

Stereoselective Organocatalytic Addition of Nucleophiles to Isoquinolinium and 3,4-dihydroisoquinolinium Ions: A Simple Approach for the Synthesis of Isoquinoline Alkaloids

Andrea Gualandi · Luca Mengozzi ·
Elisabetta Manoni · Pier Giorgio Cozzi

Received: 25 September 2014 / Accepted: 1 October 2014 / Published online: 31 October 2014
© Springer Science+Business Media New York 2014

Abstract The frequent occurrence of chiral 1-substituted-1,2,3,4-tetrahydroisoquinoline ring systems in a large number of alkaloids, possessing a broad spectrum of biological and pharmaceutical properties, has prompted out a considerable interest in their synthesis. Economical and valuable stereoselective processes based on organocatalytic transformations represent a new avenue for approaching isoquinoline alkaloids with efficiency and creativity.

Keywords Asymmetric catalysis · Homogeneous catalysis · Green chemistry

1 Introduction

Tetrahydroisoquinoline derivatives are structural motifs often occurring in natural products such as isoquinoline alkaloids, the largest group of alkaloids (Fig. 1) [1]. The tetrahydroisoquinoline skeleton is a basic building block of various types of alkaloids including benzyloisoquinolines (among them papaverine, hygenamine, laudanosine and micovarium), protopines, benzo[c]phenanthridines, protoberberines, naphthylisoquinolines, bisbenzyloisoquinolines (berbamine, dauricine, fangchinoline, pavines and isopavines), phtalide isoquinoline (bicuculline), emetine group, aporphinoid alkaloids, morphine, colchicines, and many

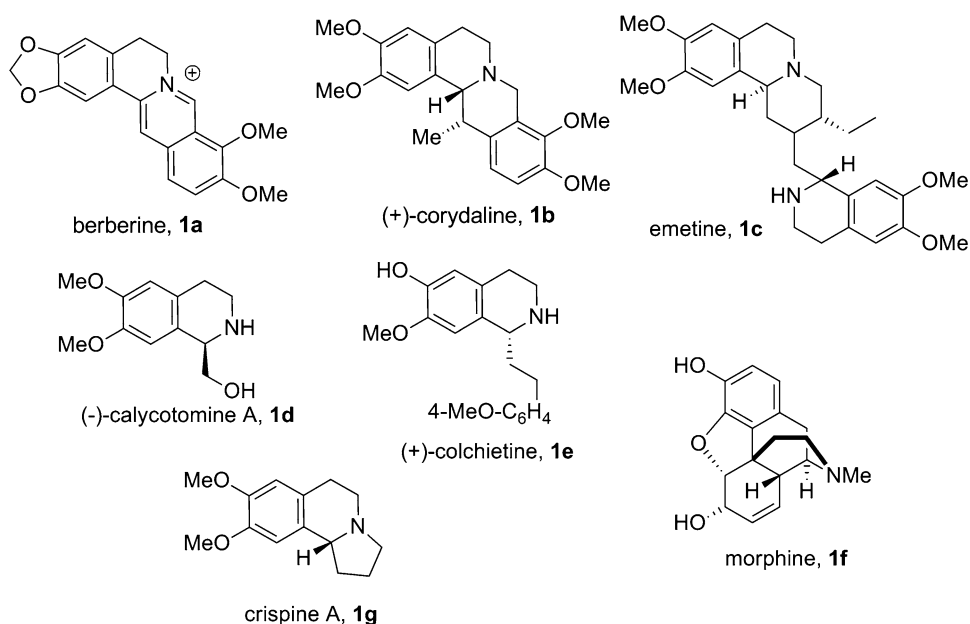
others. These natural products are found in a great variety of plants and vegetables and they often exhibit a range of pharmacologically and biological activities such as anti-tumor, antibiotic, antiviral anti-inflammatory, anticoagulation, and bronchodilation [2]. Therefore, the frequent occurrence of chiral 1-substituted-1,2,3,4-tetrahydroisoquinoline ring systems in a large number of alkaloids possessing a broad spectrum of biological and pharmaceutical properties, has led to significant increasing interest in their synthesis [3].

To date, most of the traditional synthetic approaches are based on procedures employing chiral building blocks, chiral auxiliaries, or chiral reagents [4]. In order to address issues related to economic and ecologically valuable processes, in recent years considerable effort has been directed towards the development of catalytic stereoselective transformations to obtain enantioenriched 1-substituted-tetrahydroisoquinoline frameworks with a high level of selectivity. As the biological activity of such alkaloids is often displayed by a specific stereoisomer [5], many efforts have been directed to asymmetrically functionalize isoquinolines. Many methodologies focus on the introduction of a substituent at the C1 position [6], as this stereocenter is present in most of the natural products in this compound class [7]. This chemistry was first explored by Reissert [8] using chloroformate or benzoyl chloride to activate either isoquinolines or quinolines which react via the corresponding acyl iminium ions. The enantioselective catalytic version of the Reissert reaction was introduced by Shibasaki a number of years later [9], indicating the difficulties encountered during the reaction development. Following this, a number of enantioselective metal catalysed methodologies were described [10] for these molecules, however with only moderate success. Another important approach to consider for these compounds is the efficient

A. Gualandi (✉) · L. Mengozzi · E. Manoni · P. G. Cozzi (✉)
Dipartimento di Chimica “G. Ciamician”, ALMA MATER
STUDIORUM, University of Bologna, Via Selmi 2,
40126 Bologna, Italy
e-mail: andrea.gualandi10@unibo.it

P. G. Cozzi
e-mail: Piergiorgio.cozzi@unibo.it

Fig. 1 Some pharmaceutically relevant 1-substituted tetrahydroquinolines



asymmetric hydrogenation [11] and asymmetric transfer hydrogenation [12] of 1-substituted-3,4-dihydroisoquinolines (DHIQ). These methodologies are able to conjugate operational efficiency with atom economy. However, despite the advances in asymmetric hydrogenations and the maturity of the technique, only relatively few catalytic systems operating with high selectivity have been reported in the literature, and the asymmetric reduction of 1-aryl-substituted-3,4-DHIQs has only been described in few cases and it is still considered a challenge in the field of asymmetric hydrogenation [13]. The major problem associated with the cited methodologies is the use of metals. Although the impact of metal-based catalysts on chemical synthesis cannot be understated, expensive methodologies and toxicity are often associated with the use of metals. The advent of organocatalysis in 2000 [14, 15] introduced new concepts in catalysis, making possible to design new processes with different experimental procedures, allowing the development of complementary methods able to reduce costs, energy, and chemical waste. The benefits associated with organocatalysis rely on the use of organic molecules, moisture and oxygen stable, and prepared from available precursors, often aminoacids, alkaloids, or from other natural sources already available as single enantiomers. These organic catalysts, or as are now called “organocatalysts” are able to play a specific role in the reaction. It is now well established that organocatalysts are able to promote a reaction and transmit the stereochemical information through generic modes of catalyst activation, induction and reactivity. In a such generic activation mode the reactive specie, that can participate in many reaction types, is formed by the interaction of the organocatalyst with a

functional group (e.g.: ketone, aldehyde, imine, nitro, ester or an unsaturated Michael acceptor) present in the reaction mixture, in a highly organized and predictable manner. In a pioneering and inspiring paper [16] activation modes in organocatalysis have been classified, helping many new players to enter into this field and accelerating the exponential growth of the subject. The paradigm of generic activation modes allows straightforwardly the design on many new enantioselective reactions. Indeed, more than 100 organocatalytic reactions were quickly discovered from the use of only five or six activation modes. The small number of activation modes in the field of organocatalysis cannot force readers to think that all mechanisms are established and that these general principles are fully understood [17]. On the contrary more detailed mechanistic investigations and analysis will be useful for solving open problems related to some drawbacks in organocatalysis, such as the low turnover numbers that might limit the potential uses of organocatalysis for industrial applications. In our overview we will summarize the recent methodologies that are using stereoselective organocatalysis in the addition of nucleophiles to 3,4-dihydroisoquinolinium and isoquinolinium ions. Basically, an activation mode of organocatalysis is creating nucleophiles in the presence of activated electrophiles. In the end, the organocatalytic reaction is determined by the interaction of nucleophiles with electrophiles. The reaction rate can be rationalized and even predicted using the concepts developed by Mayr with his scale of reactivity [18]. The Mayr’s table can be therefore quite useful to understand and rationalize the behaviour of organocatalysis, particularly when additives and tailored reaction conditions are employed. We will try

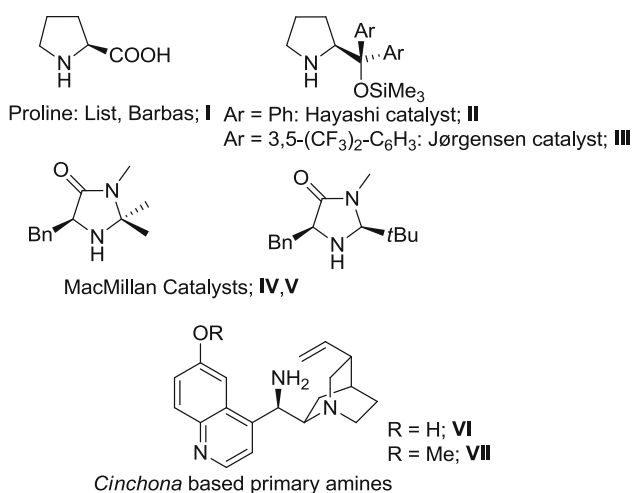


Fig. 2 Structures of the principal organocatalysts

to underline simple and useful points for this review, in a brief introduction on organocatalytic activation modes and their connection to the Mayr's scale. Few organocatalytic activation modes (enamine catalysis, hydrogen bond catalysis, and carbene catalysis) will be generally introduced and described in relation to addition to iminium and isoquinolinium ions; through this reaction useful intermediates were prepared for the synthesis of isoquinoline alkaloids or related compounds, that will be the main topic of this review.

2 Organocatalytic Activation Modes and Their Role in the Reaction with Iminium and Isoquinolinium Ions

Organocatalytic procedures and studies have grown exponentially in the last decade, and organocatalytic modes of activation are also currently employed in the synthesis of complex natural products [19] and in drug development [20]. Most of the stereoselective organocatalytic reactions are based on the basic activation modes of enamino- [21] and iminium catalysis [22], as displayed by selected secondary amines bearing a pyrrolidine core [23]. Also primary amines derived from *Cinchona* alkaloids were used in many reactions due to their properties to control nucleophilic addition [24]. To these secondary and primary amines the nickname "working-horses" [25] of enantioselective organocatalysis was assigned. Proline, proline derivatives, *Cinchona* based amine, and other five-member heterocycles (structures **I–VII**, Fig. 2) have found an extensive use in organocatalysis field. Three catalysts are worth to mention, in particular the most commonly used diaryl-pyrrolidine derivatives, the Hayashi and Jørgensen organocatalysts **II–III** [26], the MacMillan type catalysts

IV and **V** and the *Cinchona* primary amines **VI–VII**. These catalysts are normally employed when enamine or iminium activation modes are designed for the desired transformation.

2.1 Enamine Activation Mode: Enamine-Activated Reactions

When proline and proline derived catalysts are employed, the catalytic cycle depicted in Fig. 3 represents the generally accepted mechanism [27] for enamine-activated reactions. A key-step, not necessarily the rate-determining step, is the attack of an electrophile **4** to the enamine **3**. For this organocatalytic reaction the most comprehensive nucleophilicity and electrophilicity scales, presently available, can be also applied. The scale is based on Eq. 1, where electrophiles are characterized by one solvent-independent parameter *E*, and nucleophiles are characterized by two solvent-dependent parameters, the nucleophilicity parameter *N* and the sensitivity parameter *s_N* [28].

$$\log k (20^\circ\text{C}) = s_N(E + N) \quad (1)$$

The scale was constructed by reference electrophiles (benzhydrylium ions and structurally related quinone methides) and covers a reactivity range of 32 orders of magnitude. With these different reactive electrophiles Mayr and co-workers have been able to compare nucleophiles of widely differing structure and reactivity [29]. The reactivity scales could be employed for designing syntheses by applying the Mayr's rule of thumb [30] that states that "an electrophile can be expected to react with nucleophiles at room temperature when $E + N > -5$ ". The Jørgensen-Hayashi catalysts **II–III** have previously been employed to catalyse reactions of aldehydes and ketones with weak electrophiles, (for example β -nitrostyrene, $E = -13.9$), because they afford more nucleophilic enamines compared to Macmillan catalysts **IV–V**. Indeed, these less basic imidazolidinones, which yield the less nucleophilic intermediate enamines, are suitable catalysts for reactions with stronger electrophiles, such as stabilized carbenium ions [31].

In most of the reactions examined in this review, nucleophilic enamines are poured to react with electrophilic iminium ions and isoquinolinium ions. Although the isoquinolinium electrophilic parameter has not been determined yet, Klussmann [32, 33] has recently estimated the electrophilicity parameter *E* of a *N*-phenyl-3,4-dihydroisoquinolinium **6**, a key intermediate in many organocatalytic nucleophilic additions described in literature (Fig. 4). The value estimated by Klussmann between -8 and -9 , is in line with electrophilicity parameters determined by Mayr and co-workers for comparable iminium ions, which lie between -5 and -10 [34].

