



**A general overview on the organocatalytic intramolecular  
aza-Michael reaction**

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**ARTICLE TYPE****A general overview on the organocatalytic intramolecular *aza*-Michael reaction**María Sánchez-Roselló,<sup>\*a,b</sup> José Luis Aceña,<sup>c</sup> Antonio Simón-Fuentes<sup>a</sup> and Carlos del Pozo<sup>\*a</sup><sup>5</sup> Dedicated to Professor Santos Fustero on the occasion of his 65th birthday

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The organocatalytic intramolecular *aza*-Michael reaction gives entry to enantiomerically enriched nitrogen-containing heterocycles in a very simple manner. Enals, enones, conjugated esters and nitro olefins have been employed as Michael acceptors, while moderate nitrogen nucleophiles such as sulphonamides, carbamates or amides have shown to be appropriate Michael donors in this type of reaction. Additionally, the process has been performed under both covalent and non-covalent catalysis, being diaryl prolinols, imidazolidinones, thioureas and chiral binol phosphoric acids the most frequently used catalysts. The level of efficiency reached with this protocol is exemplified in the implementation of numerous tandem processes as well as in the total synthesis of several natural products.

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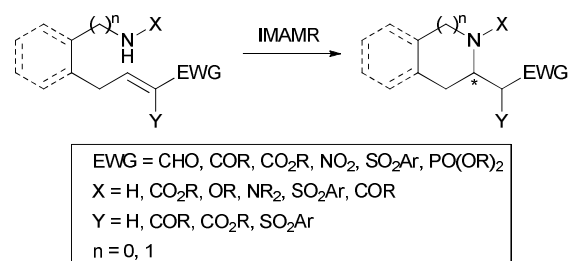
**1. Introduction**

Among the numerous carbon-carbon and carbon-heteroatom bond-forming reactions, conjugated additions play a prominent role in organic chemistry. Indeed, the 1,4-addition of nucleophilic species to alkenes substituted with electron-withdrawing groups is one of the most important and versatile chemical reactions due to the large variety of nucleophiles and alkene acceptors amenable to participate in it.

In 1887, Arthur Michael described the reaction that bears his name.<sup>1</sup> In this seminal paper, the addition of sodium malonate or sodium acetoacetate esters to  $\alpha,\beta$ -unsaturated esters was discussed. Although other examples of this type of process were observed before, A. Michael was the first chemist in recognizing the crucial importance of this transformation. For that reason, conjugate additions are generally named as Michael-type reactions.<sup>2</sup> An especially interesting kind of conjugate addition reactions involves the use of nitrogen-centered nucleophiles, the so-called *aza*-Michael reaction. In this transformation, extremely valuable synthetic intermediates are formed:  $\beta$ -amino carbonyl

derivatives, being  $\beta$ -amino acids the most representative example. A wide variety of nitrogen nucleophiles (amines, amides, oximes, carbamates, sulphonamides, hydrazines, azides or nitrogen-containing heterocycles) and Michael acceptors (conjugated aldehydes, ketones, esters, amides or nitriles, nitroolefins, vinyl sulfones or vinyl phosphonates) are good partners in this reaction. Additionally, the process can be performed under basic or acidic catalysis and even sometimes without catalyst. All these features, together with its simplicity and atom economy, convert the *aza*-Michael reaction in the most direct way to generate carbon-nitrogen bonds.

The intramolecular version of the *aza*-Michael reaction allows the preparation of nitrogen heterocycles in a single step (Scheme 1). Since *N*-heterocyclic compounds are common structural features in a great variety of biologically active substances, this transformation has found wide applicability in the synthesis of heterocycles and natural products.<sup>3</sup>

**Scheme 1** Intramolecular *aza*-Michael reaction (IMAMR)

In the conjugated addition process, the generation of one or more stereogenic centers takes place. Therefore, in the asymmetric version of the intramolecular *aza*-Michael reaction (IMAMR), enantiomerically enriched nitrogen heterocycles are

obtained. In this context, the more classical asymmetric *aza*-Michael reactions rely on the use of chiral auxiliaries, chiral starting materials, or stoichiometric amounts of chiral ligands. However, the catalytic asymmetric version still represents a significant challenge in organic synthesis.

The use of small molecules to catalyse organic transformations, the so-called organocatalysis, has witnessed an extraordinary growth since the pioneering work of MacMillan,<sup>4</sup> List and Barbas III in 2000.<sup>5</sup> Actually, this methodology is nowadays considered as the third pillar that sustains enantioselective catalysis, together with metal-mediated and biocatalytic transformations. The overwhelming success of organocatalysis has also reached the *aza*-Michael reaction. After the first efficient and general protocol for the intermolecular enantioselective organocatalytic *aza*-Michael reaction reported by MacMillan in 2006,<sup>6</sup> this reaction has been the subject of an intensive research. Several examples of analogous transformations were described soon after, mostly based on the use of conjugated aldehydes as Michael acceptors with different nucleophilic nitrogen sources, such as carbamates,<sup>7</sup> succinimides,<sup>8</sup> hydrazones,<sup>9</sup> triazoles,<sup>10</sup> tetrazoles<sup>11</sup> or indols<sup>12,13</sup> among others. Although the first organocatalytic IMAMR had been reported back in 2003,<sup>14</sup> this reaction was clearly much less studied than its intermolecular counterpart. This was probably due to the difficulties generally associated with the organocatalytic intramolecular process. The first one is the generation of both the nitrogen nucleophile and the Michael acceptor at the same time, thus avoiding a spontaneous cyclisation that may take place with free amines, oximes or hydrazones and  $\alpha,\beta$ -unsaturated aldehydes or ketones. The second problem, shared with both the inter- and intramolecular versions, is related to the catalytic system. Typically, in these transformations the activation by the catalyst occurs at the Michael acceptor, according to an enamine or iminium activation mode. Considering the amine nature of the catalysts usually employed, a possible competition between the catalyst and the nitrogen-centered nucleophile can take place. These two issues have to be overcome and, therefore, an accurate choice of the catalyst and the nitrogen nucleophile becomes a crucial factor in order to develop an efficient organocatalytic IMAMR.

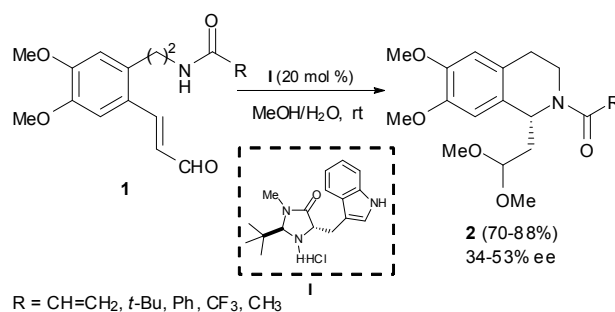
In this review, we wish to present an overview of the examples reported in the literature for carrying out the IMAMR in an enantioselective manner by using organocatalysis as the methodological approach. The review has been organised focusing on the nature of the Michael acceptor. It also includes the applications of the IMAMR in tandem protocols and ends up highlighting the use of this reaction in the synthesis of natural products. Several reviews covering the organocatalytic *aza*-Michael reaction have been published to date.<sup>15-17</sup> However, none of them is focused specifically in the intramolecular version and we consider it is relevant enough to be treated by itself, as a substantial number of reports dealing with this topic in the last three years corroborates.

## 2. Conjugated aldehydes as Michael acceptors

$\alpha,\beta$ -Unsaturated aldehydes are ubiquitous substrates in organocatalyzed reactions. They can be activated by addition of small amounts of secondary amines by means of an iminium

activation mode (LUMO activation), as it was early demonstrated by MacMillan.<sup>4</sup> In this type of activation, the organocatalyst facilitates the addition of the nucleophile to the beta-carbon shielding, at the same time, one of the enantiotopic faces of the enal. As mentioned before, in the intramolecular *aza*-Michael reaction “the nature” of the Michael acceptor determines both the type of catalysis and the choice of the nucleophilic nitrogen source. In this context, the use of nitrogen donors with moderate nucleophilicity such as carbamates or sulphonamides is crucial in the success of the process, since no spontaneous cyclisation onto the conjugated aldehyde takes place, which would compromise the enantioselectivity. Additionally, the different nucleophilicity of the catalyst and the nitrogen source avoids their competition in reacting with the starting aldehyde.

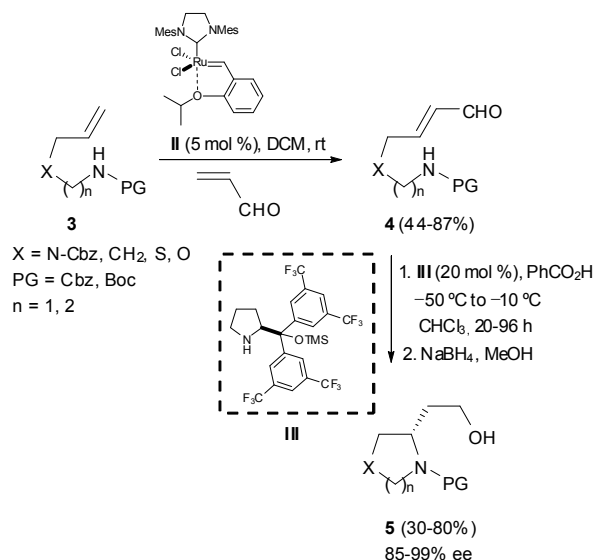
The first example of an organocatalytic IMAMR was reported by Ihara in 2003.<sup>14</sup> Dopamine derivatives **1** underwent cyclisation in the presence of chiral imidazolidinone **I** (MacMillan’s type catalyst) to render tetrahydroquinolines **2** in good yields and modest enantioselectivity. The reaction was performed in aqueous methanol and the final products were isolated as the corresponding acetals. The amide functionality was chosen as the nucleophilic nitrogen source and, due to its low nucleophilicity, the process needed 10 days to complete. (Scheme 2).



**Scheme 2** First IMAMR with enals as acceptors

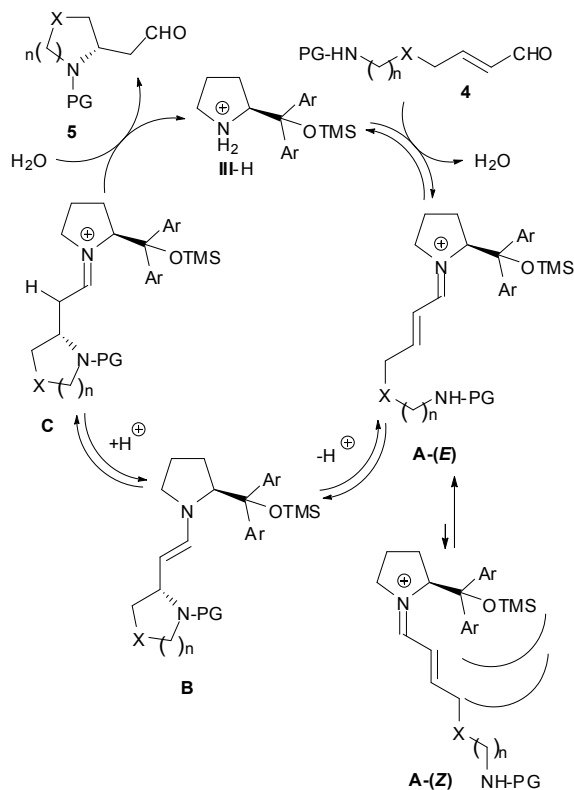
The second example was reported in 2007 and also took advantage of the iminium catalysis with secondary amines.<sup>18</sup> In this case, Jørgensen-Hayashi diaryl prolinols were the catalysts of choice and carbamates were the nucleophilic nitrogen source. These changes led to achieve excellent yields and ee’s in the IMAMR for the straightforward synthesis of several nitrogen-containing heterocycles (Scheme 3).

One of the keys for the success of this protocol was the use of the cross metathesis reaction for the generation of the IMAMR substrates **4**. They were assembled by reaction of the corresponding carbamates **3** bearing a remote olefin with acrolein in the presence of second generation Hoveyda-Grubbs catalyst **II**. The reaction proceeded at room temperature and no spontaneous cyclisation of enals **4** was detected. After optimization, we found that diarylprolinol **III** was the best catalyst for the IMAMR. Thus, reaction of substrates **4** in the presence of **III** and benzoic acid as an additive in CHCl<sub>3</sub> at temperatures ranging from -50 °C to -10 °C, afforded a small family of 5- and 6-membered ring heterocycles **5** in moderate to good yields and excellent enantioselectivities (Scheme 3).<sup>19</sup>



**Scheme 3** Asymmetric synthesis of *N*-heterocycles through cross metathesis (CM) followed by IMAMR

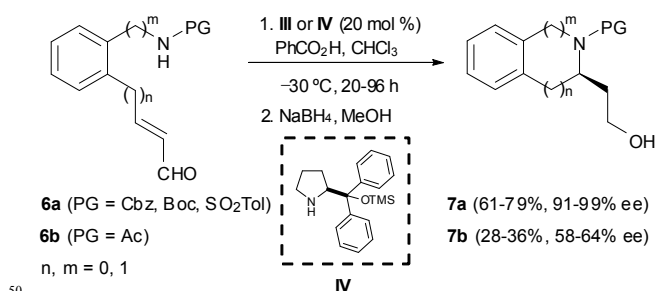
At this point it is important to mention a remarkable difference between the inter- and the intramolecular *aza*-Michael reactions. The intermolecular process usually takes place at room temperature and *N*-silyloxycarbamates are employed as the nucleophilic nitrogen source in order to enhance the nucleophilicity of the nitrogen by the alpha effect. In the intramolecular version, the activation of the carbamate is not necessary and, additionally, the reaction takes place at low temperatures, allowing for a better stereochemical control and also indicating that the intramolecular process is more favoured kinetically.



**Scheme 4** Mechanism of the IMAMR with  $\alpha,\beta$ -unsaturated aldehydes **4**

The mechanism commonly invoked to rationalize the organocatalytic conjugate addition of nitrogen nucleophiles to  $\alpha,\beta$ -unsaturated aldehydes involves activation of the substrate **4** by the catalyst through the formation of an iminium salt (**A**, Scheme 4). Among the two possible conformations of this salt, the *E*-isomer is less hindered and the *si* face is shielded by the bulky group of the catalyst. Consequently, the attack of the nitrogen nucleophile to the  $\beta$ -carbon takes place from the opposite side, giving rise to enamine intermediate **B**. Tautomeric equilibrium to intermediate **C** and hydrolysis of this iminium salt release the final product **5** and the catalytic species, thus closing the catalytic cycle (Scheme 4).<sup>20</sup>

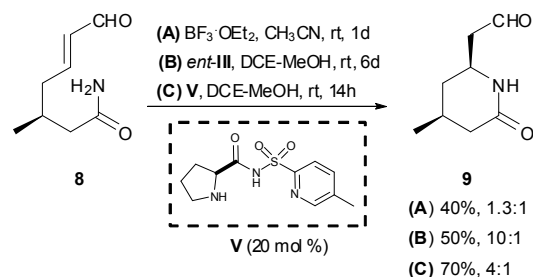
The extension of this protocol to benzofused derivatives allowed obtaining enantiomerically enriched indolines, isoindolines, tetrahydroquinolines and tetrahydroisoquinolines **7a,b** (Scheme 5).<sup>21</sup> In this case, both the fluorinated and non-fluorinated diarylprolinols **III** and **IV** were effective in the IMAMR, giving rise to excellent yields and enantioselectivities of the final products when carbamates or sulphonamides (**6a**) were used as nitrogen sources. However, the reaction with acetamides **6b** led to poor yields and enantiomeric excesses. From these results it seems clear that the decrease of the nucleophilicity of the nitrogen source in the IMAMR results in lower yields and ee values of the final products. This fact can be rationalized assuming that the conjugate addition with acetyl amides **6b** is much slower compared with carbamates (**6a**) and alternative reaction pathways promoted by protons liberated during the process (Brønsted acid catalysis) apparently became more important. This is a non-selective process that competes with the iminium activation by the organocatalyst, which translates into the decrease of the selectivity in the overall process.



**Scheme 5** IMAMR for the synthesis of benzofused nitrogen heterocycles

Very recently, Carter and co-workers found that primary amides are good partners in this reaction giving rise to  $\delta$ -lactams.<sup>22</sup> When amide **8** was cyclised in the presence of an achiral Lewis acid (Scheme 6, conditions A), no selectivity was observed in the IMAMR. The use of the enantiomer of diarylprolinol **III** (see Scheme 3) as the catalyst led to the formation of compound **9** in moderate yield and good diastereoselectivity after 6 days at room temperature (Scheme 6, conditions B),<sup>23</sup> whereas proline sulphonamide **V** accelerated the process affording the desired product **9** in 70% yield after 14 h, although with some erosion in the selectivity (Scheme 6,

conditions C).



