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# Organocatalytic Enantioselective Synthesis of Tetrahydropyridines

Yohan Dudognon,<sup>[a]</sup> Jean Rodriguez,<sup>[a]</sup> Thierry Constantieux,<sup>[a]</sup> and Xavier Bugaut<sup>†[a]</sup>

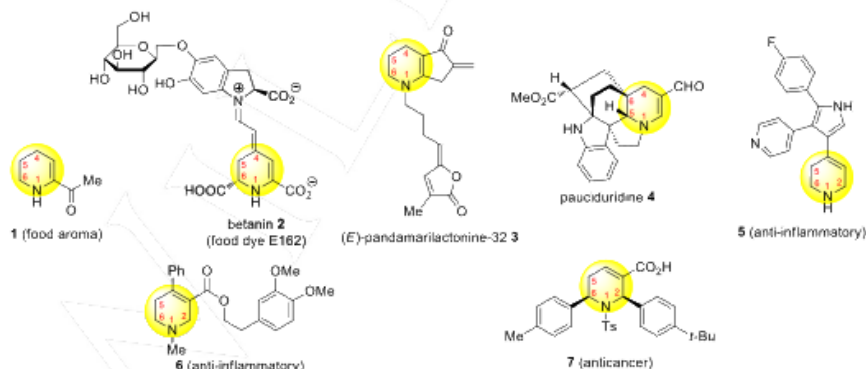
**Abstract:** Tetrahydropyridines are important heterocycles present in many molecules of natural and non-natural origins that exhibit a wide array of biological activities. With several  $sp^3$ -hybridized carbon atoms in their structure, they often include one or several stereogenic centers, whose control represents a great synthetic challenge. For the past two decades, enantioselective organocatalysis has developed as a very powerful strategy to perform the synthesis of enantioenriched compounds, including heterocycles. In this Microreview, we wish to provide the readers with a general overview about the organocatalytic strategies that have been used to achieve the preparation of diversified families of tetrahydropyridines, thereby providing elements of reflection for further developments.

## 1. Introduction

### 1.1. Significance of tetrahydropyridines

Nitrogen-containing heterocycles are among the most common structural motifs in bioactive compounds.<sup>[1]</sup> Among them, six-membered rings containing a nitrogen atom as the single heteroatom lead the dance, with piperidine and pyridine ranking at the first two positions for their frequency among U.S. FDA approved pharmaceuticals. Between these two extreme oxidation levels, partially saturated congeners, i.e. dihydro- and tetrahydropyridines (DHPs and THPs, respectively) and their

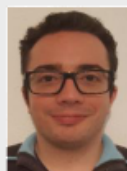
fused derivatives, also exhibit interesting bioactivities. The different regioisomers of the THP motif can be found in a large variety of natural and non-natural organic molecules of moderate to very high complexity, several of them being of industrial relevance.<sup>[2]</sup> A non-exhaustive list is presented below (Figure 1). Both 1-(1,4,5,6-tetrahydropyridin-2-yl)ethanone **1**<sup>[3]</sup> and betanin **2**<sup>[4]</sup> are used in food industry, as aroma and dye, respectively. (*E*)-Pandamarilactonine-32 **3** is an alkaloid obtained from *Pandanus amaryllifolius*, whose extracts have been used as flavors but also in traditional medicine in Southeast Asia, because of their antioxidant, antibiofilm, and anti-inflammatory activities.<sup>[5]</sup> Moreover, the THP ring can also be part of complex fused polycyclic architectures such as in pauciduridine **4**, extracted from *Kopsia pauciflora*, a tree found in Malaysian Borneo that produces a variety of indolic alkaloids with pluripotent inhibitory activities against human cancer cell lines.<sup>[6]</sup> Purely synthetic THPs are also of great interest. For example, compound **5** bearing a THP ring attached to a pyrrole nucleus can act as an anti-inflammatory agent with superior activities compared to the corresponding piperidine and pyridine analogues.<sup>[7]</sup> To finish with, ester **6** behaves as an antagonist for  $M_3$  muscarinic acetylcholine receptor, a potential target for the treatment of drug abuse,<sup>[8]</sup> whereas *N*-tosyl THP **7** is a reversible inhibitor of platelet-activating factor acetylhydrolases, thereby causing the death of cancer cells.<sup>[9]</sup>



**Figure 1.** Examples of natural and non-natural tetrahydropyridines of industrial significance and/or with bioactivities

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Yohan Dudognon was born in Bordeaux, France, in 1998. In 2013, he obtained his M. Sc. in molecular chemistry from Université Pierre et Marie Curie (Paris, France). He carried out his PhD in synthetic organic chemistry under the supervision of Dr. X. Bugaut, Prof. T. Constantieux and Prof. J. Rodriguez in the STeR&O group of Aix-Marseille Université (Marseille, France), working on the synthesis and use of original 1,3-dicarbonyls in enantioselective organocatalysis. After his defense in 2016, he joined the group of Prof. A. Fürstner at the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany).