Fig. 3 Catalytic cycle in enamine catalysis and nucleophilicity scale of chiral enamines obtained with the organocatalyst **II**, **IV** and **V**

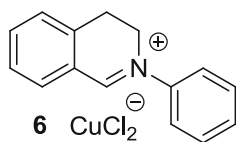
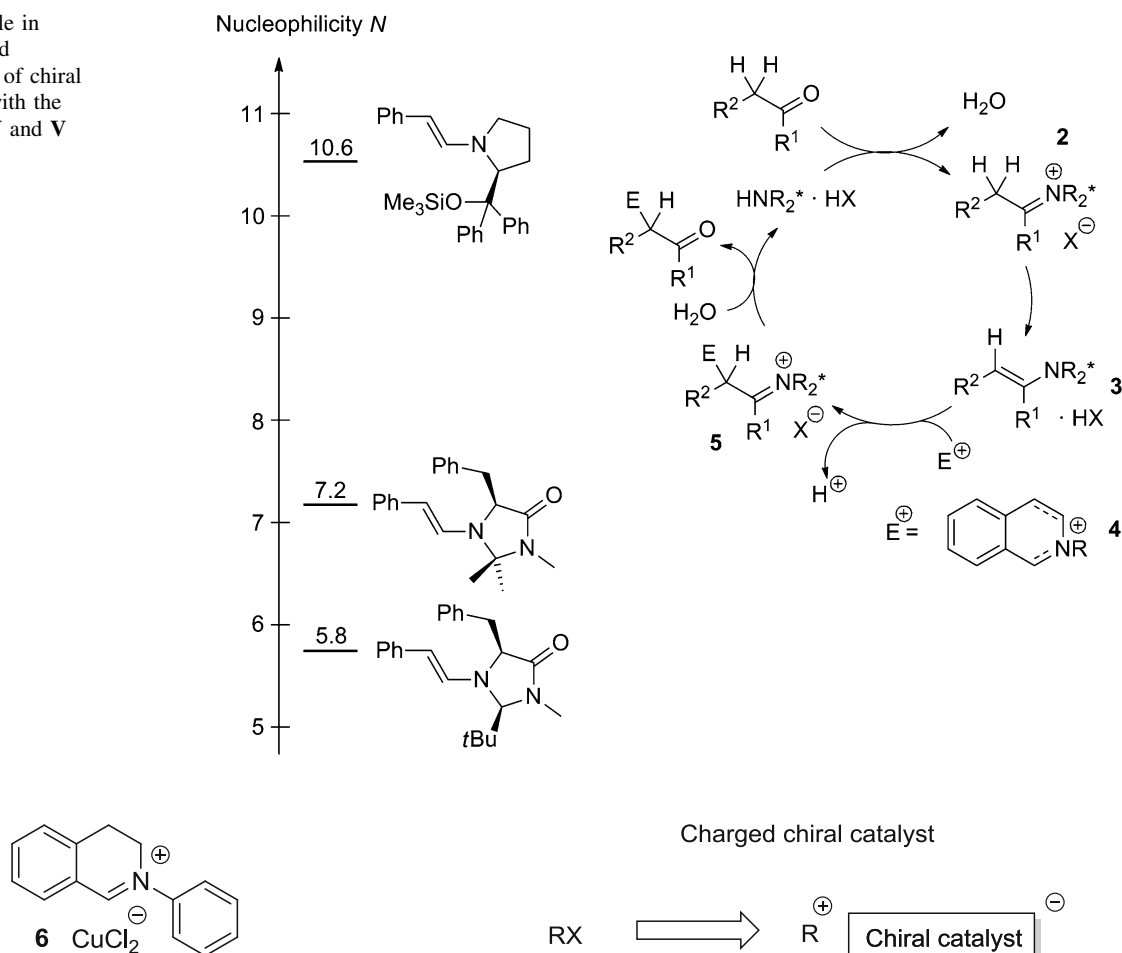


Fig. 4 Intermediates characterized by Klussmann in the oxidative nucleophilic reaction of *N*-phenyl-3,4-dihydroisoquinolinium

From the electrophilicity value determined by Klussmann it is possible to rationalize many reactions summarized in this review. It is worth mentioning that due to the low electrophilicity of the iminium derivative, it is simple to predict that only the most nucleophilic enamine derived from Hayashi-Jørgensen catalyst will be able to react with intermediates of type **6**.

2.2 Hydrogen Bond Activation Mode: the Asymmetric Counteranion-Directed Catalysis (ACDC) Ion Pairing

Organocatalyst can be designed for inducing an ion pair formation. The non-covalent binding of a chiral neutral catalyst to the intermediate ion pair (Fig. 5) can be used to transmit chiral information. Both the anion or the cation can be surrounded by the chiral ligand, and neutral or charged catalysts could be employed.

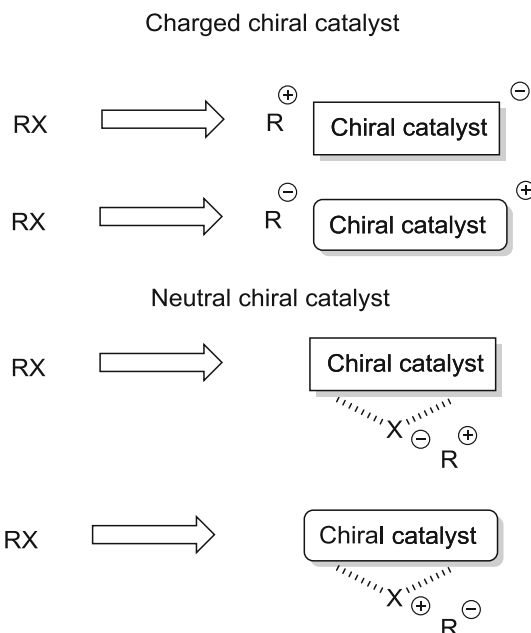
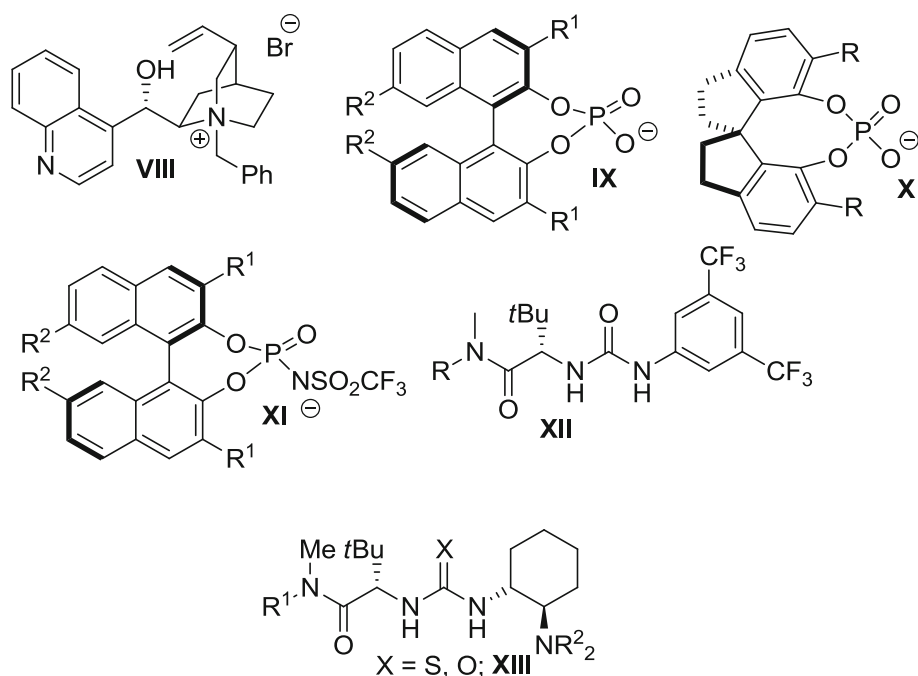


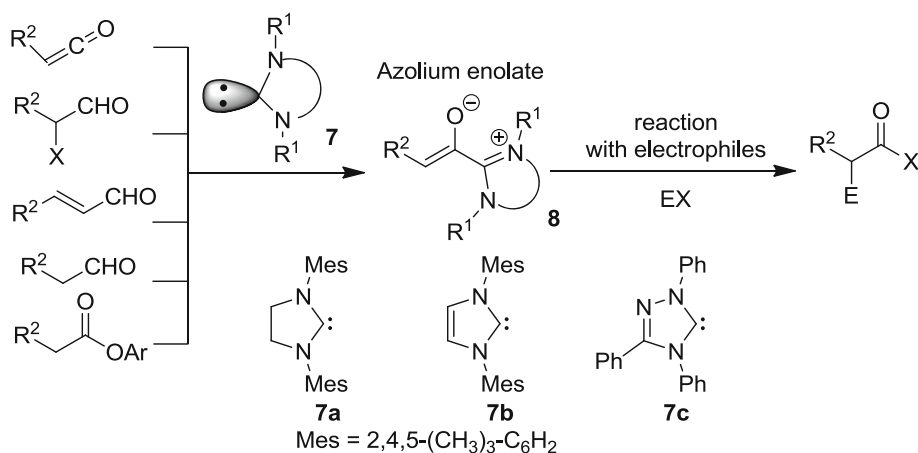
Fig. 5 Different type of chiral catalysts capable of ion-pairing

Catalysts based on designed hydrogen-bond donor groups are embracing weak interactions. Through these interactions the catalysts are able to induce ion-pairing. These interactions are inherently less directional making the transmission of the chiral information by the catalyst

Fig. 6 Chiral catalysts used as chiral counter ions



Scheme 1 Azolium enolate obtained by carbene precursors



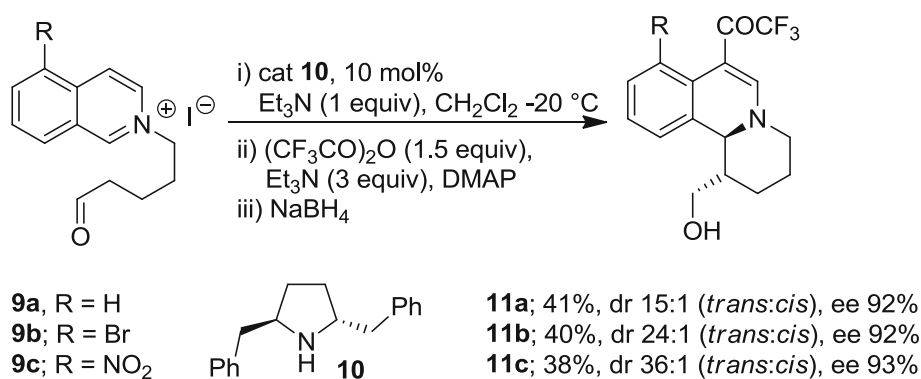
an hard task. However, by the recognition of key elements the design of these catalysts has obtained extraordinary success, by combining elements capable of inducing specific attractive or repulsive interactions in the step in which the stereoselective information is transferred. Of course, there is a quite strict connection between this activation mode and the way in which substrates are activated by enzymes [35]. Also in this field “privileged” [36] structures of small molecules emerged (Fig. 6). In the review we will illustrate the design principles and the structural importance of the elements present in the catalysts, in the case of activation of iminium ions.

2.3 Carbene Catalysis

N-heterocyclic carbenes (NHCs, **7**) have been extensively employed since their discovery as catalysts for C–C bond-forming reactions [37]. In organocatalytic reactions with ketenes, aldehydes, and esters they give rise to the formation of azolium enolates equivalents of ester enolates (Scheme 1) [38]. Such enolates are generally generated in situ and they are very useful nucleophiles in many reactions [39].

The nucleophilicity values of the NHCs were measured by Mayr [40] and do not differ from those of other organocatalysts (DABCO, DMAP, Ph_3P). However, these

Scheme 2 Alkylation of isoquinolinium salts promoted by the organocatalyst **10**



nucleophilicity differences are crucial when they are evaluated for organocatalytic reactions. For example, the triazolylidene compound **7c** has a considerably lower nucleophilicity compared with the imidazolylidene **7b**, caused by the inductive electron withdrawal due to the extra nitrogen in the triazole ring. All NHCs are significantly stronger Lewis bases than PPh₃, DMAP, and DABCO. Saturated NHCs like **7a** are rarely used as organocatalysts and this was explained by Mayr, taking into account the nucleophilicity order of the deoxy-Breslow intermediates [41]. By using the rule of thumb that combination of electrophile–nucleophile may give positive reactions at room temperature when $E > -5$, and considering that the N values for the enolate carbon of the azolium enolates **8** are between 14.4 and 15.9, it is possible to predict that they will react with N -activated imines ($-11.5 > E > -15.1$) and iminium ions ($E = -10$).

3 Organocatalytic Addition of Nucleophiles to Isoquinolinium Ions

The isoquinoline framework is present in a large number of naturally occurring and synthetic biologically active 1,2-dihydroisoquinolines and the closely related 1,2,3,4-tetrahydroisoquinolines derivatives [42]. One of the recurring features of these compounds is the presence of a stereogenic center located adjacent to the nitrogen atom (Fig. 1). As we have briefly commented catalytic stereoselective synthetic methodologies for the formation of chiral isoquinoline derivatives was only described in few approaches [43]. The pioneering use of organocatalysis employing chiral C₂-symmetric secondary amines for the diastereo- and enantioselective annulation reaction of 2-(5-oxopentyl)isoquinolinium **9** was described by Jørgensen [44]. The key concepts studied in this work were the use of isoquinolinium salts [45] in combination with the enamine catalysis. This reaction gives rise to the formation of optically active 1,2-dihydroisoquinoline derivatives **11** that contain two adjacent stereocenters together with a carbonyl

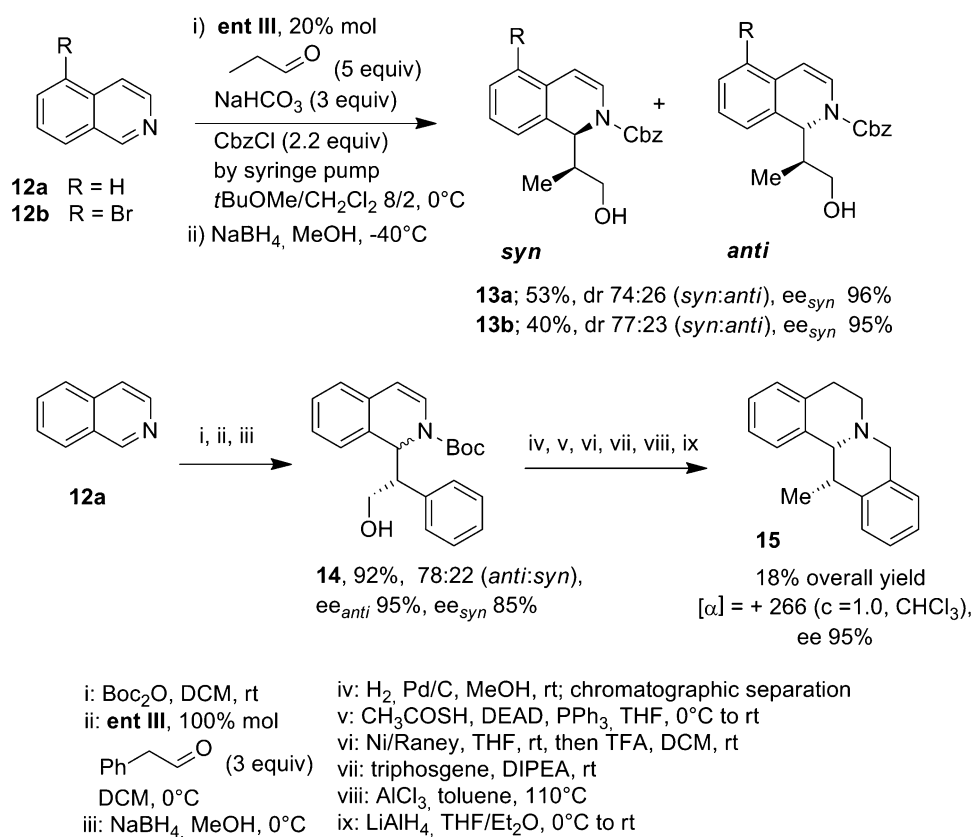
group suitable for further chemical transformations. The substrates for the intramolecular annulations reaction are stable isoquinolinium salts. (Scheme 2).

