Organocatalytic enantioselective synthesis of 1,4-dihydropyridines

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Abstract. This review aims to bring light upon a very interesting group of compounds, the 1,4-dihydropyridines (1,4-DHPs). These structures are well-known pharmacophores, used for many years to treat cardiovascular diseases because of their activity as calcium channel blockers. In addition, their potential as drugs to treat other affections has been recently exposed. The racemic synthesis of 1,4-DHPs has been well studied, while the asymmetric approaches are mainly based on the use of chiral auxiliaries or chiral resolutions. However, there are scarce examples regarding enantioselective organocatalytic methods. Herein, we will summarize the existing examples in this field of research.

Keywords: 1,4-dihydropyridine; 1,4-DHP; organocatalysis; (thio)urea; BINOL-derived phosphoric acid; aminocatalysis

1 Introduction

1,4-Dihydropyridine (1,4-DHP)[1] ring is one of the most researched scaffolds in chemistry due to the biological activity exhibited by these compounds.[2] The most remarkable use of this family of molecules is the treatment of various cardiovascular diseases because of their activity as calcium channel blockers (Figure 1).[3,4] Recently, new studies have exposed their activity as antioxidant, antidiabetic and antitumor agents.[5] Moreover, 1,4-DHPs are NAD(P)H mimetics and can be used in alkaloids synthesis.[6]

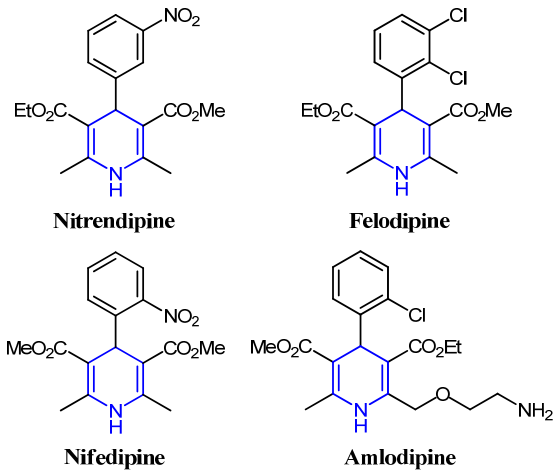
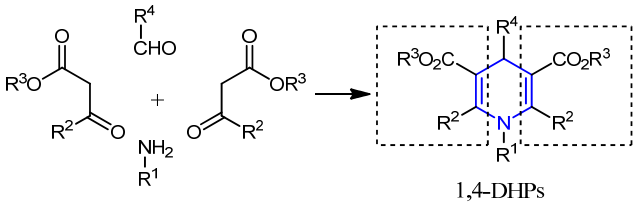


Figure 1. Drugs belonging to the group of 1,4-dihydropyridines that act as calcium channel blockers.

Therefore, it is not surprising that 1,4-DHPs synthesis had attracted the attention of numerous researchers for many years.[7] The classical synthetic methodology of these molecules is the Hantzsch condensation (Scheme 1).[8] However, only symmetrical 1,4-DHPs can be obtained through this multicomponent (MCR) route. Otherwise, a mixture of different products could be found.



Scheme 1. Hantzsch classical methodology to synthesize 1,4-DHPs based on a MCR.

The control of the enantioselectivity in biologically active compounds has proven to be crucial in their activity.[9] Thus, chemists have assumed the challenge of preparing enantiomerically enriched 1,4-DHPs, mainly using chiral reactants[10] or chiral resolution.[9a,11] Nevertheless, only a few examples of organocatalytic enantioselective syntheses of these

compounds have been developed so far (Figure 2 and Scheme 2), which are gathered on this review. These methods allow the preparation of unsymmetrical 1,4-DHPs differently substituted, being 1,2,3,4-tetrasubstituted molecules the most frequent case (Scheme 2, routes a, b and e). This is a strong example where the organocatalysis has succeed earlier and faster than the metal catalysis, since to the best of our knowledge there is not any metal-catalyzed enantioselective method to obtain these compounds. Due to the biological importance of these products and their structural complexity, their asymmetric catalytic preparation is still an active challenging task in organic synthesis.

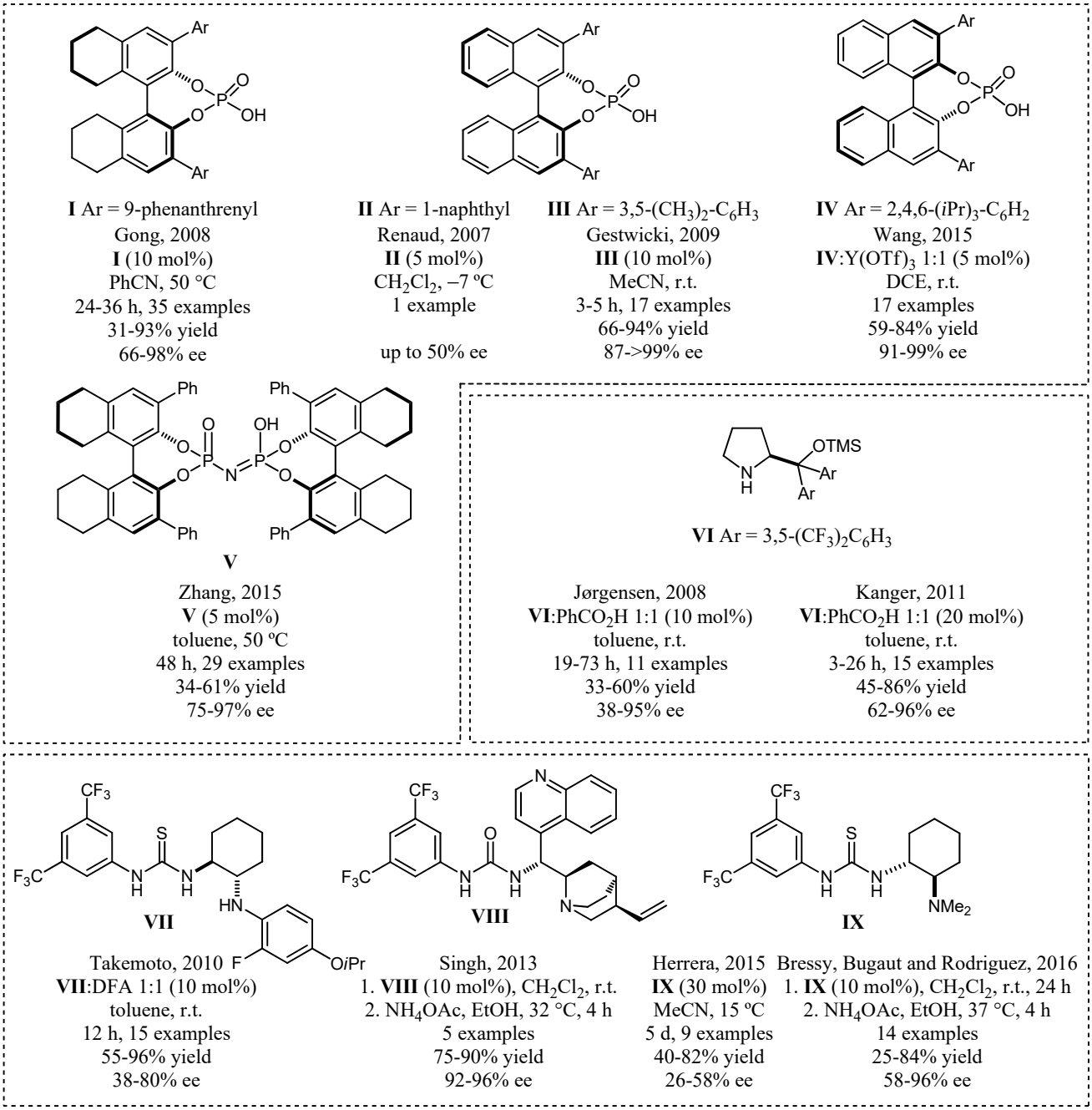
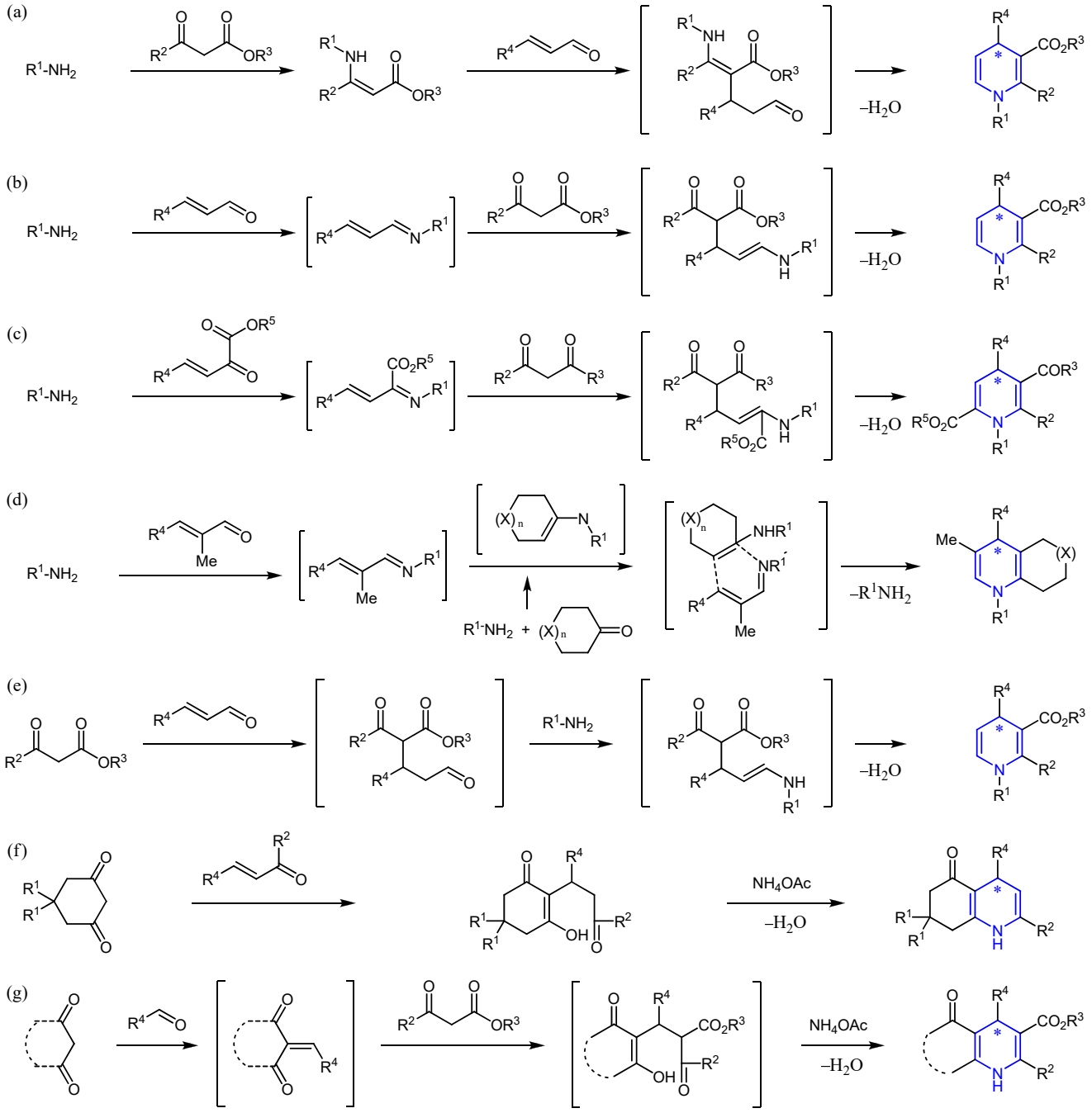


