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A novel atroposelective strategy for the synthesis of quinoline substrates

Tesi di laurea sperimentale

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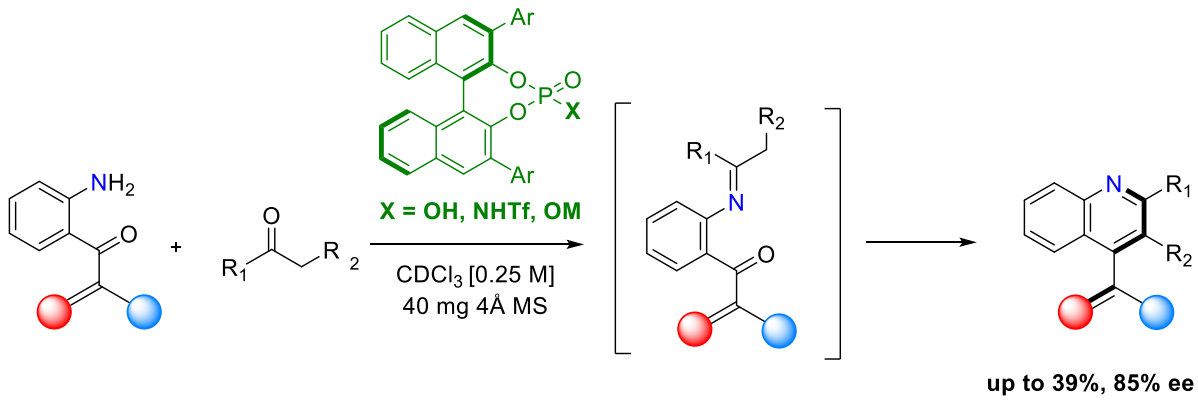
Abstract

Among heterocyclic compounds, quinoline scaffold has become an important motif for the development of new pharmacological active compounds. Since the discovery of their antimalarial properties, a large variety of quinolines was found to have interesting physiological activities and displayed attractive applications for pharmaceutical industries. In accordance to the above-mentioned features, a number of methods were developed for their synthesis but enantioselective versions are still lacking in the literature. In the past decades, this question has become even more complex, with the emergence of the less common axial chirality. Within the growing number of articles about atropisomers, the discovery of new synthetic pathways for the synthesis of enantioenriched atropisomers and their use in drug discovery has become a challenging topic in the organic chemistry scenario. In this work, the development of a novel atroposelective strategy for the synthesis of quinoline substrates has been achieved, and in order to obtain high values of enantioselectivity and yields a screening of the reaction conditions has been performed. The design of such strategy has been developed combining an already established methodology for the synthesis of heteroaromatic compounds such as a well-known Friedländer-type quinoline synthesis with chiral Brønsted acid catalysis to obtain the C-C bond formation in an enantioselective fashion.



Contents

Abbreviations

Ac	Acetyl
ACDC	Assisted counterion directed catalysis
API	Active pharmaceutical ingredient
Ar	Aryl
BINOL	1,1'-bi-2-naphtol
BPA	BINOL derived phosphoric acid
BuLi	*n*-Butyllithium
CatH	Acid catalyst
DMF	Dimethylformamide
DMSO	Dymethyl sulfoxide
ee	enantiomeric excess
Et	Ethyl
h	hour
***i*-Pr**	Isopropyl
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
L-DOPA	L-3,4-dihydroxyphenylalanine
LUMO	Lowest unoccupied molecular orbital
M	Molar (concentration)
Me	methyl
MeOH	methanol
MS	Molecular sieves
MTBE	Methyl, *tert*-butyl ether
n.a.	Not available
n.d.	Not detected
NMR	Nuclear magnetic resonance
NTPA	N-Triflyl phosphoric acid
o	*ortho*
Ph	Phenyl

***p*-TSA**	*p*-Toluensulfonic acid
RT	Room temperature
τ	Reaction time
TADDOL	α, α, α’, α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosylate
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate

1. Introduction

This work is focused on several topics of Organic chemistry and in this following section the author presents a brief introduction of all the topics that will be treated in the discussion of this thesis, introducing the reader with chemical notions and concepts, useful for the understanding of this work.

1.1 Chirality and Atropisomerism

Among all the topics of Organic chemistry, stereochemistry is one of the most interesting, especially from an industrial and pharmaceutical point of view. This matter studies the different possible position of atoms of a molecule in a three-dimensional space and how they can arrange in different ways, giving rise to stereoisomers. Among them, Enantiomers are very common: they possess at least one stereogenic element, like a stereogenic centre or axis, for which they are asymmetric molecules, that is they don't possess a symmetry plane (Fig.1).

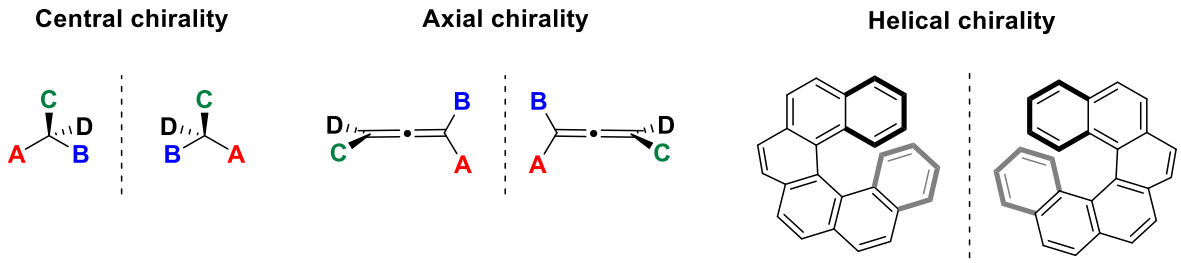


Fig. 1 – Enantiomers among different kinds of chirality

Enantiomers are chiral molecules. The term chirality was first coined by William Thomson (Lord Kelvin) in 1894, defining that chiral molecules, such as enantiomers, are non-superimposable mirror images of each other. Enantiomers have the same physical and chemical properties, except when they are in a chiral environment. This exception is the answer to why chemists are so interested in obtaining enantiopure molecules: chiral molecules react differently in Nature. Indeed, despite some may think that perfect symmetry may be found in Nature, this one is asymmetric and thus chiral. A tangible proof can be showed by considering two enantiomers: (*R*)-limonene and (*S*)-limonene may be seen as the same molecule, although depending on the chiral form, the first one smells of oranges and the second one of lemons (Fig. 2). The reason can be found in the chiral receptors of the nose

which interact in a different manner with the two enantiomers. There are a lot of these examples showing how biological receptors react differently with enantiomers.

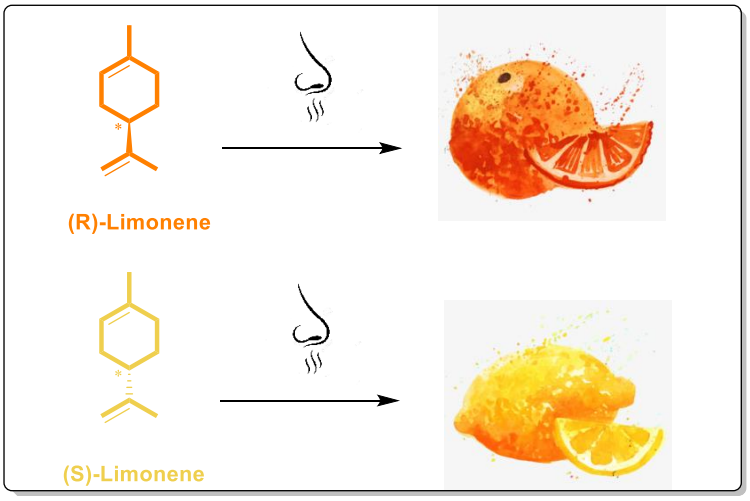


Fig. 2 - The two enantiomers of limonene

This becomes critical, when this biological behaviour of enantiomers is transferred to drug development. Since biological receptors and physiological processes are enantioselective, when a racemic drug is administered, only one of enantiomers gives the expected response, the other might give undesired and collateral effects. This is just what happened in 1957 when Thalidomide was introduced in the market as an API (Active Pharmaceutical Ingredient). The racemate was prescribed to pregnant women for morning sickness, causing limb malformation to thousands of infants. Indeed, where the (*R*)-enantiomer has sedative effects, (*S*)-enantiomer is teratogenic. This event caused many countries to tighten drug approval regulations and increased the synthesis of drugs based on only enantiopure APIs.[1]

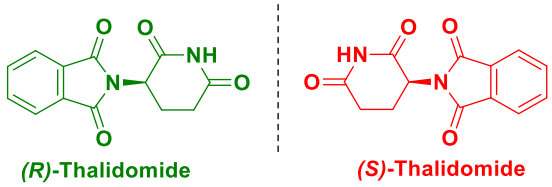


Fig. 3 - The two enantiomers of Thalidomide

Chiral molecules are not defined by the presence of a stereogenic centres, but also depending on other stereogenic elements as evident from molecules in Fig. 4. They look quite symmetrical, but they are not: the configuration of these molecules is related to the dihedral

angle which “generates”, a stereogenic axis, that may be hidden by a representation in two dimensions. Chiral compounds with a stereogenic axis, like those shown in Fig. 4, exhibit atropisomerism.[2] These are a class chiral compounds, whose enantiomers are stable rotamers, because of their restricted rotation of the single bond connecting the two naphthyl units, are stable and do not interconvert between each other. Moreover, bond rotation is time-dependent and half-life for atropisomers can vary between minutes or years, depending not only on steric hindrance, but also on electronic interactions, temperature and solvent. Thus, they are strictly defined as a pair of conformers which can interconvert with a half-life time greater than 1000 s at 25 °C.[3] If the energy given to the system is enough to overcome that barrier, for example by heating, the free rotation of the single bond may lead to a complete racemisation of a pure enantiomer over time. Because of this feature, drug development can become much more complex.

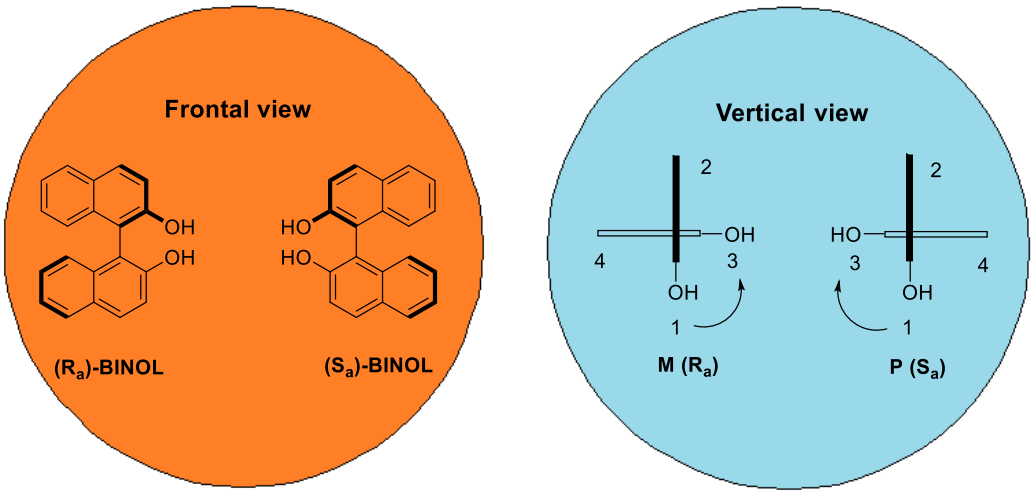


Fig. 4 - Representation and different points of view of BINOL

It is still common to refer to these enantiomers with R and S nomenclature, however a more appropriate nomenclature exists for atropisomers and in general for compounds with stereogenic axes. So, once the priority is given, following the CIP rules (the plane closer to the observer has the priority),[4] if the rotation is clockwise, the configuration is P, otherwise, if the rotation is counter clockwise, the configuration is M (Fig. 4).[5]

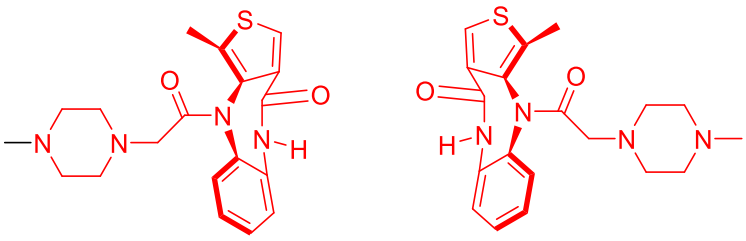


Fig. 5 - Atropisomers of Telenzepine

For decades the concept of axial chirality in rotationally hindered compounds has been relegated to the academic field. However, the situation changed with the discovery of many bioactive chiral compounds containing stereogenic axes and the discovery of many catalysts useful for asymmetric synthesis.[6,7] Furthermore, because of the different biological behaviour of enantiomers, it is important to make investigations about specific activity of each atropisomer as well. It has already been seen in Telenzepine, a selective muscarinic antagonist that has found use in the treatment of peptic ulcers,[8] as one of the two configurations (Fig. 5) is 500 times more reactive at muscarinic receptors in rat cerebral cortex.[9] Therefore, it is imperative that tools for the enantioselective synthesis of only one selected atropisomers must be studied, as it is one of the aims of this work.

1.2 Asymmetric catalysis

Based on what it has been shown in the previous section, it is clear the importance of methods capable of achieving only one enantiomer. One of the main strategies for obtaining enantiopure products is the resolution of racemates. The main drawback of this method is that the undesired enantiomer is wasted. Another common method is to exploit the chiral pool, a collection of cheap and readily available enantiopure natural products. Of course, this method can be quite cheap, but it is limited to few substrates, like amino acids, carbohydrates, and their derivatives. Finally, there is also another tool, that it has been intensively used in this work: the asymmetric synthesis. It is a branch of chemistry involved in controlling by induction the absolute stereochemistry. The induction's techniques are employed by choosing specific substrates, reagents, or catalysts, leading to highly enantioenriched products. This last method has the big advantage to synthesize only the desired enantiomer, without any waste of product (theoretically). In asymmetric synthesis chiral auxiliaries may be used to be attached to the substrate. Alternatively, a chiral reagent can be employed, to induce enantioselection, but in both cases we will need a stoichiometric amount of enantiopure substances to produce chiral auxiliaries or chiral reagents, that it can be very expensive. For this reason, the real pinnacle in achievement in asymmetric synthesis, it is to make use of asymmetric catalysis.

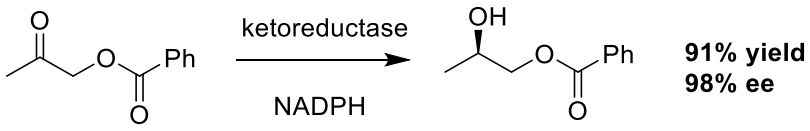


Fig. 6 - Asymmetric reduction mediated by ketoreductase bio-catalyst

For long time the generally accepted classes of efficient asymmetric catalysts where just enzymes and metal catalysts. Enzymatic reactions where considered beyond reach of non-biological catalyst. They are carried out by enzymes or whole cells, achieving high level of enantioselectivity and they are increasingly used on an industrial scale, in particular, they are favoured for hydrolytic reactions. Enzymatic catalysts are able to work in mild conditions, with the drawbacks of a narrow scope of reactions, substrates and operating conditions. However, it became clear that high level of enantioselection can also be achieved by using metal complexes.