Quite remarkably it was reported that the corresponding intermolecular reaction, activating isoquinoline with ethyl chloroformate in presence of 3-methylbutyraldehyde and various organocatalysts, gave low yield and stereoselectivity. No further details are furnished, but probably the ethyl chloroformate is deactivating the organocatalyst by formation of the corresponding carbamate. In addition, as we have previously noted, the appropriate organocatalyst needs to be employed, because of the quite low electrophilicity of the iminium salt. Indeed Jørgensen is using chiral C₂ symmetric pyrrolidine **10** for the reaction. Nucleophilicity of the enamines obtained with this organocatalyst are in the same order to those obtained with **I–III** (Scheme 2). As in the catalytic cycle iodidric acid (HI) is formed as by-product, it is necessary to use a base (Et₃N) in order to recycle the catalyst. It is also worth mentioning that the products are quite unstable and were isolated after trifluoroacetylation and reduction. The optimized conditions for the catalytic diastereo- and enantioselective reaction gave good to high conversions (70–100 %), high diastereoselectivity (up to 98:2) and excellent enantioselectivity (85–96 % ee) for neutral or electron-poor substrates. No further transformation of the products to alkaloids or natural products were described in the paper.

Cozzi and co-workers [46] recently described the activation of various isoquinolines **12** by Boc₂O or CbzCl in an organocatalytic alkylation promoted by the organocatalyst **ent III** (Scheme 3).

An important key feature of the process is the slow addition of the activating agent that is avoiding the acylation of the catalyst. The scope of the reaction is broad respect to isoquinolines and aldehydes, and the products **13** were isolated in moderate yields after reduction, avoiding further reaction. The Boc or Cbz adduct can be easily deprotected and transformed in useful intermediates. The major diastereoisomer was obtained in *syn* or *anti* configuration in function of the reaction solvent, giving the

Scheme 3 Activation of isoquinoline by CbzCl and total synthesis of a protoberberine alkaloid



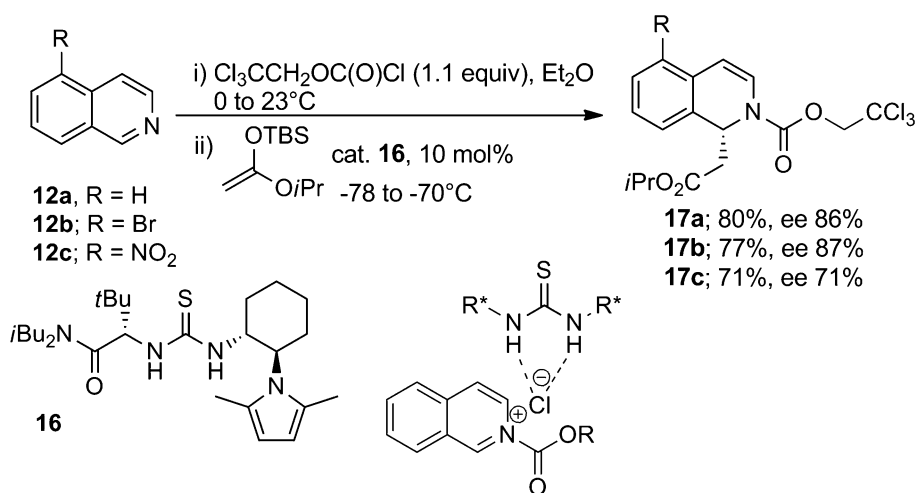
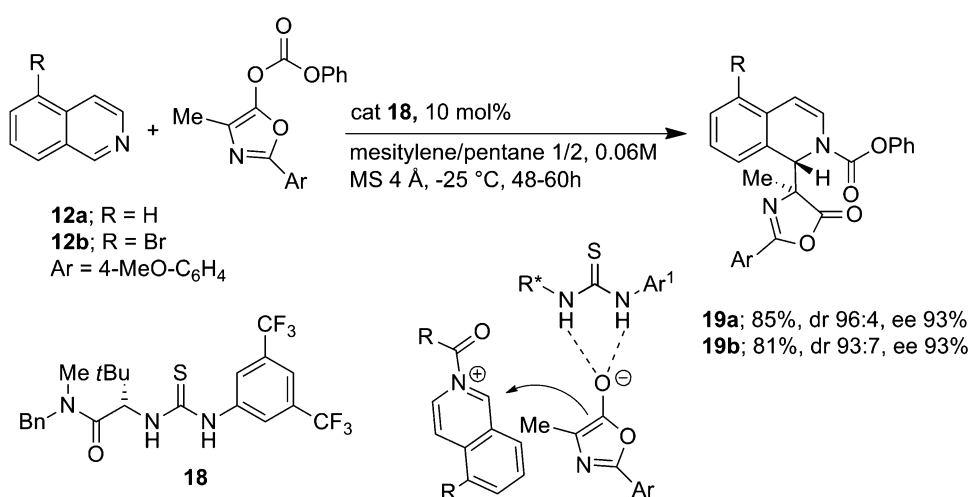
opportunity to select the desired stereoisomer depending on the reaction conditions. The *anti* diastereoisomer was favoured in CH₂Cl₂, while *t*BuOMe favoured the *syn* diastereoisomer. The first total synthesis of a 13-alkyl-protoberberine alkaloid (**15**) was described in the paper by the use of an enantioselective organocatalytic reaction as key step (Scheme 3). In order to improve stereoselectivity and yield the step was performed using a stoichiometric amount of chiral catalyst **ent III**, but the catalyst can be recovered as its stable enamine and reused for another batch without any problem. Furthermore, the compounds obtained are showing interesting anticancer properties [47], and the aldehydes obtained can be reacted by Wittig reaction to access other interesting protoberberine alkaloids [48]. An intermolecular, organocatalytic addition of silyl enolates to *N*-acylisoquinolinium was discovered by Jacobsen (Scheme 4) [49]. The organocatalyst **16** was found to catalyse the addition in good to excellent yields and enantioselectivities; the ee values obtained were sensitive to the nature of the solvent and of the activating agent, with chloroformates performing better than acetyl chloride. Also in this report the facile reduction of the intermediate to give tetrahydroisoquinoline derivatives was reported, in conjunction with the cleavage of the carbamate, giving 1-substituted tetrahydroisoquinolines with no loss

of enantiopurity. As illustrated in Scheme 4 the catalyst acts by hydrogen bonding interactions with the chloride ion formed by the activation of the isoquinoline ring.

Chiral silane diols were also able to act in anion-binding catalysis as reported by Matteson [50]. The enantiomeric excess obtained in the similar reaction of silyl ketene acetals with *N*-acylisoquinolinium ion was still quite unsatisfactory and limited to isoquinoline substituted with electron-withdrawing groups. However, the concept is quite interesting and worth to be further exploited.

Isoquinolinium intermediates can be alkylated by azanolethers in presence of a chiral hydrogen-bonding catalyst [51] as reported by Seidel. Both electrophilic and nucleophilic reaction partners are generated in situ by the efficient Steglich [52] rearrangement of *O*-acylated azalactone (Scheme 5).

The reactions were conducted in mixtures of mesitylene and pentane at -25 °C. The best result was obtained with a 1:2 mixture of mesitylene and pentane, in the presence of the thiourea catalyst **18**. Various *O*-acylated azalactones derived from different amino acids were reactive in the reported conditions furnishing the products **19** in generally high yields and levels of enantio- and diastereoselectivity with a number of differently substituted isoquinolines [53].

Scheme 4 Acyl Mannich reaction of substituted isoquinolines**Scheme 5** Addition of azlactones to isoquinolines promoted by the thiourea catalyst

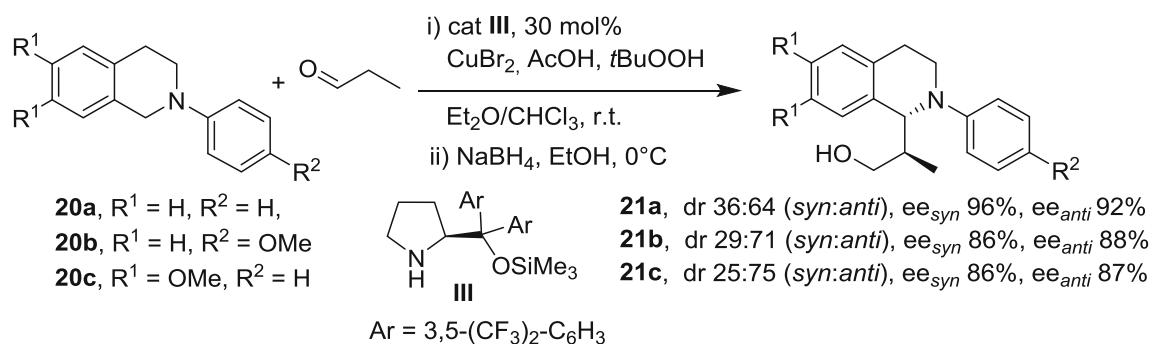
4 Organocatalytic Addition of Nucleophiles to Dihydroisoquinolinium Iminium Ion

4.1 Stereoselective Dehydrogenative Cross Coupling

The cross-dehydrogenative coupling (CDC) reaction has been extensively investigated in the last decade [54]. Various methods have been described for the generation via oxidative process of an iminium activated specie [32], formed from a tetrahydroisoquinoline derivative, but in most of the published procedures, the nucleophilic attack was not stereoselective, even when proline or proline derivatives were used as organocatalysts [55–57]. The first successful example of addition of chiral nucleophiles (enamines) through cross dehydrogenative coupling was reported by Chi [58]. As it was well discussed by Klussmann, the oxidation of *N*-aryltetrahydroisoquinolines **20** forms an electrophilic iminium derivative. Chi used a combination of *tert*-butylhydroperoxide in the presence of

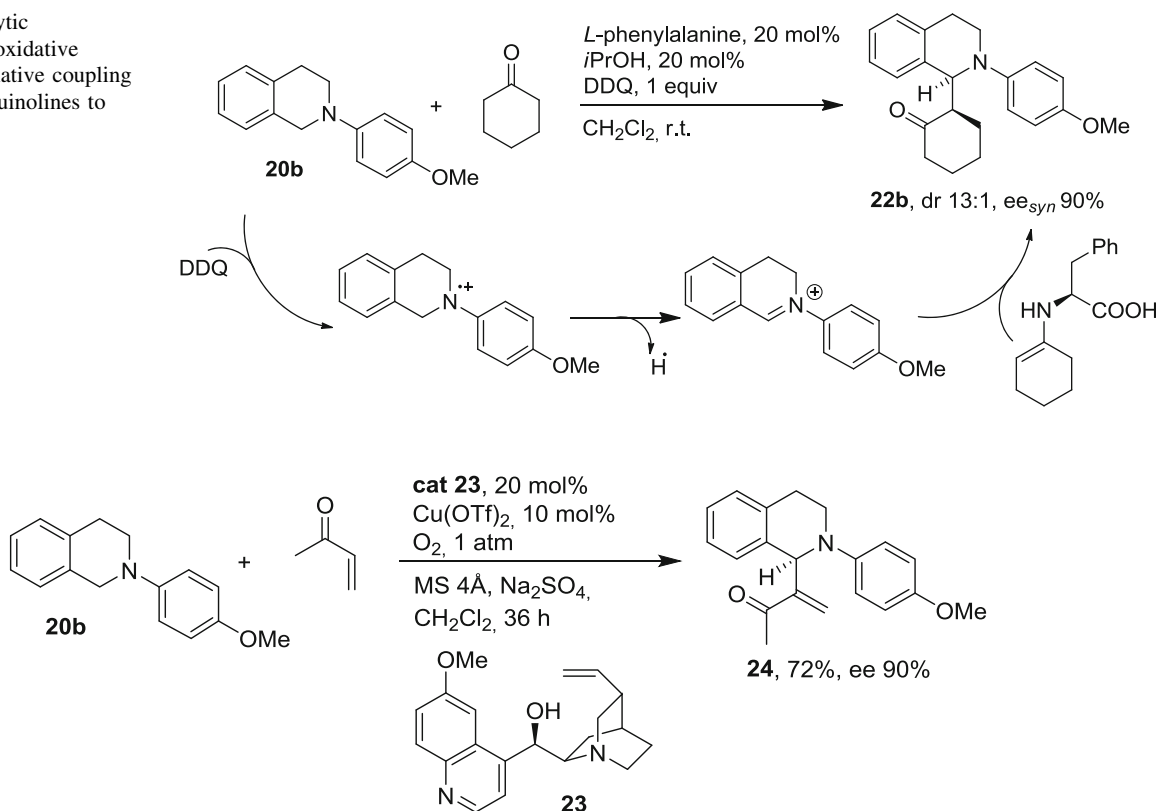
CuBr_2 to perform the oxidation, and the reaction was catalysed by the Jørgensen diarylprolinol catalyst **III** (Scheme 6). We have previously remarked that the enamines formed by **III** are more nucleophilic than the ones obtained with the other organocatalysts, and their use is related to the low electrophilicity of **6** (Fig. 4).