Figure 2. Enantioselective organocatalytic synthesis of 1,4-DHPs: Catalysts and results [**I**,[12] **II**,[13] **III**,[14] **IV**,[15] **V**,[16] **VI**,[17,18] **VII**,[19,20] **VIII**,[21] and **IX**[22,23]]



Scheme 2. Synthetic routes for chiral 1,4-DHPs [(a),[13,18-21] (b),[12] (c),[16] (d),[15] (e),[17] (f),[14] and (g)[21,23]].

The first method, developed by Renaud, dates from 2007, and yielded a modest 50% ee, using a phosphoric acid derivative as catalyst (**II**; route a).[13] Since then, different organocatalysts have been tested for this purpose, such as other phosphoric acid derivatives following multicomponent strategies (**I**,[12] **III**[14] and **V**;[16] routes b, f and c, respectively). Chiral phosphoric acid **IV** has been also used together with $Y(OTf)_3$ forming a dual catalytic system (route d).[15] Chiral (thio)ureas have been proved to be active catalysts for the synthesis of 1,4-DHPs (**VII**[19,20] routes a and b; **VIII**[21] and **IX**,[23] route g; **IX**,[22] a variant of route a). Jørgensen[17] and Kanger[18] employed aminocatalytic approaches using a diarylprolinol derivative as catalyst (**VI**; routes e and a, respectively), which leads to the formation of an iminium cation with the α,β-unsaturated carbonyl compound. Attending to the approach used to obtain the 1,4-DHPs, the current literature may be organized according to the type of organocatalyst, substrates, and synthetic route used. These three main aspects are highlighted in each case.

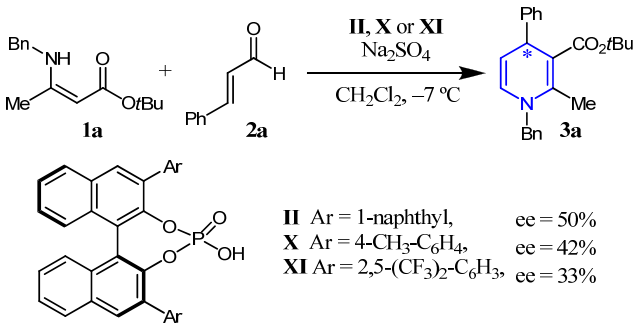
Fernando Auría-Luna was born in Zaragoza (Spain) in 1990. He obtained his B.Sc. in Chemistry in 2015 at the University of Zaragoza, Spain. Currently, he is working on his Ph.D. in Organic Chemistry at the H-OCA research group, under the supervision of Dr. Raquel P. Herrera and Dr. Eugenia Marqués-López at the ISQCH (CSIC)-University of Zaragoza. His research interest focuses on the asymmetric synthesis of new heterocyclic compounds that feature potential biological properties, by means of organocatalysis.

Dr. Eugenia Marqués-López completed her Ph.D. in Organic Chemistry (2007), under the supervision of Prof. Rosario Fenández and Prof. José M. Lassaletta, at the University of Seville, Spain. During her Ph.D. studies she worked on the field of N,N-dialkylhydrazones as N,N-dialkylamino imines surrogates and its applications in Staudinger, Mannich and Strecker-type reactions. She also worked on the synthesis of novel diene complexes, in the laboratory of Dr. John M. Brown in the CRL at Oxford University (UK; 2005). After her promotion, she joined the group of Prof. Mathias Christmann (Technische Universität Dortmund, Germany) as an Alexander von Humboldt post-doctoral fellow, where she deeply investigated dienamine catalysis (2008-2010). Later, she moved back to Spain to work in the group of Prof. Pedro Merino at the Instituto de Ciencia de Materiales de Aragón (ICMA-CSIC) (Zaragoza, Spain), as JAE-Doc postdoctoral researcher (2011). From 2011 to 2016 she held the position of an Assistant Professor at the University of Zaragoza, where she promoted to Associate Professor in September 2016. She currently develops her independent research, together with Dr. Raquel P. Herrera, focused on new catalytic methods, mainly based on asymmetric organocatalysis, at the Instituto de Síntesis Química y Catálisis Homogénea (ISQCH-CSIC) in Zaragoza (Spain).

Dr. Raquel P. Herrera was born in Alicante (Spain), in 1977. She received her B.Sc. (1999) and M.Sc. degrees (2000) at the University of Alicante, Spain, and completed her Ph.D. (1999-2003) under the supervision of Prof. Guijarro and Prof. Yus at the same university. She then took up a European postdoctoral contract with Prof. Ricci (Bologna, Italy) until March 2006, at which time she joined Prof. Lassaletta's group at the IIQ-CSIC (Seville, Spain). She was appointed as a permanent researcher (ARAID program) at the ISQCH-University of Zaragoza in January 2008 and in 2011 she obtained a permanent position as Tenured Scientist of the Spanish Council of Research (CSIC) at the same Institute. In 2012 she was awarded with the Lilly Prize to the best young scientist less than 40 ages, in Spain. Her research focuses on asymmetric organocatalysis and its applications.

