (CH); 110.8 (2CH); 55.2 ($2CH_3$); 51.4 (CHanti); 50.8 (CHsyn); 41.6 (CHanti); 41.1 (CHsyn); 25.28 (CH_3syn); 20.5 (CH_3anti); 12.1 (CH_3anti); 11.7 (CH_3syn). **HRMS** Calcd for $C_{26}H_{26}O_2$: 370.19328 $[M]^+$, found: 440.27135. **HPLC analysis** OD-H (reduction to alcohol), gradient from 99:1 (n-hexane: i-PrOH) to 90:30 in 30 min, flow 0.5mL/min. TM(maj): 18.7min; tm(maj): 18.2min; TM(min): 25.1min; tm(min): 22.6min.

(S)-2- ((R)- 1-(2-methoxynaphthalen-1-yl)-3,3-diphenylallyl)octanal (9l)



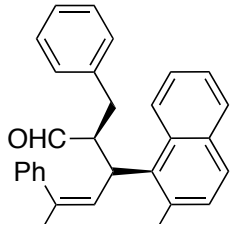
Compound was obtained **9l** as a yellow oil (71% yield, d.r 3:1, 91%syn; 68%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ** syn 9.17 (CHO, d, J = 4.4Hz); 7.75 (2H, d, J = 9.2Hz); 7.34 (2H, d, J = 7Hz); 7.28-7.22 (10H, m); 7.02 (2H, d, J = 5.4Hz); 6.92 (1H, d, J = 9.4Hz); 4.62-4-6 (1H, m); 4.00 (3H, bs); 3.32-3.30 (1H, m); 1.76-1.72 (2H, m); 1.29 (8H, m); 0.91 (3H, t, J = 6.4Hz). **^{13}C NMR (50MHz, $CDCl_3$) δsyn** 204.4 (CHO); 142.2 (C); 139.8 (2C); 132.0 (C); 130.1 (2CH); 129.5 (2C); 129.3 (CH); 129.2 (CH); 128.5 (CH); 128.4 (CH); 128.1 (4CH); 127.0 (4CH); 126.3 (CH); 123.2 (2CH); 121.9 (C); 99.8 (CH); 56.0 (CH); 56.0 (CH_3); 31.6 (CH_2); 29.4 (CH_2); 29.0 (CH_2); 27.2 (CH_2); 22.6 (CH_2); 14.1 (CH_3). **HPLC-MS:** t_r: (syn) 27.1min; m/z: 350 (M-octanal). **HRMS** Calcd for $C_{34}H_{36}O_2$: 476.27153 $[M]^+$, found: 440.27135. **HPLC analysis** IC, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30 min, flow 0.5mL/min. TM(maj): 17.7min; tm(maj): 15.8min; TM(min): 14.9min; tm(min): 13.9min.

(2R,3S)-3-(2-methoxynaphtalen-1-yl)-2-methyl-5,5-diphenylpent-4-enal (9m)



Compound **9m** was obtained as a yellow oil (75% yield, d.r 5:1, 94%syn; 87%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δ syn** 9.26 (1H, d, J=2.6Hz); 7.79-7.7 (2H, m); 7.4-7-24 (12H, m); 7.03-6.99 (2H, m); 6.94 (1H, d, J=10Hz); 4.53 (1H, m); 3.99 (3H, bs); 3.4-3.43 (1H, m); 1.22 (3H, d, J=7Hz). **^{13}C NMR (100MHz, $CDCl_3$) δsyn** 204.6 (CHO); 142.2 (2C); 139.8 (2C); 132.1 (2C); 130.1 (2CH); 130 (CH); 129.5 (C); 129.2 (CH); 129.0 (CH); 128.6 (CH); 128.4 (CH); 128.1 (CH); 128 (CH); 127.2 (CH); 127.1 (CH); 127.0 (2CH); 126.3 (2CH); 123.2 (2CH); 56.0 (CH_3+CH); 49.4 (CH); 13.5 (CH_3). **HRMS** Calcd for $C_{29}H_{26}O_2$: 406.19328 $[M]^+$, found: 406.19344. **HPLC analysis** IC, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30 min, flow 0.5mL/min. TM(maj): 19.3min; tm(maj): 18.7min; TM(min): 15.9min; tm(min): 15.1.

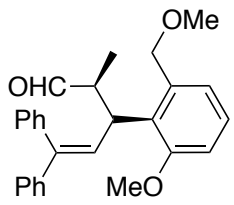
(2R,3S)-3-(2-methoxynaphtalen-1-yl)-2-benzyl-5,5-diphenylpent-4-enal (9n)



To a solution of the corresponding alcohol **8** (R_1 = 2-OMe-1-Naphthyl) (0.1mmol, 1eq) in DCM (1mL) were added MacMillan's catalyst **3** TFA (0.02mmol, 20mol%) and aldehyde (0.3mmol, 3eq) at 0°C. The mixture was stirred until no further

conversion took place (monitored by TLC) at the same temperature. Then the reaction was quenched with water. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2: cyclohexane: Et_2O = 7:3), to obtain **9n** as a yellow oil (73% yield, d.r 20:1, 99%syn; 55%anti). **^{1}H NMR (200MHz, $CDCl_3$) δ syn** 9.3 (1H, d, J=3Hz); 7.78-7.7 (2H, m); 7.36-7.01 (19H, m); 6.97 (1H, d, J=9.8Hz); 4.65 (1H, m); 4.0 (3H, bs); 3.7 (1H, m); 3.0 (2H, d, J = 7Hz)**. ^{13}C NMR (50MHz, $CDCl_3$) δsyn** 203.5 (CHO); 142.2 (2C); 139.8 (C); 139.4 (2C); 132.2 (C); 130.2 (2CH); 129.6 (C); 129.4 (CH); 129.1 (3CH); 128.5 (3CH); 128.2 (3CH); 127.3 (2CH); 127.2 (3CH); 126.4 (CH); 126.2 (CH); 123.4 (2CH); 121.3 (C); 113.4 (CH); 56.7 (CH); 56.1 (CH_3+CH); 29.8 (CH_2). **HRMS** Calcd for $C_{35}H_{30}O_2$: 482.22458 $[M]^+$, found: 406.19344. **HPLC analysis** ODH, gradient from 99:1 (*n*-hexane:i-PrOH) to 90:10 in 30 min, flow 0.5mL/min. TM(maj): 26.2min; tm(maj): 24.0min; TM(min): 19.1min; tm(min): 20.1min.

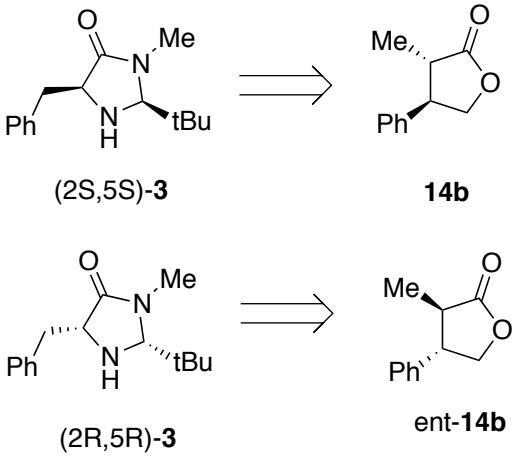
(2R,3S)- 3-(2-methoxy-6-(methoxymethyl)phenyl)-2-methyl-5,5-diphenylpent-4-enal (9o)



Following the same procedure described for **9n**, compound **9o** was obtained as a yellow oil (75% yield, d.r 11:1, 96%syn; 85%anti ee). **^{1}H NMR (200MHz, $CDCl_3$) δsyn** 9.31 (1H, d, J=2.2Hz), 7.43-7.13 (11H, m); 6.92-6.79 (3H, m); 3.93 (3H, s); 3.84 (1H, t, J = 9.8Hz); 3.6-3.4 (2H, m);3.31-3.24 (1H, m); 3.02 (3H, s); 1.20 (3H, d, J= 7Hz). **^{13}C NMR (100MHz, $CDCl_3$) δ syn** 205.2 (CHO); 142.2 (2C); 140.1 (C); 136.9 (2C); 130.0 (1CH); 129.9 (2CH); 128.6 (2CH); 128.4 (C); 128.1 (2CH); 127.5 (CH); 127.1 (CH); 127.0 (CH); 126.9 (2CH); 122.2 (CH); 111.5 (CH); 72.8 (CH_2); 57.5 (CH); 55.3 ($2CH_3O$); 30.9 (CH); 13.3 (CH_3). **ESI-MS** m/z: 423 (M+Na). **HPLC analysis** IC (reduction to alcohol), gradient from 99:1 (*n*-hexane: i-PrOH) to 90:10 in 30 min, flow 0.5 mL/min. TM(maj): 30.1min; tm(maj): 31.4min; TM(min): 25.1 min; tm(min): 24.6min.

Determination of relative and absolute configuration

Compounds **14b** and **15b** were prepared from **9b** through the sequence described in scheme 6; compounds **ent-14b** and **ent-15b** were prepared from **ent-9b**, obtained by using **ent-3** ((2*S*,5*S*)-(−)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone) as catalyst. The relative *anti* and *syn* configurations were assigned respectively to compounds **14b**, **ent-14b** and **15b**, **ent-15b** by comparison with published ^{1}H-NMR spectra (see ref.30 of the Communication). The major isomers **14** and **ent-14** were used for the determination of the absolute configuration by means of TD-DFT calculations of the Electronic Circular Dichroism (ECD) spectra.



ECD spectra. UV absorption spectra were recorded at 25 °C in the 190-300 nm spectral region in acetonitrile by means of Perkin-Elmer Lambda 45 spectrophotometer. The cell path length was 0.1 mm, concentration was 5.7 mM for **14b** and 6.3 mM for **ent-14b**. CD spectra were recorded at 25°C in acetonitrile by employing a Jasco J-810 spectropolarimeter, in the range 190-300 nm, with the same concentration and path lengths of 0.2 mm. The values are expressed in terms of the molar circular dichroism Δε, expressed as L $mol^{-1}cm^{-1}$.

Preliminary conformational analysis.

A preliminary conformational analysis was performed at the SCC-DFTB level of theory ("mio-0-1" parameter set)[31] to allow a fast exploration of the conformational space of the two *anti* stereoisomers. By means of geometry optimisations and short molecular dynamics runs, carried out with the with the DFTB package,[31] the presence of two stable conformers was ascertained for each stereoisomer. In all cases the conformational isomers correspond to puckering isomers where the phenyl-substituted carbon (C4) atom lies, respectively, above or below the plane defined by the 5-membered ring (see Figure S1).

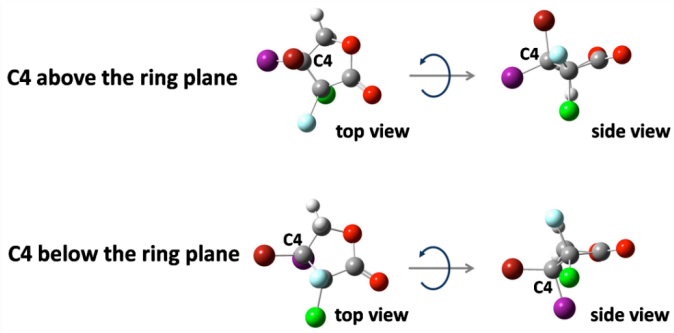


Figure S1. Graphical representations of the two puckering conformations assumed by the modelled compounds. Generic substituent groups attached to C4 and C5 are represented by spheres of different colours (C3: ice blue and green; C4: dark red and purple).

The DFTB optimised structures of the four stable isomers (two conformers for each of the two stereoisomers, see Figure S2) found in the preliminary study were used for the following investigations.

Accurate conformational investigation. The structure of the four isomers has been subjected to geometry optimization in search for local minima of the potential energy surface (PES). The nature of the found critical points was then ascertained by means of frequency calculations. All calculations have been performed with the Gaussian 03[32] (G03.E01) software package at the DFT(B3LYP)/6-31+g* level using the default convergence criteria; [33-35] solvent effects due to the presence of acetonitrile were taken into account by using the SCRF-CPCM[36-38] method. All DFT optimized geometries, represented in S2, resulted to be similar to those obtained at the SCC-DFTB level, but DFT energy differences are generally considered more accurate and thus reported here (Table S1). After all critical points have been confirmed as minima on the PES by frequency calculations (no imaginary frequency value has been found) a local conformational investigation was performed to exclude recondite shallow minima overlooked by the optimization procedure. To this purpose the puckering of C4 was constrained while a relaxed scan was performed on the dihedral angle centred on the bond connecting the phenyl group to the 4-membered ring. For all four isomers no other minimum was found by rotating the phenyl group, thus confirming that the conformational freedom of all stereoisomer is limited to the two considered puckering conformers.

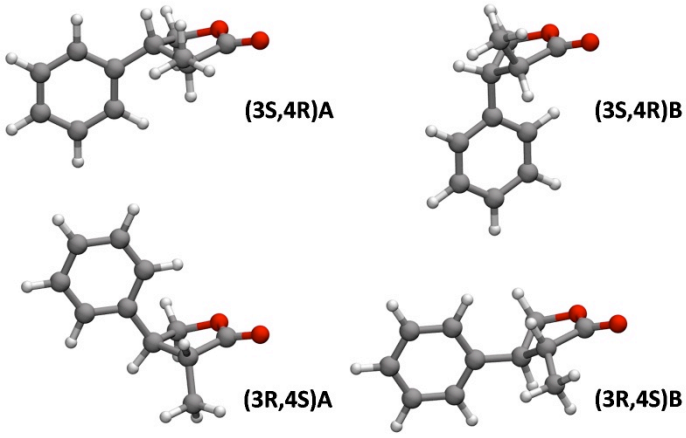


Figure S2. DFT(B3LYP)/6-31+g* optimised geometries of the two puckering conformers (A,B) of the *anti* stereoisomers (3S,4R) and (3R,4S).

Table S1. Energy values computed at the DFT(B3LYP)/6-31+g* level for the four isomers. Energy (E), zero-point energy (ZPE), Gibbs energy correction (G corr.), zero-point corrected energy (E+ZPE),

Gibbs free energy (G), Gibbs free energy difference with respect the more stable isomer (3B), frequency value of the fist normal modes (ν_1, ν_2, ν_3).

	E (hartree)	**ZPE (hartree)**	**G corr. (hartree)**	**E+ZPE (hartree)**	**G (hartree)**	**ΔG (kcal mol^{-1})**	**ν_1 (cm^{-1})**	**ν_2 (cm^{-1})**	**ν_3 (cm^{-1})**
(3S,4R)A	-576.884053	0.206815	0.168974	-576.677238	-576.715079	0.09	39.7642	61.9151	88.5092
(3S,4R)B	-576.879912	0.206980	0.168594	-576.672932	-576.711318	2.45	24.7361	50.3873	93.8375
(3R,4S)A	-576.879748	0.206824	0.167581	-576.672924	-576.712167	1.91	14.8603	34.9199	94.5158
(3R,4S)B	-576.884172	0.206778	0.168956	-576.677394	-576.715216	0.00	39.7877	63.2234	89.1317

The ECD spectra for the four isomers were computed [39-46] at the TD-DFT(B3LYP)/6-31+g* level using the previously optimised geometries. 40 transitions have been used to cover the interesting absorption range. Spectra have been obtained by using the SpecDis software[47] setting a bandwidth γ = 0.16 eV.[44, 48, 49] For each stereoisomer the spectrum was obtained by adding the spectra of the two conformers A and B, according to Boltzmann weights computed by their relative Gibbs free energy (Table S2).[47] For both enantiomers the resulting spectrum is dominated by the component due to the conformer where the phenyl group is placed in and equatorial position, namely (3S,4R)A and (4S,3R)A (Figure S3,S4).

The obtained spectra have been compared with those measured experimentally for **14** and **ent-14**; As shown in Table S2, the ECD spectrum calculated for the (3S,4R) configuration matched the profile and relative intensities of the experimental spectrum of **14**, while the ECD spectrum calculated for the (3R,4S) configuration was in agreement with the experimental spectrum of **ent-14.** Consequently, the absolute (3S,4R) configuration was assigned to compound **14** and the (3R,4S) configuration to compound **ent-14**. As a result, the (3S,4S) and (3R,4R) configurations were attributed to the minor *syn* isomers **15** and **ent-15**, respectively.

The absolute configurations of all other products were assigned on the basis of regularity in their NMR spectra and of the assumption of a common mechanistic path.

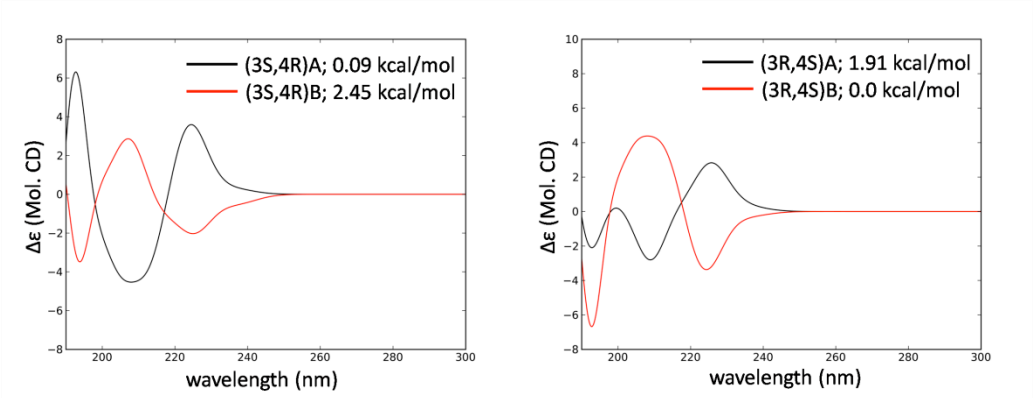


Figure S3. Calculated Optical Rotation for the two conformers of each enantiomer.

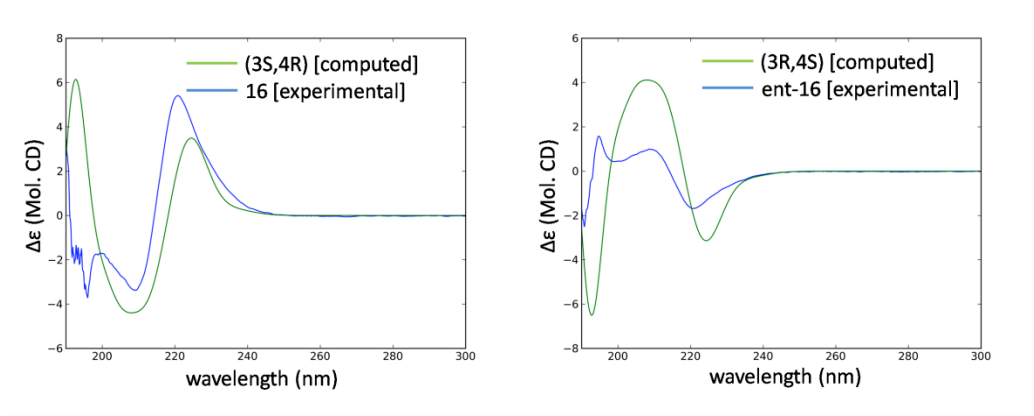
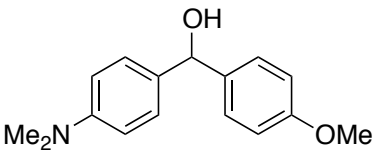


Figure S4. Comparison between experimental and computed Optical rotation.

Indium (III) promoted Organocatalytic enantioselective α-alkylation of aldehydes with Benzhylic and benzhydrylic alcohols.

Starting materials

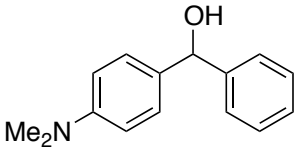
(4-(dimethylamino)phenyl)(4-methoxyphenyl)methanol



A vial equipped with a magnetic stir bar under inert atmosphere was charges with p-bromoanisole (1mmol, 125µL), in 0.5mL THF at -78°C. The mixture was stirred and a solution of n-BuLi (2.5M in THF, 0.500mL) was added slowly. The yellow solution was warmed slowly at r.t and stirring for 1 hour at the same temperature. After the solution was cooled at 0°C and p-N-dimethylaminobenzaldehyde (1mmol, 149mg) was added. The solution was warmed at r.t and stirring until no further conversion take place (controlled by TLC). The reaction was worked up with aq solution of NH_4Cl. The organic layer was separated and washed several times with acid water and the aqueous layer was extracted twice with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtain an orange oil. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O; 7:3) to afford the product as a white solid. (70% Yield.) **^{1}H**

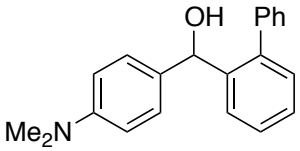
NMR (400MHz,$CDCl_3$) δ 7.30 (d, 2H, J = 8.7Hz); 7.22 (d, 2H, J = 8.3Hz), 6.87 (d, 2H, J = 8.7Hz), 6.70 (d, 2H, J = 8.7Hz), 5.75 (m, 1H), 3.80 (s, 3H; OCH_3), 2.94 (s, 6H, $N(CH_3)_2$), 1.56 (s, OH). **^{13}C NMR (50MHz,$CDCl_3$) δ** 158.8, 136.6 127.6 (3C), 127.5 (3C), 113.5(2C), 112,5 (2C), 75.6, 55.2, 40.7(2C)

4-(dimethylamino)phenyl)(phenyl)methanol (18)



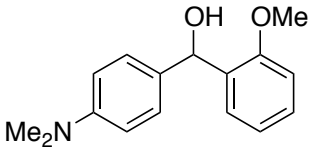
A vial equipped with magnetic stir bar and under innert atmosphere was charged with phenylmagnesium bromide (0.2mmol, 1.0M in THF) in anhydrous THF (0.1 M) The solution was stirred during 5 minuts at 0°C, and p-N-dimethylaminobenzaldehyde (0.2mmol, 30mg) was added at the same temperature, and the mixture was warmed at r.t and stirring until no further conversion took place (controlled by TLC). The reaction was worked up with H_2O. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtain a yellow oil. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O; 7:3) give **18** as yellow oil. (Yield 90%). **^{1}H NMR (400MHz,$CDCl_3$) δ** 7.38 (d, 2H, J = 6.4Hz); 7.31 (t, 2H, J = 7.2Hz); 7.23 (m, 1H); 7.20 (d, 2H, J = 8.4Hz); 6.68 (d, 2H, J = 8.8Hz); 5.76 (s, 1H); 2.92 (s, 6H); 2.00 (s, OH). **^{13}C NMR (50MHz,$CDCl_3$) δ** 150.0; 144; 131.8; 128.1 (2C); 127.6 (2C); 126.9(2C); 126.2; 112.4 (2C); 75.8; 40.5; 40.4.

biphenyl-2-yl(4-(dimethylamino)phenyl)methanol (19)



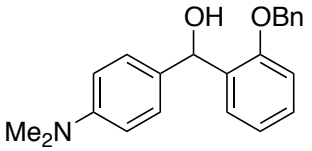
A vial equipped with magnetic stir bar and under inert atmosphere was charged with 2-bromodiphenyl (1mmol, 233mg) and anhydrous THF (1M, 1mL). The solution was stirred at -78°C for 5minuts, and a solution of n-BuLi (0.5mL, 2.5M in hexane) was added slowly. The mixture was warmed at 0°C and stirring during 1 hours. After p-N-dimethylaminobenzadldehyde (1mmol, 149mg) was added at the same temperature and the solution was warmed at r.t and stirring until no further conversion took place (controlled by TLC). The reaction was worked up with NH_4Cl aq solution. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure give **19** a yellow oil. The residue was purified by flash chromatography (SiO_2; cyclohexane:Et_2O; 7:3). Yiled 90%. **^{1}H NMR (400MHz, $CDCl_3$) δ** 7.62 (d, 1H, J = 7.6Hz); 7.39-7.32 (m, 5H); 7.23-7.20 (m, 3H); 7.06 (d, 2H, J = 6.8Hz); 6.78 (d, 2H, J = 7.6Hz); 5.86 (bs, 1H,); 3.75 (s,6H); 2.18 (s, 1H, OH). **^{13}C NMR (50MHz, $CDCl_3$) δ** 158.7 (C); 141.2 (C); 141.1 (C); 140.8 (C); 136.1 (C); 129.9 (CH); 129.3 (3CH); 128.1 (CH); 128.05 (CH); 128.0 (CH); 127.8 (CH); 127.2 (CH); 127.1 (CH); 126.9 (CH); 113.5 (CH); 113.6 (CH); 72.1 (CH); 55.3 (CH_3); 55.2 (CH_3).

(4-(dimethylamino)phenyl)(2-methoxyphenyl)methanol



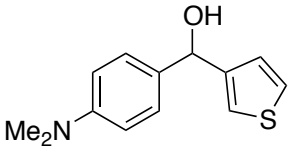
According at the same procedure from compound **19** using 1-bromo-2-methoxybenzene. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the product as a yellow oil (80% yield) **^{1}H NMR (200MHz, $CDCl_3$) δ** 7.4 -7.26 (m, 4H); 7.1-6.8 (m, 2H); 6.74 (d, 2H, J = 8.8Hz); 6.1 (s, 1H); 3.83 (s, 3H); 2.95 (s, 6H). **^{13}C NMR (50MHz,$CDCl_3$) δ** 156.6 (C); 149.8 (C); 132.4 (C); 131.3 (C); 128.2 (1CH); 127.5 (3CH); 120.5 (CH); 112.2 (2CH); 110.4 (CH); 71.1 (CH); 55.3 (OCH_3); 40.5 (2 CH_3)

(2-(benzyloxy)phenyl)(4-(dimethylamino)phenyl)methanol.



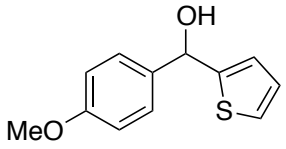
According at the Grignard procedure using 4-N,N-dimethylaniline magnesium bromide solution (1.1eq, 0.5M in THF) at 0°C in 1mL THF was slowly added (1eq) of 2-(benzyloxy)benzaldehyde. The residue was purified by flash chromatographic (SiO_2, cyclohexane: EtOAc, 7:3) to afford the product as a yellow solid. **^{1}H NMR (200MHz, $CDCl_3$) δ** 7.47-7.24 (m, 9H); 7.06-6.94 (m, 2H); 6.74 (d, 2H, J = 8.8Hz); 6.09 (s, 1H); 5.08 (s, 2H); 2.98 (s, 6H). **^{13}C NMR (125MHz,$CDCl_3$) δ** 155.6 (C); 149.9 (C); 136.6 (C); 132.2 (C); 131.5 (C); 128.4 (2CH); 128.2 (CH); 127.8 (CH); 127.6 (2CH); 127.5(CH); 127.3(2H); 120.8(CH); 112.3 (2CH); 111.7 (CH); 71.9 (CH); 69.9 (CH_2); 40.7 (CH_3); 40.6 (CH_3).

(4-(dimethylamino)phenyl)(thiophen-3-yl)methanol



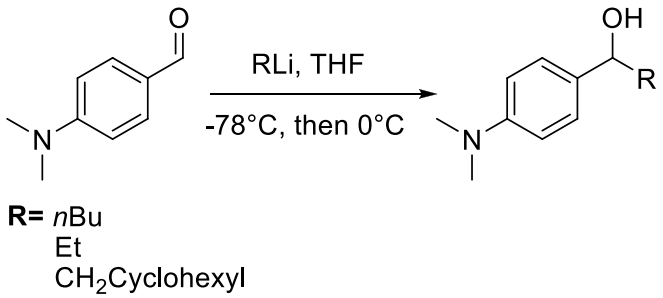
A vial equipped with magnetic stir bar and under inert atmosphere was charged with 3-bromothiophene (1mmol, Xmg) and anhydrous THF (1M, 1mL). The solution was stirred at -78°C for 5minuts, and a solution of n-BuLi (2.5M in hexane, 0.500mL) was added slowly. The mixture was stirred during 1 hours at the same temperature. After p-N-dimethylaminobenzadldehyde (1mmol, 149mg) was slowly added at the same temperature and the solution was warmed at 0°C and stirring until no further conversion took place (controlled by TLC). The reaction was worked up with saturated solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtaining a yellow oil. The residue was purified by flash chromatography (SiO_2; cyclohexane: Et_2O, 7:3) to afford the product as an orange solid (60% yield). **^{1}H NMR (400MHz,$CDCl_3$) δ** 7.28 (d, 2H, J = 8.4Hz); 7.24-7.20 (m, 1H); 6.9 (1H, t, J = 4Hz); 6.8 (d, 1H, J = 3.4Hz); 6.71 (d, 1H, J = 8.4Hz); 6.70 (d, 1H, J = 8.8Hz); 5.94 (s, 1H); 2.94 (s, 6H), 2.44 (bs, OH). **^{13}C NMR (50MHz,$CDCl_3$) δ** 150.3 (C); 148.8. (C); 131.2 (C); 127.4 (2CH); 126.5 (CH); 124.8 (CH); 124.3 (CH); 112.3 (2CH); 72.3 (CH); 40.6 ($2CH_3$)

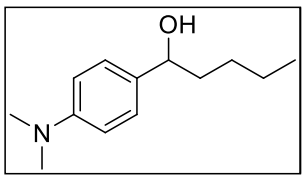
(4-methoxyphenyl)(thiophen-2-yl)methanol



A vial equipped with magnetic stir bar and under inert atmosphere was charged with 2-iodothiophene (4.4 mmol, 487 ml) and anhydrous THF (5 mL). the solution was stirred at -78º C for 5 minutes, and a solution of *n*-BuLi (2.5 M in hexane, 1.9 mL) was added slowly. The mixture was stirred during 1 hours at the same temperature. After *p*-OMe-benzaldehyde (3.67 mmol, 500 mg) was slowly added at the same temperature and the solution was warmed at 0º C and stirring until no further conversion took place (controlled by TLC). The reaction was worked up with saturated solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtain yellow oil. The residue was purified by flash chromatography (SiO_2; cyclohexane: EtOAc, 8:2) obtain the desired product as an white solid, 60% yield. **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 7.38 (d, *J* = 8.7 Hz, 2H); 7.26 (dd, *J* = 4.7 Hz, *J* = 5.9 Hz, 1H), 6.95 (dd, *J* = 3.5 Hz, *J* = 5.1 Hz, 1H); 6.91 (d, *J* = 8.7 Hz, 1H); 6.89 (m, 1H); 6.03 (d, *J* = 3.5 Hz, 1H); 3.82 (s, 3H); 2.38 (d, *J* = 3.9 Hz, 1H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 159.1 (C); 148.4. (C); 135.4 (C); 127.6 (2CH); 126.5 (CH); 125.0 (CH); 124.5 (CH); 113.7 (2CH); 71.8 (CH); 55.1 ($2CH_3$). ESI-MS: *m/z* = 203.1 $[M-H_2O]^+$, 243.1 $[M+Na]^+$.

Synthesis of alcohols from benzylic alcohols

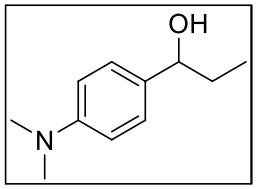




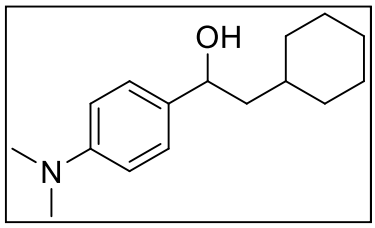
To a solution of 4-(dimethylamino)benzaldehyde (1.34 mmol, 200 mg) in anhydrous THF (5 ml) at -78 °C, *n*-BuLi (2.5 M in hexane, 1.34 mmol, 540 mL) was added dropwise at -78°C. After that, the solution was wormed up and stirred at 0 °C until complete consumption of the aldehyde (TLC) and water (2 mL) was added. The solvent was evaporated under reduced pressure, CH_2Cl_2 (10 mL) was added and the organic phases were extracted with CH_2Cl_2 (2 x 10 mL). The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated.

Flash chromatography (cyclohexane/ethyl acetate = 9/1) of the residue give the desired alcohol in 75% yield (207mg). Yellowish liquid; **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 0.90 (t, *J* = 7.1 Hz, 3H), 1.24 (m, 1H), 1.36 (m, 2H), 1.70 (m, 1H), 1.83 (m, 2H), 4.57 (t, *J* = 6,7 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.23

(d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** *δ* 14.0, 22.6, 28.2, 38.4, 40.6 (2C), 74.4, 112.5 (2C), 127.8 (2C), 132.9, 150.1; ESI-MS: *m/z* = 208.2 $[M+H]^+$, 230.1 $[M+Na]^+$, 437.3 $[2M+Na]^+$.

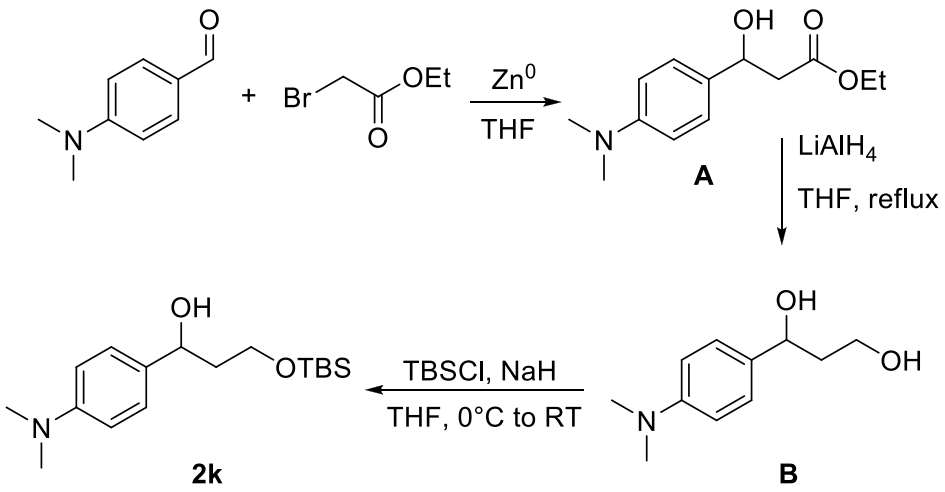


To a solution of 4-(dimethylamino)benzaldehyde (1.0 mmol, 149 mg) in anhydrous THF (1 ml) at 0 °C, EtMgBr (1.0 M in THF, 1.1 mmol, 1.1 mL) was added dropwise at 0°C. After that, the solution was stirred at 0 °C until complete consumption of the aldehyde (TLC) and water (1 mL) was added. The solvent was evaporated under reduced pressure, CH_2Cl_2 (10 mL) was added and the organic phases were extracted with CH_2Cl_2 (2 x 10 mL). The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (cyclohexane/ethyl acetate = 9/1) of the residue give the desired alcohol in 93% yield (167 mg). Colorless oil; yield: 192 mg (80%); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 0.92 (t, *J* = 7.5 Hz, 3H), 1.74 (m, 1H), 1.84 (m, 1H) ,2.03 (bs, 1H), 2.96 (s, 6H), 4.49 (t, *J* = 6.7 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** *δ* 10.3, 31.4, 40.6 (2C), 75.7, 112.5 (2C), 126.9 (2C), 132.6, 150.1; ESI-MS: *m/z* = 180.2 $[M+H]^+$.

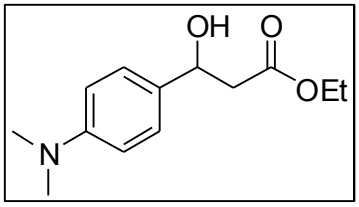


To a solution of (bromomethyl)cyclohexane (1.34 mmol, 200 ml) in anhydrous THF (15 ml) at -78 °C, *n*-BuLi (2.5 M in hexane, 1.34 mmol, 540 mL) was added dropwise at -78°C. After 1 hour, a solution of 4-(dimethylamino)benzaldehyde (1.34 mmol, 200 mg) in anhydrous THF (4 ml) was added dropwise and stirred at 0 °C until complete consumption of the aldehyde (TLC). 20 ml of water was added and the organic phase was extract with EtOAc (3x). The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (cyclohexane/ethyl acetate = 9/1) of the residue give the desired alcohol in 83 % yield: 277 mg. Yellow oil **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 0.92 (t, *J* = 7.1 Hz, 2H), 1.02 (dq, *J* = 12.9 Hz, *J* = 15.3 Hz, 1H), 1.13-1.29 (m, 2H), 1.29-1.45 (m, 3H), 1.60-1.73 (m, 2H), 1.74-1.85 (m, 2H), 1.86-1.93 (m, 1H), 2.39 (bs, 1H), 2.95 (s, 6H), 4.53 (t, *J* = 6.7 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** *δ* 22.5, 25.6, 26.0, 28.0, 31.5, 38.3, 39.8, 40.5 (2C), 74.6, 112.4 (2C), 126.7 (2C), 133.0, 149.8; ESI-MS: *m/z* = 248.3 $[M+H]^+$, 270.2 $[M+Na]^+$, 517.3 $[2M+Na]^+$.

Synthesis of alcohol



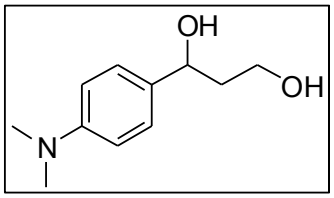
In a three-neck round botton flask charged with nitrogen, to a suspension of metal Zn (6.0 mmol, 390 mg) in anhydrous THF (3.0 ml), TMSCl (0.96 mmol, 121 ml) was added at room temperature and the reaction was put under reflux three times. After 15 minutes, ethyl 2-bromoacetate (6.0 mmol, 665 ml) was added dropwise and the reaction was left under reflux until the complete consumption of metal zink. The solution was cooled down at rt, than a solution of 4-(dimethylamino)benzaldehyde (6.9 mmol, 446 mg) in dry THF (30ml) was added dropwise. After 2.5 hours, AcOEt was added and the resulting mixture was filtered. The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (cyclohexane/ethyl acetate = 9/1) of the residue give **A** in 25% yield (348 mg).



(A): colourless oil; yield: 192 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.28 (t, J = 7.1 Hz, 3H), 2.68 (dd, J = 3.9 Hz, J = 16.1 Hz, 1H), 2.79 (dd, J = 9.4 Hz, J = 16.1 Hz, 1H), 2.95 (s, 6H), 3.00 (d, J = 3.2 Hz), 4.19 (q, J = 7.1 Hz, 2H), 5.06 (dt, J = 3.5 Hz, J = 9.4 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H**); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.2, 40.6 (2C), 43.3, 60.7, 70.2, 112.5 (2C), 126.7 (2C), 130.4, 150.3, 172.5; ESI-MS: m/z = 238.3 $[M+H]^+$, 260.1 $[M+Na]^+$, 497.3 $[2M+Na]^+$.

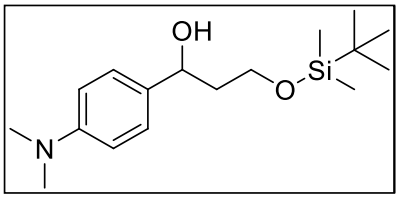
In a two-neck round-bottom flask charged under nitrogen, **A** (0.73 mmol, 174 mg) was dissolved in dry THF (2 ml). The resulting solution was warm up to 60°C, then $LiAlH_4$ (1.10 mmol, 42 mg) dissolved in dry THF (3 ml) was added dropwise. After two hours, the mixture was cooled down to RT and the reaction was followed by TLC, until completion.

Flash chromatography (cyclohexane/ethyl acetate = 4/6) of the residue give **B** in 80% yield (192 mg).