The products were obtained in 31–71 % yield but with low diastereoselectivity, although the enantioselectivity was in general quite good. The aldehyde compounds, as the adducts obtained by Jørgensen [44], suffered of low stability, and they were reduced to their corresponding alcohols to avoid racemization and decomposition. Although the authors reported the use of 4-MeO-C₆H₄ (PMP) as aryl group (**20b**), they did not report an effective procedure for its cleavage. This appears a limitation in the methodology. The procedure was extended to the addition of ketones by the work of Wang and co-workers [59]. *N*-aryl tetrahydroisoquinolines **20** were coupled with cyclic ketones with *L*-phenylalanine as chiral catalyst in the presence of



Scheme 6 Dehydrogenative stereoselective coupling catalysed by Jørgensen catalyst **III**

Scheme 7 Catalytic enantioselective oxidative cross-dehydrogenative coupling of tetrahydroisoquinolines to ketones



Scheme 8 Enantioselective dehydrogenative coupling of tetrahydroisoquinoline with unsaturated alkenes

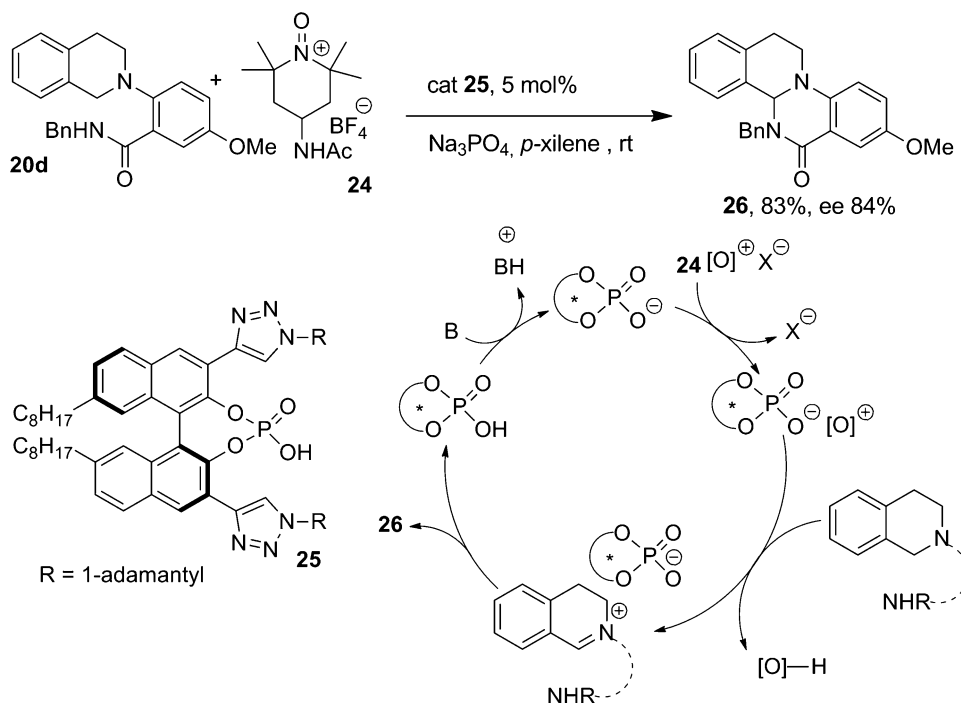
anhydrous *i*PrOH as additive, and 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant (Scheme 7). The scope of the reaction was tested with different substrates, and the reaction proceeded well to afford the products in good yields and from good to excellent diastereo- and enantioselectivities. The use of ketones was limited to cyclohexanone derivatives, while the *N*-aryl group was varied considerably. The absolute and relative configuration of the newly formed stereocenters was firmly established by X-ray analysis.

The possible reaction mechanism is illustrated in Scheme 7. For many of the transformation discussed in this

section a single-electron transfer (SET) induced by DDQ is assumed [60]. Quenching experiment with 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) were reducing the yield of the coupling showing the probable presence of radical cation. Wang also explored the possibility of using cooperative organocatalysis in a different reaction describing an aerobic oxidative aza-Baylis–Hillman reaction of *N*-aryl-tetrahydroisoquinolines **20** (Scheme 8) [61].

The oxidation was carried out with a combination of Cu(OTf)₂ and 1 atm of molecular O₂ as oxidant system, and quinine **23** was used as the catalyst. For this reaction the scope was quite large concerning the *N*-substitution of

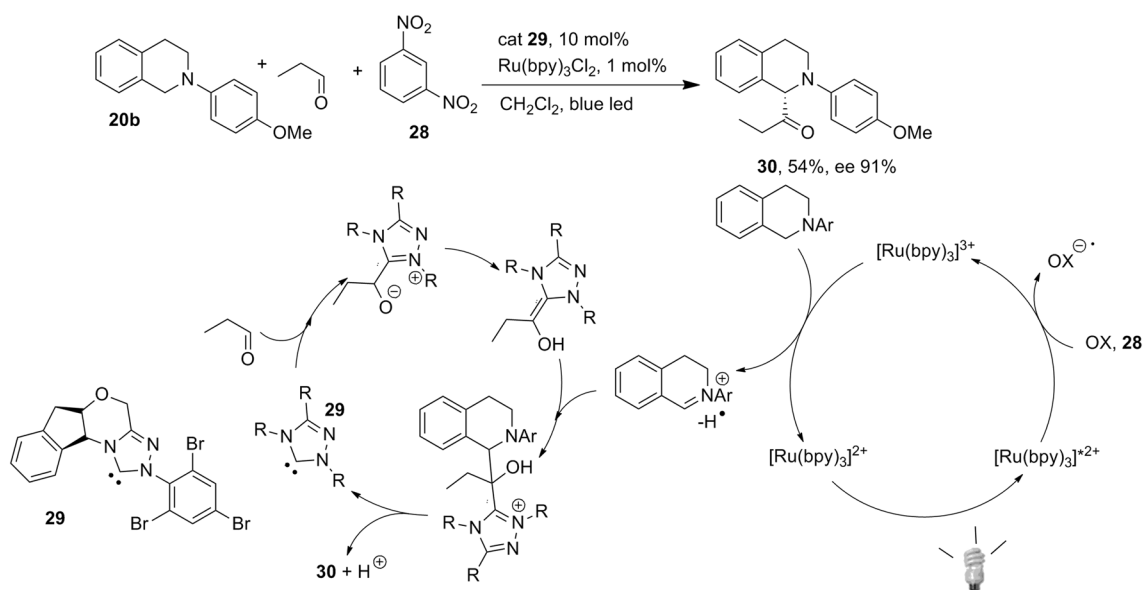
Scheme 9 Enantioselective cross dehydrogenative intramolecular coupling of tethered tetrahydroquinoline promoted by chiral triazole-containing phosphoric acid



tetrahydroisoquinolines. The desired products were obtained in 47–82 % yields and 69–99 % enantiomeric excess for the reaction with various olefins. The presence of methoxy groups on the 6,7-position or chlorine on the 7-position of the tetrahydroisoquinoline ring did not influence the reaction outcome. Methylvinylketone and acrylonitrile were also tested giving excellent results. The absolute configuration of a key product was established by single-crystal X-ray diffraction, and the configuration of the others adducts was established by analogy. The deprotection or application of these products as key intermediates in synthesis was not disclosed. Toste applied the chiral counter anion catalysis in an example in which he described the synthesis of a C–N bond-forming reaction to produce 1,2,3,4-tetrahydroisoquinoline-derived cyclic aminals [62]. The stereoselective reaction is promoted by the formation of a chiral phosphate that undergoes anion exchange with an appropriately chosen cationic oxidant. The generation of the iminium by oxidation and the subsequent anion exchange allows the formation of a tight chiral ion-pair. The phosphate chiral catalyst is re-generated after the nucleophilic addition (Scheme 9).

Amide-tethered tetrahydroisoquinoline **20d** are cyclized in the presence of the oxoammonium salt **24**. A careful design of the chiral phosphoric acid was necessary in order to achieve good selectivity. The guide principle was the inspection of the needs to perform a reaction with such chiral Brønsted acids. In first instance, a bulky group needs to be installed in 3,3' positions of the BINOL backbone.

As in this case the presence of bulkyness was not enough to guarantee a good stereoselection, an “enzyme like” secondary interaction with substrate was introduced in the catalyst design. The 1,2,3-triazole moiety was chosen because of its ability to perform hydrogen bond together with its modularity and facile introduction by click chemistry [63]. A series of 3,3'-triazoly-BINOL-phosphoric acids **25** were prepared and evaluated for the reaction, and through the fine tuning of the catalyst structure, excellent enantioselectivities and conversions were observed. The enantioselective oxidative C–H functionalization of tetrahydroisoquinoline derivatives can be achieved by the use of another powerful concept. Organocatalytic photoredox catalysis has been quite recently introduced by the pioneering work of MacMillan [64] and photocatalytic transformations emerged recently as a powerful tool for organic synthesis [65]. Two key transformations were recently described in which the stereoselective addition of chiral nucleophiles to tetrahydroisoquinolines is achieved through photocatalysis. The first report is the combination of photoredox catalysis with *N*-heterocyclic carbene catalysis developed by Rovis [66]. In the introductory section, we have highlighted the role of carbene catalysis in the generation of acyl anion or homoenolate equivalents from aldehydes under very mild conditions. These species have been demonstrated to be competent nucleophiles in a large variety of reactions [67, 68]. The nucleophilicity of carbene enolates measured by Mayr is sufficient for the reaction with iminium intermediates, and the possibility of



Scheme 10 Asymmetric acylation of tetrahydroisoquinoline mediated by photoredox catalysis in the presence of a chiral carbene

the reaction is quite predictable. However, the difficulties in the oxidative coupling is determined by the possibility to oxidize the Breslow intermediate to unproductive pathways [69]. As illustrated in Scheme 10, the irradiation of $[\text{Ru}(\text{bpy})_3]^{2+}$ with blue light populates the $[\text{Ru}(\text{bpy})_3]^{2+*}$ excited state, giving rise to a powerful oxidant or reductant. If the oxidant $[\text{Ru}(\text{bpy})_3]^{3+}$ (1.29 V vs SCE) is generated by reduction of an oxidative quencher, this specie is capable of a single-electron oxidation of a *N*-aryl tetrahydroisoquinoline, giving after hydrogen atom abstraction, a radical intermediate that is further oxidized to the activated iminium. This electrophile is then intercepted by the nucleophilic Breslow intermediate obtained by reaction of the aldehyde with the carbene catalyst.

The reaction is possible using $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ as the photocatalyst in the presence of *m*-dinitrobenzene (*m*-DNB) **28** as the oxidant and chiral NHC **29** under irradiation with blue light. A careful optimization of the catalyst was necessary, giving optimal yields and high enantioselectivity (92 % ee) for a series of various functionalized α -amino ketones.

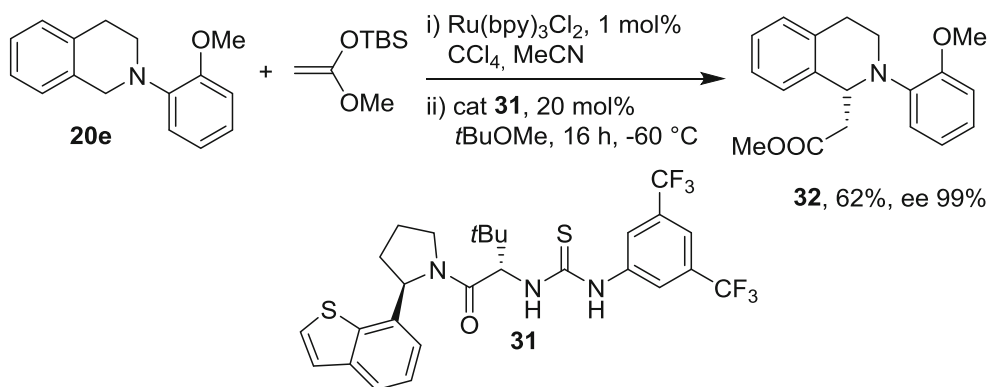
Irradiation of photoactive catalysts and asymmetric anion-binding catalysis can also be merged in a quite interesting and innovative process. Jacobsen and Stephenson have described the stereoselective addition of not prochiral silyl ketene acetal to isoquinoline by the use of chiral anion-binding catalysts in combination with photocatalysis (Scheme 11). In this transformation the photocatalysed oxidation is generating a reactive specie that is trapped by a chiral H-bond donor catalyst, chiral thiourea

31. The stoichiometric oxidant that is used in this reaction is CCl_4 [70].

The reaction is realized in two steps: in the first one the formation of a stable iminium is achieved by the use of photocatalysis in a polar solvent (MeCN) that allows the solubilisation of the photocatalyst. Then the solvent is switched to *t*BuOMe for the stereoselective reaction conducted at low temperature. Unfortunately electron rich dehydroisoquinoline are affording moderate to low enantiomeric excesses. Instead of many papers published on this subject, the authors were able to describe a new protocol for *N*-dearylation of the products to provide derivatives that could be used in alkaloid synthesis. The *ortho* methoxy derivative was deprotected in good yield by the use of a specific reagent, $[\text{Fe}(\text{bpy})_3](\text{PF}_6)_2$. Application of other standard oxidative protocol (CAN, $\text{PhI}(\text{TFA})_2$, or DDQ) led to low yields or extensive decomposition via over-oxidation.