2 BINOL-derived phosphoric acid mediated organocatalysis

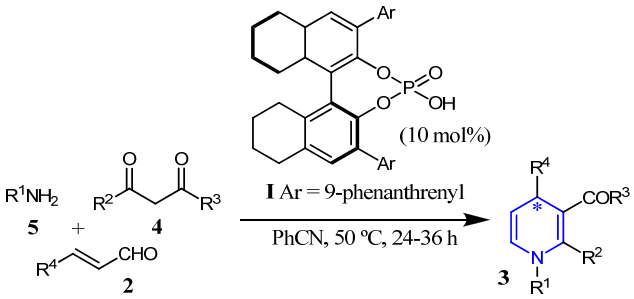
In 2007, Renaud and coworkers published a methodology to synthesize DHPs, following the synthetic route (a), as depicted in Scheme 2, based on the Michael addition of β-enaminoesters to α,β-unsaturated aldehydes followed by a cyclization.[13] According to the literature, the authors anticipated that a Brønsted acid could promote the reaction through the activation of α,β-unsaturated aldehydes *via* hydrogen bonding.[24] Following this hypothesis, a variety of substituted 1,4-DHPs using a non-chiral phosphoric acid derivative as catalyst was first synthesized. Additionally, three chiral BINOL-derived phosphoric acids (**II**, **X** and **XI**) were tested in a single reaction of (*Z*)-*tert*-butyl 3-(benzylamino)but-2-enoate (**1a**) and cinnamaldehyde (**2a**), achieving the final product **3a** with moderate enantioselectivity, up to 50% ee (Scheme 3).



Scheme 3. Pioneering enantioselective organocatalytic synthesis of 1,4-DHP **3a** catalyzed by the chiral BINOL-phosphoric acid derivatives **II**, **X** and **XI**.[13]

This work represents one of the first developed attempts following an asymmetric catalytic approach to obtain this kind of promising molecules. Although with a narrow scope, the authors successfully applied the potential of Brønsted acid catalysts, setting a significant precedent for many other scientists in this field of research.

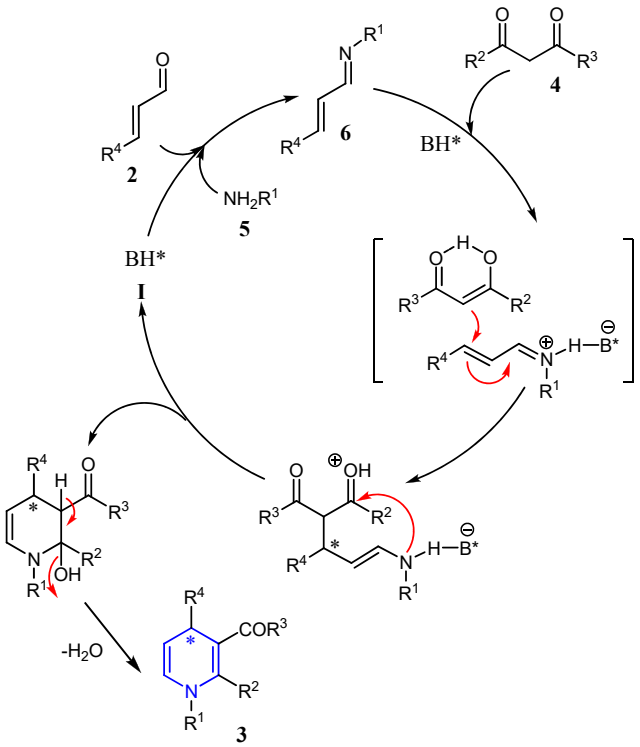
One year later, Gong's group reported another procedure using the chiral BINOL-derived phosphoric acid **I** for the three component synthesis of enantiomerically enriched 1,4-DHPs **3** with good yields (31-93%) and good to excellent enantioselectivity (66-98% ee) (Scheme 4).[12] Furthermore, the authors provided possible outputs to their products such as the synthesis of other interesting chiral heterocyclic compounds (a tetrahydropyridine and two piperidines).[25] The selected route (b), shown in Scheme 2, is based on a three-component cyclization of 1,3-dicarbonyl compounds **4**, primary amines **5** and α,β-unsaturated aldehydes **2**.



R^1 = 3-MeO-C_6H_4, 4-MeO-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4
R^2 = Me, Et
R^3 = OMe, OEt, O*i*Pr, Oallyl, Me
R^4 = Ph, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2,3-Cl_2-C_6H_3, 2-MeO-C_6H_4, 2-Cl-C_6H_4, 2-CF_3-C_6H_4, 2-Br-C_6H_4, *n*Pr

Scheme 4. Enantioselective organocatalytic synthesis of 1,4-DHPs **3** catalyzed by the chiral BINOL-phosphoric acid derivative **I**.[12]

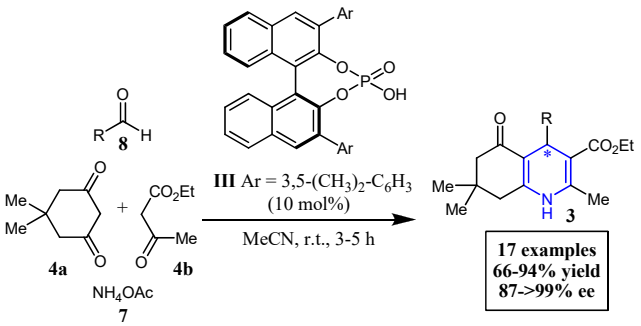
The proposed mechanism would begin with the condensation between the α,β-unsaturated aldehyde **2** and the primary amine **5** to form a conjugated imine **6** (Scheme 5). Later, the acidic catalyst **I** would activate the imine **6** by means of hydrogen bonding and, then, the 1,3-dicarbonyl compound **4** would attack the β position of the imine **6**. Finally, a cyclization followed by dehydration would produce the optically active DHP ring.



Scheme 5. Plausible reaction mechanism.

Additionally, the authors enhanced the importance of their methodology applying the resulting 1,4-DHPs **3** in the synthesis of other optically active heterocyclic compounds.

Gestwicki and coworkers reported in 2009 a third way for the synthesis of important DHPs catalyzed by chiral BINOL-phosphoric acid derivatives **III**. They developed an enantioselective organocatalytic Hantzsch synthesis starting from two different dicarbonyl compounds (dimedone **4a** and ethyl acetoacetate **4b**), giving rise to non-symmetric products **3** with good to excellent yields (66-94%) and excellent enantioselectivity (87->99% ee) in very short reaction times (3-5 hours, Scheme 6).[14] The reactants together with ammonium acetate (NH_4OAc, **7**) and benzaldehyde derivatives **8** would react for instance through the route (f), as depicted in Scheme 2. The best enantioselectivities were reached using aromatic aldehydes, in contrast to the lack of enantioselectivity observed with aliphatic ones.

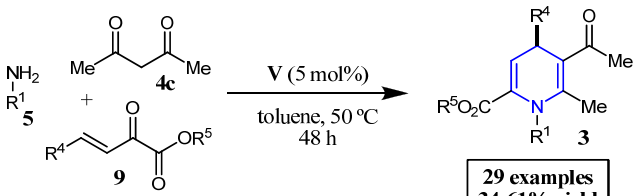


R = Me, Ph, 2,4-Cl_2-C_6H_3, 4-Br-C_6H_4, 3,5-$(MeO)_2$-C_6H_3, 3-F-C_6H_4, 4-$(Me)_2N$-C_6H_4, 2-CF_3-C_6H_4, 2,5-F_2-C_6H_3, 4-*t*Bu-C_6H_4, 2-naphthyl, 2-CN-C_6H_4, 3,4-$(OH)_2$-C_6H_3, Ph-CH_2CH_2-, 2-Cl-C_6H_4, 4-Ph-C_6H_4, $C_2H_5CH(CH_3)$-

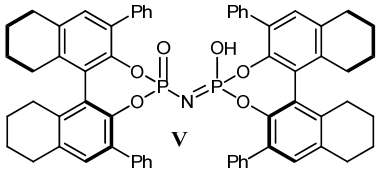
Scheme 6. Hantzsch synthesis of 1,4-DHPs **3** catalyzed by the chiral BINOL-phosphoric acid derivative **III**.[14]

Interestingly, the structural core of 4-aryl-functionalized products obtained in this approach could provide many synthetic and pharmaceutical applications. The most relevant aspect of this work lies in the fact that this procedure represents the first enantioselective catalytic four-component Hantzsch reaction to afford the non-symmetric chiral products.