Jean Rodriguez, after studying chemistry at the University of Aix-Marseille (France), completed his Ph.D. as a CNRS researcher with Prof. B. Waegell and Prof. P. Brun in 1987. After a postdoctoral position in Prof. Peter Vollhardt's group at the University of Berkeley with a NATO fellowship, he completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-7313-iSm2. In 1998 he was awarded the ACROS prize in Organic Chemistry, and in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society and was named Distinguished Senior Member (2013) of the French Chemical Society. His current research interests include the development of new multiple bond-forming transformations based on domino and multicomponent reactions, and their application in stereoselective synthesis with a recent focus on new enantioselective organocatalyzed transformations involving the reactivity of 1,2- and 1,3-dicarbonyl compounds.



Thierry Constantieux was born in Pau (France) in 1968. After studying chemistry at the University Bordeaux I, he completed his PhD under the supervision of Dr. J.-P. Picard and Dr. J. Duroguez in 1994. In 1995, he was appointed Assistant-Professor at University of Aix-Marseille III (France). He completed his Habilitation in 2004, at Aix-Marseille Université (France), where he is currently full professor of organic chemistry. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially enantioselective organocatalyzed cascades and domino multicomponent reactions from 1,3-dicarbonyl compounds, and their applications in heterocyclic chemistry. Since 2012, he is the scientific coordinator of one of the four research teams (STEREO team, 14 permanent people) of Institut des Sciences Moléculaires de Marseille (iSm2). In 2015, he has been

elected as Director of the Doctoral School of Chemical Sciences, at Aix-Marseille Université.



Xavier Bugaut studied chemistry the Ecole Nationale Supérieure de Chimie de Montpellier (France) and carried out his doctoral work on the synthesis of landomycinone under the supervision of Dr. Emmanuel Roulland, at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette (France). He then joined the group of Prof. Frank Glorius at the Westfälische-Wilhelms Universität Münster (Germany) as a postdoctoral fellow, focusing on the development of new NHC-catalyzed transformations. In October 2011, he was appointed Maître de Conférences (equivalent to assistant professor) at Aix-Marseille Université (France). His current research interests include enantioselective organocatalysis, with a focus on its application to multicomponent reactions and to the control of axial chirality.



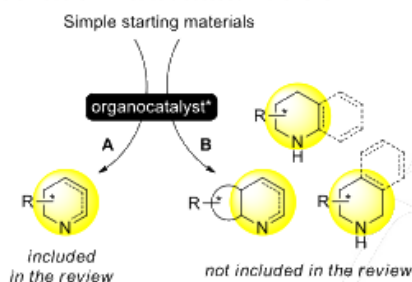
Since both DHPs and THPs non-planar rings comprise Csp<sup>3</sup> carbon atoms, many of them are chiral. Of course, their biological activities depend on the absolute and relative configurations of their stereogenic elements, rendering necessary the development of methods to control them. Over the past twenty years or so, organocatalysis, that is to say the use of small organic molecules able to catalyze transformations, has emerged as an extremely powerful strategy to achieve stereocontrol.<sup>[10]</sup> Through a variety of activation modes involving covalent and/or non-covalent interactions with their substrates, organocatalysts can decrease the activation barriers of transformations while tightly controlling the position of the reaction partners in the transition state of the enantiodiscriminating step.<sup>[11]</sup> Moreover, since they obviate the use of transition metals and are often tolerant towards water, oxygen and many functional groups, organocatalysts are easy to handle and interesting tools in the context of green chemistry. More specifically, organocatalysis is an especially efficient tool for the preparation of nitrogen-containing heterocycles.<sup>[12]</sup> If the application of enantioselective organocatalysis to the synthesis of 1,4-DHPs has been recently reviewed,<sup>[13]</sup> there is no comprehensive discussion on the preparation of the related enantioenriched THPs.<sup>[12]</sup>

## 1.2. Scope and organization of the review

In this review, we aim at providing the readers with an overview of the synthetic strategies that exist to prepare chiral enantioenriched THPs from simple starting materials in the

presence of a chiral organocatalyst. Numerous disconnections and activation strategies exist and they deliver different regioisomers depending on the position of the double bond. It appeared to us that the enantiodiscriminating step involved in the construction of the THP ring is the key event in the process and we selected this criterion to sort the transformations (Scheme 1A). We put 1,2-additions on the one hand and 1,4-additions on the other hand. In the former section, the reactions are sorted based on the nature of the nucleophile, whereas we found it clearer to organize the second section depending on the nature of the electrophile.