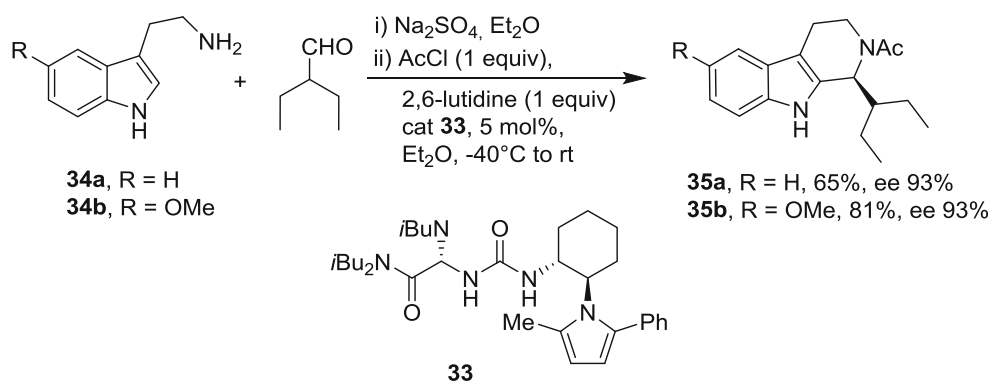
4.2 Pictet-Spengler Via Hydrogen Bond Activation

The Pictet-Spengler reaction was discovered in 1911 and it is now widely used for the synthesis of a large variety of heterocyclic compounds named alkaloids [71]. The first enantioselective catalytic Pictet-Spengler reaction was described by Jacobsen (Scheme 12) [72]. Formation of the reactive acyliminium is realized in situ by activation with AcCl . After a careful optimization of the structure of the catalyst and of the reactions conditions the methodology was applied to a series of aliphatic aldehydes, giving the desired products in good yields and stereoselectivity. Unfortunately the

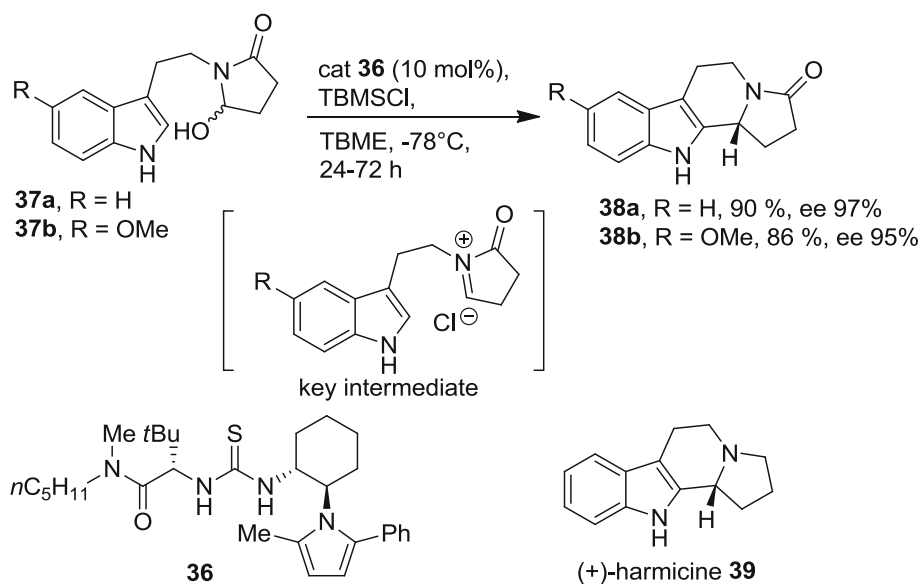


Scheme 11 Photocatalytic reaction of isoquinoline with a silyl ketene acetal promoted by a chiral thiourea catalyst

Scheme 12 Asymmetric acyl Pictet-Spengler reaction catalysed by chiral thiourea catalyst **33**



Scheme 13 Asymmetric cyclization of the hydroxyl lactam **37** promoted by the thiourea catalyst **36**



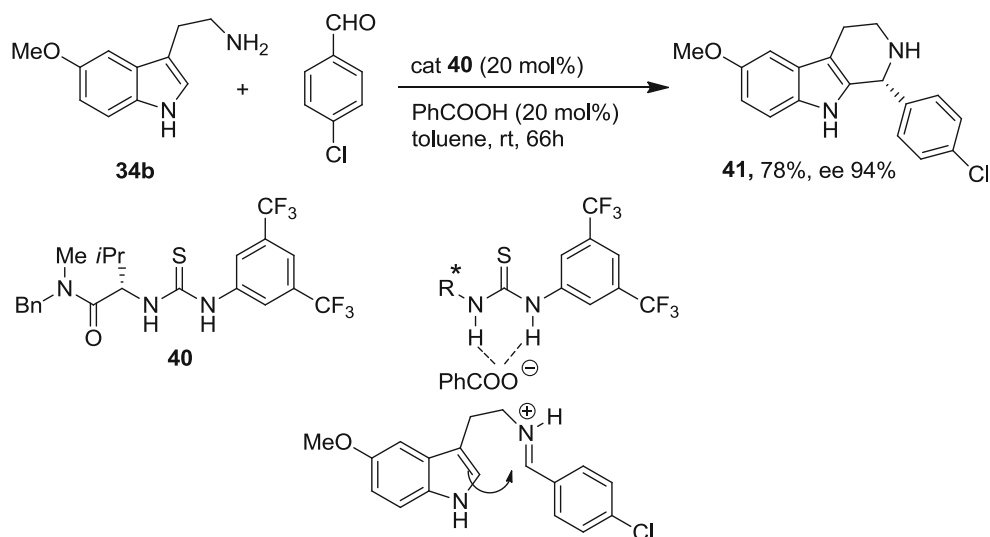
stereoselective variants of the Pictet-Spengler reaction are limited to tryptamine and tryptamine derivatives **34**.

Jacobsen disclosed an enantioselective variant of the Pictet-Spengler reaction of 3-indolyl-tethered hydroxylactams catalysed by chiral thiourea **36**. The cationic *N*-

acyliminium intermediate was obtained after the treatment of hydroxylactam **37** with TMSCl (Scheme 13) [73].

The chlorolactam intermediate in the presence of the thiourea afforded an ion pair catalyst complex after a chloride dissociation induced by the catalyst. Thus the

Scheme 14 Thiourea and benzoic acid catalysed Pictet-Spengler reaction with activated tryptamines



anion binding properties of the thiourea catalyst are quite important for activating the chlorolactam substrate. In a kinetic analysis performed on the episulfonium opening reaction [74] Jacobsen was able to indicate the rate determining step, that was the enantio-determining step as well. The conclusions highlighted in the paper can be translated to other reactions promoted by chiral thiourea catalysts. Thiourea catalysts are able to stabilize an anion by binding, and to activate the nucleophilic indole via a catalyst amide-indole N–H interaction. Thioureas possessing donating aromatic groups, such as the catalyst **36**, are able to stabilize the transition state through a cation- π interaction with the aromatic ring. The cyclized products were obtained in yields of 51–94 % with ees ranging from 81 to 99 %. In particular by the use of this methodology, the alkaloid (+)-harmicine **39** was prepared in four steps from tryptamine in 62 % overall yield and 97 % ee. However, the reaction was limited to the use of aliphatic aldehydes.

A careful design of the catalyst allowed the development of an enantioselective catalytic Pictet–Spengler reaction with a broad substrate scope for tryptamines [75]. Under the optimized reaction conditions, with simple catalyst **40** prepared in three steps, a series of substituted benzaldehydes were condensed. The presence of a suitable Brønsted acid, namely benzoic acid in catalytic amount (20 mol%) is important in order to promote the reaction with aromatic aldehydes (Scheme 14). The reaction rate was enhanced by the use of electron rich tryptamines.

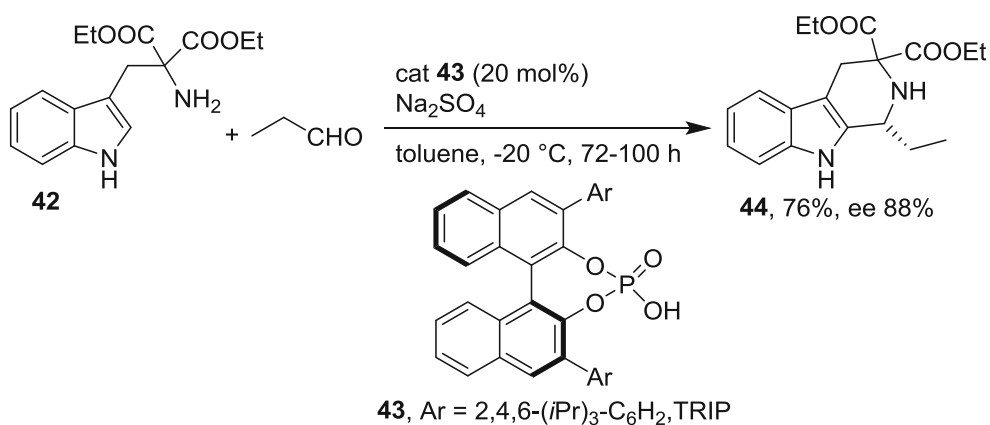
List and co-workers in 2006, observing that the catalytic Pictet–Spengler was assumed to involve chiral, hydrogen-bond assisted iminium ion pairs, explored the use of phosphates as chiral anions [76]. Taking advantage of the Thorpe–Ingold effect for forcing the cyclization they used a tailored geminal disubstituted tryptamine substrates in the presence of a chiral organic Brønsted acid (Scheme 15).

They found that the chiral phosphoric acid **43**, now called TRIP, gave the highest enantioselectivity in the Pictet–Spengler cyclisation. The reaction was effective with aliphatic and aromatic aldehydes affording the desired products in good yields and ees varying from 62 to 96 %.

The presence of geminal substituents to allow the cyclization was found unnecessary by Hiemstra, that described Pictet–Spengler reactions of *N*-sulfonyl **45a** [77] and benzyl **45b** [78] tryptamines (Scheme 16).

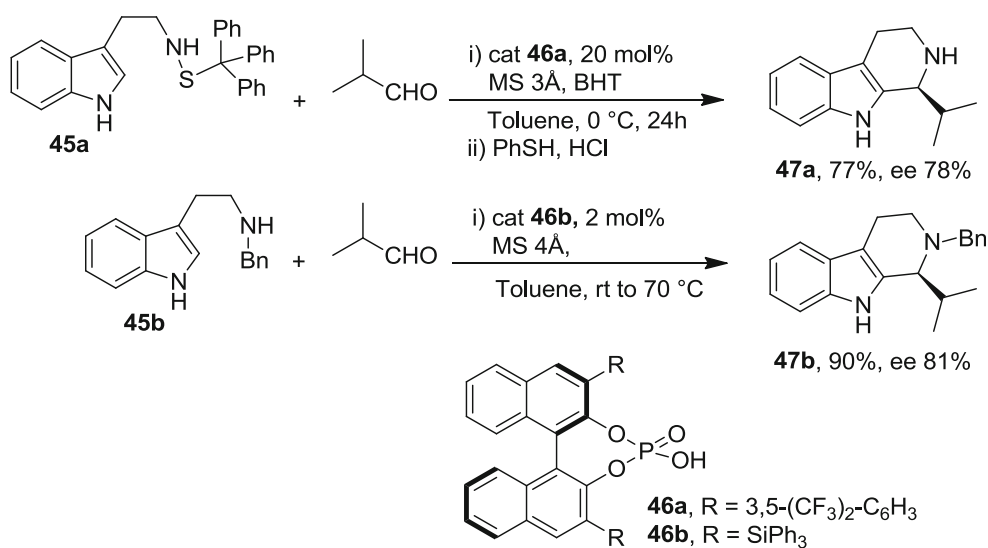
The bulkier *N*-tritylsulfonyl group requires careful conditions and the presence of radical scavenger (3,5-di(*tert*-butyl)-4-hydroxytoluene, BHT) and molecular sieves. It is important to point out that a different phosphoric acid is here necessary to reach good level of stereoselectivity, pointing out the delicate balance of steric and electronic effects in these reactions. The obtained products were directly deprotected in a one-pot procedure. The enantiomeric excesses obtained with aromatic and aliphatic aldehydes were however in the range between 72–86 %. In the case of benzyl tryptamines [77] the enantiomeric excesses obtained were above 80 % for *p*-substituted aromatic aldehydes. The catalyst that gave the highest selectivity in this case was 3,3'-triphenylsilyl substituted phosphoric acid **46a**. This approach was used by Hiemstra in the total synthesis of alkaloids. The catalyzed Pictet–Spengler reaction of the derivative **48** with methyl 5-oxo-2-(phenylseleno)pentanoate in the presence of phosphoric acid **49** gave the corresponding product (Scheme 17) that was converted, by nine-steps, to (+)-yohimbine **51** [79].

Another quite interesting total synthesis of the indole alkaloids (–)-mitragynine **55**, (+)-paynantheine **56** and (+)-speciogynine **57** was reported by Maarseveen and Hiemstra (Scheme 18) [80]. These compounds were synthesized in nine steps from 4-methoxytryptamine by enantioselective catalyzed Pictet–Spengler reaction as one

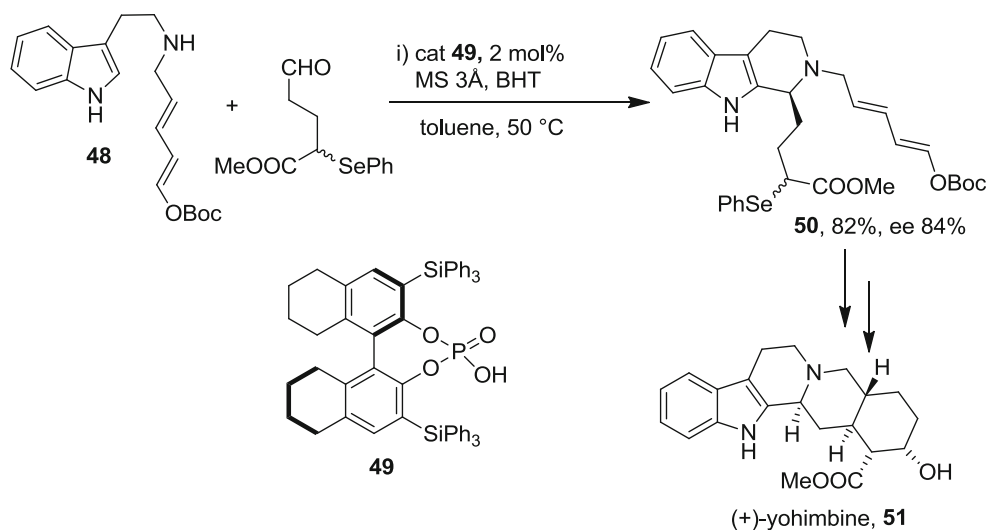


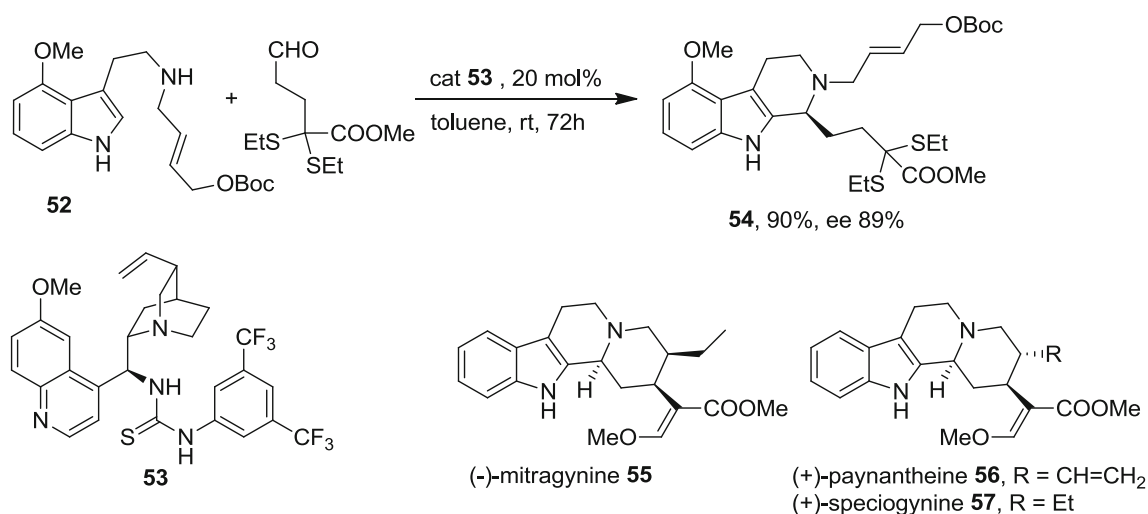
Scheme 15 Catalytic asymmetric Pictet-Spengler reaction promoted by the chiral phosphoric acid TRIP