In 2015, Zhang's group reported an enantioselective cyclization between β,γ-unsaturated α-ketoesters **9**, arylamines **5** and acetylacetone **4c**, giving rise to penta-substituted 1,4-DHPs **3** with moderate yields (34-61%) and good to excellent selectivity (75-97% ee, Scheme 7).[16] The reaction is catalyzed by the H_8-BINOL type chiral imidodiphosphoric acid **V** with better activity than a normal chiral phosphoric acid.[26]



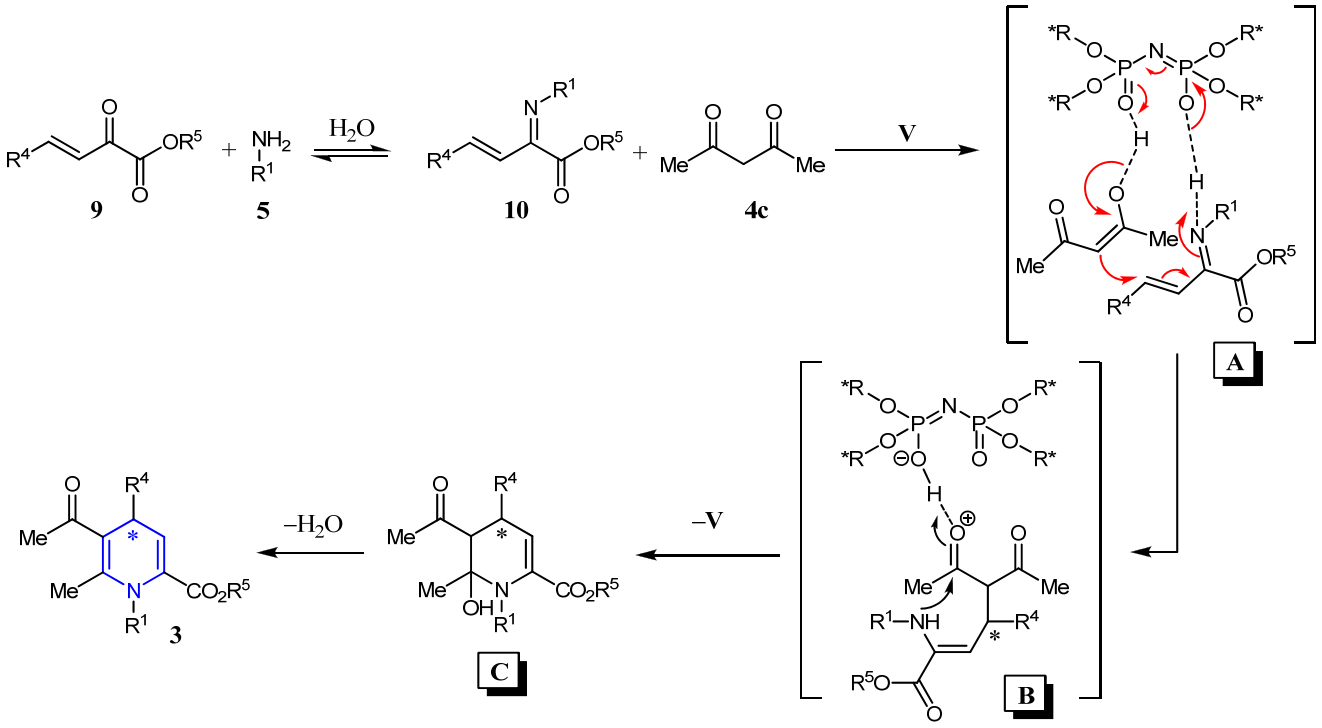
R^1 = 3-F-C_6H_4, 3-Cl-C_6H_4, 3-Br-C_6H_4
R^4 = 4-NO_2-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 3,4-Cl_2-C_6H_3, 4-Me-C_6H_4, 3-NO_2-C_6H_4
R^5 = Bn, *i*Pr, Me, Et



Scheme 7. 1,4-DHPs synthesis developed by Zhang's group.[16]

Better values of enantioselectivity were achieved when enones with electron-withdrawing groups on the aromatic ring were used in the process. Although the enantioselectivity could be further improved decreasing the reaction temperature to 40 ºC, the yield of the process was negatively affected.

The reaction pathway would be understood as depicted in the route (c) of Scheme 2, which is analogous to route (b) but with β,γ-unsaturated α-ketoesters **9** instead of α,β-unsaturated aldehydes **2**. The authors suggested a bifunctional activation of the imine β,γ-unsaturated α-iminoester intermediate **10** and the enol form of the acetylacetone **4c**, as shown in Scheme 8 (**A**). After the Michael addition between both reagents, the new generated intermediate **B** is activated through the carbonyl group of the acetylacetone **4c**. Subsequently, the amino group attacks the carbonyl group to produce the cyclic intermediate **C**. Finally, optically active 1,4-DHPs **3** are generated via dehydration of intermediate **C** (Scheme 8). Taking in mind the lack of procedures affording greater variety on the substitution patterns and the important role played by the C6 substituent on the conformation of 1,4-DHPs, the authors introduced this new imidophosphoric acid derivative **V** as a plausible solution to the limited enantioselectivities obtained with common chiral phosphoric acids.

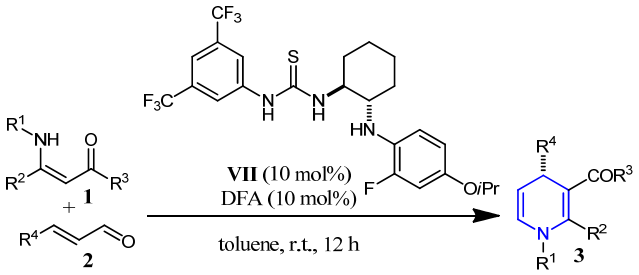


Scheme 8. Mechanism for the cyclization reaction in the presence of catalyst **V**.

3 (Thio)urea mediated organocatalysis

In 2010, Takemoto *et al.* published two key works introducing an organoammonium salt formed by a Brønsted acid (HX) and a thiourea catalyst, a new family of bifunctional catalysts.[27] This catalytic complex was used to afford the desired chiral 1,4-DHPs extending the procedures reported so far.[19,20] The authors described a Brønsted acid (difluoroacetic acid, DFA)-thiourea **VII** co-catalyzed asymmetric cycloaddition of β-enaminoesters **1** and α,β-unsaturated aldehydes **2** through the route (a) shown

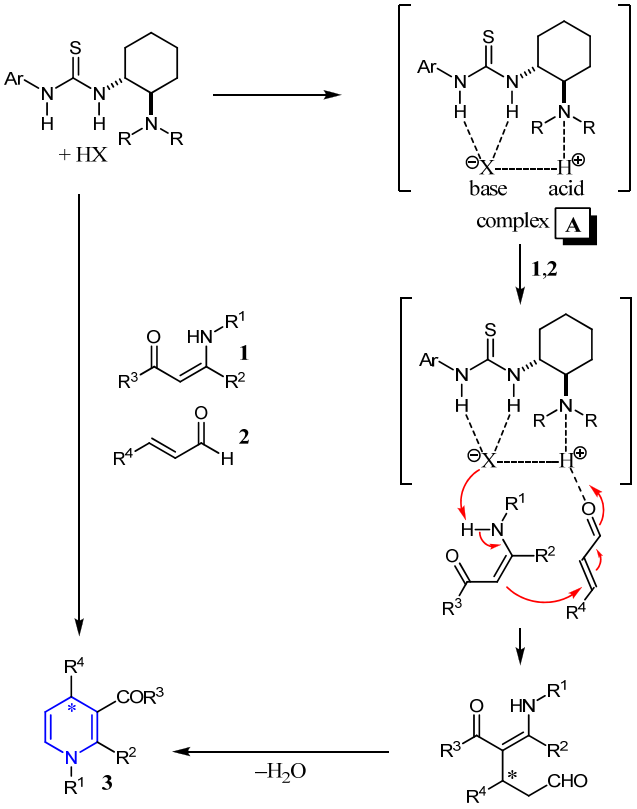
in Scheme 2. With the optimal conditions in hand, this strategy afforded functionalized 5,6-unsubstituted 1,4-DHPs **3** with good to excellent yields (55-96%) and good enantioselectivities (38-80% ee, Scheme 9).