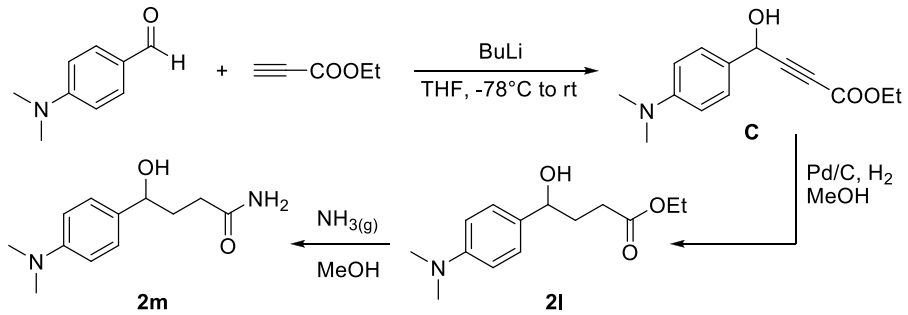
(B): colourless oil; yield: 192 mg (80%); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 2.00-2.12 (m, 1H), 1.86-1.96(m, 1H), 2.49 (bs, 2H), 2.96 (s, 6H), 3.86 (dd, *J* = 5.1 Hz, *J* = 5.9 Hz, 2H), 4.87 (dd, *J* = 3.54 Hz, *J* = 9.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H**); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 40.3, 40.6 (2C), 61.6, 74.4, 112.5 (2C), 126.7 (2C), 128.6, 150.3; ESI-MS: *m/z* =196.2 $[M+H]^+$, 218.1 $[M+Na]^+$, 413.3 $[2M+Na]^+$.

To a solution of **B** (0.25 mmol, 48.8 mg) in THF (1.0 mL) at 0°C, NaH (60% in mineral oil) (0.23 mmol, 9.2 mg) was added. After 30 minutes, TBSCl (0.23 mmol, 34.5 mg) was added and the reaction was stirred at 0°C for 2 hours. The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (cyclohexane/ethyl acetate = 7/3) of the residue give **2k** in 89% yield (68.7 mg).



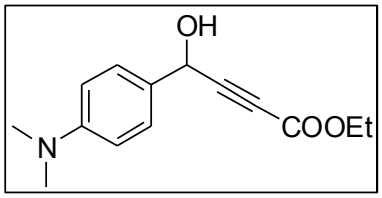
affording the desired alcohol as a yellow oil; yied: 68.7 mg (89%); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= -0.08 (s, 6H), 0.92 (s, 9H),1.83-1.91 (m, 1H), 1.91-2.02 (m, 1H), 2.92 (s, 6H), 3.40 (bs, 1H), 3. 82 (m, 2H), 4.84 (dd, *J* = 3.5 Hz, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J*= 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= -5.5 (2C), 18.1, 25.9 (3C), 40.7 (2C), 62.1, 73.4, 112.5 (2C), 126.6 (2C), 132.6, 150; ESI-MS: *m/z* = 292.3 $[M-OH]^+$, 310.3 $[M+H]^+$, 332.1 $[M+Na]^+$, 641.3 $[2M+Na]^+$.

Synthesis of products



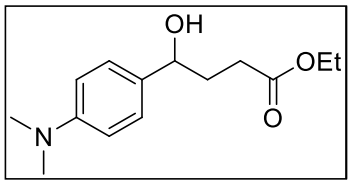
A solution of of *n*BuLi (2.5M in Hexane, 3.36 ml) in 2 ml of dry THF was added dropwise to a solution of 4-(dimethylamino)benzaldehyde (500 mg, 3.35 mmol) and ethyl propiolate (850 ml, 8.4 mmol) in dry THF (5ml), at -78°C. The reaction was stirred for 3 hours and than water (5 ml) was added The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce

pressure. Flash chromatography (cyclohexane/ethyl acetate = 8/2) of the residue give **C** in 61% yield (505 mg).



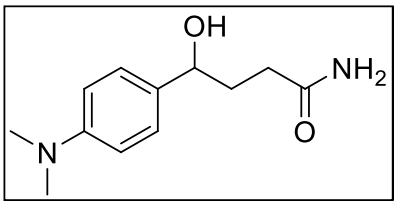
Affording the desired alcohol as a yellow oil; yield: 505 mg (61%); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.31 (t, J = 7.5 Hz), 2.96 (s, 6H), 4.24 (q, J = 7.5 Hz, 2H), 5.48 (bs, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 14.0, 40.0 (2C), 62.0, 64.2, 77.5, 86.8, 112.3 (2C), 125.1, 127.9 (2C), 132.0, 154.3; ESI-MS: m/z = 403.1 $[M+Na]^+$, 783.3 $[2M+Na]^+$.

To a solution of **C** (0.5 mmol, 125 mg) in MeOH (3 mL), Pd/C (10% wt, 13mg) was added and the reaction was keep under H_2 atmosphere (1 atm). After 21 hours the reaction was filtered through a Celite pad and the organic layer was separated and concentrated under reduce pressure. Flash chromatography: (cyclohexane/Et_2O= 8/2) mixture to give **2l** (90%, 117 mg) as yellow oil.



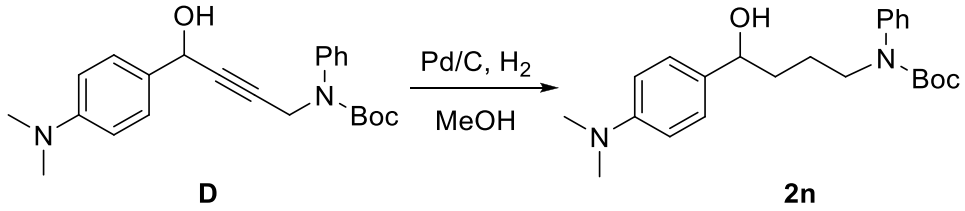
Affording the desired alcohol as a yellow oil; yield: 117 mg (90%); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C):** δ 1.26 (t, J = 7,5 Hz 1H), 2.01 (bs, 1H), 1.99-2.18 (m, 2H), 2.40 (ddd, J = 8.3 Hz, J = 2.7 Hz, J = 2.0 Hz, 2H), 2.95 (s, 6H), 4.13 (q, J = 7.1 Hz, 2H), 4.65 (dd, J = 5.5 Hz, J = 7.1 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 7.23 (d, J= 8.7 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.2, 30.9, 33.6, 40.6 (2C), 60.4, 73.4, 112.5 (2C), 126.8 (2C), 131.9, 150.3, 173.9; ESI-MS: m/z = 234.2 $[M-OH]^+$, 252.2 $[M+H]^+$, 274.1 $[M+Na]^+$, 525.2 $[2M+Na]^+$.

$NH_{3(g)}$ was bubbled for 10 minutes to a solution of **2l** (0.55 mmol, 138 mg) in MeOH (3 mL). After 21 hours the reaction was concentrated under reduce pressure and the product was purify by flash chromatography: (AcOEt/MeOH= 9/1) to afford the product **2m** (95%, 119 mg) as yellow oil.

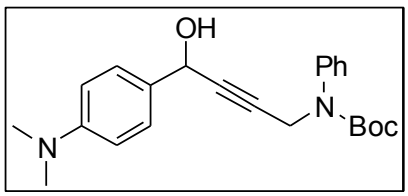


Affording the desired alcohol as a yellow oil; yield 119 mg (95%); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 2.04 (m, 2H), 2.32 (m, 2H), 2.93 (s, 6H), 4.65 (t, J = 5.2 Hz, 1H), 5.71 (bs, 1H), 5.87 (bs, 1H), 6.70 (d, J = 8.8 Hz, 2H), 7.21 (d, J= 8.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 32.3, 34.2, 40.7 (2C), 73.1, 112.7 (2C), 126.8 (2C), 132.4, 150.3, 176.6; ESI-MS: m/z = 205.2 $[M-OH]^+$, 223.3 $[M+H]^+$, 245.1 $[M+Na]^+$, 467.3 $[2M+Na]^+$.

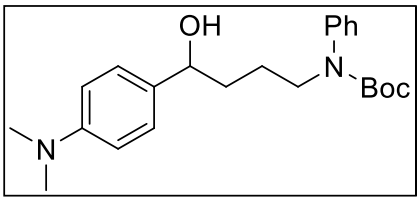
Synthesis of product



D **2n**



The compound **D** was prepared adding alkyne derivate (prepared according to the literature procedure [i]) to 4-(dimethylamino)benzaldehyde. Orange oil; yield: 94%. **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.41 (s, 9H), 2.91 (s, 6H), 4.44 (d, J = 1.6 Hz, 2H), 5.32 (bs, 1H), 6.64 (m, 2H), 7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 28.2, 40.0, 40.5 (2C), 64.3, 80.9, 82.2, 84.0, 112.3 (2C), 126.2, 126.5, 127.8, 128.3 (2C), 128.6 (2C), 142.0, 150.6, 154.1; ESI-MS: m/z = 286 $[M\text{-}OH]^-$, 403.1 $[M+Na]^+$, 783.3 $[2M+Na]^+$.

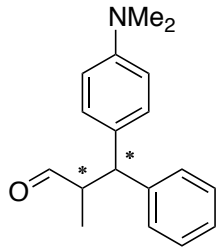


To a solution of **D** (0.34 mmol, 129 mg) in MeOH (3 mL), Pd/C (10% wt, 13 mg) was added and the reaction was keep under H_2 atmosphere (1 atm). After 21 hours the reaction was filtered through a Celite pad and the organic layer was separated and concentrated under reduce pressure. Flash chromatography: (cyclohexane/Et_2O= 8/2) mixture to give the desired alcohol in (90%, 117 mg) as orange oil; **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.42 (s, 9H), 1.50-1.61 (m, 1H), 1.61-1.76 (m, 2H), 1.76-1.85 (m, 1H), 2.95 (s, 6H), 3.57-3.77 (m, 2H), , 4.58 (dd, J = 5.5 Hz, J = 7.5 Hz, 1H), 6.71 (d, J = 9.1 Hz, 2H), 7.12 (m, 3H), 7.19 (d, J= 8.7 Hz, 2H); 7.32 (t, J = 7.9 Hz, 2H) **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 25.0, 28.3 (3C), 35.6, 40.7 (2C), 49.7, 74.0, 80.0, 112.6 (2C), 125.9 (2C), 126.8 (2C), 127.1, 128.7 (2C), 132.6, 142.4, 150.2, 154.8; ESI-MS: m/z = 367.3 $[M\text{-}OH]^+$, 407.1 $[M+Na]^+$, 791.3 $[2M+Na]^+$.

General Procedure for the enantioslelectivity α-alkylation benzylic benzydrylic alcohols

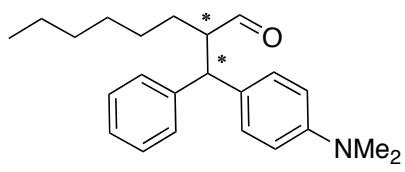
A vial was added alcohol (0.1mmol, 1eq), catalyst (20mol%, 0.02mmol), and aldehyde (0.3mmo, 3eq) in anhydrous hexane (0.1M), at 0°C. The mixture was stirred and a solution of $In(OTf)_3$ (20mol%, 0.33M in CH_3CN) was added. The solution was stirred for 8 hours at 0°C. The reaction was worked up with H_2O. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtain an orange oil. The residue was purified by flash chromatography (SiO_2; cyclohexane:diethylether; 9:1)

3-(4-(dimethylamino)phenyl)-2-methyl-3-phenylpropanal (table6, entry 1).



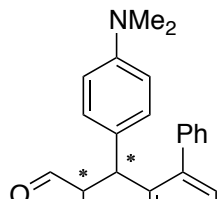
Prepared according to the general procedure the compound was purified by flash chromatography column (SiO_2, cyclohexane: diethyl ether, 9:1) afforded the desired product as a colourless oil (**80% yield, d.r---, 98maj:96min% ee**) The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel OD-H column: gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 16.3min, *τM(mino) r* = 15.5min, *τm(majo)r* = 18.1min, *τm(min)r* = 24.1min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.58 (d, 2H, J = 3.3Hz, 2 CHO), 7.30-7.23 (m, 8H, HAr), 7.19-7.10 (m, 6H, HAr), 6.66 (t, 4H, J = 8.9Hz), 3.99 (d, $1H_{min}$, J = 10.9Hz), 3.98 (d, $1H_{maj}$, J = 11.1Hz), 3.29-3.19 (m, $2H_{maj+min}$, CH), 2.91 (s, $6H_{min}$, $(CH_3)_2N$), 2.89 (s, $6H_{maj}$, $(CH_3)_2N$), 1.06 (d, $3H_{min}$, J = 6.9Hz), 1.02 (d, 3H, J = 6.65Hz) **^{13}C NMR (125 MHz, $CDCl_3$) δ** 204.7 (2CHO), 149.3 (2), 142.9 (2), 129.8 (2), 128.7, 128.6, 128.61(4), 128.0 (4), 127.9 (2), 126.4, 126.3, 112.8 (2), 112.8 (2), 52.6 (2), 50.2 (2), 40.5 (2), 29.6 (2), 13.7$_{maj}$, 13.5$_{min}$. **HPLC-MS** calcul for ($C_{18}H_{21}NO$) ($M+H^+$) 268, (M+Na+) 290 , t_m = 10.6min, t_M = 10.7min.

2-((4-(dimethylamino)phenyl)(phenyl)methyl)octanal (table 6, entry2)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 9:1) to afford the desired product as a colourless oil (**85% yield, d.r --, 89maj:81min% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel OD-H column: gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 17.0 min, *τM(mino) r* = 16.3 min, *τm(majo)r* = 18.1min, *τm(min)r* = 25.6min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.47 (d, 2H, J = 4.4Hz, CHO), 7.30-7.24 (m, 8H, HAr), 7.19-7.13 (m, 2H, HAr), 7.12 (d, 4H, J = 8.5Hz, HAr), 6.67 (d, $2H_{min}$, J = 8.5Hz), 6.63 (d, $2H_{maj}$, J = 8.9Hz), 4.03 (d, 2H, J = 11.3Hz), 3.16-3.08 (m, $2H_{min+maj}$), 2.91 (s, $6H_{min}$), 2.88 (s, $6H_{maj}$), 1.59-1.49 (m, 2H), 1.44-1.34 (m, 2H), 1.33-1.15 (m, 16H), 0.85 (t, $3H_{maj}$, J = 7.15Hz), 0.84 (t, $3H_{min}$, J = 7.0Hz). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 204.6 (2CHO), 149.3 (2C), 143.0 (2C), 134.6 (2C) 129.8 (2CH), 128.6 (2CH), 128.67 (2CH), 128.5 (2CH), 127.9 (2CH), 126.3 (2CH), 112.8 (2CH),112.7 (2CH), 112.77 (2CH), 55.8 (2CH), 51.5 (2CH), 40.5 ($2CH_3$), 40.4 ($2CH_3$), 31.4 ($2CH_2$), 29.1 ($2CH_2$), 28.6 ($2CH_2$), 26.8 ($2CH_2$), 22.46 ($2CH_2$); 13.9 ($2CH_3$) **HPLC-MS** calcu. for ($C_{23}H_{31}NO$) (M+H) 338 ($M+Na^+$) 360 t_M = 15.6 min, t_m = 14.7min

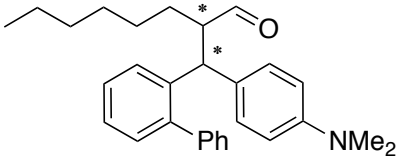
3-(biphenyl-2-yl)-3-(4-(dimethylamino)phenyl)-2-methylpropanal (table 6, entry 3)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a colourless oil (**90% yield ,d.r 5:1, 99maj:83min% ee**) The ee was determined

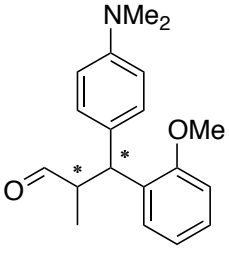
directly with crude product by **HPLC analysis** Daicel Chiralcel OD-H column:gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 19.1 min, *τM(mino) r* = 20.8 min, *τm(majo)r* = 21.6 min, *τm(min)r* = 23.8 min. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.47 (d, 1Hmaj, J = 3.38Hz), 9.33 (d, 1Hmin, J = 3.3Hz), 7.68 (d, 1H, J = 8.0Hz), 7.55 (d, 1H, J = 8.0Hz); 7.49-7-30 (m, 9H), 7.25-7.13 (m, 7H), 7.03 (d, 2H, J = 8.6Hz), 6.88 (d, 2H, J = 8.6Hz), 6.64 (d, $2H_{min}$, J = 9.1Hz), 6.6 (d, $2H_{maj}$, J = 9.1Hz), 4.18 (d, $1H_{min}$, J = 11.3Hz), 4.05 (d, $1H_{maj}$, J = 11.0Hz), 3.29-3.13 (m, $2H_{maj+min}$), 2.90 (s, $6H_{maj}$), 2,89 (s, $6H_{min}$), 0.94 (d, $3H_{min}$, J = 6.9Hz), 0.88 (d, $3H_{maj}$, J = 6.9Hz) **^{13}C NMR (50MHz, $CDCl_3$) δ** 204.7 (2CHOmaj+min); 149.1 (2C); 142.2; 141.6; 140.2 (2C); 130.3 (2C); 129.6 (2C); 129.5 (2C); 129.0 (4C); 128.7 (4C); 127.9 (4C); 127.8 (4C); 127.2 (2C); 127.0 (2C); 126.1 (2C); 112.6 (4C); 51.7 (2C); 47.7 (2C); 40.6 (4C); 13.5 (2C). **HPLC-MS** calcu. for ($C_{24}H_{25}NO$) (M+H) 286 t_M = 4.3min.

2-(biphenyl-2-yl(4-(dimethylamino)phenyl)methyl)octanal (table 6, entry 4)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to affor the desired product as a colourless oil (**66%yield, d.r 3:1, 93maj:71min%ee**). The ee was determined directly with crude product from alcohol by **HPLC analysis** Daicel Chiralcel OD-H column: (Reduction to alcohol) gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 19.2 min, *τM(mino) r* = 23.8 min, *τm(majo)r* = 28.1 min, *τm(min)r* = 26.5 min **^{1}HNMR (200MHz,$CDCl_3$) δ** 9.38(d, 1Hmin,J = 4.8Hz); 9.25 (d, $1H_{maj}$, J = 4.4Hz); 7.53-7.34 (m, 9H); 7.28-7.14 (m, 9H); 6.95 (d, $2H_{maj}$,J = 8.6Hz); 6.91(d, $2H_{min}$,J = 7.6Hz); 6.63 (d, $2H_{min}$, J = 7Hz); 6.59 (d, $2H_{maj}$, J = 8.8Hz); 4.24 (d, $1H_{maj}$, J = 11.4Hz); 4.14 (d, $1H_{min}$, J = 11,4Hz); 3.0 (m, $2H_{maj+min}$); 2.93 (s, $6H_{min}$); 2.89 (s, $6H_{maj}$); 1.46-1.18 (m, 20H); 0.871 (t, $6H_{maj+min}$, J = 7.8Hz). **^{13}C NMR (50MHz,$CDCl_3$) δ** 204.7 (2CHO); 149.2 (2C); 142.5 (2C); 141.7 (2C); 140.2 (2C); 130.2 (2C); 129.7 (4C); 128.8 (4C); 127.9 (6C); 127.5; 127.0 (3C); 126.7 (2C); 125.8 (2C); 112.7 (4C); 57.4 (C_{min}); 57.1 (C_{maj}); 46.4 (C_{min}); 46.1 (C_{maj}); 40.5 (4C); 31.5 (2C); 29.6; 29.1 (2C); 28.4 (2C); 26.9; 22.5 (2C); 14.3 (C_{min}); 14.0 (C_{maj}). **HPLC-MS** calcu.from alcohol for ($C_{29}H_{37}NO$) (M+H) 416 t_M = 15.8min, t_m= 16.4min

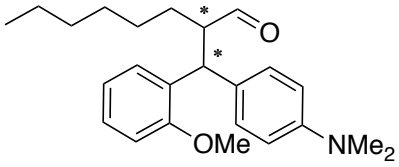
3-(4-(dimethylamino)phenyl)-3-(2-methoxyphenyl)-2-methylpropanal (table 6, entry 5)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a yellow oil (**70% yield,d.r 2:1, 98maj:91min% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel IB column: gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 18.2 min, *τM(mino) r* = 20.2 min, *τm(majo)r* = 21.4 min, *τm(min)r* = 25.0 min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.59 (d, $1H_{min}$, J = 3.2Hz), 9.48 (d, $1H_{maj}$, J = 3.2Hz), 7.19-7.11 (m, 8H), 6.90 (t, 2H, J = 7.7Hz), 6.85 (d, 1H, J = 8.3Hz), 6.80 (d, 1H, J = 8.3Hz), 6.67 (

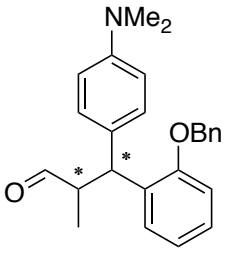
d, 2H$_{maj}$, J = 8.7Hz), 6.64 (d, 2H$_{min}$, J = 8.7Hz), 4.61 (d, 1H$_{min}$, J = 10.7Hz), 4.46 (d, 1H$_{maj}$, J = 11.2Hz), 3.83 (s, 3H$_{min}$, OCH$_3$), 3.79 (s, 3H$_{maj}$, OCH$_3$), 3.31-3.24 (m, 1H$_{min}$), 3.23-3.16 (m, 1H$_{maj}$), 2.91 (s, 6H), 2.89 (s, 6H), 1.04 (d, 3H$_{maj}$, J = 6.6Hz), 0.99 (d, 3H$_{min}$, J = 6.6Hz) **^{13}C NMR (125 MHz, CDCl$_3$) δ** 205.3 (CHO$_{min}$), 205.1 (CHO$_{maj}$), 157.0 (C), 156.5 (C), 149.1 (C), 149.0 (C), 131.3 (C), 131.2 (C), 130.0 (C), 129.6 (C), 129.1 (2CH), 129.0 (2CH), 128.4 (2CH), 128.2 (2CH), 127.4 (1CH), 127.2 (1CH), 120.7 (2CH), 112.6 (2CH), 110.7 (2CH), 55.3 (2CH$_3$), 50.1 (CH), 49.7 (CH), 44.5 (CH), 44.2 (CH), 40.5 (4CH$_3$), 13.6 (CH$_{3min}$); 13.2 (CH$_{3maj}$). **HPLC –MS** calcu. for $C_{19}H_{23}NO_2$ (M+H$^+$) 298 t$_{min}$ = 10.7 min, t$_{maj}$ = 10.9min.

2-((4-(dimethylamino)phenyl)(2-methoxyphenyl)methyl)octanal (table 6, entry 6)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a yellow oil (**86% yield,d.r 1:1, 90:88% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel OD-H column:gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 17.4 min, *τM(mino) r* = 21.0 min, *τm(majo)r* = 19.0 min, *τm(min)r* = 25.4min. **^{1}H NMR (400 MHz, CDCl$_3$) δ** 9.4 (d, 1H$_{min}$, J = 4.2Hz), 9.39 (d, 1H$_{maj}$, J = 4.6Hz), 7.2-7.0 (m, 8H), 6.8 (t, 2H, J = 7.5Hz), 6.78 (d, 2H, J = 8.3Hz), 6.6 (d, 2H$_{maj}$, J = 7.7Hz), 6.6 (d, 2H$_{min}$, J = 8.2Hz), 4.6 (d, 1H$_{min}$, J = 11.9Hz), 4.5 (d, 1H$_{maj}$, J = 11.5Hz), 3.8 (s, 3H$_{min}$), 3.7 (s, 3H$_{maj}$), 3.2-3.1 (m, 1H$_{min}$), 3.1-3-0 (m, 1H$_{maj}$), 2.9 (s, 6H$_{maj}$), 2.8 (s, 6H$_{min}$), 1.7-1.6 (20H, m), 0.8 (t, 3H$_{min}$, J = 5.1Hz), 0.84 (t, 3H$_{maj}$, J = 7.1Hz). **^{13}C NMR (50MHz,CDCl$_3$) δ** 205.2 (2CHO); 157.0 (2C); 149.2 (2C); 131.3 (2C); 130.0 (2C); 129.1 (2CH); 129.0 (2CH); 128.4 (CH); 128.1 (CH); 127.2 (2CH); 120.8 (2CH); 112.7 (4CH); 110.9 (2CH); 55.4 (CH$_3$); 55.3 (CH$_3$); 43.4 (2CH); 43.1 (CH); 43.0 (CH); 40.6 (4CH$_3$); 31.6 (CH$_2$); 31.5 (CH$_2$); 30.7 (CH$_2$); 29.7 (CH$_2$); 29.1 (CH$_2$); 28.2 (CH$_2$); 26.8 (CH$_2$); 24.7 (CH$_2$); 22.6 (CH$_2$); 22.5 (CH$_2$); 14.0 (2CH$_3$). **HPLC –MS** calcu. for $C_{24}H_{33}NO_2$ (M+H$^+$) 368 (M+H+Na) 390, t$_{maj}$ = 15.0min

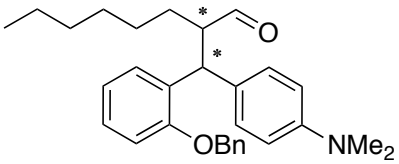
3-(2-(benzyloxy)phenyl)-3-(4-(dimethylamino)phenyl)-2-methylpropanal (table 6, entry 9)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a yellow oil (**60% yield, d.r 1:1, 94:95% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel IC column: gradien from 99:1 n-thexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 23.6 min, *τM(mino) r* = 24.7 min, *τm(majo)r* = 33.4 min, *τm(min)r* = 38.7 min. **^{1}H NMR (400MHz, CDCl$_3$) δ** 9.48 (d, 1H, J = 2.4Hz); 9.40 (d, 1H, J = 2.8Hz); 7.39 -7.14 (m, 12H); 7.05 (d, 2H, J = 8.4Hz); 7.03 (d, 2H, J = 8.4Hz); 6.86-6.81 (m, 2H,); 6.77 (d, 2H, J = 7.6Hz); 6.85 (d, 2H, J = 6.4Hz); 6.56 (d, 2H, J = 8.8Hz); 6.54 (d, 2H, J= 10.4Hz); 4.99 (s, 2H); 4.95 (s , 2H); 4.56 (d, 1H, J = 10.8Hz); 4.41 (d, 1H, J = 11.6Hz); 3.21-3.17 (m, 1H); 3.15-3.10 (m, 1H); 2.83 (s, 6H); 2.81 (s, 6H); 0.94 (d, 6H, J = 6.8Hz). **^{13}C NMR (125,CDCl$_3$) δ** 205.3 (CHO); 205.0 (CHO); 156.1 (C); 155.7 (C); 149.2 (2C);

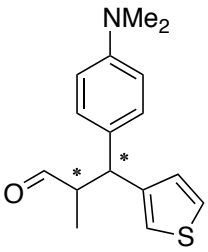
137.1 (2C); 131.6 (C); 131.4 (C); 129.9 (C); 129.5 (C); 129.3 (2CH); 129.1 (2CH); 128.5 (2CH); 128.4 (3CH); 128.3 (CH); 128.1 (CH); 127.8 (CH); 127.8 (CH); 127.5 (2CH); 127.4 (2CH); 127.2 (CH); 121.0 (2CH); 112.7 (2CH); 112.6 (CH); 112.6 (CH); 112.1 (2CH); 70.2 (CH_2); 70.13 (CH_2); 50.1 (CH); 49.6 (CH); 44.5 (CH); 44.4 (CH); 40.6 (4CH_3); 13.7 (CH_3); 13.4 (CH_3). **HPLC-MS** calcul. $C_{25}H_{27}NO_2$

2-(biphenyl-2-yl(4-(dimethylamino)phenyl)methyl)octanal (table 6, entry 10)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to affor the desired product as a yellow oil (**79% yield, d.r 1:1, 90:81% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel OD-H column: gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 19.9 min, *τM(mino) r* = 23.8 min, *τm(majo)r* = 21.6 min, *τm(min)r* = 28.0 min. **^{1}H NMR (400MHz, $CDCl_3$) δ** 9.38 (d, 1H_{maj}, J = 4.4Hz); 9.29 (d, 1H_{min}, J = 4.8Hz); 7.31-7.16 (m, 12H); 7.09-6.99 (m, 3H); 6.84-6.80 (m, 3 H); 6.81 (d, 2H_{maj}, J = 8.4Hz); 6.74 (d, 2H_{min}, J = 8.4Hz); 6.56 (d, 2H_{min}, J = 8.4Hz); 6.52 (d, 2H_{maj}, J = 8.8Hz); 4.99 (s, 2H_{maj}); 4.94 (s, 2H_{min}); 4.62 (d, 1H_{maj}, J = 10.8Hz); 4.49 (d, 1H_{min}, J = 11.6Hz); 3.07 (m, 1H_{maj}); 3.00 (m, 1H_{min}); 2.82 (s, 6H_{min}); 2.79 (s, 6H_{maj}); 1.48-1.27 (m, 4H); 1.18-1.08 (m, 16H); 0.81 (t, 3H_{min}, J = 7.2Hz); 0.73 (t, 3H_{maj}, J = 7.6Hz). **^{13}C NMR (50MHz,$CDCl_3$) δ** 205.2(CHO_{maj}); 204.9 (CHO_{min}); 156.1 (2C); 149.2 (2C); 137.1 (2C); 131.4 (2C); 129.7 (2C); 129.3 (2C); 129.1 (2C); 128.5 (2C); 128.4 (2C); 128.1 (2C); 127.8 (2C); 127.5 (2C); 127.4 (2C); 127.2 (2C); 121.0 (2C); 112.7 (2C); 112.6 (2C); 112.1 (C); 112.0 (C); 70.1 (2C); 55.9 (C); 55.3 (C); 43.1 (2C); 40.6 (2C); 40.5 (2C); 31.5; 30.9; 29.7; 29.2; 28.5; 28.3; 26.9; 26.8; 22.6; 22.4; 14.0 (2C). HPLC-MS calcul.for $C_{30}H_{37}NO_2$ ($M+H^+$) 444 ($M+Na^+$) 466 t_M= 18.0min, t_m = 18.4.

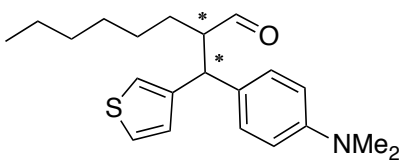
3-(4-(dimethylamino)phenyl)-2-methyl-3-(thiophen-3-yl)propanal (table 6, entry 7)



Prepared according to the general procedure. The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a colourless oil (**84% yield, d.r 2:1, 93%maj:90min% ee**). The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel IA column gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 8 nm: *τM(majo)r* = 21.7 min, *τM(mino) r* = 24.3 min, *τm(majo)r* = 28.7 min, *τm(min)r* = 23.1 min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.67 (d, 1Hmaj, J = 3Hz), 9.57 (d, 1Hmin, J = 2.9Hz), 7.18-7.0 (m, 6H), 7.13 (d, 2Hmaj, J = 8.3Hz), 6.92-6.89 (m, 2H), 6.70-6.66 (m, 4H), 4.32 (d, 1Hmaj, J = 10.2Hz), 4.31 (d, 1Hmin , J = 9.9Hz), 3.19-3.08 (2H,m), 2.94 (s, 6Hmaj), 2,92 (s, 6Hmin), 1.12 (d, 3H, J = 6.8Hz), 1.02 (d, 3H, J = 6.8Hz). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 204.1 (CHO_{maj}), 204.0 (CHO_{min}), 149.5 (C_{maj}), 149.2 (C_{min}), 147.1 (C_{maj}), 146.8 (C_{min}), 132.7 (C_{min}), 129.4 (CH_{min}), 129.3 (CH), 129.2 (C_{maj}), 128.7 (2CH), 128.6 (CH), 126.6 (CH), 126.5 (CH), 124.2 (CH), 124.0 (2CH), 112.7 (CH), 112.6 (2CH), 112.4

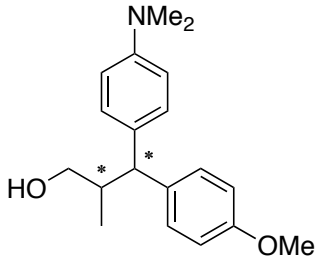
(CH), 52.0 (CH_{maj}), 51.9 (CH_{min}), 48.0 (CH), 47.2 (CH), 40.5 ($2CH_3$), 40.4 ($2CH_3$), 13.5 (CH_{3min}), 13.4 (CH_{3maj}). **HPLC-MS calcu**. for $C_{16}H_{19}NOS$ ($M+H^+$) 274, tmin = 10.3min, tmaj = 10.4min.

2-((4-(dimethylamino)phenyl)(thiophen-3-yl)methyl)octanal (table 6, entry 8)

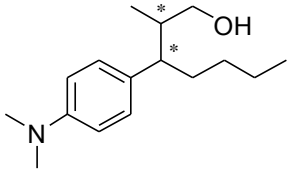


Prepared according to the general procedure The residue was purified by flash chromatography (SiO_2, cyclohexane: Et_2O, 7:3) to afford the desired product as a colourless oil (**70% yield,d.r 1.5:1, 88%maj:80%min ee**) The ee was determined directly with crude product by **HPLC analysis** Daicel Chiralcel IC column:gradient from 99:1 n-hexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 8 nm: *τM(majo)r* = 20.4 min, *τM(mino) r* = 19.5 min, *τm(majo)r* = 28.1 min, *τm(min)r* = 36.0 min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.58 (d, 1H,J = 4.3Hz), 9.46 (d, 1H, J = 4.3Hz), 7.15-7.05 (m, 8H), 6.92-6.86 (m, 2H), 3.96 (d, 2H, J = 8.8Hz), 6.65 (d, 2H, J = 8.8Hz), 4.33 (d, $1H_{maj}$, J = 10.4Hz), 4.32 (d, $1H_{min}$, J = 10.2Hz), 3.10-2.96 (m, 2H), 2.93 (s, 6H, $N(CH_3)_2$), 2.90 (s, 6H, $N(CH_3)_2$), 1.69-1.39 (m, 4H), 1.39-1.14 (m, 16H), 0.85 (t, 3H, J = 6.5Hz), 0.84 (t, 3H, J = 7.0Hz). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 204.2 (CHO_{maj}), 203.9 (CHO_{min}), 149.5 (2C), 147.1 (C), 147.0 (C), 129.3 (C), 129.2 (C), 128.7 (4CH), 126.6 (2CH), 124.4 (2CH), 124.0 (2CH), 112.7 (4CH), 57.4 (2CH), 46.9 (CH), 46.3 (CH), 40.4 ($2CH_3$), 31.5 ($2CH_2$), 29.6 (CH_2), 29.1 ($2CH_2$), 28.6 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.7 ($2CH_2$), 22.4 ($2CH_2$), 14.0 ($2CH_3$). **HPLC-MS** calcul.for $C_{21}H_{29}NO_S$ ($M+H^+$) 344 (M+Na+)366, t_M = 14.9min, t_m = 14.3min

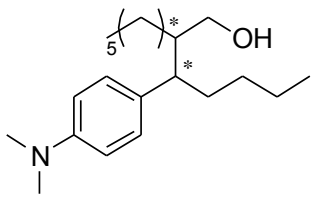
Prepared according to the general procedure. The residue was diluted with MeOH at 0°C for 5 minuts



stirring and 2 eq of $NaBH_4$ was slowly added. The reaction was quenched with water and concentrated under reduce pressure. The crude solution was extracted twice times with EtOAc. The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography (SiO_2; cyclohexane:Et_2O; 7:3) to afford the desired product as a yellow oil **(85% yield, d.r 2:1, 95:92 %ee**) The ee was determined by **HPLC analysis** Daicel Chiralcel IC column:gradient from 99:1 n-thexane/*i*-PrOH to 90:10 in 30 min, flow rate 0.50 mL/min, 30°C, λ = 254, 4 nm: *τM(majo)r* = 39.2 min, *τM(mino) r* = 40.3 min, *τm(majo)r* = 43.0 min, *τm(min)r* = 42.3 min. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.21 (d, 2H, J= 8.6Hz), 7.20 (d, 2H, J = 8.6Hz), 7.15 (d, 2H, J = 8.6Hz); 7.14 (d, 2H, J = 8.6Hz), 6.81 (d, 2H, J = 8.4Hz), 6.80 (d, 2H, J = 8.6Hz), 6.67 (d, 2H, J = 8.7Hz), 6.66 (d, 2H, J = 8.8Hz), 3.76 (s, 3H, OMe_{maj}), 3.75 (s, 3H, OMe_{min}), 3.61-3-53 (m, 2H, CH_2OH), 3.57 (d, 1H, J= 10.8Hz), 3.55 (d, 1H, J = 11.2Hz), 3.44-3.37 (m, 2H, CH_2OH), 2.89 (s, 6H, NMe_{2min}), 2.87 (s, 6H, NMe_2maj), 1.58 (s,OH, 2H), 0.96 (d, 3H, J = 6.6Hz), 0.93 (d, 3H, J = 6.7Hz) **^{1}H NMR (50 MHz, $CDCl_3$) δ** 149.1; 136.8, 132.2, 128.5 (2), 128.6(2), 128.3, 114.0, 113.8, 113.0, 112.8, 67.0 (2), 55.1, 53.8, 40.6, 39.5, 16.3 (2).

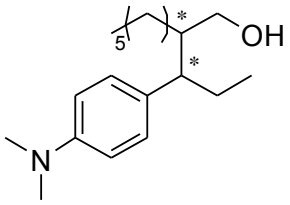


Prepared according to the genereal procedure. The residue was purified by flash chromatography (SiO2, cyclohexane: EtOAc = 8:2) to afford the desired product as a yellowish oil; yield 94%; d.r.= 4.5:1 ratio (*anti*:*syn*). Anti diastereisomer ee = 98% : Syn diasterisomer ee = 90% ee. was determined was determined by integration of RCHO ^{1}H NMR signal: δ_{anti}= 9.66 (d, *J* = 3.2 Hz, 1H), δ_{syn}= 9.56 (d, *J* = 2.4 Hz, 1H). The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH from 99:1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 23.5 min., *τmajor* = 31.7 min; *Syn* diasteroisomer *τmajor* = 27.4 min., *τminor* = 30.8 min. **^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ_{anti}** 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H), 1.09-1.17 (m, 2H), 1.19-1.27 (m, 4H), 1.66 (q, *J* = 7.9 Hz, 2H), 1.82-1.91 (m, 1H), 2.33 (m, 1H), 2.58-2.63 (m, 1H), 2.93 (s, 6H), 3.44 (dd, *J* = 4.7 Hz, *J* = 5.9 Hz, 1H), 3.53 (dd, *J* = 6.3 Hz, *J* = 10.6 Hz, 1H), 6.70 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H), 7.02 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H); **δ_{syn}**= 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H), 1.09-1.17 (m, 2H), 1.19-1.27 (m, 4H), 1.66 (q, *J* = 7.9 Hz, 2H), 1.82-1.91 (m, 1H), 2.33 (m, 1H), 2.58-2.63 (m, 1H), 2.93 (s, 6H), 3.26 (dd *J* = 4.7 Hz, *J* = 5.9 Hz, 1H), 3.45 (dd *J* = (dd, *J* = 6.3 Hz, *J* = 10.6 Hz, 1H), 6.70 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H), 7.02 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** =14.0, 22.8, 30.1, 32.8, 40.8 (2C), 41.7, 45.9, 47.8, 66.7, 112.5 (2C), 129.3 (2C), 130.9, 149.0; **δ_{syn}** = 14.0, 22.8, 29.7, 31.9, 40.8 (2C), 41.7, 45.9, 47.8, 67.1, 112.8 (2C), 128.7 (2C), 130.9, 149.0; ESI-MS: *m/z* = 250.2 $[M+H]^+$.