Scheme 16 Differently protected tryptamines in effective Pictet-Spengler reaction promoted by chiral phosphoric acids



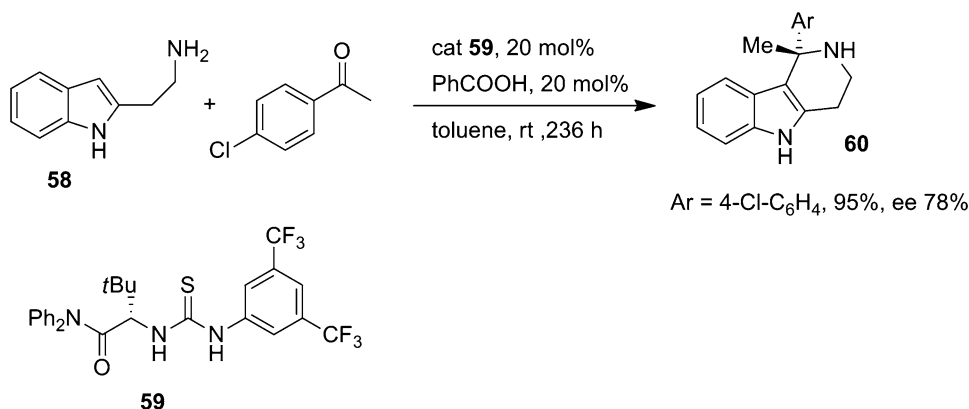
Scheme 17 Enantioselective approach to (+)-yohimbine **51** through an asymmetric Pictet-Spengler reaction





Scheme 18 A simple prepared thiourea catalyst from quinine as effective catalyst for Pictet-Spengler reactions

Scheme 19 Thiourea/benzoic acid catalyzed iso-Pictet-Spengler reaction



of the key steps. Interestingly, in the described transformation, the structure of the alkaloids influenced the choice of the chiral catalyst employed for the Pictet-Spengler reaction. As thioureas are the catalysts of choice with more nucleophilic indole systems the authors screened commercially available catalysts and they found that a simple prepared chiral catalyst **53** derived from quinine was the most effective.

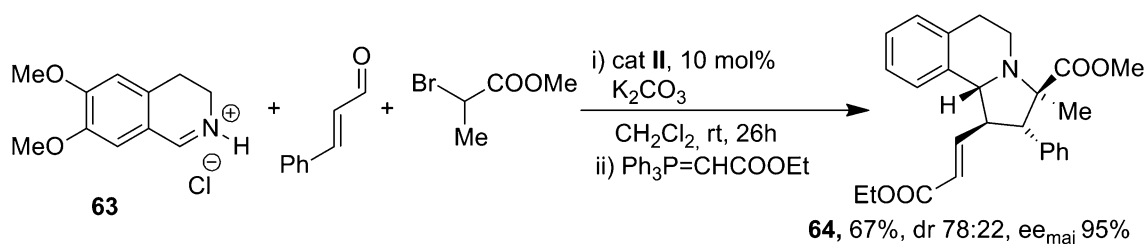
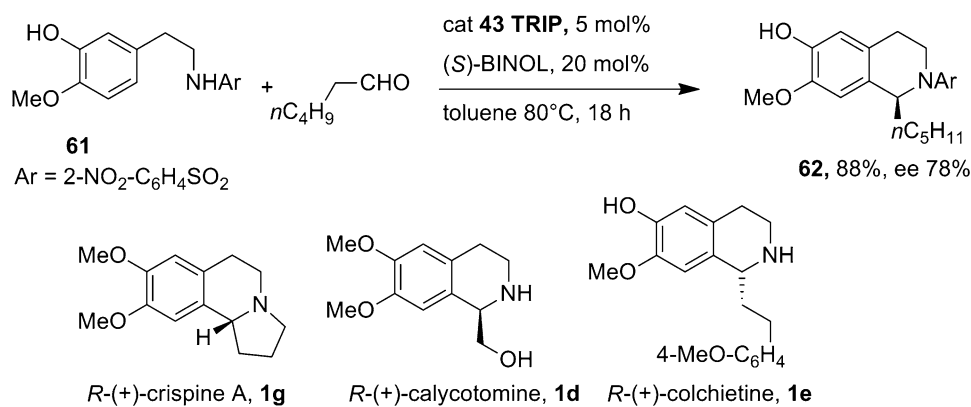
The one-pot condensation of isotryptamines and aldehydes that gave enantiomerically enriched 4-substituted tetrahydro- γ -carbolines was reported by Jacobsen [81] (Scheme 19).

Also in this report, a chiral thiourea **59**/benzoic acid dual catalyst system was used to promote the reaction with aliphatic and aromatic aldehydes. Remarkably, also ketone substrates were successfully applied to this iso-Pictet-Spengler protocol. In a single example, *p*-chloroacetophenone was treated under the catalytic conditions. Even if a prolonged reaction time (14 days) is needed, the desired

tetrahydro- γ -carboline **60** is obtained in 95 % yield and 76 % ee. Although in many cases the enantiomeric excesses were not excellent, simple trituration or crystallization was sufficient to rise the enantiomeric excesses.

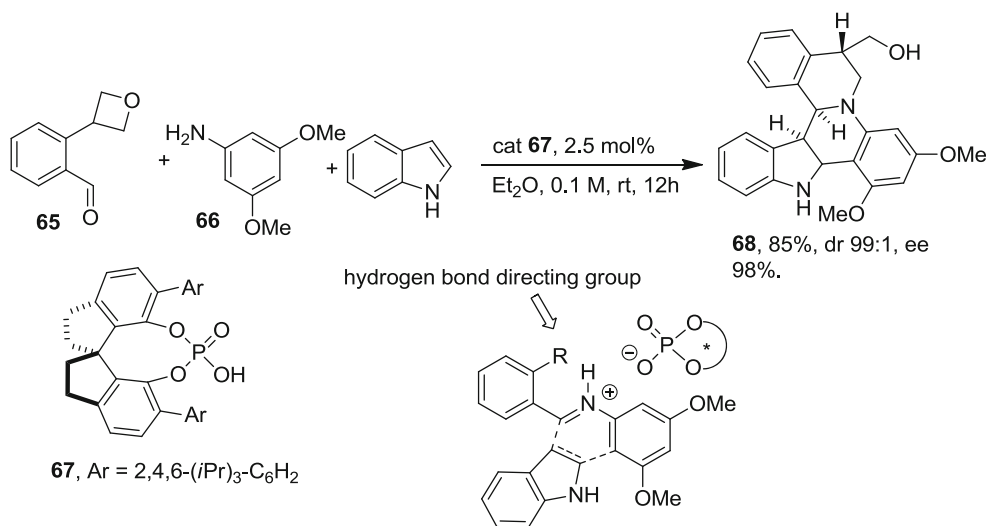
Most of the examples reported for the organocatalytic stereoselective Pictet-Spengler reaction have been restricted to tryptamines and tryptamines derivatives. This observation is not a surprise as a quick inspection in the Mayr scale can give a clear idea of the higher nucleophilicity of indole systems compared to benzene rings. In addition, the hydrogen bonding properties of the indole N–H can improve the control in the transition state with hydrogen bond forming catalysts. Recently, Hiemstra and co-workers [82] have disclosed a remarkable result showing that a series of 1-substituted 1,2,3,4-tetrahydroisoquinolines **62** can be prepared from *N*-(*o*-nitrophenylsulfenyl)-2-phenylethylamines through (*S*)-BINOL and (*R*)-TRIP phosphoric acid **43** catalyzed asymmetric Pictet-Spengler reactions. By using this new methodology the natural products (*R*)-

Scheme 20 An effective TRIP catalyzed Pictet-Spengler reaction that gave tetraisoquinolines intermediates for the synthesis of natural alkaloids



Scheme 21 Three component reaction promoted by Jørgensen catalyst **II**

Scheme 22 Three component aza-Diels–Alder reaction of indole promoted by oxetane containing aldehyde



crispine A **1g**, (R) -calycotomine **1d** and (R) -colchietine **1e** (Scheme 20) were obtained.

5 Organocatalytic Multicomponent Reactions

Multicomponent reactions (MCRs) are a quite useful strategy for the approach to heterocyclic compounds, particularly in the case of nitrogen containing heterocycles [83]. Several approaches to isoquinoline derivatives through organocatalytic asymmetric MCRs to access enantioenriched complex

molecules were reported. The pyrrolo-isoquinoline moiety, that is present in the alkaloid families of erythrines [84] and lamellarins [85], is one of the structures that can be accessed through a multicomponent reaction. In 2012 Jørgensen reported [86] a three-component organocatalytic asymmetric reaction of imines, α -bromoesters or α -bromoketones with α,β -unsaturated aldehydes to give optically active pyrrolo-isoquinolines **64**, with excellent enantioselectivity for a large number of substituents showing broad scope for this reaction (Scheme 21). Computational studies shed light on the reaction pathway that proceeded in a stepwise manner.

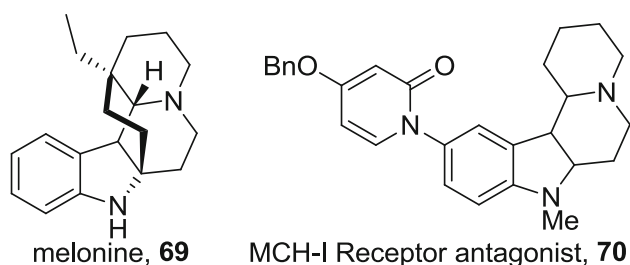


Fig. 7 Biologically active products that can be accessed through an asymmetric three components aza-Diels–Alder reaction

Zhu and Sun published a catalytic asymmetric three-component aza-Diels–Alder reaction using indole as the dienophile (Scheme 22) [87]. The presence of a directing group on the aldehyde **65** as hydrogen bond acceptor is mandatory for the success of the reaction.

The chiral phosphoric acid catalyst is involved in multiple hydrogen bonds and the oxetane moiety is also involved in the hydrogen bond recognition. Remarkably the isoquinoline indole-alkaloid-type polycyclic **68** products of the multicomponent reaction possess a core structure that is recognizable in melonine **69** and an MCH-I receptor antagonist **70** (Fig. 7).

3-Indolylmethanol derivatives have found many uses in organocatalysis as precursors of stabilized vinyliminium or carbocation intermediates species [88] that can be generated in the presence of a Lewis or Brønsted acid (LA or BH). Shi, Tu and co-workers have used isatin-derived 3-indolylmethanols **71** as dipolarophiles for a formal catalytic asymmetric [3+3] cycloaddition with azomethine ylides [89]. The desired spiro[indoline-3,4'-pyridoindoles] **73**, were obtained in moderate diastereoselection but in

excellent enantiomeric excess (up to 93 %, yield >99 %) (Scheme 23). Chiral phosphoric acids are promoting the reaction through the formation of a stabilized vinyliminium in tight contact with the phosphate anion. Among all the catalysts tested for the reaction the acid **72** bearing bulky 9-phenanthrenyl group at the 3,3'-positions of the BINOL backbone exhibited the higher catalytic activity, when the reaction was performed in dichloroethane.

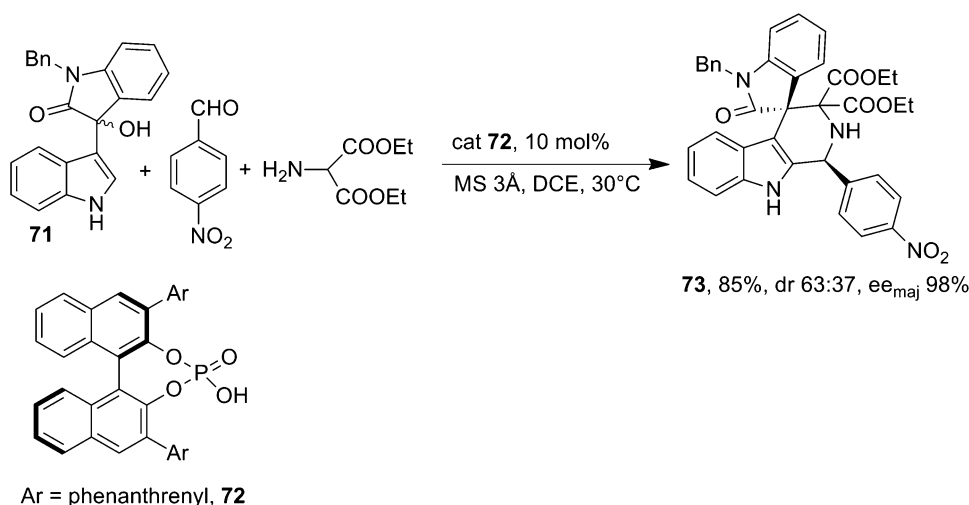
In a similar fashion, Gong and Luo described a multi-component reaction that occurred with *p*-nitrobenzaldehyde, diethyl 2-aminomalonate, and 3-indolyl(aryl)methanols [90]. A formal, highly diastereoselective, chiral catalyst-controlled aza-Diels–Alder reaction between a 6-methoxy-tryptamine-derived dihydro- β -carboline **74** and an enantio-enriched substituted dienone **75** was described by Jacobsen (Scheme 24) [91, 92]. The key tetracyclic intermediate **77** was used for the total synthesis of (+)-reserpine **78**.