There exist also reactions where the organocatalyst controls stereogenic elements at the periphery of the THP rather than within the ring (Scheme 1B).<sup>[14]</sup> Moreover, numerous organocatalytic transformations allow the preparation of fused polycyclic systems, where the double bond of the six-membered nitrogen heterocycle is shared with a carbocyclic or heterocyclic aromatic ring (tetrahydroquinolines, tetrahydro- $\beta$ -carboline, etc.).<sup>[15]</sup> For the sake of clarity and conciseness, those transformations will not be discussed in this review



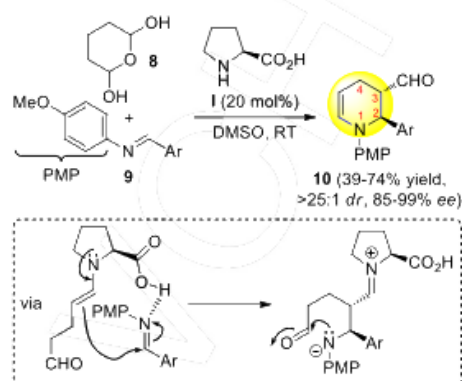
Scheme 1. Scope of the review.

## 2. 1,2-Additions

### 2.1. Additions of enolates and related species

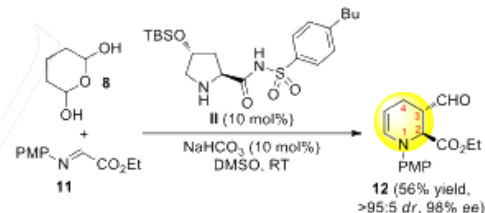
The Mannich reaction that consists in the addition of an enol or enolate to an imine is one of the most useful transformations, not only in organic synthesis in general, but also more specifically in organocatalysis.<sup>[16]</sup> The first strategy to attain THPs via a Mannich reaction was to use 1,5-dialdehydes synthetic equivalents in the presence of proline derivatives. In 2008, Xu and co-workers showed that inexpensive aqueous tetrahydro-2H-pyran-2,6-diol (**8**) could interact with (S)-proline (**1**) to afford an intermediate enamine able to trap diversely substituted *N*-(*p*-methoxyphenyl)aldimines **9** (Scheme 2).<sup>[17]</sup> The initial Mannich reaction is followed by hemiaminal formation and dehydration to afford 1,2,3,4-THPs **10** in moderate yields but with complete diastereoselectivities and very high enantiomeric excesses. Notably, catalysts that do not bear an acidic proton failed to provide the product, pointing towards a bifunctional activation mode where the carboxylic acid function interacts with the

nitrogen atom of the imine. The aldimines obtained from enals or aliphatic aldehydes performed very poorly compared to their aromatic congeners.



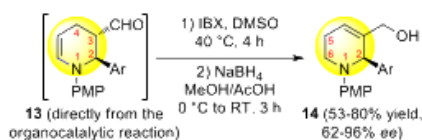
Scheme 2. Synthesis of THPs by (S)-proline-catalyzed Mannich reaction of tetrahydro-2H-pyran-2,6-diol (**8**).<sup>[17]</sup>

Further studies showed that silylated *N*-sulfonyl-4-hydroxyprolinamide **II** was also a potent catalyst to achieve the same transformation starting from ethyl glyoxylate-derived imine **11** to afford 1,2,3,4-THP **12** with similar results (Scheme 3).<sup>[18]</sup> It should be noted that  $\text{NaHCO}_3$  as an additive led to a dramatic increase of the enantioselectivity.



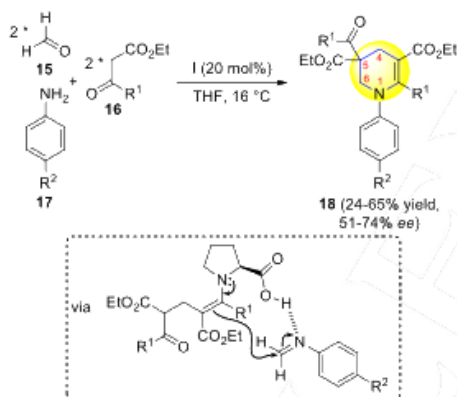
Scheme 3. Synthesis of THPs from tetrahydro-2H-pyran-2,6-diol (**8**) with silylated *N*-sulfonyl-4-hydroxyprolinamide **II** as catalyst.<sup>[18]</sup>

A third study using this strategy showed that the reaction could be conveniently carried out with *in situ* formation of the imine from the aldehyde and the amine.<sup>[19]</sup> Interestingly the 1,2,3,4-THP **13** obtained initially could be converted into the corresponding 1,2,5,6-THP **14** via a one-pot oxidation-reduction sequence (Scheme 4). These compounds could then serve as intermediates for the synthesis of several biologically active nitrogen-containing heterocycles.