Scheme 6 IMAMR on chiral primary amide **8**

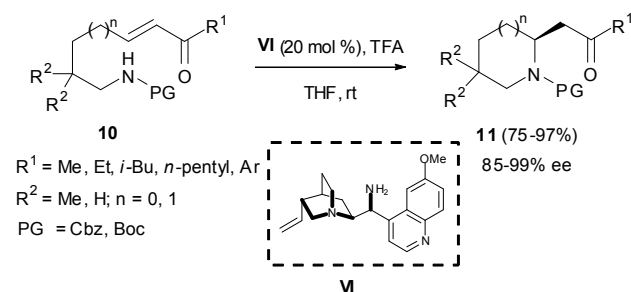
### 3. Conjugated ketones as Michael acceptors

Although asymmetric aminocatalysis has been proven to be a powerful tool for the enantioselective functionalization of carbonyl compounds, the iminium activation of unsaturated ketones has been far less developed than their aldehyde counterparts. The equilibrium constants for the iminium ion formation are greatly influenced by steric constraints. The steric congestion associated with the formation of iminium ions from ketones and the secondary amines usually employed as catalysts, together with lower electronic affinity of ketones toward iminium formation and the issues associated with the more difficult control of the iminium geometry could explain this tendency.

The incorporation of chiral primary amines as catalysts was crucial for the application of classical activation modes in aminocatalysis with secondary amines (proline, diaryl prolinols or imidazolidinones) to more sterically demanding ketones.<sup>24</sup> Particularly, the incorporation of a primary amine function to the privileged framework of Cinchona alkaloids, simple organic molecules provided by Nature, played a prominent role in the last few years, allowing to expand the utility of aminocatalysis.<sup>25</sup> Recently, MacMillan highlighted the privileged nature of quinine-derived primary amines: these catalysts provided by far the best enantioselectivity (>90% ee) in the  $\alpha$ -fluorination reaction of ketones among 250 different catalysts screened.<sup>26</sup>

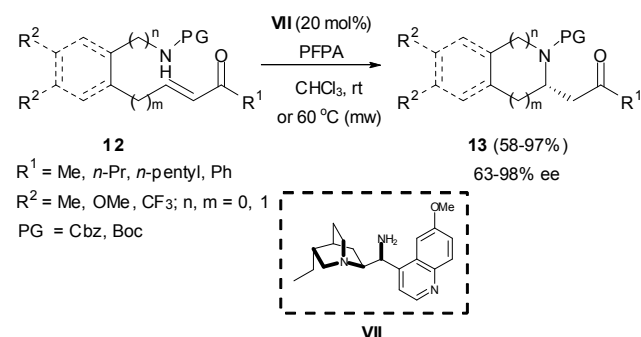
Regarding the *aza*-Michael reaction with conjugated ketones as Michael acceptors, the first organocatalytic enantioselective example was independently reported by Deng<sup>27</sup> and Melchiorre<sup>28</sup> in its intermolecular version. The combination of a 9-amino Cinchona alkaloid derivative and trifluoroacetic acid (TFA) or *D*-*N*-Boc-phenylglycine as co-catalysts led the authors to perform the enantioselective addition of *N*-silyloxycarbamates to conjugated ketones in excellent yields and ee's. In the case of the intramolecular version, the first general method of this protocol was reported three years later (2011) by Chen and Fan<sup>29</sup> and Fustero's research group almost simultaneously.<sup>30</sup> Both methods took advantage of the ability of 9-amino-9-deoxy-*epi*-(hydro)quinine to efficiently catalyse the IMAMR of ketones. Thus, conjugated ketones **10** underwent the reaction in the presence of catalyst **VI** and TFA as a co-catalyst in THF at room temperature to render heterocycles **11** in good yields and enantioselectivities (Scheme 7). The process was very efficient in the formation of 6-membered rings (>90% ee) while the formation of the corresponding pyrrolidines took place with

diminished enantioselectivity (80% ee).<sup>29</sup>



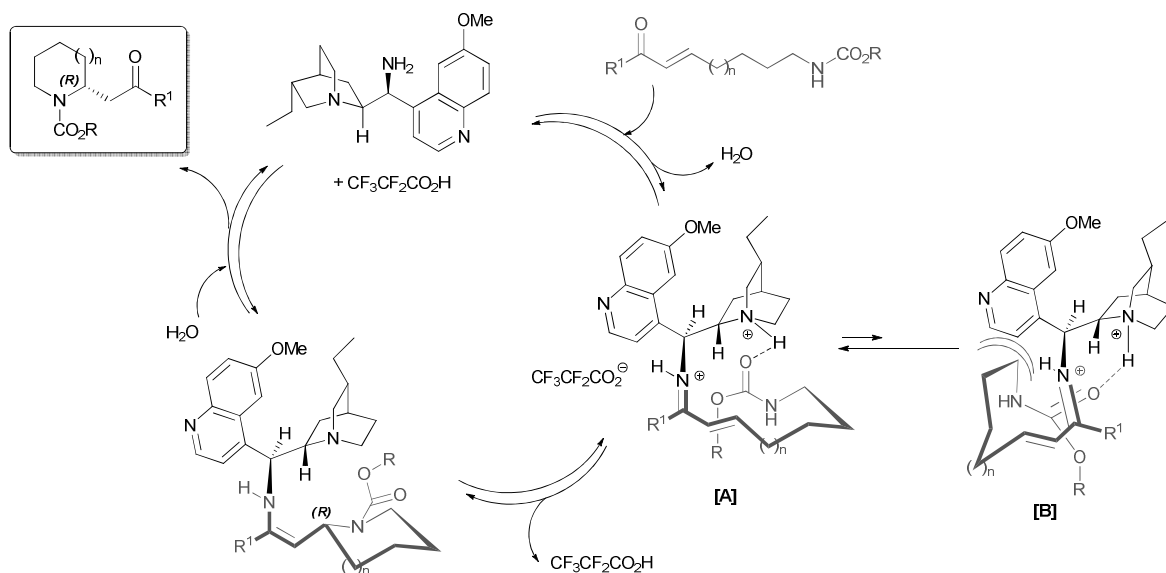
50 Scheme 7 IMAMR with conjugated ketones as acceptors (1)

This reaction was also very efficient in  $\text{CHCl}_3$  using pentafluoropropionic acid (PFPA) as a co-catalyst. Additionally, the protocol was extended to the organocatalyzed IMAMR on benzofused derivatives, allowing the synthesis of enantiomerically enriched indolines, isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines (Scheme 8).<sup>30</sup> It is worth noting that the presence of electron donating substituents (**12**,  $\text{R}^2 = \text{OMe}$ ), especially with aniline derivatives (**12**,  $n = 0$ ), enhances the nucleophilicity of the nitrogen thus improving enantioselection (>95% ee), while the presence of electron withdrawing substituents (**12**,  $\text{R}^2 = \text{CF}_3$ ) produces the opposite effect (63-68% ee). In addition, the process can be performed under microwave irradiation affording, after 1h at 60 °C, the desired products with comparable yields and enantioselectivities to those observed in the rt process.<sup>30</sup>



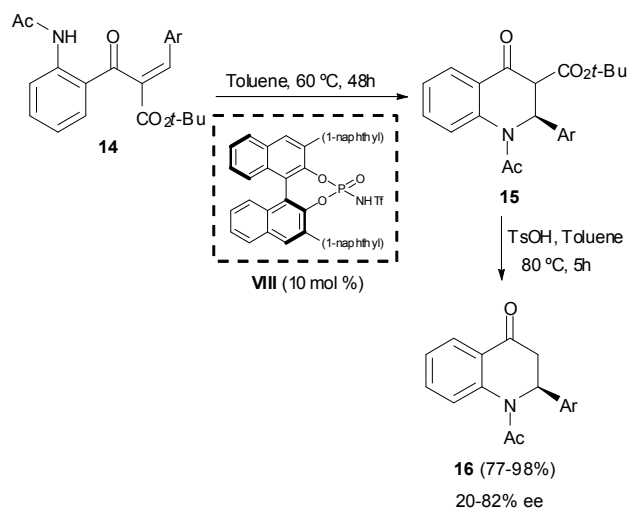
Scheme 8 IMAMR with conjugated ketones as acceptors (2)

As mentioned before, the mechanism commonly invoked to rationalize the organocatalytic conjugate additions of nitrogen nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds involves activation of the Michael acceptor by the catalyst through the formation of an iminium ion, thereby facilitating the intramolecular addition of the nucleophile to the  $\beta$ -carbon. Thus, the initial reaction of the primary amine (catalyst) with an enone gives rise to the corresponding iminium ion intermediate under acidic conditions (no reaction takes place in the absence of the acid).<sup>30</sup> Simultaneously, the quinuclidine nitrogen would be protonated and a hydrogen bond interaction would be established with the carbamate carbonyl oxygen, indicating the bifunctional nature of catalyst **VII**.<sup>31</sup> In this conformation, the attack of the nitrogen nucleophile would take place onto the *Re* face of the less sterically constrained (*E*)-iminium transition state **A** to furnish the *aza*-Michael product after hydrolysis in its *R* absolute configuration (Scheme 9).



**Scheme 9** Mechanism commonly accepted for the IMAMR with enones catalysed by 9-amino-9-deoxy-*epi*-hydroquinine.

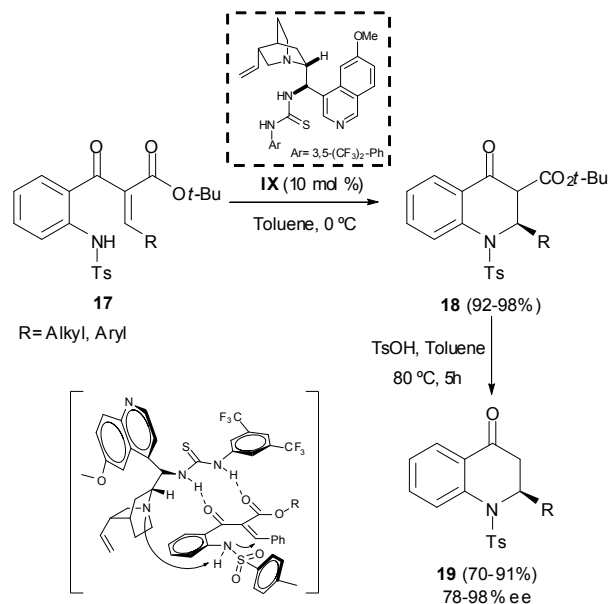
The aforementioned general methods for the IMAMR with ketones as Michael acceptors were described in 2011, however the first example was reported by You at the beginning of 2010.<sup>32</sup> It involved the use of substrate **14** bearing an acetamide as nitrogen source and a conjugated keto-ester as Michael acceptor with a chiral Brønsted acid as the catalyst. The authors envisioned that the presence of the keto-ester moiety would enhance the electrophilicity of the Michael acceptor. After heating compounds **14** in the presence of chiral *N*-triflyl binolphosphoramidate **VIII** in toluene at 60 °C during 48 h, good yields of the corresponding dihydroquinolones **15** were obtained. Decarboxylation of **15** by heating in toluene and *p*-toluenesulfonic acid rendered final dihydroquinolones **16** in good yields and moderate enantioselectivities (Scheme 10).



**Scheme 10** Synthesis of dihydroquinolones through an IMAMR on conjugated keto-ester derivatives (1)

This methodology for the preparation of the biologically relevant dihydroquinolone substructure was later improved by Lu.<sup>33</sup> The use of sulphonamides as nucleophilic nitrogen source, in combination with chiral thiourea **IX** as catalyst, led the authors

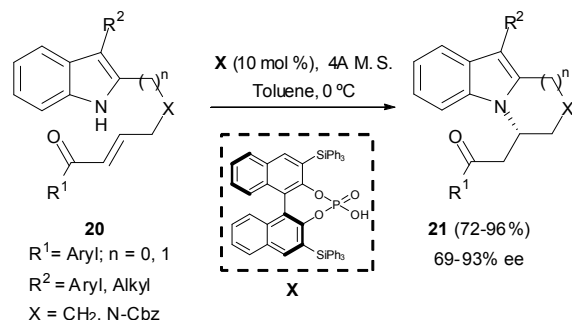
to perform the cyclization at 0 °C in very good yields and excellent levels of enantioselectivity. Subsequent decarboxylation afforded final products **19** in very good yields (Scheme 11). In the proposed transition state of this process, compound **17** interacts with the thiourea group of the catalyst through hydrogen bonds. Additionally, the tertiary amine of a quinuclidine moiety also present in the catalyst removes the acidic sulphonamide proton and promotes the diastereoselective nucleophilic attack to render quinolones **18** (Scheme 11).



**Scheme 11** Synthesis of dihydroquinolones through an IMAMR on conjugated keto-ester derivatives (2)

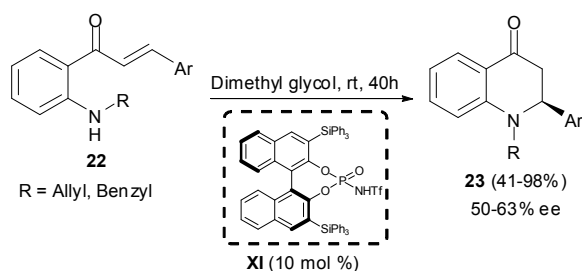
Almost at the same time, the nucleophilic addition of an indolic nitrogen to aromatic ketones catalysed by a chiral Brønsted acid was reported.<sup>34</sup> Thus, indole derivatives **20** bearing a remote chalcone functionality in the 2 position underwent the IMAMR in the presence of binol phosphoric acid **X** and molecular sieves in

toluene at 0 °C. Tricyclic indoles **21** were obtained in good yields and excellent ee's (Scheme 12).



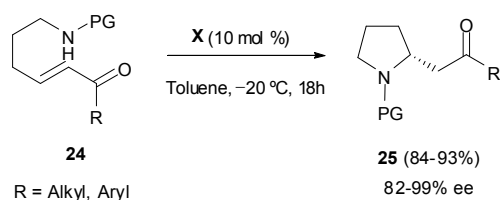
**Scheme 12** IMAMR on 2,3-disubstituted indole derivatives **20**

In 2012 Rueping reported a different methodology for the synthesis of dihydroquinolones also based on an IMAMR as the key step. Starting from *N*-allyl or *N*-benzyl anilines **22** substituted with a chalcone moiety in the *ortho* position, the cyclisation in the presence of chiral *N*-triflyl binolphosphoramidate **XI** in dimethyl glycol at room temperature afforded dihydroquinolones **23** in moderate to very good yields and moderate enantioselectivities (Scheme 13).<sup>35</sup>



**Scheme 13** IMAMR on conjugated ketone derivatives for the synthesis of dihydroquinolones **23**

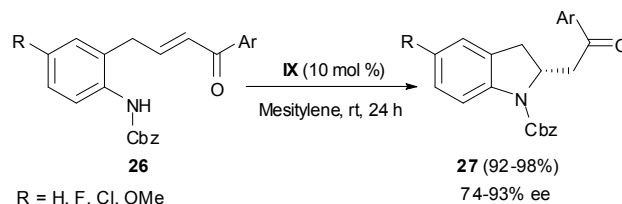
As mentioned before, the synthesis of pyrrolidines employing amino quinine-derived catalyst **VI** (see Scheme 7) was less efficient in terms of enantioselectivity than their piperidine analogues. From the observation that this cyclization takes place in the presence of catalytic amounts of TFA, Yu and co-workers envisioned that the use of a chiral Brønsted acid would enhance the selectivity of the process. After some optimization, the authors found that enone carbamates **24** underwent the IMAMR in the presence of chiral binol phosphoric acid **X** (see Scheme 12) to render the desired pyrrolidines **25** with improved enantioselectivities (Scheme 14).<sup>36</sup>



**Scheme 14** Synthesis of pyrrolidines through an IMAMR catalysed by phosphoric acid **X**

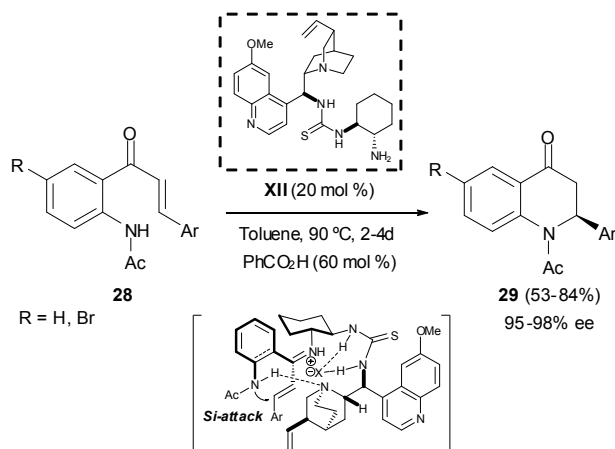
Matsubara and Asano described in 2013 the synthesis of indolines by means of a non-covalent type catalysis. In this work, substituted *N*-benzyloxycarbonyl anilines **26** cyclised at room

temperature in the presence of bifunctional quinine-derived thiourea **IX** (see Scheme 11) giving rise to the final indolines **27** in good yields and enantioselectivities.<sup>37</sup> It is important to point out that best results were obtained with aromatic conjugated ketones as Michael acceptors (Scheme 15).