R^1 = 4-MeO-C_6H_4, 3,4-$(MeO)_2$-C_6H_3, 4-Cl-C_6H_4, Bn, 4-MeO-C_6H_3-CH_2
R^2 = H, Me, Ph
R^3 = OEt, O*t*Bu, Ph
R^4 = Ph, 4-NO_2-C_6H_4, 4-MeO-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4

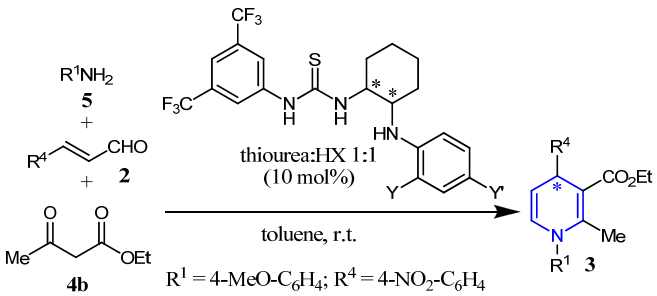
Scheme 9. Thiourea **VII** catalyzed 1,4-DHPs synthesis.[19]

The authors hypothesized that a mixture of thiourea **VII** and a Brønsted acid in a 1:1 ratio, could produce an ammonium salt complex **A** (Scheme 10). In this salt **A**, the conjugate base would be anchored to the thiourea moiety by hydrogen bonds,[28] and it could represent a new family of bifunctional catalysts. In the proposed mechanism the α,β-unsaturated aldehyde **2** and β-enaminoester **1** would be activated by both the ammonium proton and the conjugate base (X^-), respectively, promoting a 1,4-conjugated addition in a chiral environment. A further intramolecular cyclization and dehydration would furnish the desired optically active 1,4-DHP **3**. The interest of this strategy relies on the possibility of modulating the acidity-basicity of the catalytic species just changing the strength of the acid.



Scheme 10. Proposed reaction mechanism through the formation of an ammonium salt complex **A**.

Later, the same research group reported an expanded study of the effect of the catalytic complex (thiourea:Brønsted acid) in a *pseudo* three-component version of the previous cyclization reaction (Scheme 11).[20] In this case, the β-ketoester (ethyl acetoacetate, **4b**) reacts with the α,β-unsaturated imine, previously formed from the α,β-unsaturated aldehyde **2** and the amine **5**, following the route (b) depicted in Scheme 2. It is noteworthy to remark that both enantiomers of the final product can be obtained using the same thiourea catalyst and changing the Brønsted acid, as shown in Scheme 11.



R^1 = 4-MeO-C_6H_4; R^4 = 4-NO_2-C_6H_4

(*S*,*S*)-**VII**	[Y = F, Y' = O*i*Pr]	: DFA	48 h	**64% yield, 50% ee (*R*)**
(*S*,*S*)-**VII**	[Y = F, Y' = O*i*Pr]	: TfOH	60 h	**82% yield, 20% ee (*S*)**
(*S*,*S*)-**XII**	[Y = F, Y' = OMe]	: DFA	48 h	**53% yield, 43% ee (*R*)**
(*S*,*S*)-**XII**	[Y = F, Y' = OMe]	: TfOH	48 h	**82% yield, 50% ee (*S*)**
(*R*,*R*)-**XIII**	[Y = OMe, Y' = H]	: HBF_4	72 h	**52% yield, 69% ee (*R*)**

Scheme 11. Effect of the catalytic complex (thiourea:Brønsted acid) in a *pseudo* three-component version of the Takemoto's 1,4-DHPs synthesis.[20]

To shed light, the authors proposed different transition states (TS) involved in two plausible reaction pathways, routes (a) (**TS-A**, Figure 3) and (b) (**TS-B**, Figure 3), when a weaker Brønsted acid (DFA) is used as an additive, where the true catalytic species is an ammonium salt complex, formed with the thiourea and the acid. A new mechanism for the route (b) is also introduced when a stronger Brønsted acid is used (HBF_4, **TS-C**, Figure 3), taking place through the formation of an ion pair complex of the acid with the thiourea. Thus, in the case of **TS-A**, the starting aldehyde and the enamine are activated in a bifunctional way through the ammonium proton and the conjugate base of the additive (X^-), respectively. Then, the obtained Michael product would undergo an intramolecular cyclization and dehydration to give the final DHP. A similar bifunctional activation is described for **TS-B**, but in this case, coordinating the preformed α,β-unsaturated imine **6** and the β-ketoester **4**, respectively. In both cases, (*S*)-product is obtained. Regarding **TS-C**, the nucleophile is approached from the less-hindered upper side (*re*-face) to the (*Z*)-imine **6**, which is coordinated with the ammonium proton of the ion-pair complex as well as proposed for weaker Brønsted acids such as DFA in **TS-B**. This pathway would lead to the (*R*)-product.

Takemoto *et al.* have completed a very remarkable work in many aspects. They have envisioned a pioneering approach to the synthesis of unsymmetrical 1,4-DHPs using the novel thiourea catalysts as described above. Their co-catalyzed system has both complexity in its structure and simplicity on the subjacent idea, making it a nice methodology from our point of view. They have performed a very detailed work, with high versatility and effectiveness.

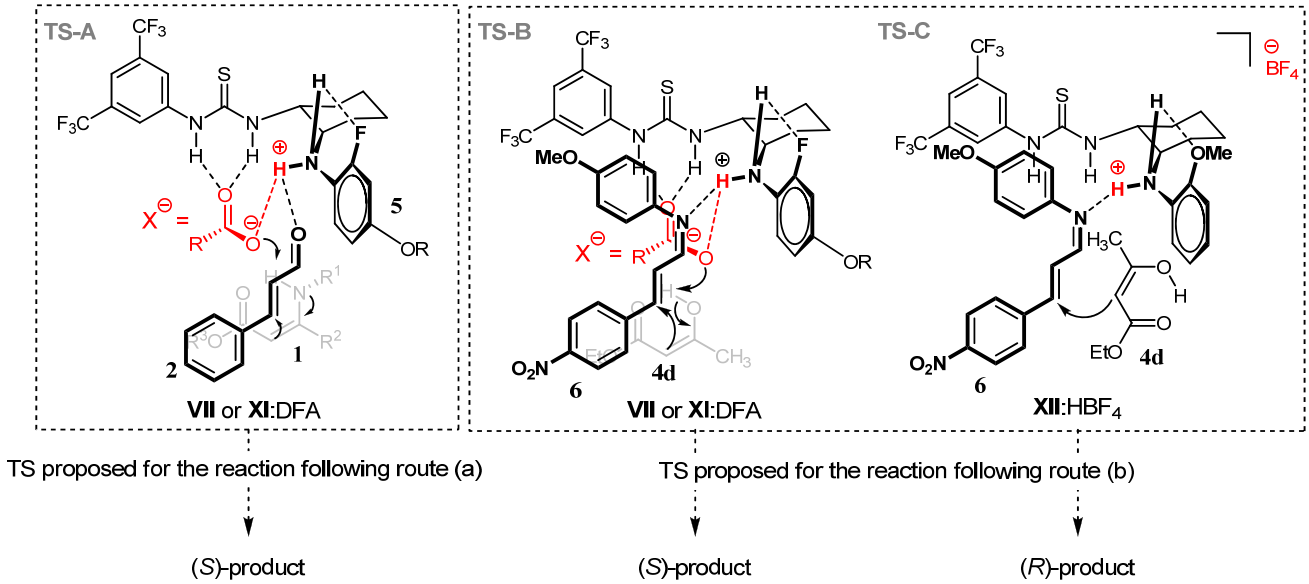
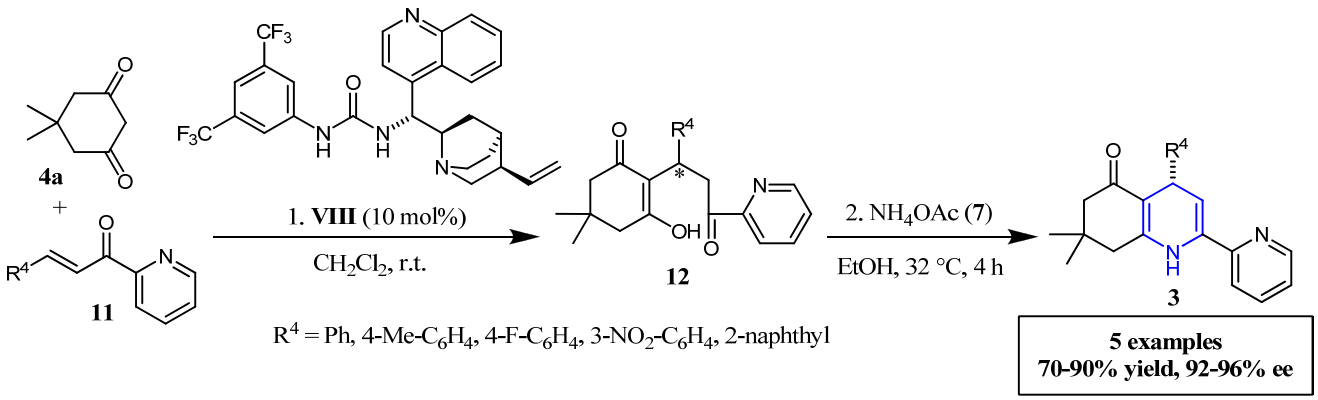