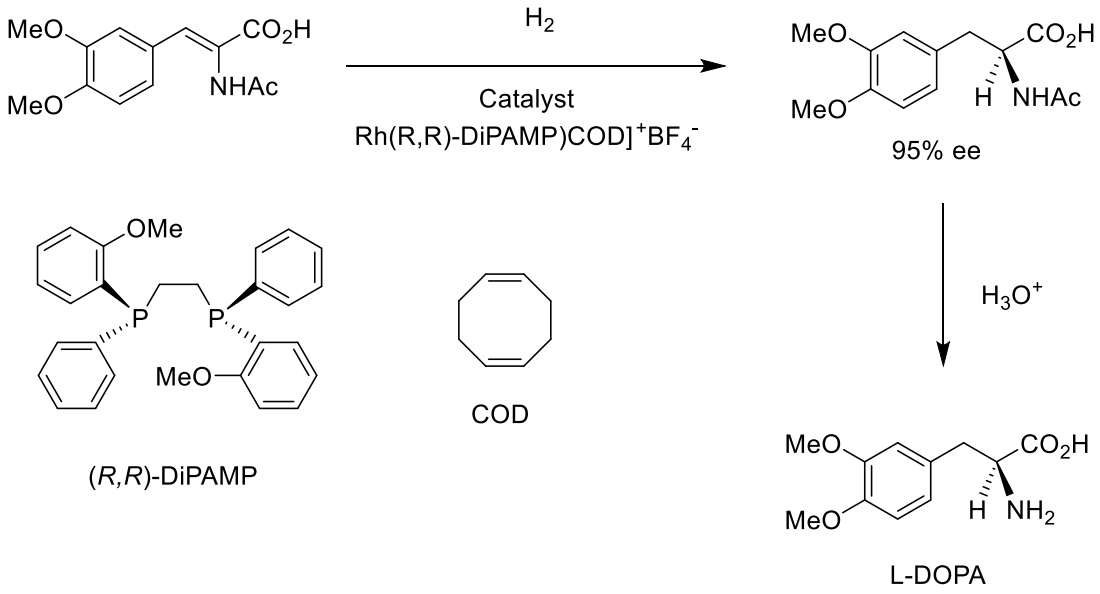


Fig. 7 - The Monsanto synthesis of L-DOPA using catalytic asymmetric hydrogenation

An early success was achieved in the synthesis of L-DOPA (Fig. 7), a rare amino acid that is effective in the treatment of Parkinson's disease. This compound was synthesized by Monsanto employing a chiral transition metal complex in 1974.[10] The big drawback of metal catalysts is that they may leach possible toxic traces of heavy metals in the product, with also high expenses for metal costs and management of toxic wastes, besides expenses for the catalyst synthesis.

Along with metal complexes and enzymes, another category of catalyst emerged in this new century: Organocatalysis. This new branch promotes the acceleration of chemical reactions using substoichiometric amount of organic molecules acting as catalyst. Organic catalysts are cheap and eco-friendly and they do not require harsh working conditions of reaction. This new area is a hot topic in chemical research and it is seeing an exponential development.[11]

1.3 Organocatalysis: history and development

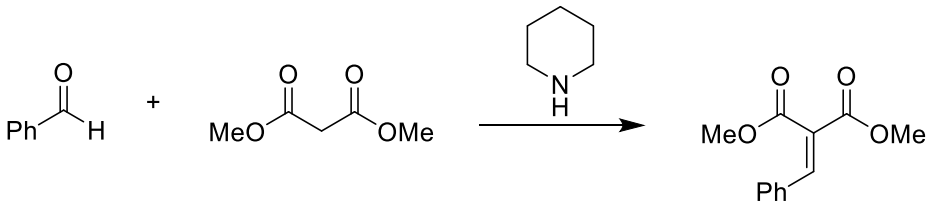


Fig. 8 - First organocatalytic reaction conducted by Emil Knoevenagel in 1896

This term, organocatalysis, is nowadays a commonly accepted word to describe the use of small organic molecules as catalyst for organic transformations. The name was coined by David W. C. MacMillan in 2000,[12] a date that represents the beginning of the era of this new branch of catalysis. It now takes part among the pillars of asymmetric synthesis, together with bio- and metal catalysis. The fast and easy development of this area can be easily explained, because of the several advantages offered to researchers from this kind of catalysts, such as: ease of use, with mild reaction conditions and economically convenient; usually insensitive to moisture or air; often easily isolated from natural sources. Therefore, they are accessible and inexpensive to prepare, and often the processes in which are involved are environmentally friendly. Moreover, the need in industrial production for removal of impurities related to toxic metal catalysis from the waste stream, it has a huge financial impact and it could be avoided with the use of organocatalysis. Performing chemical transformations with small amounts of organic molecules is not a novel concept: organocatalytic transformation were developed prior to organometallic ones. It was in 1896 the origins of small organic molecules acting as catalyst, thanks to the earliest works of Emil Knoevenagel (Fig. 8).[13] In these works, he studied the use of primary and secondary amines for the aldol condensation of β-ketoesters or malonates with aldehydes or ketones. Another great discovery in the history of organocatalysis was the work of Dakin in 1910, regarding the catalytic activity of primary amino acids in the Knoevenagel reaction.[14] Twenty years later, Khun and Hoffer found that secondary amines could also catalyze the cross aldol reaction between different aldehydes.[15] Another very important point in history, reported by Bredig in 1913,[16] was the groundbreaking discovery of the addition of HCN to benzaldehyde in the presence of Cinchona alkaloid catalyst to obtain mandelonitrile with less than 10% ee. Following his footsteps, Pracejus developed the first reactions with

good enantioselectivity, reporting the addition of methanol to methyl phenyl ketene catalysed by O-acetyl quinine (Fig. 9).[17]

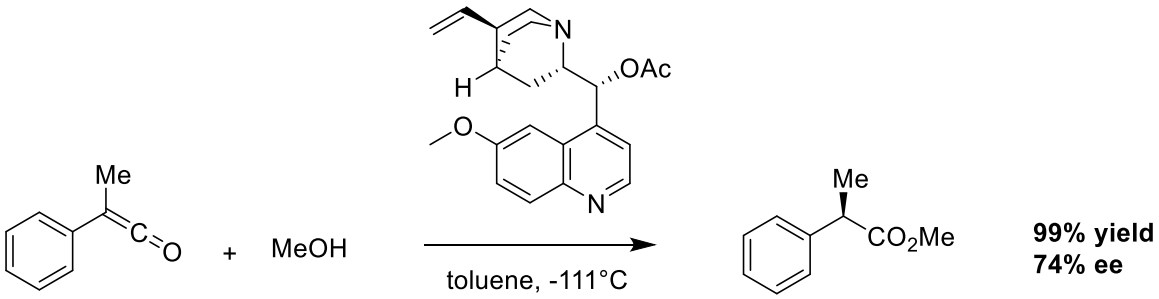


Fig. 9 - First example of Cinchona's alkaloids catalysed reaction with high enantioselectivity

Another important contribution in the field of organocatalysis was made by G. Stork with his work on preformed enamine chemistry (Fig.10).[18]

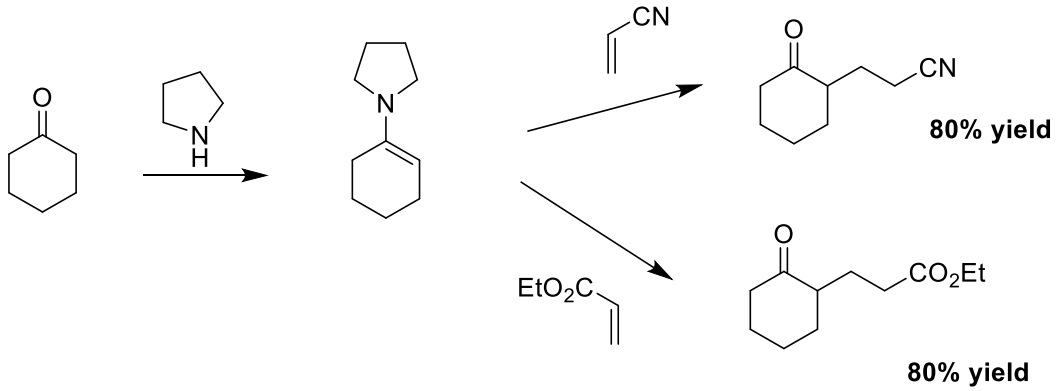


Fig. 10 - Early work of Stork's research group with preformed enamines

The research made by Stork's research group, inspired further studies by Wieland and Miescher, and also by Woodward, on the intramolecular aldol reaction of diketones and dialdehydes. They studied the application of the intramolecular aldol reaction, catalysed by secondary amine salts for the synthesis of steroids and believed that the aldolization proceeded via enamine intermediates.[19]

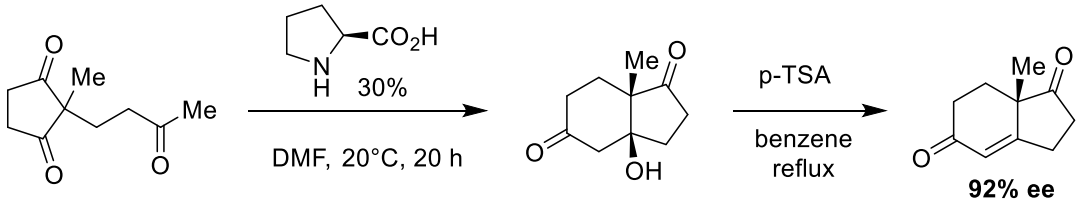


Fig. 11 - The Hajos-Parrish reaction in 1974

Based on these previous works, Eder, Sauer and Wiechert in 1971 and Hajos and Parrish in 1974, independently developed the first asymmetric amine-catalyzed aldolization with proline as catalyst (Fig. 11).[20] None of them proposed the enamine mechanism for the reaction. Later, one of the most brilliant work on iminium catalysis before its rebirth in 2000 was conducted by Woodward. He applied proline catalysis in a triple organocascade addition reaction consisting of a deracemization and an intramolecular aldol reaction leading to the synthesis of erythromycin (Fig. 12).[21]

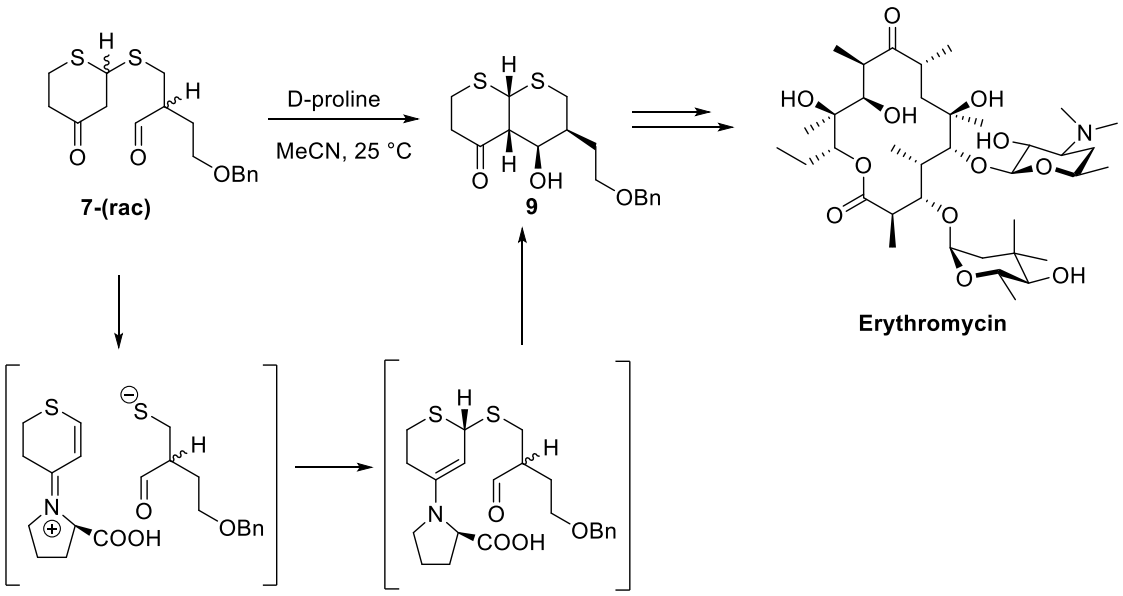


Fig. 12 – Key step for Woodward's synthesis of erythromycin

After this, yet another important discovery has been made in the 1980s: Agami and co-workers studied the application of proline in an enol-endo aldolization reaction and their mechanistic studies showed nonlinear and dilution effects that suggested the involvement of two molecules of proline in the transition state.[22] These are just a few of the milestones in the history of organocatalysis. The so called "renaissance" of organocatalysis came with the simultaneous works of List, Barbas and Lerner in enamine chemistry and MacMillan in iminium ion chemistry in 2000 (Fig. 13).[23]

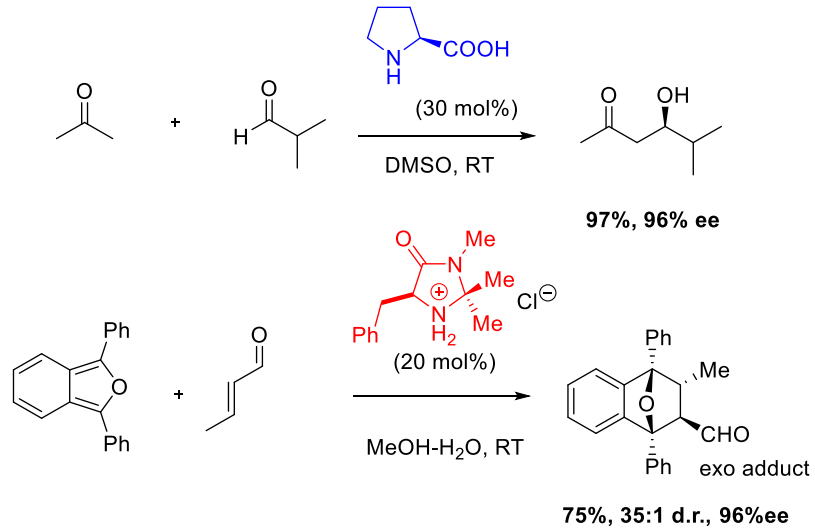


Fig. 13 - The works on enamine catalysis by List and iminium ion catalysis by MacMillan in 2000

Since then, enormous efforts have been made by the chemical community toward the development of new catalysts and methodologies without the use of metals (Fig. 14).

It is now clear the importance of organocatalysis, owing to the number of studies reported in the literature, and moreover, providing new activation modes and new powerful methodologies.