**Scheme 15** Synthesis of 2-substituted indolines through an IMAMR with conjugated ketones as acceptors

The last example of an IMAMR with conjugated ketones as Michael acceptors has been very recently reported. In this work, amino chalcones **28** underwent a 6-*endo* IMAMR in the presence of bifunctional thiourea **XII** and benzoic acid as a co-catalyst to render *aza*-flavanones **29** in good yields and excellent enantioselectivities.<sup>38</sup> Among the different *N*-protections employed, the acetamide gave the best results, even though it was necessary to heat the reaction at 90 °C for several days to obtain the yields depicted in Scheme 16. This example is a nice combination of an iminium-type activation of the Michael acceptor with a non-covalent activation (hydrogen bonding) of the nitrogen nucleophile.



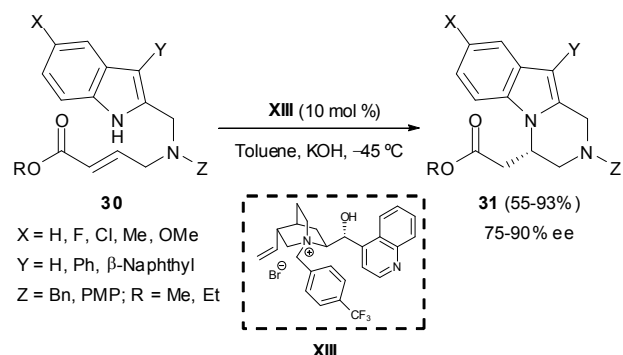
**Scheme 16** Synthesis of *aza*-flavanones **29** through an IMAMR on conjugated ketones **28**

#### 4. Conjugated amides, esters and thioesters as Michael acceptors

Ester functionality plays a central role in biological and synthetic organic transformations. However, its organocatalytic activation via iminium/enamine intermediates is not possible (like in the aldehyde or ketone analogues). Precisely the activation of the Michael acceptor is the usual way to proceed in the IMAMR, which explains why the use of conjugated esters in this process still remains a big challenge. Other types of activation are required being non-covalent catalysis the appropriate choice in most cases.

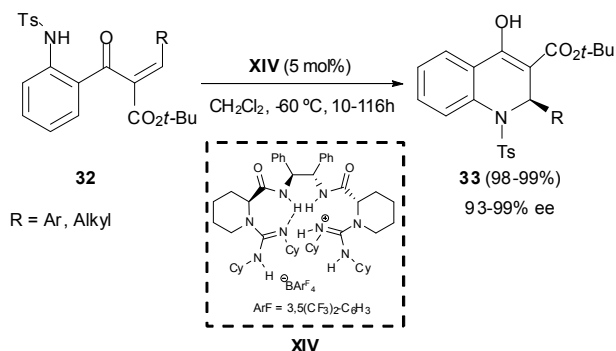
The first example of an IMAMR with conjugated esters as

Michael acceptors was reported in 2008 by Bandini and Umani-Ronchi.<sup>39</sup> It involved the addition of indolic nitrogens by means of phase transfer catalysis with cinchona-derived salts. Thus, indole derivatives **30** underwent cyclisation in the presence of *N*-benzylcinchonidinium bromide **XIII** and KOH at  $-45\text{ }^{\circ}\text{C}$  furnishing tricyclic derivatives **31** in good yields and enantioselectivities up to 90% (Scheme 17). The enantiodiscrimination was ascribed to the formation of a tight ion pair between the ammonium salt of the quinuclidine ring and the nucleophilic indolate intermediate. Free hydroxyl group in catalyst **XIII** resulted crucial to maintain the ee values, together with the presence of an electron-withdrawing substituent at the benzyl group, since they are known to favour tighter contact ion pairing. A detailed mechanistic study combining theoretical and experimental investigations was carried out by the authors, providing the aforementioned key aspects of the reaction outcome.<sup>40</sup>



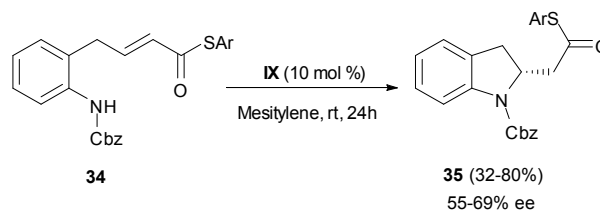
**Scheme 17** First example of an organocatalytic IMAMR with conjugated esters as acceptors

Liu and Feng reported the preparation of optically active 2,3-dihydroquinolin-4-one scaffolds using conjugated keto esters as Michael acceptors. Tosyl amides **32** reacted in dichloromethane at  $-60\text{ }^{\circ}\text{C}$  in the presence of chiral bisguanidinium salt **XIV** to afford tautomerized dihydroquinolones **33** in excellent yields and enantioselectivity (Scheme 18).<sup>41</sup> The presence of the keto ester functionality increased the electrophilicity of the  $\beta$ -carbon for the Michael addition and, at the same time, provided more sites for potential interactions with the catalyst. In this context, the use of polar solvents was translated into a dramatic decline of the selectivity, probably due to the adverse effect on the hydrogen bonding interactions between the substrate and the catalyst.



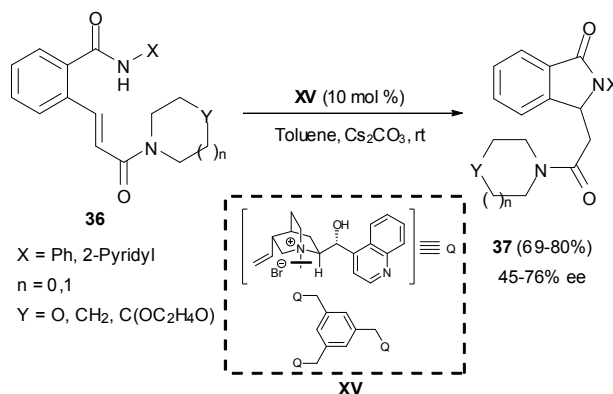
**Scheme 18** Organocatalytic asymmetric IMAMR for the synthesis of 2,3-dihydroquinolin-4-one derivatives

Conjugated thioesters have been also employed as Michael acceptors in the IMAMR. Asano and Matsubara extended their synthesis of indolines to these types of acceptors, using quinine-derived thiourea **IX** (see Scheme 11) as the catalyst (Scheme 19).<sup>37</sup> However, yields and enantioselectivities of indolines **35** were lower compared to the reaction with aromatic ketones as Michael acceptors (see Scheme 15).



**Scheme 19** Synthesis of 2-substituted indolines through an IMAMR with conjugated thioesters as acceptors

The last example in this series was reported at the end of 2013 by Deniau and Michon.<sup>42</sup> It involved the use of conjugated amides as Michael acceptors and amides as nucleophilic nitrogen source. Substituted benzamides **36** reacted under phase transfer catalysis conditions in toluene at room temperature in the presence of Cs<sub>2</sub>CO<sub>3</sub> as a base and oligomeric cinchonidinium salt **XV** as the catalyst to furnish isoindolinones **37** in good yields and moderate enantioselectivity (Scheme 20). These compounds are useful intermediates in the synthesis of benzodiazepine-receptor agonists.



**Scheme 20** Organocatalytic IMAMR employing conjugated amides as Michael acceptors

It is worth mentioning that all examples showed in this section are limited in scope, and a general method to perform this transformation on conjugated esters as Michael acceptors still remains a pending task for organic chemists.

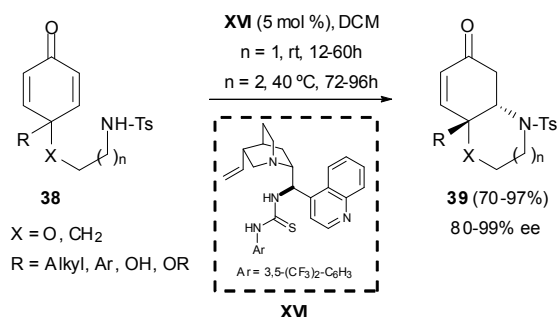
## 5. Application of the organocatalytic IMAMR in desymmetrization processes

Asymmetric desymmetrization is the modification of a molecule that results in the loss of one or more symmetry elements thus converting prochiral precursors into chiral products. Although desymmetrization processes are commonly used strategies to generate enantioenriched compounds, its application in organocatalysis is still very limited. Efforts in this area were mostly devoted to anhydrides as starting materials. Regarding the IMAMR, two examples of this transformation in



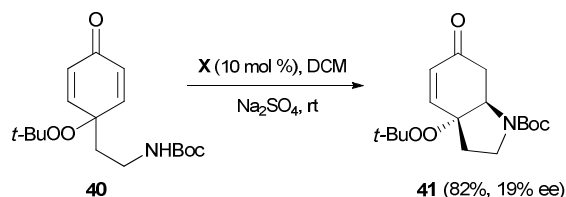
desymmetrization processes have been reported to date.

In 2011, You developed a cinchonine-derived thiourea catalysed desymmetrization of cyclohexadienones *via* asymmetric *aza*-Michael reaction.<sup>43</sup> The starting substrates **38** were previously obtained by oxidative dearomatization of the corresponding phenol derivatives. Therefore, dearomatized cyclohexadienones **38** reacted with catalyst **XVI** in dichloromethane to afford bicyclic pyrrolidine and morpholine derivatives **39** in excellent yields and ee's (Scheme 21). Nitrogen protecting group played a crucial role in both selectivity and reactivity. The tosyl group provided the best results, reaching almost complete levels of enantioselection, while substrates bearing a Boc protecting group were unreactive.



**Scheme 21** Asymmetric desymmetrization *via* IMAMR (1)

A closely related example started again with a dearomatization process that rendered symmetric ketone **40**. In this case, the nucleophilic nitrogen source in the IMAMR was a Boc-carbamate and the catalyst employed was chiral binol phosphoric acid **X** (see Scheme 12), affording the desired bicyclic pyrrolidine **41** in good yield although quite low enantioselectivity (Scheme 22).<sup>44</sup>



**Scheme 22** Asymmetric desymmetrization *via* IMAMR (2)

## 6. Organocatalytic tandem processes involving an IMAMR

One of the most important goals for organic chemists in the last few decades has been the development of new stereoselective methodologies for the synthesis of optically pure molecules that bear diversity in their structures. This search has been driven in part by the growing demand for chiral drugs due, in turn, to the increased control of the enantiopurity of drug candidates. In this context, the interest in combining asymmetric organocatalytic processes with tandem reactions is obvious, since multiple stereogenic centers could be created in only one synthetic step. Additionally, these tandem sequences provide, in general, attractive and efficient routes to key building blocks for the synthesis of complex organic molecules. Organocatalyzed reactions have been combined in a huge number of conceivable manners, which explains why tandem or domino organocatalytic

processes have reached an extraordinary level of efficiency.<sup>45-47</sup>

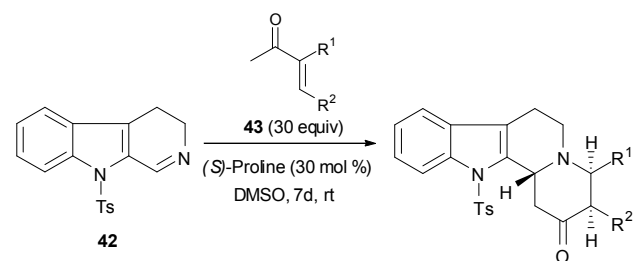
The *aza*-Michael reaction is a common transformation employed in tandem protocols, being its intramolecular version mostly restricted to at least the second step of the tandem sequence. To date, only two examples of tandem reactions starting with an IMAMR have been described. It is important to point out that intramolecular *aza*-Michael processes being part of a tandem protocol are much more abundant than the individual reactions mentioned in sections 1-5. As stated in the Introduction, one of the problems associated with the organocatalytic IMAMR is the generation of the Michael acceptor in the presence of the nucleophilic nitrogen source. In tandem protocols, this nitrogen source can be generated *in situ* by means of other organocatalyzed reaction, which facilitates the overall process.

In order to clarify this section, it will be divided according to the reaction that is coupled with the IMAMR.

### 6.1. Tandem Mannich-IMAMR

The combination of the Mannich reaction with an IMAMR can be noticed as a formal *aza*-Diels Alder reaction. However, this sequence of reactions typically follows a stepwise mechanism that involves a tandem Mannich-IMAMR, by means of enamine-type catalysis or non-covalent catalysis.

The first example of this sequence was reported by Ohsawa in 2003.<sup>48</sup> The imine functionality of 9-tosyl-3,4-dihydro- $\beta$ -carboline **42** reacted with methyl vinyl ketone in the presence of (*S*)-proline to afford, after 7 days at room temperature, tetracyclic derivative **44a** in good yield and excellent ee (Scheme 23). This strategy was later extended to substituted conjugated ketones **43**, giving rise to the desired pyridone rings **44b-c** as single diastereoisomers in good yields (Scheme 23).<sup>49</sup> A large excess of ketones **43** (30 equiv) was needed in order to obtain good yields, which suggested that the first addition step (Mannich reaction) is the rate-determining step. Compound **44c** was an advanced intermediate in the total synthesis of the natural product *ent-dihydrocorynantheol* (see Section 7).

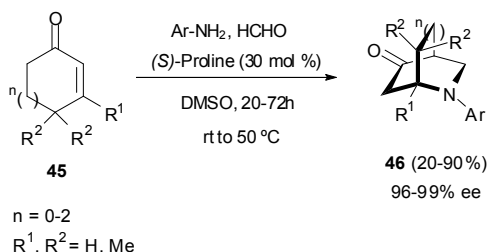


**44a** (R<sup>1</sup> = H, R<sup>2</sup> = H): 76%, 92% ee  
**44b** [R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>4</sub>]: 91%, 96% ee  
**44c** (R<sup>1</sup> = H, R<sup>2</sup> = Et): 85%, 99% ee

**Scheme 23** Mannich-IMAMR tandem process for the synthesis of indole tetracyclic derivatives

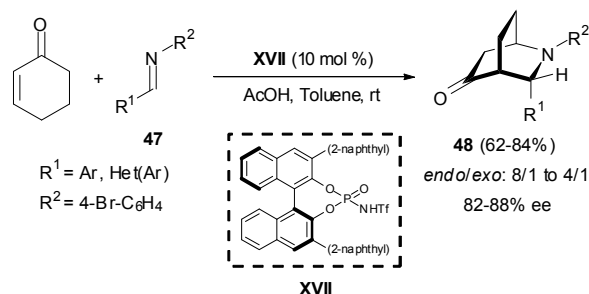
In 2006, Cordova described the direct Mannich reaction of aqueous formaldehyde, aromatic imines and cyclic conjugated ketones **45** in DMSO in the presence of (*S*)-proline as the catalyst.<sup>50</sup> The Mannich adduct underwent the IMAMR in a tandem fashion over the conjugated ketone generating, in a single step, nitrogenated bicycles **46** in variable yields and excellent enantioselectivities (up to 96%) (Scheme 24). Aromatic amines

bearing electron-donating groups gave the best results, while electron-withdrawing groups provided only moderate yields of the final adducts. Additionally, the size of the starting cyclic ketone affected dramatically the process, the cyclopentenone giving the desired product in only 10% yield. Finally, the process was very sensitive to steric hindrance at R<sup>1</sup> as with a substituent distinct than hydrogen the IMAMR did not take place and the Mannich adduct was isolated instead.



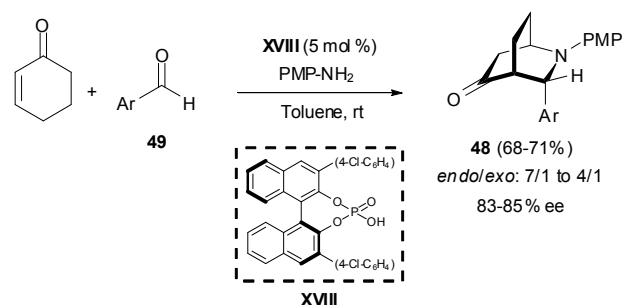
**Scheme 24** Mannich-IMAMR tandem process for the synthesis of azabicyclic ketones (1)

Soon after, Rueping found that this tandem protocol could be also catalysed by chiral BINOL phosphoric acids.<sup>51</sup> In this way, cyclohexenone reacted with aromatic or heteroaromatic imines **47** in toluene at room temperature, in the presence of BINOL-derived catalyst **XVII** with acetic acid as a co-catalyst, to render isoquinuclidines **48** in good yields, moderate diastereoselectivity and good enantioselectivity (Scheme 25). It is important to mention that this Mannich-*aza* Michael reaction combines two Brønsted acids, one chiral and another achiral. Both of them cooperatively activate the enone and the aldimine thus enabling the formation of the final products **48** in a stereoselective manner.