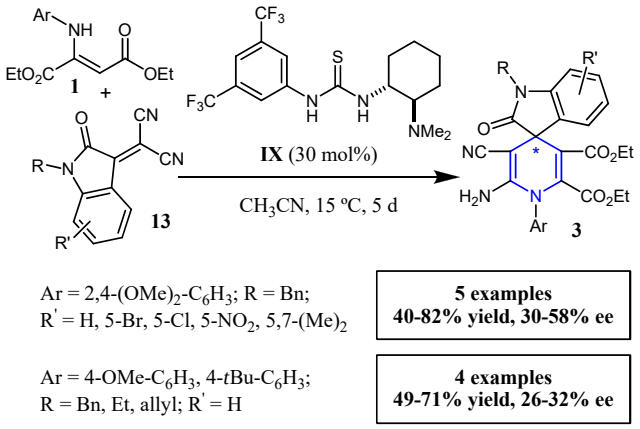
Figure 3. Activation of the substrates by the thiourea: Brønsted acid complex following both routes, (a) and (b).

Singh and coworkers reported an asymmetric synthesis of 1,4-DHPs using chiral urea **VIII** (Scheme 12),[21] following a 2-steps strategy (route (g), Scheme 2). The first step is the synthesis of the Michael adduct **12**, catalyzed by chiral urea **VIII**, and after purification and treatment with NH_4OAc (**7**) the DHP ring is formed to give the corresponding final products **3** with good yields (70-90%) and very good enantioselectivity (92-96% ee).



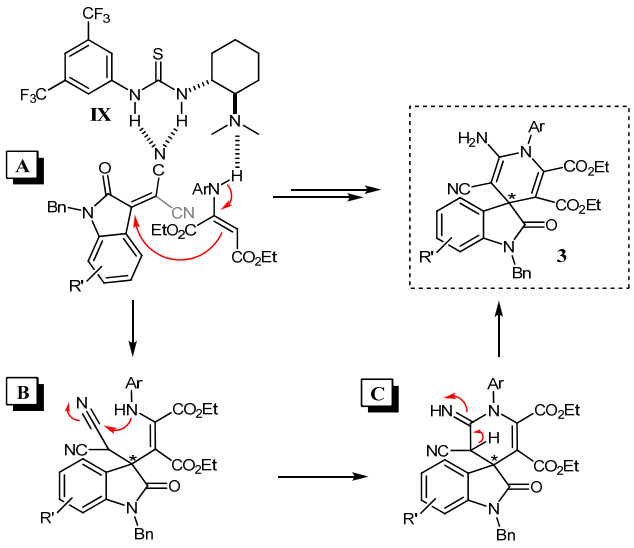
Scheme 12. Two steps synthesis of chiral 1,4-DHPs **3**, catalyzed by urea **VIII**.[21]

Herrera and coworkers reported in 2015 one of the most recent asymmetric organocatalytic example of 1,4-DHPs synthesis. They performed a strategy which is a variant of route (a) of Scheme 2, where an α,β-unsaturated malononitrile **13** is used as Michael acceptor instead of the commonly used α,β-unsaturated carbonyl compound (Scheme 13).[22]



Scheme 13. Synthesis of highly substituted chiral 2-oxospiro-1,4-DHPs **3**.[22]

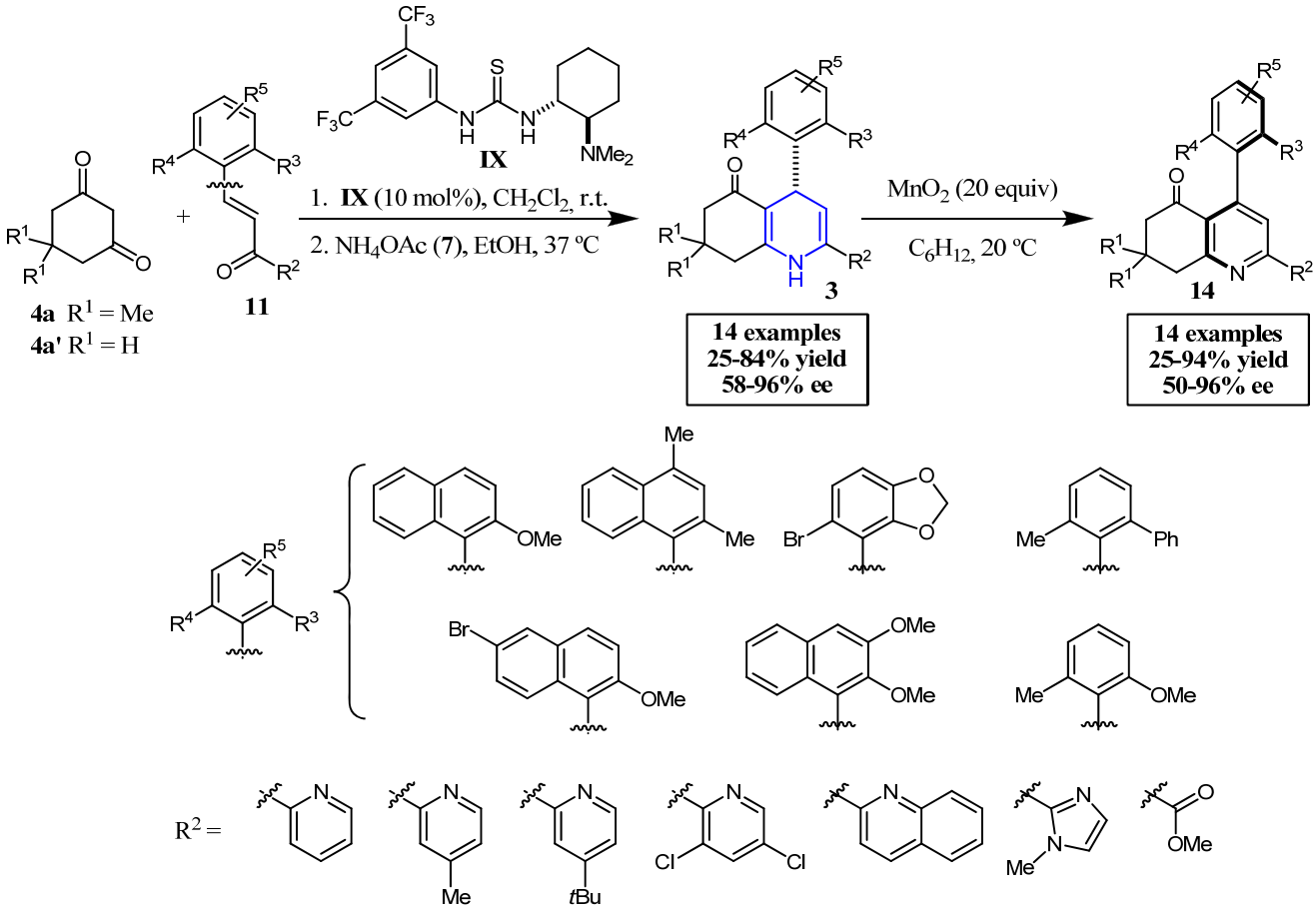
Specifically, the authors described the reaction of enamines **1** with isatin-derived methylenemalononitriles **13**, catalyzed by Takemoto's thiourea **IX**, which would activate the substrates in a bifunctional fashion as depicted in Scheme 14. The formation of hydrogen bonds between the thiourea moiety and the Michael acceptor is suggested, while the basic tertiary amine of the catalyst would interact with the acidic hydrogen of the enamine, enhancing its nucleophilicity (Scheme 14, A). Final products are obtained after cyclization (B) and tautomerization (C). This method allows the preparation of spirooxyndoles **3**, a structural motif present in numerous natural products with intriguing biological activity. The presence of both scaffolds confers a high complexity to the structure, creating a new spirocycle on the C4, a family of molecules which has attracted much attention in the last years.[29]



Scheme 14. Mechanistic hypothesis proposed by Herrera.[22]

In 2016, Bressy, Bugaut, Rodriguez *et al.* developed a two steps synthesis of DHPs, following route (g, Scheme 2),[23] analogous to that developed by Singh (Scheme 12).[21] The first step is an enantioselective Michael addition of dimedones **4** to β-aryl-2-enoylpyridines **11** catalyzed by means of hydrogen bonding with the same thiourea used before for Herrera's group (**IX**) (Scheme 15). The purified Michael adduct was then submitted to a second step, reacting with NH_4OAc (**7**) in ethanol at 37 ºC to give the corresponding chiral DHPs **3** with moderate to good yields (25-84%) and good to excellent ee (58-96% ee) (Scheme 15). However, the actual goal of their work was to try a chirality conversion towards axially chiral 4-arylpyridines **14**. This kind of processes was postulated long ago and nowadays is attracting further attention. The authors have taken advantage of the dihydropyridine-pyridine REDOX

reaction and, fortunately, they have developed an efficient synthetic route to axially chiral 4-arylpyridines **14**. Thus, the obtained DHPs **3** were later oxidized with manganese dioxide (MnO_2) to the corresponding axially chiral 4-arylpyridines **14** (Scheme 15).[30] Regarding this objective, the authors achieved total conversions in some cases and high enantioselectivities (50-96% ee). Moreover, variations on the substitution pattern of the 2-pyridyl group (R^2) with different electron-donating or electron-withdrawing groups were also possible.