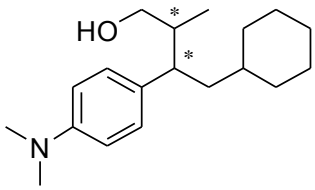


Prepared according at the general procedure was obtained the desired product as a yellowish oil; yield 94% d.r.= 2:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signal δ_{anti}= 9.55 (d, *J* = 4.4 Hz, 1H), δ_{syn}= 9.43 (d, *J* = 4.0 Hz, 1H). The title compound was isolated by flash column chromatography (SiO_2, Cyclohexane:ether = 8/2) as mixture of diastereoisomers. The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 2:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 92%; *Syn* diastereoisomer ee= 86%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH fron 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 17.7 min., *τmajor* = 25.4 min; *Syn* diasteroisomer *τmajor* = 21.6 min., *τminor* = 23.8 min. **^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}**= 0.83 (t, *J* = 7.5, 3H), 0.85 (t, *J* = 7.5 Hz, 3H), 1.03-1.15 (m, 2H), 1.16-1.44 (m, 10H), 1.53-1.77 (m, 2H), 1.95-2.13 (m, 1H), 2.26-2.40 (m, 1H), 2.43-2.49 (m, 1H), 2.69 (dd, *J* = 6.7 Hz, *J* = 14.2 Hz, 1H), 2.93 (s, 6H), 3.54 (dd, *J* = 5.9 Hz, *J* = 10.6 Hz, 1H), 3.66 (dd, *J* = 3 Hz, *J* = 11.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H); **δ_{syn}**= 0.81 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H), 1.03-1.15 (m, 2H), 1.16-1.44 (m, 10H), 1.53-1.77 (m, 2H), 1.95-2.13 (m, 1H), 2.26-2.40 (m, 1H), 2.43-2.49 (m, 1H), 2.69 (dd, *J* = 6.7 Hz, *J* = 14.2 Hz, 1H), 2.93 (s, 6H), 3.36 (dd, *J* = 4.7 Hz, *J* = 11.0 Hz, 1H), 3.51 (dd, *J* = 4.7 Hz, *J* = 11.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}**= 14.0, 14.1, 22.7, 22.9, 27.6, 29.6, 30.2, 31.8, 32.9, 40.8

(2C), 41.7, 45.3, 46.1, 63.5, 112.6 (2C), 129.2 (2C), 131.5, 148.9**;** $\boldsymbol{\delta_{syn}}$= 14.0, 14.1, 22.6, 22.8, 27.7, 29.8, 30.0, 31.9, 32.9, 40.7 (2C), 41.7, 45.3, 46.5, 63.8, 112.8 (2C), 128.8 (2C), 131.5, 148.9; EI-MS: *m/z* = 302.9 $[M\text{-}OH]^+$, 320.3 $[M+H]^+$, 342.4 $[M+Na]^+$.

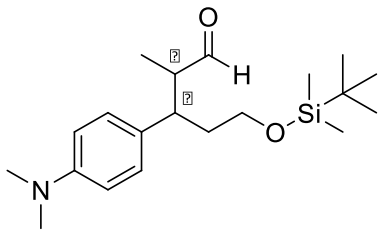


Prepared according at the general procedure was obtained the desired product as a colourless oil; yield 90% d.r.= 3:1 ratio (*anti*-**5i**:*syn*-**5i**) was determined was determined by integration of RCHO ^{1}H NMR signal δ_{anti}= 9.50 (d, *J* = 4.4 Hz, 1H), δ_{syn}= 9.39 (d, *J* = 4.0 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 3:1 ratio (*anti*-**5i**:*syn*-**5i**). *Anti* diastereoisomer ee = 76%; *Syn* diastereoisomer ee= 94%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH fron 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 19.9 min., *τmajor* = 29.6 min; *Syn* diasteroisomer *τmajor* = 24.2 min., *τminor* = 26.2 min**. ^{1}H-NMR (400 MHz, $CDCl_3$, 25°C):** $\boldsymbol{\delta_{anti}}$= 0.77 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 1.19-1.36 (m, 10H), 1.56-1.74 (m, 3H), 2.59 (m, 1H), 2.93 (s, 6H), 3.55 (dd, *J* = 5.8 Hz, *J* = 10.0 Hz, 1H), 3.67 (dd, *J* = 4.1 Hz, *J* = 10.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H); $\boldsymbol{\delta_{syn}}$= 0.73 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 1.19-1.36 (m, 10H), 1.56-1.74 (m, 3H), 2.37 (m, 1H), 2.93 (s, 6H), 3.37 (dd, *J* = 4.4 Hz, *J* = 10.0 Hz, 1H), 3.50 (dd, *J* = 4.7 Hz, *J* = 10.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)**: $\boldsymbol{\delta_{anti}}$= 12.6, 14.1, 22.6, 25.3, 27.6, 29.6, 31.8, 40.8 (2C), 45.8, 47.3, 63.4, 112.6 (2C), 129.2 (2C), 132.0, 148.8**;** $\boldsymbol{\delta_{syn}}$= 12.5, 14.1, 22.6, 25.3, 27.6, 29.6, 31.8, 40.8 (2C), 45.8, 47.3, 63.8, 112.8 (2C), 128.9 (2C), 132.0, 148.8; ESI-MS: *m/z* = 292.3 $[M+H]^+$, 314.3 $[M+Na]^+$.

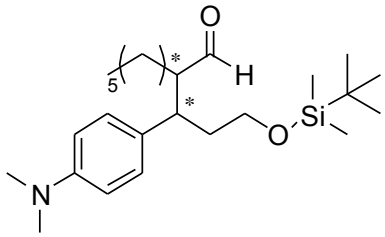


According at the general procedure was obtained the desired product as a yellowish oil; yield 88%; d.r.= 5:1 ratio (*anti*-:*syn*-) was determined was determined by integration of RCHO ^{1}H NMR signal δ_{anti}= 9.68 (d, *J* = 3.4 Hz, 1H), δ_{syn}= 9.57 (d, *J* = 2.2 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/AcOEt = 8/2) as mixture of diastereoisomers in 5:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 92%; *Syn* diastereoisomer ee= 86%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH from 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 22.9 min., *τmajor* = 30.8 min; *Syn* diasteroisomer *τmajor* = 26.7 min., *τminor* = 30.0 min; **^{1}H NMR (400 MHz, $CDCl_3$, 25°C):** $\boldsymbol{\delta_{anti}}$= 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 2H), 1.07-1.17 (m, 2H), 1.18-1.35 (m, 6H), 1.66 (q, *J* = 7.9 Hz, 2H), 1.82-1.91 (m, 1H), 2.30-2.36 (m, 1H), 2.57-2.63 (m, 1H), 2.93 (s, 6H), 3.44 (dd, *J* = 4.7 Hz, *J* = 5.9 Hz, 1H), 3.53 (dd, *J* = 6.3 Hz, *J* = 10.6 Hz, 1H), 6.69 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H), 7.01 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H**);** $\boldsymbol{\delta_{syn}}$ **=** 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 2H), 1.07-1.17 (m, 2H), 1.18-1.35 (m, 6H), 1.66 (q, *J* = 7.9 Hz, 2H), 1.82-1.91 (m, 1H), 2.30-2.36 (m, 1H), 2.57-2.63 (m, 1H), 2.93 (s, 6H), 3.26 (dd *J* = 6.3 Hz, *J* = 10.6 Hz, 1H), 3.44 (dd, *J* = 6.3 Hz, *J* = 10.6 Hz, 1H), 6.69 (dd, *J* = 2.4 Hz, *J* = 9.1 Hz, 2H), 7.01 (dd, *J*

= 2.4 Hz, *J* = 9.1 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = 14.0, 22.8 (2C), 29,7, 30.1 (2C) , 32.4, 32.8 , 40.8 (2C), 46.0, 47.8, 66.7, 112.4 (2C), 128.7 (2C), 129.3, 149.0**; δ_{syn}** = 13.5, 22.8 (2C), 29,7, 30.1 (2C) , 32.4, 32.8 , 40.8 (2C), 46.0, 47.8, 67.1, 112.4 (2C), 128.7 (2C), 129.3, 149.0; ESI-MS: *m/z* = 290.3 $[M+H]^+$.

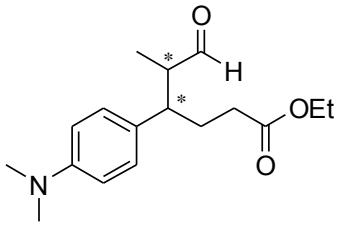


Prepared according at the general procedure was obtained the desired product as a yellowish oil; yield 85%; d.r.= 6:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signals δ_{anti}= 9.65 (d, *J* = 3.5 Hz, 1H), δ_{syn}= 9.56 (d, *J* = 2.4 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 6:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 99%; *Syn* diastereoisomer ee= 86%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 98/2, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 12.3 min., *τmajor* = 12.6 min; *Syn* diasteroisomer *τmajor* = 15.3 min., *τminor* = 20.9 min.^{1}H **NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = -0.03 (s, 6H), 0.87 (s, 9H), 0.89 (d, *J* = 7.8 Hz, 3H), 1.77-1.93 (m, 2H), 2.48-2.61 (m, 1H), 2.94 (s, 6H), 3.00-3.06 (m, 1H), 3.33-3.42 (m, 1H), 3.45-3.55 (m, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 9.65 (d, *J* = 3.5 Hz, 1H); **δ_{syn}** = -0.02 (s, 6H), 0.87 (s, 9H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.77-1.93 (m, 2H), 2.48-2.61 (m, 1H), 2.93 (s, 6H), 3.00-3.06 (m, 1H), 3.33-3.42 (m, 1H), 3.45-3.55 (m, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 9.56 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = -5.4 (2C), 12.0, 25.3 (3C), 29.7, 37.2, 40.7 (2C), 41.7, 52.1, 60.7, 112.7 (2C), 128.9, 129.0 (2C), 149.6, 205.5; **δ_{syn}** = -5.4 (2C), 12.0, 25.9 (3C), 29.7, 37.2, 40.7 (2C), 41.7, 52.1, 60.7, 112.7 (2C), 128.9, 129.0 (2C), 149.6, 205.5; ESI-MS: *m/z* = 350.3 $[M+H]^+$, 372.2 $[M+Na]^+$, 721.3 $[2M+Na]^+$.

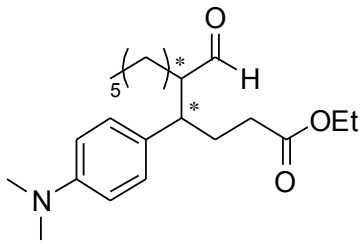


According at the general procedure was obtained the desired product as a colourless oil; yield 60% d.r.= 3:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signal δ_{anti}= 9.55 (d, *J* = 4.7 Hz, 1H), δ_{syn}= 9.43 (d, *J* = 3.9 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 3:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 96%; *Syn* diastereoisomer ee= 92%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 98/2, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 8.5 min., *τmajor* = 9.0 min; *Syn* diasteroisomer *τmajor* = 12.4 min., *τminor* = 17.8 min.**^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = -0.04 (s, 6H), 0.83 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 1.13-1.44 (m, 5H), 1.48-1.70 (m, 3H), 1.70-1.85 (m, 2H), 1.94-2.10 (m, 1H), 2.31-2.46 (m, 2H), 2.94 (s, 6H), 2.95-3.03 (m, 1H), 3.27-3.33 (m, 1H), 3.41-3.46 (m, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 9.1 Hz, 2H), 9.55 (d, *J* = 4.7 Hz, 1H**); δ_{syn}** =

-0.02 (s, 6H), 0.83 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H),1.13-1.44 (m, 5H), 1.48-1.70 (m, 3H), 1.70-1.85 (m, 2H), 1.94-2.10 (m, 1H), 2.31-2.46 (m, 2H), 2.92 (s, 6H), 2.95-3.03 (m, 1H), 3.35-3.41 (m, 1H), 3.50-3.55 (m, 1H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 9.1 Hz, 2H), 9.43 (d, *J* = 3.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = -5.4 (2C), 14.0, 18.2, 22.5, 25.9 (3C), 27.1, 27.5, 29.1, 31.6, 37.4, 40.7 (2C), 41.0, 58.0, 60.5, 112.7 (2C), 127.0, 129.0 (2C), 149.4, 206.0**; δ_{syn}** = -5.4 (2C), 14.0, 18.2, 22.6, 25.9 (3C), 27.2, 27.6, 29.3, 31.6, 37.4, 40.7 (2C), 41.0, 58.0, 60.5, 112.6 (2C), 127.0, 129.0 (2C), 149.4, 206.0; EI-MS: *m/z* = 306.4 $[M\text{-}TBS]^+$, 633.3 $[(2M\text{-}TBS)+Na]^+$.

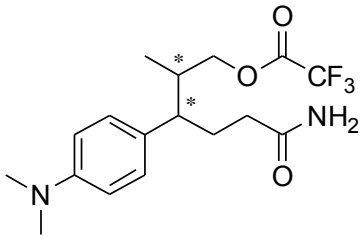


Prepared accordign at the general procedure was obtained the desired product as an orange oil; yield 45%; d.r.= 6:1 ratio (*anti*:*syn*) was determined was determined by integration of RC<u>H</u>O ^{1}H NMR signals δ_{anti}= 9.68 (d, *J* = 3.5 Hz, 1H), δ_{syn}= 9.52 (d, *J* = 2.4 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 7/3) as mixture of diastereoisomers in 6:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 97%; *Syn* diastereoisomer ee= 82%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 85/15 for 16 min, than from 85/15 to 70/30 in 14 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τmajor* = 33.2 min., *τminor* = 35.9 min; *Syn* diasteroisomer *τmajor* = 31.7 min., *τminor* = 37.4 min.**^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = 0.89 (d, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.83-1.94 (m, 1H), 1.95-2.09 (m, 1H), 2.10-2.17 (m, 1H), 2.26-2.39 (m, 1H), 2.51-2.63 (m, 1H), 2.77-2.85 (m, 1H), 2.94 (s, 6H), 4.07 (q, *J* = 7.1 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 9.68 (d, *J* = 3.5 Hz, 1H); **δ_{syn} =** 0.88 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.83-1.94 (m, 1H), 1.95-2.09 (m, 1H), 2.10-2.17 (m, 1H), 2.26-2.39 (m, 1H), 2.51-2.63 (m, 1H), 2.77-2.85 (m, 1H), 2.73 (s, 6H), 4.08 (q, *J* = 7.1 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 9.52 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = 12.3, 14.2, 29.7, 32.4, 40.6 (2C), 45.0, 52.3, 60.2, 112.7 (2C), 127.8, 129.0 (2C), 149.6, 173.4, 205.1; **δ_{syn}** = 12.3, 14.1, 29.4, 31.9, 40.6 (2C), 45.0, 52.3, 60.2, 112.8 (2C), 127.8, 128.8 (2C), 149.6, 173.4, 205.0; ESI-MS: *m/z* = 292.3 $[M+H]^+$, 314.1 $[M+Na]^+$, 605.3 $[2M+Na]^+$.

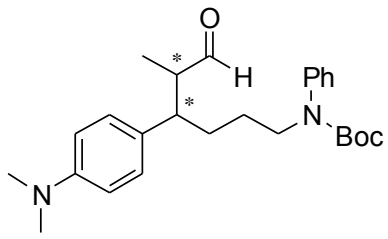


Prepared according at the general product was obtained the desired product as a colourless oil; yield 60% d.r.= 2.5:1 ratio (*anti*:*syn*) was determined was determined by integration of RC<u>H</u>O ^{1}H NMR signal δ_{anti}= 9.59 (d, *J* = 4.7 Hz, 1H), δ_{syn}= 9.40 (d, *J* = 3.9 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 2.5:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 96%; *Syn* diastereoisomer ee= 91%. The ee was determined by HPLC analysis Daicel Chiralcel IB column: hexane/*i*-PrOH fron 99/1 to 80/20 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τmajor* = 18.2 min., *τminor* = 18.8 min; *Syn* diasteroisomer

τmajor = 20.8 min., *τminor* = 22.7 min. **^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}**= 0.82 (t, *J* = 7.1 Hz, 3H), 1.06-1.18 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.24-1.35 (m, 4H), 1.57-1.70 (m, 2H), 1.77-1.87 (m, 1H), 1.88-1.97 (m, 1H), 2.02-2.12 (m, 2H), 2.10-2.16 (m ,1H), 2.35 (t, *J* = 7.5 Hz, 1H), 2.38-2.48 (m, 1H), 2.77 (ddd, *J* = 3.5 Hz, *J* = 5.9 Hz, *J* = 9.4 Hz, 1H), 2.94 (s, 6H), 4.06 (q, *J* = 7.1 Hz, 2H), 6.70 (d, *J* = 9.1 Hz, 2H), 6.98 (d, *J* = 9.1 Hz, 2H), 9.59 (d, *J* = 4.7 Hz, 1H); **δ_{syn}**= 0.87 (t, *J* = 7.1 Hz, 3H), 1.06-1.18 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.24-1.35 (m, 4H), 1.57-1.70 (m, 2H), 1.77-1.87 (m, 1H), 1.88-1.97 (m, 1H), 2.02-2.12 (m, 2H), 2.10-2.16 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 1H), 2.38-2.48 (m, 1H), 2.77 (ddd, *J* = 3.5 Hz, *J* = 5.9 Hz, *J* = 9.4 Hz, 1H), 2.92 (s, 6H), 4.08 (q, *J* = 7.1 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 9.1 Hz, 2H), 9.40 (d, *J* = 3.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}**= 14.0, 14.2, 22.5, 27.6, 29.6, 31.5, 32.0, 32.2, 40.6 (2C), 44.3, 45.0, 58.0, 60.2, 112.8 (2C), 128.2, 128.9 (2C), 149.5, 173.3, 205.6**; δ_{syn}=** 14.0, 14.2, 22.5, 27.7, 29.7, 31.6, 32.0, 32.2, 40.6 (2C), 44.3, 45.0, 58.0, 60.2, 112.7 (2C), 128.2, 129.0 (2C), 149.5, 173.5, 205.3; EI-MS: *m/z* (%) = 362.3 $[M+H]^+$, 384.2 $[M+Na]^+$, 745.4 $[2M+Na]^+$.

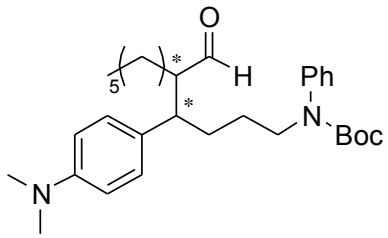


According at the general procedure was obtained the desired product as a yellow oil; yield 88%; d.r.= 5.5:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signals δ_{anti}= 9.68 (d, *J* = 2.8 Hz, 1H), δ_{syn}= 9.50 (d, *J* = 2.4 Hz, 1H). The title compound was isolated by flash column chromatography (EtOAc/MeOH= 9/1) as mixture of diastereoisomers in 5.5:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 90%; *Syn* diastereoisomer ee= 71%. The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH from 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 31.4 min., *τmajor* = 33.8 min; *Syn* diasteroisomer *τmajor* = 26.8 min., *τminor* = 29.6 min.; **^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = 0.88 (d, *J* = 7.1 Hz, 3H), 1.93-2.11 (m, 3H), 2.12-2.28 (m, 2H), 2.70-2.80 (m, 1H), 3.02 (s, 6H), 4.19 (dd, *J* = 6.7 Hz, *J* = 19.7 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H); **δ_{syn}** = 1.15 (d, *J* = 6.7 Hz, 3H), 1.79-1.90 (m, 1H), 1.93-2.11 (m, 2H), 2.12-2.28 (m, 2H), 2.50-2.58 (m, 1H), 3.01 (s, 6H), 4.01 (ddd, *J* = 6.7 Hz, *J* = 10.6 Hz, *J* = 81.4 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H); ^{13}C **NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = 14.0, 22.8 (2C), 29,7, 30.1 (2C) , 32.4, 32.8 , 40.8 (2C), 46.0, 47.8, 66.7, 112.4 (2C), 128.7 (2C), 129.3, 149.0; **δ_{syn}** = 13.5, 22.8 (2C), 29,7, 30.1 (2C) , 32.4, 32.8 , 40.8 (2C), 46.0, 47.8, 67.1, 112.4 (2C), 128.7 (2C), 129.3, 149.0; ESI-MS: *m/z* = ESI-MS: *m/z* = 292.3 $[M+H]^+$, 314.1 $[M+Na]^+$, 605.3 $[2M+Na]^+$.



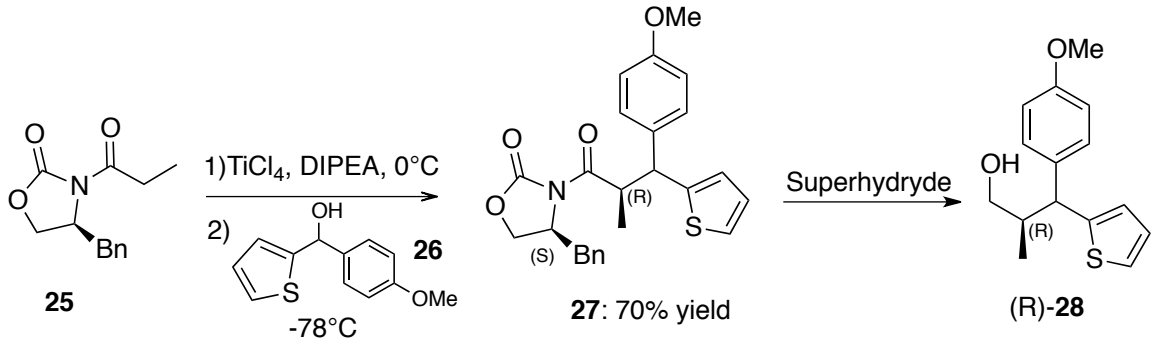
According at the general procedure was obtained the desired product as an orange oil; yield 92%; d.r.= 4.5:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signals δ_{anti}= 9.61 (d, *J* = 3.5 Hz, 1H), δ_{syn}= 9.51 (d, *J* = 2.4 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 4.5:1 ratio (*anti*:*syn*). *Anti*

diastereoisomer ee = 95%; *Syn* diastereoisomer ee= 97%. The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH from 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 21.3 min., *τmajor* = 22.1 min; *Syn* diasteroisomer *τmajor* = 25.0 min., *τminor* = 27.8 min. **^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = 0.86 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 9H), 1.54-1.77 (m, 4H), 2.27-2.38 (m, 1H), 2.44-2.56 (m, 1H), 2.73-2.81 (m, 1H), 2.93 (s, 6H), 3.58-3.70 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 7.08 (bd, *J* = 7.5 Hz, 2H), 7.17 (tt, *J* = 5.9 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 4.5 Hz, 2H), 9.61 (d, *J* = 3.5 Hz, 1H); δ_{syn} = 0.88 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 9H), 1.54-1.77 (m, 4H), 2.27-2.38 (m, 1H), 2.44-2.56 (m, 1H), 2.73-2.81 (m, 1H), 2.93 (s, 6H), 3.58-3.70 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.08 (bd, *J* = 7.5 Hz, 2H), 7.17 (tt, *J* = 5.9 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 4.5 Hz, 2H), 9.51 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = 12.1, 14.1, 22.7, 28.3 (3C), 31.2, 40.7 (2C), 45.1, 52.4, 77.2, 80.0, 112.7 (2C), 125.9 (2C), 128.6 (2C), 128.8, 129.0 (2C), 142.4, 149.4, 154.7, 205.4; δ_{syn} = 12.1, 14.1, 22.7, 28.3 (3C), 31.2, 40.7 (2C), 45.1, 52.4, 77.2, 80.0, 112.7 (2C), 125.9 (2C), 128.6 (2C), 128.8, 129.0 (2C), 142.4, 149.4, 154.7, 205.4; ESI-MS: *m/z* = 447.2 $[M+Na]^+$, 871.4 $[2M+Na]^+$.



According at the general procedure was obtained the desired product as a dark yellow oil; yield 75% d.r.= 2.5:1 ratio (*anti*:*syn*) was determined was determined by integration of RCHO ^{1}H NMR signal δ_{anti}= 9.52 (d, *J* = 4.7 Hz, 1H), δ_{syn}= 9.39 (d, *J* = 3.9 Hz, 1H). The title compound was isolated by flash column chromatography (Cyclohexane/ether = 8/2) as mixture of diastereoisomers in 2.5:1 ratio (*anti*:*syn*). *Anti* diastereoisomer ee = 96%; *Syn* diastereoisomer ee= 91%. The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH fron 99/1 to 90/10 in 30 min, flow rate 0.50 mL/min., 30°C, λ = 214, 254 nm: *Anti* diasteroisomer *τminor* = 17.3 min., *τmajor* = 18.1 min; *Syn* diasteroisomer *τmajor* = 19.7 min., *τminor* = 23.0 min. **^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti}** = 0.82 (t, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 5.9 Hz, 3H), 1.22-1.33 (m, 3H), 1.39 (s, 9H), 1.49-1.58 (m, 4H), 1.58-1.67 (m, 2H), 2.28-2.41 (m, 2H), 2.66-2.75 (m, 1H), 2.94 (s, 6H), 3.42-3.50 (m, 1H), 3.56-3.67 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.06 (bd, *J* = 7.5 Hz, 2H), 7.14-7.19 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 9.52 (d, *J* = 4.7 Hz, 1H); δ_{syn} = 0.82 (t, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 1.22-1.33 (m, 3H), 1.40 (s, 9H), 1.49-1.58 (m, 4H), 1.67-1-79 (m, 2H), 2.28-2.41 (m, 2H), 2.66-2.75(m, 1H), 2.92 (s, 6H), 3.50-3.56 (m, 1H), 3.56-3.67 (m, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.09 (bd, *J* = 8.7 Hz, 2H), 7.14-7.19 (m, 1H), 7.30 (d, *J* = 4.7 Hz, 2H), 9.39 (d, *J* = 3.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti}** = 14.0, 22.5, 27.1, 27.3, 27.6, 28.3 (3C), 29.1, 29.7, 31.5, 31.6, 40.7 (2C), 44.2, 57.4, 80.0, 112.8 (2C), 125.8 (2C), 127.0, 128.6 (2C), 128.8, 129.0 (2C), 142.4, 149.4, 154.7, 205.9; δ_{syn} = 14.0, 22.6, 27.1, 27.3, 27.6, 28.3 (3C), 29.1, 29.7, 31.5, 31.6, 40.6 (2C), 45.2, 58.2, 80.0, 112.7 (2C), 125.9 (2C), 127.0, 128.6 (2C), 128.8, 129.0 (2C), 142.4, 149.4, 154.7, 205.6; ESI-MS: *m/z* = 495.4 $[M+H]^+$, 517.3. $[M+Na]^+$.

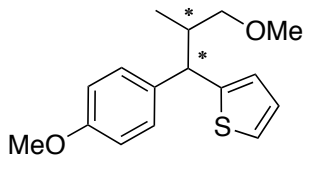
Absolute and relative configuration



(4*S*)-4-benzyl-3-((2*R*)-3-(4-methoxyphenyl)-2-methyl-3-(thiophen-2-yl)propanoyl)oxazolidin-2-one (27)

To a dry flask under argon was charged with 0.1mmol of acyloxazolidinone in anhydrous DCM, and the solution was cooled to 0°C. $TiCl_4$ was slowly added and the solution allowed stired for 5 minuts, to the yellow suspension was addes diisopropylamine (1.1mmol). The red-dark titanium enolate stirred for 20 minuts at 0°C, then was cooled at -78°C. Then the alcohol **26** (1.1mmol) was added and the result mixture was stirred for 1h at -78°C and after was warmed at 0°C. The rection was worked up with saturated solution of ammonium chloride, and the layers were separated. The organic layer was dried over sodium sulfate filtred and concentrate. ^{1}H NMR analysis showed the two diasterisomers (d.r ratio 2:1). The crude was charged with 0.1M THF in a flash. The solution was stirred at 0°C for 5 minuts then was treated with SuperHydrided (0.10mL of a solution 1M in THF). After 60 minuts, the reactions was worked up with water and diluted with AcOEt. The organic layer was dried over sodium sulfate and concentrated in vacuo. Purfiction throught flash chromatography column (SiO2, cyclohexane: EtOAc; 7:3) affording **28** in 85 yield, d.r 2:1, 95% : 92% ee.

To a solution of **28** (0.06 mmol, 15.6 mg) in anhydrous DMF (0.5 ml) at rt, oxone (0.1 mmol, 60mg)

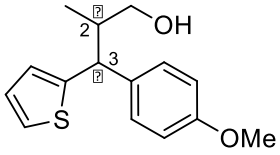


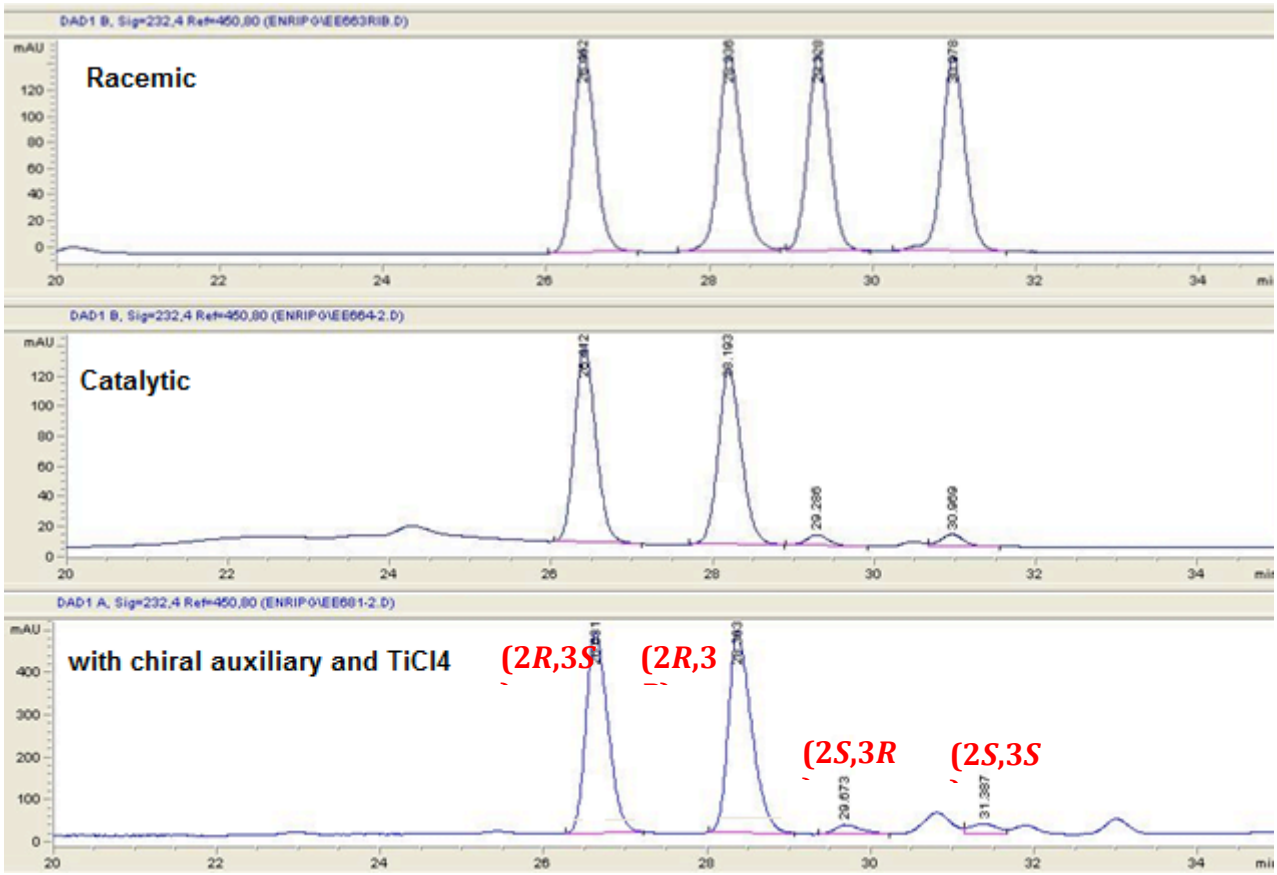
was added in one portion and stirred at rt overnight. 1N HCl was used to dissolve the salts and EtOAc was added to extract the product. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. The crude was dissolved in dry DCM (1.0 ml) and cool down to 0°C. Some drops of (Trimethylsilyl)diazomethane solution (2.0 M in hexane) was added and the solution was stirred at rt and monitored by TLC. The crude was concentrated *in vacuo* and the product was purify by flash chromatography (SiO_2, cyclohexane:EtOAc = 9/1) to give 13.0 mg of desired product in 75% yield

^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti} = 1.08 (d, *J* = 7.1 Hz, 3H), 3.15-3.26 (m, 1H), 3.60 (s, 3H), 3.79 (s, 3H), 4.36 (d, *J* = 12.2 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.88-6.94 (m, 2H), 7.09-7.17 (m, 1H), 7.21 (d, *J* = 8.7 Hz, 2H); δ_{syn} = 1.22 (d, *J* = 7.1 Hz, 3H), 3.15-3.26 (m, 1H), 3.47 (s, 3H), 3.77 (s, 3H), 4.33 (d, *J* = 11.8

Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.88-6.94 (m, 2H), 7.09-7.17 (m, 1H), 7.25 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti} = 16.9, 46.6, 49.2, 51.7, 55.2, 114.1 (2C), 123.9, 124.6, 126.4, 129.1 (2C), 133.8, 147.4, 158.5, 176.0; δ_{syn} = 16.9, 46.7, 49.8, 51.6, 55.2, 113.8 (2C), 123.8, 124.1, 126.6, 128.6 (2C), 134.9, 146.3, 158.3, 175.6 ; ESI-MS: m/z = 291.2 $[M+H]^+$, 313.1 $[M+Na]^+$.

Absolute configuration HPLC traces





VI. References

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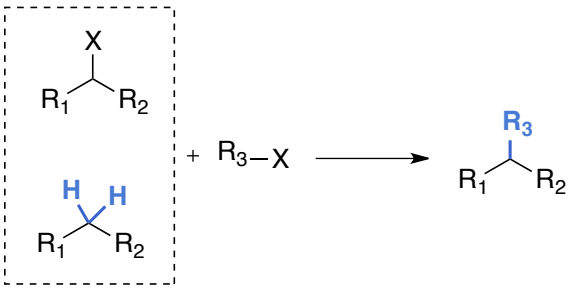
Chapter 3. Catalytic stereoselective benzylic C-H functionalization by oxidative C-H activation and organocatalysis.

I. Introduction

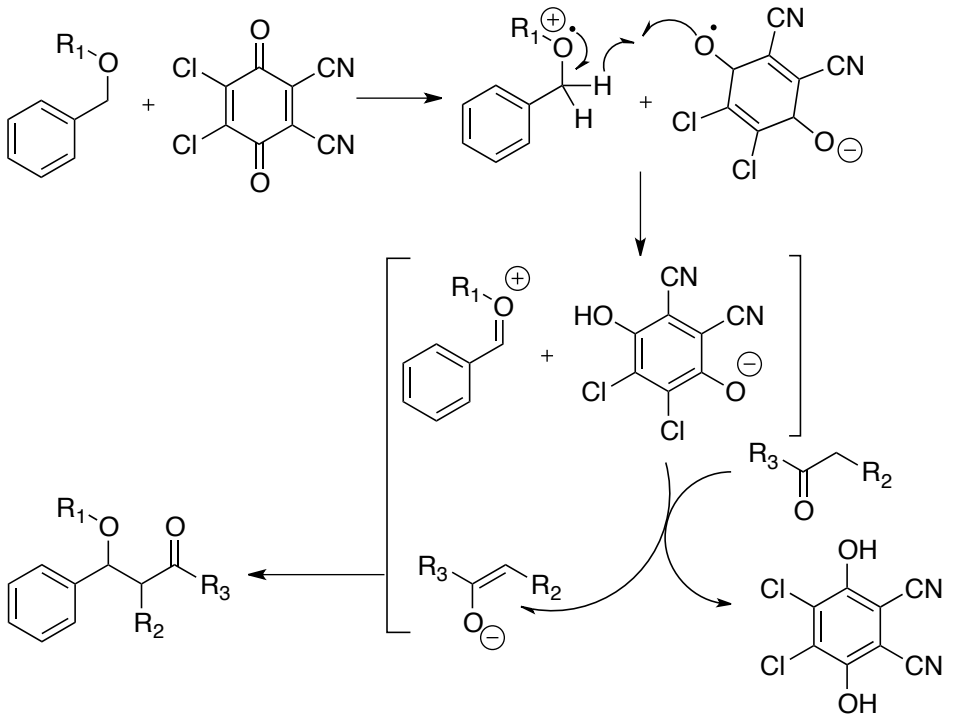
C-H activation

The activation of C-H bond has attracted in organic synthesis for their potential economic and ecologic advantages. In the field of asymmetric catalysis, enantioselective C-C bond formation via the activation of C-H bond has been a new strategy to obtain enantiomerically pure compounds without any type of functional group, this because the C-H bond is not considered as a functional group in organic synthesis. Thus, the presences of heteroatoms such as oxygen, halogen or unsaturation are required for install new functionality. Selective C-H bond functionalization has introduced as a novel synthetic strategy that provides direct access to a series of structural analogous.



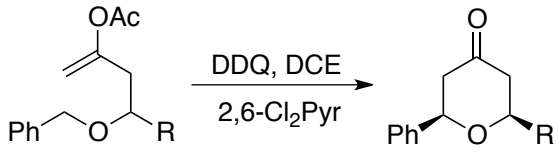
Scheme 1. Alternative way for the C-C bond formation

The development of various transition metal catalyzed coupling reactions was studied for the approach in the stereoselective intermolecular C-H functionalization methods. Sames and co workers[1] reported a review where they described the functionalization of C-H bond in complex organic substrates catalyzed by transition metal catalyst. Two types of transition metal mediated transformations have appeared as innovative methodologies for selective C-H functionalization in complex organic substrates.[2] The first method described as C-H activation involves insertion of a metal into a C-H bond.[3] The second method is the C-H insertion of metal bound carbenes or nitriles. [4] On the other hand, metal free coupling reactions has emerged as interesting synthetic methodologies.[5] Several groups have developed various cross-dehydrogenative-coupling (CDC) reactions for forming C-C bonds through two different C-H bonds. Zhang and co-workers[6] reported a highly efficient CDC reaction between benzyl ether and ketone mediated by DDQ without metal, the role of DDQ in the reaction was a dehydrogenating reagent and the reagent was also able to activate the carbonyl towards the addition. (Scheme2)



Scheme 2. Mechanism CDC reaction mediate by DDQ.