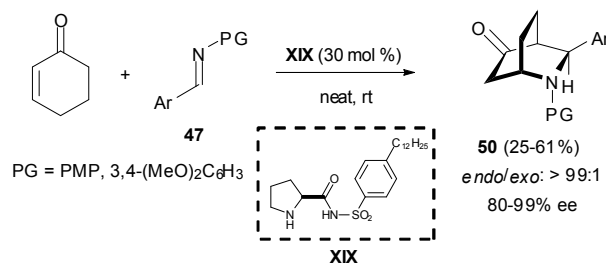
**Scheme 25** Mannich-IMAMR tandem process for the synthesis of azabicyclic ketones (2)

Independently and almost simultaneously, Gong reported an analogous protocol to the one described by Rueping. The main difference was the use of the chiral binol phosphoric acid **XVIII** as the catalyst and the absence of acetic acid in the process.<sup>52</sup> Additionally, Gong found that this transformation could be also performed in a direct way, using a three-component reaction (cyclohexenone, *p*-anisidine and aromatic aldehydes **49**) to yield the final products **48** with comparable results to those obtained in the reaction with the corresponding pre-formed imines (Scheme 26).



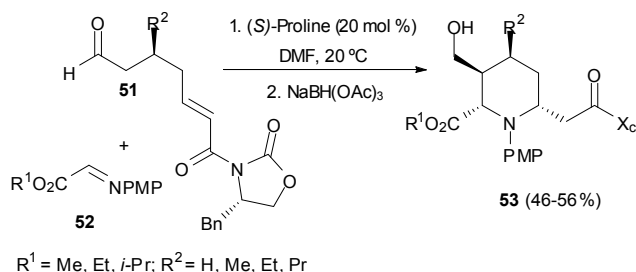
**Scheme 26** Mannich-IMAMR tandem process for the synthesis of azabicyclic ketones (3)

In the same context, three years later Carter reported a complementary protocol to the ones described in Schemes 25 and 26. The use of *p*-dodecylphenylsulfonamide-based proline derivative **XIX** (designed to improve solubility properties of proline derivatives in non-polar media) was translated into a total inversion of the selectivity, giving rise to the exclusive formation of the *exo* adduct.<sup>53</sup> In this way, aromatic imines **47** reacted in cyclohexenone as solvent to render final isoquinuclidines **50** in moderate yields and excellent diastereo- and enantioselectivity (Scheme 27). It is important to point out that aliphatic imines followed a divergent reaction pathway and bicyclo[2.2.2]octanes were formed instead.



**Scheme 27** Mannich-IMAMR tandem process for the synthesis of azabicyclic ketones (4)

The synthesis of highly substituted pipercolic esters through a proline-catalyzed domino Mannich-IMAMR was described by Schneider in 2008.<sup>54</sup> Aldehydes **51** reacted with imino esters **52** in DMF at -20 °C in the presence of (*S*)-proline to afford, after reduction of the aldehyde moiety, pipercolic esters **53** as single diastereoisomers although in moderate yields. Three stereocenters were simultaneously generated during the process with complete selectivity (Scheme 28).

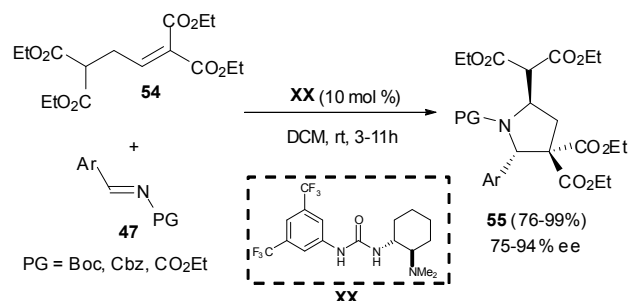


**Scheme 28** Mannich-IMAMR tandem process for the synthesis of highly substituted pipercolic esters **53**

When this reaction was performed with (*R*)-proline, a 2:1 mixture of diastereoisomers with respect to the 6-position was

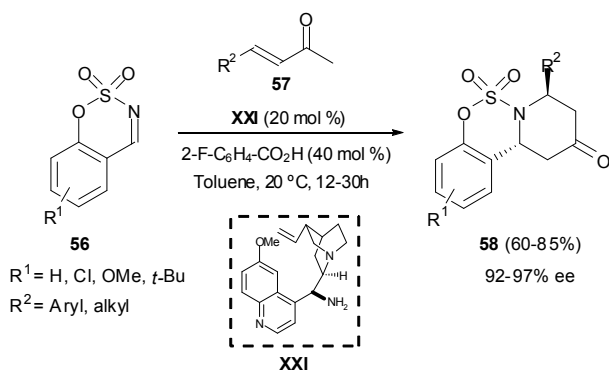
observed, suggesting that the initial Mannich reaction is a catalyst-controlled process whereas the IMAMR apparently proceeds under substrate control.

Another example of this tandem sequence involved the reaction of  $\gamma$ -malonate-substituted  $\alpha,\beta$ -unsaturated esters **54** with alkoxy-carbonyl-protected aryl aldimines **47** in the presence of Takemoto catalyst **XX** to furnish highly substituted pyrrolidines **55** in good yields and excellent diastereo- and enantioselectivities (Scheme 29).<sup>55</sup> The presence of an additional ester group in the Michael acceptor was crucial for the success of the tandem protocol: a regular conjugated ester interrupted the process in the first step (Mannich reaction) and the IMAMR did not take place.



**Scheme 29** Mannich-IMAMR tandem process for the synthesis of highly substituted pyrrolidines **55**

The last example within this series was reported in 2013. *N*-Sulfonylimines **56** reacted with conjugated ketones **57** in the presence of quinidine-derived primary amine **XXI** and *o*-fluorobenzoic acid as a co-catalyst in toluene at room temperature, affording sulfamate-fused 2,6-disubstituted piperidin-4-ones **58** in good yields and excellent diastereo- and enantioselectivities (Scheme 30).<sup>56</sup> The process is compatible with aromatic and aliphatic substituents at the ketone moiety and electron donating or withdrawing groups in the aromatic ring.

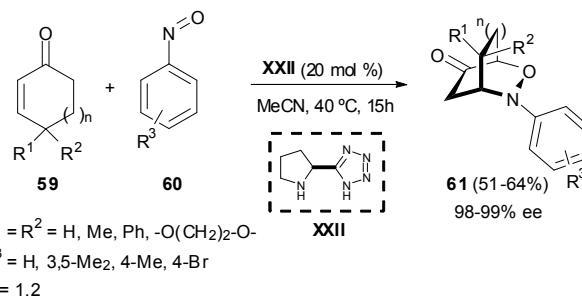


**Scheme 30** Mannich-IMAMR tandem process for the synthesis of sulfamate-fused 2,6-disubstituted piperidin-4-ones **58**

## 6.2. Tandem $\alpha$ -aminoxylation-IMAMR

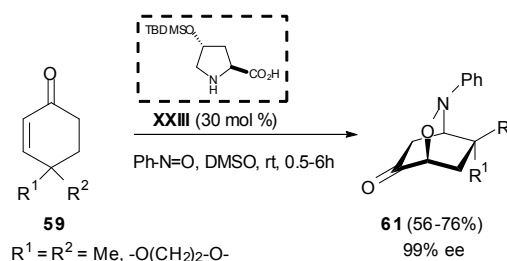
As occurred with the Mannich reaction, the  $\alpha$ -aminoxylation (also called *O*-nitroso aldol reaction) of carbonyl compounds generates a nitrogen nucleophile that can react with double bonds substituted with electron withdrawing groups in an intramolecular fashion. This tandem process generates nitroso Diels-Alder adducts with the opposite regiochemistry of that of the normal nitroso Diels-Alder reaction.

The first example of this sequence was reported by Yamamoto and co-workers in 2004. Based on the excellent results provided by pyrrolidine-based tetrazoles as catalysts in the *O*-nitroso aldol reaction, its combination with an IMAMR in a tandem process was logical. The reaction of conjugated ketones **59** with aromatic nitroso compounds **60** in the presence of tetrazole derivative **XXII** led to the formation of bicycles **61** in moderate yields and remarkable enantioselectivity (Scheme 31).<sup>57,58</sup>



**Scheme 31** Tandem asymmetric  $\alpha$ -aminoxylation-IMAMR for the synthesis of bicycles **61** (1)

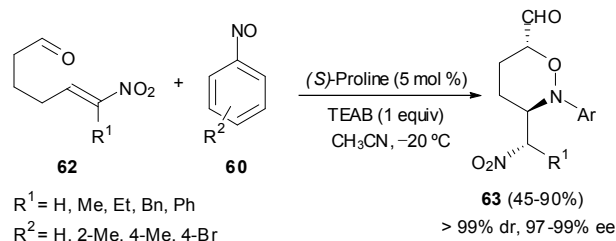
Hayashi took advantage of this tandem protocol to demonstrate the benefits of using *trans*-4-*tert*-butyldimethylsilyloxy-(*S*)-proline **XXIII** in asymmetric synthesis.<sup>59</sup> Catalyst **XXIII** accelerated the reaction of ketones **59** with nitrosobenzene dramatically, with a reduced amount of catalyst in comparison to proline itself, probably due to its solubility problems. Bicycles **61** were synthesized in moderate to good yields and complete enantioselectivity (Scheme 32).



**Scheme 32** Tandem asymmetric  $\alpha$ -aminoxylation-IMAMR for the synthesis of bicycles **61** (2)

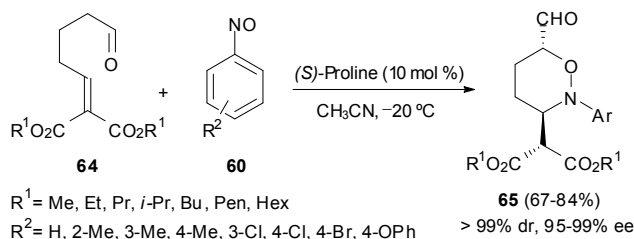
In 2008 Zhong and co-workers reported the first example of a direct tandem  $\alpha$ -aminoxylation/*aza*-Michael reaction involving aldehydes.<sup>60</sup> A chemoselectivity problem had to be addressed in this work: after the aminoxylation step, the newly generated amine functionality could react either with the starting aldehyde or the Michael acceptor. This was circumvented employing nitroalkenes, since they are recognized among the most reactive Michael acceptors, and employing diluted reaction conditions thus favouring the intramolecular reaction. In this manner, aldehydes **62** bearing nitroalkenes in a remote position reacted with nitroso aromatic compounds **60** in acetonitrile at  $-20$  °C, in the presence of (*S*)-proline, to afford tetrahydro-1,2-oxazines **63** in good yields and excellent diastereo- and enantioselectivities (Scheme 33). The origin of the high stereoselectivity derives from the  $\alpha$ -aminoxylation reaction, which is known to proceed with high enantioselectivity, while the IMAMR seems to be controlled by the substrate. Additionally, it is important to note that, in the presence of 1 equivalent of tetraethylammonium bromide

(TEAB), a catalyst loading of 5 mol% could be used without any loss in the ee and dr values.



**Scheme 33** First example of a tandem  $\alpha$ -aminoxylation-IMAMR involving aldehydes

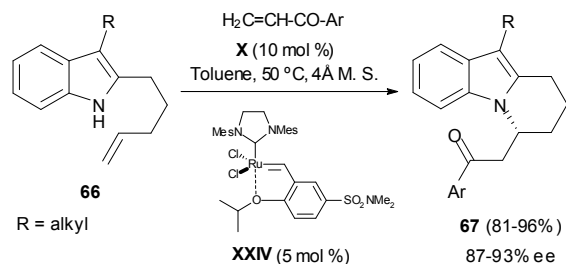
An extension of this tandem protocol to ene-malonates as Michael acceptors was also reported.<sup>61</sup> Aldehydes **64** bearing a conjugated diester moiety reacted with nitroso compounds **60** in acetonitrile at  $-20\text{ }^\circ\text{C}$ , in the presence of (*S*)-proline, to afford the corresponding tetrahydro-1,2-oxazines **65** in good yields and remarkable diastereo- and enantioselectivities (Scheme 34).



**Scheme 34** Tandem  $\alpha$ -aminoxylation-IMAMR for the synthesis of tetrahydro-1,2-oxazines **65**

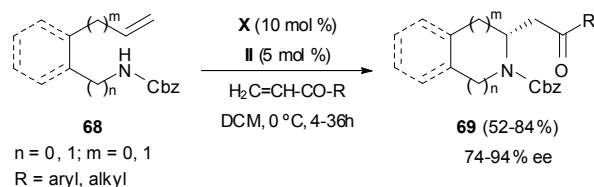
### 6.3. Tandem cross-metathesis-IMAMR

The first example that illustrated the synthetic utility of combining a cross metathesis (CM) reaction with an IMAMR was reported in 2007.<sup>62</sup> It involved the use of carbamates bearing a remote olefin which reacted with conjugated ketones in the presence of second generation Hoveyda-Grubbs catalyst and  $\text{BF}_3\cdot\text{OEt}_2$  as a co-catalyst. In the field of organocatalysis, this tandem protocol was described by You and co-workers in 2010.<sup>34</sup> They took advantage of the synergistic combination of a ruthenium carbene with a chiral Brønsted acid, demonstrating the complementarity of transition metal catalysis and organocatalysis. In this work, indole derivatives **66** reacted with aromatic ketones in the presence of chiral binol phosphoric acid **X** (see Scheme 12) and Zhan-1B catalyst **XXIV** in toluene at  $50\text{ }^\circ\text{C}$ , furnishing tricyclic indole derivatives **67** in good yields and excellent enantioselectivity (Scheme 35).



**Scheme 35** First example of a tandem cross metathesis-IMAMR

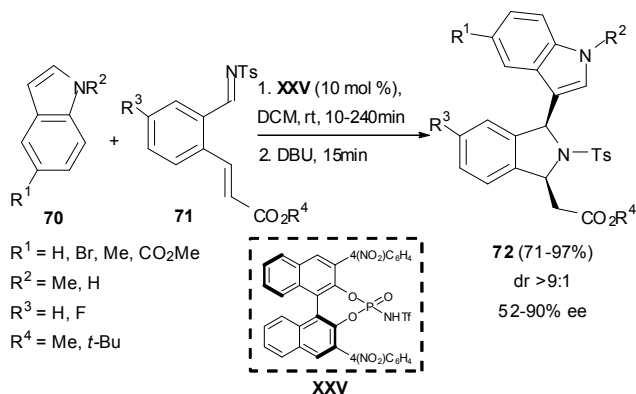
Inspired by this work, Yu and co-workers extended this methodology to the formation of five membered rings.<sup>63</sup> The combination of chiral binol phosphoric acid **X** (see Scheme 12) and second generation Hoveyda-Grubbs catalyst **II** (see Scheme 3) was employed in the reaction of carbamates **68** and conjugated ketones. The optimal conditions involved the use of dichloromethane at  $0\text{ }^\circ\text{C}$ , affording the corresponding pyrrolidines **69** in good yields and enantioselectivity. Additionally, benzofused derivatives were also suitable substrates for this tandem protocol: indolines ( $n = 0, m = 1$ ) and isoindolines ( $n = 1, m = 0$ ) were obtained in a very efficient manner (Scheme 36).



**Scheme 36** Tandem cross metathesis-IMAMR for the synthesis of five-membered *N*-heterocycles

### 6.4. Tandem aza-Friedel-Crafts-IMAMR

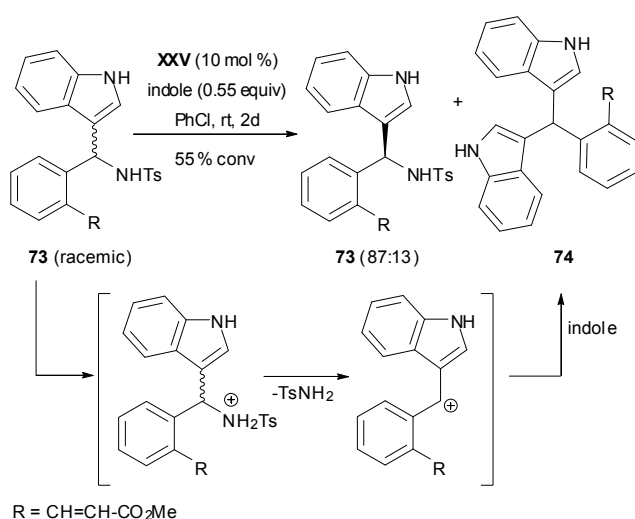
Chiral BINOL phosphoric acids have proven to be very efficient catalysts in the addition of aromatic and heteroaromatic nucleus to imines. These *aza*-Friedel-Crafts processes generate enantiomerically enriched amines, which can participate in an IMAMR. Enders and co-workers reported a one-pot protocol involving these two transformations to yield highly substituted isoindolines.<sup>64</sup> Thus, substituted indoles **70** reacted with *N*-tosyliminoenones **71** in dichloromethane at room temperature with chiral *N*-triflyl phosphoramidate **XXV** as the catalyst, to afford the *aza*-Friedel-Crafts adducts. Addition of catalytic amounts of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) promoted the IMAMR that took place in a stereoselective manner to afford the final isoindolines **72** in good yields and enantioselectivities (Scheme 37). The best results were obtained with unsubstituted indole derivatives (**70**,  $\text{R}^2 = \text{H}$ ) while a dramatic decrease in enantioselectivity was observed with substituted indoles (**70**,  $\text{R}^2 = \text{Me}$ , 22% ee), indicating that the N-H bond would be involved in the stereochemical outcome through hydrogen bond interactions.