Scheme 15. Synthesis of axially chiral 4-arylpyridines **14**.[23]

The working hypothesis was to carry out a conversion of the classic chirality from the 1,4-DHPs **3** to the axial chirality of the 4-aryl-pyridines **14**, by means of an oxidation (Figure 4). The authors envisioned that the chirality conversion depended on the ability of the oxidant to efficiently discriminate between the two conformers, which were in a fast equilibrium (Figure 4). The absolute configuration observed in the final chiral 4-aryl-pyridines **14** is in agreement with a preferred oxidation for the less stable conformer *ap*-(*S*)-**3**, presumably because of a greater accessibility to the hydride on position 4 of the 1,4-dihydropyridine.

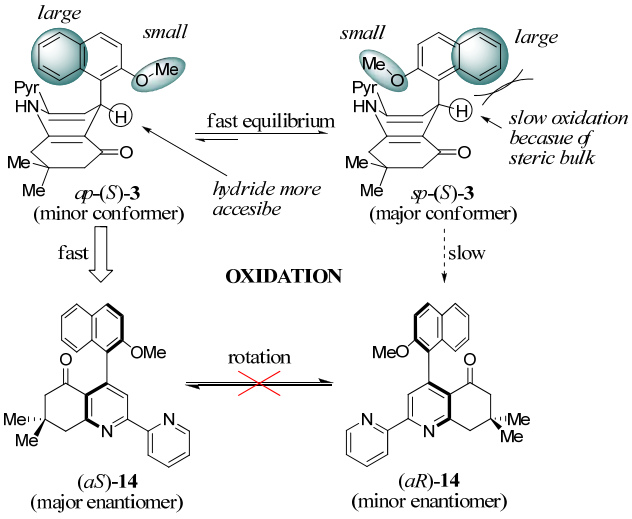
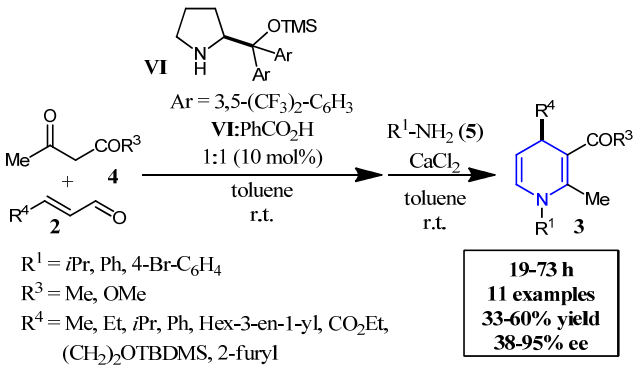


Figure 4. Chirality conversion explanation.[23]

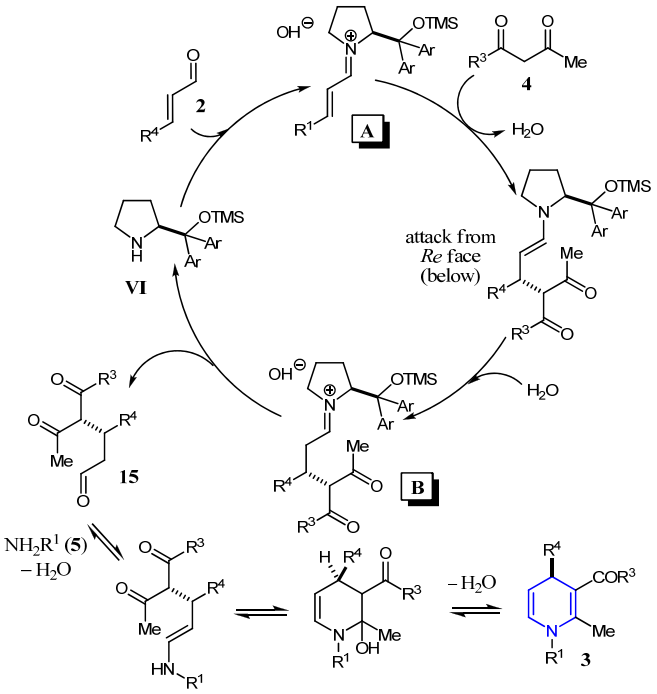
4 Aminocatalysis

In 2008, Jørgensen *et al.* investigated a different approach using aminocatalysis instead of hydrogen bonding catalysis to promote the synthesis of 1,4-DHPs (Scheme 16).[17] They developed a one-pot protocol using α,β-unsaturated aldehydes **2**, β-diketones or β-ketoesters **4** and primary amines **5**, catalyzed by diarylprolinol derivative **VI** and benzoic acid ($PhCO_2H$) as additive, that would proceed through route (e) of Scheme 2. A wide range of chiral DHPs **3** was synthesized and the properties as reducing agents were tested for some of them.



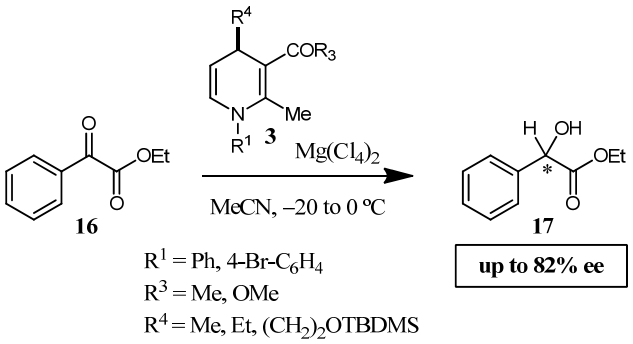
Scheme 16. Aminocatalytic 1,4-DHPs synthesis. TBDMS = *tert*-butyldimethylsilyl.[17]

This approach represents a different strategy, considering the type of catalyst used. This was the first method using this family of catalysis on the synthesis of chiral unsymmetrical 1,4-DHPs. First, the prolinol catalyst derivative **VI** would activate the aldehyde **2** and then, the dicarbonyl compound **4** would attack the β position of the iminium ion **A** in an enantioselective style (Scheme 17). The absolute stereochemistry in final products **3** is controlled by a *Re*-face attack of the nucleophile. Subsequently, the iminium ion **B** would be hydrolyzed and the catalyst released. The primary amine **5** would condensate on a second step with the intermediate **15**. Finally, a cyclization would close the DHP ring. This protocol produces chiral 1,4-DHPs **3** with moderated yields (33-60%) and moderate to excellent enantioselectivity (38-95% ee).



Scheme 17. Proposed reaction mechanism by Jørgensen.[17]

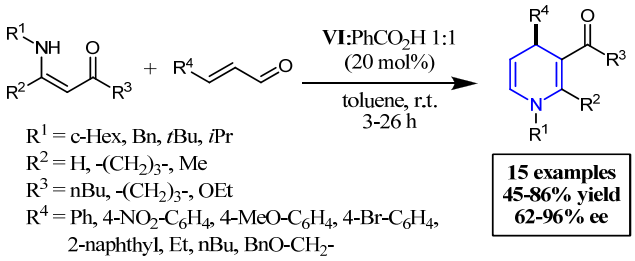
It is worth noting that the produced DHPs **3** were tested for their reductive abilities in asymmetric hydride-transfer reactions.[31] The authors tried to reduce ethyl benzoylformate (**16**) in the corresponding alcohol **17**, achieving full conversions and good enantioselectivity (up to 82% ee, Scheme 18).



Scheme 18. Reduction of ethyl benzoylformate (**16**) using DHPs.