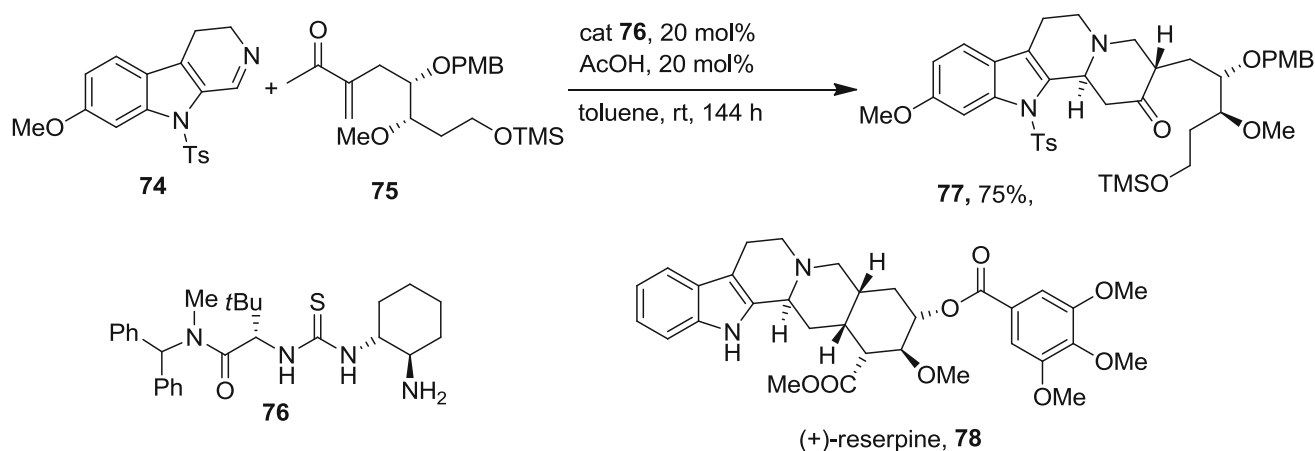
6 Amido Alkylation via Chiral Brønsted Acids

The intramolecular attack on *N*-acyliminium ion electrophiles by π nucleophiles can be used as a privileged methodology for the stereoselective construction of isoquinoline ring systems, by a cascade sequence. Taking inspiration from gold(I)-catalysed chemistry, Dixon group identified a strategy based on the use of phosphoric acids [93] for efficient *N*-acyliminium cyclization [94–97]. First the reaction was optimized by studying the condensation of a keto amide intermediate, and when the most selective chiral phosphoric acid was found, the enantioselective *N*-acyliminium cyclization cascade was realized (Scheme 25).

Different 5 or 6 membered unsaturated ring lactones and tryptamine derivatives were treated in toluene at 110 °C in

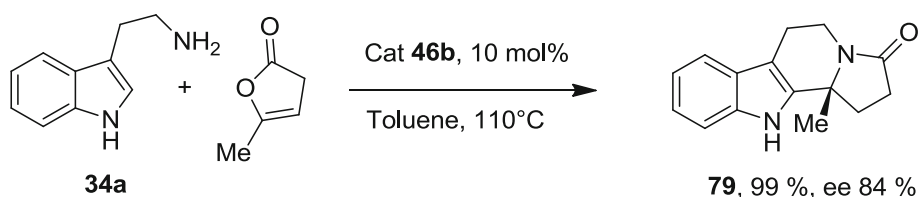
Scheme 23 Multicomponent reaction with 3-indolyl-methanol



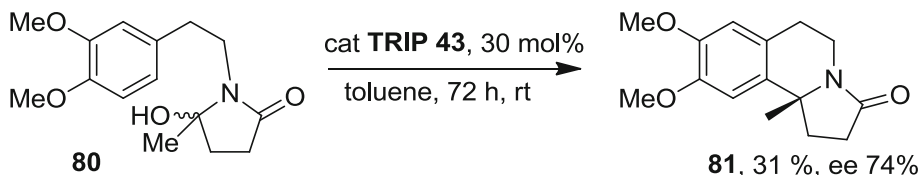


Scheme 24 Stereoselective approach to reserpine through a diastereoselective, catalyzed controlled, formal aza-Diels–Alder reaction

Scheme 25 Cyclization cascade promoted by chiral phosphoric acid **46b**



Scheme 26 Stereoselective amido alkylation promoted by TRIP

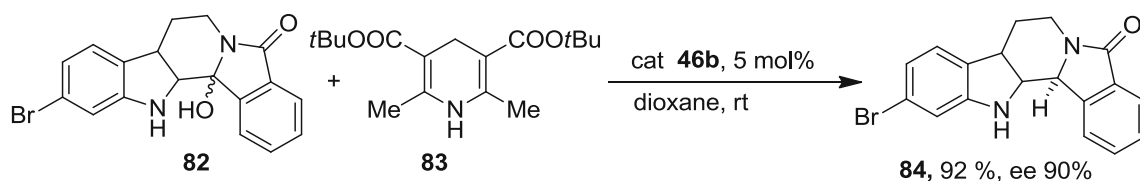


the presence of 10 mol% of chiral catalyst **46b**. It is noteworthy that the high temperature is not depriving the stereoselective reaction. The yields obtained were in the range of 63–99 % while the stereoselectivities were in between 72–99 %. The high diastereo- and enantiocontrol observed in the reaction can be rationalized by a fast, reversible formation of the diastereomeric *N*-acyliminium salts followed by rate determining ring closure. As we have pointed out, the intramolecular Pictet–Spengler reaction promoted by chiral thioureas requires electron rich heteroaromatic systems, as indoles or pyrroles. However, Lete and co-workers reported the intramolecular Friedel–Crafts-type α -amidoalkylation using benzene derivatives as internal nucleophile to give functionalized tetrahydroisoquinoline derivatives **81** bearing a quaternary stereocenter (Scheme 26) [98].

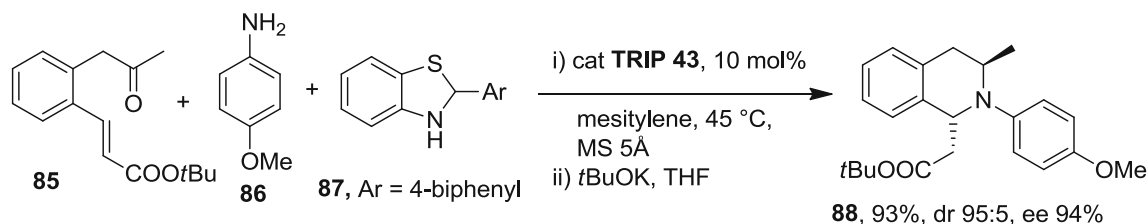
The use of chiral phosphoric acids [99, 100] in this chemistry through the formation of a *N*-acyliminium intermediate surrounded by chiral base anion gave, unfortunately, only moderate results. The reaction is sluggish

and the yields are quite modest. The low nucleophilicity of the benzene aromatic substrates is probably responsible for the moderate success. Related to this reaction are the results reported by You [101], who has applied the formation of iminium promoted by a chiral phosphoric acid to a series of tetrahydro- β -carboline **82**. The derivatives **84** were obtained in 68–94 % yield and up to 90 % ee (Scheme 27).

The reaction uses Hantzsch ester **83** as reductant. Its ability to behave as hydride donor was established in organocatalysis in various reactions [102], and it is strictly correlated to the nucleophilicity of hydride donors [103]. As it is well reported by Mayr the nucleophilicity of the hydrides are well suited for reacting with the iminium ions generated by Brønsted acids. In conjunction with this chemistry Enders reported a three-component reductive amination using another hydride donor, the substituted benzothiazoline **87** derivative, to obtain 1,3-disubstituted tetrahydroisoquinolines **88** in high yields and stereoselectivities (Scheme 28) [104].

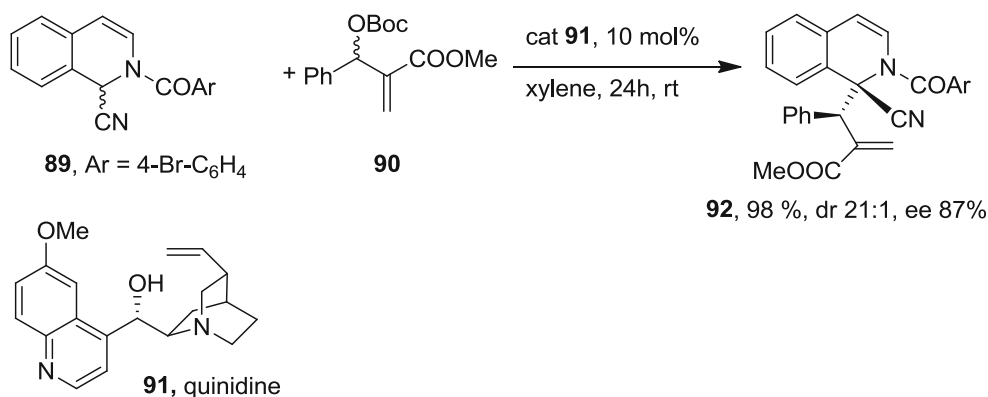


Scheme 27 Chiral phosphoric acid catalyzed transfer hydrogenation of hydrolactams



Scheme 28 Reductive amination aza-Michael reaction

Scheme 29 Alkylation of a Reissert compounds to produce 1-substituted isoquinolines



7 Reissert Adduct in Stereoselective Organocatalysis

Reissert adducts, that can be simply obtained by catalytic addition of cyanide anion to isoquinoline, can be the precursors of a wide range of functionalities. They can be easily alkylated by electrophiles and we will illustrate the use of phase transfer catalysis (PTC) in the enantioselective alkylation of Reissert compounds, derived from various isoquinolines by the use of acyl chlorides or chloroformates as activating agents. A practical and stereoselective asymmetric allylic alkylation of 1,2-dihydro-Reissert compounds **89** was described by Zhang [105] disclosing a novel protocol to access highly functionalized 1,2-dihydro-isoquinolines **92** bearing adjacent quaternary and tertiary stereocenters (Scheme 29).

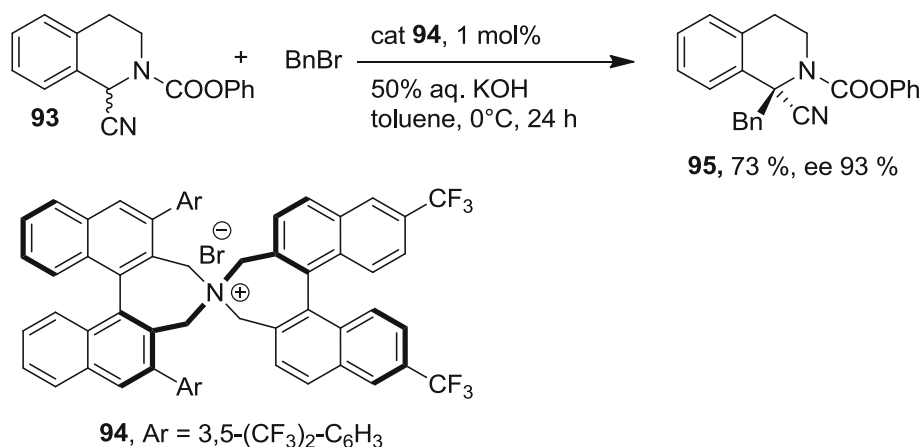
The substrate for the allylic alkylation **89** is a useful and studied precursor in organocatalysis, due to the studies made by Chen and coworkers [106] and other groups [107]. The Lewis base-catalysed asymmetric allylic alkylation reactions in which Reissert adducts are used as substrates is often promoted by *Cinchona* alkaloid derivatives. The

tertiary amino group of the quinidine alkaloid activates the substrates **89**, that further reacts with suitable electrophiles through a push-pull mechanism in a chiral environment. The reaction proceeded smoothly and provided the desired product in good yield with excellent diastereoselectivity and high enantioselectivity (85 % ee) in the presence of 10 mol% quinidine **91**, while the opposite enantiomer can be obtained by using 10 mol% quinine. The absolute configuration was firmly established by X-ray analysis of a product derivative. Although the presence of various functional groups, the authors have not investigated the uses of these adducts in the synthesis of natural alkaloids.

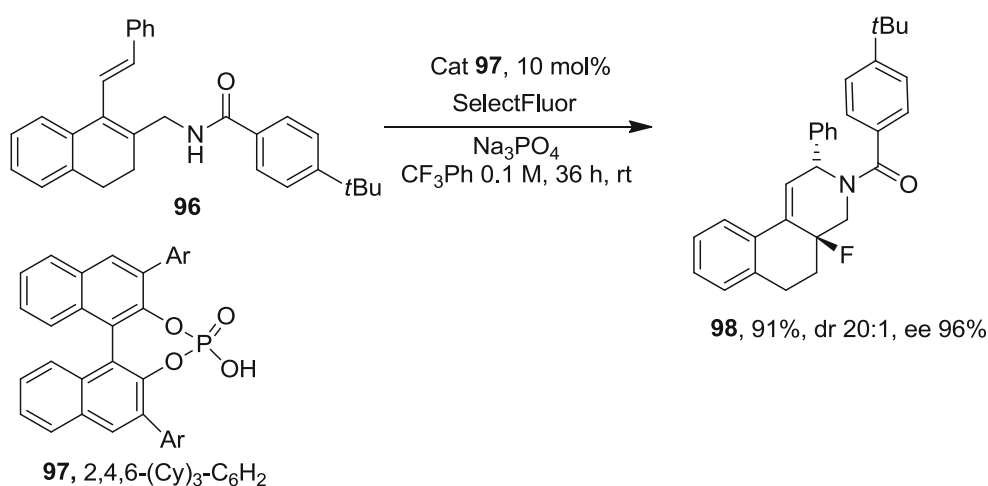
8 Phase Transfer Catalysis with Iminium in the Approach to Isoquinoline Derivatives

Maruoka has recognized the practical and effective PTC [108] when applied to the synthesis of 1,1-disubstituted tetrahydroisoquinolines. A highly efficient catalytic asymmetric synthesis of 1,1-disubstituted tetrahydroisoquinolines

Scheme 30 Asymmetric alkylation of 1-cyanotetrahydroisoquinolines promoted by PTC



Scheme 31 Enantioselective PTC fluoroamination in the synthesis of isoquinolines



was reported by Maruoka starting from the Reissert compounds via asymmetric alkylation or Michael addition [109]. The reaction is promoted by the use of *N*-spiro-type chiral phase-transfer catalyst **94** possessing the 3,5-bis(trifluoromethyl)phenyl groups and trifluoromethyl groups onto 3,3'-positions of one and the 6,6'-positions of one of the binaphthyl units (Scheme 30).

Benzylic bromides with different steric and electronic properties can be employed obtaining the corresponding products **95** in high yield and ees (84–94 % ee).