**Scheme 37** First example of organocatalyzed asymmetric synthesis of 1,3-disubstituted isoindolines

Further investigation of this sequence led to the discovery of a remarkable Brønsted acid catalysed stereoablative kinetic

resolution.<sup>64</sup> In this manner, the enantiomeric ratio of final isoindolines **72** increased when longer reaction times were used in the Friedel-Crafts reaction. At the same time, yield of the final product decreased as increased the presence of a side product, the achiral bis-indol **74** (Scheme 38). When racemic Friedel-Crafts product **73** was treated with chiral BINOL phosphoramidate **XXV** and 0.55 equiv of indole, after 2 days, unreacted **73** was isolated in enantiomerically enriched manner (er 87:13). This observation was explained through an initial protonation of the tosyl amide by the catalyst followed by preferential dissociation of tosyl amide from one of the diastereoisomers. The resulting carbocation was irreversibly trapped by indole to afford product **74** (Scheme 38). Consequently, the stereoablative destruction of the minor enantiomer occurred during the process. With these results, conditions showed in Scheme 37 were revised and, after extending reaction times of the Friedel-Crafts event, final isoindolines **72** were obtained in 99% ee with a minimal erosion of the final yield.

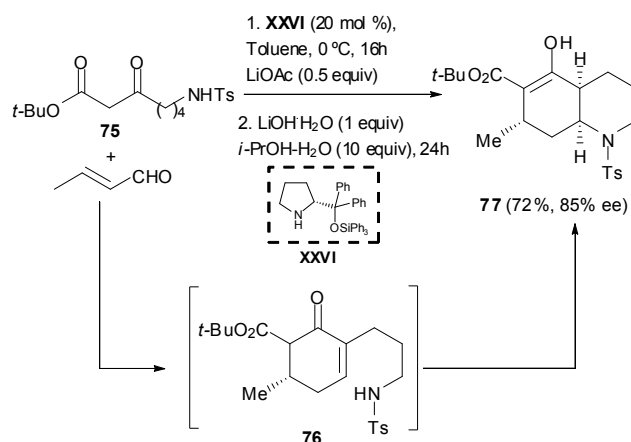


**Scheme 38** Brønsted acid catalysed stereoablative kinetic resolution

### 6.5. Tandem Robinson annulation-IMAMR

The organocatalytic sequence Robinson annulation-IMAMR was developed by Bonjoch and Bradshaw in their efforts to access the heterocyclic structure of the *Lycopodium* family alkaloids. The authors tuned this synthetic approach up, which allowed a rapid assembly to 5-oxo-decahydroquinolines in a diastereo- an enantioselective manner in a single chemical step. Keto ester **75** bearing a remote tosyl amide reacted with crotonaldehyde in the presence of diarylprolinol **XXVI** as the catalyst in toluene at 0 °C to afford the Robinson annulation product **76**. This was *in situ* treated with LiOH in a mixture *i*-PrOH-H<sub>2</sub>O promoting the IMAMR to render the *aza*-bicyclic core **77** in 72% yield and 85% ee (Scheme 39).<sup>65</sup> In this process two C-C bonds, one C-N bond and three stereogenic centers were generated in a single step. The presence of the ester group in substrate **75** was crucial for the success of the process: it stabilized the final compound by forming the enolic tautomer and preventing the ring opening through a retro-*aza*-Michael reaction in the basic reaction media

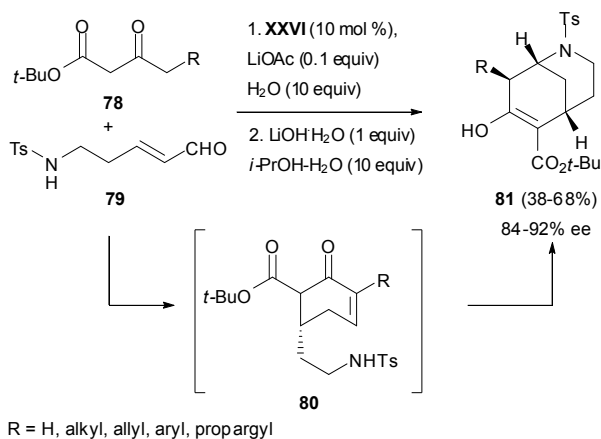
or in the purification step (silica gel chromatography).



**Scheme 39** One-pot tandem organocatalyzed synthesis of decahydroquinolines *via* tandem Robinson-IMAMR

After a decarboxylation step on compound **77**, a series of configurationally controlled equilibration processes provided synthetic access to 7-methyl-5-oxodecahydroquinolines corresponding to the three main types of phlegmarine alkaloids (types A–C) as well as the unnatural type D (see Section 7).<sup>66</sup>

This tandem sequence was also employed to access the morphan scaffold (2-azabicyclo[3.3.1]nonane), present in many complex and biologically active natural products as well as medicinal compounds of significant interest. Starting keto esters **78** were treated with the conjugated aldehyde **79** bearing a remote tosyl amide in the presence of chiral diaryl prolinol **XXVI**. Solvent free conditions gave the best results in terms of yield and enantioselectivity in the synthesis of bicyclic derivatives **81** after effecting the IMAMR by basic treatment of intermediate **80** (Scheme 40).<sup>67</sup>

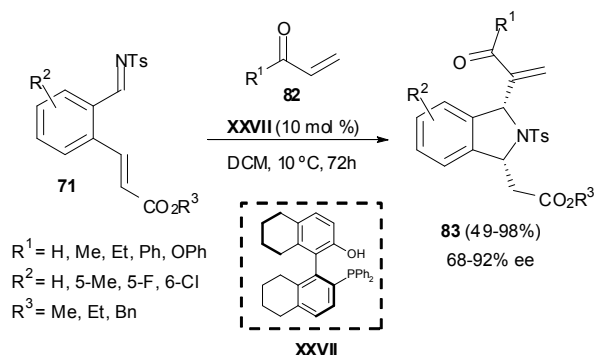


**Scheme 40** Organocatalyzed synthesis of enantioenriched morphans

### 6.6. Tandem *aza*-Morita-Baylis-Hillman-IMAMR

The enantioselective *aza*-Morita-Baylis-Hillman (*aza*-MBH) reaction generates enantiomerically enriched allyl amines, valuable building blocks in asymmetric synthesis. Among the catalysts employed in this process, BINOL-derived phosphines **70** are probably the most ubiquitous. On the other hand, this process

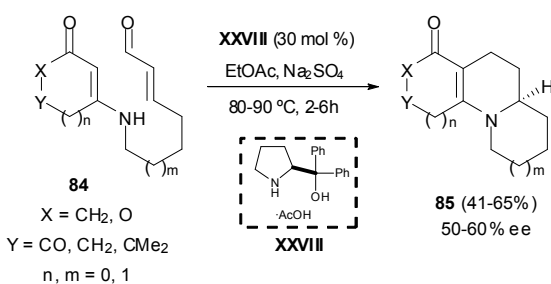
generates a nucleophilic nitrogen source, suitable for further transformations in a tandem fashion. To date, only one example of the organocatalytic tandem *aza*-MBH-IMAMR has been reported. It was described by Sasai in 2010 and involved the use of *N*-tosyl iminoenones **71** and conjugated ketones or esters **82** with chiral phosphine **XXVII** as the catalyst in dichloromethane at 10 °C. Under these conditions, *cis*-substituted isoindolines **83** were obtained in general good yields and enantioselectivity (Scheme 41).<sup>68</sup>



**Scheme 41** Tandem *aza*-MBH-IMAMR for the synthesis of disubstituted isoindolines **83**

### 6.7. Miscellaneous tandem processes involving an IMAMR

The first example of an organocatalytic tandem process that involved an IMAMR and do not fall into the aforementioned categories was an annulation reaction using vinylogous amides and  $\alpha,\beta$ -unsaturated iminium salts. Reported by Hsung, it represents a formal [3+3] cycloaddition with net formation of two  $\sigma$ -bonds and a new stereocenter adjacent to the nitrogen atom.<sup>69</sup> This is the first example of a tandem protocol that starts with an IMAMR. Vinylogous amides **84** underwent cyclization in the presence of chiral diarylprolinol **XXVIII** in EtOAc at 80-90 °C to render tricyclic derivatives **85** in moderate yields and enantioselectivity (Scheme 42).

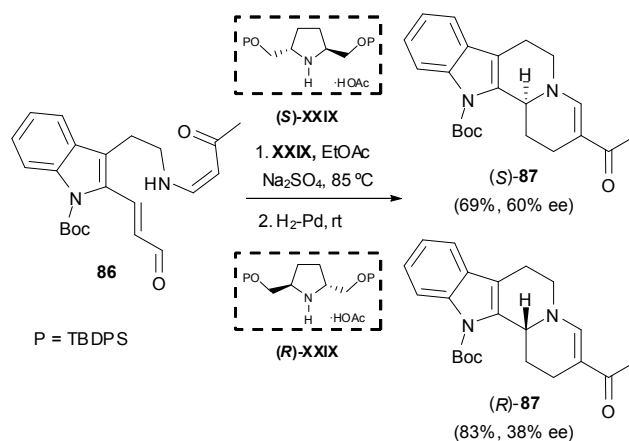


**Scheme 42** Enantioselective intramolecular formal *aza*-[3 + 3] cycloaddition (1)

Mechanistically the overall process constitutes a tandem Knoevenagel condensation- $6\pi$ -electron electrocyclic ring-closure involving a 1-azatriene intermediate. However, the first step can be considered as an IMAMR with an iminium activation by the catalyst, being this the step where the stereochemical induction most likely occurred. Subsequent enamine attack to the aldehyde, tautomerization and elimination would explain the formation of the final products.

The same strategy was employed in the total synthesis of the

indoloquinolizidine alkaloid *deplancheine* (see Section 7) for the construction of the cycles C and D of the polyheterocyclic framework.<sup>70</sup> In this case, the enantioselective formal *aza*-[3+3]-cycloaddition was performed with chiral pyrrolidine **XXIX** as the catalyst. Indole-derived vinylogous amide **86** reacted with (*S*)-**XXIX** in refluxing ethyl acetate to render, after an additional hydrogenation step, the (*S*)-enantiomer of tetracyclic derivative **87** in good yield and moderate enantioselectivity. The use of the (*R*)-enantiomer of the catalyst rendered compound (*R*)-**87** albeit with a noticeable drop of the enantioselectivity (Scheme 43).



**Scheme 43** Enantioselective intramolecular formal *aza*-[3+3] cycloaddition (2)

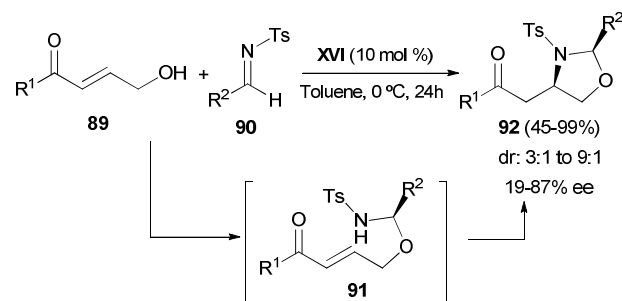
Another example in this series was related to the preparation of brominated dihydroquinolones **88**. Besides the IMAMR performed on tosyl amides **32** (see Scheme 18), the same authors also carried out a tandem IMAMR-bromination process.<sup>41</sup> This constitutes the second example of an organocatalytic tandem protocol that starts with an IMAMR. Substrates **32** were treated with chiral bis-guanidinium salt **XIV** (see Scheme 18) and NBS in dichloromethane at -20 °C giving rise to dihydroquinolones **88** in good yields and generally excellent diastereo- and enantioselectivities (Scheme 44). The tandem protocol needed much longer reaction times than the initial IMAMR to complete (4 days); however, the addition of 4Å molecular sieves reduced reaction times notably.



**Scheme 44** Synthesis of brominated dihydroquinolones *via* tandem IMAMR-bromination

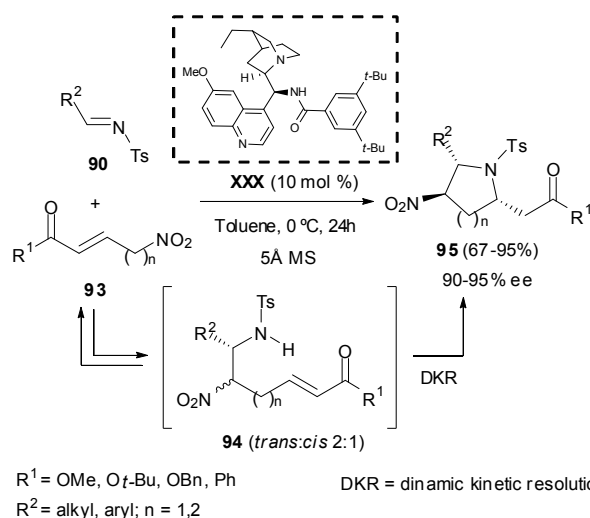
In 2013 Matsubara and Asano described a novel synthetic route to optically active 1,3-oxazolidines *via* formal [3 + 2] cycloaddition in the presence of Cinchona alkaloid-thiourea-based bifunctional organocatalysts.<sup>71</sup> Conjugated ketones **89** bearing a remote hydroxyl group reacted with tosyl imines **90** to render hemiaminal intermediates **91** in toluene at 0 °C in the presence of chiral thiourea **XVI** (see Scheme 21). This hemiaminal underwent IMAMR spontaneously, yielding

enantioenriched 1,3-oxazolindines **92** (Scheme 45). The major limitation of this protocol was its moderate stereoselectivity.



**Scheme 45** Asymmetric synthesis of 1,3-oxazolindines via IMAMR

Recently, Huang reported a tandem protocol for the synthesis of polysubstituted pyrrolidines and piperidines with up to three stereogenic centers involving an *aza*-Henry-IMAMR sequence.<sup>72</sup> Conjugated ketones or esters **93** bearing a remote nitro group reacted with tosyl imines **90** in the presence of Cinchona alkaloid amide-derived organocatalyst **XXX** in toluene at 0 °C to render heterocycles **95** in good yields and excellent diastereo- and enantioselectivities (Scheme 46). It is important to point out that tosyl imines are not usually good partners in the enantioselective *aza*-Henry reaction due to the high reactivity of these imines. However, the analogous *N*-Boc derived imines were unreactive under these conditions. On the other hand, 5 Å molecular sieves were found to significantly accelerate the *aza*-Michael cyclization without eroding the product ee.



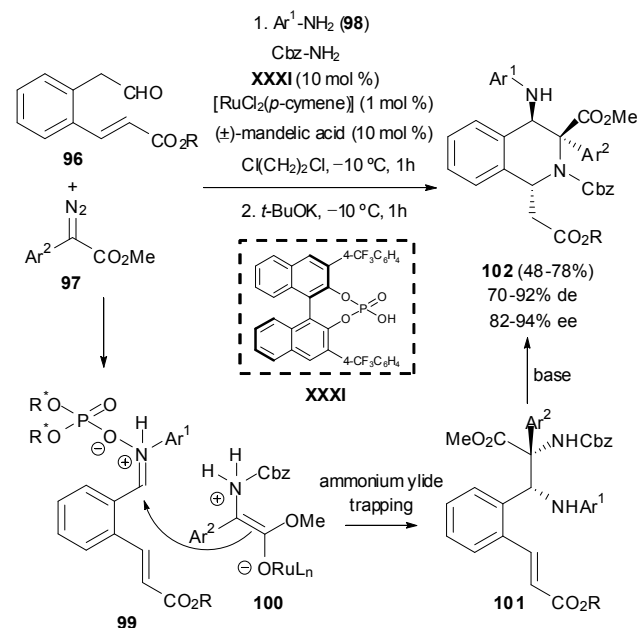
**Scheme 46** Tandem *aza*-Henry-IMAMR for the asymmetric synthesis of polysubstituted pyrrolidines and piperidines

NMR experiments revealed that the initial *aza*-Henry reaction was modestly diastereoselective, giving rise to a mixture of *trans/cis* products **94** in a *ca.* 2:1 ratio. The authors observed that only the *trans* *aza*-Henry adduct underwent subsequent cyclisation. These experiments indicate that the present cascade takes advantage of a first reversible step (the *aza*-Henry reaction) and a second dynamic kinetic resolution (DKR) step (the IMAMR on the *trans* isomer). The synergistic combination of both processes is translated in the synthesis of pyrrolidine and

piperidine analogues with excellent selectivity.

Finally, this year Liu and Hu developed an enantioselective multicomponent process that can be viewed as a tandem Mannich-type reaction-IMAMR catalysed by a ruthenium complex and a chiral BINOL phosphoric acid in what is called an orthogonal relay catalytic protocol.<sup>73</sup> This is an example of a synergistic combination of organocatalysis and transition metal catalysis. It involved the use of conjugated esters **96**, aryl diazo esters **97**, aryl amines **98** and benzyl carbamate as starting materials, and led to the synthesis of 1,3,4-tetrasubstituted tetrahydroisoquinolines (Scheme 47).