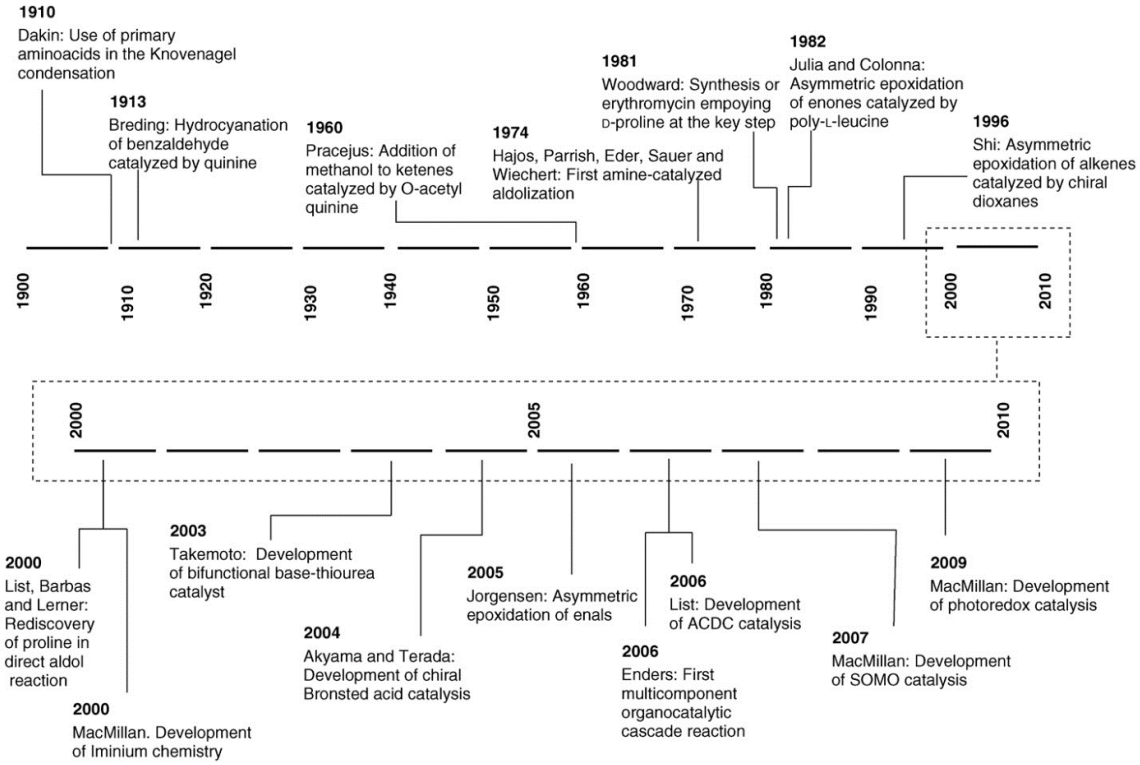


Fig. 14 - Detailed timeline of Organocatalysis

1.4 Organocatalysis: Brønsted acids

Fig. 15 – Lewis and Brønsted acid catalysis

Reactions for the formation of C-C, C-O and C-N bonds catalysed by Lewis acid have been acknowledged since a long time as very important strategies for the synthesis of organic molecules. The concept behind the activation of various chemical functional groups, such as carbonyl, imine, alkene and alkyne moieties, is lowering the energy of the LUMO molecular orbital due to the coordination with Lewis acids and thus accelerating the nucleophilic attack.[24] Despite their good activity, metal Lewis acids are generally sensitive to moisture, indeed they are also usually prepared in situ to prevent degradation and employed directly.[25] However, water-tolerant Lewis acids were developed, such as lanthanide triflates.[26] They may also be combined with chiral ligand to achieve enantioselective versions of Lewis acid catalysed reactions. In contrast to Lewis-acid catalysts, Brønsted acids, being underestimated in the 20th century, are now also valid choices as catalysts, even though they have been always been employed for the formation and cleavage of C-O bonds, such as hydrolysis and formation of esters and acetals.[27] Indeed, Brønsted acids emerged as efficient catalysts for a range of carbon-carbon bond formation reactions.[28] They activate carbonyl, imine, alkene, alkyne and hydroxy group, promoting the nucleophilic addition. Nowadays, Brønsted acid catalysis is an innovative method to afford enantioenriched products using a catalytic amount of a chiral organic molecule bearing an acidic functionality. The first example was the reaction reported in 1998 by Jacobsen and co-workers (Fig.16), achieving an enantioselective Strecker reaction catalysed by peptide-based thiourea derivatives, acting as hydrogen-bond donor catalysts.[29] This first landmark contributed to intensify interest in Brønsted acid catalysis for enantioselective reactions, for which they have not been employed until that moment. This achievement has clearly indicated as chiral Brønsted acid enables discrimination between the enantiotopic faces of an imine substrate opening up a new avenue in enantioselective catalysis without the use of metal chiral Lewis acid.

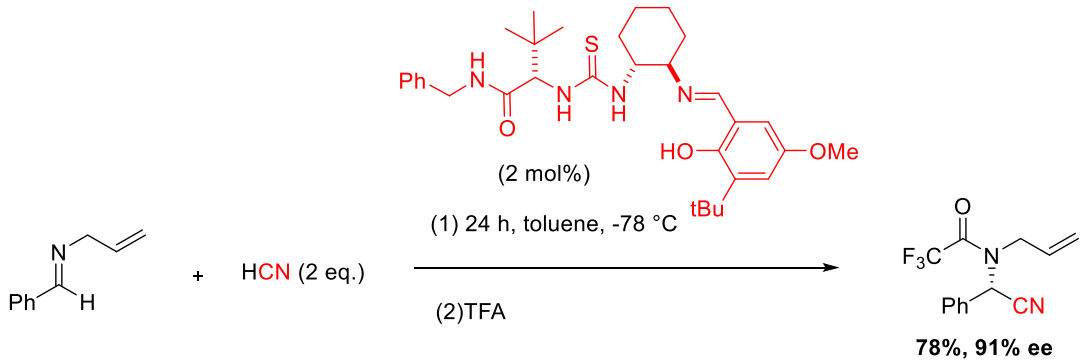


Fig. 16 - Enantioselective organocatalytic Strecker reaction by Jacobsen and co-workers in 1998

Another milestone was the excellent work by Rawal and co-workers in 2003, using TADDOL as the chiral Brønsted acid catalyst to achieve an enantioselective hetero-Diels-Alder reaction (Fig. 17).[30] These first two discoveries in Brønsted acid catalysis have strongly influenced current studies on the development of new Brønsted acid catalysts. However, the acidity of thioureas and aliphatic alcohols are rather weak.

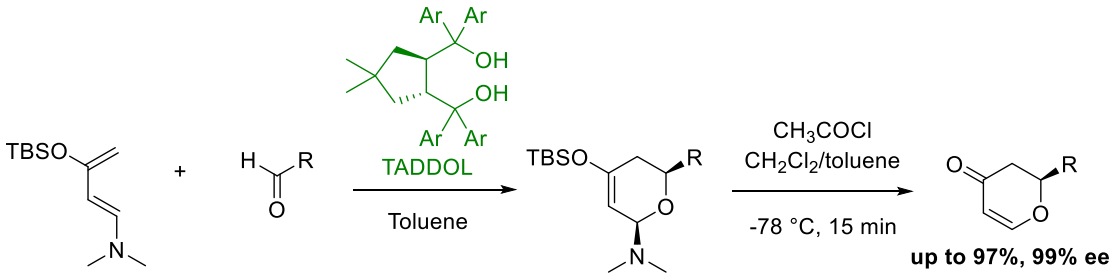


Fig. 17 – Asymmetric hetero-Diels-Alder by Rawal and co-workers in 2003

An innovative approach to the development of chiral Brønsted acid was independently published by Akiyama and Terada.[31] Highly enantioselective transformations using 1,1-bi-2,2'-naphthol (BINOL)-derived mono-phosphoric acids (BPAs) as chiral Brønsted acid catalysts were demonstrated by these two research groups (Fig. 18). Given all these different Brønsted acid catalysis, thiourea and TADDOL derivatives can be classified as neutral compounds while phosphoric acids can be considered as strong acids and because of their different acidity, they show different activation modes and different types of acid catalysis.

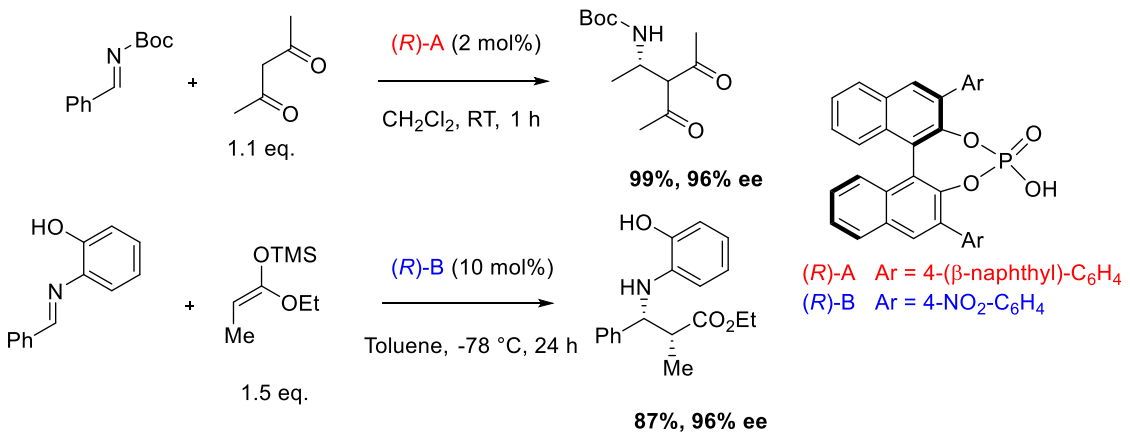


Fig. 18 - Terada and Akiyama's Mannich -type reaction

Indeed, neutral compounds, or weak acids, preferer to activate substrates via hydrogen bonding-general acid catalysis and stronger acid may prefer to activate via Brønsted acid-specific acid catalysis (Fig.19).

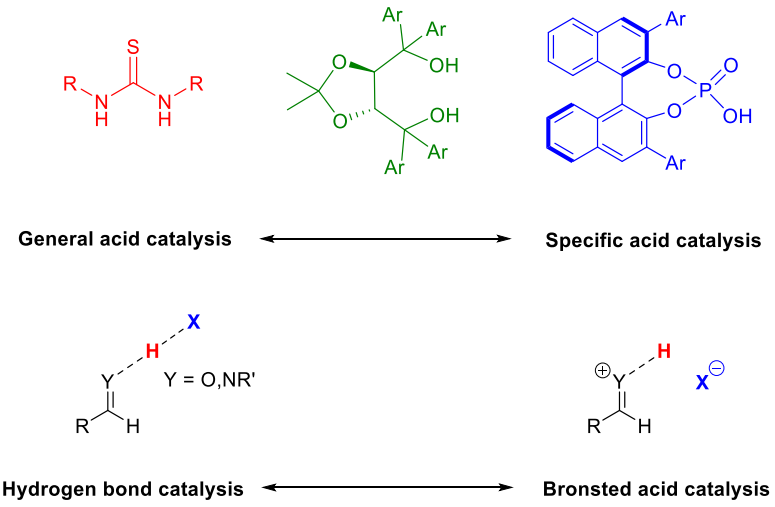


Fig. 19 - Different modes of substrate activation and types of acid catalysis

Nonetheless, in this distinction of activation modes, there is no clear borderline between hydrogen bond catalysis and Brønsted acid catalysis,[32] and further studies are required to improve the knowledge in this field. However, the key concept to realizing enantioselective catalysis using a chiral Brønsted acid is the hydrogen bonding interaction between a protonated substrate and the chiral conjugate base. Thus, the organic transformations proceed under a chiral environment created by the chiral conjugated base, which exists in the vicinity of the substrate through hydrogen bonding interactions.

1.5 BINOL-derived phosphoric acids (BPAs), *N*-triflylphosphoramides (NTPAs) and derived metal complexes

In the vast field of Brønsted acid organocatalysis, BINOL-derived phosphoric acids (BPAs) are the most employed. They achieved this status by being highly versatile catalysts and are able to catalyze a plethora of asymmetric transformations typically using operationally simple and mild conditions. In 2013 alone, over 100 research articles were published, which utilized them as catalysts for synthetic procedures.[33] The core structure of these phosphoric acids is a rigid BINOL core, which acts as chiral unit in the catalyst design (Fig. 20).

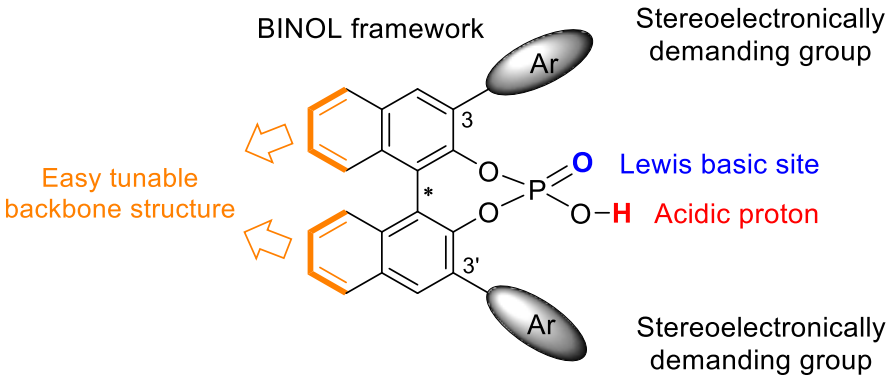


Fig. 20 - BINOL-derived phosphoric acid structure and chemical features

This scaffold is usually modified in the 3 and 3' positions with sterically demanding aryl moieties with diverse electronic properties. These big substituents are shielding the active site of the catalyst, namely the acidic proton, and are responsible of the control of stereochemical induction in asymmetric reactions. Another feature of BINOL-derived phosphoric acids is that their chiral BINOL framework can be modified to change drastically the properties of the catalysts. Usually the BINOL framework is modified in order to change the steric demand achieving a better enantioselection, where the H8-BPA is a good example. Anyway, more incredible tuning of this framework can be performed, like the astonishing work by Rueping and co-workers, with the development of a recyclable heterogeneous phosphoric acid catalysis,[34] and also by Toy and co-workers, with the development of a homogeneous phosphoric acid catalysis, recyclable by precipitation (Fig. 21).[35]

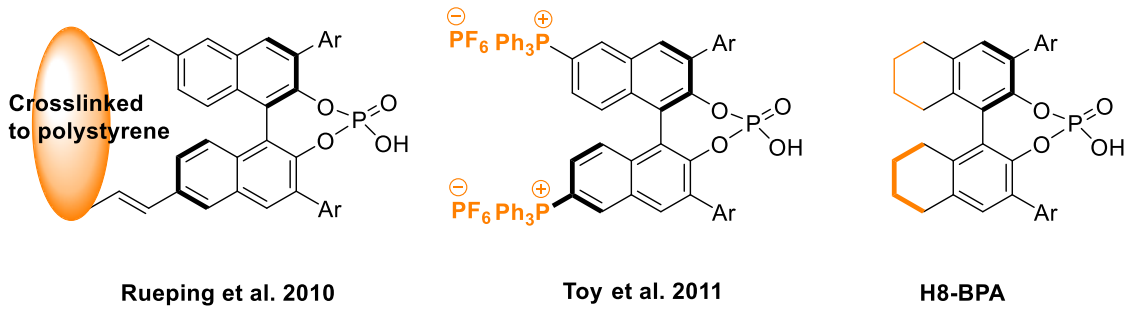


Fig. 21 - Backbone structure tunings of BPAs

Regarding the activation of electrophiles like imines, the formation of a chiral contact ion pair between the chiral acid and the substrate is generally assumed.[36] In the case of carbonyl activation, the existence of a contact ion pair is less probable because of the low basicity of the oxygen atom. A dynamic state which can be described as an equilibrium between the formation of a hydrogen bonding and a contact ion pair complex is more likely during the activation of carbonyl groups. However, the *p*K_a difference between the Brønsted acid catalyst and the carbonyl function that determines which activation mode is more populated in the equilibrium of these two activated species. As example, Terada found that if the acid employed is too strong, like sulfonic acids, it is difficult to maintain hydrogen bonding interactions between a protonated substrate and the conjugated base,[37] leading to a loose anionic chiral pocket, and thus, to a decrease in the enantioselection of the reaction. Phosphoric acids have relatively strong but appropriate acidity,[38] that they are expected to capture electrophilic component through hydrogen bonding interactions without the formation of a loose ion-pairs.