A new concept for the chiral-anion phase-transfer catalysis was reported by Toste [110] in the synthesis of octahydroisoquinoline derivatives [111]. Respect to the previous described methodologies, in which the counter ion is surrounding the nucleophiles in a homogeneous solution, the strategy developed by Toste is able to bring an insoluble cationic reagent into the solution. An electrophilic fluorinating reagent (Selectfluor), insoluble in nonpolar media, is brought into an apolar solution by the anion exchange with a lipophilic, bulky chiral phosphate anion. With this strategy an enantioselective 1,4-

aminofluorocyclization of 1,3-dienes **96** that gave in good yield and stereoselectivity benz[*f*]isoquinolines **98** through an 6-*endo-trig* cyclization was described (Scheme 31).

9 Conclusion and Perspective

In this brief and limited overview we have presented a few of the activation modes that can be used in designing successful organocatalytic reactions to access isoquinoline derivatives in a stereocontrolled manner. Many other activations modes, such as dienamine [112], trienamine [113] and tetraenamine [114] catalysis, SOMO reactions [115] and β -activation of simple aldehyde substrates [116] will be certainly explored in near future in the synthesis of useful intermediates. Stereoselective addition of ketones [117] and γ -alkylation with unsaturated aldehydes [118] to isoquinolinium are possible and will be presented. All these reactions, that occurred in simple and scalable conditions, will certainly help medicinal chemists to prepare analogous

of alkaloids, leading to the discovery of new effective and powerful drugs.

References

- Shamma M (1972) *The Isoquinoline Alkaloids*, Vol 25. Academic Press, London or Verlag Chemie, Weinheim
- Kittakoop P, Mahidol C, Ruchirawat S (2014) *Curr Top Med Chem* 14:239
- Hesse M (2002) *Alkaloids: nature's curse or blessing?* Wiley-VCH, Weinheim
- Rozwadowska MD (1994) *Heterocycles* 39:903
- Czarnocki Z, Siwicka A, Szawalko J (2005) *Curr Org Chem* 2:301
- Ahamed M, Todd MH (2010) *Eur J Org Chem* 31:5935–5942
- Bentley KW (2006) *Nat Prod Rep* 23: 444 and previous reviews in this series
- Reissert A (1905) *Ber Dtsch Chem Ges* 38:1603
- Takamura M, Funabashi K, Kanai M, Shibasaki M (2001) *J Am Chem Soc* 123:6801
- Lin W, Cao T, Fan W, Han Y, Kuang J, Luo H, Miao B, Tang X, Yu Q, Yuan W, Zhang J, Zhu C, Ma S (2014) *Angew Chem Int Ed* 53:277 and references therein
- Ye ZS, Guo RN, Cai XF, Chen MW, Shi L, Zhou YG (2013) *Angew Chem Int Ed* 52:3685
- Wu Z, Perez M, Scalone M, Ayad T, Ratovelomanana-Vidal V (2013) *Angew Chem Int Ed* 52:4925
- Wilson YM, Dürrenberger M, Nogueira ES, Ward TR (2014) *J Am Chem Soc* 136:8928
- List B, Lerner RA, Barbas III CF (2000) *J Am Chem Soc* 122:2395
- Ahrendt KA, Borths JC, MacMillan DWC (2000) *J Am Chem Soc* 122:4243
- MacMillan DWC (2008) *Nature* 455:304
- Burés J, Dingwall P, Armstrong A, Blackmond DG (2014) *Angew Chem Int Ed* 53:8700
- Mayr H, Lakhdar S, Maji B, Ofial AR (2012) *Beilstein J Org Chem* 8:1458
- Marquès-López E, Herrera RP, Christmann M (2010) *Nat Prod Rep* 27:1138
- Ricci A (2014) *ISRN Org Chem*. doi:10.1155/2014/531695
- Mukherjee S, Yang JW, Hoffmann S, List B (2007) *Chem Rev* 107:5471
- Erkkilä A, Majander I, Pihko PM (2007) *Chem Rev* 107:5416
- Petruzzello D, Stenta M, Mazzanti A, Cozzi PG (2013) *Chem Eur J* 19:7696
- Moran A, Hamilton A, Bo C, Melchiorre P (2013) *J Am Chem Soc* 135:9091
- Seebach D, Groselj U, Badine DM, Schweizer WB, Beck AK (2008) *Helv Chim Acta* 91:1999
- Palomo C, Mielgo A (2006) *Angew Chem Int Ed* 45:7876
- Hoang L, Bahmanyar S, Houk KN, List B (2003) *J Am Chem Soc* 125:16
- Mayr H, Bug T, Gotta MF, Hering N, Irrgang B, Janker B, Kempf B, Loos R, Ofial AR, Remennikov G, Schimmel H (2001) *J Am Chem Soc* 123:9500
- Mayr H, Ofial AR (2008) *J Phys Org Chem* 21:584
- Mayr H, Kempf B, Ofial AR (2003) *Acc Chem Res* 36:66
- Gualandi A, Cozzi PG (2013) *Synlett* 24:281
- Boess E, Schmitz C, Klussmann M (2012) *J Am Chem Soc* 134:5317
- Boess E, Sureshkumar D, Sud A, Wirtz C, Farès C, Klussmann M (2011) *J Am Chem Soc* 133:8106
- Lakhdar S, Tokuyasu T, Mayr H (2008) *Angew Chem Int Ed* 47:8723
- Knowles RR, Jacobsen EN (2010) *PNAS* 107:20668
- Yoon TP, Jacobsen EN (2003) *Science* 299:1691
- Enders D, Niemeier O, Henseler A (2007) *Chem Rev* 107:5606
- Morrill LC, Smith AD (2014) *Chem Soc Rev* 43:6214
- Grossmann A, Enders D (2012) *Angew Chem Int Ed* 51:314
- Maji B, Mayr H (2013) *Angew Chem Int Ed* 52:11163
- Maji B, Mayr H (2012) *Angew Chem Int Ed* 51:10408
- Phillipson JD, Roberts MF, Zenk MH (eds) (1985) *The chemistry and biology of isoquinoline alkaloids*. Springer Verlag, Berlin
- Chrzanowska M, Rozwadowska MD (2004) *Chem Rev* 104:3341
- Frisch K, Landa A, Saaby S, Jørgensen KA (2005) *Angew Chem Int Ed* 44:6058
- Akiba K, Nakatani M, Wada M, Yamamoto Y (1985) *J Org Chem* 50:63
- Mengozi L, Gualandi A, Cozzi PG (2014) *Chem Sci* 5:3915
- Calonghi N, Naso F, Mengozzi L, Gualandi A, Cozzi PG, unpublished results
- Mattioli EJ, Mengozzi L, Gualandi A, Cozzi PG, unpublished results
- Taylor MS, Tokunaga N, Jacobsen EN (2005) *Angew Chem Int Ed* 44:6700
- Schafer AG, Wieting JM, Fisher TJ, Mattson AE (2013) *Angew Chem Int Ed* 52:11321
- De Kanta C, Mittal N, Seidel D (2011) *J Am Chem Soc* 133:16802
- Höfle G, Steglich W, Vorbrüggen H (1978) *Angew Chem Int Ed Engl* 17:569
- De Kante C, Seidel D (2011) *J Am Chem Soc* 133:14538
- Girard SA, Knauber T, Li CJ (2014) *Angew Chem Int Ed* 53:74
- Cherevatskaya M, Neumann M, Fuldner S, Harlander C, Kümmel S, Dankesreiter S, Pfitzner A, Zeitler K, König B (2012) *Angew Chem Int Ed* 51:4062
- Dhineshkumar J, Lamani M, Alagiri K, Prabhu KR (2013) *Org Lett* 15:1092
- Xue Q, Xie J, Jin H, Cheng Y, Zhu C (2013) *Org Biomol Chem* 11:1606
- Zhang J, Tiwari B, Xing C, Chen X, Chi YR (2012) *Angew Chem Int Ed* 51:3649
- Zhang G, Ma Y, Wang S, Kong W, Wang R (2013) *Chem Sci* 4:2645
- Shi Z, Zhang C, Tang C, Jiao N (2012) *Chem Soc Rev* 41:3381
- Zhang G, Ma Y, Wang S, Zhang Y, Wang R (2012) *J Am Chem Soc* 134:12334
- Neel AJ, Hehn JP, Triplet PF, Toste FD (2013) *J Am Chem Soc* 135:14044
- Hein JE, Fokin VV (2010) *Chem Soc Rev* 39:1302
- Nicewicz D, MacMillan DWC (2008) *Science* 322:77
- Prier CK, Rankic DA, MacMillan DWC (2013) *Chem Rev* 113:5322
- Di Rocco DA, Rovis T (2012) *J Am Chem Soc* 134:8094
- Ryan SJ, Candish L, Lupton DW (2013) *Chem Soc Rev* 42:4906
- Vora HU, Rovis T (2011) *Aldrichimica Acta* 44:3
- For the chemistry related of carbene intermediate oxidation, see: Mo J, Shen L, Chi RY (2013) *Angew Chem Int Ed* 52:8588
- Bergonzini G, Schindler CS, Wallentin CJ, Jacobsen EN, Stephenson CRJ (2014) *Chem Sci* 5:112
- Stöckigt J, Antonchick AP, Wu F, Waldmann H (2011) *Angew Chem Int Ed* 50:8538
- Taylor MS, Jacobsen EN (2004) *J Am Chem Soc* 126:10558
- Raheem IT, Thiara PS, Peterson EA, Jacobsen EN (2007) *J Am Chem Soc* 129:13404
- Lin S, Jacobsen EN (2012) *Nature Chem* 4:817

75. Klausen RS, Jacobsen EN (2009) *Org Lett* 11:887
76. Seayad J, Seayad AM, List B (2006) *J Am Chem Soc* 128:1086
77. Wanner MJ, Van der Haas RNS, De Cuba KR, Van Maarseveen JH, Hiemstra H (2007) *Angew Chem Int Ed* 46:7485
78. Sewgobind NV, Wanner MJ, Ingemann S, De Gelder R, Van Maarseveen JH, Hiemstra H (2008) *J Org Chem* 73:6405
79. Herlé B, Wanner MJ, Van Maarseveen JH, Hiemstra H (2011) *J Org Chem* 76:8907
80. Kerschgens IP, Claveau E, Wanner MJ, Ingemann S, Van Maarseveen JH, Hiemstra H (2012) *Chem Comm* 48:12243
81. Lee Y, Klausen RS, Jacobsen EN (2011) *Org Lett* 13:5564
82. Mons E, Wanner MJ, Ingemann S, Van Maarseveen JH, Hiemstra H (2014) *J Org Chem* 79:7380
83. Ruijter E, Scheffelaar R, Orru RVA (2011) *Angew Chem Int Ed* 50:6234
84. Ozawa M, Kawamata S, Etoh T, Hayashi M, Komiyama K, Kishida A, Kuroda C, Ohsaki A (2010) *Chem Pharm Bull* 58:1119
85. Pla D, Albericio F, Álvarez M (2011) *Med Chem Commun* 2:689
86. Fraile A, Scarpino Schietroma DM, Albrecht A, Davis RL, Jørgensen KA (2012) *Chem Eur J* 18:2773
87. Chen Z, Wang B, Wang Z, Zhu G, Sun J (2013) *Ang Chem Int Ed* 52:2027
88. Cozzi PG, Benfatti F, Zoli L (2009) *Angew Chem Int Ed* 48:1313
89. Shi F, Zhu RY, Dai W, Wang CS, Tu SJ (2014) *Chem Eur J* 20:2597
90. Huang J, Luo S, Gong L (2013) *Acta Chim Sin* 71:879
91. Lalonde MP, McGowan MA, Rajapaksa NS, Jacobsen EN (2013) *J Am Chem Soc* 135:1891
92. Rajapaksa NS, McGowan MA, Rienzo M, Jacobsen EN (2013) *Org Lett* 15:706
93. Terada M (2011) *Curr Org Chem* 15:2227
94. Muratore ME, Holloway CA, Pilling AW, Storer RI, Trevitt G, Dixon DJ (2009) *J Am Chem Soc* 131:10796
95. Muratore ME, Shi L, Pilling AW, Storer RI, Dixon DJ (2012) *Chem Comm* 48:6351
96. Holloway CA, Muratore ME, Storer RI, Dixon DJ (2010) *Org Lett* 12:4720
97. Aillaud I, Barber DM, Thompson AL, Dixon DJ (2013) *Org Lett* 15:2946
98. Gómez-SanJuan A, Sotomayor N, Lete E (2012) *Tetrahedron Lett* 53:2157
99. Terada M (2010) *Synthesis* 12:1929
100. Akiyama T (2007) *Chem Rev* 107:5744
101. Yin Q, Wang SG, You SL (2013) *Org Lett* 15:2688
102. Zheng C, You SL (2012) *Chem Soc Rev* 41:2498
103. Horn M, Schappele LH, Lang-Wittkowski G, Mayr H, Ofial AR (2013) *Chem Eur J* 19:249
104. Enders D, Liebich JX, Raabe G (2010) *Chem Eur J* 16:9763
105. Qin TY, Liao WW, Zhang JY, Zhang SXA (2013) *Org Biomol Chem* 11:984
106. Liu TY, Xie M, Chen YC (2012) *Chem Soc Rev* 41:4101
107. Rios R (2012) *Catal Sci Technol* 2:267
108. Shirakawa S, Maruoka K (2013) *Ang Chem Int Ed* 52:4312
109. Shirakawa S, Liu K, Ito H, Le TN, Maruoka K (2011) *Adv Synth Catal* 353:2614
110. Rauniyar V, Lackner AD, Hamilton GL, Toste FD (2011) *Science* 334:1681
111. Shunatona HP, Früh N, Wang YM, Rauniyar V, Toste FD (2013) *Angew Chem Int Ed* 52:7724
112. Albrecht L, Dickmeiss G, Acosta FC, Rodríguez-Escrich C, Davis RL, Jørgensen KA (2012) *J Am Chem Soc* 134:2543
113. Kumar I, Ramaraju P, Mir NA (2013) *Org Biomol Chem* 11:709
114. Stiller J, Poulsen PH, Cruz DC, Dourado J, Davis RL, Jørgensen KA (2014) *Chem Sci* 5:2052
115. Devery JJ III, Conrad JC, MacMillan DWC, Flowers RA II (2010) *Angew Chem Int Ed* 49:6106
116. Pirnot MT, Rankic DA, Martin DBC, MacMillan DWC (2013) *Science* 339:1593
117. Benelli C, Gualandi A, Mengozzi L, Cozzi PG, manuscript in preparation
118. Gualandi A, Mengozzi L, Cozzi PG, manuscript in preparation