Ruthenium complexes have been reported to be effective catalysts for the decomposition of diazo compounds. The mechanism involved the formation of a ruthenium-associated ammonium ylide **100** by means of the reaction of benzyl carbamate with a ruthenium carbene, in turn formed by reaction of diazo compound **97** and the ruthenium catalyst. Ammonium ylide **100** was trapped with the iminium ion **99**, *in situ* formed by the chiral BINOL phosphoric acid **XXXI** after the imine formation between the aldehyde functionality in **96** and the aryl amine **98**. A Mannich-type addition of iminium ylide **100** to the bifunctional and chiral iminium species **99** rendered enantiomerically enriched adduct **101**, which was cyclized *in situ* by addition of potassium *tert*-butoxide to the reaction media. This sequence afforded tetrahydroisoquinolines **102** with the simultaneous generation of three stereocenters, one of them quaternary, in good yields, diastereo- and enantioselectivity (Scheme 47).



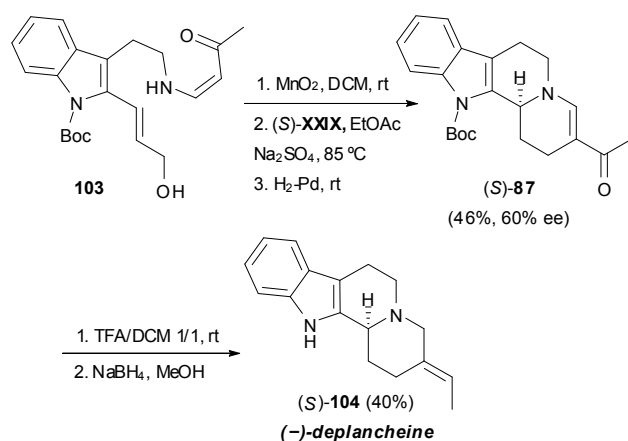
**Scheme 47** Synthesis of 1,3,4-tetrasubstituted tetrahydroisoquinolines via four-component Mannich/cascade *aza*-Michael reaction.

## 7. Application of the IMAMR to natural product synthesis

Recent achievements in the organocatalytic IMAMR showed along this review have demonstrated the utility of this methodology for the synthesis of enantiomerically enriched five

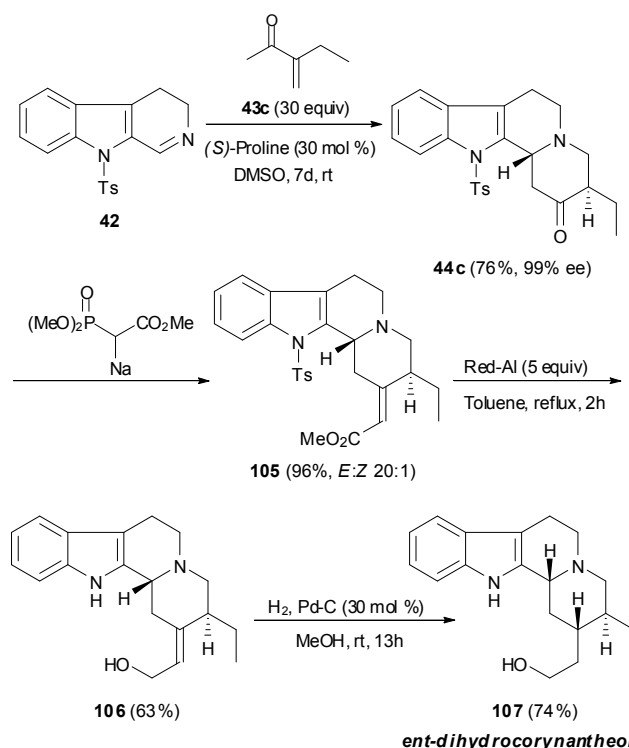
and six membered nitrogen-containing heterocycles. By definition, alkaloids are one of the widest classes of natural products that incorporate a basic nitrogen atom in their structure, and the IMAMR has been widely employed in multistep synthesis of this kind of natural products containing pyrrolidine and piperidine scaffolds and their analogues.

The first natural product that was synthesized taking advantage of an organocatalytic IMAMR was the indoloquinolizidine derived alkaloid *deplancheine*. The enantioselective intramolecular formal *aza*-[3+3] cycloaddition developed by Hsung was employed as key step.<sup>70</sup> After oxidation of allylic alcohol **103**, the conjugated aldehyde was subjected to the initial IMAMR catalysed by chiral pyrrolidine (*S*)-**XXIX** to render, after the second cyclisation step (see Scheme 43) and hydrogenation of the double bond, tetracycle **87** in moderate enantioselectivity with simultaneous generation of the C and D rings. Removal of the Boc-protecting group with TFA followed by NaBH<sub>4</sub> reduction afforded the natural product (*-*)-*deplancheine* **104** (Scheme 48).



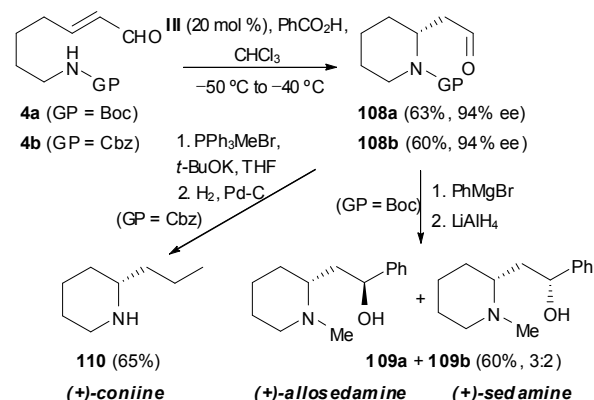
**Scheme 48** Asymmetric synthesis of (*-*)-*deplancheine*

A second example of a natural product synthesized by means of an organocatalytic IMAMR was the indole derived alkaloid *ent-dihydrocorynantheol*. Reported by Itoh,<sup>49</sup> it involved a tandem Mannich-IMAMR protocol on  $\beta$ -carboline **42** with unsaturated ketone **43c** in the presence of (*S*)-proline as the catalyst (see Scheme 23). The tetracyclic derivative **44c** was transformed in three steps into the natural product. Horner-Wadsworth-Emmons olefination of the ketone moiety afforded conjugated ester **105**, which was reduced with Red-Al to allylic alcohol **106** with concomitant elimination of the tosyl group. Catalytic hydrogenation afforded the enantiomer of the natural product *ent-dihydrocorynantheol* **107** with complete selectivity in the generation of the newly created stereocenter (Scheme 49).



**Scheme 49** Asymmetric synthesis of *ent-dihydrocorynantheol*

In 2007, the synthetic utility of the organocatalytic IMAMR with enals as Michael acceptors was illustrated with the synthesis of three piperidine alkaloids.<sup>18</sup> Conjugated aldehydes **4a,b** underwent cyclisation *via* IMAMR in the presence of fluorinated diarylprolinol **III** (see Scheme 3) and benzoic acid as a co-catalyst at  $-50^\circ\text{C}$  to give piperidine aldehydes **108a,b** in good yield and excellent ee. Addition of PhMgBr to **108a** followed by carbamate reduction with LiAlH<sub>4</sub> afforded a separable 3:2 mixture of diastereoisomeric alkaloids (*+*)-*allosedamine* **109a** and (*+*)-*sedamine* **109b**. On the other hand, Wittig reaction on **108b** followed by hydrogenation of the double bond furnished alkaloid (*+*)-*coniine* **110** in excellent overall yield (Scheme 50).

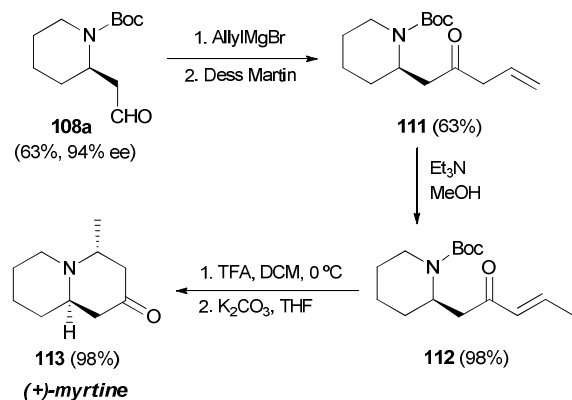


**Scheme 50** Asymmetric synthesis of (*+*)-*allosedamine*, (*+*)-*sedamine* and (*+*)-*coniine*

Three quinolizidine alkaloids were also synthesized taking advantage of our developed methodology for the organocatalytic IMAMR with enals (see Scheme 3). Thus, starting from piperidine aldehyde **108a**, the total synthesis of (*+*)-*myrtine*, (*-*)-

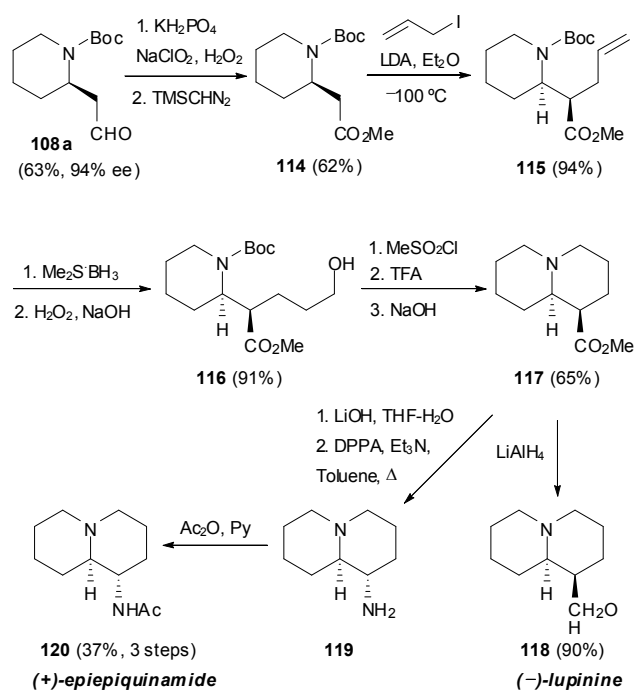


*lupinine* and (+)-*epiepipiquinamide* was successfully accomplished in 2011.<sup>74</sup> For the synthesis of *myrtine*, aldehyde **108a** was treated with allylmagnesium bromide followed by oxidation with Dess-Martin periodinane. Then, the double bond of ketone **111** was nicely isomerized with Et<sub>3</sub>N in MeOH in almost quantitative yield. Removal of the Boc protecting group in compound **112** gave an appropriate substrate for a second IMAMR that took place in a completely selective manner (substrate-controlled process) upon basification, to afford the final product (+)-*myrtine* **113** in excellent yield (Scheme 51).



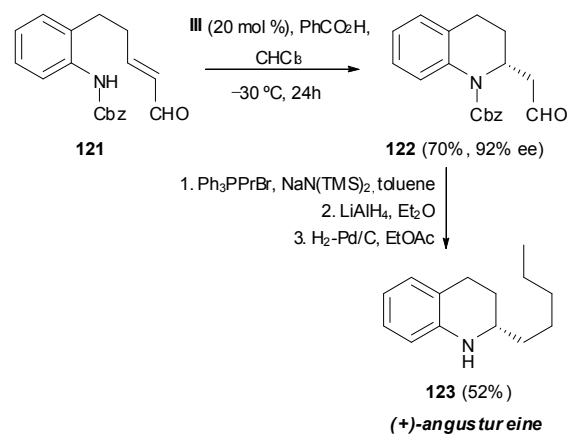
**Scheme 51** Asymmetric synthesis of (+)-*myrtine*

On the other hand, aldehyde **108a** was oxidized and esterified to give methyl ester **114**. Alkylation at the alpha position of the ester was performed with LDA and allyl iodide at -100 °C in a complete selective manner. Then, hydroboration followed by oxidation of the double bond afforded alcohol **116** that was transformed into ester **117** bearing the quinolizidine skeleton. This was achieved through a sequence involving mesylation, removal of the Boc protecting group and cyclization upon basification. Reduction of the ester moiety afforded (-)-*lupinine* **118** in very good yield. Alternatively, saponification of ester **117** (that took place with complete epimerization of the alpha stereocenter) followed by Curtius rearrangement and acetylation of the resulting amine **119** led to (+)-*epiepipiquinamide* **120** in acceptable yield (Scheme 52).<sup>74</sup>



**Scheme 52** Asymmetric synthesis of (-)-*lupinine* and (+)-*epiepipiquinamide*

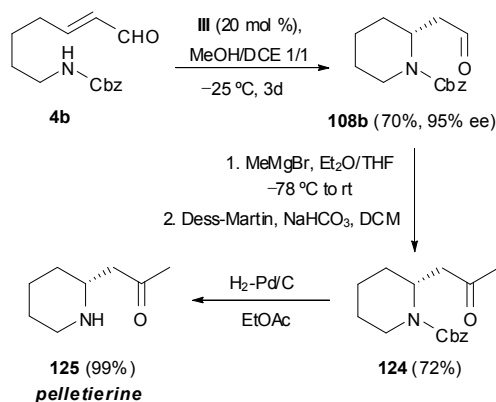
The same organocatalytic methodology applied to benzofused derivatives allowed a straightforward synthesis of the tetrahydroquinoline alkaloid (+)-*angustureine*. Aniline derivative **121** bearing a remote conjugated aldehyde was subjected to the organocatalyzed IMAMR in the presence of diaryl prolinol **III** and benzoic acid as a co-catalyst (see Schemes 3 and 5) to give tetrahydroquinoline aldehyde **122** in 70% yield and 92% ee. Wittig reaction, carbamate reduction and double bond hydrogenation rendered enantiomerically enriched compound (+)-*angustureine* **123** (Scheme 53).<sup>21</sup>



**Scheme 53** Asymmetric synthesis of (+)-*angustureine*

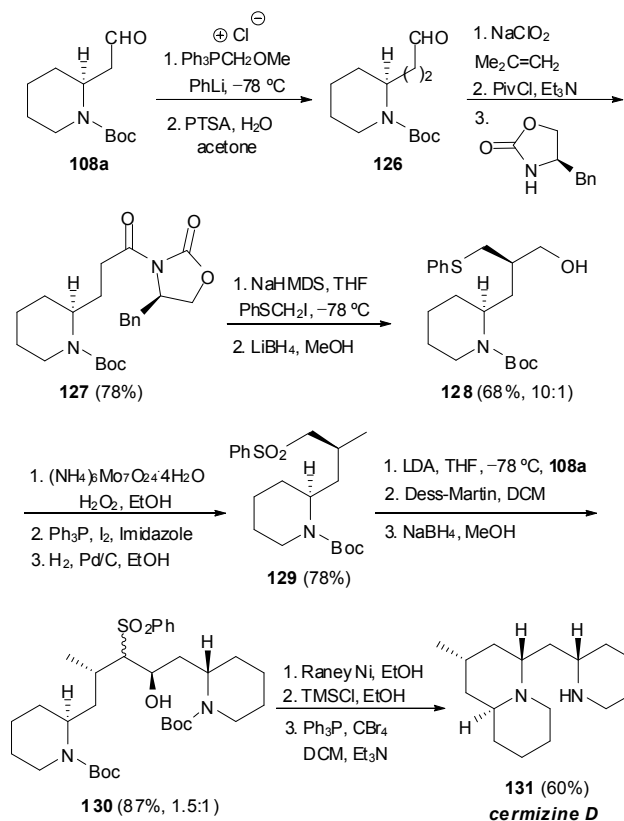
Again an organocatalytic IMAMR with enals as Michael acceptors was employed by Carter and co-workers in the total synthesis of piperidine alkaloid *pelletierine*. In this case, conjugated aldehyde **4b** reacted in a 1:1 mixture of 1,2-dichloroethane (DCE):MeOH at -25 °C during three days in the presence of diarylprolinol **III** (without the need of any additive) to render piperidine aldehyde **108b**.<sup>19</sup> Addition of MeMgBr and

subsequent *in situ* oxidation gave rise to ketone **124**. Finally, Cbz deprotection efficiently rendered the natural product *pelletierine* **125** (Scheme 54).