Furthermore, Floreancig and co-workers[7] reported the intramolecular nucleophilic attack on transiently -formed oxocarbenium ions that promoted a diastereoselective cyclization. In their work demonstrated the tolerance and application of DDQ- mediated C-H bond activation and subsequent C-C bond formation to annulation reactions requires that nucleophile be stable toward DDQ. (Scheme 3)

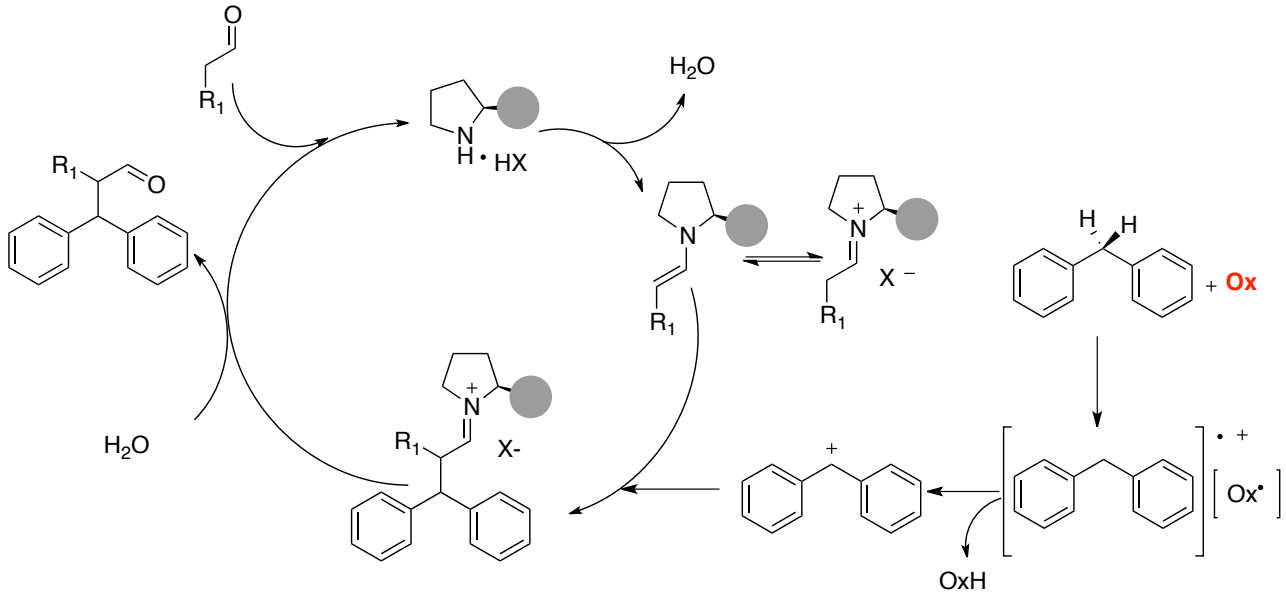


Scheme 3. Oxidative C-H bond activation.

Over the past years, my group was involved in the development of stereoselective S_N1 type reactions, merging two concepts enamine catalysis and Mayr's electophilicity scale to generated stereoselective α-alkylation of aldehydes.[8] This allowed to use stabilized carbocations generated by benzylic alcohols in situ that reacted with the enamine catalyst that generated enantioselective α-alkylation of aldehydes.[9] However, the carbocation can be generated under oxidative conditions by a benzylic C-H bond activation and the organocatalytic reactions can be merged with oxidants. With these two concepts a new approach in the stereoselective α-alkylation of aldehydes is developed with C-H functionalization.

II. Results and Discussion

Some challenges need to be addressed in merging the organocatalysis and C-H functionalization. The generation of water during the cycle organocatalytic, that could react with the carbocation. Other point was to choose alkyl aromatic compounds with weak C-H bonds to easily generate the carbocation through oxidant conditions. However the stability of the carbocation was also important for this type of reactions. (Scheme 4)

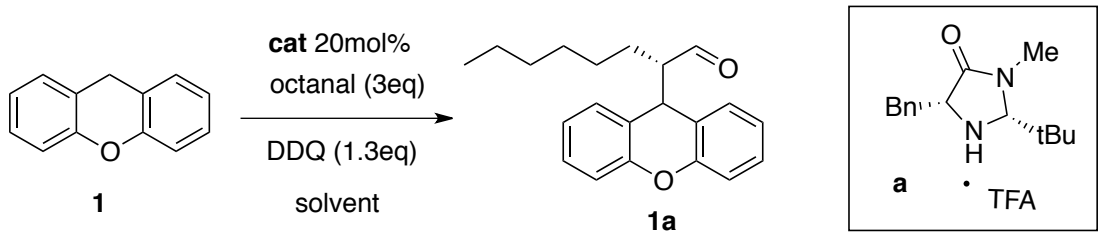


Scheme 4. Hypothesis about the cycle organocatalytic

The model reaction was performed under inert atmosphere using 1eq. of xanthene, 3 eq. of octanal, 20mol% of secondary amine as catalyst and 1.3eq. of DDQ as oxidant in the reaction. As already mentioned before DDQ mediate the cross dehydrogenation coupling reaction between nucleophiles and benzylic substrates.

On the other hand, the scope of organocatalysis mediated reactions is expanding in the last years and new chiral organocatalysts have been developed by several groups[10] The chiral diphenylprolinol TBS ether catalyst developed by two groups independently, on of them Jørgensen group and other was Hayashi and co-workers, did not prove good stereoselectivity in the reaction conditions.[11] MacMillan group[12] developed a new type of catalyst imidazolidinone derivatives that promoted a good stereoselectivity for our reaction. The catalyst **a** (2S, 5R)-5-benzyl-2-(tert-butyl)-3-methylimidazolidin-4-one · TFA performed better than other MacMillan type catalysts studied in the reaction. Furthermore the reaction was efficiently promoted by using polar aprotic solvent such as nitromethane or dichloromethane. The rule played by DDQ was crucial. In fact DDQ was powerful enough as oxidant to generate the carbocation, but no enough to oxidize the transient enamine formed by the MacMillan catalyst during the catalytic cycle: In catalysis is well know that strong oxidant used

in combination of organocatalysis are able to promote what is called SOMO catalysis.[13] In fact, other oxidants, such as $K_3Fe(CN)_6$, $Fe(acac)_3$, $K_2S_2O_8$, AgOTf, $Cu(OAc)_2$, and CAN that were investigated for the reaction have failed to produce the desired product. We have observed instead byproducts derived from the by oxidation of the substrate **1** to the corresponding xanthone. We have also observed with strong oxidant complete decomposition of the MacMillan catalyst and no conversion into the desired product **1a**.



Entry	Temp (°C)	Solvent	Time(h)	Y (%)[a]	ee (%)[b]
1	r.t	CH_3CN	1	Traces	---
2	r.t	DMF	1	---	---
3	r.t	DCM	0.5	62	45
4	r.t	CH_3NO_2	0.5	50	70
5	0	DCM	3	81	69
6	0	CH_3NO_2	3	55	56
8	-25	DCM	4	65	77
9[c]	-25	DCM	4	90	79
10[d]	-25	DCM	4	52	70
11[e]	-25	DCM	4	74	70

[a] Isolated yield after chromatographic purification. [b] Evaluated by chiral HPLC analysis. [c] The reaction was performed under nitrogen with degassed solvents and adding portion wise the oxidant. [d] the reaction was carried out using 15mol% of MacMillan catalyst. [e] The reaction was carried out without TFA as additive.

Table 1 Organocatalytic functionalization C-H activation with compound **1**

When the reaction was performed at low temperature (-25 °C) it was observed an increase in enantioselectivity and moderated decrease in yield (table1, entry 8, 65% yield, 77% ee). The addition of DDQ in two portions increased the yield, but without compromising the enantioselectivity (table 1, entry 9). The addition of oxidant by syringe pump stopped the reaction, and no conversion of product

was observed. Without the addition of 20mol % of TFA as co-catalyst, the enantioselectivity decreased (table 1, entry 11, 70% ee). When the reaction was carried under nitrogen atmosphere with degassed solvent the product **1a** as isolated in high yield and enantioselectivity (table 1, entry 9, 90%, 79% ee). With the optimised reaction conditions other substrates and unfunctionalized aldehydes were investigated.

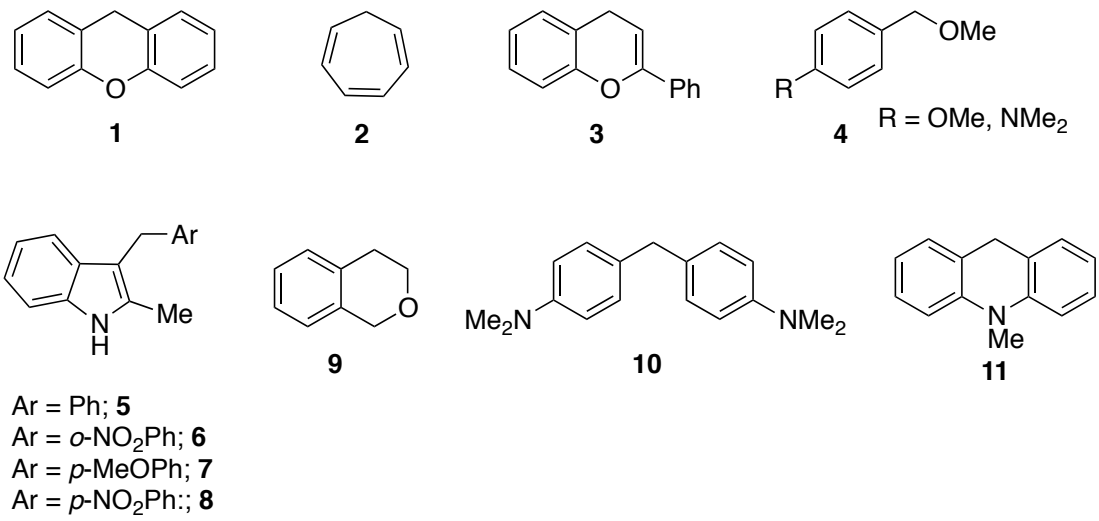
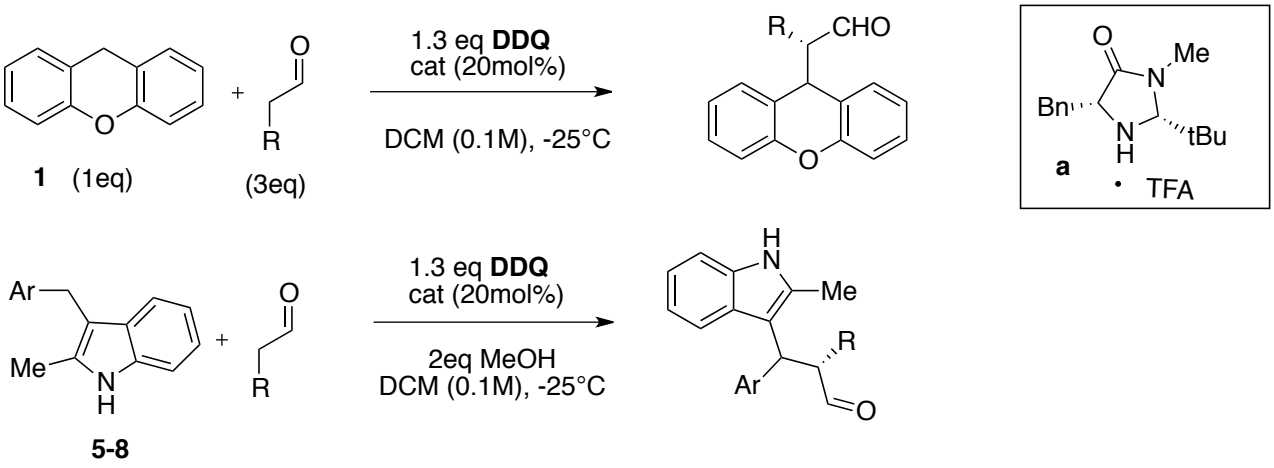


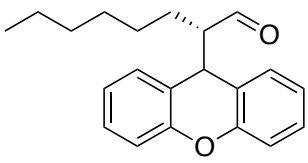
Figure 1. Substrates tested in the stereoselective benzylic C-H functionalization

Not all the substrates had the same behaviour in the oxidative C-H activation with DDQ. Substrates **2-3** gave the desired products. Substrate **9** was not reactive in the reaction conditions. Another substrates were **11-10** that only promoted byproducts of reaction. On the other hand, xanthene **1** reacted smoothly with different aldehydes, resulting in high yield and good enantioselectivity (table 2, entries 1-6, 79-68% ee). The indole derivatives **5-8** were prepared as reported in literature from the reaction of 2-methyl indole with aromatic aldehydes in presence of Et_3SiH and TFA, and the substrates were used in the reaction.[14] The reaction with indole derivatives was very fast, and only operating at low temperatures and addition of 2 equiv. of methanol, it was possible to obtain the desired product in moderated yield (Table 2, entry 7-13, 57-30% yield).

Scheme 5. Organocatalytic C-H activation with compounds **1** and **5-8**

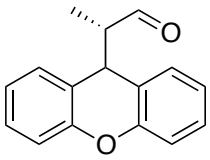


1



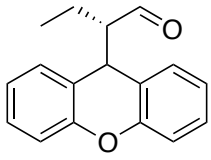
90%, 79% ee

2



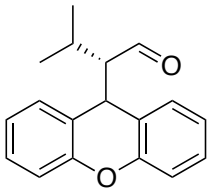
75%, 68% ee

3



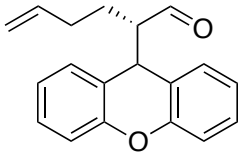
50%, 78% ee

4



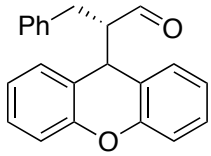
66%, 68% ee

5



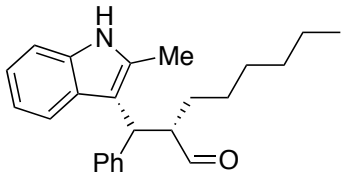
90%, 78% ee

6



30%, 74% ee

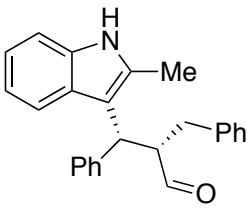
7



50%, d.r 1:1

82 *anti*: 62 *syn* % ee

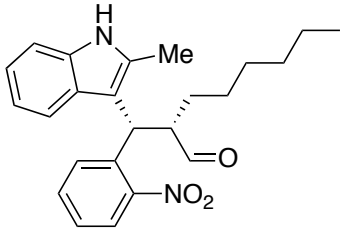
8



40%, d.r 1:1

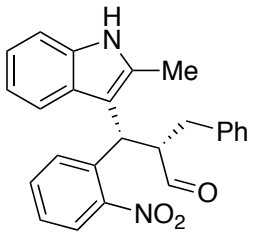
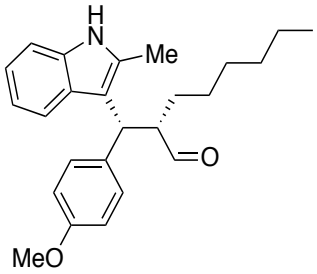
69 *anti*: 59 *syn* % ee

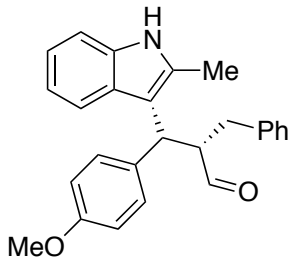
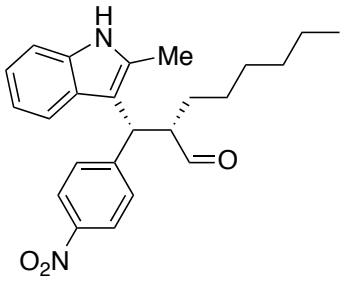
9



57%, d.r 1:9

86 *syn* % ee

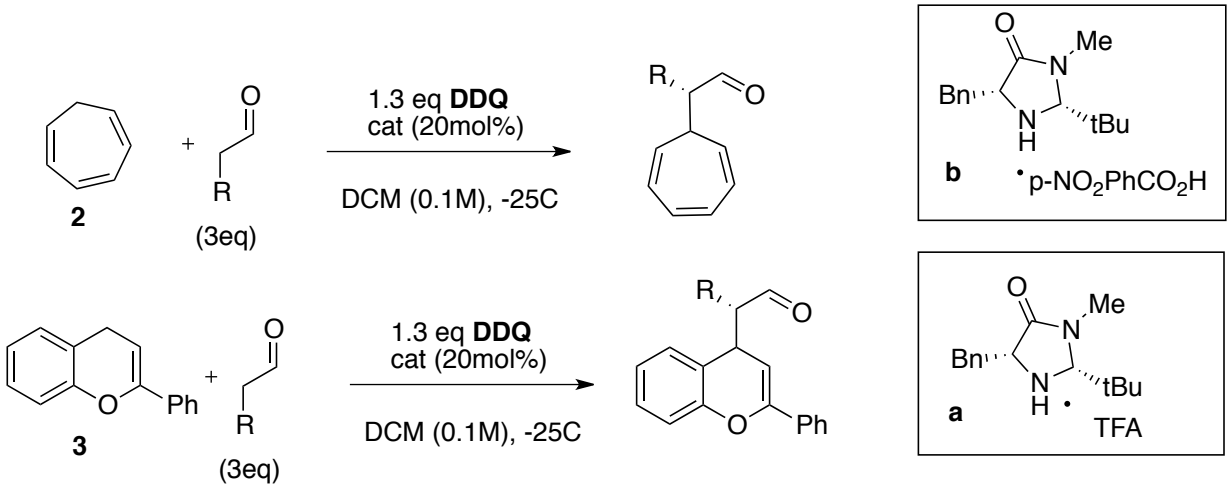
10		11	
	57%, d.r 1:9		33%, d.r 1:1
	60 *anti*: 77 *syn* % ee		66 *anti*: 65 *syn* % ee

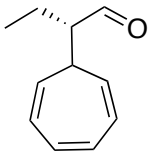
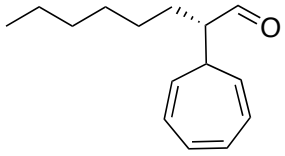
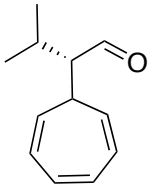
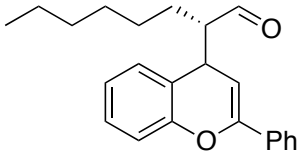
12		13	
	55%, d.r 3:1		40%, d.r 1:1
	74 *anti*: 50 *syn* % ee		86 *anti*: 79 *syn* % ee

All the reactions were performed at -25°C under nitrogen with anhydrous solvents. DDQ was added in portions. The Yield after chromatography purification. For all the reactions the d.r ratio was determined by ^{1}HNMR spectroscopic analysis. The enantiomeric excess determined by chiral HPLC analysis of the isolated products or of the corresponding alcohol.

Table 2. Representative Stereoselective C-H functionalization by oxidative CH activation and organocatalysis .

Oxidation of 1,3,5-cycloheptatrienene **2** gave the stable tropylium cation, but in performing the reaction using 20 mol% TFA as co-catalyst the enantioselectivity decreased to 16% ee. However the counter ion of the catalyst was crucial in order to obtain a good enantiomeric excess, and by the use of MacMillan catalyst with p-NO_2PhCOOH as co-catalyst, the alkylation of product was isolate in moderated yield and low enantioselectivity (table 3, entry 1-3, 90-30, 38-70 % ee). The substrate **3** was prepared according at the literature by a reduction of the corresponding flavylium salt,[15] The procedure led to the formation of a mixture of two products, one the desired product and the other the specie reduce from flavylium salt: Is important to note that the separation by chromatography of the two products was difficult, possibly due to π-stacking interaction between aromatic system of the two products. Using the mixture obtained by a partial purification as a starting material, the desired product was obtained in moderated enantioselectivity and poor yield (table 3, entry 4, 30%, d.r. 3:1, 74 anti: 50 syn % ee).



1		2	
	30%, 38% ee		90%, 46% ee
3		4	
	30%, 70% ee		30%, d.r 3:1 74 *anti*: 50 *syn* % ee

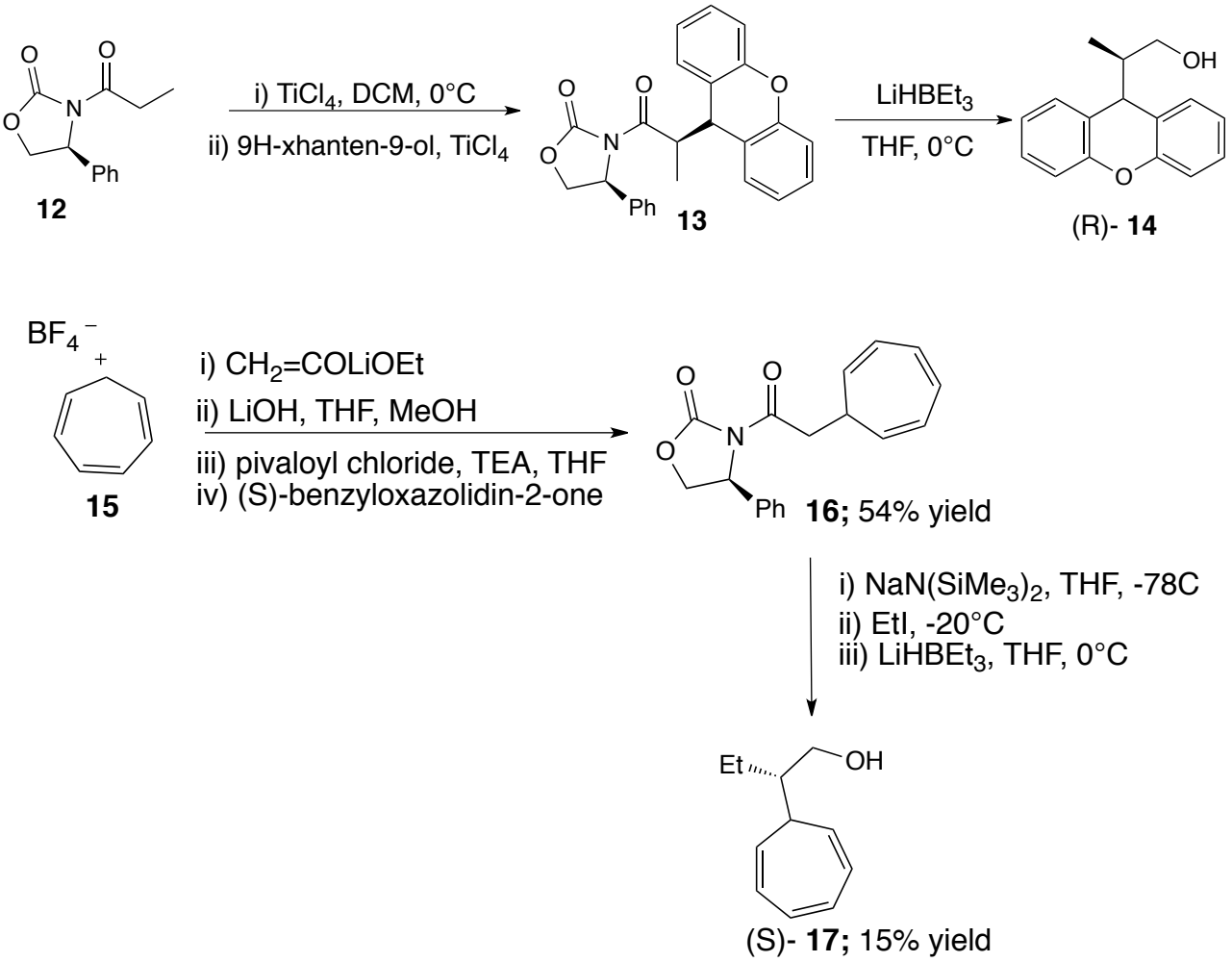
All the reactions were performed at -25°C under nitrogen with anhydrous solvents. DDQ was added in portions.

Table 3. Organocatalytic C-H activation with compounds **2-3**

Determination of absolute configuration

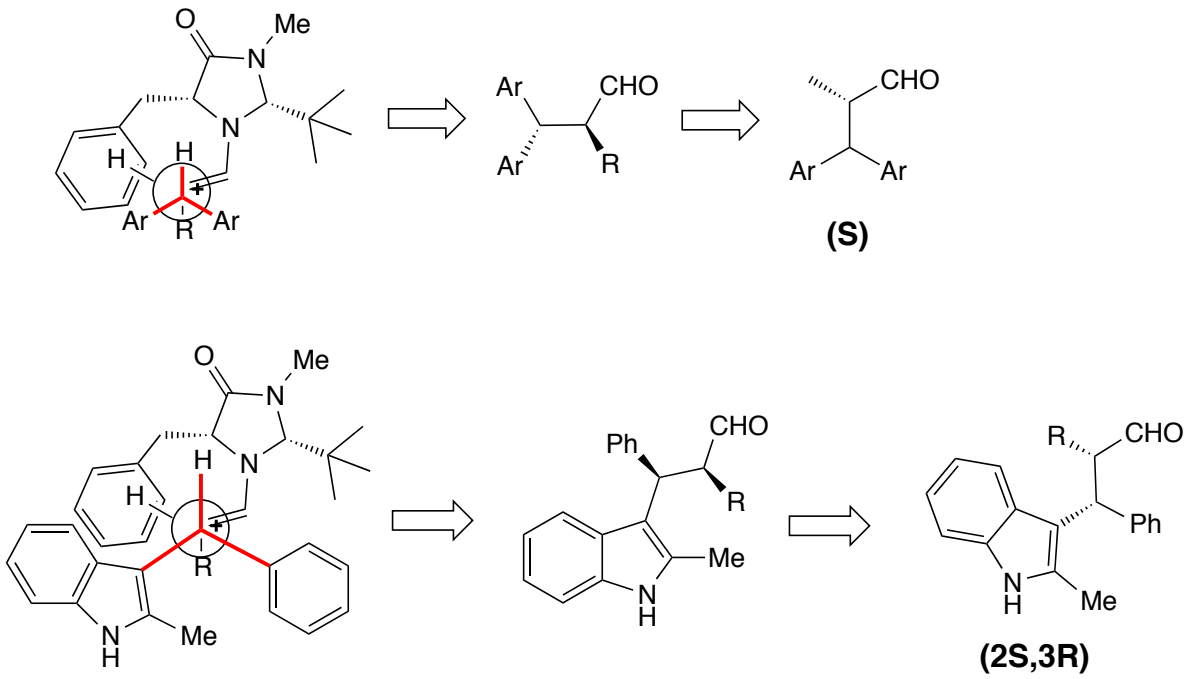
The absolute configuration of the products derivatives from xanthene **1** and from 1,3,5-cycloheptatriene (table 2, entry 2; table 3, entry 1) were established by chemical correlation through alkylation of oxazolidinone derivatives.[16] From the enolization procedure of chiral oxazolidinone described by of Evans, the 9H-xanthen-9-ol was treated with titanium enolate derived from the *N*-propionyl oxazolidinone, and the product was reduced with Super Hydride in THF to afford the (R)-alcohol **14.**[17] (Scheme 6) The absolute configuration for the product derivative from alcohol **2** was assigned by correlation to know derivatives obtain using a methodology reported by Evans. The (S)-

alcohol **17**, obtained using the Evans aldol chemistry was then reduced to the correspondent (S) -**17** (Scheme 6), enantiomer of the alcohol obtained in the alkylation procedure (table 3, entry 1).



Scheme 6. Assignment of absolute configuration by chemical correlation

The absolute configuration of the product derived from alcohols **5-8** was assigned by comparison of the elution order of the product from a chiral phase HPLC column reported by Melchiorre group.[18] The major diastereoisomer obtained in the reaction was the syn isomer. In all cases the configuration of the isolated products were in agreement with the addition of carbocation from the less hindered face of the enamine. (Scheme 7)



Scheme 7. Stereochemical models

III. Conclusion

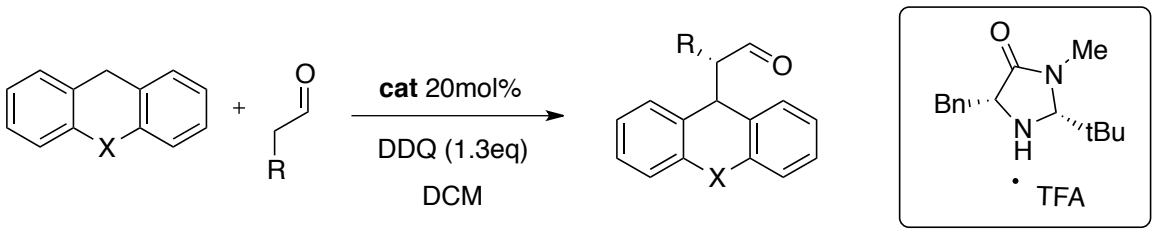
The development of stereoselective intermolecular dehydrogenation α-alkylation of aldehyde via benzylic C-H bond activation has emerged as a new strategy in the building of active organic compounds, merging enamine catalysis with oxidative C-H activation. The limitations in this new reaction have been the small arrange of substrates that can perform the reaction, an only alkyl aromatic compound with weak C-H was tolerance in the reaction conditions. In addition tnother weak point is the stoichiometric amount of oxidant necessary to activated the C-H bond. Quite recently, a group reported the use of oxygen in these reactions.

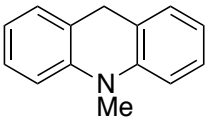
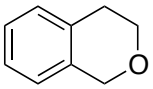
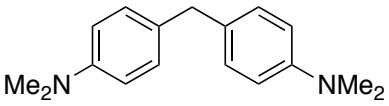
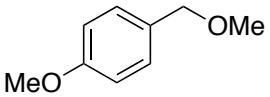
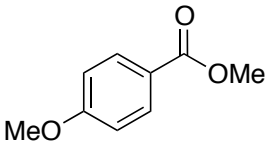
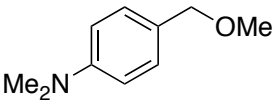
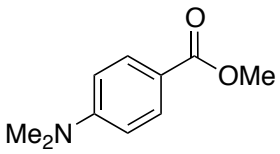
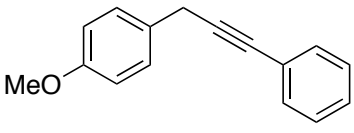
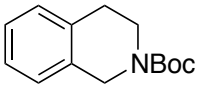
On the other hand, the tolerance of DDQ with enamine catalysts emerge a new approach in the catalytic stereoselective α-alkylation of aldehydes with the use of oxidants. The possibility in the future to use catalytic amount of oxidant or inexpensive and simple oxidants has been studying in our group. Recently, Jiao and co-workers [19] reported the stereoselective dehydrogenation α-alkylation of aldehydes using molecule of oxygen as oxidant with efficiently enantioselectivity up to 93% ee.

IV. Experimental section

Additional tables

All the substrates in the table 4 were tested in the direct organocatalytic C-H alkylation using the MacMillan catalyst in presence of DDQ (1.3eq) at 0°C following the general procedure A. All the reactions were run for 4 hours.



entry	substrate	Product
1		Not characterized by-products
2		Starting material
3		Not characterized by products
4		 (45%)
5		 (63%)
6		Not characterized by-prodducts
7		Starting material

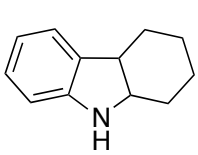
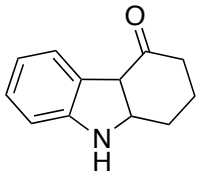
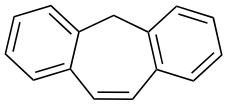
8		 (61%)
9		Starting material
10		Starting material

Table 4. Stereoselective α-alkylation with aldehydes via benzylic C-H bond activation.

entry	T(°C)	Additive, 20mol%	Yield (%)	ee (%)
1	RT	TFA	---	---
2	-25	TFA	91	16
3	-25	p-NO_2PhCO_2H	90	46
4	-25	1,3,5-MeOPhCOOH	27	44
5	-25	---	82	40
6	-25	CF_3CH_2OH	32	20
7	-25	N-Boc-Phe-OH	n.d	20
8	-25	proline	---	0

Table 5. Reaction of n-octanal with 1,3,5-cycloheptatriene performed with different co-catalysts.

Synthetic procedures

Procedure A. Substrates **1** and **3**.

In a two-necked flask containing degassed DCM (1 mL), the organocatalyst **a** (20 mol %), the aldehyde (3 eq., 0.3 mmol) and compound **1** or **3** (0.1mmol) are added under nitrogen at r.t. and the solution was stirred at r.t. for 5 min. After cooling to -25°C, DDQ (1.3 eq.) was added portion wise (3 portions) during 1 hour, and the solution was stirred at -25°C for 4 h. The reaction was quenched with water,

and the organic phase was separated. The aqueous phase was extracted twice with DCM; the organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude reaction mixture, that was purified by flash chromatography (SiO2, cyclohexane/Et_2O = 9/1 for the product from 1, n-hexane/ Et_2O = 95/5 for the producst from 3).

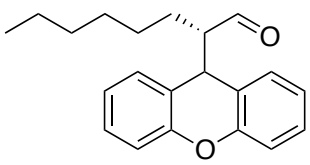
Procedure B. Substrate **2**.

In a two-necked flask containing degassed DCM (1 mL), the organocatalyst **b** (20 mol %), the aldehyde (3 eq., 0.3 mmol) and compound **2** (0.1mmol) are added under nitrogen at r.t. and the solution was stirred at r.t. for 5 min. After cooling to -25°C, DDQ (1.3 eq.) was added portion wise (3 portions) during 1 hour, and the solution was stirred at -25°C for 4 h. The reaction was quenched with water, and the organic phase was separated. The aqueous phase was extracted twice with DCM; the organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude reaction mixture, that was purified by flash chromatography (SiO_2; cyclohexane/Et_2O = 9/1).

Procedure C. Substrates **5-8**.

In a two-necked flask containing degassed DCM (1 mL), the organocatalyst **a** (20 mol %), the aldehyde (3 eq., 0.3 mmol), MeOH (2eq., 0.2 mmol) and compound **5-8** (0.1 mmol) are added under nitrogen at r.t. and the solution was stirred at r.t. for 5 min. After cooling to -25°C, DDQ (1.3 eq.) was added and the solution was stirred at -25°C for 4 h. The reaction was quenched with water, and the organic phase was separated. The aqueous phase was extracted twice with DCM; the organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude reaction mixture, that was purified by flash chromatography (SiO_2; cyclohexane/AcOEt, gradient from 9/1 to 8/2).

2-(*9H*-xanthen-9-yl)octanal (table 2, entry 1)

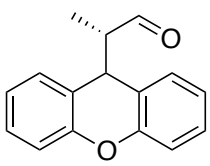


$C_{21}H_{24}O_2$ FW = 308.41

$[a]_D$ = + 17.1 (c 0.35, $CHCl_3$)

According at the procedure A was afforded the desired product in 90% yield, 79% ee. **^{1}H NMR** ($CDCl_3$, 200MHz) δ 0.83 (3H, t, J = 6.6Hz), 0.98-1.60 (10H, m), 2.51-2.57 (1H, m), 4.49 (1H, d, J = 4.8Hz), 7.04-7.32 (8H, m), 9.65 (1H, d, J = 2.6Hz). **^{13}C NMR** ($CDCl_3$, 50MHz) δ 13.9, 22.4, 25.4, 25.4, 27.4, 29.1, 31.4, 40.1, 60.6, 116.7, 116.8, 123.4, 123.5, 128.2 (2C), 128.3 (2C), 128.7 (2C), 128.9 (2C), 204.0. **ESI-MS**: r.t: 15.1 min; m/z: 331 ($M+Na^+$), **HPLC analysis** (reduced to the corresponding alcohol) OF: gradient from 99:1 (*n*-hexane: i-PrOH) to 90:10 in 30min, flow 0.5mL/min. T_M: 18.2 min; t_m:20.5min.

2-(9H-xanthen-9-yl)propanal (table 2, entry 2)



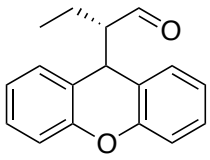
$C_{16}H_{14}O_2$ Fw = 238.28

$[\alpha]_D$ = +7.6 (c 1.1, $CHCl_3$).

Colorless oil.

According at the procedure A was afforded the desired product in 75% yield, 68 % ee. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.93 (3H, d, J = 7.4 Hz), 2.67-2.76 (1H, m), 4.64 (1H, d, J = 4.0 Hz), 7.02-7.32 (8H, m); 9.78 (1H, s). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ: 9.4, 39.7, 55.8, 116.6, 118.0, 121.5, 123.3, 123.4, 123.6, 128.2, 128.3, 128.6, 129.0, 152.9, 153.1, 203.7. **GC-MS:** rt: 19.2 min; *m/z*: 238(5), 183(12), 182(146), 181(1000), 180(12), 165(13), 153(15), 152(112), 151(39), 150(14), 127(15), 126(15), 77(10), 76(11), 63(7). **HPLC** analysis: Chiracel IC: 99:1 (*n*-hexane: *i*-PrOH), flow 0.7mL/min. t_m:12.2 min; T_M: 11.7 min. **HRMS** Calcd for $C_{17}H_{16}O_2$: 238.09938, $[M]^+$, found: 238.0991.

2-(*9H*-xanthen-9-yl)butanal (table 2, entry 3)



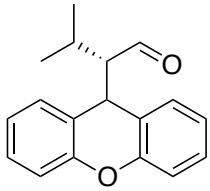
$C_{17}H_{16}O_2$ Fw = 252.31

$[\alpha]_D$ = +19.5 (c 1.2, $CHCl_3$).

Colorless oil.

According at the procedure A was afforded the desired product in 50% yield, 78%ee. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.84 (3H, t, J = 7.5 Hz), 1.45-1.65 (2H, m), 2.42-2.53 (1H, m), 4.49 (1H, d, J = 4.4 Hz); 7.04-7.32 (8H, m); 9.67 (1H, d, J = 2.6 Hz). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 12.0, 18.7, 40.0, 62.3, 116.7, 116.8, 122.2, 123.2, 123.4, 123.5, 128.2, 128.3, 128.7, 128.9, 152.9, 153.0, 204.5. **GC-MS**: rt: 22.7 min; *m/z*: 252(5), 207(9), 205(7), 196(5), 183(17), 182(18), 181(1000), 180(13), 165(10), 153(18), 152(116), 151(38), 150(14), 139(6), 91(9), 77(9), 76(15), 75(9),70(9), 69(9), 63(10). **HPLC** analysis (derivatized to alcohol): Chiracel OF: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. tm:23.3 min; TM: 21.4 min. **HRMS** Calcd for $C_{17}H_{16}O_2$: 252.11503, $[M]^+$, found: 252.1151.

3-methyl-2-(*9H*-xanthen-9-yl)butanal (table 2, entry 4)



$C_{18}H_{18}O_2$ Fw = 266.33

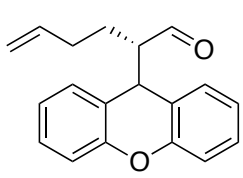
$[\alpha]_D$ = + 10.5 (c 0.38, $CHCl_3$).

White solid. Mp=46.2-48.5°C

According at the procedure A was obtained the desired product in 66% yield and 68%ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.90 (3H, d, J = 6.8 Hz), 1.11 (3H, d, J = 6.8Hz), 1.94-2.03 (1H,m), 2.31 (1H, ddd, J= 4.0, 6.0, 6.8Hz), 4.50 (1H, d, J = 6.0 Hz), 7.07-7.13 (4H, m), 7.24-7.28 (4H, m), 9.52 (1H, d, J =4.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 19.3, 21.7, 26.1, 38.2, 66.2, 116.7, 116.8, 123.1, 123.3, 123.5, 124.0, 128.1, 128.2, 128.7, 128.8, 152.9, 153.2, 204.4. **GC-MS:** rt: 26.4 min; *m/z*: 266(2), 223(8), 205(8), 183(16), 182(166), 181(1000), 180(11), 165(12), 153(13), 152(100), 151(31), 150(12),

127(12), 126(10), 76(8), 63(7). **HPLC** analysis: Chiracel IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. t_m:14.8 min; T_M: 15.9 min. **HRMS** Calcd for $C_{18}H_{18}O_2$: 266.13068, $[M]^+$, found: 266.1307.