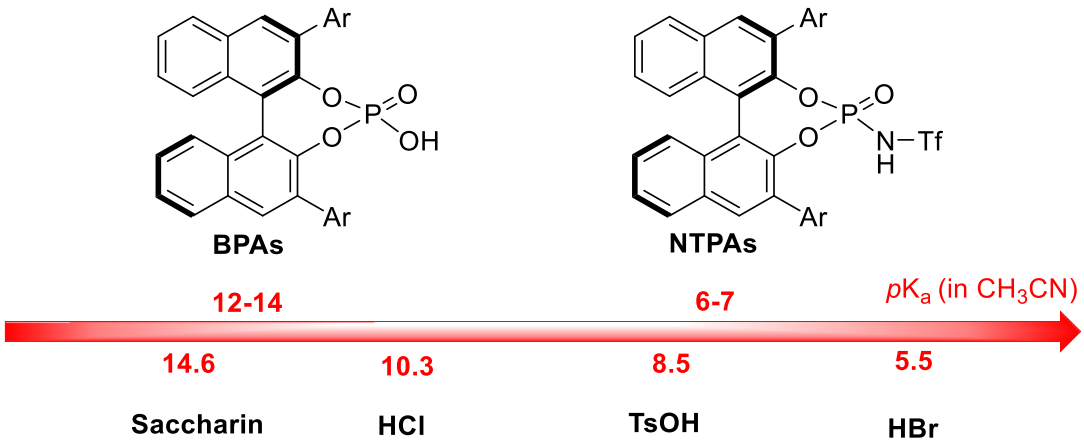


Fig. 22 - Acidity scale for organic Brønsted acid catalyst compared with common acid

BINOL phosphoric acids have estimated *p*Ka values between 1 and 2 (13-14 in CH_3CN) and due their limited acidity their substrate scope is generally limited to rather basic electrophiles, such as imines.[39] For this reason, Yamamoto and co-workers started to design modified phosphoric acids in a way to lower their *p*Ka values. The major approach to the development of highly acidic Brønsted acids is the introduction of strong electro-withdrawing groups into existing acidic scaffolds. This led to the successful development of the related BINOL-derived *N*-triflylphosphoramides (NTPAs) with estimated *p*Ka values between 6 and 7 in CH_3CN (see Fig. 22). NTPAs exhibit most of the features described for BPA, except for they possess a slightly different acidic proton, both from a steric and acidic point of view. This new typology of chiral Brønsted acid was employed in an asymmetric Diels-Alder reaction, becoming the first example in which a chiral Brønsted acid catalyst activates a ketone in a highly stereochemically controlled fashion (Fig.23).[40] Under the same conditions, the equivalent phosphoric acid was inactive which demonstrates the higher acidity and activity of the phosphoramide catalyst.

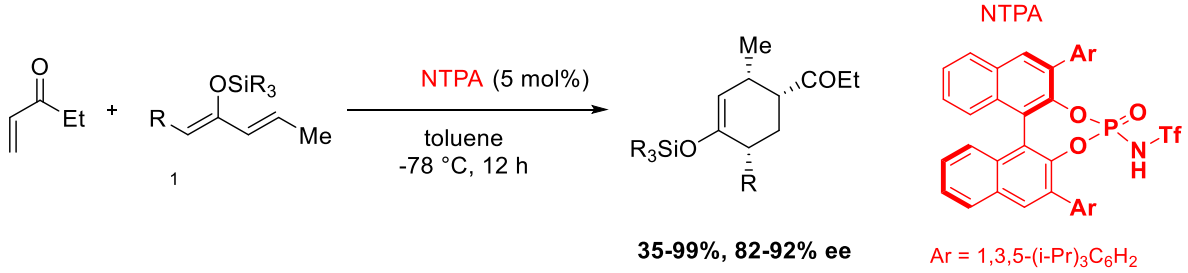


Fig. 23 - First asymmetric Brønsted acid catalysed Diels-Alder By Yamamoto and Nakashima in 2006

It is important to put an emphasis on the fact that in general, the more acidic catalyst have higher reaction rate constants and give higher yields but it should be pointed out that the enantioselectivity depends on the catalyst architecture.[41] Nevertheless, activation (and thus reactivity) can be directly correlated to acidity if no catalyst inhibition occurs.

Another emerging and very powerful class of catalysts are metal phosphate catalysts.[42] In these metal phosphates, the phosphoric acid acts as a phosphate anionic ligand for the metal core which behaves as a proper Lewis acid. The phosphoric acid still retains its Lewis basic site for useful further inductions of substrates. However, the mechanism of catalysis of these compounds is still uncertain.

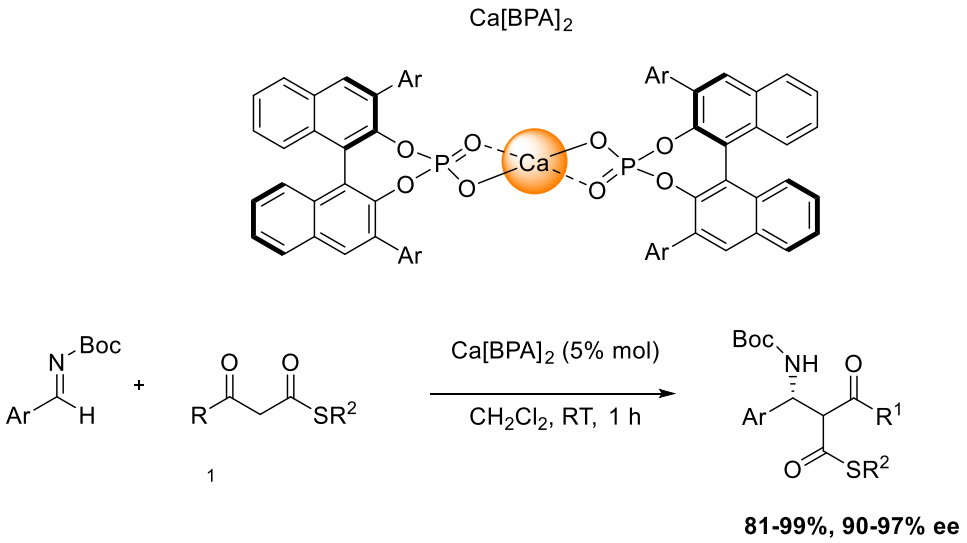


Fig. 24 - Enantioselective Mannich reaction catalysed by BPA derived m by Ishihara et al in 2010

The discovery of these catalysts came out in 2010, when Ishihara published an article about a very interesting observation. He found that chiral phosphoric acid purified over silica gel had a strong tendency to form metal salts. These salts were able to catalyse the same reactions of the corresponding phosphoric acid however giving rise to alteration of yields enantioselectivity, and even absolute stereo-configuration. Despite this, Ishihara found that these salts could in fact be advantageous when used in their pure form. Then, he studied a Mannich reaction catalysed by a calcium phosphate, and obtained good yields and excellent enantioselectivities (Fig. 24). In contrast, the free acids tested performed with only moderate selectivity.[43] After that, chemists aware of this discovery published several works, involving other metal phosphates with different metals.[44] It is now recognised the enormous potential of this class of organocatalysts combined with metals, that they represent a novel catalytic framework for novel methodologies to perform organic reactions in an enantioselective fashion.

1.6 Quinoline scaffolds in drug development

Quinoline is a heterocyclic aromatic compound and a weak tertiary base. It was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge and this source still remains the principal source of commercial quinoline.[45] This scaffold has found many applications in different chemical domains, such as pharmaceuticals, agrochemicals, dyestuffs, and materials, and has wide occurrence among natural products such as alkaloids. It is also employed to chelated metallic ions as *N*-donor ligands. Yet, it is one of the most studied heterocyclic scaffolds in medicinal chemistry, for its broad spectrum of biological activities in diverse therapeutic areas.[46] The importance of this molecule in antimalarial drug development is well documented. Indeed, the well know antimalarial natural products quinine and quinidine alkaloids isolated from Cinchona bark comprise also quinoline scaffold.[47] Recently quinolines substrates have also gained recognition as important privileged scaffolds for the development of new therapeutics in cancer and tuberculosis. This molecule has been reported to possess activity also as antiprotozoal, antipsychotics, anti-inflammatory, antioxidant, anti-HIV, antifungal, and for treatment of neurodegenerative disease (like Alzheimer's disease).[48] Camptothecin is a quinoline alkaloid discovered in 1966 by Wall and Wani through a systematic screening of natural products for anticancer drugs. In fact, two comptothecin analogues namely topotecan and irinotecan have been approved for clinical use for cancer chemotherapy (Fig.25).[49]

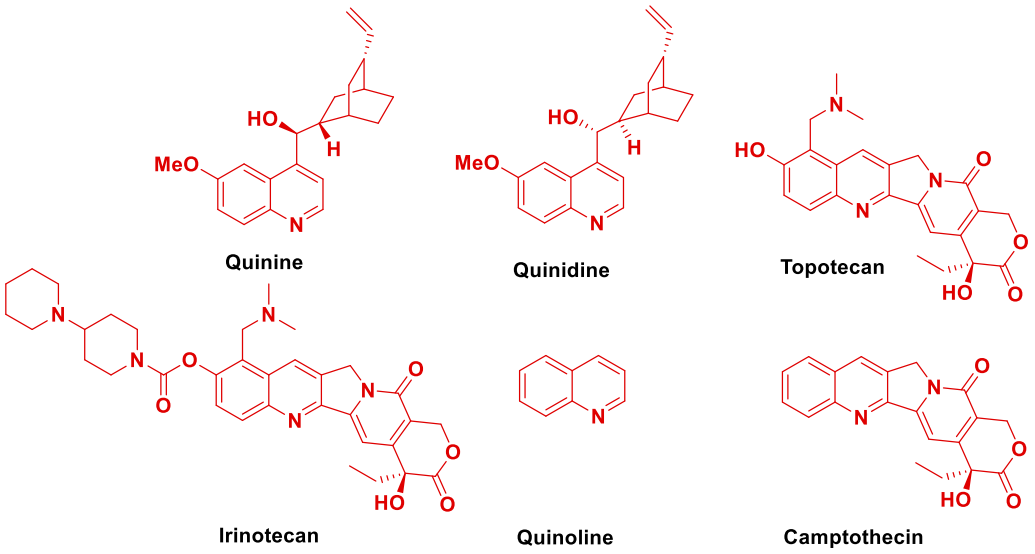
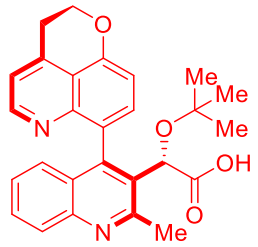


Fig. 25 - Quinoline and quinoline-based drugs

Quinoline is also part of several clinically used drugs, where their major occurrence is among antimalarial drugs. The aminoquinoline scaffolds has been a backbone of antimalarial drugs since 1940s. In this class, chloroquine was the first drug discovered in 1934 by Hans Andersag and co-workers at the Bayer laboratories.[50]

Quinoline scaffolds have found useful also for the treatment of the acquired immunodeficiency syndrome (AIDS) and the human immunodeficiency virus (HIV), that are considered a significant global problem.[51] The advent of multidrug cocktails of different drug classes has transformed this disease into what is now considered treatable chronic infection. Aside from these advances, drug resistances are emerging as threats to these therapeutic advancements. Therefore, the advent of new therapeutic approaches is required to keep this disease under control. In this context, the HIV-integrase inhibitor 1 (Fig. 26), a quinoline-based allosteric integrase inhibitor is being investigated for HIV treatment.[52] This molecule, respect to all other showed above, has a chiral centre but also has a chiral axis. In contrast to traditional stereogenic centres, the axially chiral unit can readily interconvert depending on the degree of steric impairment. If the stereogenic axis is thermally stable, the drug candidate would then necessitate the synthesis of a single atropisomers, as it is the case for the HIV integrase inhibitor 1.



HIV integrase inhibitor 1

Fig. 26 - An atropisomeric quinoline-based drug for HIV treatment

Hence, seen different classes of quinoline-based drug scaffolds, the discovery of more efficient and versatile new routes for their synthesis is one of the hottest areas in organic chemistry,[53] and moreover, it is very important to investigate new enantioselective routes for the synthesis of unconventional atropoisomeric drugs.

1.7 Atroposelective synthesis of quinoline - State of the art

In this work it has been proposed a novel organocatalytic strategy, to obtain an atropisomeric quinoline substrate with high enantioselectivity by Friedländer reaction. The use of such arene-forming reaction, combined with the application of chiral Brønsted acid organocatalysts, in a way to obtained highly enantioenriched atropisomers, it has been inspired by novel works and previous existing reactions that will be showed in this section, along with the conceptual design of the catalytic strategy employed.

1.7.1 Quinoline synthesis by Friedländer annulation

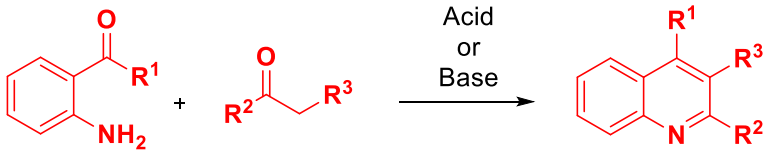


Fig. 27 - General Friedländer reaction

Because of their unique pharmaceutical importance, continuous development in the synthesis of new quinoline derivatives is a growing sector of research. Indeed, there is a number of methods for the synthesis of quinolines reported so far: Dobner, Skraup, Pfitzinger and Friedländer methods.[54] Among them, the Friedländer reaction is still one of the simplest methods. This reaction is a cyclecondensation of 2-amino-substituted aromatic aldehydes or ketones with carbonyl derivatives containing active methylene group. It is catalyzed by high temperatures, acids or bases. Acid catalysis is more effective than base catalysis, while using temperature to accelerate the reaction suffers of low selectivity, leading to a majority of non-Friedländer product. The mechanism of this reaction it has been for long time uncertain. As showed in Fig.28 two possible pathways are possible. However, thanks to the work of Javanshir, pathway II has proven to be the mechanism of choice by DFT method.[55]

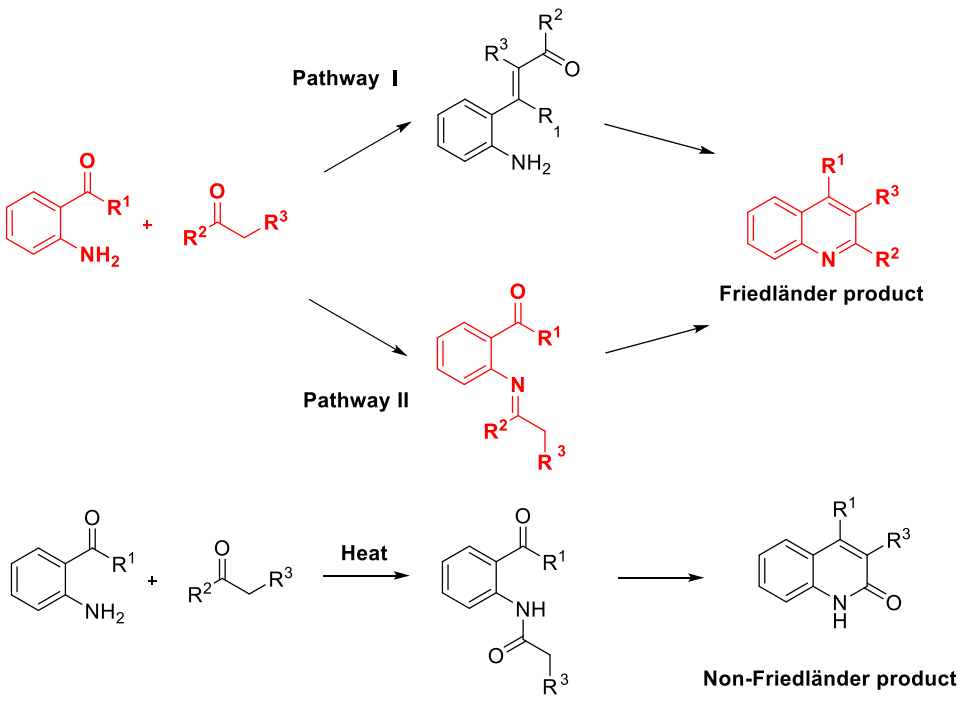


Fig. 28 - Different reaction pathways of Friedländer reaction

In recent years, a very good work has been carried out by Seidel and Li which reported the first catalytic enantioselective Friedländer reaction. Enamine catalysis allowed the formation of the desired product in good yields and excellent levels of enantioselectivity from the reaction of 4-substituted cyclohexanones with *o*-aminobenzaldehydes. (Fig.29).[56]