5 **Scheme 54** Asymmetric synthesis of *pelletierine*

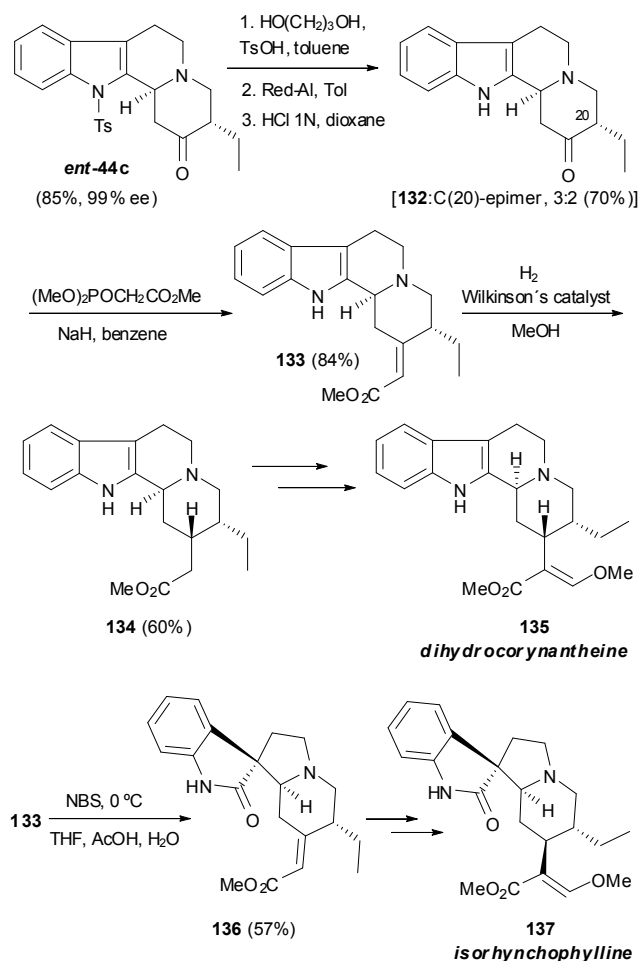
The same authors employed piperidine aldehyde **108a** for the preparation of the alkaloid *cermizine D*. A highly convergent route was designed from **108a** (synthesized following an IMAMR mediated by diaryl prolinol **III**, see Scheme 54) as starting  
10 substrate for the preparation of the two halves of the molecule.<sup>75</sup> The aldehyde moiety was homologated through a Wittig-type reaction to aldehyde **126** that was in turn oxidized and coupled with a chiral oxazolidinone to generate compound **127** in good yield. The sodium anion of this compound was alkylated in a stereoselective manner with PhSCH<sub>2</sub>I and the oxazolidinone was reduced to give alcohol **128**. Sulfide oxidation and further deoxygenation afforded sulfone **129** which was deprotonated with LDA. At this point, a second molecule of the starting aldehyde **108a** was added, and the corresponding hydroxyl sulfone was obtained as a mixture of diastereoisomers. The undesired isomer was recycled *via* oxidation followed by NaBH<sub>4</sub> reduction, affording again a 1.5:1 mixture of diastereoisomers **130**. Then, desulfurization with Raney Ni yielded an unstable alcohol that was cyclized under Mitsunobu conditions to furnish the desired  
15 alkaloid *cermizine D* **131** (Scheme 55).



**Scheme 55** Asymmetric synthesis of *cermizine D*

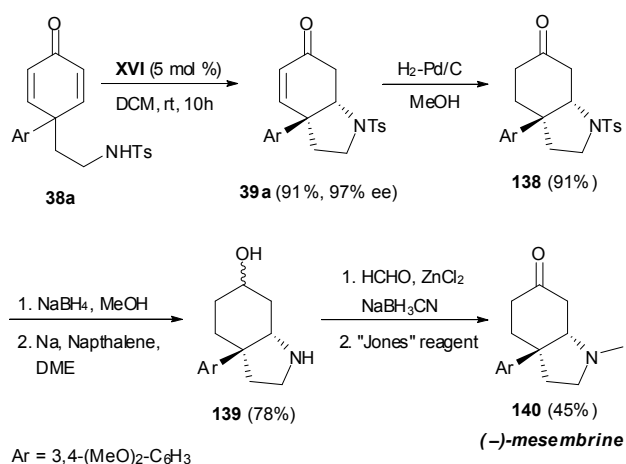
In 2010, Itoh and co-workers applied their proline-catalyzed tandem Mannich-IMAMR with cyclic ketones (see Scheme 23) to the formal synthesis of corynanthe-type indole alkaloids *dihydrocorynantheine* and *isorhynchophylline*. After the tandem reaction on  $\beta$ -carboline **42**, in this case employing (*R*)-proline as the catalyst (see Scheme 23), tetracyclic indole derivative *ent-44c* was efficiently obtained.<sup>76</sup> The elimination of the tosyl group attached to the nitrogen atom revealed to be troublesome at late stages of the synthesis and it was performed at this point. To this end, the carbonyl group was protected as its cyclic acetal and then reduced with Red-Al. Release of the carbonyl functionality in acidic media afforded deprotected compound **132** as a 3:2  
30 mixture of epimers at C-20. Without separation of diastereoisomers, **132** was subjected to the Horner-Wadsworth-Emmons reaction and, in the basic conditions, one epimer isomerized to the thermodynamically more stable compound **133**. Hydrogenation of the conjugated ester with Wilkinson's catalyst  
45 was completely stereoselective, affording **134** as single diastereoisomer. Condensation with methyl formate followed by methylation with diazomethane completed the synthesis of *dihydrocorynantheine* **135** as it was previously described (Scheme 56).<sup>77,78</sup> Intermediate product **133** was employed to perform the total synthesis of *isorhynchophylline*. The key step was the transformation of the tetracyclic structure into the spirocyclic ring system of the natural product. This transformation, previously reported by Taylor,<sup>79</sup> was first attempted on ketone **132**, however  
55 further Wittig-type reaction was unsuccessful. Therefore, the NBS mediated ring contraction was performed on conjugated ester **133**. In this manner, compound **136** was isolated in 57%

yield as a single diastereoisomer, which was finally converted into *isorhynchophylline* **137** in three steps (Scheme 56).<sup>77,78</sup>



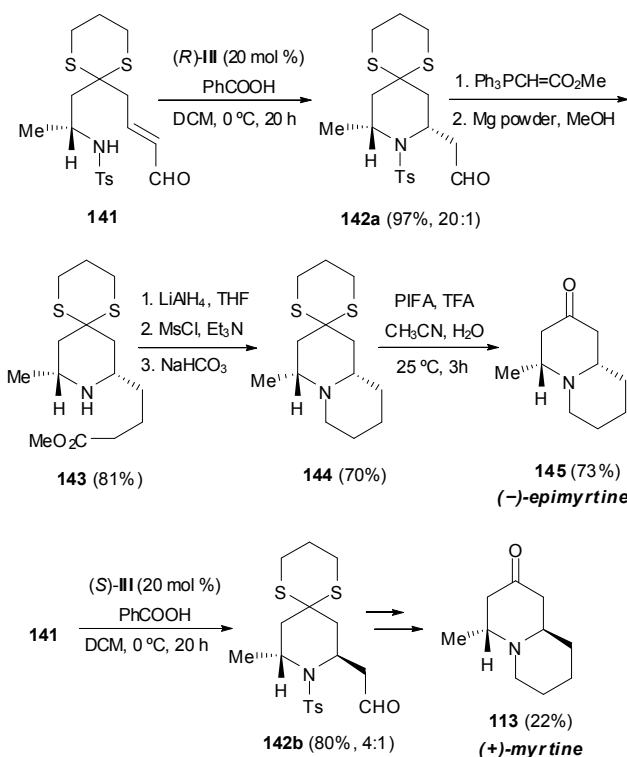
**Scheme 56** Asymmetric synthesis of *dihydrocorynantheine* and *isorhynchophylline*

In 2011, You described the total synthesis of *(-)-mesembrine* employing as the key step a desymmetrization reaction produced by an organocatalytic IMAMR.<sup>43</sup> The main challenge in the design of this synthetic protocol was the installation of the quaternary stereocenter that contains the aryl moiety. This issue was nicely solved by means of the desymmetrization process on substrate **38a**. IMAMR in the presence of chiral thiourea **XVI** (see Scheme 21) afforded bicycle **39a** in very good yield and excellent ee. Double bond hydrogenation afforded compound **138**, which was reduced to the corresponding alcohol and deprotected to give free amine **139** that was *N*-methylated and re-oxidated to render alkaloid *(-)-mesembrine* **140** in 35% yield from **38a** (Scheme 57).



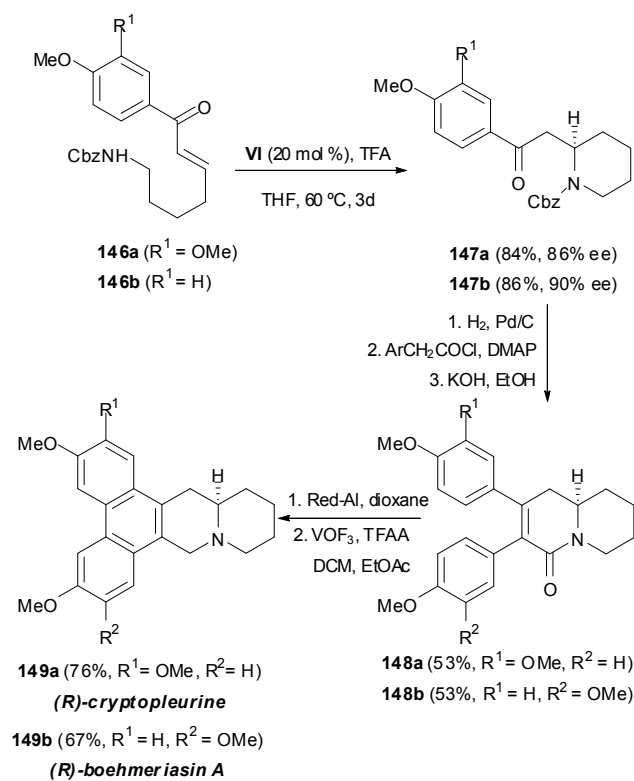
**Scheme 57** Asymmetric synthesis of *(-)-mesembrine*

A diastereodivergent synthesis of *(+)-myrtine* and *(-)-epimyrtine* was reported in 2011 by Hong and co-workers by means of a stereoselective IMAMR.<sup>80</sup> Initially, chiral dithiane **141** bearing the enal functionality was subjected to the IMAMR under basic conditions, but the reaction took place with poor selectivity. However, when the reaction was performed in the presence of chiral diarylprolinol (*R*)-**III** (see Scheme 3) in dichloromethane at 0 °C, the IMAMR proceeded with excellent diastereoselectivity (20:1) affording *cis*-2,6-disubstituted piperidine **142a** in excellent yield. It is important to mention that the authors performed also the reaction with the (*Z*)-enal isomer of **141** but the reaction was less selective. The organocatalytic IMAMR in the presence of (*S*)-**III** gave a 4:1 mixture of diastereoisomers, indicating that enal **141** and diaryl prolinol (*R*)-**III** formed the matched pair. To continue the synthesis of the natural product, **142a** was subjected to Wittig olefination followed by *N*-deprotection with Mg in methanol. Ester **143** was then converted into the quinolizidine skeleton **144** through the sequence involving reduction of the ester moiety, mesylation of the resulting alcohol and cyclisation upon basification. Finally, dithiane deprotection with bis(trifluoroacetoxy)iody benzene (PIFA) afforded *(-)-epimyrtine* **145**. An analogous sequence on the *trans*-2,6-disubstituted piperidine **142b** gave rise to *(+)-myrtine* **113** in 22% overall yield (Scheme 58).



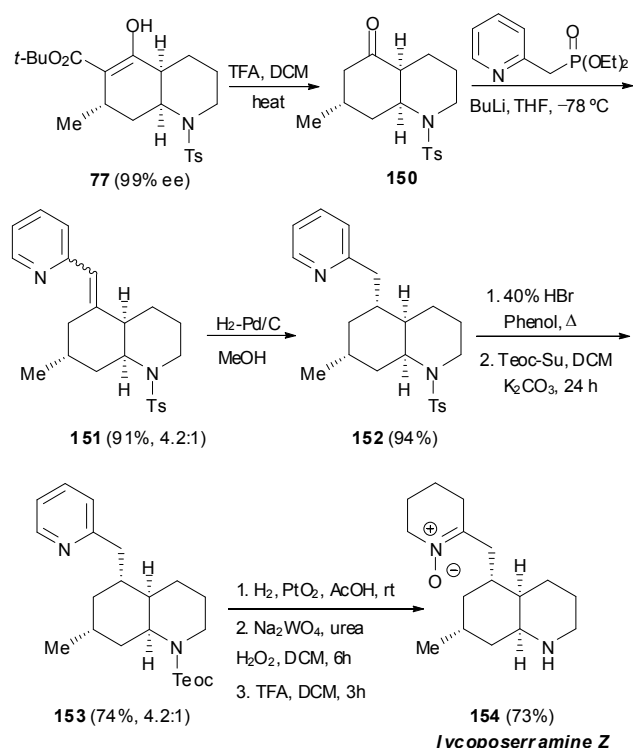
**Scheme 58** Asymmetric synthesis of (+)-myrtine and (-)-epimyrtime

The enantioselective synthesis of phenanthroquinolizidine alkaloids *cryptopleurine* and *boehmeriasin A* employing an organocatalytic IMAMR with aromatic ketones as Michael acceptors was reported by Yu and co-workers in 2012.<sup>81</sup> With the substrates for the IMAMR **146a,b** in hand, first attempts were performed with quinine-derived primary amine **VI** (see Scheme 7) at room temperature, however low conversions were reached even after one week. When the reaction was heated at 60 °C, full conversions were achieved after three days with good enantioselectivity. Next, removal of the Cbz protecting group of piperidines **147a,b** followed by reaction with the corresponding acyl chlorides and subsequent intramolecular aldol addition gave rise to bicyclic derivatives **148a,b**. Reduction of the amide bond with Red-Al and oxidative coupling with VOF<sub>3</sub> rendered final alkaloids *cryptopleurine* **149** and *boehmeriasin A* **149b** in an efficient manner (Scheme 59).



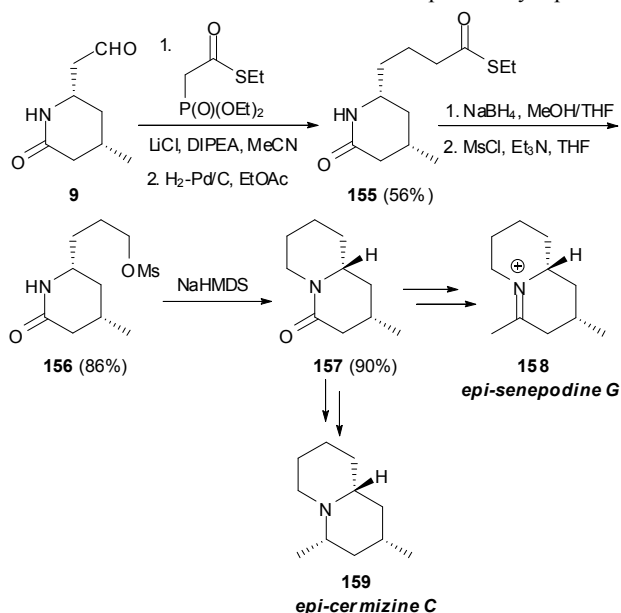
**Scheme 59** Asymmetric synthesis of *cryptopleurine* and *boehmeriasin A*

Bonjoch and Bradshaw designed a very elegant synthesis of lycopodium alkaloid *lycposerramine Z* following an organocatalytic tandem Robinson annulation-IMAMR.<sup>65</sup> With this strategy, they obtained bicycle **77** in 85% ee (see Scheme 39), which was enriched until 99% ee after recrystallization. Ester deprotection with TFA and azeotropic removal of TFA with toluene induced decarboxylation to afford ketone **150** which was used in the subsequent Horner-Wadsworth-Emmons reaction to give vinyl pyridine **151** in excellent yield (three steps) as a 4.2:1 mixture of *E/Z* isomers. The setting of all stereogenic centers was achieved by stereoselective hydrogenation of the double bond assisted for the methyl group present in the molecule. Next, tosyl group of **152** was removed with HBr and re-protected with Teoc. The pyridine ring of **153** was reduced with H<sub>2</sub> and PtO<sub>2</sub> as catalyst to the corresponding piperidine, which was *in situ* oxidized to the nitrone functionality. Finally, removal of the Teoc protecting group with TFA afforded the desired natural product *lycposerramine Z* **154** (Scheme 60).