2-(*9H*-xanthen-9-yl)hex-5-enal (table 2, entry5)



$C_{19}H_{18}O_2$ Fw = 278.35

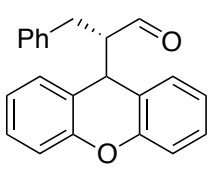
$[\alpha]_D$ = + 2.3 (c 0.48, $CHCl_3$).

Colorless oil.

According at the same procedure A was afforded the desired product in 90% yield, 78% ee **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.43-1.49 (1H,m), 160-1.69 (1H, m), 1.85-1.91 (1H, m), 1.96-2.02 (1H, m), 2.60 (1H, ddt, J= 2.4, 4.4, 9.6 Hz), 4.50 (1H, d, J= 4.4 Hz), 4.84 (1H, d, J=17.2 Hz), 4.89 (1H, d, J=10.4 Hz), 5.57 (1H, ddt, J= 3.2, 10.4, 17.2 Hz), 7.04-7.12 (4H, m), 7.21-7.28 (4H, m), 9.67 (1H, d, J=2.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.4, 31.3, 39.9, 59.9, 115.5, 116.7, 116.8, 122.9 (2C), 123.4, 123.6, 128.3, 128.4, 128.7, 128.9, 137.3, 152.8 (2C), 204.2. **GC-MS:** rt: 30.2 min; *m/z*: 278(4), 207(14), 183(11), 182(138), 181(1000), 180(10), 153(14), 152(86), 151(23), 127(10), 126(9), 77(7). **HPLC** analysis (derivatized to alcohol) Chiracel IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. t_m:27.8 min; T_M: 29.0 min.

HRMS Calcd for $C_{19}H_{18}O_2$: 278.13068, $[M]^+$, found: 268.1308.

3-phenyl-2-(*9H*-xanthen-9-yl)propanal (table 2, entry 6)



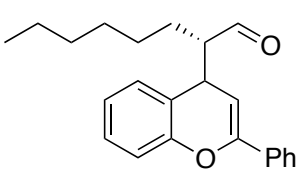
$C_{22}H_{18}O_2$ Fw =314.38

$[\alpha]_D$ = + 100.0 (c 0.30, $CHCl_3$).

White solid.Mp= 84-89 °C

According at the procedure A was afforded the desired product in 30% yeild and 74%ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.68-2.90(2H, m), 2.98-3.08 (1H,m), 4.63 (1H, d, J = 7.2 Hz), 7.01 (2H, d, J=8.0Hz), 7.11-7.36 (11H, m), 9.68 (1H, d, J = 3.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 31.2, 39.5, 62.4, 116.7, 116.8, 121.7, 122.6, 123.5, 123.6, 126.3 (2C), 128.2, 128.4, 128.5, 128.6 (2C), 128.8, 128.9, 138.7, 152.8, 152.9, 203.4. **ESI-MS:** rt: 12.7 min; *m/z*: 313 ($M-H_2+1$), 335 ($M-H_2+Na^+$). **HPLC** analysis: Chiracel IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. t_m:17.1 min; T_M: 16.3 min. **HRMS** Calcd for $C_{22}H_{18}O_2$: 314.13068, $[M]^+$, found: 314.1307.

(2*S*)-(2-phenyl-4*H*-chromen-4-yl) octanal (table 3, entry 4)

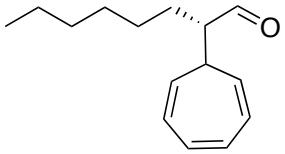


$C_{23}H_{26}O_2$ Fw = 334.45

Colorless oil.

According at the procedure A was afforded the desired product in 30% yield, d.r 2:1, 10%maj: 62%min ee **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.82 (3H M, t, J = 7.2 Hz), 0.88 (3H m, t, J = 7.2 Hz), 0.91-1.45 (16H, m), 1.61-1.73 (2H m, m), 1.73-1.80 (2H M, m), 2.58-2.62 (1H m, m), 2.62-2.66 (1H M, m), 4.06 (1H m, t, J=4.4Hz), 4.22 (1H M, t, J=4.4Hz), 5.38 (1H M, d, J= 4.8Hz), 5.55 (1H m, d, J= 4.8Hz), 7.07-7.26 (6H, m), 7.24 (1H M + 1H m, t, J=5.8Hz), 7.33-7.40 (6H, m), 7.69 (4H, d, J=6.8Hz), 9.72 (1H m, d, J=2.4Hz), 9.84 (1H M, d, J=2.4Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (major) 13.9, 24.9(2C), 27.8, 29.1, 31.4, 35.0, 59.5, 96.6, 116.7, 116.8, 121.3, 123.7, 124.7, 124.8, 127.9, 128.3, 128.4, 128.7, 133.8, 150.6, 152.5, 204.4. **ESI-MS:** rt: 17.3 min; *m/z*: 335 (M+1), 357 ($M+Na^+$). **HPLC** analysis: Chiracel IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. tm (major):12.8 min; TM (major): 14.6 min. tm (minor):15.7 min; TM (minor): 13.8 min. **HRMS** Calcd for $C_{24}H_{26}O_2$: 334.19328, $[M]^+$, found: 334.1935**.**

(S)-2- (cyclohepta -2,4,6-trien-1-yl) (table 3, entry 2)



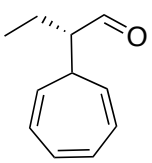
$C_{15}H_{22}O$ Fw = 218.33

$[\alpha]_D$ = + 8.4 (c 0.90, $CHCl_3$).

Colorless oil.

According the procedure B was afforded the desired product in 90 % yield, 46% ee. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ: 0.88 (3H, t, J = 6.6 Hz), 1.09-1.44 (8H, m), 1.53-1.81 (2H, m), 1.81-2.07 (1H, m), 2.52-2.69 (1H, m), 5.23 (2H, pseudo t, J = 7.2 Hz), 6.24 (2H, m), 6.69 (2H, pseudo t, J = 2.8 Hz), 9.64 (1H, d, J = 3.4Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ: 14.1, 23.6, 29.1, 29.3, 31.8, 34.4, 38.8, 54.0, 122.2, 123.1, 125.6, 125.7, 131.0, 131.1, 204.7. **GC-MS:** rt: 14.7 min; *m/z*: 218(5), 147(7), 133(45), 129(19), 128(10), 118(6), 117(28), 116(9), 115(32), 105(40), 104(12), 103(17), 92(92), 91(1000), 90(6), 79(17), 78(29), 77(34), 69(6), 65(46), 55(22), 51(11). **HPLC** analysis: Chiracel OD-H: 99:1 (*n*-hexane: *i*-PrOH), flow 0.6mL/min. tm:21.1 min; TM: 19.2 min. **HRMS** Calcd for $C_{15}H_{22}O_2$: 218.16706, $[M]^+$, found: 218.1672.

(S)-2-(cyclohepta-2,4,6-trien-1-yl)butanal (table 3, entry 1)



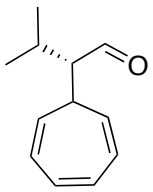
$C_{11}H_{14}O$ Fw = 162.23

$[\alpha]_D$ = + 2.7 (c 0.67, $CHCl_3$).

Colorless oil.

According at the procedure B was afforded the desired product 30% yield, 38 % ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.94 (3H, t, J = 7.2 Hz), 1.74-1.84 (2H, m), 1.97-2.02 (1H, m), 2.54-2.60 (1H, m), 5.24 (2H, dt, J = 5.6, 10.0 Hz), 6.25 (2H, tt, J = 2.8, 10.0 Hz), 6.69 (2H, pseudo t, J = 2.8 Hz), 9.65 (1H, d, J = 3.6Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 11.5, 20.2, 38.5, 55.1, 122.1, 123.1, 125.6, 125.8, 131.0, 131.1, 204.5. **GC-MS:** rt: 9.3 min; *m/z*: 162(3), 133(16), 131(7), 128(7), 117(14), 115(29), 105(40), 104(10), 103(20), 92(85), 91(1000), 89(20), 79(18), 78(57), 77(55), 65(77), 63(28), 62(9),55(24), 51(29). **HPLC** analysis: Chiracel OD-H: 99:1 (*n*-hexane: *i*-PrOH), flow 0.6mL/min. tm: 28.6min; TM: 26.9min. **HRMS** Calcd for $C_{11}H_{14}O$: 162.10447, $[M]^+$, found: 162.1045**.**

(*S*)-2- (cyclohepta-2,4,6-trien-1-yl)-3-methylbutanal (table 3, entry 3)



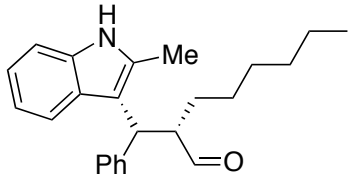
$C_{12}H_{16}O$ Fw = 176.25

$[\alpha]_D$ = + 8.8 (c 0.51, $CHCl_3$).

Colorless oil.

According to the procedure B was afforded the desired product in 30%yield, 79% ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.95 (3H, d, J = 7.2 Hz), 1.06 (3H, d, J=7.2Hz), 2.05-2.12 (1H, m), 2.25-2.33 (1H, m), 2.50 (1H, m), 5.21 (2H, dd, J=6.0, 9.2 Hz), 6.24 (2H, pseudo tt, J=2.8, 9.2 Hz), 6.70 (2H, dd, J=2.8 Hz), 9.78 (1H, d, J = 4.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 18.6, 21.2, 21.5, 37.3, 59.0, 122.0, 122.7, 125.4, 125.5, 130.9, 131.0, 205.7.**GC-MS:** rt: 10.2 min; *m/z*: 176(5), 174(6), 134(10), 133(94), 131(20), 129(11), 128(17), 117(18), 116(11), 115(50), 105(59), 104(12), 92(114), 91(1000), 90(9), 89(21), 79(39), 78(59), 77(70), 65(80), 63(24), 55(38), 53(17), 52(14), 51(38), 50(12). **HPLC** analysis: Chiracel OD-H: 99:1 (hexane: i-PrOH), flow 0.6mL/min. tm:29.0min; TM: 24.9min. **HRMS** Calcd for $C_{12}H_{16}O$: 176.12012, $[M]^+$, found: 176.1200.

(*S*)-2-((*R*)- (2-methyl-1*H*-indol-3-yl)(phenyl)methyl)octanal (table2, entry 7)



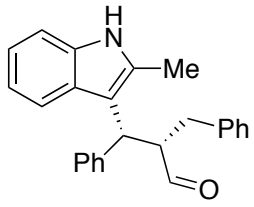
$C_{24}H_{29}NO$ Fw = 347.49

Colorless oil.

According at the procedure C was afforded the desired product in 50% yield, d.r 1:1, 82% *anti*: 62% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.79 (3Hanti, t, J=7.2Hz), 0.86 (3Hsyn, t, J=7.2Hz), 1.09-1.28 (16H, m), 1.48-1.54 (2H, m), 1.54-1.62 (2H, m), 2.42 (3Hsyn, s), 2.44 (3Hanti, s), 3.50-3.61 (2H,m), 4.34 (1Hsyn, d, J = 11.6 Hz), 4.46 (1Hanti, d, J = 11.6 Hz), 7.05-7.41 (18H, m), 7.74 (1Hsyn, bs), 7.80 (1Hanti, bs), 9.42 (1Hsyn, d, J = 4.4 Hz), 9.63 (1Hanti, d, J = 4.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (anti+syn): 13.9(2C), 14.0(2C), 22.4, 22.5, 26.7, 27.0, 28.7, 29.2, 29.3, 29.7, 31.4, 31.5, 43.1, 43.9, 54.3, 54.4, 110.3, 110.4, 112.1 (2C), 118.8, 119.0, 119.5, 119.6, 121.0, 121.1, 126.3 (2C), 127.9, 128.0 (2C), 128.1, 128.2, 128.5, 128.6 (2C), 131.2 (2C), 131.6 (2C), 135.3 (2C), 142.5, 142.6, 204.2, 205.5. **ESI MS**: rt: 13.7 min; *m/z*:

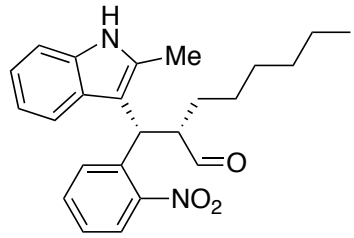
348 ($M+H^+$); 370 ($M+Na^+$). **HPLC** analysis Chiracel IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. TM (*anti*): 31.6 min; tm (*anti*): 23.8 min; TM (*syn*): 21.0 min; tm (*syn*): 24.5 min; **HRMS** Calcd for $C_{17}H_{16}O_2$: 347.22491, $[M]^+$, found: 347.2247.

(2*S*,3R)-2-benzyl-3-(2-methyl-1*H*-indol-3-yl)-3-phenylpropanal (table 2, entry 8)



According at the procedure C was afforded the desired product in 40% yield, d.r 1:1, 69%*syn*: 59% *anti* ee. Analysis data are reported in ref. 18

(*S*)-2-((R)-(2-methyl-1*H*-indol-3-yl)(2-nitrophenyl)methyl)octanal (table 2, entry 9)



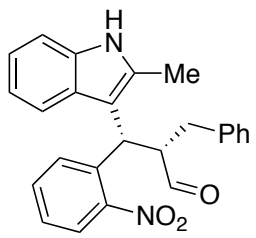
$C_{24}H_{28}N_2O_3$ Fw = 392.49

$[\alpha]_D$ = +113.0 (c 0.60, $CHCl_3$).

Yellow oil.

According at the procedure C was afforded the desired product in 57%yield, d.r 1:9; 86% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (*syn*) 0.86 (3H, t, J=7.2Hz),1.17-1.32 (8H, m), 1.49-1.57 (1H, m), 1.73-1.80 (1H,m), 2.38 (3H, s), 3.45-3.52 (1H,m), 5.22 (1H, d, J = 10.8 Hz), 7.00-7.09 (2H, m), 7.18 (1H, d, J=7.2Hz), 7.30 (1H, t, J=8.0Hz), 7.49-7.59 (2H,m), 7.63 (1H, dd, J=1.2, 8.0Hz), 7.85 (1Hsyn, bs), 7.87 (1H, d, J=8.0Hz), 9.38 (1H, d, J = 4.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (*syn*): 12.4, 14.0, 22.5, 26.9, 28.8, 29.1, 31.5, 37.3, 54.6, 110.0, 110.6, 118.7, 119.8, 121.3, 124.4, 127.1, 127.2, 129.3, 132.3, 132.7, 135.3, 136.5, 150.3, 203.2. **ESI MS**: rt: 12.9 min (syn); *m/z*: 393 ($M+H^+$); 415 ($M+Na^+$). **HPLC** analysis: Chiracel IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 1.0mL/min. TM (*syn*): 24.1 min; tm (*syn*): 17.7min. **HRMS** Calcd for $C_{24}H_{28}N_2O_3$: 392.20999, $[M]^+$, found: 392.2098.

(2*S*, 3R)-2-benzyl-3-(2-methyl-1*H*-indol-3-yl)-3-(2-nitrophenyl)propanal (table 2, entry 10)



$C_{25}H_{22}N_2O_3$ Fw = 398.45

$[\alpha]_D$ = +131.0 (c 0.27, $CHCl_3$).

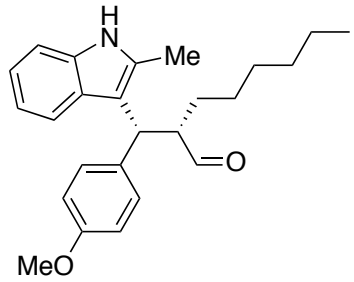
Yellow oil.

According at the procedure C was afforded the desired product in 57% yield, d.r 1:9, 60% *anti*: 77% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (*syn*) 2.36 (3H, s), 2.87 (1H, dd, J=3.6, 14.0 Hz), 3.18 (1H, dd, J=10.4, 14.0 Hz), 3.99 (1H, ddd, J= 3.6, 10.4, 10.8 Hz), 5.27 (1H, d,

J= 10.8 Hz), 6.97-7.26 (9H, m), 7.34 (1H, t, J=8.0Hz), 7.56 (1H, t, J=8.0 Hz), 7.66 (1H, d, J=8.0 Hz), 7.82 (1H, bs), 7.99 (1H, d, J= 8.0Hz), 9.43 (1H, d, J= 3.6Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 12.2, 35.0, 37.8, 55.6, 109.4, 110.7, 118.6, 119.9, 121.3, 124.5, 126.5, 127.0, 128.5, 128.6 (2C), 128.8 (2C), 129.3, 132.3, 132.9, 135.4, 136.2, 138.4, 150.5, 203.0.

ESI MS: rt: 10.9(syn) min; *m/z*: 399 ($M+H^+$); 421 ($M+Na^+$). **HPLC** analysis Chiracel IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min. TM (*syn*): 40.4 min; tm (*syn*): 33.9min; TM (*anti*): 43.0 min; tm (*anti*): 28.7min. **HRMS** Calcd for $C_{25}H_{22}N_2O_3$: 398.16034, $[M]^+$, found: 398.1602.

(S)-2-((R)-(4-methoxyphenyl)(2-methyl-1*H*-indol-3-yl)methyl)octanal (table 2, entry 11)

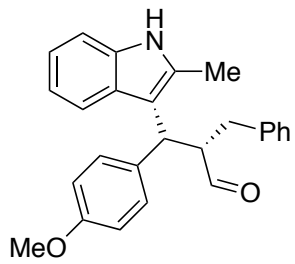


$C_{25}H_{31}NO_2$ Fw = 377.52

Colorless oil.

According at the procedure C was affored the desired product in 33% yield, d.r 1:1, 66% *anti*: 65% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.79 (3Hanti, t, J=7.2Hz), 0.86 (3Hsyn, t, J=7.2Hz),1.09-1.28 (16H, m), 1.46-1.66 (4H, m), 2.42 (3Hsyn, s), 2.44 (3Hanti, s), 3.43-3.55 (2H,m), 3.72 (3Hanti, s), 3.75 (3Hsyn, s), 4.28 (1Hsyn, d, J = 11.6 Hz), 4.40 (1Hanti, d, J = 11.6 Hz), 6.76 (2Hanti, d, J=8.4Hz), 6.81 (2Hsyn, d, J=8.4Hz), 7.02-7.11 (4H, m), 7.19-7.31 (6H,m), 7.62 (1Hanti, d, J=7.6Hz), 7.67 (1Hsyn, d, J=7.6Hz), 7.74 (1Hsyn, bs), 7.79 (1Hanti, bs), 9.40 (1Hsyn, d, J = 4.4 Hz), 9.60 (1Hanti, d, J = 4.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (*anti+syn*) 12.4, 12.8, 14.0 (2C), 22.5 (2C), 26.7, 27.0, 28.7 (2C), 29.2, 29.3, 31.5, 31.6, 42.2, 43.1, 54.5, 54.6, 55.1, 55.2, 110.3, 110.4, 112.4 (2C), 112.6 (2C), 113.8 (2C), 113.9 (2C), 118.7, 119.0, 119.4, 119.5, 121.0, 121.1, 127.4 (2C), 128.9 (2C), 129.0 (2C), 131.1, 131.4, 134.8, 135.4, 157.9 (2C), 204.3, 205.6. **ESI MS**: rt: 12.5 and 13.0 min; *m/z*: 400 ($M+Na^+$). **HPLC** analysis: Chiracel IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 8:2 in 30min, flow 0.5mL/min. TM (anti): 22.2 min; tm (anti): 20.4min; TM (syn): 24.0min; tm (syn): 25.8min. **HRMS** Calcd for $C_{25}H_{31}NO_2$: 377.23548, $[M]^+$, found: 377.2353.

(2*S*, 3R)- 2-benzyl-3-(4-methoxyphenyl)-3-(2-methyl-1*H*-indol-3-yl)propanal (table 2, entry 12)



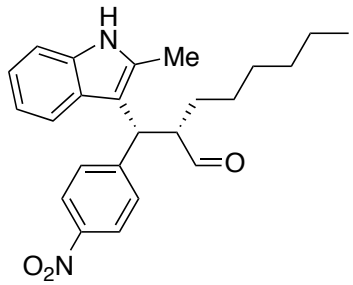
$C_{26}H_{25}NO_2$ Fw = 383.48

Yellow oil.

According at the procedure C was afforded the desired product in 55% yield, d.r 3:1, 74% *anti*: 50% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.38 (3Hsyn, s), 2.40 (3Hanti, s), 2.68-3.07 (4H, m), 3.72 (3Hanti, s), 3.78 (3Hsyn, s), 3.89-4.00 (2H, m), 4.37 (1Hsyn, d, J= 11.2 Hz), 4.46 (1Hanti, d, J= 11.2 Hz), 6.77 (2Hanti, dd, J=2.4, 6.8 Hz), 6.87 (2Hsyn, dd, J=2.4, 6.8 Hz), 6.99.7.43 (22H, m), 7.78 (1Hsyn, bs), 7.87 (1Hanti, bs), 9.47 (1Hsyn, d, J = 3.6 Hz), 9.68 (1Hanti, d, J = 3.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (*syn+anti*) 12.3, 12.5, 35.3, 35.4, 42.6(2C), 43.5(2C), 55.7, 56.4, 110.5, 110.6, 111.9, 112.2, 113.9(2C), 114.1(2C), 118.9, 119.0, 119.5, 119.6, 121.0, 121.1, 126.2, 126.3, 126.4, 127.2, 127.4, 128.2, 128.3(4C), 128.4, 128.5 (2C), 128.9, 129.0, 129.1, 131.2, 131.8, 134.3, 134.5, 135.3, 135.5, 138.6, 139.0, 157.9, 158.0, 204.5, 205.5.**ESI MS**: rt: 10.8 and 11.2 min; *m/z*: 384 ($M+H^+$); 406 ($M+Na^+$). **HPLC** analysis IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5 mL/min. TM (anti): 45.8 min; tm (anti): 48.0 min; TM (syn): 42.8 min; tm (syn): 34.1 min. **HRMS** Calcd for $C_{26}H_{25}NO_2$: 383.18853, $[M]^+$, found: 383.1884.

(*S*)-2-((R)- (2-methyl-1*H*-indol-3-yl)(4-nitrophenyl)methyl)octanal (table 2, entry 13)



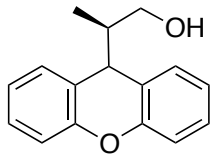
$C_{24}H_{28}N_2O_3$ Fw = 392.49

Yellow oil.

According at the same procedure C was afforded the desired product in 40% yield, d.r 1:1 and 86% *anti*: 79% *syn* ee. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.77-0.91 (6H, m), 1.34-1.45 (16H, m), 1.46-1.51 (2H, m), 1.52-1.62 (2H, m), 2.42 (3Hsyn, s), 2.44 (3Hanti, s), 3.49-3.58 (1Hsyn, m), 3.61-3.68 (1Hanti, m), 4.45 (1Hsyn, d, J = 11.2 Hz), 4.56 (1Hanti, d, J = 11.2 Hz), 7.03-7.14 (4H, m), 7.18-7.34 (4H,m), 7.50 (2Hanti, d, J=8.8 Hz), 7.54 (2Hsyn, d, J=8.8 Hz), 7.89 (1Hsyn, bs), 7.93 (1Hanti, bs), 8.07 (2Hanti, d, J=8.8 Hz), 8.13 (2Hsyn, d, J=8.8 Hz), 9.44 (1Hsyn, d, J = 4.0 Hz), 9.68 (1Hanti, d, J = 4.0 Hz).**^{13}C NMR** ($CDCl_3$, 100 MHz) δ (syn+anti) 12.7 (2C), 14.0 (2C), 22.6 (2C), 26.4, 26.9, 29.1, 29.3, 29.4, 29.7, 31.5, 31.6, 42.4, 43.9, 53.8, 54.0, 110.7 (2C), 118.4, 118.5, 119.9, 120.0, 121.4, 121.5, 123.8 (2C), 123.9 (2C), 128.7 (4C), 127.0 (2C), 131.8 (2C), 132.0 (2C), 135.3 (2C), 150.2 (2C), 150.4 (2C), 203.3, 204.5. **ESI MS**: rt: 12.4 and 12.7 min; *m/z*: 393 ($M+H^+$). **HPLC** analysis IC: gradient from 99:1 (*n*-hexane: *i*-PrOH) to 90:10 in 30min, flow 1.0 mL/min. TM (anti): 40.9 min; tm (anti): 31.8 min; TM (syn): 29.3 min; tm (syn): 27.7 min. **HRMS** Calcd for $C_{24}H_{28}N_2O_3$: 392.20999, $[M]^+$, found: 392.2098 .

Determination of the absolute configuration

Synthesis of (R)-2-(*9H*-xanthen-9-yl)propanol (14)

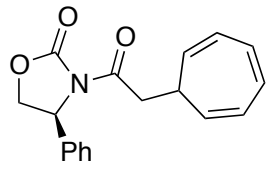


To a solution of N-propionyl oxazolidinone **12** (20 mg, 0.1mmol) in CH_2Cl_2 (2mL) a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.1mL) was added, followed by DIPEA (0.020mL, 0.12mmol). The resulting violet solution was stirred at 0°C for 30 m, then 9H-Xanthen-9-ol (20 mg, 0.1mmol), immediately followed by 0.1mL of a 1M solution of $TiCl_4$ in CH_2Cl_2, were added. The titanium enolate was immediately decolorized and after few minutes a yellow suspension was formed. The slurry was stirred 2 h at 0 °C

then quenched with water and diluted with Et_2O (6 mL). The TiO_2 formed was filtered off and the organic phase was separated. The aqueous phase was extracted with ether, then the organic phases were reunited, dried over Na_2SO_4 and evaporated under reduced pressure. The crude reaction mixture containing 9H-Xanthen-9-ol, propionyl oxazolidinone and the desired products were transferred to a flask and THF (3mL) was added. The solution was stirred at 0 °C for 5 minutes then was treated with SuperHydride (0.20mL of a solution 1M in THF). After 60 min, the reaction was quenched with water and diluted with AcOEt. The separated organic phase was dried over sodium sulfate and concentrated in vacuo. Purification by preparative TLC (5:5 cyclohexane/Et_2O) afforded **14** (3 mg, yield=12% over 2 steps).

^{1}H NMR ($CDCl_3$, 200MHz) **δ** 0.65 (3H, t, J=7.0 Hz), 1.50 (1H, bs), 2.0 (1H, m), 3.40-3.59 (2H,m), 4.23 (1H, J=4.2 Hz), 7.03-7.12 (4H,m) 7.19-7.29 (4H, m). **HPLC** analysis IC: gradient from 99:1 (hexane: *i*-PrOH) to 90:10 in 30min, flow 0.5mL/min: TM= 27.5min, tm=30.5min (ee=99%).

Synthesis of (S)-4-benzyl-3-(2-((2Z,4Z,6Z)-cyclohepta-2,4,6-trienyl)acetyl)oxazolidin-2-one (16)



To a solution of diisopropylamine (185 mL, 1.32 mmol) in 12 mL of dry THF under nitrogen, *n*-butyllithium (492 mL of a 2.5M solution in hexanes, 1.23 mmol) was added at 0°C and the resulting solution was stirred for 10 min. Then the flask was cooled to -78°C, EtOAc (119 mL, 1.2 mmol) was added and the solution was stirred at the same temperature for 60min.

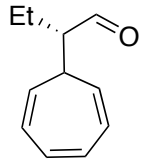
In a second flask, tropylium tetrafluoroborate **15** (178mg, 1mmol) and TEA (139 mL, 1mmol) were suspended in 1.5mL of dry THF and the mixture was cooled to -78°C. Then the content of this second flask was slowly transferred by cannula into the solution of the preformed lithium enolate, while keeping the temperature at -78°C. The reaction was allowed to warm during 1h, then it was quenched with water and extracted with EtOAc. The combined organic phases were dried on sodium sulfate and concentrated in vacuo. The crude product was the dissolved in a mixture of THF/MeOH/H_2O (3.6/1/1, total volume: 15mL) and lithium hydroxyde (114mg, 3 mmol) was added at r.t. After 1h, the reaction was diluted with EtOAc and acidified with 1M HCl. After the extraction, the organic fraction was dried over sodium sulfate and concentrated in vacuo affording 81mg of 2-((2Z,4Z,6Z)-cyclohepta-2,4,6-trienyl)acetic acid (Y=54% over 2 steps).

The carboxylic acid (81 mg, 0.54 mmol) was dissolved in dry THF (4.0 mL) and TEA (139 μL, 1.0 mmol) and cooled to –78 °C according to the procedure described by MacMillan at al. in *Science*, **2007**, *316*, 582. Pivaloyl chloride (74 μL, 0.6 mmol) was added and the reaction was gradually warmed to 0 °C over 90 min. (*S*)-4-benzyloxazolidin-2-one (89 mg, 0.54 mmol) was added followed by lithium chloride (64 mg, 1.5 mmol) and the reaction was warmed to ambient temperature and stirred for 72h. The solution was diluted with ethyl acetate and washed with water, the organic phase was dried over

sodium sulfate and concentrated in vacuo. Purification by flash chromatography (SiO_2, 9:1 cyclohexane/EtOAc) afforded **16** (90 mg, Y=54%).

^{1}H NMR ($CDCl_3$, 200MHz) δ 2.30-2.42 (1H, m), 2.80 (1H, dd, J=9.6, 13.2 Hz), 3.24-3.45 (3H, m), 4.08-4.27 (2H, m), 4.65-4.76 (1H, m), 5.29 (2H, pseudo t, J=7.0 Hz), 6.25 (2H, d, J=9.0Hz), 6.70 (2H, pseudo t, J=2.6 Hz), 7.20-7.35 (5H, m).

Synthesis of (S)-2-((2Z,4Z,6Z)-cyclohepta-2,4,6-trienyl)butan-1-ol (17)



Compound **16** was dissolved in THF (4 mL) and cooled to –78 °C. $NaN(SiMe_3)_2$ (700 µL, 0.7 mmol) was added and the reaction was stirred for 1 h. Iodoethane (150 µL, 1.88 mmol) was then added and the reaction was warmed to –20 °C over 4 h, then it was quenched with a saturated NH_4Cl aqueous solution (5 mL). The reaction was diluted with EtOAc and the organic phase was washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude mixture obtained was diluted with 400 µL of dry THF, cooled to 0°C and treated with SuperHydride (0.29mL of a solution 1M in THF). After 30 min, the reaction was quenched with water and diluted with EtOAc. The separated organic phase was dried over sodium sulfate and concentrated in vacuo. Purification by preparative TLC (7:3 cyclohexane/EtOAc) afforded **17** (7 mg, Y=15% over 2 steps).

^{1}H NMR ($CDCl_3$, 200MHz) δ 0.96 (3H, t, J=7.4 Hz), 1.39-1.70 (3H, m), 1.70-1.88 (1H, m), 3.81 (2H, d, J=4.8 Hz), 5.28-5.37 (2H, m), 6.21-6.25 (2H, m), 6.68 (2H, pseudo t, J=3.4 Hz).

HPLC analysis OD-H 99:1 (*n*-hexane: i-PrOH), flow 0.6mL/min. Tm = 28.6 min, TM = 26.9min (ee = 90 %)

V . References

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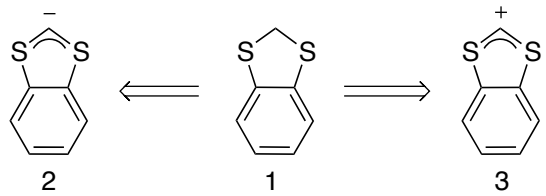
Chapter 4. Stereoselective α-alkylation of aldehydes with 1.3-benzodithiolylium tetrafluoroborate salt.

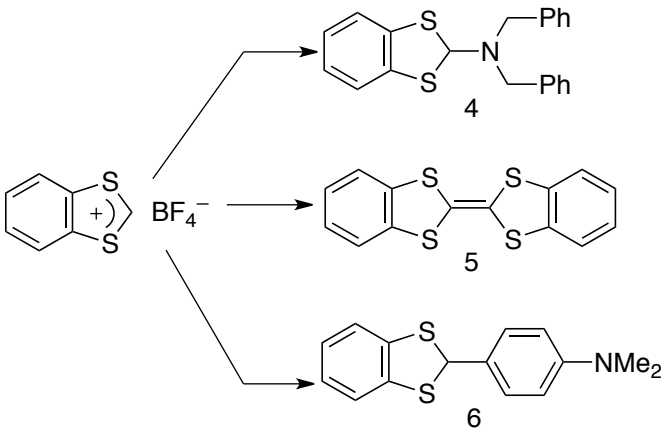
I. Introduction

1,3-benzodithiole heterocycle is a substrate that can offer considerable appeal in terms of C-C bond forming because of the relative ease with which both corresponding carbanionic **2** and carbocationic **3** forms can be designed.[1] The stability of carbocation **3** is between that of the tropylium and tritylium carbenium salts.[2]



Scheme 1

In 1976, Hoshino and co-workers[3] reported the synthesis of 1,3-benzodithiolylium salts, through treatment of a solution of 2-isopentyloxy-1,3-benzodithiole in acetic anhydride and the correspondent HX acid to give the 1,3-benzothiolylium salt. The behaviour of 1,3-benzodithiolylium salts with nucleophiles has been studied with secondary amine such as dibenzylamine that react with the salt to give the compound **4**. The treatment of tetrafluoroborate salt with triethyl amine in acetonitrile gave the compound **5**, where the reaction was performed through a base –catalyzed deprotonation and subsequent reaction of the carbene with the tetrafluoroborate salt followed by deprotection. The electrophilic substitution with electron rich aromatic compounds reacted with 1,3-benzodithiolyium to give the correspondent products in good yields. These studies about the reactivity of 1,3-benzodithiolylium tetrafluoroborate toward a wide variety of nucleophiles reagents demonstrated the stability and solubility in polar solvent of the tetrafluoroborate salt.

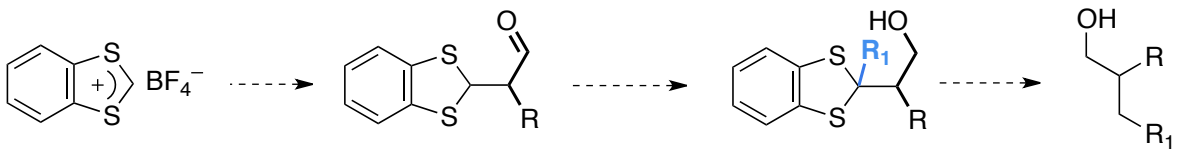


Scheme2. Reactivity of tetrafluoroborate salt with nucleophiles.

New methodologies have been studied for α-alkylation of aldehydes using secondary amine.[4]

As was discussed in the Chapter 2 and 3 S_N1 type reactions can give important contribution to solving the problem of α-alkylation of aldehydes.[5] However, one important problem remains to be solved. The alkylation of aldehydes with allylic, benzylic, Benzhidrylic substrates are certainly useful and interesting,[6] but the application of the methodology in total synthesis of natural product is quite difficult. In total synthesis the introduction of methyl or alkyl chain to an α position of aldehyde is crucial. Unfortunately, until now in organocatalysis there was not possibility to introduce a methyl or alkyl chain by using organocatalysts with simple alkyl halide (methyl iodide) reagents.

According at the use of stable and isolate carbenium ion in stereoselective α-alkylation has been investigated the use of heteoatom-stabilized carbenium ion such as the commercially available 1,3-benzoditholylium tetrafluoroborate. The stereoselective α-alkylation of aldehyde with **3** BF_4 salt not only can give the product, the introduction of 1,3-benzodithiol group in stereoselective fashion can also allow the generation of an anionic or cationic equivalent. Furthermore, deprotection of 1,3-benzothiole with Raney Ni can afford the direct access to a methyl group.

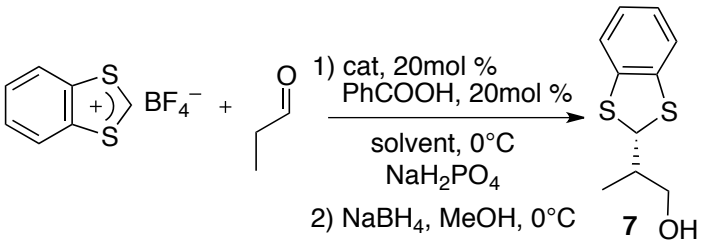


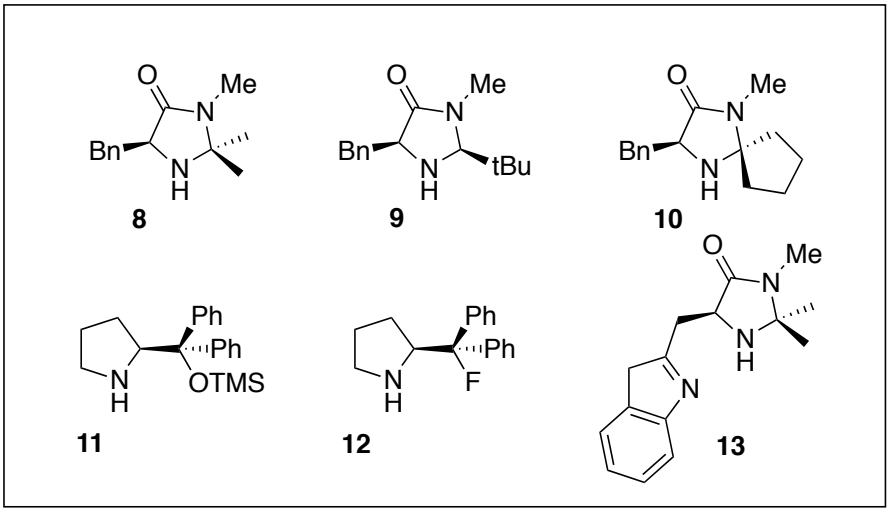
Scheme 3. Hypothesis about the functionalization of 1,3-benzodithiol group

II. Results and discussion

The direct α-alkylation reaction of propionaldehyde with 1,3-benzodithiolylium tetrafluoroborate salt and stoichiometric amount of base, which capture the HBF_4 liberated by the reaction of the carbenium ion was selected as the model reaction. Different base and organocatalysts were tested in the reaction. The nature of the base was important in the reaction, the use of organic base such as 1,6-dimethylpyridine, DABCO or triethylamine afforded the desired product in poor yields because of side reactions, formation of the tetrathioflulvalene **5** induce by the formation of the correspondent carbene. Therefore the use of inorganic bases were more suitable for the reaction. NaH_2PO_4 was found the most efficiently base in yielding. Then, different catalysts and solvents were tested in order to improve both yield and enantiomeric excesses. Proline derivatives in general gave poor results in this reaction. Meanwhile, the use of imidazolidinone derivatives **8** and **10** were found to catalyze the direct α-alkylation of aldehydes in moderated yield and enantioselectivity (table1, entry 1,3). The reaction was further optimized by screening of different solvents, using imidazolidinone derivatives as catalyst into the reaction. The water as solvent gave the optimal results in enantioselectivity. (table 1, entry 6-9). Delighted by these initials results, a mixture of solvents were tested using the catalyst **8**. The desired product **7** was produced with 96% enantioselectivity and 96 % yield in a 1:1 mixture of CH_3CN and H_2O. (table 1, entry 12).

The stability of the 1,3-benzodithiolyium carbenium is high in the presence of water and no decomposition was observed in the reaction.