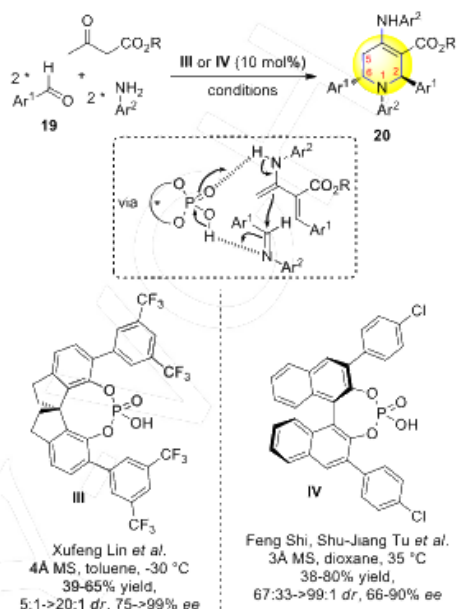
**Scheme 4.** One-pot conversion of the 1,2,3,4-THPs **13** into 1,2,5,6-THPs **14**.<sup>[19]</sup>

There exists also other possibilities of combination of an aldehyde, an amine and a third partner in the presence of an organocatalyst to prepare chiral enantioenriched THPs.<sup>[20]</sup> Two molecules of linear  $\beta$ -ketoesters **16**, two molecules of formaldehyde (**15**) and substituted anilines **17** could assemble in a *pseudo*-five-component reaction, in the presence of proline **I** to deliver 1,4,5,6-THPs **18** in moderate yields and enantiomeric excesses, the absolute configuration of which has not been determined (Scheme 5).<sup>[21]</sup> The authors claim that the enantioselective step consists in the addition of a chiral but not configurationally stable proline-derived enamine to the imine.



**Scheme 5.** Proline-catalyzed pseudo-five-component synthesis of 1,4,5,6-THPs **18**.<sup>[21]</sup>

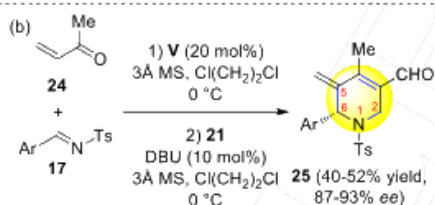
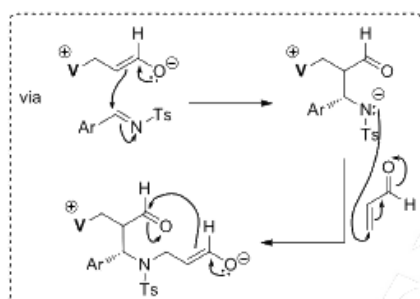
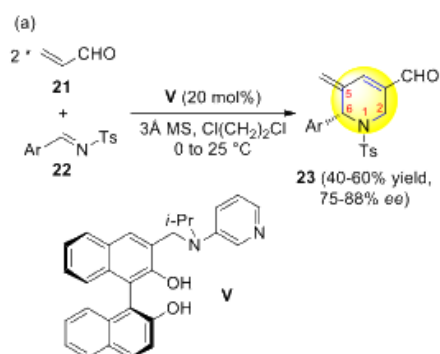
A similar combination of starting materials, with aromatic aldehydes **19** replacing formaldehyde, in the presence of phosphoric acids **III** or **IV** could deliver highly substituted 1,2,5,6-THPs **20** with very good enantiomeric excesses (Scheme 6).<sup>[22]</sup> Both reaction intermediates involved in the stereodetermining step could be isolated from reactions that did not reach full conversion and allowed to propose a detailed mechanism, where the catalyst acts in a bifunctional fashion by protonating the imine and interacting with the enamine hydrogen atom, thereby increasing its nucleophilicity.<sup>[21b]</sup> The authors of this study could also show that lower enantioselectivity was observed when the reaction was carried out in a stepwise fashion instead of the multicomponent protocol, a rather common observation in such transformations.<sup>[23]</sup>