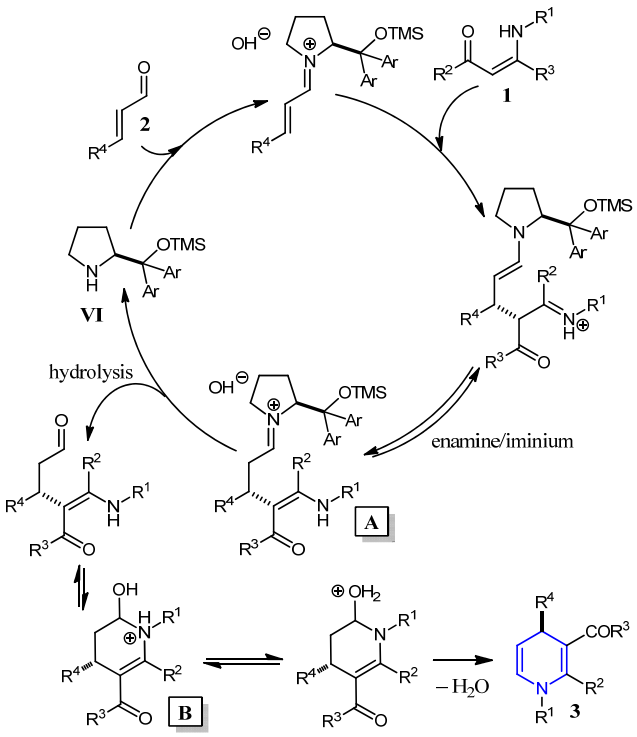
In 2011, Kanger and coworkers reported another approach by means of aminocatalysis, using the same catalytic system reported by Jørgensen's group,[17] *i.e.*, **VI**:$PhCO_2H$ (Scheme 19).[18] However, in this new example the β-enaminones and the β-enaminoesters **1** were preformed previously to the reaction with α,β-unsaturated aldehydes **2**. The authors developed a general procedure giving access to unsymmetrical

1,4-DHPs **3** with good yields (45-86%) and excellent enantioselectivities (62-96% ee).



Scheme 19. Aminocatalytic 1,4-DHPs synthesis developed by Kanger's group.[18]

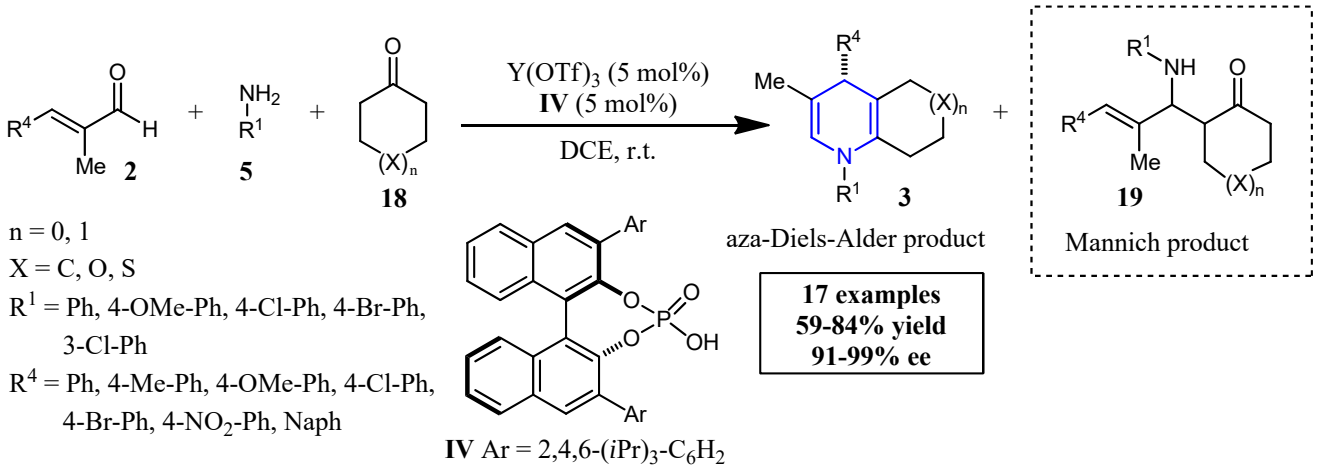
As previously proposed in Scheme 17, the stereoselectivity of the reaction would be determined in the first Michael addition reaction of enaminones **1** over the α,β-unsaturated aldehydes **2** (Scheme 20). The following hydrolysis of the iminium intermediate **A** leads to a further intramolecular cyclization, yielding a six-membered heterocycle **B**. After a proton transfer and a final dehydration, the most favored 1,4-DHPs **3** are obtained. Although this work is based on the previous one reported by Jørgensen's group,[17] this method differs in its approach. Herein, the reagents are preformed to have a better control over the enantioselective step of the process and for a better understanding of the system (route a, Scheme 2).



Scheme 20. Proposed cascade reaction by Kanger.[18]

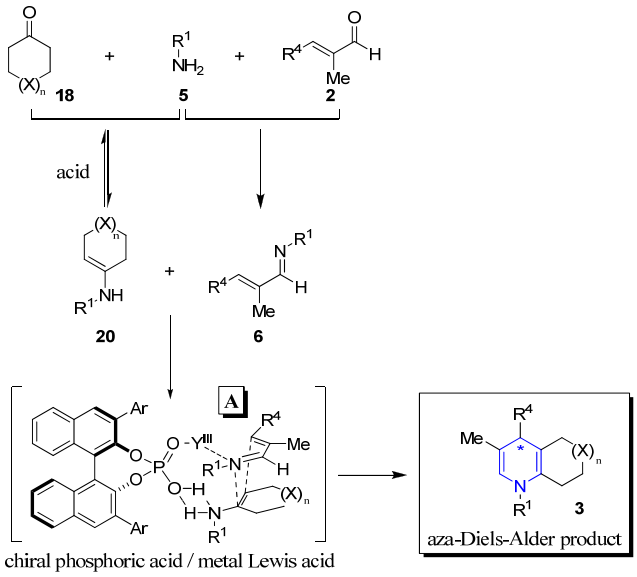
5 Dual catalysis

In 2015, Wang's group reported an interesting system with a high complexity to obtain 1,4-DHPs through route (d) of Scheme 2.[15] The goal was to combine three types of catalysis (enamine, Brønsted acid and Lewis acid catalysis) −named that as a "*trio* catalytic system"− on a cooperative manner to promote an aza-Diels-Alder (ADA) reaction. The desired DHPs **3** were obtained with good yields (59-84%) and excellent enantioselectivities (91-99% ee) as shown in Scheme 21.



Scheme 21. "*Trio* catalytic system" to promote DHPs **3**.

In the proposed mechanism, first, the aniline **5** would condensate with the aldehyde **2** and with the ketone **18** (Scheme 22). Thus, an activated enamine **20** (enamine catalysis) and a conjugated imine **6** would be formed in this initial step. Next, both species would be activated by a dual catalytic system **A**, composed of the BINOL derived phosphoric acid **IV** as a Brønsted acid, and $Y(OTf)_3$, as a Lewis acid (Scheme 22). Both acidic species would work in a synergic way as a sole catalyst, promoting the aza-Diels-Alder reaction.



Scheme 22. "*Trio* catalytic system" to promote the synthesis of DHPs **3**.

However, a Mannich reaction could take place on the same conditions as shown in Scheme 21, therefore, the authors tried to minimize the Mannich product **19** and, in the meantime, to maximize the yield and the ee of the ADA product **3**. This is the most complex system developed to date on the search of chiral unsymmetrical 1,4-DHPs.

The authors have confronted several challenges in addition to improving their results. Their system involves a delicate equilibrium between three types of catalysts working as a single and flawless machine. They have introduced a very challenging concept on this field and we believe that their hypothesis will be of great help in forthcoming asymmetric transformations.

6 Summary and outlook

We have described and discussed the existent reports involving asymmetric organocatalysis in the preparation of optically active 1,4-DHPs. We expect to have disclosed to the reader the wide variety of approaches and routes, which can lead to these important compounds and the stunning complexity of their structure.

Until now, there were only scarce methods exploiting asymmetric catalysis to produce chiral unsymmetrically substituted 1,4-DHPs. Thanks to the efforts done, not only by the researchers mentioned on this review, this scientific field has begun to boost interest and investigation. Nevertheless, with the recent advances over the potential properties of these molecules in medicinal chemistry and regarding the evident advantages of the catalytic methodologies over other approaches, there is a long road to go and a chief development of new catalytic asymmetric processes is needed. We expect a raise on the number of publications on this field in the near future and we would like that this review encourages other researchers to investigate and to contribute in this promising area.

Acknowledgements

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