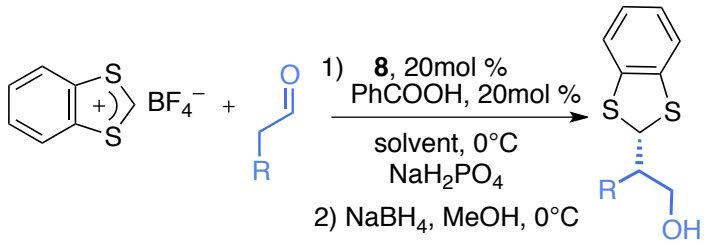


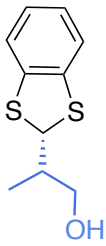
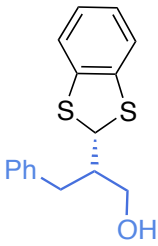
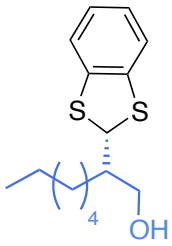
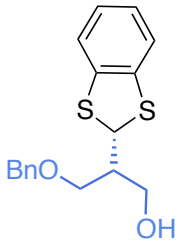
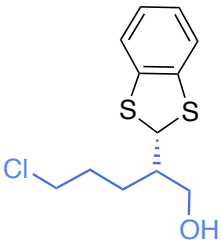
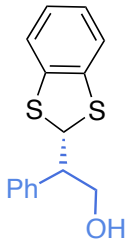
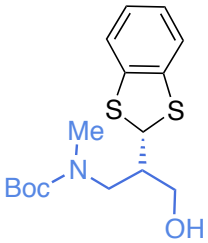
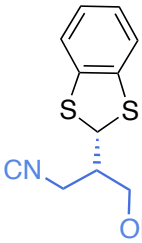
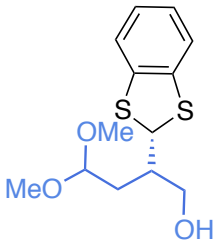
entry[a]	cat (20mol%)	solvent	Yield (%)[b]	ee (%)[c]
1	8	DCM	90	50
2	9	DCM	87	6
3	10	DCM	30	30
4	11	DCM	26	25
5	12	DCM	50	40
6	8	H_2O	54	87
7	9	H_2O	51	36
8	10	H_2O	42	80
9	13	H_2O	73	72
10	8	CH_3CN	76	80
11	8	H_2O/ CH_3CN 9:1	82	91
12	8	H_2O/ CH_3CN 1:1	96	96
13	8	H_2O/ THF 1:1	44	63

[a] the reaction were performed at 0°C with 1 eq of 1,3-benzodithiozolylium salt, 3 eq of propanal in presence of 20 mol % of catalyst, and 1 eq of NaH_2PO_4, 20 mol % benzoic acid was used as co-catalyst and the reactions were run until completion as determined by TLC. [b] Yield after chromatographic purification. [c] Determined by analysis of isolated products by HPLC on chiral phase.

Table 1.

Under the optimal conditions, the scope of 1,3-benzodithiolylium salt has revealed with a different aldehydes employed in this formylation reaction. (Table 2, entries 1-9, 97-92%ee) Moreover this protocol was tolerant to a broad array of functionalized aldehydes that incorporate heteroatoms substituents such as chloro, and cyano groups, amides and acetales. (Table 2, entries 4-9).



1		2	
	96%, 96 % ee		85%, 96% ee
3		4	
	96%, 96% ee		62%, 92% ee
5		6	
	93%, 94% ee		90%, 97% ee
7		8	
	61%, 97% ee		90%, 92% ee
9			
	84%, 96% ee		

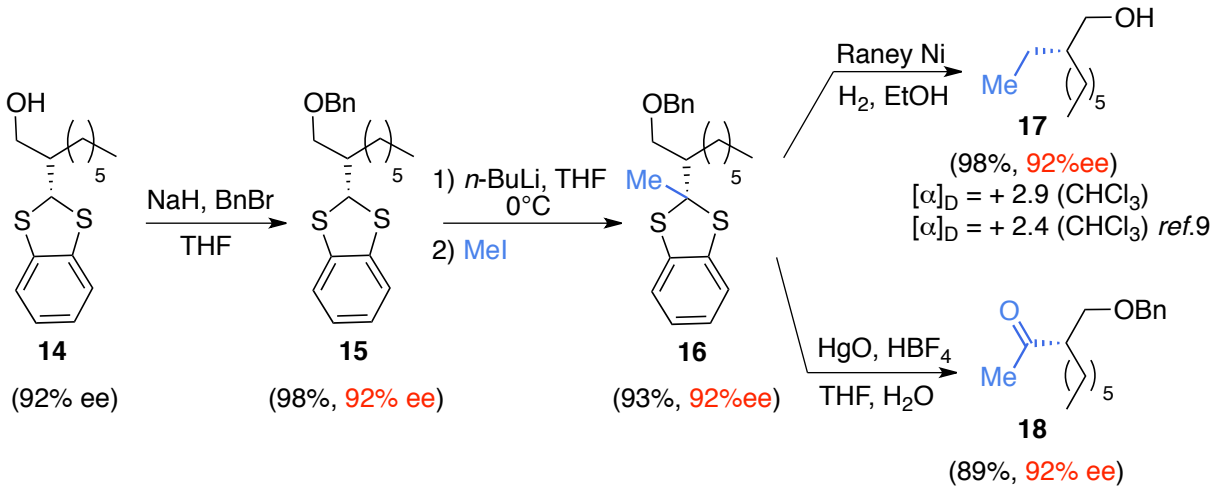
All the reaction were performed at 0°C with 1 eq of 1,3-benzodithiozolylium salt, 3 eq of aldehyde in presence of 20 mol % of catalyst, and 1 eq of NaH_2PO_4, 20 mol % benzoic acid was used as co-catalyst and the reactions were run until completion as determined by TLC. Yield after chromatographic purification. Determined by analysis of isolated products by HPLC on chiral phase.

Table2. Organocatalytic alkylation of functionalized aldehydes with 1,3-benzodithiolylium salt

While regard to the application and operational advantages of the formylation reaction,[7] it was important mentioned: a) The new formylation provides a straightforward access to a variety of precursors and b) all the alkylations were performed under aerobic conditions using wet solvents and inexpensive and available starting materials.

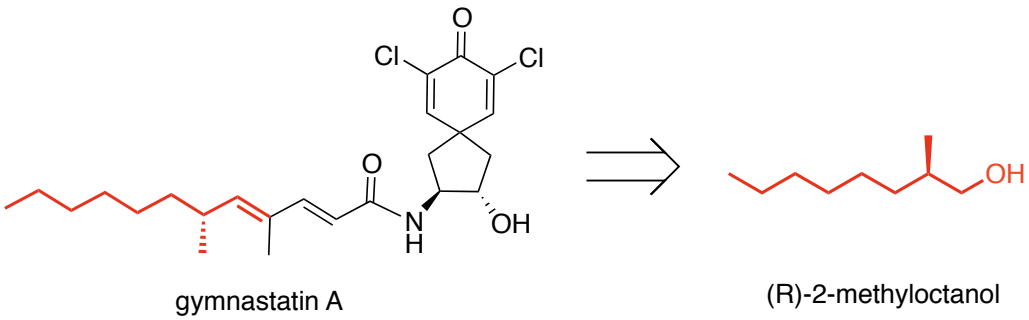
Moreover, the 1,3-benzodithiol adduct can be removed by Raney Nickel in the presence of hydrogen to promote access to a methyl group. Thus this procedure could be a useful methodology in the synthesis of product naturals and provides a new approach for the stereoselective α-methylation of aldehydes.

This novel enantioselective formylation reaction provides a highly versatile in chiral building blocks for variety of different synthetic transformations leading to optically active compounds. Some example is illustrated in the scheme 4. Protection of the alcohol **14** with NaH and BnBr afforded the corresponding compound **15** in 98% yield without decrease in optical purity. The compound **15** was lithiated with *n*-BuLi and treated with one agent alkylant such as MeI. The alkylation reaction afforded the product **16** in high yield and without loss of ee. Furthermore, the product **16** was transformed in product **17**, after treatment with Raney Ni, without any decrease in optical purity (98%, 92%ee). On the other hand, the adduct **16** could be also transformed into the correspondent ketone by treatment of the 1,3-benzodithiol adducts with HgO in presence of HBF_4 to afford the product **18** with high yield, enantioselectivity (89%, 92% ee).[8]



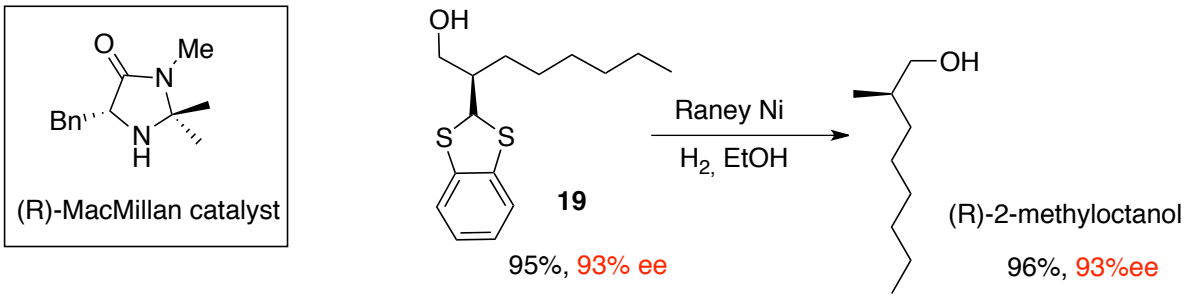
Scheme 4. Synthetic transformations

To increase the scope in the α-methylation of aldehydes was applicated this new methodology in the preparation of a key intermediate in the synthesis of gymnastatian A. Gymnastatin A was isolate from a stain of *Gymnasella dankaliensis* originally separated from *Sponge Halichondira Japonica*. Among the Gynmastatin A exhibited inhibition against P388 cancer cells.[10]



Scheme 5. Intermediate for the synthesis of Gymnastatin A

The synthesis of (R)-2-methyloctanol can be possible with the new methodology of stereoselective α-methylation of aldehydes. Alkylation of octanal with 1,3-benzodithiolyium salt was catalyzed by the (R)-MacMillan catalyst **8** to afford the desired product **19** in 95% yield and 93% ee. Then product **20** was treated with Raney Ni, without protection of alcohol to obtain the (R)-2-methyloctanol in 96% yield and the same stereoselectivity.

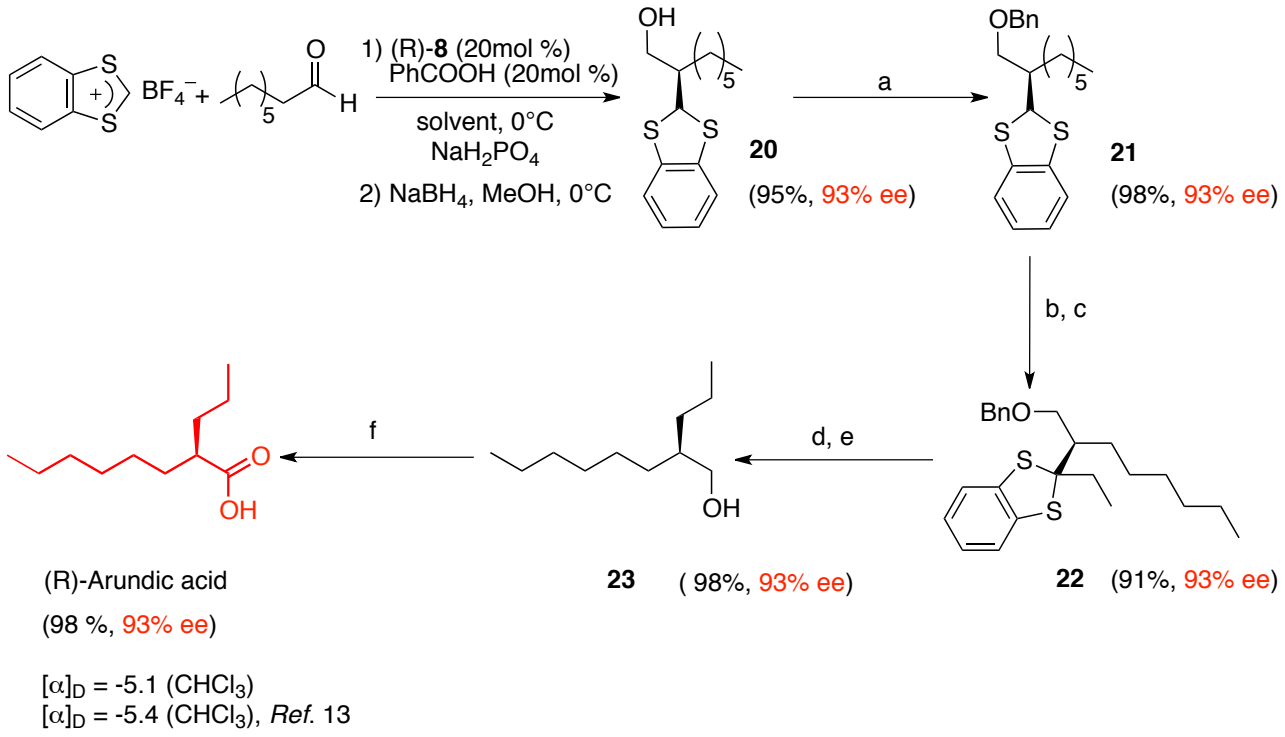


Scheme 6. Synthesis of (R)-2-methyloctanol

Other potential agent possible to prepared from the stereoselective α-methylation of aldehydes was the Arundic acid which was discovered by Minase Research Institute of Ono Pharmaceutical CO-Ltd., Osaka, during a screening process and was called the name Ono-2506 the (R)-Arundic acid is currently undergoing phase II development for the treatment of acute ischemic stroke as well as clinical development for other neurodegenerative diseases including Alzheimer's disease and Parkison's disease.[11]

To synthesize the (R)- Arundic acid was treated 1,3-benzodithiozolylium salt with hexanal and (R)-MacMillan catalyst followed by a reduction of aldehyde with $NaBH_4$ /MeOH to afford the desired alcohol **20** in 91% yield, 93%ee. Then the alcohol **20** was treated with NaH and BnBr to afford the intermediated **21** with 93% ee. Then the derivative **21** was metalated with *n*-BuLi at 0°C and then alkylated to obtain **22** in 91% yield and 93%ee After successive treatment with Raney Ni/H_2 and

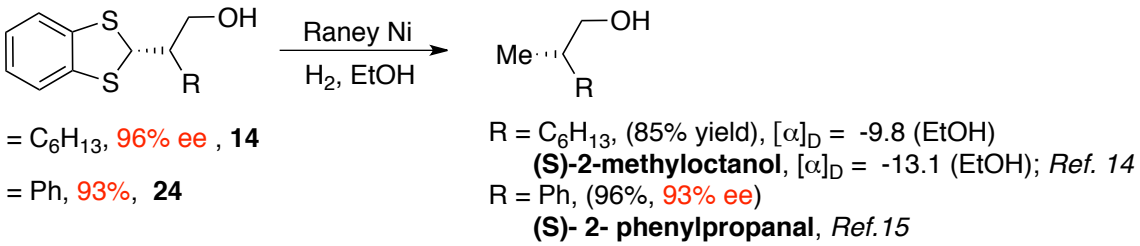
hydrogenolysis of the benzyl group with hydrogen Pd/C catalyst, afforded the alcohol **23** in quantitative yield 98% and without loss the enantioselectivity. The alcohol **23** was also easily transformed into (R)- arundic acid after oxidation treatment[12] in high yield (98%), without loss the optical purity.



Scheme 7. The enantioselective synthesis of arundic acid, with organocatalytic formylation
a)NaH, BnBr in THF; b) *n*-BuLi in THF, 0°C ; c) EtI, 98% (two steps); d) Raney Ni/H_2 in EtOH; e) H_2, Pd/C, 91% (two steps); f) $NaClO_2$, NaClO (cat.), TEMPO (cat.) in MeCN/buffer pH 6.7, 98%. TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl.

Determination of Absolute configuration

The absolute configurations of the products were determined through the transformation of the compound **15** and **25** into the correspondent products (S)- methyloctanol and (S)- 2-phenylpropanal with Raney Ni. The absolute configuration of (S)-methyloctanol was reported by comparison with the reported optical rotation value. While the absolute configuration of 2-phenylpropanal was compared with the HPLC analysis reported in the literature.[14,15]



R = C_6H_{13}, 96% ee , **14**

R = Ph, 93%, **24**

R = C_6H_{13}, (85% yield), $[\alpha]_D$ = -9.8 (EtOH)
(S)-2-methyloctanol, $[\alpha]_D$ = -13.1 (EtOH); *Ref. 14*
R = Ph, (96%, 93% ee)
(S)- 2- phenylpropanal, *Ref.15*

Scheme 8. Determination of absolute configuration

III. Conclusion

The S_N1 type reaction has appeared as a new methodology in the asymmetric organocatalysis. In this this work was reported a simple and practical asymmetric α-alkylation using 1,3-benzodithiolylium salt commercially available. This novel methodology has opened new frontiers in the stereoselective α addition of a formyl group to aldehyde. The novelty in this method has been the tolerance of the 1,3-benzodithiolylium into the reaction conditions and the capacity of transformation of 1,3-benzodithiol group by either metalation with *n*-BuLi and successive alkylation, or the possibility to reduce with Raney Ni affording stereoselective α methylation of aldehydes.

Quite remarkably, the reaction was tolerance a broad range of functionalized aldehydes and was applied successfully to the synthesis of chiral compounds. Furthermore the possibility to induce the formation of carbocation in presence of water, merging metal catalysis and organocatalysis can open new frontiers in the field of organocatalysis.

IV.Experimental section

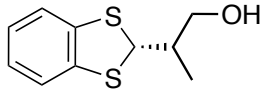
Enantioselective α-alkylation of aldehydes

General procedure

A vial was charged with (S)-**8** catalyst (0.02 mmol, 0.005 g), benzoic acid (0.02 mmol, 0.002 g), acetonitrile (0.25 mL) and water (0.25 mL). The mixture was cooled at 0°C, 1,3-benzodithiolylium tetrafluoroborate (0.1 mmol, 0.024 g), NaH_2PO_4 (0.1 mmol, 0.012 g) and propanal (0.3 mmol, 11 mL) were added. The mixture was stirred for 24 hours at the same temperature, the organic solvent was evaporated and the mixture was diluted with Et_2O (3mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 3 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure.

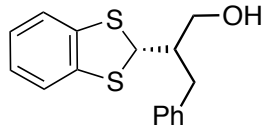
The residue was diluted in MeOH (1 mL) and $NaBH_4$ (0.4 mmol, 0.015 g) was slowly added at 0 °C. After 30 minutes, the reaction was quenched with water (0.2 mL) and concentrated in vacuo. The residue was extracted with AcOEt (3 x 5 mL), dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, cyclohexane/ethyl acetate) of the residue affording the desired product.

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)propan-1-ol. (table 2, entry 1)



According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (85% yield, 96% ee). The ee was determined by HPLC analysis Daicel Chiralcel IC column: *n*-hexane/*i*-PrOH 95:5, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 20.7 min., *τminor* = 19.1 min; $[\alpha]_D^{20}$=+4.6 (*c*=0.9 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 1.06 (d, J = 6.8 Hz, 3H), 2.11 (m, 1H), 3.69 (d, J = 5.2 Hz, 2H), 5.13 (d, J = 6.0 Hz, 1H), 7.01 (dd, J = 3.3 Hz, J = 5.8 Hz, 2H), 7.21 (dd, J = 3.1 Hz, J = 5.9 Hz, 2H); **^{13}C NMR (25 MHz, $CDCl_3$, 25°C)** δ 13.2, 43.6, 56.5, 64.8, 121.9, 122.0, 125.4 (2C), 137.7 (2C); **HMRS calcd** for $C_{10}H_{12}OS_2$: 212.0330; found 346.2327.

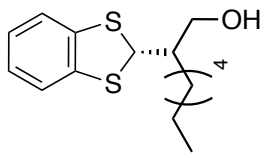
(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-3-phenylpropan-1-ol. (table 2, entry 2)



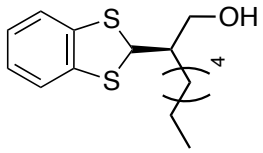
According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (85% yield, 96% ee) ; The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 95:5, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 24.3 min., *τminor* = 21.5 min; $[\alpha]_D^{20}$=+34.7 (*c*=1.3 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.57 (bs, 1H), 2.18-2.25 (m, 1H), 2.69-2.76 (m, 1H), 2.97 (dd, J = 5.4 Hz, J = 13.7 Hz, 1H), 3.66-3.70 (m, 1H), 3.75 (dd, J = 4.5 Hz, J = 11.2 Hz, 1H), 5.17 (d, J = 5.8 Hz, 1H), 7.02-7.04 (m, 2H); 7.18-7.25 (m, 5H), 7.26-7.32 (m, 2H); **^{13}C NMR (25 MHz, $CDCl_3$, 25°C)** ***δ*** 34.1, 50.3, 55.4, 61.7, 122.2, 125.6 (2C), 127.0,

126.4, 128.5, 128.7 (2C), 129.3, 137.7, 137.8, 139.4; **HMRS calcd** for $C_{16}H_{16}OS_2$: 288.0643; found 288.0640.

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)octan-1-ol. (table 2, entry 3)

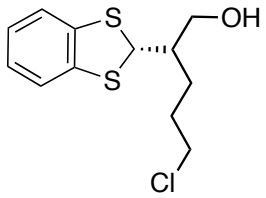


According at the same procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (96%ee, 94% ee). The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 95:5, flow rate 0.50 mL/min, 30°C, λ = 254, 262 nm: *τmajor* = 16.6 min., *τminor* = 15.5 min; $[\alpha]_D^{20}$=+17.7 (*c*=1.1 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.89 (t, J = 7.0 Hz, 3H), 2.25-1.32 (m, 8H), 139-1.46 (m, 1H), 1.53-1.60 (m, 1H), 1.77 (bs, 1H), 1.92 (m, 1H), 3.74 (dd, J = 5.6 Hz, J = 11.3 Hz, 1H), 3.83 (dd, J = 4.1 Hz, J = 11.3 Hz, 1H), 5.20 (d, J = 6.5 Hz, 1H), 7.01 (dd, J = 3.3 Hz, J = 5.8 Hz, 2H), 7.20 (dd, J = 3.1 Hz, J = 5.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C**) *δ* 14.0, 22.5, 27.1, 28.1, 29.3, 31.6, 47.6, 56.6, 62.4, 122.0 (2C), 125.3, 125.4, 137.6, 137.7; HMRS calcd for $C_{15}H_{22}OS_2$: 281.1112; found 282.1114.



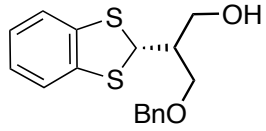
$[\alpha]_D^{20}$=-14.1 (*c*=0.7 in $CHCl_3$). NMR spectra were identical to those of **(*S*)- 2-(benzo[*d*][1,3]dithiol-2-yl)octan-1-ol**

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-5-chloropentan-1-ol. (table 2, entry 5)



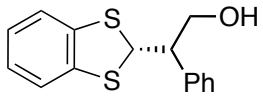
According at the same procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 7/3) as colourless oil (93% yield, 94% ee); The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 15.9 min., *τminor* = 12.3 min; $[\alpha]_D^{20}$=+21.5 (c=1.3 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.58-1.65 (m, 2H), 1.70-1.78 (m, 1H), 1.80-1.88 (m, 1H), 1.93 (m, 1H), 3.53 (m, 2H), 3.75 (dd, J = 5.3 Hz, J = 11.4 Hz, 1H), 3.87 (dd, J = 4.2 Hz, J = 11.4 Hz, 1H), 5.16 (d, J = 6.6 Hz, 1H), 7.03 (dd, J = 3.5 Hz, J = 6.0 Hz, 2H), 7.20-7.22 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 30.4, 44.8, 47.3, 56.1, 62.1, 122.1, 125.5 (2C), 125.6 (2C), 137.4 (2C); **HMRS calcd** for $C_{12}H_{15}ClOS_2$: 274.0253; found 274.0253.

(*S*)-2-(benzo[*d*][1,3]dithiol-2-yl)-3-(benzyloxy)propan-1-ol (table 2, entry 4)



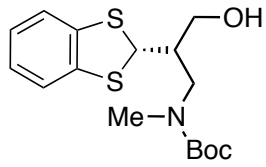
According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (62% yield, 92% ee). The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 28.5 min., *τminor* = 23.0 min; $[\alpha]_D^{20}$=+27.5 (*c*=0.4 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 2.18 (m, 1H), 2.32 (bs, 1H), 3.74 (dd, J = 4.0 Hz, J = 9.7 Hz, 1H), 3.87-3.91 (m, 2H), 3.97 (dd, J = 4.9 Hz, J = 11.2 Hz, 1H), 4.52 (s, 2H), 5.21 (d, J = 8.6 Hz, 1H), 7.00-7.04 (m, 2H), 7.20-7.23 (m, 2H), 7.31-7.34 (m, 2H), 7.36-7.39 (m, 3H); **^{13}C NMR (25 MHz, $CDCl_3$, 25°C)** δ 47.6, 52.9, 62.9, 70.3, 73.7, 122.2, 122.4, 125.5 (2C), 127.0, 127.7, 127.9, 128.5 (2C), 137.5, 137.6 (2C); **HMRS calcd** for $C_{17}H_{18}O_2S_2$: 318.0748; found 346.2327.

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-2-phenylethanol. (table 2, entry 6)



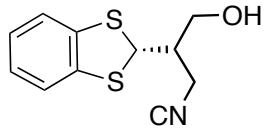
According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (90% yield, 97% ee). The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 96:4, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 34.5 min., *τminor* = 35.7 min; $[\alpha]_D^{20}$=+22.6 (*c*=0.2 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 3.33 (ddd, J = 4.9 Hz, J = 6.1 Hz, J = 9.5 Hz, 1H), 4.00-4.08 (m, 2H), 5.34 (d, J = 9.5 Hz, 1H), 6.97-7.02 (m, 2H), 7.10-7.13 (m, 1H), 7.19-7.21 (m, 1H), 7.26-7.36 (m, 5H); **^{13}C NMR (25 MHz, $CDCl_3$, 25°C)** δ 54.9, 56.2, 64.4, 122.2, 122.3, 125.4, 125.6, 127.7 (2C), 128.4, 128.6, 128.8 (2C), 137.2, 139.1**; HMRS calcd** for $C_{15}H_{14}OS_2$: 274.0486; found 346.2327.

(*R*)-*tert*-butyl (2-(benzo[*d*][1,3]dithiol-2-yl)-3-hydroxypropyl)(methyl)carbamate. (table 2, enty 7)



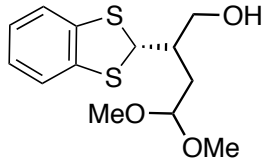
According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 7/3) as colourless oil (61% yield, 97% ee). The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 85:15, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 14.6 min., *τminor* = 10.9 min; $[\alpha]_D^{20}$=-63.7 (*c*=1.1 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.47 (s, 9H), 2.05 (m, 1H), 2.83 (s, 3H), 3.22 (dd, J = 4.1 Hz, J = 14.1 Hz, 1H), 3.52 (d, J = 14.1 Hz, 1H), 3.73-3.85 (m, 2H), 5.00 (d, J = 9.5 Hz, 1H), 7.02-7.04 (m, 2H), 7.22-7.24 (m, 2H); **^{13}C NMR (25 MHz, $CDCl_3$, 25°C)** *δ* 28.3 (3C), 34.9, 45.9, 46.9, 54.3, 59.4, 80.6, 122.3, 122.4, 125.5, 126.6, 137.3 (2C), 157.5; **HMRS calcd** for $C_{16}H_{23}NO_3S_2$: 341.1119; found 346.2327.

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-3-isocyanopropan-1-ol. (table 2, entry 8)



According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 8/2) as colourless oil (90% yield, 92% ee). The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 21.2 min., *τminor* = 18.1 min; $[\alpha]_D^{20}$=+10.4 (*c*=0.6 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 1.57 (bs, 1H), 2.25-2.33 (m, 1H), 2.61 (dd, J = 8.7 Hz, J = 16.7 Hz, 1H), 2.77 (dd, J = 4.5 Hz, J = 17.1 Hz, 1H), 3.88-3.97 (m, 2H), 5.06 (d, J = 6.9 Hz, 1H), 7.06 (dd, J = 3.2 Hz, J = 5.7 Hz, 2H), 7.24 (dd, J = 3.1 Hz, J = 5.9 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 16.2, 45.6, 53.5, 61.0, 118.2, 122.4, 122.5, 126.0 (2C), 136.3, 136.7; **HMRS calcd** for $C_{11}H_{11}NOS_2$: 237.282; found 346.2327

(*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-4,4-dimethoxybutan-1-ol. (table 2, entry 9)



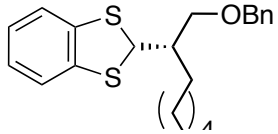
According at the general procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 8/2) as colourless oil (84% yield, 96% ee) The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 30°C, λ = 232, 254 nm: *τmajor* = 22.7 min., *τminor* = 17.7 min; $[\alpha]_D^{20}$=+3.0 (*c*=0.7 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.81 (ddd, J = 5.4 Hz, J = 8.8 Hz, J = 14.3 Hz, 1H), 1.99-2.05 (m, 1H), 2.10 (m, 1H), 3.32 (s, 3H), 3.35 (s, 3H), 3.74 (m, 1H), 3.82 (m, 1H), 4.49 (t, J = 5.3 Hz, 1H), 5.16 (d, J = 6.8 Hz, 1H), 7.01 (dd, J = 3.3 Hz, J = 5.7 Hz, 2H), 7.20 (d, J = 3.3 Hz, J = 5.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 31.5, 44.5, 52.6, 54.0, 56.2, 62.7, 103.5, 122.0, 122.1, 125.4, 125.5, 137.5, 137.6**; HMRS calcd** for $C_{13}H_{18}O_3S_2$: 286.0697; found 346.2327.

Alkylation of benzodithiol compounds

Protection of hydroxyl group

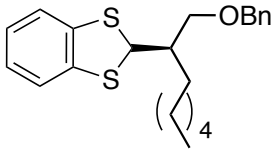
To a suspension of NaH (0.4 mmol, 0.017 g of a 60% suspension in mineral oil) in anhydrous THF (3 mL) a solution of (*S*)-**14** (0.2 mmol, 0.060 g) in THF (1 mL) was slowly added at 0°C. After 30 minutes benzylbromide (0.3 mmol, 38 mL) was added and the mixture was stirred at room temperature for 18 hours. Water (5 mL) was slowly added and the mixture was diluted with Et_2O (3mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure.

Flash chromatography (cyclohexane/ethyl acetate, 9/1) of the residue afforded product as a colourless oil (*S*)-**15** in 98% yield .



$[\alpha]_D^{20}$=+23.6 (*c*=1.1 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** *δ* 0.89 (t, J = 6.0 Hz, 3H), 1.24-1.35 (m, 8H), 1.46 (m,1H), 1.63 (m, 1H), 2.02 (m, 1H), 3.43

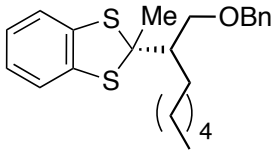
(dd, J = 5.6 Hz, J = 9.5 Hz, 1H), 3.65 (dd, J = 4.4 Hz, J = 9.5 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 5.27 (d, J = 7.2 Hz, 1H), 7.00 (dd, J = 2.8 Hz, J = 5.6 Hz, 2H), 7.31-7.40 (m, 2H), 6.98-7.02 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.1, 22.5, 27.2, 27.8, 29.3, 31.6, 46.3, 56.3, 69.3, 73.2, 121.8, 121.9, 125.2 (2C), 127.5, 127.6, 128.3, 137.8, 138.2, 138.8**; HMRS calcd** for $C_{22}H_{28}OS_2$: 372.1582; found 346.2327.



(R)- 15 : $[\alpha]_D^{20}$=-29.5 (*c*=1.0 in $CHCl_3$); NMR spectra were identical to those of (*S*)-**(16)**.

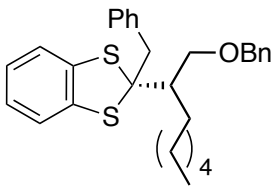
General Procedure for Alkylation

A solution of *n*BuLi (0.022 mmol, 88 mL, 2.5 M in hexanes) was added dropwise to a solution of (*S*)-**(15)** (0.2 mmol, 0.076 g) in anhydrous in THF (2 mL) at 0°C. The mixture turns to orange colour. After 5 minutes methyl iodide (0.4 mol, 20 mL) was added and the solution became colourless. The solution was stirred for 5 minutes and then water (1 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. Flash chromatography (cyclohexane/ethyl acetate) affording the product

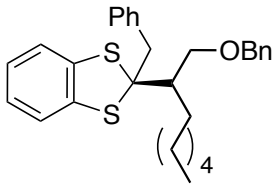


The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (S)-**16** (93% yield) $[\alpha]_D^{20}$=+12.5 (*c*=1.7 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.91 (t, J= 6.6 Hz, 3H), 1.29- 1.39 (m, 8H), 1.54- 1.63 (m, 1H), 1.66-1.72 (m, 1H), 1.88 (s, 3H), 2.35-2.41 (m, 1H), 3.66 (d, J=4.5 Hz, 2H), 4.55 (AB, J=8.6Hz, J= 11.9 Hz, 2H), 7.00- 7.02 (m,2H), 7.19 (d, J= 5.7 Hz, 1H), 7.20 (d, J= 5.7 Hz, 1H), 7.28-7.34 (m, 1H); 7.35-7.41 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.1, 22.6, 28.2, 28.3, 29.3, 30.2, 31.7, 48.5, 70.4, 73.1, 73.7, 122.4, 122.5, 125.2 (2C), 127.5 (2C), 127.6 (2C), 128.3, 137.6, 138.2, 138.3; **HMRS calcd** for $C_{23}H_{30}OS_2$: 386.1738; found 386.1737.

The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (92% yield). $[\alpha]_D^{20}$=+10.6 (*c*=1.05 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.90 (t, *J*= 6.2 Hz, 3H), 1.20-1.40 (m, 8H), 1.57-1.69 (m, 1H), 1.78-1.89 (m, 1H), 2.31-2.39 (m, 1H), 3.31 (d, *J*= 14.0 Hz, 1H), 3.38 (d, J= 14.0 Hz, 1H), 3.68-3.75 (dd, *J*= 3.3 Hz, *J*= 10.2 Hz, 1H), 3.80-3.85 (m, 1H). 4.53 (d, *J*= 11.0 Hz, 2H), 6.83- 6.87 (m, 2H), 6.97-7.00 (m, 2H), 7.10-7.18 (m, 2H),



7.28-7.42 (m, 8H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.1, 22.6, 28.4, 29.4, 30.6, 31.7, 46.2, 27.6, 70.7, 73.1, 8.0, 121.7 (2C), 124.8, 126.6, 127.2 (2C), 127.6, 127.7, 128.4 (2C), 128.7, 129.0, 130.4 (2C), 136.3, 126.3, 138.2, 138.3; **HMRS calcd** for $C_{29}H_{34}OS_2$: 465.2051; found 346.2327.



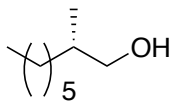
The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil (91% yield) $[\alpha]_D^{20}$=-22.1 (*c*=1.0 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.90 (t, J= 6.6 Hz, 3H), 1.08 (t, J= 7.2 Hz, 3H), 1.24-1.37 (m, 7H), 1.40-1.49 (m, 1H), 1.53-1.62 (m, 1H), 1.77-1.85 (m, 1H), 2.12 (q, J= 7.1 Hz, 2H), 2.23-2.28 (m, 1H), 3.62 (dd, J= 4.0 Hz, J= 10.4 Hz, 1H), 3.77 (dd, J= 4.5 Hz, J= 9.8 Hz, 1H), 4.52 (s, 2H), 6.95-6.98 (m, 2H), 7.11-7.14 (m, 2H), 7.29-7.38 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 9.9, 14.1, 22.6, 28.3, 29.4, 30.3, 31.7, 34.6, 47.3, 70.5, 73.1, 78.6, 121.6, 121.7, 124.9 (2C), 127.5 (2C), 127.6, 128.3 (2C), 138.2, 138.3, 138.6; **HMRS calcd** for $C_{24}H_{32}OSi_2$: 400.1895; found 400.1896.

Reductive removal of benzothiol group

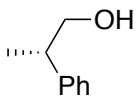
General Procedure

To a solution of **16** (0.05 mmol, 0.020 g) in ethanol (3 mL), Ni-Raney (0.450g slurry in water) was added and the reaction was keep under H_2 atmosphere (1 atm). After 3h the reaction mixture was filtered through a Celite pad and the organic solvent was removed under reduce pressure. The residue was diluited with AcOEt, the organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure.

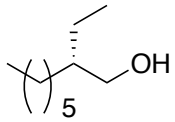
Flash chromatography (Cyclohexane/diethyl ether, 9/1) of the residue afforded the desired product.



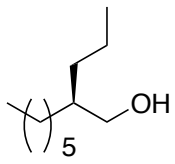
(*S*)- 2-methyloctanol and **(*R*)-** were already reported[16]



Absolute configuration was assigned by comparison of retention time with the reference literature[18]



(S)-17 product was already reported[19]



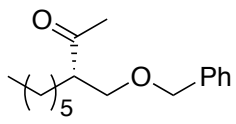
According at the procedure the desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil **(R)- 23** (98% yield) $[\alpha]_D^{20}$=-22.1 (*c*=1.0 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.87-0.93 (m,

6H), 1.24-1.34 (m, 14H), 1.48 (m, 1H), 1.58 (bs, 1H), 3.54 (d, J= 5.5 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.1, 14.4, 20.0, 22.6, 26.8, 29.7, 30.9, 31.8, 33.2, 40.2, 65.7; **HMRS calcd** for $C_{11}H_{24}O$: 172.1827; found 400.1896.

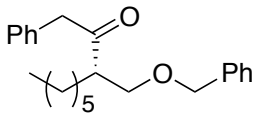
Oxidative removal of benzothiol group

General procedure[20]

To a suspension of HgO (0.1 mmol, 0.022 g) in THF (2 mL) a 40% solution of HBF_4 in water (0.05 mL) was added. After 2 minutes a solution of **16** (0.05 mmol, 0.020 g) was slowly added and the precipitated dissolved. After 30 minutes a saturated solution of $NaHCO_3$ was slowly added at 0°C until basic pH. The solid was filtered through a pad of Celite, the organic solvent was evaporated and the residue was diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure.
Flash chromatography (SiO_2, cyclohexane/ethyl acetate) of the residue gave the product.



According with the procedure the desired product was isolated by flash column chromatography (SiO_2, cyclohexane/ethyl acetate = 8/2) as colourless oil **(S)- 18** (89% yield, 92% ee). The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 95:5, flow rate 0.50 mL/min, 30°C, λ = 210, 254 nm: *τmajor* = 13.1 min., *τminor* = 13.8 min; $[\alpha]_D^{20}$=-90.9 (*c*=0.4 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 1.16 (t, J= 6.7 Hz, 3H), 1.43-1.62 (m, 6H), 1.64-1.73 (m, 2H), 1.82-1.92 (m, 2H), 2.46 (s, 3H), 3.07-3.13 (m, 1H), 3.80 (dd, J= 5.0 Hz, J= 9.0 Hz, 1H), 3.89 (t, J= 8.7 Hz, 1H), 4.76 (s, 2H), 7.54-7.64 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.0, 22.5, 27.2, 28.5, 29.3, 30.0, 31.6, 53.0, 71.2, 73.2, 127.5 (2C), 127.6, 128.4 (2C), 138.1, 211.5; **HMRS calcd** for $C_{17}H_{26}O_2$: 262.1933; found 262.1929



According at the same procedure the desired product was isolated by flash column chromatography (SiO_2, cyclohexane/ethyl acetate = 7/3) as colourless oil (85% yield, 88% ee); The ee was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 95:5, flow rate 0.50 mL/min, 30°C, λ = 210, 254 nm: *τmajor* = 16.5 min., *τminor* = 15.4 min; $[\alpha]_D^{20}$=-117.0 (*c*=0.4 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$, 25°C)** δ 0.86 (t, *J*= 6.8 Hz, 3H), 1.12-1.47 (m, 8H), 1.54-1.63 (m, 1H), 1.64-1.74 (m, 1H), 2.95-3.02 (m, 1H), 3.49-3.54 (m, 1H), 3.59-3.63 (m, 1H), 3.75 (d, *J*= 15.5 Hz, 1H), 3.82 (d, *J*= 15.7 Hz, 1H), 4.46 (s, 2H), 7.18 (d, *J*= 7.5 Hz, 2H), 7.25-7.37 (m, 8H); **^{13}C NMR (100 MHz, $CDCl_3$, 25°C)** δ 14.0, 22.5, 27.2, 29.3, 29.7, 31.5, 50.8, 51.3, 71.8, 73.3, 126.8 (2C), 127.6 (2C), 127.7 (2C), 128.4 (2C), 128.5 (2C), 129.8, 138.1, 210.6; **HMRS calcd** for $C_{23}H_{30}O_2$: 338.2246; found 338.2247.