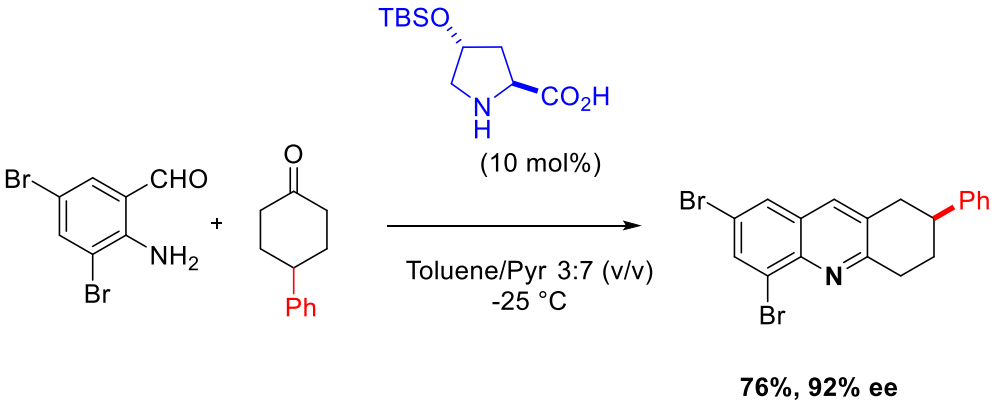


Fig. 29 - Enantioselective organocatalytic Friedländer annulation by Li and co-workers in 2010

1.7.2 Atropisomers by arene-forming reaction

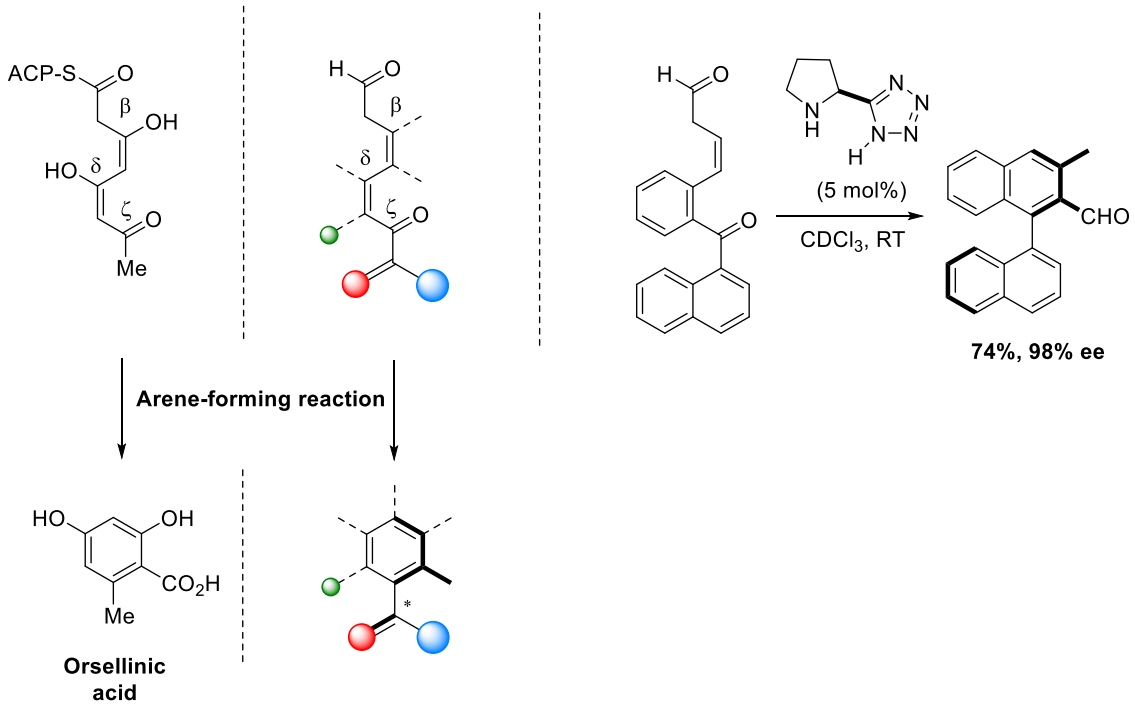


Fig. 30 - General concept for arene-forming reactions and Atroposelective synthesis of chiral binaphthyl systems, developed by Sparr and co-workers in 2014

Sparr and co-workers, fascinated by biosynthetic machinery of a prototypical arene-forming aldol condensation of aromatic polyketide orsellinic acid, stated to design stereoselective arene-forming aldol condensations as a synthetic concept for the synthesis of stable atropisomers.[57] They thought that to enable operational simple catalysis, the substrate ideally bears an aldehyde, which generates an activated enamine intermediate by aminocatalysis and then the ς-keto group provides a means for the formation of a six-membered ring. Then, carbonyl moieties in σ- and β-position, are replaceable by different alkene or aryl groups and allow substrate diversification. To create configurationally stable atropisomers upon arene formation, two different substituents are installed at the terminal position. By combining these considerations with a viable substrate synthesis, various atropoisomeric scaffolds may be conveniently prepared in enantioenriched form by catalytic stereoselective arene-forming aldol condensation. Indeed, they developed a stereoselective arene-forming aldol condensation of ketoaldehydes with a proline-derived catalyst, affording the corresponding atropisomeric biaryl in high yields and enantiomeric excess (Fig.30).[58]

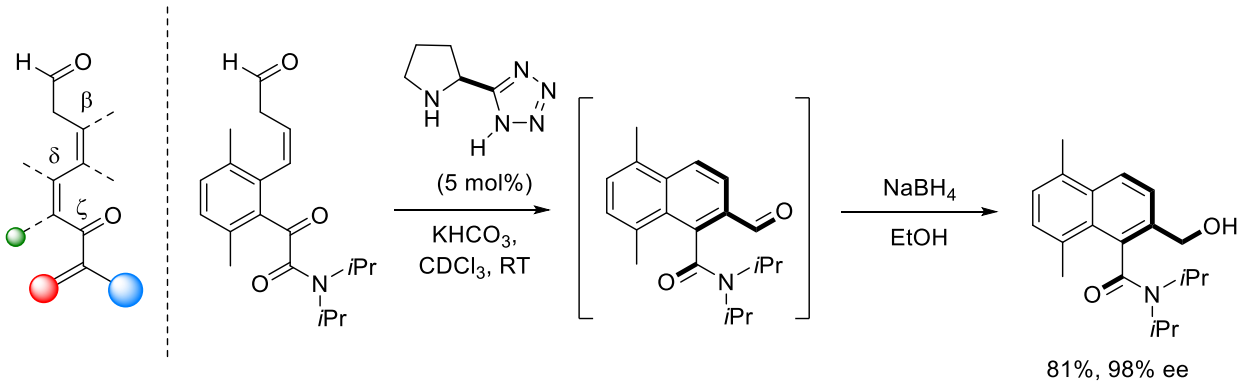


Fig. 31 - Atroposelective synthesis of chiral amide by Sparr and co-workers in 2016

It is then clear how thanks to this strategy Sparr was able to pursue very quickly another novel synthesis. He elaborated a stereoselective synthesis of axially chiral aromatic amides by the seteroselective arene-forming aldol condensation, yet in high yields and enantioselectivity using pyrrolidinyl tetrazole (Fig. 31).[59]

Another important work was developed by Tan, using an earth-abundant metal combined with an organocatalyst, in the synthesis of arylpyrroles, a motif largely found among natural products. He obtained high yields and enantioselectivity by using a chiral phosphoric acid, with iron (III) triflate as a Lewis acid, leading to an axially chiral arylpyrrole, because the restricted rotation around the C-N bond. In this case the presence of an *ortho* substituent on the pyrrole moiety was sufficient to ensure the configurational stability of the stereogenic axis (Fig. 32).[60]

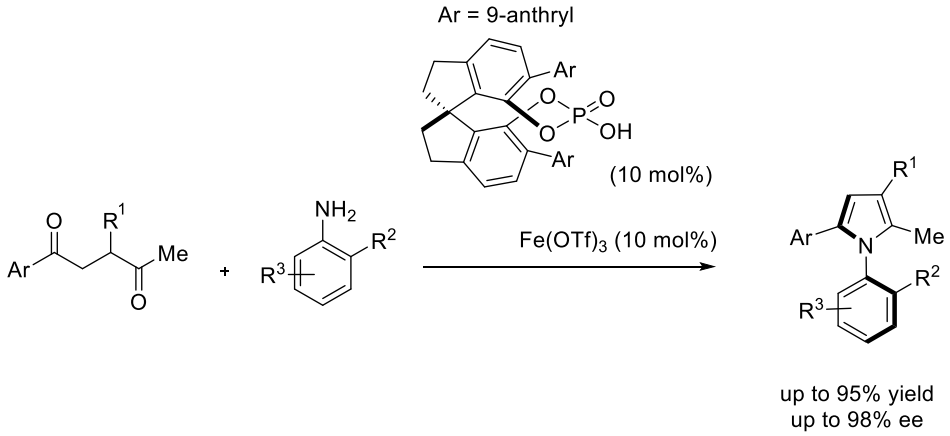


Fig. 32 - Atroposelective Paal-Knorr for the synthesis of arlpyrrole derivatives by Tan et al. in 2017

1.7.3 Design of the reaction

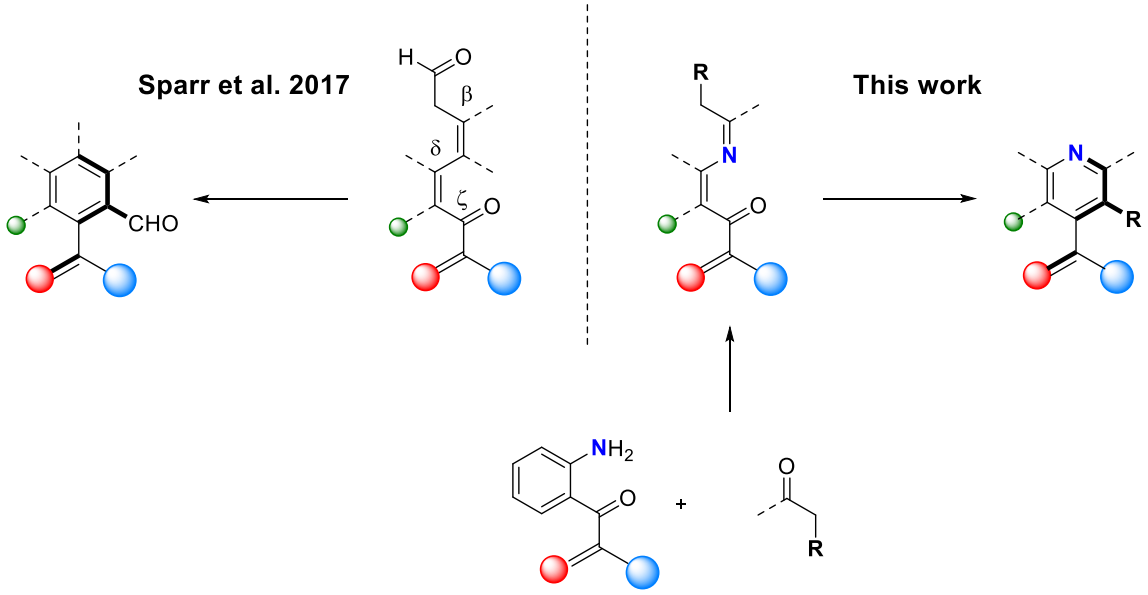


Fig. 33 - Comparison of design strategy with the work of C. Sparr and co-workers

The initial idea behind this work, was to synthesize a very hindered biaryl system, like a binaphthyl in Sparr's work, but containing a heteroatom, such as in the work of Tan. In order to create a novel strategy, we decided to focus our attention to the formation of a binaphthyl core containing a quinolinic unit. We envisioned then, the Friedländer annulation seemed a feasible reaction to obtain the desired atropisomer,[61] since it allows to employ *o*-aminoarylketones, which could possibly bear a very bulky substituents on the ketone, being a favourable substrate for our reaction to form a stable atropisomer (Fig. 33). Then, once established possible substrate and reagent to accomplish this design, we went for an acid catalysed Friedländer reaction. The base catalysed Friedländer reactions could not be used since suitable only for *o*-aminoarylaldehydes.[62] At the end, the accomplishment of such idea comes with the use of a privileged BPA, such as TRIP,[63] to achieve the desired outcome with a very high enantiomeric excess. This final step reminds the previous mentioned work, reflecting an atroposelective version of the Friedländer reaction.[64] Aware of these concepts, the design started to concretize by synthesizing the substrate.

2. Aim of the work

The aim of this work will be to combine the state of the art in this rather still unknown field of enantioselective aromatization and the already established importance of the resulting structure by synthesizing enantioenriched quinoline via an unprecedented atroposelective Friedländer-type heteroannulation. The fulfilment of such aim could be possible by the employment of the novel and fast-growing area of organocatalysis, choosing chiral phosphoric acids and analogues as Brønsted acid to be the best tool for the accomplishment of such goal. Therefore, exploiting fine-tuning of the chosen starting materials and of the catalytic system the best conditions in term of reaction yield and enantiomeric excess will be investigated (Fig. 34).