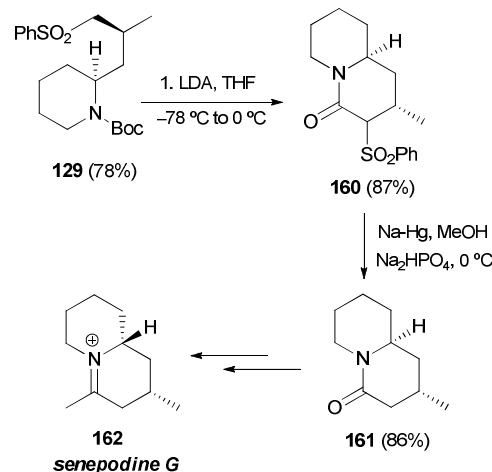
**Scheme 60** Asymmetric synthesis of *lycoposerramine Z*

In 2013, Carter succeeded in applying his methodology for the organocatalytic IMAMR with primary amides (see Scheme 6) to the formal synthesis of *epi-senepodine G* and *epi-cermizine C*. Hence, piperidone **9** was transformed into thioester **155** by means of a Horner-Wadsworth-Emmons reaction followed by double bond hydrogenation. The thioester group was reduced with sodium borohydride and converted into mesylate **156**, which cyclised to the quinolizidine skeleton **157** upon treatment with NaHMDS (Scheme 61).<sup>22</sup> The transformation of advanced intermediate **157** into the two alkaloids was previously reported.<sup>82</sup>



**Scheme 61** Asymmetric synthesis of *episepodine G* and *epicermizine C*

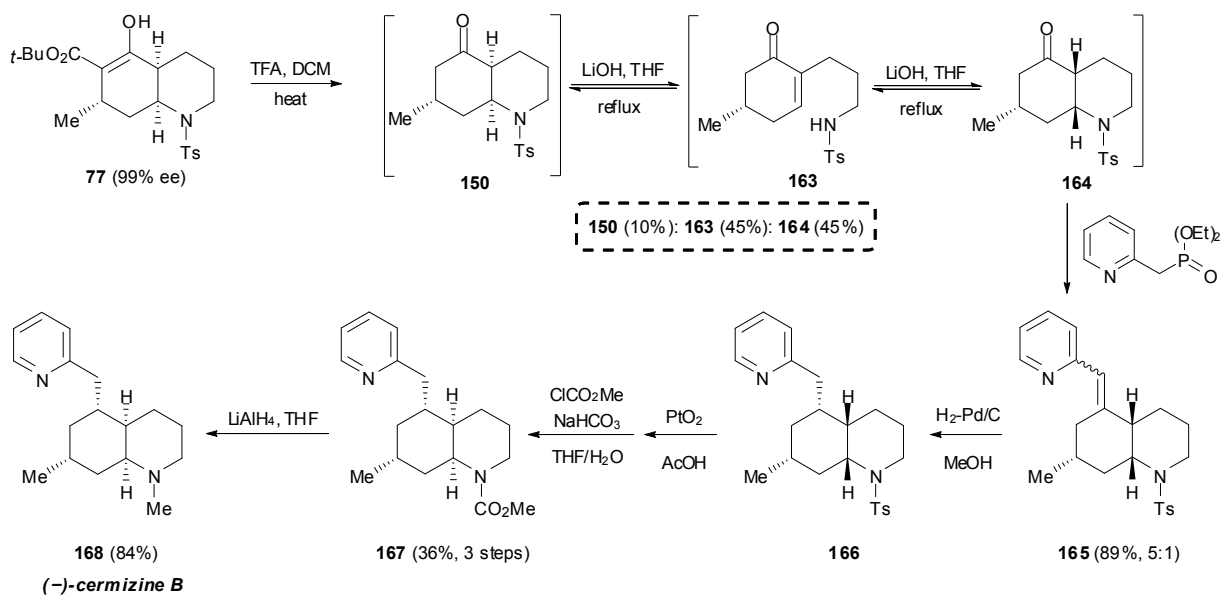
One of the intermediates employed by Carter in the total synthesis of *cermizine D* (see Scheme 55) was employed also in the formal synthesis of the quinolizidine alkaloid *senepodine G*.<sup>22</sup> Thus, when sulfone **129** was treated with LDA at  $-78\text{ }^\circ\text{C}$  and the temperature was allowed to reach room temperature, bicyclic sulfone **160** was obtained in good yield. Treatment with sodium amalgam rendered intermediate **161** for the synthesis of *senepodine G* **162** (Scheme 64).<sup>82</sup>



**Scheme 62** Asymmetric synthesis of *senepodine G*

The last example in this section was reported very recently by Bradshaw and Bonjoch taking advantage of their previously developed methodology concerning a tandem organocatalytic Robinson annulation-IMAMR (see Scheme 39). These authors developed a “pot economy” synthesis of the *Lycopodium* alkaloid (*-*)*cermizine B* in gram scale (Scheme 63).<sup>83</sup> Their elegant protocol was based on three consecutive tandem reactions which were finally combined in a single sequence. Starting material **77** was synthesized according to the tandem sequence described in Scheme 39 with some improvements: only 5% of catalyst loading was employed and, at the end of the process, the reaction mixture was treated with a sulfonic acid resin which eliminated the basic residues and no work-up of the reaction mixture was necessary, allowing also for the recovery of the catalyst. Bicycle **77** was treated with TFA and heated to promote the decarboxylation process. Solvent was removed and ketone **150** was redissolved in THF and treated with LiOH. Under these basic conditions, the retro *aza*-Michael reaction occurred to give **163**, which again underwent cyclization to the more stable decahydroquinoline **164**. At this point, a mixture of compounds **149**, **163** and **164** was detected, however this problem was overcome by addition of the pyridyl phosphonate since the Horner-Wadsworth-Emmons reaction was irreversible, shifting the equilibrium and leading to the formation of **165** as a 5:1 mixture of *cis:trans* isomers. Next, the hydrogenation of the double bond took place in both isomers to render the same diastereoisomer **166**. Solvents were removed and the *N*-protecting group was removed with acetic acid in the presence of PtO<sub>2</sub>. The corresponding free amine obtained was transformed into carbamate **167** and finally, reduction of the carbamate with LiAlH<sub>4</sub> gave the natural product **168** in 20% overall yield. It is important to point out that the three tandem reactions were performed in a one pot manner until compound

167, allowing the authors to perform the whole sequence in gram scale.



Scheme 63 Asymmetric synthesis of (-)-cermizine B

## Conclusions

The organocatalytic version of the IMAMR enables a straightforward preparation of enantiomerically enriched pyrrolidine and piperidine scaffolds and their analogues. These scaffolds are present in a wide variety of natural products and biologically relevant compounds. Since the first efficient example reported in 2007, great achievements have been made and several methodologies for the conjugate addition of nitrogen nucleophiles to enals and enones have been described. To this end, both covalent and non-covalent catalysis have been employed being diaryl prolinols, quinine-derived primary amines and thioureas and chiral BINOL phosphoric acids the most common catalysts of choice. Regarding the nucleophilic nitrogen source, in general we can state that those with moderate nucleophilicity that avoid spontaneous cyclization, such as carbamates and sulphonamides, are the most adequate. However, it is important to point out that a general method for the IMAMR with conjugated esters as Michael acceptors remained elusive to date, being in this context the main gap that has to be filled in the future.

On the other hand, the organocatalytic combination of several reactions in a tandem manner allows for the generation of multiple stereogenic centers in a single step. The organocatalytic IMAMR has been combined with a wide variety of different reactions like *oxa*-Michael, *aza*-Henry, Mannich, *aza*-Morita-Baylis-Hillman, cross metathesis, Robinson annulation or alpha amination among others, allowing the generation of complex polycyclic structures in a quite simple manner. Most of these tandem protocols generate the nucleophilic nitrogen source in a first step and it is subsequently trapped with an  $\alpha,\beta$ -unsaturated functionality. In this context, the design of more tandem processes starting with an IMAMR is still underdeveloped and it is one of the future directions of research.

Finally, we can anticipate that we witness in the future more applications of these methodologies (either in a single step or in a

tandem manner) for the synthesis of natural products with increasing complexity.

## Notes and references

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- 1 A. Michael, *Prakt. Chem.*, 1887, **35**, 349.
- 2 T. Tokoroyama, *Eur. J. Org. Chem.*, 2010, 2009.
- 3 Z. Amara, J. Caron and D. Joseph, *Nat. Prod. Rep.*, 2013, **30**, 1211.
- 4 K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243.
- 5 B. List, R. A. Lerner and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
- 6 Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328.
- 7 J. Vesely, I. Ibrahim, R. Ríos, G.-L. Zhao, Y. Xu and A. Córdova, *Tetrahedron Lett.*, 2007, **48**, 2193.
- 8 H. Jiang, J. B. Nielsen, M. Nielsen and K. A. Jørgensen, *Chem. Eur. J.*, 2007, **13**, 9068.
- 9 D. Perdicchia and K. A. Jørgensen, *J. Org. Chem.*, 2007, **72**, 3565.
- 10 P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983.
- 11 U. Uría, J. L. Vicario, D. Badía and L. Carrillo, *Chem. Commun.*, 2007, 2509.
- 12 D. Enders, A. Greb, K. Deckers, P. Selig, C. Merckens, *Chem. Eur. J.* 2012, **18**, 10226.
- 13 D. Enders, C. Joie, K. Deckers, *Chem. Eur. J.* 2013, **19**, 10818.
- 14 K. Takasu, S. Maiti and M. Ihara, *Heterocycles*, 2003, **59**, 51.
- 15 D. Enders, C. Wang and J. X. Liebich, *Chem. Eur. J.*, 2009, **15**, 11058.
- 16 E. Reyes, M. Fernández, U. Uría, J. L. Vicario, D. Badía and L. Carrillo, *Curr. Org. Chem.*, 2012, **16**, 521.
- 17 J. Wang, P. Li, P. Y. Choi, A. S. C. Chan and F. Y. Kwong, *Chem. Cat. Chem.*, 2012, **4**, 917.
- 18 S. Fustero, D. Jiménez, J. Moscardó, S. Catalán and C. del Pozo, *Org. Lett.*, 2007, **9**, 5283.

- 19 At the beginning of 2008 Carter described a slightly different protocol. A mixture of MeOH/dichloroethane was used as solvent and the process was performed without additive. E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett and R. G. Carter, *J. Org. Chem.*, 2008, **73**, 5155.
- 20 The mechanism of the intermolecular addition of nitrogen heterocycles to conjugated aldehydes have been the subject of theoretical calculations, in order to support the presence of the intermediates showed in Scheme 4. In this context, see: S. Lakhdar, M. Baydia and H. Mayr, *Chem. Commun.*, 2012, **48**, 4504 and reference 10.
- 21 S. Fustero, J. Moscardó, D. Jiménez, M. D. Pérez-Carrión, M. Sánchez-Roselló and C. del Pozo, *Chem. Eur. J.*, 2008, **14**, 9868.
- 22 N. Veerasamy, E. C. Carlson, N. D. Collett, M. Saha and R. C. Carter, *J. Org. Chem.*, 2013, **78**, 4779.
- 23 With catalyst **III** a 1:1 mixture of diastereoisomers was obtained, indicating that the reaction with *ent*-**III** gives rise to the matched product.
- 24 G. Bartoli and P. Melchiorre, *Synlett*, 2008, 1759.
- 25 P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 9748.
- 26 P. Kwiatkowski, T. D. Beeson, J. C. Conrad and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2011, **133**, 1738.
- 27 X. Lu and L. Deng, *Angew. Chem., Int. Ed.*, 2008, **47**, 7710.
- 28 F. Pesciaiolli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2008, **47**, 8703.
- 29 J.-D. Liu, Y.-C. Chen, G.-B. Zhang, Z.-Q. Li, P. Chen, J.-Y. Du, Y.-Q. Tu and C.-A. Fan, *Adv. Synth. Catal.*, 2011, **353**, 2721.
- 30 S. Fustero, C. del Pozo, C. Mulet, R. Lázaro and M. Sánchez-Roselló, *Chem. Eur. J.*, 2011, **17**, 14267.
- 31 A recent theoretical study related to the activation of enones by catalyst **VI** was recently reported, confirming its bifunctional nature: A. Morán, A. Hamilton, C. Bo and P. Melchiorre, *J. Am. Chem. Soc.*, 2013, **135**, 9091.
- 32 Z. Feng, Q.-L. Xu, L.-X. Dai and S.-L. You, *Heterocycles*, 2010, **80**, 765.
- 33 X. Lu and Y. Liu, *Org. Lett.*, 2010, **12**, 5592.
- 34 Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666.
- 35 M. Rueping, S. A. Moreth and M. Bolte, *Z. Naturforsch.*, 2012, **67b**, 1021.
- 36 H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666.
- 37 R. Miyaji, K. Asano and S. Matsubara, *Org. Lett.*, 2013, **15**, 3658.
- 38 S. Chen, L. Zhao and S. You, *Adv. Synth. Catal.*, 2014, **356**, 982.
- 39 M. Bandini, A. Eichholzer, M. Tragni and A. Umami-Ronchi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3238.
- 40 M. Bandini, A. Bottoni, A. Eichholzer, G. P. Miscione and M. Stenta, *Chem. Eur. J.*, 2010, **16**, 12462.
- 41 X. Xiao, X. Liu, S. Dong, Y. Cai, L. Ling and X. Feng, *Chem. Eur. J.*, 2012, **18**, 15922.
- 42 R. Sallio, R. Lebrun, N. Schifano-Faux, J.-F. Goossens, F. Agbossou-Niederconr, E. Deniau and C. Michon, *Synlett*, 2013, **24**, 1785.
- 43 Q. Gu and S.-L. You, *Chem. Sci.*, 2011, **2**, 1519.
- 44 M. O. Ratnikov, L. E. Farkas and M. P. Doyle, *J. Org. Chem.*, 2012, **77**, 10294.
- 45 C. Grondal, M. Jeanty and D. Enders, *Nature Chem.*, 2010, **2**, 167.
- 46 L. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492.
- 47 H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237.
- 48 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2003, **5**, 4301.
- 49 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2006, **8**, 1533.
- 50 H. Sundén, I. Ibrahim, L. Eriksson and A. Cordova, *Angew. Chem., Int. Ed.*, 2005, **44**, 4877.
- 51 M. Rueping and C. Azap, *Angew. Chem., Int. Ed.*, 2006, **45**, 7832.
- 52 H. Liu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Org. Lett.*, 2006, **8**, 6023.
- 53 H. Yang and R. G. Carter, *J. Org. Chem.*, 2009, **74**, 5151.
- 54 S. Khaliel, M. V. Nandakumar, S. Krautscheid and C. Schneider, *Synlett*, 2008, 2705.
- 55 D. Enders, D. P. Göddertz, C. Beceño and G. Raabe, *Adv. Synth. Catal.*, 2010, **352**, 2863.
- 56 Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang and L. He, *Org. Lett.*, 2013, **15**, 6090.
- 57 Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5692.
- 58 N. Momiyama, Y. Yamamoto, and H. Yamamoto, *J. Am. Chem. Soc.*, 2007, **129**, 1190.
- 59 Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji and D. Hashizume, *Adv. Synth. Catal.*, 2004, **346**, 1435.
- 60 M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, *Angew. Chem., Int. Ed.*, 2008, **47**, 10087.
- 61 D. Zu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett.*, 2008, **10**, 4585.
- 62 S. Fustero, D. Jiménez, M. Sánchez-Roselló and C. del Pozo, *J. Am. Chem. Soc.*, 2007, **129**, 6700.
- 63 H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666.
- 64 D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661.
- 65 B. Bradshaw, C. Luque-Corredera and J. Bonjoch, *Org. Lett.*, 2013, **15**, 326.
- 66 B. Bradshaw, C. Luque-Corredera, G. Savorit, C. Catiuela, R. Dorel, C. Bo and J. Bonjoch, *Chem. Eur. J.*, 2013, **19**, 13881.
- 67 B. Bradshaw, C. Parra and J. Bonjoch, *Org. Lett.*, 2013, **15**, 2458.
- 68 S. Takizawa, N. Inoue, S. Hirata and H. Sasai, *Angew. Chem., Int. Ed.*, 2010, **49**, 9725.
- 69 A. I. Gerasyuto, R. P. Hsung, N. Sydorenko and B. Slafer, *J. Org. Chem.*, 2005, **70**, 4248.
- 70 N. Sydorenko, C. A. Zificsak, A. I. Gerasyuto and R. P. Hsung, *Org. Biomol. Chem.*, 2005, **3**, 2140.
- 71 Y. Fukata, K. Asano and S. Matsubara, *Chem. Lett.*, 2013, **42**, 355.
- 72 T. Cheng, S. Meng and Y. Huang, *Org. Lett.*, 2013, **15**, 1958.
- 73 J. Jiang, X. Ma, C. Ji, Z. Guo, T. Shi, S. Liu and W. Hu, *Chem. Eur. J.*, 2014, **20**, 1505.
- 74 S. Fustero, J. Moscardó, M. Sánchez-Roselló, S. Flores, M. Guerola and C. del Pozo, *Tetrahedron*, 2011, **67**, 7412.
- 75 N. Veerasamy, E. C. Carlson and R. G. Carter, *Org. Lett.*, 2012, **14**, 1596.
- 76 K. Nagata, H. Ishikawa, A. Tanaka, M. Miyazaki, T. Kanemitsu and T. Itoh, *Heterocycles*, 2010, **81**, 1791.
- 77 L. F. Tietze and Y. Zhou, *Angew. Chem., Int. Ed.*, 1999, **38**, 2045.
- 78 M. Amat, A. Gómez-Esqué, C. Escolano, M. M. M. Santos, E. Molins and J. Bosch, *J. Org. Chem.*, 2009, **74**, 1205.
- 79 N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 3871.
- 80 Y. Ying, H. Kim and H. Hong, *Org. Lett.*, 2011, **13**, 796.
- 81 C. Zeng, H. Liu, M. Zhang, J. Guo, S. Jiang and S. Yu, *Synlett*, 2012, 2251.
- 82 B. Snider and J. F. Grabowski, *J. Org. Chem.*, 2007, **72**, 1039.
- 83 B. Bradshaw, C. Luque-Corredera and J. Bonjoch, *Chem. Commun.* 2014, **50**, 7099.