**Scheme 6.** Phosphoric acid-catalyzed pseudo-five-component synthesis of 1,2,5,6-THPs **20**.<sup>[22]</sup>

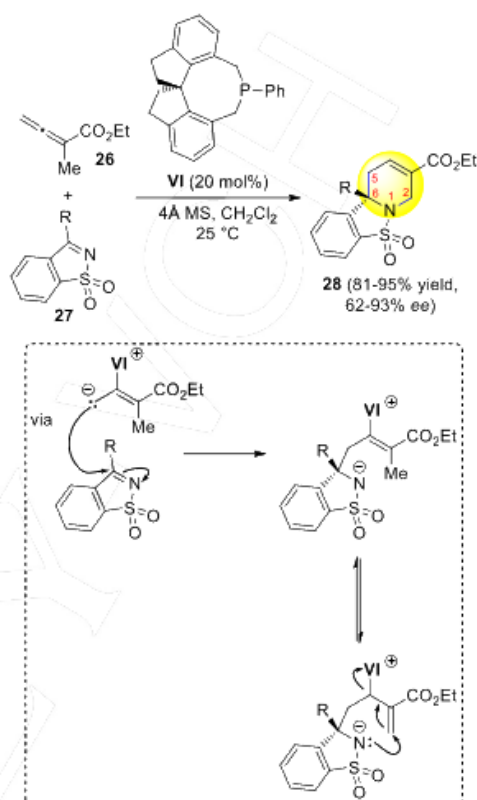
Enolates can also be generated indirectly in the presence of an organocatalyst and then trap enantioselectively an imine to initiate a cascade towards enantioenriched THPs. The *aza*-Baylis-Hillman reaction consists in the combination of a Michael acceptor and an imine in the presence of a Lewis basic catalyst.<sup>[24]</sup> The polyfunctional pyridine **V** that is flanked with a BINOL unit could control the enantioselectivity in the *aza*-Baylis-Hillman reaction of acrolein (**21**) with *N*-tosylaldimines **22** through conjugate addition of the nucleophilic catalyst and creation of a hydrogen-bonding network between the BINOL moiety and the Lewis-basic atoms of the substrates (Scheme 7a).<sup>[25]</sup> The resulting intermediates could trap a second molecule of acrolein through an *aza*-Michael addition, and cyclization followed by dehydration afforded 1,2,5,6-THPs **23**. Products were isolated in moderate yields and enantiomeric excesses. The reaction could also be performed in a sequential fashion with the replacement of acrolein by methyl vinyl ketone (**24**) in the *aza*-Baylis-Hillman reaction. Acrolein (**21**) was added in a second step in the presence of a sub-stoichiometric amount to DBU to deliver THP products **25** with an additional methyl substituent at position 4 (Scheme 7b). Notably, this modification was also accompanied by a significant improvement of enantiocontrol.





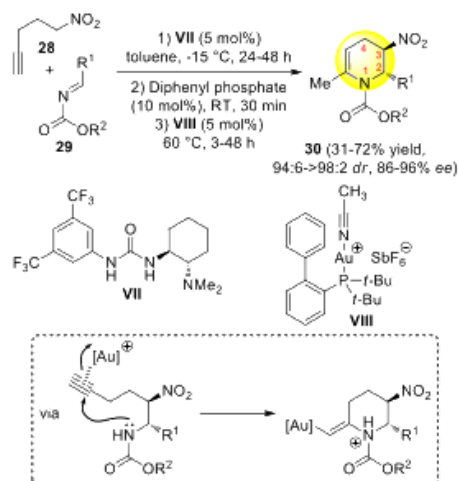
**Scheme 7.** Synthesis of 1,2,5,6-THPs **23** and **25** via an enantioselective aza-Baylis-Hillman reaction.<sup>[25]</sup>

In a similar fashion, allenates could give rise to vinylogous enolates when they are treated with nucleophilic catalysts. In this way, allenate **26** could be combined with chiral phosphine **VI** and the resulting vinylogous enolate could add to saccharin-derived ketimines **27** (Scheme 8).<sup>[26]</sup> Tautomerism and allylic substitution with expulsion of the catalyst delivered 1,2,5,6-THPs **28** in good yields and moderate to high enantioselectivities.



**Scheme 8.** Synthesis of 1,2,5,6-THPs **28** from allenate **26** and ketimine **27** in the presence of nucleophilic catalyst **VI**.<sup>[26]</sup>