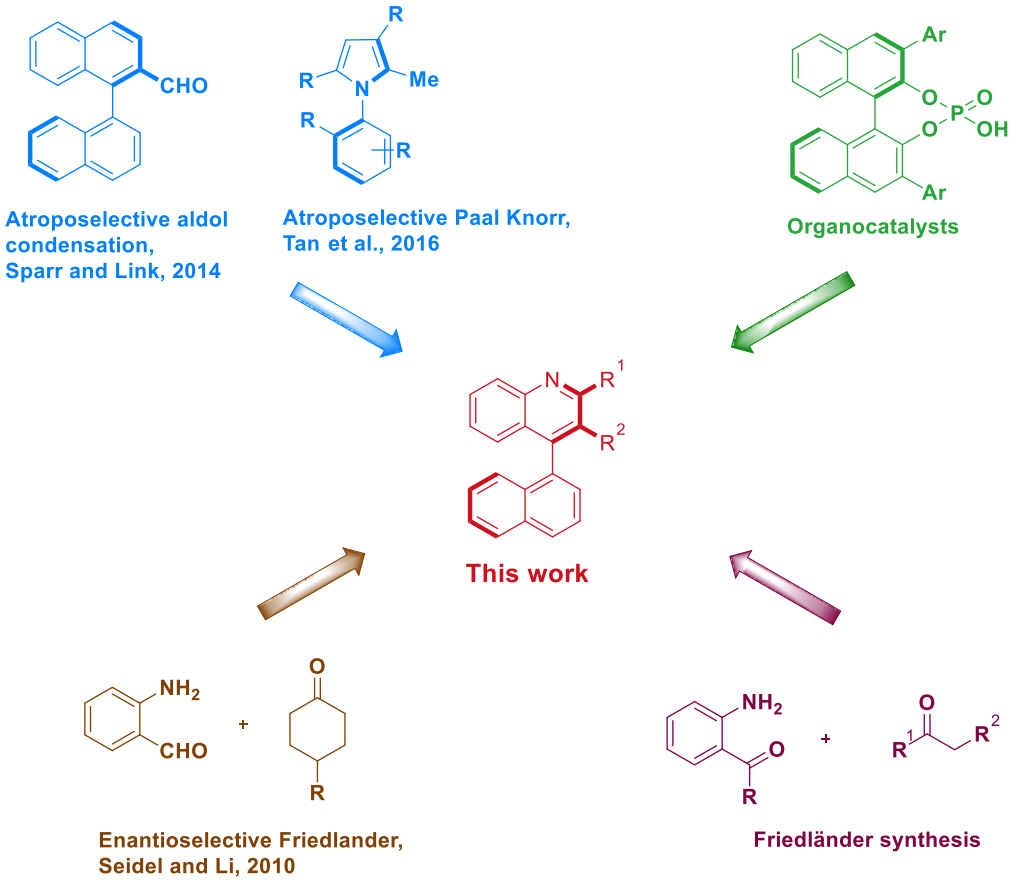


Fig. 34 - Previous works and concepts combined, inspiring for the design of this novel atroposelective strategy

3. Results and discussion[I,II]

3.1 Synthesis of the substrate

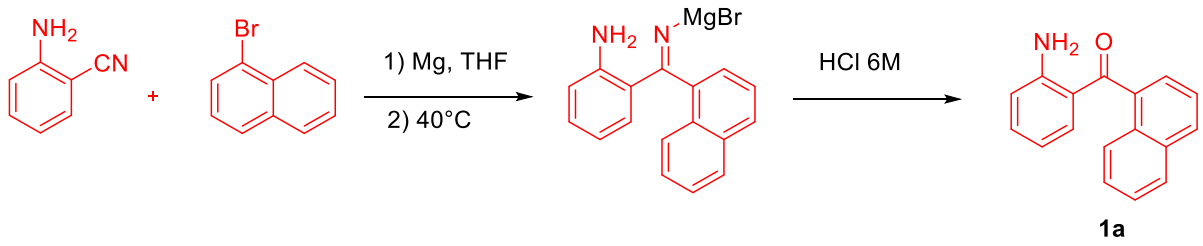


Fig. 35 – Synthesis of the substrate

We found in the literature a similar procedure for the synthesis of the desired substrate, which employed less bulky substituent, such as a phenyl instead of a naphthyl, and so the reaction has been also be optimised in a way to obtain the wanted product in high yields. The synthesis is composed by a Grignard reaction in THF, between a 2-aminobenzonitrile and 1-bromonaphthalene, followed by hydrolysis of the formed imine to give the desired substrate **1a**. During the hydrolysis, it was important to work under very acidic conditions to guarantee full conversion of the imine to the ketone, and after the addition of *o*-aminonitrile to the Grignard reagent, to keep at 40 °C the reaction vessel to allow the attack of the nitrile group. With these small precautions we obtained the desired substrate in good yields (65%) and the product **1a** has been confirmed by ^{1}H-NMR analysis.

[I] Please, note that in all the reaction schemes, do not intend to show the absolute configuration of atropisomeric products, since it has not yet been determined. The purpose of such chiral indication is only to express the axial chirality of the molecule.

[II] See Experimental section for further details about procedure, methods and characterisation of products

3.2 Proof of concept, choice of reaction conditions and initial solvent screening

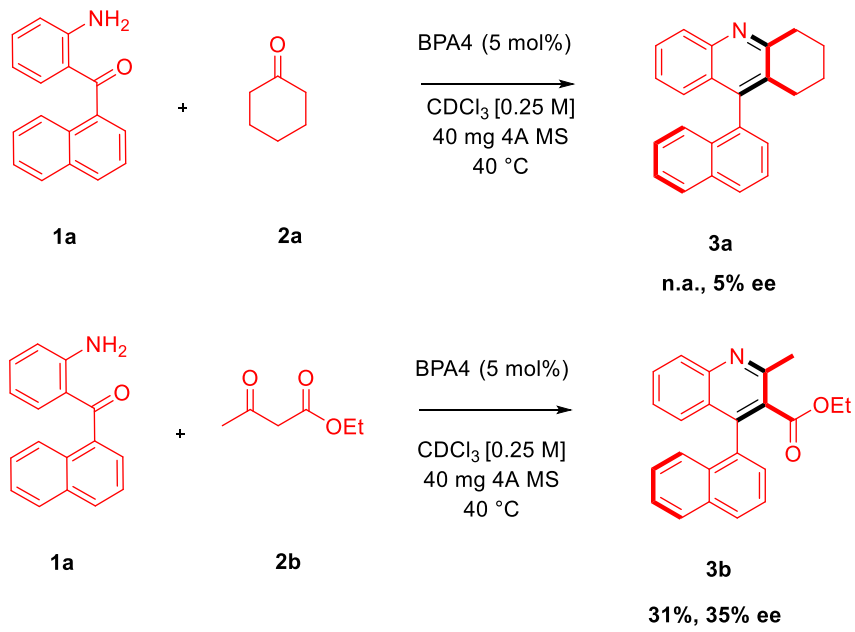
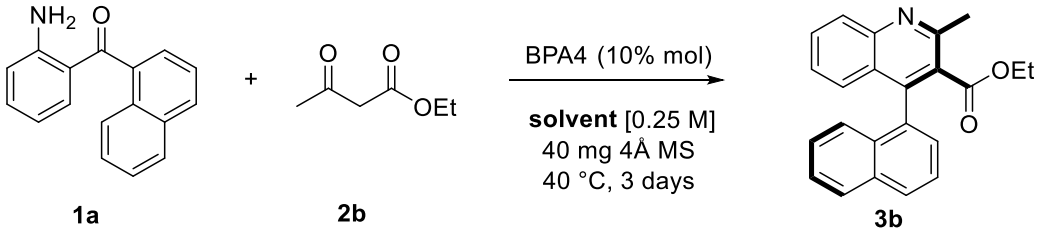


Fig. 36 - First synthesis of the desired atropisomeric product

Once the substrate has been obtained, we started with the first attempts of the synthesis. We decided to use cyclohexanone (**2a**) as the ketone and diphenylphosphate as an achiral organocatalyst. The latter possess the same reactivity as the more expensive BPA and also allows to obtain the racemic mixture of the product, that is used as a reference in the HPLC analysis of the enantiomers. We adopted common and mild conditions, with the aid of molecular sieves (MS) and $CDCl_3$ as the solvent. The initial synthesis proceeded smoothly, and seemed to be immediately successful by TLC, with further confirmation of NMR analysis, affording poor but acceptable yield, and no by-products have been observed. We then started with the synthesis using **BPA4**. The reaction proceeded forward this time too, but we obtained always poor yields and very low ee% (almost a racemic mixture of enantiomers). So, we repeated the reaction again with a different ketone, hoping to increase yields and enantioselectivity, with another very common ketone employed in the Friedländer reaction, the ethylacetoacetate (**2b**).

Tab. 1 – Initial solvent screening



Entry	Solvent	Yield (%)	ee (%)
1	$CDCl_3$	31	35
2	CH_2Cl_2	31	26
3	THF	22	26
4	Toluene	48	26
5	$PhCF_3$	25	21
6	MTBE	30	14
7	CH_3CN	4	23
8[b]	DMSO	n.d.	n.d.

[a] 55 °C; [b] 3 days reaction time; [c] RT

We obtained poor yields, but higher enantioselections. Then we evaluated the configurational stability of such atropisomers. We determined the enantiomeric excess of **3b** before and after putting the reaction vessel in a hot bath at 60 °C for 12 h, and no change in the ee% have been recorded, considering it a very stable atropisomer. We then started to work with ketone **2b**, performing an initial screening of aprotic solvents to use for the establishment of a common procedure to follow during the development. Surprisingly, $CDCl_3$ showed to be already a good solvent for enantioselection, while toluene gave higher yields (Tab. 1, entry 1 and 4). It has

also been seen as an increase of the polarity of the solvent, leads to a decrease in both enantioselectivity and yield, where strong polar aprotic solvent such as DMSO and acetonitrile, gave no reaction at all or very poor yield. Indeed, this behaviour can be explained because Brønsted acid catalysis is a type of non-covalent catalysis, working mainly by hydrogen bonding interactions. Therefore, modification of such delicate electronic catalytic environment is easily corrupted by other charges, partial and especially formal, present in solution.

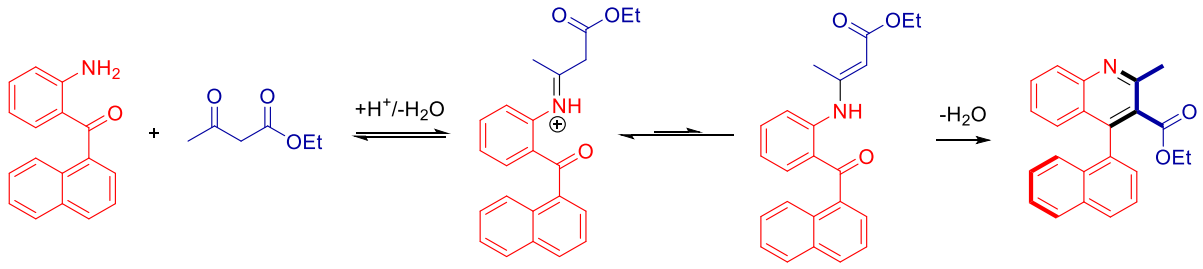


Fig. 37 - Mechanism of Friedländer annulation reaction

At this point we started to think to the reasons of such low reactivity. Looking to the mechanism of the reaction (Fig. 37), an explanation could be the presence of several equilibrium states, some of them not even productive, such as the formation of the Z-enamine. The Z-enamine is believed to have higher activation energy because it would form the product in its hydrated form (before the final dehydration) with the hydroxyl group in *gauche*-position with the hydrogen in α, forming an intermediate with the water elimination much less favoured, since the elimination at the *anti*-position is much faster due to better orbital overlapping, observable in a Newman representation (Fig. 38). The rate determining step of the reaction could be possibly attributed to the annulation step of the enamine, requiring high energy for such intramolecular movement to achieve the ring formation. Another factor for low reactivity is probably the temperature, that it is too low, especially with the use of such bulky substrate, indeed many of these kinds of reactions are performed at higher temperatures. However, an increase in temperature would favour the reaction, but compromising enantioselectivity by lowering the energy gap between the two transition states leading to the different atropisomers.

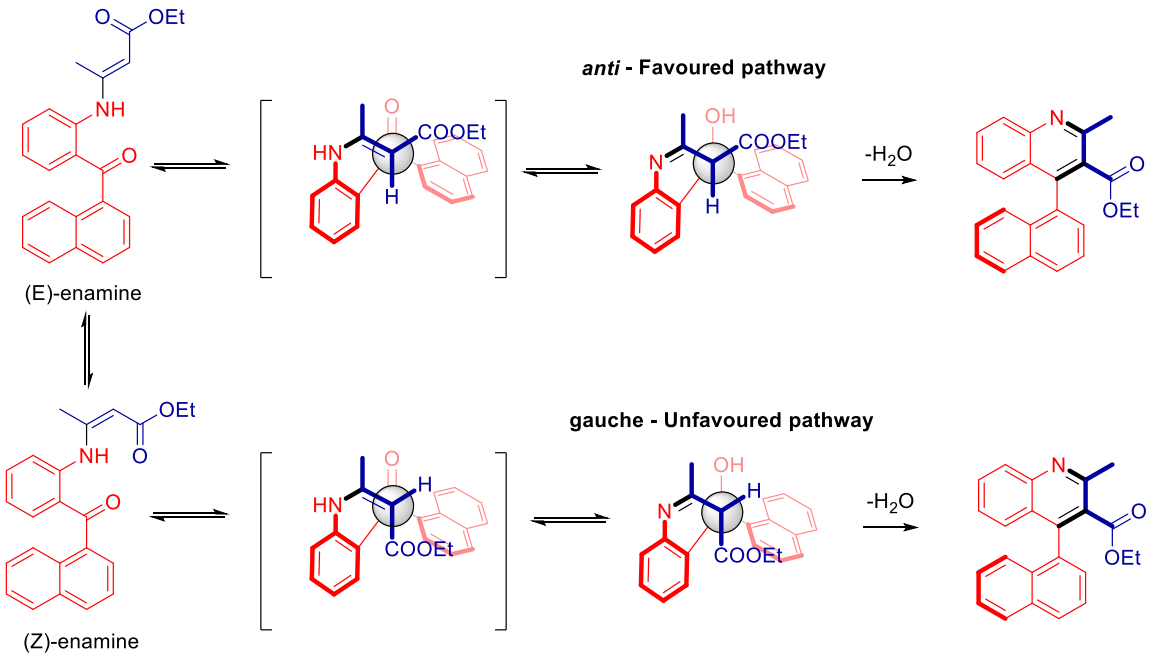


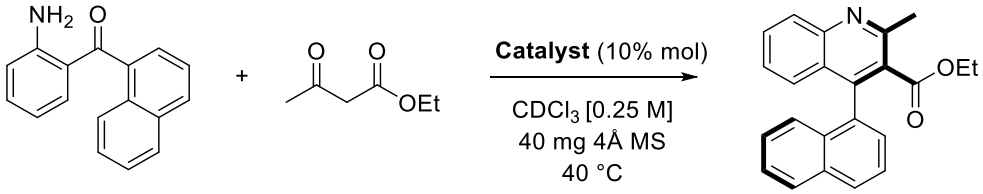
Fig. 38 – Reaction pathways assumed in this work

Furthermore, the possible partial salt formation between the amine moiety and the BPA could be causing a limitation in the rate of the reaction. Thereafter, in order to increase ee%, we started to screen different catalysts (Tab.2), using metal phosphate complexes[III], switching from a Brønsted acid catalysis to a Lewis acid catalysis. Still, we were only able to increase very slightly the ee%. We didn't try other BPAs (except entry 9), because **BPA4** is considered a very good enantioselective catalyst and also the most versatile we used it for the screening of other ketones.

During the catalyst screening we also tried different entries varying reaction conditions. It has been seen as keeping the reaction at 40 °C or a RT didn't show any change in ee%, and a slightly higher yield at higher temperature (Tab. 2, entries 2 and 4). We also tried to increase yield and enantioselectivity by adding an additive, a cationic resin to grant an easier proton transfer during the reaction but it seemed to be a bad choice in this case (tab. 2, entry 6), lowering both yield and ee%. The same behaviour has been observed by the absence of Molecular sieves (MS) (Tab. 2, entry 7).