Oxidation to arundic acid[21]

A 1 mL flask equipped with a magnetic stir bar was charged with an alcohol **23** (0.5mmol, 0.009 g) in CH_3CN (0.25 mL). A solution of $NaClO_2$ (0.1 mmol, 0.009 g), TEMPO (0.01mmol, 0.001g) in H_2O (0.05 mL), 0.67 M sodium phosphate buffer (pH 6.7, 0.200 mL) and a solution of dilute NaOCl, prepared by diluting household bleach with 25 μL of water, were added. The mixture was stirred at 35°C. for 7 hours and was cooled to 0°C. Water (0.25 mL) and $NaHCO_3$ aq. were added until pH 8.0. Na_2SO_3 (0.12mmol, 0.015 g) was added and the mixture was vigorously stirred 30 min. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). HCl (0.1M) was added to the aqueous phase until pH= 2 and AcOEt was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure to give **(R)-arundic acid** in 98% yield. Spectroscopical data are in according with the literature[22]

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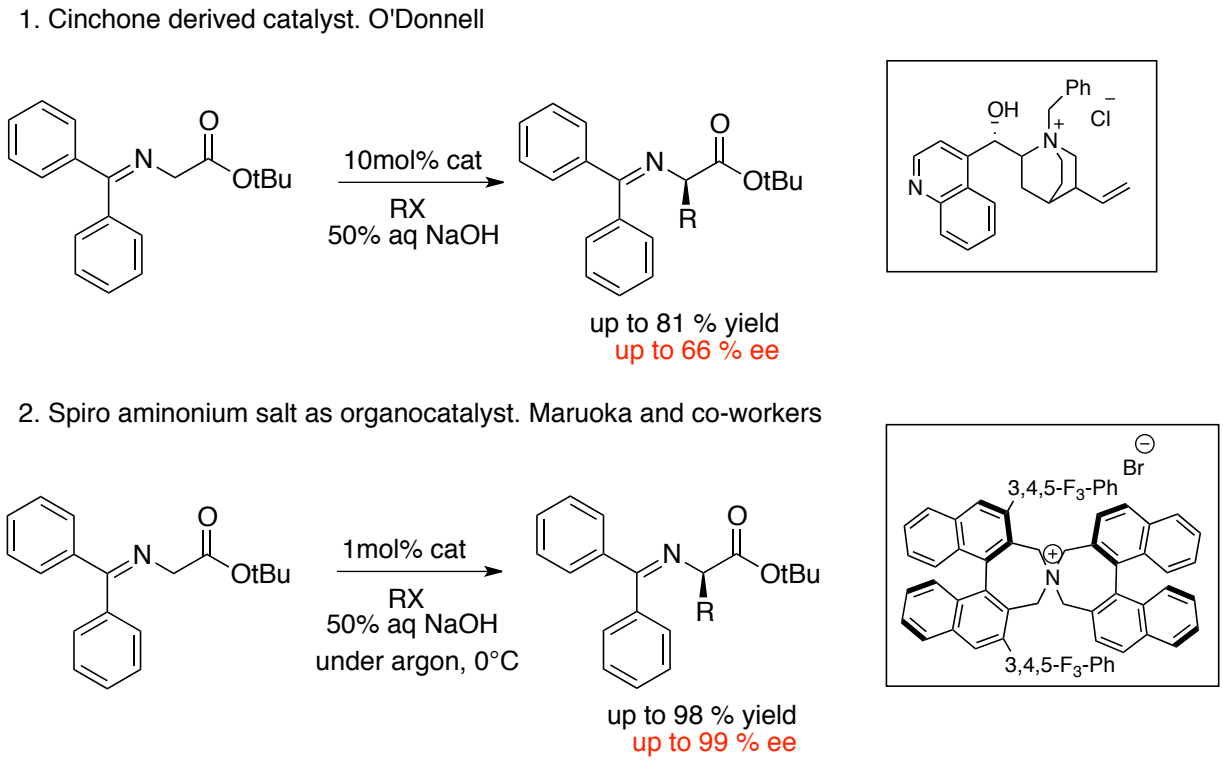
Chapter 5. Stereoselective α-alkylation of ketone *via* S_N1 Type.

I. Introduction

The asymmetric alkylation of ketone enolate represented one of the most challenging reactions in asymmetric catalysis. The use of auxiliars chirals in α-alkylation of ketone was a goal in the synthesis of chiral compounds and product naturals. The asymmetric alkylation of ketone enolate represented one of the most challenging reactions for asymmetric catalysis. [1]Several groups have studied the stereoselective alkylation of ketone with performed or in situ generated metal enolate.[2]

Organocatalysis has opened new frontiers in the world of organic chemistry.[3] New mode of activation has set up such as enamine catalysis[4a], iminium catalysis[4b], SOMO catalysis[4c], hydrogen bonding[4d] and new reactions have been discovered. Several groups have studied the stereoselective α-alkylation of aldehydes with enamine catalysis.[5] But limiting process in organocatalysis have studied the catalytic alkylation of ketone because of side reactions such as N,O-alkylation, Cannizzaro reaction[6] or enolation reaction can take place so fast in acidic conditions to promoted the racemization of the product. Furthermore ketone again the aldehydes are less reactive. Only few strategies in organocatalysis have reported the alkylation of ketones, one of them was the asymmetric phase transfer catalyzed[7] other the intramolecular alkylation of aldehydes with alkyl halides promoted by a chiral amine catalyst by List group.[8] MacMillan group with SOMO catalysis introduced the direct stereoselective α-allylation of ketones with allyl silanes.[9]



Scheme 1. Phase transfer catalysts

Recently our group has reported a simple and practical asymmetric α-alkylation of aldehydes using 1,3-benzodithiolylium salt obtaining high stereoselectivity.[10]

In view of this approach for the development of α-methylation of aldehydes using 1,3-benzodithiolylium salt was realized in an indirect way; by the use of a stabilized carbenium ions and by the successive reduction with Raney Ni. We were interested in developing the same straightforward alkylation of ketone, and we try to use similar reaction conditions and investigate the same reagents. Preliminary studies with 1,3-benzodithiolyium salt give unsatisfactory results with ketones using the same conditions that were used in the α-alkylation with aldehydes. After several trials and attempts we discovered a major problem in the use of the benzodithiolylium tetrafluoborate with ketone. Traces of fluoroboric acid liberates during the reaction or by storing the carbocation were active in promoting the reaction with the ketone. The easy formation of the corresponding enol form of the ketone was responsible for the fast background reaction. The reaction was settled with many organocatalysts and in the presence of bases, but the reaction conditions found were not reproducible. Therefore, we have investigated the possibility to use other carbenium ions for the stereoselective α-alkylation of ketone. We have prepared many formylation reagents based on different stabilized carbenium and we have tested them in reaction with cyclopentanone. Finally, we have demonstrated that 3-methyl benzothiazolium iodide was the most efficient carbenium ion providing the desired alkylation product in moderate yields.

The carbenium ion from benzothiazole is a useful electrophile used in synthetic transformations and can be easy prepared by alkylation of the nitrogen atom with methyl iodide. The scaffold used for the formylation is an aromatic heterocyclic thermally stable compound, and it is considered an electron poor aromatic compound. Some drugs contain benzothiazole such as Rizuole that is used in the treatment of amyotrophic lateral sclerosis.[11]

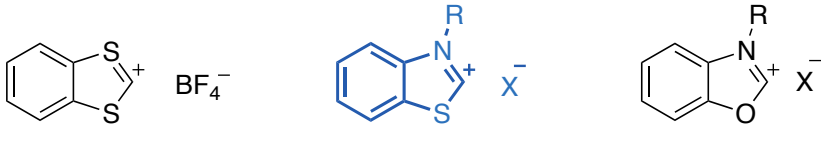
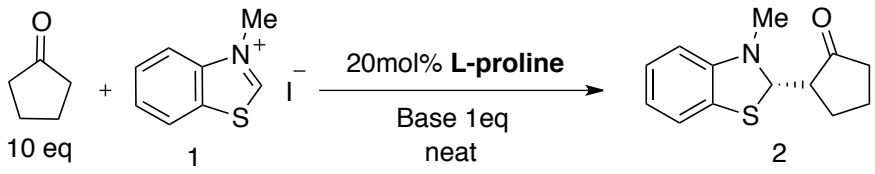


Figure 1. Stabilized carbeniums

II. Results and discussion

Inspired by the studies with α-alkylation of aldehydes with stabilized carbenium ions was hypothesized the use of 1 equiv. of base to capture the acid generated in the reaction. The first experiments began using 1equiv. of 3-methylbenzothiazolium iodide **1** 20 equiv. of cylopentanone, 20mol% of L-proline and 1 equiv. of base. The reaction was performed neat. The test with different kinds of base demonstrated that inorganic base than organic base with proline as catalyst were effective in yield (60-75%). Using inorganic base such as K_2CO_3, or Na_2CO_3 was providing a high diastereoselectivity (d.r 10:1). However, in both cases studied, either inorganic or organic bases gave poor enantioselectivity; racemic product was measured for from the minor diastereisomer obtained. Furthermore using 20mol% of base the yield decrease to 10% yield. (table 1)



entry[a]	Base 1eq	Yield[b] %	d.r[c]	ee %maj[d]	ee % min[d]
1	DABCO	70	3:1	30	0
2	lutidine	70	4:1	21	0
3	DBU	60	7:1	30	0
4	TEA	75	8:1	36	0
5	K_2CO_3	60	10:1	21	0
6	Na_2CO_3	70	10:1	31	0

[a]All the reaction were performed under air with 1 eq of 1, 10 eq of ketone, 20mol% L-proline and 1 eq of base at r.t. [b] Determined after chromatographic purification [c] for all the reactions the d.r ratio measured by ^{1}NMR spectroscopy. [d] Determined by HPLC analysis.

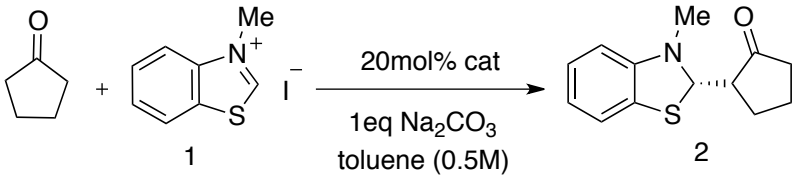
Table 1. Stereoselective α-alkylation of ketone with L-proline and different base

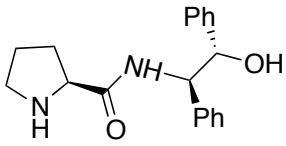
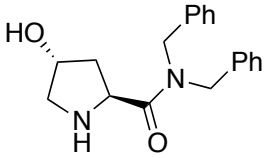
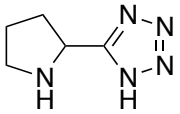
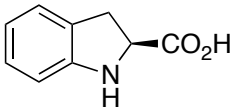
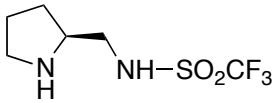
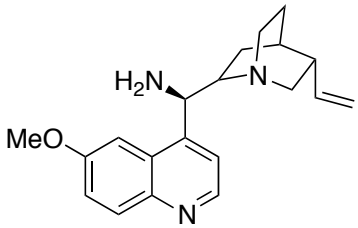
According to the previous results was examined the reaction with different secondary and primary amine catalysts, and decrease the amount of ketone. The reaction was performing using 5 equiv. of cyclopentanone, 1 eq of **1**, 20 mol % of catalyst and 1 eq Na_2CO_3 as base. The secondary amine catalysts afforded the product in low yields or without conversion into the product. (table 2, entry 1-5). On the other hand, the use of primary amine catalyst derivative from cinchona alkaloids produced

the desired α-alkylation adduct in poor yield, but notable stereocontrol (table 2, entry 6, d.r. 8:1; 95% maj: 64% min ee)

Primari amine derived from natural cinchona alkaloids have demonstrated the ability to catalyze in highly enantioselectivity Michael addition and cycloaddition reactions of α,β unsaturated ketones.[12] Moreover the cinchona alkaloids has been used as a chiral base by Wynberg and co-workers[13] in the conjugation addition reaction or as chiral quaternary ammonium salt which has served as the basis of high enantioselective phase transfer catalysis.[14] In this work alkylation has been used the 9-epi- 9-amino- 9-deoxyepi-quinidine (9 epi-QDA) as catalyst, derived from cinchona alkaloid. For the catalyst elaboration was used quinidine as starting material which was allowed to react with hydrazoic acid in a Mitsunobu reaction to provide the correpoding azide with inversion of configuration, and sequence in situ reduction of azide to afford the 9-epiQDA catalyst.[15]

Remarkably, all the catalysts gave a poor conversion of product (5%-25% yield). In order to improve the yield it was proposed to change the equivalent of ketone. Using 1 equiv. of ketone the reaction lost the stereocontrol (d.r 2:1, 23%maj: 00% min ee), instead when were used between 5 and 20 equiv. of ketone the reaction maintained the yield and enantioselectivity. (Table 3, entry 1-4)



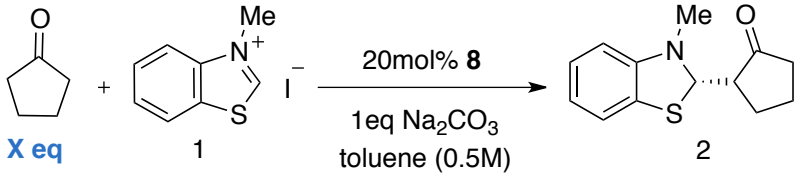
1		2	
	3; 10% yield, d.r 4:1 racemic		**4**; 10% yield, d.r 4:1 racemic
3			
	5; 5% yield, d.r 3:1 racemic		
4		5	
	6; 0% yield		**7**; 15% yield, d.r 4:1 25% maj: 0% min ee
6			
	8; 25% yield, d.r 8:1 95% maj: 64% min ee		

All the reaction were performed under air with 1 eq of **1**, 5 eq of ketone, 20mol% of catalyst and 1 eq of base at r.t. Determined after chromatographic purification. For all the reactions the d.r ratio measured by 1NMR spectroscopy. Determined by HPLC analysis

.

Table 2. Model reaction tested with primary and secondary amine catalysts.

On the other hand the use the ketone as solvent afforded the product in good diastereoselectivity but low enantioselectivity was recorded for the minor diastereoisomer (table 3, entry 5). In all case the reaction yield did not improve. However, to use 10 equiv. of ketone was chosen as optimal reaction conditions.

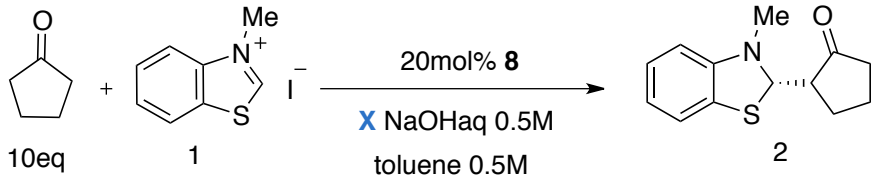


entry[a]	X eq ketone	d.r[b]	ee %[c]
1	1	2:1	23:00
2	5	6:1	57:00
3	10	4:1	97:63
4	20	4:1	96:18
5	neat	10:1	92:00

[a]All the reaction were performed under air with 1 eq of **1**, X eq of ketone, 20mol% **8**, 1 eq Na_2CO_3 and 0.5M toluene at r.t. [b] for all the reactions the d.r ratio measured by 1NMR spectroscopy. [c] Determined by HPLC analysis.

Table 3. Influence of equivalent of ketone in the reaction

According with previous works from Cozzi group with α-alkylation of aldehydes with propargylic alcohols[16] or stabilized carbenium ions[17], the presence of water was important to increase the yield and stereocontrol in the reaction. Thus, the reaction was tested with 1equiv. of NaOH aq 0.5M as base and 20mol% of catalyst **8**, without afforded the desired product **2**. In decrease the equivalents of base using 0.5 eq. of NaOH aq 0.5M , the reaction improved in 60% yield and maintaining the enantioselectivity. The reaction was proved without base losing yield (30% yield) but maintaining the diastereoselectivity and racemization of minor isomer was observed (table 4). Moreover, the concentration was an important parameter in the reaction, the optimal conditions was with toluene 0.5M, providing a good chemical yield and enantioselectivity. The reaction less concentrate gave a poor yield.



entry[a]	eq of Base	Yield[b] %	d.r[c]	ee % maj[d]	ee% min[d]
1	1	---	---	---	---
2	0.5	60	8:1	93	56
3	---	30	8:1	97	0

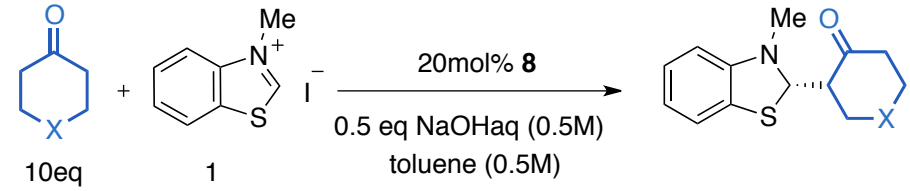
[a]All the reaction were performed under air with 1 eq of **1**, 10 eq of ketone, 20mol% **8** and X eq of NaOH aq 0.5M, at r.t. [b] Determined after chromatographic purification [c] for all the reactions the d.r ratio measured by 1NMR spectroscopy. [d] Determined by HPLC analysis.

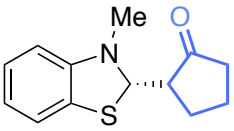
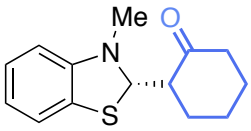
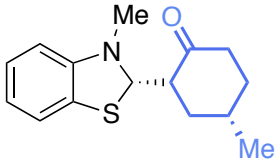
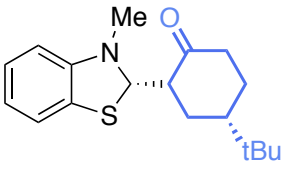
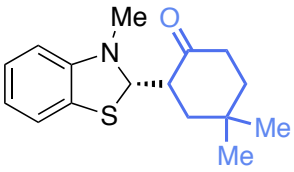
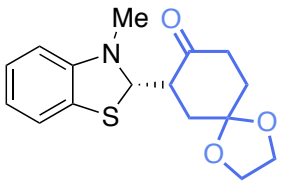
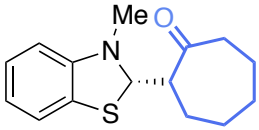
Table 4. Test of solution aq. NaOH 0.5M as base

The limitation in this reaction was the conversion that was around 30-60% yield. To increase the conversion, higher temperatures were applied. Unfortunately, no increase in conversion was observed and the carbocation seemed to degrade. At lower reaction temperatures, the conversion dropped drastically. Using polar solvents such as *i*PrOH, H_2O, and MeOH resulted in a decrease in conversion.

Further investigations were conducted by studying the behaviour of benzothiazolium iodide at different pH range, using different buffer solutions (controlled by ^1H NMR in $CDCl_3$) demonstrated that the stability of the carbocation was quite high. In fact, after 24 hours stirring in an acid or base solution, the carbocation was stable The stability of carbocations in polar and apolar solvents was also controlled by NMR, and no degradation after 24 hours occurred by stirring in the different solvents.

Finally the α alkylation of ketones using 3-methylbenzothiazolium iodide was applied with a large range of ketones, but only limited to unfunctionalized cyclic ketones gave the desired product in moderate yield and stereoselectivity. (table 5, enrty 1-8, d.r. up to 8:1, up to 93% maj and 56%min ee) Linear, functionalized ketones were unreactive in the reaction conditions.



1	2	3	
			
60% yield, d.r 8:1	54% yield, d.r 4:1	30% yield, d.r 4:1	
93%maj: 56% min ee	89% maj, 0% min	81%maj: 65%min ee	
4	5	6	
			
40% yield, d.r 3:1	20% yield, d.r 4:1	27% yield, d.r 5:1	
88%maj:7% min ee	95%maj: 36% min ee	85%maj: 13%min ee	
7			
			
30% yield, d.r 8:1			
87%maj ee			

All the reaction were performed under air with 1 eq of **1**, 10 eq of ketone, 20mol% **8**, 50%mol of NaOH aq 0.5M and 0.5M of toluene at r.t. The yield were determined after chromatographic purification For all the reactions the d.r ratio measured by 1NMR spectroscopy. The excess enantiomerics were determined by HPLC analysis.

Table 5 Stereoselective α-alkylation of cycle ketones with 3-methylbenzothiazolium iodide

Remarkably, the possibility to remove the benzothiazoline group could adopt a new approach to α-methylation of ketones. The hydrolysis of benzothiazoline was accomplished under neutral conditions using $AgNO_3$ in a solution of CH_3CN-phosphate buffer (pH = 7, 0.05M)- H_2O (15:3:5) at 0 °C.[18] In such a conditions the benzothiazoline is transformed in the corresponding aldehyde. Before to liberate the aldehyde the ketones was reduced to alcohol with $NaBH_4$ in MeOH at 0°C, in order to avoid the racemization and degradation of the product.

Absolute configuration

The major diastereoisomer was afforded the products in excellent enantiomeric excess, while the minor diastereoisomer was isolated with low or no entamieric exess. The diastereoselection of the reaction is dependant by the approaching mode of the cation to the enamine. However, is still difficult suggesting a preferential conformation of the enamine derived by Cinchona alkaloids. Thus, we have performed analysis through NMR studies. ^{1}H NMR analysis on the product (table 5, **entry 3**) in order to attribute the relative configuration of the majoritary diastereoisomer. From the multiplicity of the H^2 proton signal it was possible stablished the equatorial position of the benzothiazole group. The positive NOE response experienced by the four H^3 and H^5 protons, when the methyl frequency was irradiated confirmed the syn relative configuration between the methyl in γ position and the benzothiazole. (Figure 2, see E.P for further details)

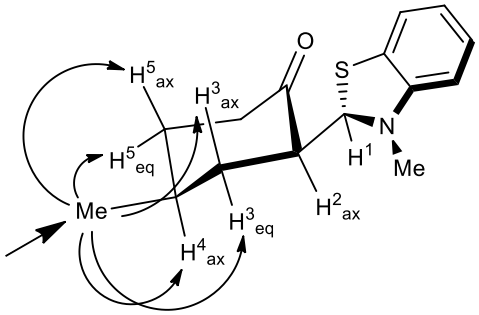


Figure 2. Observed NOEs for the analyzed diasteroisomer

Unfortunately, the direct long range NOEs between the H^2 and H^4 in 1,3-diaxial position was not clear, due to the overlapping with the H^3_{eq} and H^5_{eq} signals. The analysis was less clear for the compound (table 5, **entry 4**), in which some protons were overlapping in the ^{1}H NMR spectra, due to the presence of the *tert*butyl substituent. Considering the partial results obtained and that the *tert*butyl group is more bulky compare to the methyl, we can assume that also for the compound (table 5, **entry 4**), a *syn* product was obtained where the *ter*butyl and benzothiazolyl group are both in equatorial position. For the derivatives (table5, **entry 3, 4**) only two of the possible four diasteroisomers were observed, and the more stable *syn* diequatorial diastereoisomer was obtained in both cases.[19] We have followed the reaction by sampling amounts of the crude reaction mixture over the time and studying the dr of the reaction by ^{1}H NMR and HPLC analysis. We had no evidence of diastereoisomers equilibration or changes in the dr over the reaction time.

The stereochemical outcome of the reaction was probably determined by the hindrance of the *N*-methylbenzothiazolium iodide in the approach to the primary enamine. At this time we can only suggest a speculative model for interpreting the result of the reaction that is represented in the Figure

3. The absolute configuration of the newly formed stereogenic center was established through chemical correlation to a known product (Scheme 2), and the absolute configuration of the major diastereoisomer was assigned by analogy to allproducts (table 5, entry 1-7).

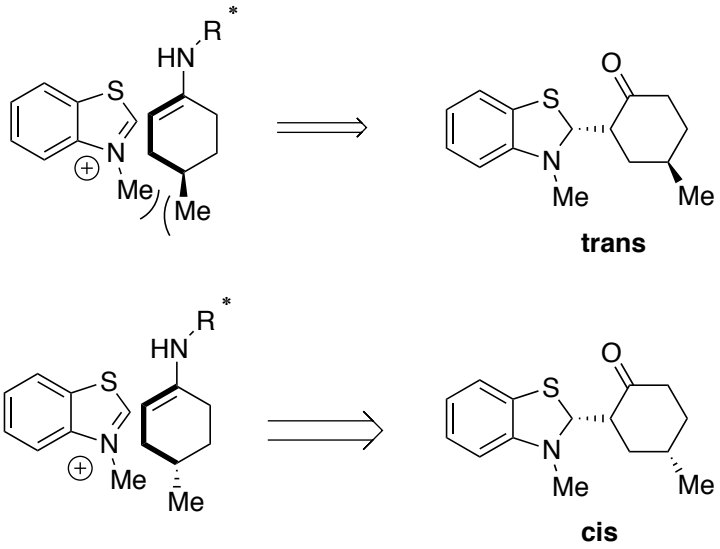
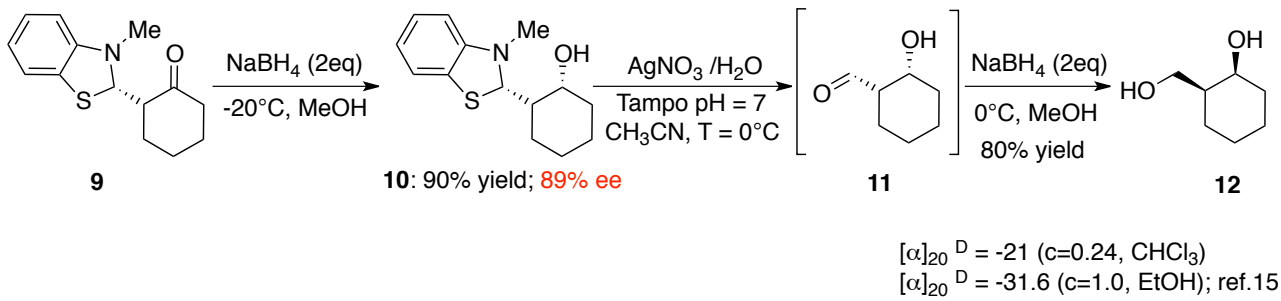


Figure 3. Model for the stereochemical course of the reaction

The absolute configuration for the products were determined through the transformation of adduct **9** to the corresponding alcohol **10** by reduction with $NaBH_4$ at -20°C**,** the reaction was completely diastereoselective and only syn adduct was isolated. The presence of the bulky benzothiazolyl group at the 2-position resulting in an equatorial attack by the hydride.[20] The relative syn configuration between the benzothiazoline and the OH bond was assigned on the basis of the NOE 1H NMR analysis. Yhe hydrolysis of benzothiazoline in acoording to the procedure reported by Chikashita group[21] and it get in high yield the pure but unstable aldehyde **11**, that was immediately reduced by $NaBH_4$ to the known (1R, 2R)-2-hydroxycyclohexanemethanol **12**.[22]



$[\alpha]_{20}{}^{D}$ = -21 (c=0.24, $CHCl_3$)
$[\alpha]_{20}{}^{D}$ = -31.6 (c=1.0, EtOH); ref.15

Scheme 2. Synthesis for the absolute configuration

III. Conclusion

Here has been reported the firstα alkylation of ketone with 3-methylbenzothiazolium iodide. In terms of conversion was obtained poor yields into the desired product. It was important to note that in some case only one cycle was performed in the catalytic cycle providing the desired product in 20% yield. Moreover, in this new protocol only was able employed cycle ketones limiting the scope of the reaction.

Remarkably was the possibility to cleavage the benzothiazoline group through oxidative procedure maintaining the stereoselectivity and promoting β-hydroxy-cyclohexanone carbonyl derivatives potential intermediates in product naturals.

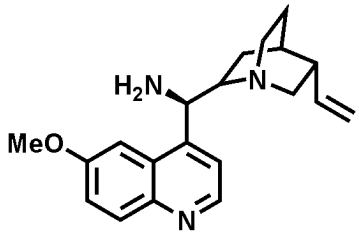
IV. Experimental section

Starting materials

Ketone: cyclopentanone, cyclohexanone, 4,4-dimethylcyclohexanone, 4-dimethylcyclohexanone, 4-tert-buthylcyclohexanone, 1,4-cyclohexanedione monoethylen acetal, cycloheptanone are commercially availables.

3-methylbenzothiazolium iodide salt. A flash with benzothiazole (1eq, 10 mmol) and (1.2eq, 12mmol) iodomethane was stirred 24 hours at room temperature until observe a yellow precipitate. The yellow solid was collected by filtration and washed several times with ether: DCM (1:1), and finally dried in a vacuum obtain the compound 3-methylbenzothiazolium iodide salt in 90% yield. [23]

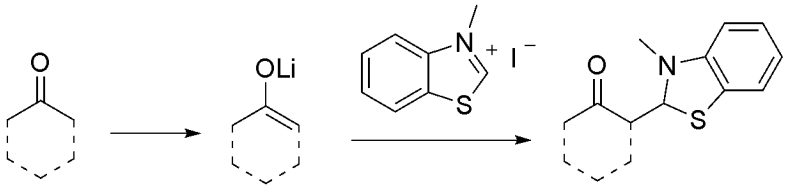
Catalysts 8 used in the screening are commercially availables.



9-amino-(9-dioxy-epi-quinidine) (9-epiQDA) the catalyst was prepared from quinidine according to the procedure of Connon's[15]. The crude was purified by chromatographic column (SiO_2, DCM:MeOH:NH_3, 9:1:1) to obtain 9-epiQDA as yellowish viscous oil.

Racemic samples

Direct reaction of lithium enolates with 3-methylbenzothiazolium iodide salt gave the racemic α-alkylation of ketones. [24]



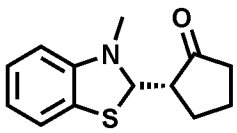
A freshly solution of LDA (1.1eq, 0.11mmol) in anhydrous THF (0.1M) in a flask equipped with a magnetic stir bar under inert atmosphere was cooled at -78°C for 5minuts and ketone (1eq, 0.1mmol) was added. The mixture was stirred for 30 minuts, then the solution was cooled at 0°C and stirring for 10 minuts, and 3-methylbenzothiazolium iodide salt (1eq, 0.1mmol, 27.7mg) was added and the mixture was warmed at r.t and stirring until no further conversion took place (controlled by TLC). The

reaction was quenched with saturated NH_4Cl aq. solution. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The collected organic layers were dried over Na_2SO_4 and concentrated under reduce pressure to give an orange oil. The residue was purified by flash chromatography.

General procedure for the asymmetric α- alkylation of ketone with 3-methylbenzothiazolium iodide salt

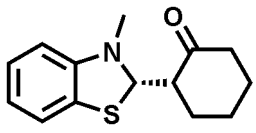
A vial equipped with magnetic stir bar and charged with 3-methylbenzothiazolium iodide salt (1eq, 0.1mmol, 27.7mg), 20 mol% of freshly prepared chincona primary amine, ketone (10eq, 10mmol) and 0.2 mL of anhydrous toluene (0.5M). Then a solution of NaOH aq (0.5M, 100µL) was added and the mixture was stirred for 24 hours at room temperature. The reaction was quenched with water. The organic layer was separated, and the aqueous layer was extracted twice times with DCM. The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. The enantioselectivity was determined either by chiral HPLC analysis, using the crude product. The product was purified by flash chromatography silica gel to give yield/ conversion.

(*S*)-2-((R)-3-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)cyclopentanone (table 5, entry 1)



According at the same procedure. The product was purified by flash chromatography column (SiO_2, cyclohexane: acetone=7/3) to give a yellow solid (60% yield, d.r 8:1, 94 % maj: 55 % min ee). The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH gradient from 99:1 to 90:10 in 30 min, flow rate 0.5mL/min, 35°C, λ = 230nm, *TM(maj)* = 32.2.min, *TM(min)* = 40.8 min, *tm(maj)* = 27.2 min, *tm(min)* = 24.5 min . HPLC-MS calcul for ($C_{13}H_{15}NOS$) (M+H^+ 234), (M+Na 255) t_{Maj} = 9.9 min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.98 (d, 1H, J = 7.5Hz, 1ArH), 6.95 (t, 1H, J = 7.6Hz, 1ArH), 6.63 (t, 1H, J = 7.6Hz, 1ArH), 6.31 (d, 1H, J = 7.6Hz, 1ArH), 5.60 (d, 1H, J = 3.8Hz, NCHS), 2.87-2.82 (m, 1H, 0=CCH), 2.85 (s, 3H, NCH_3), 2.32 (dd, 1H, J = 18.2, 6.8Hz, CH_2), 2.18-2.01 (m, 3H, CH_2CH_2), 1.97- 1.90 (m, 1H, CH_2), 1.82-1.68 (m, 1H, CH_2), **^{13}C NMR (125 MHz, $CDCl_3$) δ** 218.0 (CO), 147.9 (C), 125.5 (C); 125.6 (CH), 121.2 (CH), 118.4 (CH), 106.6 (CH), 71.9 (CH), 53.5 (CH), 39.0 (CH_2), 33.4 (CH_3), 23.4 (CH_2), 20.4 (CH_2).

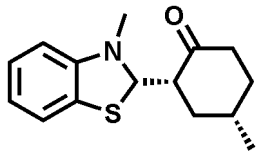
2 -(S)- (N-methylbenzothiazolium)cyclohexanone (table 5, entry 2)



According at the same procedure the product was purified by flash chromatography column (SiO_2, cyclohexane: acetone=7/3) to give a yellow oil (54% yield, d.r 4:1, 89 % maj: 0 % min ee). The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH gradient from 99:1 to

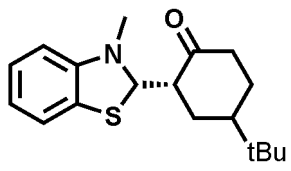
90:10 in 30 min, flow rate 0.5mL/min, 40°C, λ = 254nm, *TM(maj)* = 37.1.min, *TM(min)* = 39.9 min, *tm(maj)* = 28.8 min, *tm(min)* = 25.5 min . HPLC-MS calcul for ($C_{14}H_{17}NOS$) ($M+H^+$) 248, t_{Maj} = 9.76 **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.97 (d, 1H, J = 7.4Hz, 1HAr), 6.92 (t, 1H, J = 7.8Hz, 1HAr), 6.61 (t, 1H, J = 7.8Hz, 1HAr), 6.33 (d, 1H, J = 7.8Hz, 1HAr), 5.55 (d, 1H, J = 3.5Hz, NCHS), 2.94-2.88 (m, 1H, O=CCH), 2.84 (s, 3H, NCH_3), 2.46 (dm, 1H, J = 12.7Hz, $O=CCH_2$), 2.33-2.25 (m, 1H, CH_2), 2.11-2.00 (m, 2H, CH_2), 1.97-1.89 (m, 2H, CH_2), 1.73 -1.62 (m, 2H, CH_2).**^{13}C NMR (125 MHz, $CDCl_3$) δ** 211.2 (CO), 148.5 (C), 126.9 (C), 124.1 (CH), 120.8 (CH), 118.3 (CH), 106.9 (CH), 71.8 (CH), 54.4 (CH), 42.2 (CH_2), 34.7 (CH_3), 26.9 (CH_2), 26.1 (CH_2), 24.2 (CH_2).

(2*S*,4*S*)-4-methyl-2-((R)-3-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)cyclohexanone (table 5, entry 3)



Prepared according to the general procedure. The product was isolated by flash chromatography (SiO_2, cyclohexane: acetone=7/3) to give a yellow oil (30% yield, d.r 4:1, 81% maj: 65 %min ee). The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH 90:10, flow rate 0.5mL/min, 35°C, λ = 230nm, *TM(maj)* = 23.6min, *TM(min)* = 25.2min, *tm(maj)* = 26.5min, *tm(min)* = 28.8min. HPLC-MS calcul for ($C_{15}H_{19}NOS$) ($M+H^+$) 261; t_{Maj} = 11.0 min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.97 (d, 1H, J = 7.6 Hz, 1ArH), 6.93 (t, 1H, J = 7.6, 1ArH), 6.61 (t,1H, J = 7.6 Hz, 1HAr), 6.34 (d, 1H, J =7.6Hz, 1HAr), 5.53 (d, 1H, J = 3.5 Hz, NCHS), 2.97 (dt, 1H, J = 12.8, 4.0 Hz, O=CCH), 2.82 (s, 3H, NCH_3), 2.42-2.32 (m, 2H, $O=CCH_2CH_2$), 2.04-1.93 (m,·2H, CH_3CH,CH_2), 1.70 (t,1H, J = 13Hz, CH_2), 1.48-1.35 (m, 2H, CH_2), 1.03 (d, 3H, J = 6.2Hz, CH_3CH) **^{13}C NMR (125 MHz, $CDCl_3$) δ** 211.3 (CO), 148.5 (C), 126.9 (C), 125.0 (CH), 120.9 (CH), 118.6 (CH), 107.1 (CH), 71.8 (CH), 53.1 (CH), 41.6 (CH_2), 35.0 (CH_2), 34.8 (CH_3), 34.1 (CH_2), 31.2 (CH), 21.4 (CH_3).

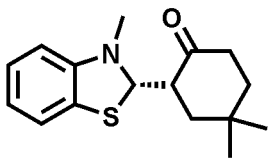
4-tert-butyl-2-(3-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)cyclohexanone (table 5, entry 4)



According at the same procedure. The product was purified by flash chromatography column (SiO_2, cyclohexane: acetone=7/3) to give a yellow oil.(40% yield, d.r 3:1, 88 % maj: 7 % min ee) The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH gradient from 99:1 to 90:10 in 30 min, flow rate 0.5mL/min, 35°C, λ = 230nm, *TM(maj)* = 37.2.min, *TM(min)* = 34.6 min, *tm(maj)* = 28.0 min, *tm(min)* = 23.9 min . HPLC-MS calcul for ($C_{18}H_{25}NOS$) ($M+H^+$ 304), (M+Na 326) t_{Maj} = 15.8 min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.99 (t, 1H, J = 7.6Hz, 1HAr), 6.93 (t, 1H, J = 7.6Hz, 1HAr), 6.63 (t, 1H, J = 7.6Hz, 1HAr), 6.36 (d, 1H, J = 7.9Hz; 1HAr), 5.51 (d, 1H, J = 3.6Hz, NCHS), 2.94 (ddd, 1H, J= 12.5, 4.2, 4.2 Hz, O=CCH), 2.81 (s, 3H, NCH_3), 2.48 (ddd, 1H, J = 14.2, 4.1, 4.1 Hz, CH), 2.33 (td, 1H, J = 14.0, 6 Hz, CH), 2.13-2.04 (m, 2H,CH_2), 1.73-1.63 (m, 1H,

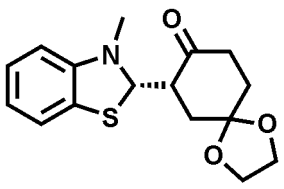
CH), 1.61-1.42 (m, 2H, CH_2), 0.88 (s, 9H, CCH_3).**^{13}C NMR (125 MHz, $CDCl_3$) δ** 211.6 (CO), 148.7, 127.0, 125.0, 121.0, 118.6, 107.3, 72.3, 53.3, 46.4, 41.7, 34.9, 32.6, 30.9, 29.7, 27.8, 27.6, 27.3.