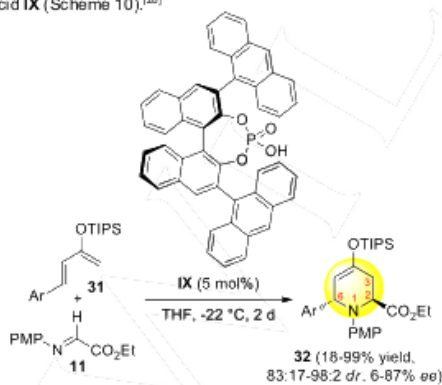
In a similar fashion to enolizable carbonyl compounds, nitroalkanes can also be deprotonated in a position to afford nucleophilic nitronates. This reactivity was exploited by the group of Dixon in a one-pot synthesis of 1,2,3,4-THPs **30** from  $\omega$ -nitroalkyne **28** and *N*-Boc or *N*-Cbz aldimines **29** (Scheme 9).<sup>[27]</sup> At first, bifunctional urea catalyst **VII** could promote an enantio- and diastereoselective nitro-Mannich reaction. After the addition of diphenyl phosphate as a quenching additive to neutralize the basic organocatalyst, Echavarren's gold catalyst enabled an intramolecular hydroamination reaction with 6-exo-dig cyclization followed by protodemetalation. The final products were obtained with very high stereoselectivities after migration of the olefin inside the six-membered ring. It should be noted that non-terminal alkynes were compatible with the first step but failed in the cyclization step.



**Scheme 9.** Synthesis of 1,2,3,4-THPs **30** by a combination of organocatalysis and gold catalysis.<sup>[27]</sup>

## 2.2. Additions of electron-rich olefins

Electron-rich olefinic systems are nucleophilic enough to add to imines activated by chiral Brønsted acids. If one of these two functionalities is conjugated with an additional alkene that can also participate in the reaction, then it becomes possible to achieve formal (4+2) cycloadditions to obtain enantioenriched THPs. In 2015, Enders and co-workers engaged ethyl glyoxylate imine **11** with different electron-rich dienes **31** in a normal demand Diels-Alder reaction in the presence of BINOL-derived phosphoric acid **IX** (Scheme 10).<sup>[28]</sup>

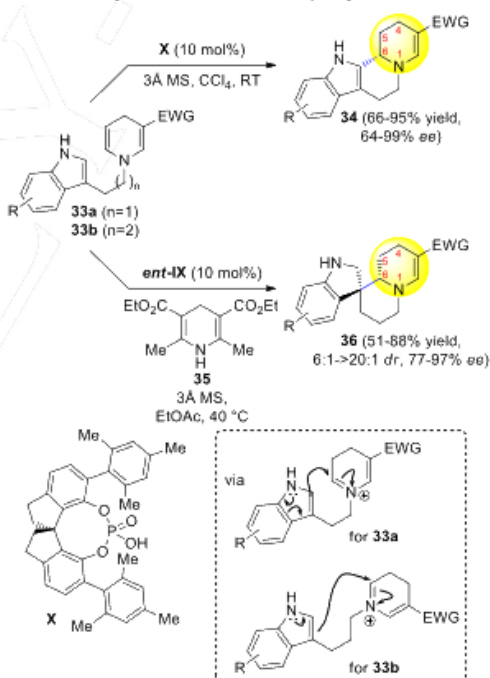


**Scheme 10.** Synthesis of 1,2,3,6-THPs **32** by a phosphoric acid-catalyzed Diels-Alder reaction.<sup>[28]</sup>

Original 1,2,3,6-THPs **32** were isolated in rather good yields and stereoselectivities except when the aromatic ring on the diene bore an *ortho* substituent or was replaced by a furan ring.

## 2.3. Additions of electron-rich aromatic compounds

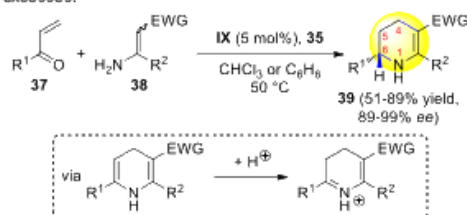
The organocatalytic addition of electron-rich aromatic compounds to iminium ions, known as the Pictet-Spengler reaction, is also a possible alternative to prepare enantioenriched THPs, as illustrated by the recent work from the group of You (Scheme 11).<sup>[29]</sup> Starting from substrate **33a** or its homologue **33b** in the presence of catalyst **X** or *ent*-**IX**, respectively, cyclization at the position 2 or 3 of the indole could be observed. By this way, both fused 1,4,5,6-THPs **34** and spiro 1,4,5,6-THPs **36** were prepared in high yields and enantiomeric excesses. The electron-withdrawing group on the DHP ring was essential for the reaction sequence and dictated the regioselectivity of the isomerization that occurred at the most electron-rich enamine. Moreover, in the second reaction, Hantzsch ester **35** was added to reduce the intermediate cyclic imine obtained after spirocyclization.