[III] Characterisation of Metal complexes containing titanium has never been reported yet in the literature. Therefore, in this work we will referer to them simply as $Ti[BPAn]_2$

Tab. 2 – Initial screening of catalysts



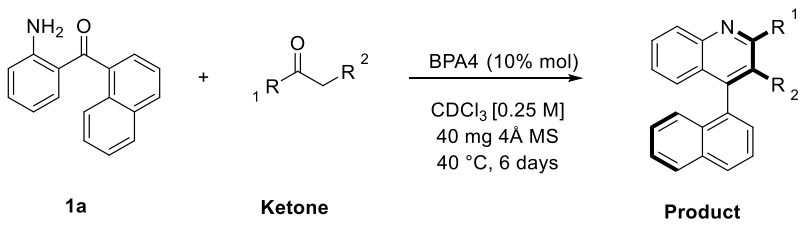
1a **2b** **3b**

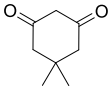
Entry	Catalyst	Yield (%)	ee (%)	τ
1	Sr[BPA4]$_2$	12	7	1 week
2	Ti[BPA4]$_2$	39	39	44 h
3[a]	Mg[BPA4]$_2$	25	32[b]	48h
4[a]	Ti[BPA4]$_2$	33	38	48h
5[c]	Ti[BPA4]$_2$	19	30	48h
6[c]	Mg[(R)-BPA4]$_2$[e]	7	21	84h
7	Mg[(R)-BPA4]$_2$[e]	n.a.	41	48h
8	BPA4	31	34	18h
9	(S)-BPA7	26	2	18h
10	Ca[BPA4]$_2$	33	24	4 days
11[a,f]	BPA4	38	34	25h

[a] Reaction at RT; [b] ee% pre-column = 35 [c] without Molecular Sieves (MS); [d] using 25mg of Cationic resin Amberlite IRC-50; [e] Catalyst prepared [f] Reaction under blue led light

3.3 Ketone screening

Tab. 3 – Ketone screening



Entry	Ketone	Product	Yield %	ee %
1[a,b]	**2a** 	**3a**	n.a.	5
2[b]	**2b** R^1=CH_3 R^2=COOEt	**3b**	31	36
3	**2c** R^1=CH_3 R^2=COOMe	**3c**	43	28
4	**2d** R^1=Ph R^2=COOMe	n.d.	n.d.	n.d.
5	**2e** R^1=CH_3 R^2=COO*i*-Pr	**3e**	48	31
6	**2f** R^1=CH_3 R^2=COOBn	**3f**	68	32
7	**2g** R^1=CH_2Ph R^2=H	n.d.	n.d.	n.d.
8	**2h** 	**3h**	63	33
9	**2i** R^1=CH_3 R^2=$COCH_3$	**3i**	29	31
10	**2j** R^1=CH_3 R^2=OH	**3j**	17	74
11	**2k** R^1=Ph R^2=OH	n.d.	n.d.	n.d.
12	**2l** R^1=Ph R^2=NO_2	n.d.	n.d.	n.d.

[a] 55°C; [b] 3 days reaction time; [c] RT

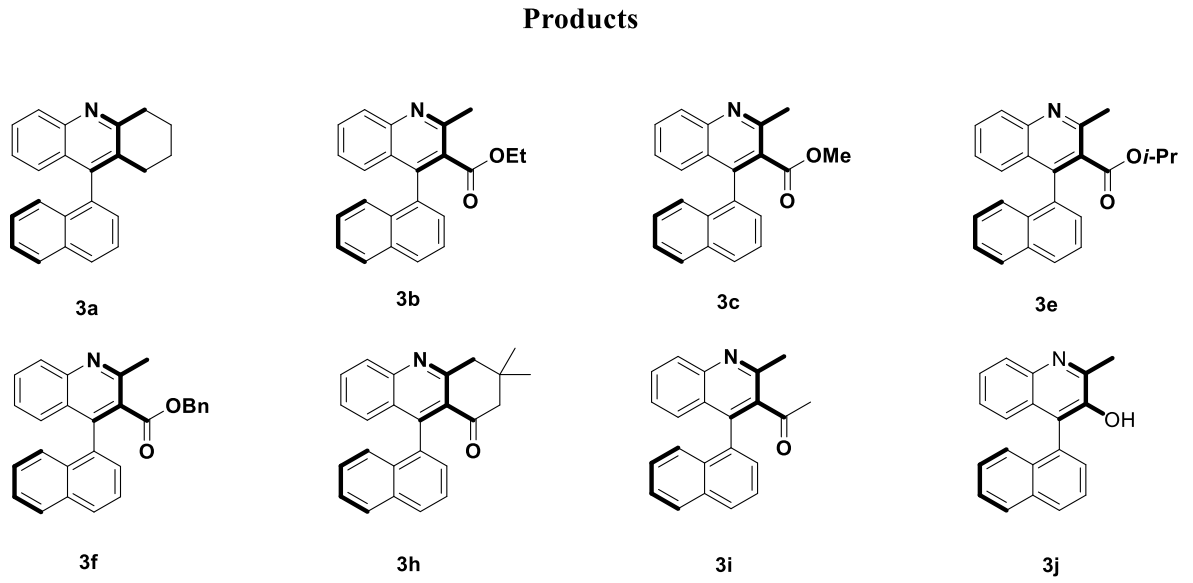


Fig. 39 - Various products isolated and confirmed by NMR analysis in this work

We were looking to find a ketone that it could possibly perform better in enantioselectivity, but also in reactivity, with BPAs. We thought that also finding an astonishing increase in reactivity could potentially lead to higher enantioselectivity by drastically lowering the temperature, as it can been observed in many examples in literature. We began the screening of different ketones. And after numerous entries, we achieved a good enantioselectivity with ketone **2j** (Tab. 3, entry 10). Comparing these results with those obtained with other ketones, the difference is abyssal. This behaviour could be easily explained, since the presence of a hydroxyl moiety probably favour a bidentate transition state with the BPA, granting a much better enantiotopic induction during the arene-forming transition state of the reaction (Fig. 40). Another plausible explanation, it may be always due to the hydroxylic group, because it could be a source of achiral proton, granting better ee% and yield as it has already been observed in other works in presence of phenol, although it is a much less acidic proton. Further studies on the catalytic mechanism, with the help of DFT calculations and NMR spectroscopy as well, are required to confirm any of this hypothesis and for a deeper understanding of the topic. After, we observed that increasing the steric hindrance of the group directly connected to the α-methylene, the yield has seen a proportional increase (Tab. 2, entries 3,5,6,7,8). This is due to a kind of gem-diol effect, where the presence of bulky substituents greatly increases the formation of the ring, because of the increasing chain strain.

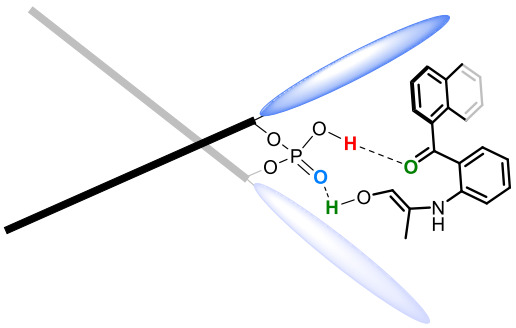


Fig. 40 - Bidentate transition state of a general BPA with hydroxyacetone (2l)

This effect is opposite to the presence of bulkier group to the other side of the ketone, where the presence of a phenyl group completely suppresses the reactivity of the reaction, probably not even allowing the formation of the initial imine. However, if an aldehyde is employed, such as propionaldehyde, the lack of steric hindrance on one side of the enamine probably enhance the stability of the Z-enamine, in order to completely suppress the reaction, since when this experiment was tried, no formation of products has been observed. One very interesting discovery was the observation of a by-product (Fig.41) in TLC in entry 9 with ketone **2i**. The by-product was then successfully isolated and immediately analysed and the structure confirmed by NMR spectroscopy. This is not only a by-product, but it is also an intermediate of the reaction. Then, we tried to use the intermediate as starting substrate of the reaction, possibly obtaining a better enantioselection beginning from that point of the reaction. Unfortunately, the isolated intermediate quickly performs hydrolysis to give starting reagents and it was impossible to deploy this new strategy.

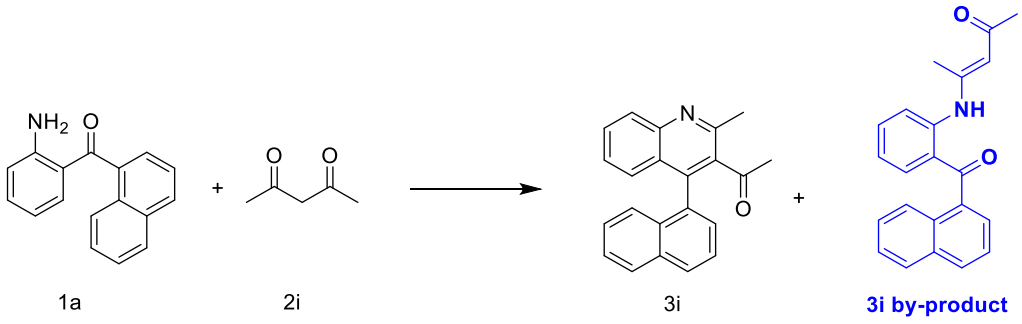
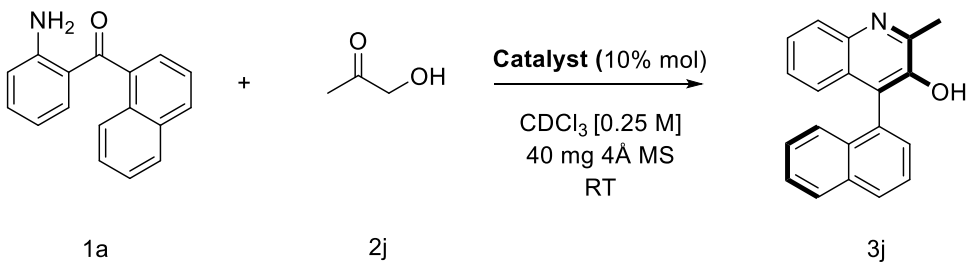


Fig. 41 - Encountered by-product in entry 9 during ketone screening

3.4 Catalyst screening

Tab. 4 – Catalyst screening



1a 2j 3j

Entry	Catalyst	Yield (%)	ee (%)	τ
1	Ti[BPA4]$_2$	18	80	6 days
2	Ca[BPA4]$_2$	17	10	40h
3	Mg[BPA4]$_2$	20	1	7 days
4	Sr[BPA4]$_2$	21	26	7 days
5	NTPA4	22	78	40h
6	BPA6	26	66	40h
7	NTPA5	18	33	40h
8	Ti[BPA6]$_2$	17	57	3 days
9	Ti((H8)-BPA6]$_2$	17	49	3 days
10	BPA4	17	74	3 days
11	NTPA1	n.a.	17	3 days
12	NTPA2	22	30	3 days
13	NTPA6	28	83	3 days
14	NTPA5	24	72	3 days
15	NTPA3	25	48	3 days
16[a]	BPA4	22	82	18h

[a] 12 equivalents of ketone

After the astonishing finding that hydroxyketone is a good suitable ketone for this synthesis, probably interacting with a bidentate approach during the transition state, we started the screening of different catalysts, in order to improve enantioselectivity. We then started to use

metal phosphate complexes, prepared in situ, hoping to improve ee%. We found out that **Ti[BPA4]$_2$** (Tab.4, entry 1) was able to conduct the reaction in good enantioselection, reaching 80% ee. This clearly shows how perfectly titanium performs well in this particular kind of reaction, indeed even with **2b** gave the highest enantioselection among other catalysts (Tab.2, entry 2). Trying to achieve a still better enantioselectivity, we continued to screen different catalysts, such as NTPAs. Their higher acidity didn't show to have any effect on the reaction. However, the employment of **NTPA6** (Tab.4, entry 13), a much simpler catalyst respect to metal complexes, surprisingly raised again the enantiomeric excess until 83. It is interesting also to notice as BPAs and respective NTPAs, do not show the same trend in order of enantioselection. Indeed, where **BPA4** gave better ee% over **BPA6** (Tab.4, entry 10 and 6), this behaviour is inverted using with respective **NTPA4** and **NTPA6** (Tab.4, entry 13 and 5). Predicting outcomes or trends with the use of metal complexes, it's unlikely predictable, in both orders of enantioselection and yields, and serendipity in these cases seems to be crucial to find the right metal and the right combination of BPAs as ligands.

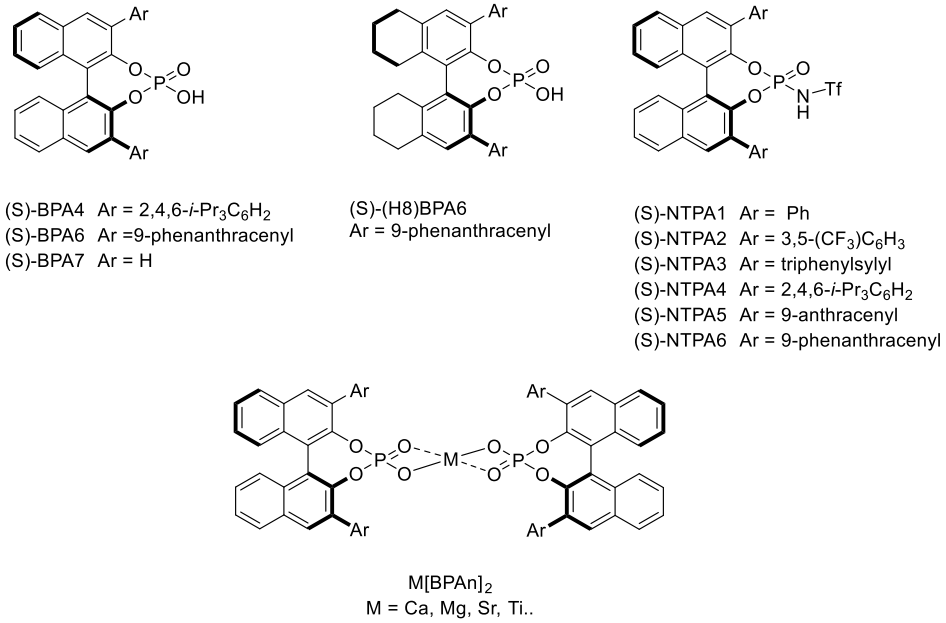


Fig. 42 - Different catalyst employed in this work

3.5 Optimisation of reaction conditions

Very content of this results obtained until this point, we started to evaluate reaction conditions in order to improve ee% and we found out that with an excess of the ketone **2j** of 12 equivalents (Tab. 4, entry 16), both yield and enantioselectivity greatly increased using **BPA4** (TRIP), maybe due to the increase of the achiral proton source from the hydroxyl moiety of **2j** (Fig.43).

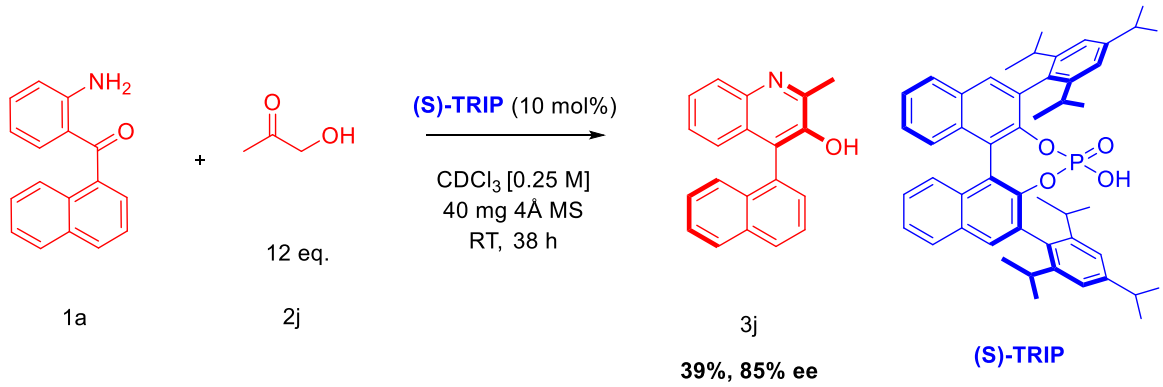


Fig. 43 - Orgnocatalytic Friedländer reaction with optimised reaction conditions

3.6 Future development

The study of the reaction explored in this work is still currently ongoing. New achievements are expected to be reached soon, such as optimisation of enantiomeric excess, yield and reaction times and especially those regarding the employment of this reaction with a greater number of substrates, allowing to cover a large scope for the synthesis of substituted atropisomeric quinolines.