(R)-4,4-dimethyl-2-((S)-3-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)cyclohexanone (table 5, entry 5)



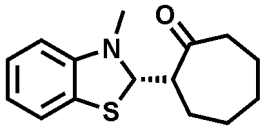
Prepared according at the same procedure. The product was isolated by flash chromatography column (SiO_2, cyclohexane: acetone=7/3) to give a yellow oil (20% yield, d.r 4:1, 95 % maj: 36 % min ee).The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IA column hexane/i-PrOH gradient from 99:1 to 90:10 in 30 min, flow rate 0.5mL/min, 35°C, λ = 230nm, *TM(maj)* = 20.9.min, *TM(min)* = 19.8 min, *tm(maj)* = 15.8 min, *tm(min)* = 14.6 min. . HPLC-MS calcul for ($C_{16}H_{21}NOS$) (M 275), t_{Maj} = 11.8min, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.97 (d, 1H, J = 7.3Hz, 1ArH), 6.92 (t, 1H, J = 7.3Hz, 1HAr), 6.61 (t, 1H, J = 7.3Hz, 1HAr), 6.32 (d, 1H, J = 7.7Hz, 1HAr), 5.58 (d, 1H, J = 3.5Hz, NCHS), 3.07 (dd, 1H, J = 7.6, 3.8Hz, 0=CCH), 2.81 (s, 3H, NCH_3), 2.51-2.42 (m, 1H, $O=CCH_2$), 2.33 (ddd,1H, J = 15, 4.7, 2.9 Hz, $O=CCHCH_2$), 1.92 (t, 1H, J = 13.4Hz, $O=CHCCH_2$), 1.74- 1.63 (m, 3H, CH_2CH_2, $O=CCH_2$), 1.21 (s, 3H, CCH_3), 1.02 (s, 3H, CCH_3) **^{13}C NMR (125 MHz, $CDCl_3$) δ** 211.7 (CO), 148.5 (C), 126.8 (C), 125.0 (CH), 121.0 (CH), 118.3 (CH), 106.8 (CH), 71.8 (CH), 49.7 (CH), 38.9 (CH_2), 38.3 (CH_2), 34.4 (CH3), 31.5 (CH_3), 30.2 (CH_2), 29.6 (C), 24.6 (CH_3).

(R)-7-((S)-3-methyl-2,3-dihydrobenzo[*d*] thiazol-2-yl)-1.4-dioxaspiro [4.5]decan-8-one (table 5, entry 6)



According at the same procedure the compound was purified by flash chromatography (SiO2, cyclohexane: acetone = 9:1) to give a yellow oil (27% yield, d.r 5:1, 85%maj; 13%min ee). The ee was determined directly with crude product by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH 90:10 , flow rate 0.5mL/min, 35°C, λ = 232nm, *TM(maj)* = 30.0 min, *TM(min)* = 25.3 min, *tm(maj)* = 16.5 min, *tm(min)* = 19.0 min . HPLC-MS calcul for ($C_{16}H_{19}NO_3S$) ($M+H^+$ 306), (M+Na 328) t_{Maj} = 10.0 min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.96 (d, 1H, J = 7.5Hz, 1HAr), 6.92 (t, 1H, J = 7.5Hz, 1HAr), 6.60 (t, 1H, J = 7.5 Hz, 1HAr), 6.32 (d, 1H, J = 7.8Hz, 1HAr), 5.59 (d, 1H, J = 3.4Hz, SCHN), 4.05-4.02 (m, 2H, OCH_2), 4.00-3.96 (m, 2H, OCH_2), 3.29 (dt, 1H, J = 12.8, 5.4Hz, O=CCH), 2.83 (s, 3H, NCH_3), 2.70-2.61 (m, 1H, CH_2), 2.43 (dt, 1H, J = 14.9, 4.5Hz, CH_2), 2.30 (t, 1H, J = 13.0 Hz, CH_2), 2.04-1.93 (m, 3H, CH_2CH).**^{13}C NMR (50 MHz, $CDCl_3$) δ** 209.7 (CO), 148.3, 126.5, 125.1, 121.1, 118.4, 107.7, 106.9, 71.4, 64.7, 64.6, 50.5, 38,4, 34.5, 33.8, 33.4.

2-(3-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)cycloheptanone (table 5, entry 7)

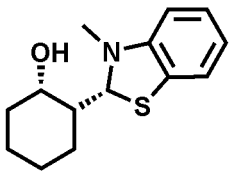


According at the same procedure. The compound was purified by flash chromatography (SiO_2, cyclohexane: acetone = 9:1) to give a yellow oil (30% yield, d.r 8:1, 87%maj ee). The ee was determined directly with crude product to reduction to alcohol by HPLC analysis Daciel Chiralcel IC column hexane/i-PrOH gradient from 99:1 to 90:10 in 30 min, flow rate 0.5mL/min, 35°C, λ = 230nm, *TM(maj)* = 32.8 min*, TM(min)* = 29.2 min*.* HPLC-MS calcul for ($C_{15}H_{19}NOS$) ($M+H^+$ 262) t_{Maj} = 10.6 min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.01 (d, 1H, J = 7.8Hz), 6.94 (t, 1H, J = 7.8Hz), 6.69 (t, 1H, J = 7.4Hz), 6.47 (d, 1H, J = 8.1Hz), 5.12 (d, 1H, J = 5.5Hz); 4.21 (bs, 1H), 2.80 (s, 3H), 2.03-1.99 (m, 1H), 1.83-1.75 (m, 2H), 1.71-1.27 (m, 6H).

Absolut configuration

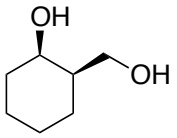
The absolute configuration was assigned by comparation of [α] in literature[19]

(1S, 2R)-2-((S)-3-methyl-2,3 –dihydrobenzo[d]thiazol-2-yl)cyclohexanol (10)



The residu of 2 -(S)- (N-methylbenzothiazolium)cyclohexanone was diluted in MeOH at 0°C and $NaBH_4$ (2eq) was added slowly. The mixture was stirred. After 30 min the reaction was worked up with H_2O and concentrated in vacuo. The residue was extracted twice times with AcOEt, dried over Na_2SO_4 and concentrated The crude was purified by flash chromatography (SiO_2, cyclohexane/Et_2O = 7:3) to isolate the maj. diasterisomer (90% yield). HPLC-MS calcul for ($C_{14}H_{19}NOS$) ($M+H^+$ 250) t_M = 9.9min **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.05 (d, 1H, J = 7.5Hz, 1HAr), 6.96 (t, 1H, J = 7.7Hz, 1HAr), 6.72 (t, 1H, J = 7.4Hz, 1HAr), 6.54 (d, 1H, J = 7.7Hz, 1HAr), 4.99 (d, 1H, J = 6.2H, NCHS), 4.23 (bs, 1H, CHOH), 2.94 (s, 3H, NCH3), 2.11 (s, 1H, OH), 2.08- 2.01 (m, 1H, CH_2CHOH), 1.85 -1.74 (m,3H, CHCHOH, CH_2), 1.68-1.57 (m, 3H, $CHCH_2$, CH_2), 1.54-1.45 (m, 2H, CH_2CHOH, CH_2CH) **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.4, 125.5, 125.0, 121.2, 120.3, 110.8, 78.1, 67.5, 47.5, 39.3, 33.5, 25.3, 22.9, 20.2.

(1R, 2R)-2-(hydroxydimethyl)cyclohexanol (12)



The hydrolysis of benzothiazolines into ketones was prepared according to the procedure of Itoh's.[18]

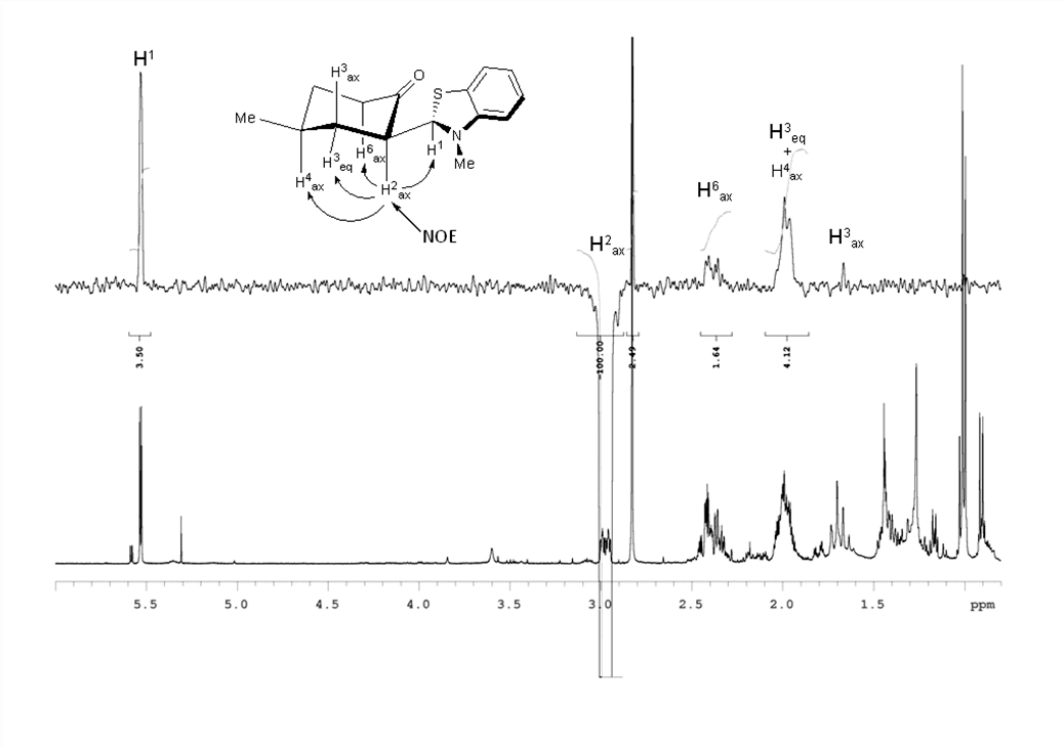
A flask equipped with a magnetic stir bar and charged with (1S, 2R)-2-((S)-3-methyl-2,3 –dihydrobenzo[d]thiazol-2-yl)cyclohexanol benzothiazolie (1) (1eq, 0.05mmol) in CH_3CN (0.8mL) and 0.05M phosphate buffer (0.1mL) the mixture was stirred at 0°C for 10 min. At same temperature was added a solution of $AgNO_3$ (1.5eq, 14 mmol),with H_2O (0.1mL), the resulting yellow solution was stirred for 15 min.and $AgNO_3$ (1.5eq, 14mg) dissolved in water (0.1mL) was added at 0°C. After 15 minuts, at the same temperature Et_3N (10µL) was added to neutralized HNO_3 formed

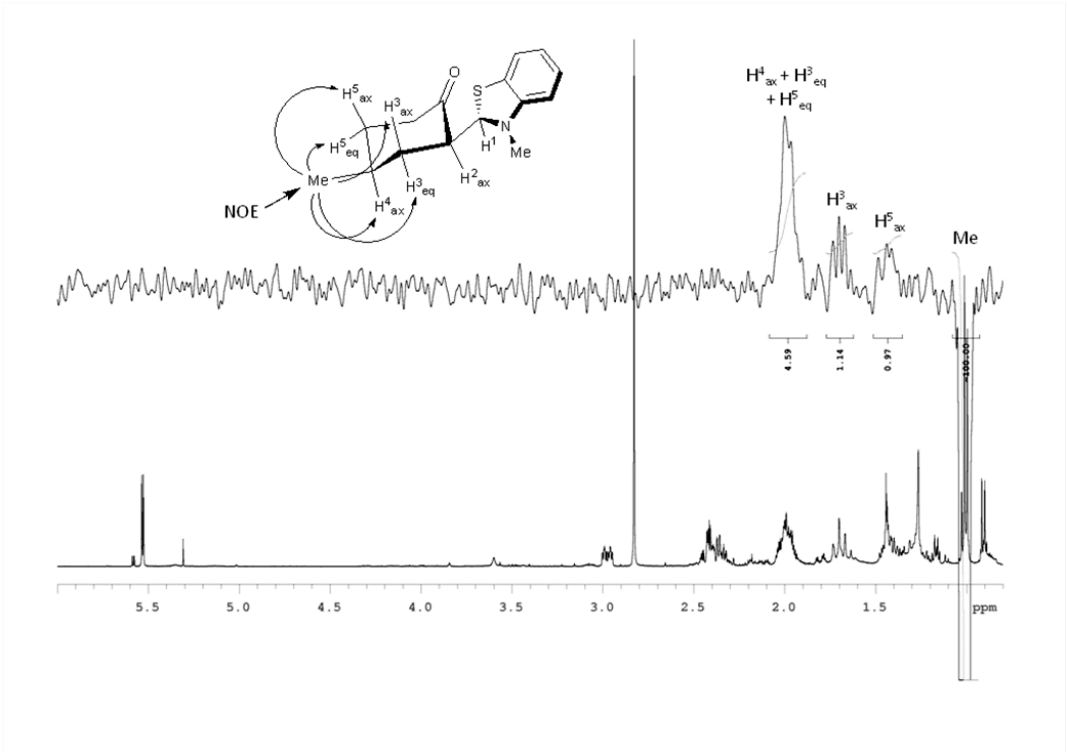
in solution and stirring was continued for 5 minuts. satured aq NaCl solution was added to the reaction mixture and filtered through Celite. The filtrated was extracted with Et_2O. Removal solvent afford almost pure **but unstable aldehyde** over extended time periode at r.t.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H, CHO), 4.28 (bs, 1H, 0=CCH), 2.47-2.48 (m, 1H, CHOH), 1.84-1.66 (m, 4H, CH_2CH_2), 1.84-1.66 (m, 1H, CH_2), 1.49-1.35 (m, 3H, CH_2, CH_2)

The crude product was dissolved in MeOH and 1.5 eq of $NaBH_4$ was slowly added at 0°C. The reaction was controlled by TLC until total conversion and followed by aqueous work-up. The organic layer was separated, and the aqueous layer was extracted twice times with EtOAc. The collected organic were dried over Na_2SO_4 and concentrated under reduce pressure to obtain a pure dialcohol. The mixture was purified by flash chromatography (SiO_2, cyclohexane: ethyl acetate = 7:3) to give the product (80% yield) $[\alpha]_D^{20}$ = -21 (c= 0.24 in $CHCl_3$) **^{1}H NMR (400 MHz, $CDCl_3$) δ** 4.16 (s, 1H, CHOH), 3.76 (bs, 2H, CH_2OH), 2.17 (s, 2H, OH), 1.82 -1.76 (m, 1H, $CHCH_2OH$), 1.71-1.21 (m, 8H, $CH_2CH_2CH_2CH_2$). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 70.0 (CHOH), 66.4 (CH_2OH), 42.4 ($CHCH_2OH$), 33.0, 24.9, 23.4, 20.4.

Experiment for the atribution of the relative stereochemistry

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Me
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H^3_{ax}
H^5_{eq}
H^3_{eq}
H^4_{ax}
H^2_{ax}
H^1
N
S
O
$H^4_{ax} + H^3_{eq} + H^5_{eq}$
H^3_{ax}
H^5_{ax}
Me
4.59
1.14
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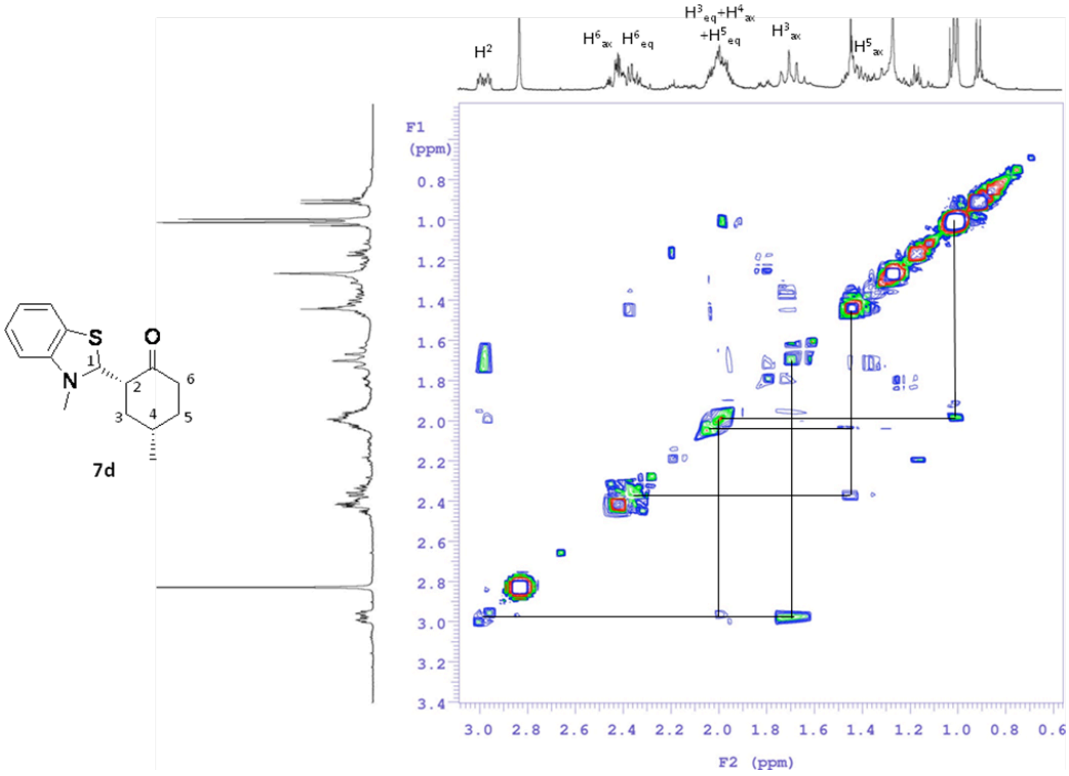
100.00
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


H^2
H^6_{ax}
H^6_{eq}
$H^3_{eq}+H^4_{ax}+H^5_{eq}$
H^3_{ax}
H^5_{ax}
F1 (ppm)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
F2 (ppm)
S
O
N
1
2
3
4
5
6
7d

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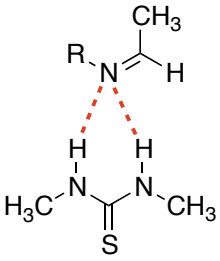
Chapter 6. Stereoselective S_N1 type reaction using chiral phosphoric acid as catalyst.

I. Introduction

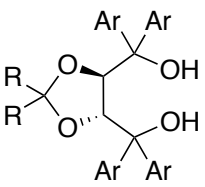
Hydrogen bonding catalysis

The field of organocatalysis discovered the use small organic molecule to perform C-C bond or C-heteroatom with high enantioselectivity.[1] Chiral hydrogen bond donors catalyst emerged as a new mode of activation in organocatalysis, the concept was the activation of electrophiles through the H bonding between catalyst and electrophile.[2] But the introduction of H bond donors as a new concept in organocatalysis not appeared until 1990s. In 1998, one work from Sigman and Jacobsen[3] reported the stereoselective hydrocyanation reaction with imines derived catalyzed by urea and thiourea derivatives. Studies about the mechanism of reaction revealed that the interaction between catalyst and electrophile takes places via a dual H bond. [4] Moreover preliminary studies about the mechanism of proline catalyst shown the importance of H-bonding in asymmetric catalysis[5], inspiring the design of new class of bifunctional H-bonding catalyst, one of them were the chiral Brønsted acids, which have been classified into two catagories:

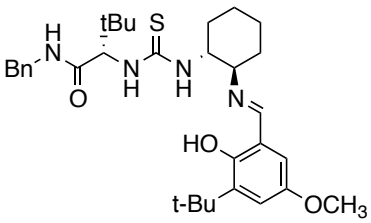


1. **Neutral Brønsted acids such as urea or TADDOL.**

Representative work was presented by Takemoto and co-workers[6] that reported the enantioselective thiol conjugate addition reaction catalyzed by urea catalyst. In this work was presented the ability of the urea catalyst to activate electrophiles in highly enantioselective transformations. Another publication that presented this peculiar ability was the enantioselective reaction with activation of ketone and aldehydes electrophiles toward nucleophilic attack by the use of TADDOL derivatives as catalyst. Rawal and co-workers reported that TADDOL catalyst in the vinylogous Mukaiyama reaction of dienol ethers with reactive aldehydes.[7]



Rawal, 2003
hetero Diels Alder reaction

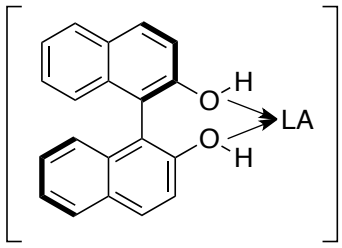


Jacobsen, 1998
Strecker Reaction

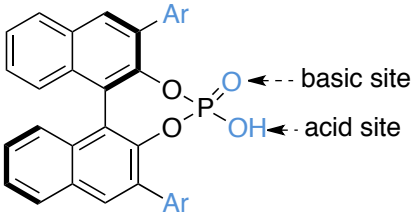
Figure 1. Brønsted acids catalysts

In this chapter the discussion is focused in the chiral Phosphoric acids and Super acids, which have recently emerged as a new class of organocatalysts[2] for enantioselective C-C bond forming reactions.

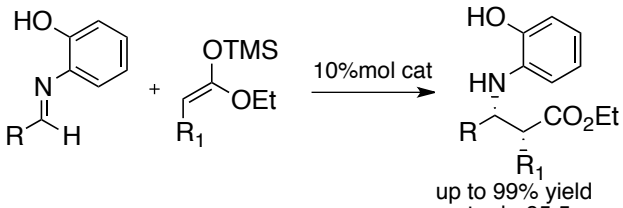
2.Stronger Brønsted acids such as chiral Phosphoric acids or BINOL derivatives.



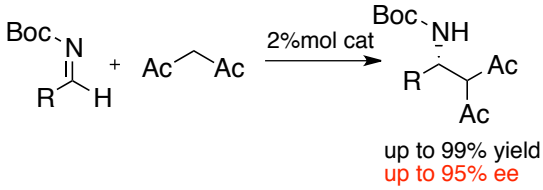
The introduction of chiral Brønsted acid was presented by Yamamoto and Ishihara[8] that proposed the concept of combining Lewis acid with chiral phenol increasing the H acidity from the catalyst. From this seminal work several groups developed new BINOL catalyst, and new reactions were performed using these new chiral Brønsted acids combining chiral BINOL catalyst and Lewis acids. Other generation of Brønsted acids were then introduced by using the same framework. These Brønsted acids are the chiral phosphoric acids derived from (R)-BINOL. The pioneers in the use of this novel catalysts in organocatalysis were the Akiyama[9] and Terada groups[10] that independently reported reactions promoted by chiral phosphoric acids. They reported the first Mannich reaction using chiral phosphoric acids. Studies about the reaction mechanism have been carried out and have determined that chiral phosphoric acid acts as a bifunctional catalyst. The phosphoric acid has in fact a Brønsted acid site and Lewis- basic site that are both acting in promoting the reactions. Moreover many of the described phosphoric acids are bearing 3,3-substituents on the BINOL framework. These substituents, sometimes very bulky are playing also an important role in the enantiodeterming step.[11]



1. Addition of Silyl ketene Acetals to N-Aryl Imines. Akiyama group



2.Direct Mannich reaction. Terada group

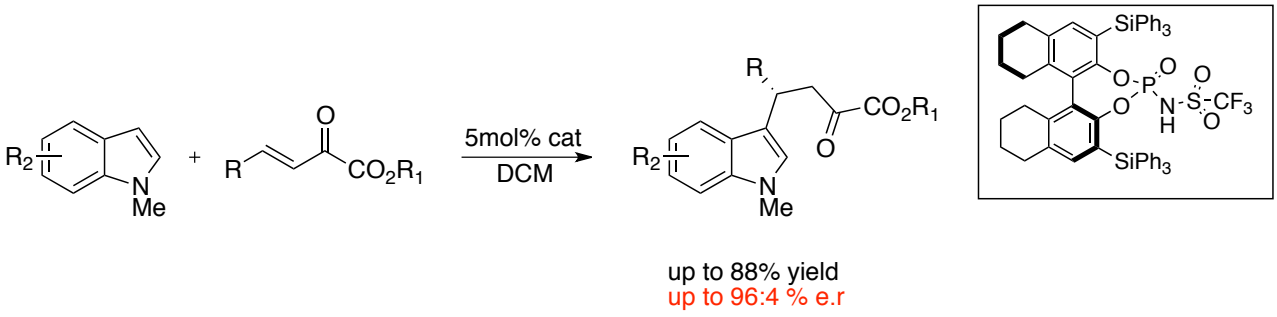


Scheme 1

In the work presented for the Mannich reaction is also important to mention that phosphoric acids have a great affinity for electrophiles such as imines. On the basis of experimental results a nine-member transition state between catalyst and substrates is proposed, where the phosphate catalyst is able to have two point of coordination: the hydrogen atom of the phosphoric acid is able to activate the imines as a Brønsted acid; the phosphory oxygen acts as a Brønsted base activating the nucleophile.[12] From these studies, other reactions was developed using chiral Brønsted acids such as Aza Friedel-Crafts alkylation[13], Pictet Spengler reaction[14], Strecker reaction[15], Aza Diels Alder reaction[16], Aza ene reaction[17] In addition transfer hydrogenation reactions using Hantzsch ester as cofactor with chiral phosphoric acids were reported by the Rueping group[18] and by the List group[19] in two independent works.

The design of new chiral phosphoric acid catalyst, by increasing the acidity of the Brønsted acid group, allowed new developments in the field of chiral phosphoric acids. N-phosphinyl phosphoramide (STRIP) was developed as a novel Brønsted acid and was applied in the catalytic asymmetric acetalizations by List and co- workers.[20] The Antilla group[21] synthesized a phosphoric acid derivative from (S)-VAPOL that was applied in the formation of aminals by addition of sulfonamide to aldimines. Other type of catalysts was N-tritfyl phosphoramide derivatives or Super acids. Yamamoto and co-workers[22] designed these stronger chiral Brønsted acids to extend the scope of this catalyst in other reactions, as Diels Alder reaction of α,β-unsaturated ketone or the Nazarov cyclization repored by Rueping group.[23]

The Direct substitution of alcohols has emerged as a power methodology in the C-C bond forming reaction. Cozzi group[24] reported the stereoselective α-alkylation of aldehydes through S_N1 type reaction between stable carbocations and enamine. Other innovative work reported by my group was the the α-allylation of aldehydes with allylic alcohols, merging two concepts enamine catalysis and In(III).[25] One of the first observation about the possibility to perform stereoselective organocatalytic S_N1-type reaction was disclosed by Rueping in 2008. [26] In examining the reaction of N-methyl indole with an unsaturated keto-ester in the presence of Brønsted, the catalytic amounts of N-triflylphosphoramide resulted in the formation of products. The scope of the reaction was to promote the 1,4-addition of indole to the unsaturated compounds. However, beside the desired product, an interesting bisindole was isolated.



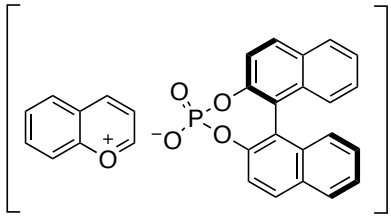
Scheme 2. Brønsted acid catalyzed enantioselective 1,4-addition

The product shows a remarkable exhibits atropisomerism determined by the rotation barrier about the bonds to the quaternary carbon bond.[27] By optimizing the reaction with different bistriflammides and by varying the temperature, solvent, catalyst loading, and concentration, the bis indole was obtained with a remarkable 72% ee. In the supposed mechanism, a stabilized vinylic carbenium indolyl intermediate is supposed, that undergoes a S_N1 reaction by formation of a diastereoisomeric ion pair.

The discrimination of the face of the chiral carbenium ion is determined by the hindrance of the flanking group. In the case of the chiral Brønsted acids, the chiral counter ion formed after effective protonation or partially donation of the proton, is surrounding the cationic intermediate created. One face of the intermediate is effectively covered by the chiral counter ion and the nucleophiles is reacting with the less covered face.

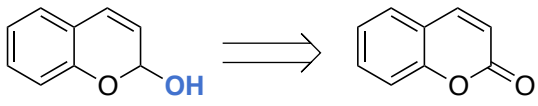
My last 4 months my research field has developed in the group of Dr. Magnus Rueping, the research was focused on selective S_N1 type reaction that can be developed by using phosphoric acids.

We supposed that the combination of chiral Brønsted acids with coumarine derivatives was able to form stabilized carbocations from the starting alcohols that can react with different nucleophiles. The idea that we tried to follow was to generate ionic intermediated formed by



the reaction of the electrophile **1** and the phosphoric acid catalyst, able to control the attack of the nucleophile with high stereoselectivity.

2-H-chromen-ol-derivative from coumarine was used as a model substrate for this reaction. The synthesis **1** was a simple reduction of the carbonyl group with DIBAL in DCM at -78°C. Coumarine is easy to use, cheap, and innocuous benzopyran that constitute the core skeleton of flavonoids compounds.



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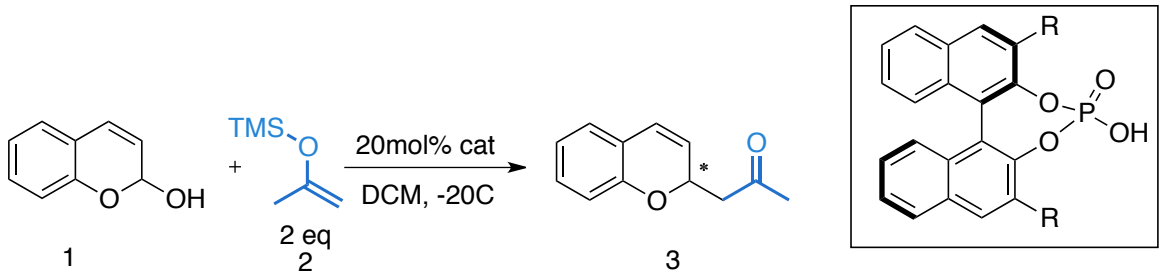
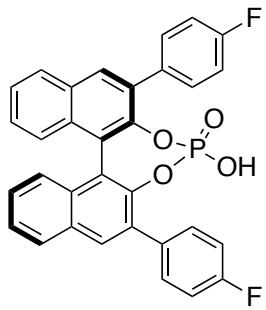
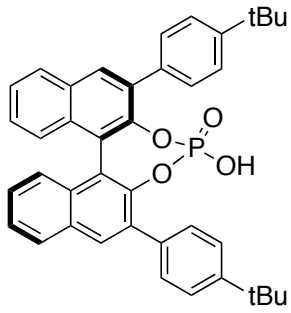
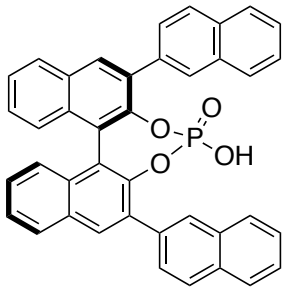
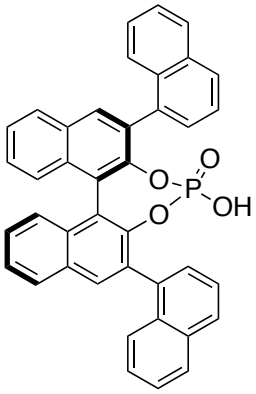
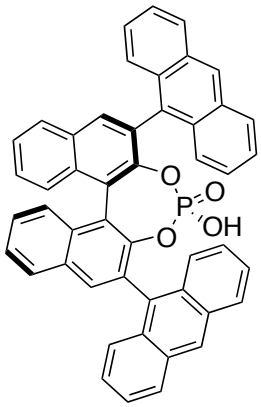
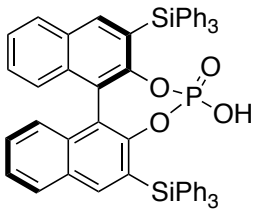
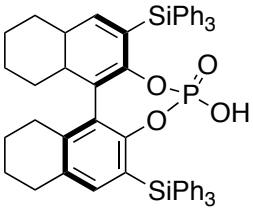
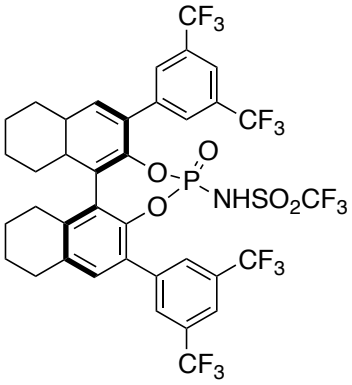
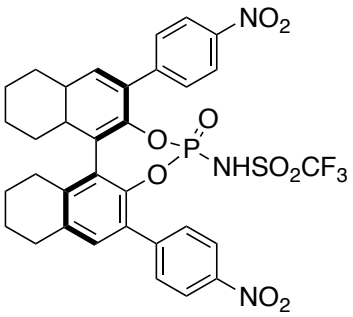
II. Results and discussion

Different nucleophiles were tested in this catalytic alkylation reaction with chiral Phosphoric acids. Silyl Enol ehters are important intermediated in the organic synthesis, and they can be prepared from ketones with strong base followed by a silylating agent. These silyl enolates react as nucleophiles, and they are commonly used in Mannich reactions, Mukaiyama aldol reaction, Michael reactions and Lewis acids mediated alkylations. In our preliminary investigation we have used 1-phenyl-1-(trimethylsilyloxy)ethylene ether **2** as nucleophile in this in the presence of 2H-chromen-2-ol **1** as electrophile the reaction. The reaction was studied in the presence of 20mol% of chiral phosphoric acid. The preliminary results obtained at r.t with 2eq of nucleophile revealed a poor stereocontrol into the reaction, thus was decided to decrease the temperature in order to increase the enantioselectivity. The model reaction was tested with different chiral phosphoric acids at -20 °C affording the product in moderated yield and again poor enantioselectivity (50% yield; 27% ee), the use of Super acids in the reaction increased the conversion into product (80% yield) and the reaction was more fast compare the use of chiral phosphoric acids.



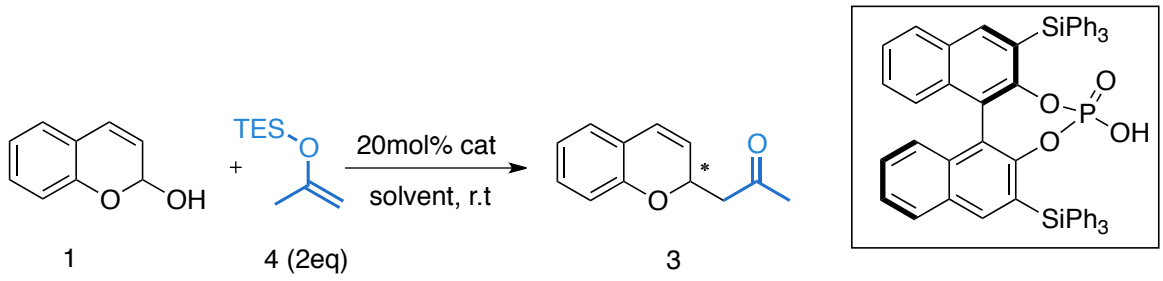
1			
	50% yield; 0% ee	50% yield; 0% ee	45% yield; 27% ee

4 	5 	6 
50% yield; 0% ee	45% yield; 13% ee	50% yield; 20% ee
7 	8 	9 
44% yield; 21%ee	80% yield; 0% ee	80% yield; 0% ee

All the reaction were performed under air with 1 eq of **1**, 2 eq of enolate, 20mol% of catalyst in DCM at -20°C. The yields were determined after chromatographic purification. Enantiomeric excess were determined by HPLC analysis

After catalyst screening it was tested the reaction with different solvents. The $CHCl_3$ was the more suitable solvent furnished 31% ee, apolar solvent as toluene decrease the enantioselectivity. Using the best catalyst (table1, entry 6) in $CHCl_3$ the desired product was obtained in 50% yield and 36% ee. The Super acids family was then used and the conversion was increased to expense of the enantioselectivity.

In order to obtain a better stereocontrol, more hindered silylenolates were considered to use in the reaction. For this reason the silyl enolate **4** bearing a more hindered silyl group was synthesized. However, the reaction afforded the desired product in poor conversion and enantioselectivity. The use of chiral phosphoric acids with increased hindrance at the 3,3-substituent such as the phenanthrene derivative gave 26% ee with toluene as solvent, but the conversion towards the desired product was rather poor.

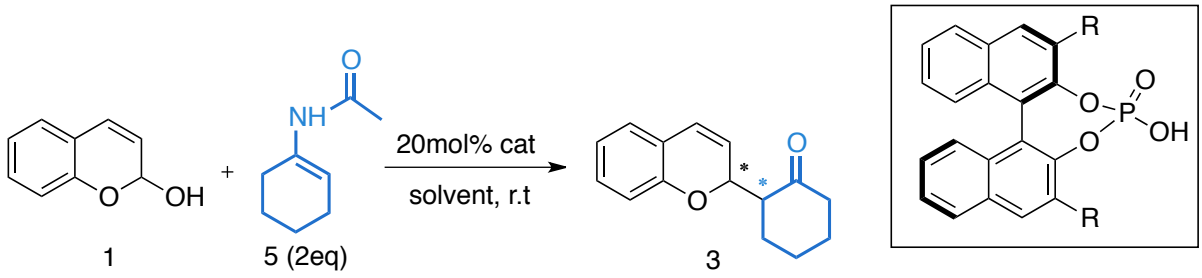


1 4 (2eq) 3

DCM 14% ee
CH_3CN 10% ee
$CHCl_3$ 0% ee
toluene 17% ee

We have also investigated the possibility to use chiral phosphoric acid salt with the aim to increase the enantioselectivity of the reactions in function of the effect of the counter ion. Also in this case poor enantioselectivity was achieved with the catalyst.

With the poor results with enolates was turned the attention to enamides as nucleophile in the reaction. The model reaction was using 2 eq of enamide and 1 eq of 2H-chromen-2-ol and 20mol% catalyst in DCM at r.t temperature, after 24 hours not total conversion (controlled by TLC) presence of product. The limitation with enamine as nucleophile was the poor reactivity affording the product in 30-40% yield, d.r 1:1, 34:22 % ee, thus not possible made the reaction at low temperatures.



1 5 (2eq) 3

The use of aldehydes or ketones as nucleophiles gave the desired product but not presence of stereocontrol in the reaction.

III. Conclusion

The limitation in this alkylation reaction has been the compatibility between nucleophile and electrophile. The formation of the carbocation in the reaction gave other by-product, moreover the desired product was performing with poor stereocontrol into the reaction. When we have performed the reaction with different nucleophiles such as enamine, ketone or aldehydes that can be able to be activated by H-bond the reactivity between the substrate was quite limited with poor yields and enantioselectivity. In the future could be considerate new approach for this alkylation reaction using other electrophiles as a potential carbocations.

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