**Scheme 11.** Synthesis of fused or spiro 1,4,5,6-THPs by cyclization of indoles to 1,4-dihydropyridine-derived iminium ions.<sup>[29]</sup>

## 2.4. Additions of hydrides

An intuitive synthetic pathway towards enantioenriched THPs is to achieve an enantioselective reduction of DHPs. In 2008, Rueping and Antonchick combined enamines **38** flanked with an electron-withdrawing group at the  $\beta$  position with enones **37** in the presence of Brønsted acid **IX** (Scheme 12).<sup>[30]</sup> The intermediate DHPs then underwent protonation from the catalyst to deliver the intermediate iminium ion associated with the chiral conjugated base. Reduction by hydride transfer from Hantzsch ester **35** afforded the 1,4,5,6-THPs **39** with excellent enantiomeric excesses.



**Scheme 12.** Synthesis of 1,4,5,6-THPs **39** by formation of DHPs and enantioselective reduction by hydride transfer.<sup>[30]</sup>

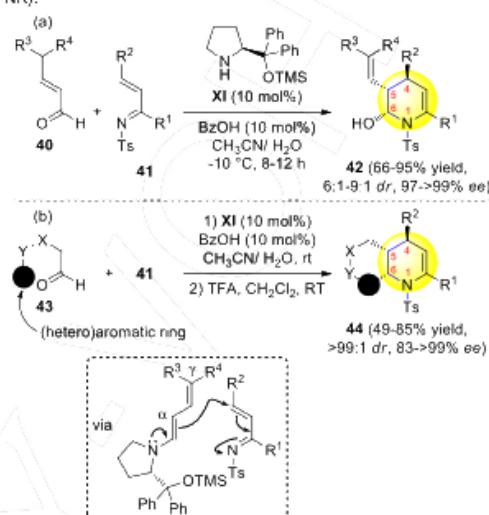
## 3. 1,4-Additions

Conjugate additions are ubiquitous in the literature concerning enantioselective organocatalysis and they can accommodate a very broad variety of substrates and activation modes. For this reason, it is not surprising that conjugate additions to imines, carbonyl compounds and nitroolefins have developed as one of the most popular strategies to prepare enantioenriched THPs.

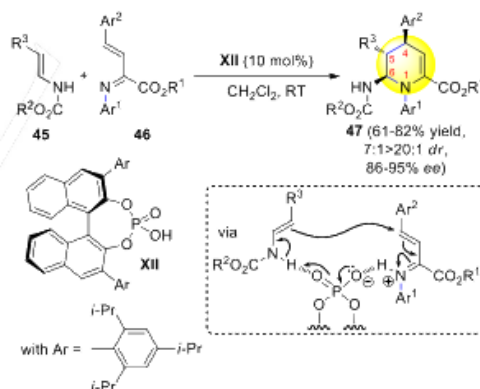
### 3.1. Additions to imines

$\alpha,\beta$ -Unsaturated imines can furnish four atoms to be integrated within the THP structure. In 2009, the group of Chen showed that they could be intercepted in a domino sequence by aldehydes under secondary amine catalysis. Dienamine formation from enals **40** combined with Hayashi-Jørgensen catalyst **XI** and conjugate addition to  $\alpha,\beta$ -unsaturated *N*-tosylimine **41** was followed by trapping of the aldehyde function by the nucleophilic nitrogen atom to afford 5-alkenyl-6-hydroxy-1,4,5,6-THP **42** (Scheme 13a).<sup>[31]</sup> Almost complete  $\alpha/\gamma$  regioselectivity was obtained during the dienamine addition and extremely high enantioselectivities (>97% ee) were observed throughout the whole substrate scope. On the contrary, MacMillan-type catalyst oriented the reactivity towards the  $\gamma$  position but with moderate stereoselectivities. For some examples, PCC oxidation of **42** into the corresponding lactam was necessary to allow complete characterization of the products. Two years later, the same group showed that aldehydes **43** bearing a suitably positioned electron-rich (hetero)aromatic ring could participate in the reaction (Scheme 13b).<sup>[32]</sup> Dehydration followed by Friedel-Crafts-type trapping of the iminium ion delivered bicyclic 1,4,5,6-THPs **44** with

excellent yields and stereoselectivities. The linker X-Y could be composed only of carbon atoms or different heteroatoms (O, S, NR).