4. Conclusions

At the end of this work it was possible to establish a new atroposelective route to obtain quinoline substrates up to 39% of yield and 85% of enantiomeric excess. This achievement was reached thanks the employ of a highly enantioselective Brønsted acid organocatalyst. This catalyst combined with this arene-forming reaction was the real pinnacle we were able to obtain, creating a new strategy for the synthesis of this peculiar substrates. Nonetheless, we were not able to reach high yields with short reaction times, as this problem encountered may be attributed to the higher activation energy required for the Friedländer reaction, respect to common organic reactions. The outcome of this discovery is expected to be in the field of drug development, increasing the number of methods for the synthesis of quinolines, with particular regard those with a chiral axis. Furthermore, the unprecedent employ of such organocatalysts has not been explored yet. Therefore, within this work we also showed how organocatalysts can be very versatile, even to be employed in this kind of reaction pathway. This work can be also recognised as another step forward in the exploration of chiral Brønsted acid organocatalysis.

5. Experimental session

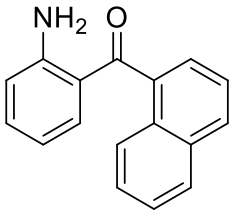
5.1 General information

The ^{1}H NMR spectra were recorded at 300 and 400MHz. The chemical shift (σ) are given in ppm relative to the signals of internal standard TMS. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[65] Organic solutions were concentrated under reduced pressure on a rotary evaporator. BPA and NTPA employed were synthesised following literature procedures.[66,67] The enantiomeric ratio was determined by Chiral HPLC analysis on an Agilent 1100-series instrumentation, using column Daicel Chiralpack AD-H or IC with *i*-PrOH/hexane as eluent mixture of solvents. HPLC traces of the products were compared to quasi racemic mixture obtained by an analogue reaction for the synthesis of the same product but using an achiral catalyst. All reactions were carried out in air and using undistilled solvent without any precautions to exclude moisture unless otherwise noted. Commercial grade reagents and solvent were used without further purification.

5.2 Synthesis of substrates

(2-aminophenyl)(naphthalen-1-yl)methanone (1a)

The product has been synthesized following a modified procedure from the literature.[68] All



1a

the glassware used for this reaction has been kept in stove for at least 12 h; the reaction was done under nitrogen; THF used was distilled. In a 250ml three-neck round bottom flask with refrigeration column was first prepared the Grignard reagent, by dropping with a funnel a solution 1.0 M of 1-naphtylbromide in THF (9.2 ml, 0.62 g, 30 mmol, 3 eq., in 30 ml of THF) on magnesium turning (pre-activated with HCl and stored in stove) under stirring. Add the solution slowly in a way to let the reaction auto sustain, observable by the formation of bubbles, with the help of a heat gun. Then, the reaction was kept at 0 °C with an ice bath, and then a solution 1.0 M of aminobenzonitrile (1.2 g, 10 ml, 1 eq., in 10 ml of THF) was added drop wisely. The bath was then removed, and the reaction was placed at 40 °C to react for 24h. After the reaction was quenched pouring directly ice and

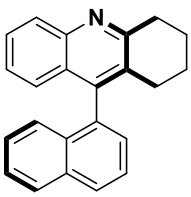
then adding 10 ml of HCl 6M. After we neutralised with Na_2CO_3, we added ethyl acetate and we separated the two layers. The crude product has been purified with flash chromatographic column (hexane/ethylacetate 9:1) and then dried overh $MgSO_4$, to afford 65% of yield of product as a yellow powder.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 – 7.83 (m, 3H), 7.55 – 7.40 (m, 4H), 7.30 – 7.18 (m, 2H), 6.74 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.45 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.62, 151.00, 138.36, 135.17, 134.92, 133.54, 130.58, 129.75, 128.28, 126.81, 126.25, 125.63, 125.58, 124.61, 119.01, 117.06, 115.78.

5.3 General procedure (GP1) for the catalytic reaction for the synthesis of product 3

In a 2 ml HPLC vial, was placed first the catalysts in 10 mol% (0.005 mmol, 0.1 eq.) with the magnetic anchor, then in sequence were placed 12.4 mg of substrate 1a (0.05 mmol, 1 eq.), 40 mg of 4 Å Molecular Sieves (MS), ketone 2 (0.1 mmol, 2 eq.), 0.2 ml of solvent. Then the vial was closed with its cap and let to react for determined temperature and time, as specified in the screening tables reported. After, the reaction goes through a plug to quench the reaction, eluting with 20 ml of CH_2Cl_2/EtOAc 1:1, and then purified by flash chromatographic column, as specified underneath for each product in GP1.

9-(naphthalen-1-yl)-1,2,3,4-tetrahydroacridine (3a)

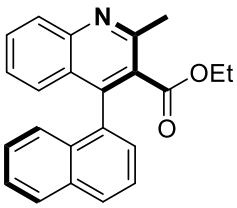


3a

The products 3a was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8.5:1.5) to give a yellow product. HPLC conditions: AD-H, 1.0 ml/min, hexane/*i*-PrOH 90:10, 25 °C, R_T of enantiomers are at 5.53 and 6.06 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.61 (t, *J* = 7.7 Hz, 1H), 7.36 – 7.17 (m, 6H), 7.13 – 6.94 (m, 2H), 6.73 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.44 (td, *J* = 7.5, 6.9, 1.1 Hz, 1H), 1.23 (d, *J* = 7.5 Hz, 4H), 1.17 (d, *J* = 6.7 Hz, 2H), 0.92 (d, *J* = 6.8 Hz, 2H).

ethyl-2-methyl-4-(naphthalen-1-yl)quinoline-3-carboxylate (3b)

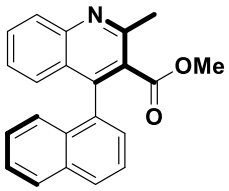


3b

The products 3b was synthesized following GP1 and then purified by flash chromatographic column (hexane/EtOAc 8.5:1) to give a yellow product. HPLC conditions: AD-H, 1.0 ml/min, hexane/*i*-PrOH 95:5, 25 °C, R_T of enantiomers are at 6.26 and 6.84 minutes.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.97 (dt, *J* = 8.4, 1.1 Hz, 1H), 7.93 (ddd, *J* = 8.1, 1.3, 0.6 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.39 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.32 (dtd, *J* = 8.0, 6.7, 1.3 Hz, 2H), 7.27 – 7.21 (m, 2H), 3.81 (qq, *J* = 10.7, 7.1 Hz, 2H), 2.86 (s, 3H), 0.51 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.95, 155.04, 147.18, 145.75, 133.37, 133.20, 132.07, 130.59, 128.97, 128.58 (d, *J* = 4.9 Hz), 128.40, 128.11, 127.30, 126.88, 126.66, 126.48, 126.27, 126.19, 125.95, 125.04, 61.07, 23.78, 13.11.

Methyl-2-methyl-4-(naphthalen-1-yl)quinoline-3-carboxylate (3c)

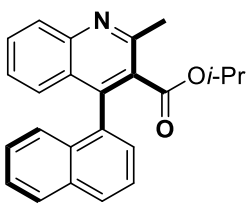


3c

The products 3c was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product. HPLC conditions: AD-H, 1.0 ml/min, hexane/*i*-PrOH 90:10, 25 °C, R_T of enantiomers are at 6.70 and 7.46 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.5 Hz, 1H), 7.95 (dd, *J* = 11.0, 8.2 Hz, 2H), 7.72 (ddd, *J* = 8.1, 6.5, 1.3 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.49 (ddd, *J* = 7.7, 6.4, 1.2 Hz, 1H), 7.40 (dd, *J* = 6.8, 1.1 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.26 – 7.19 (m, 2H), 3.33 (d, *J* = 0.6 Hz, 3H), 2.84 (s, 3H).

methyl-2-methyl-4-(naphthalen-1-yl)quinoline-3-carboxylate (3e)

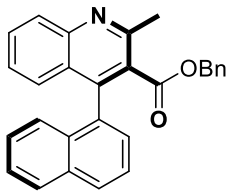


3e

The products 3e was synthesized following GP1 and then purified by flash chromatographic column (height 18 cm, width 2 cm hexane/EtOAc 9:1) to give a yellow product. HPLC conditions: AD-H, 1.0 ml/min, hexane/*i*-PrOH 90:10, 25 °C, R_T of enantiomers are at 5.49 and 5.88 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.00 – 7.89 (m, 2H), 7.70 (ddd, *J* = 8.1, 6.4, 1.5 Hz, 1H), 7.56 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.6, 1.4 Hz, 1H), 7.39 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.32 (dtd, *J* = 7.7, 6.5, 1.3 Hz, 2H), 7.27 – 7.19 (m, 2H), 4.74 (hept, *J* = 6.3 Hz, 1H), 2.85 (s, 3H), 0.82 (d, *J* = 6.3 Hz, 3H), 0.42 (d, *J* = 6.2 Hz, 3H).

benzyl-2-methyl-4-(naphthalen-1-yl)quinoline-3-carboxylate (3f)

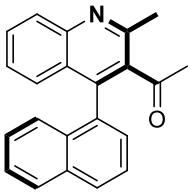


3f

The products 3f was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product. HPLC conditions: IC, 1.0 ml/min, hexane/*i*-PrOH 90:10, 25 °C, R_T of enantiomers are at 8.48 and 10.49 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.19 – 8.08 (m, 1H), 7.98 – 7.89 (m, 2H), 7.70 (ddt, *J* = 7.3, 5.7, 1.3 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 2H), 7.37 (dt, *J* = 7.1, 1.0 Hz, 2H), 7.33 – 7.14 (m, 5H), 7.13 – 7.05 (m, 2H), 6.68 – 6.61 (m, 2H), 4.88 – 4.66 (m, 2H), 2.83 (d, *J* = 0.9 Hz, 3H).

3,3-dimethyl-9-(naphthalen-1-yl)-3,4-dihydroacridin-1(2H)-one (3h)

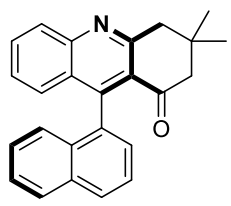


3i

The products 3h was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product. HPLC conditions: AD-H, 1 ml/min, hexane/*i*-PrOH 95:5, 25 °C, R_T of enantiomers are at 10.9 and 14.5 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.17 – 8.07 (m, 1H), 7.98 (ddt, *J* = 13.3, 8.2, 0.9 Hz, 2H), 7.74 – 7.67 (m, 1H), 7.63 – 7.55 (m, 1H), 7.55 – 7.47 (m, 1H), 7.40 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.32 – 7.24 (m, 2H), 7.20 (ddd, *J* = 8.3, 1.5, 0.6 Hz, 1H), 2.75 (d, *J* = 5.8 Hz, 3H), 1.88 (s, 3H).

(1-(2-methyl-4-(naphthalen-1-yl)quinolin-3-yl)ethan-1-one (3i)

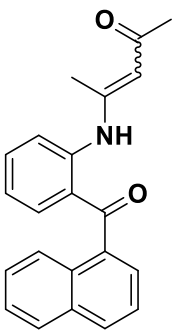


3h

The products 3i was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product. HPLC conditions: AD-H, 1 ml/min, hexane/*i*-PrOH 95:5, 25 °C, R_T of enantiomers are at 10.80 and 14.29 minutes.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.96 (tt, *J* = 7.4, 1.1 Hz, 2H), 7.75 (ddd, *J* = 8.4, 6.0, 2.3 Hz, 1H), 7.59 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.44 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.32 – 7.18 (m, 4H), 7.03 (dq, *J* = 8.4, 0.9 Hz, 1H), 3.34 (s, 2H), 2.62 – 2.37 (m, 2H), 1.17 (d, *J* = 3.6 Hz, 6H).

4-((2-(1-naphthoyl)phenyl)amino)but-3-en-2-one (3i by-product)

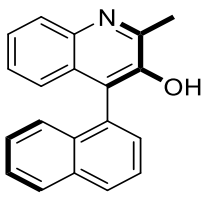


3i by-product

The by-product 3i was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.50 (s, 1H), 8.54 – 8.29 (m, 1H), 8.02 – 7.94 (m, 1H), 7.91 – 7.81 (m, 1H), 7.57 – 7.50 (m, 5H), 7.43 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.26 – 7.20 (m, 2H), 4.98 (s, 1H), 1.90 (s, 3H), 1.86 (s, 3H).

2-methyl-4-(naphthalen-1-yl)quinolin-3-ol (3j)



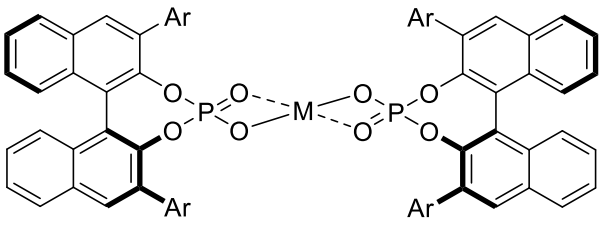
3j

The products 3j was synthesized following GP1 and then purified by flash chromatographic column (height 12 cm, width 2 cm, hexane/EtOAc 8:2) to give a yellow product. HPLC conditions: AD-H, 1 ml/min, hexane/*i*-PrOH 80:20, 25 °C, R_T of enantiomers are at 6.7 and 11.0 minutes.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.78 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.01 (ddd, *J* = 7.7, 1.9, 0.7 Hz, 1H), 7.94 (dt, *J* = 8.3, 1.2 Hz, 2H), 7.62 – 7.48 (m, 5H), 7.44 – 7.40 (m, 1H), 6.99 – 6.91 (m, 1H), 1.26 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.17, 169.59, 141.57, 137.04, 135.38, 134.81, 133.63, 131.19, 130.63, 128.54, 128.53, 127.39, 127.14, 126.61, 125.30 (d, *J* = 1.3 Hz), 124.42, 123.24, 122.16, 120.86, 25.55.

5.4 General procedure (GP2) for in situ preparation of BPA metal complexes

The product has been synthesized following a modified procedure from the literature.[69] In a HPLC vial were placed 0.005 mmol of Metal (1 eq.) and 0.01 mmol (2 eq.) of BPA ligand. Then it was added 1.5 ml of a solution of MeOH/CH_2Cl_2 in ratio 1:1 and let to react under stirring for 2 h. Then, the solvent was evaporated under flux of nitrogen and placed under vacuum pump, it was added 1 ml of CH_2Cl_2 and evaporated under flux of nitrogen and placed under vacuum once more. After the catalyst was prepared as described, the procedure for the catalytic Friedländer reaction continued as described for GP1.



$M[BPAn]_2$
M = Ca, Mg, Sr, Ti..

Fig. 442 - Metal phosphate complex

6. References

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