**Scheme 13.** Synthesis of functionalized 1,4,5,6-THPs **42** and **44** through enamine activation of aldehydes.<sup>[31,32]</sup>



**Scheme 14.** Synthesis of 6-amino-1,4,5,6-THPs **47** through inverse-electron-demand Diels-Alder reaction of *N*-alkenylcarbamates **45**.<sup>[33]</sup>

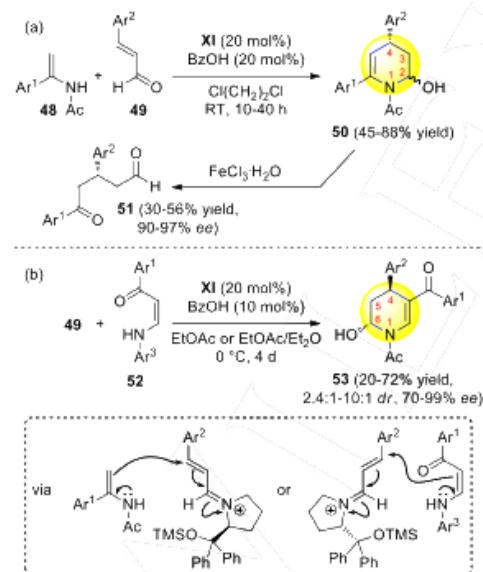
Following their initial work on inverse-electron-demand Diels-Alder reaction that afforded tetrahydroquinolines,<sup>[15d,e]</sup> the group of Masson proposed another retrosynthesis that opened a synthetic route towards 6-amino-1,4,5,6-THPs **47** from *N*-alkenylcarbamates **45** and  $\alpha,\beta$ -unsaturated *N*-arylimine **46** in the presence of TRIP catalyst **XII** (Scheme 14).<sup>[33]</sup> Products were



obtained with very good diastereo- and enantioselectivities and the mechanism is likely to proceed in a concerted fashion, with the catalyst acting in a bifunctional manner: protonation of the imine to increase its electrophilicity and deprotonation of the enamine to make it more nucleophilic.

### 3.2. Additions to carbonyl compounds

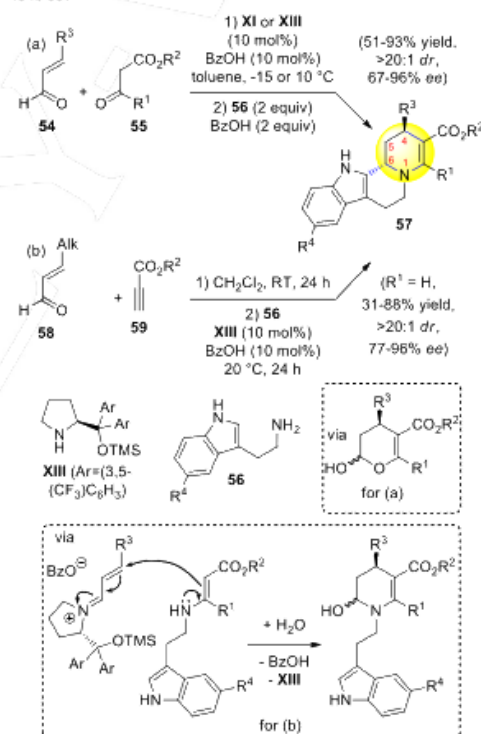
In addition to  $\alpha,\beta$ -unsaturated imines,  $\alpha,\beta$ -unsaturated carbonyl compounds can also participate in organocatalytic enantioselective 1,4-additions. Interestingly, they can combine with aminocatalysts to furnish intermediate  $\alpha,\beta$ -unsaturated iminium ions that can be trapped by nucleophiles such as enamines. In 2008, Yu, Wang and co-workers developed a formal (4+2) cycloaddition between *N*-alkenyl acetamides **48** and cinnamaldehydes **49** in the presence of proline-derived catalyst **XI** and benzoic acid as co-catalyst (Scheme 15a).<sup>[34]</sup> 2-Hydroxy-1,2,3,4-THPs **50** were formed in moderate to good yields and hydrolyzed by treatment with iron(III) chloride hydrate to allow determination of the enantiomeric excess (90–97% ee) on  $\delta$ -oxoaldehydes **51**. A few years later, the group of Enders extended this reactivity pattern to enaminketones **52** to prepare 6-hydroxy-1,4,5,6-THPs **53** in moderate yields and diastereoselectivities, but with enantiomeric excesses that could be very high for some examples (Scheme 15b).<sup>[35]</sup>



**Scheme 15.** Synthesis of hydroxyTHPs through secondary-amine catalyzed addition of enamines to enals.<sup>[34,35]</sup>

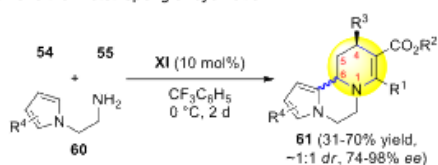
HydroxyTHPs can dehydrate to furnish the corresponding iminium ions, whose interception by nucleophiles has been well

documented. In 2010, Wu, Cao, Zhao and co-workers illustrated this strategy by mixing acetoacetates **55** with diversely substituted enals **54** ( $\text{R}^3$  being a alkyl chain, an aromatic ring or an ester) in the presence of proline-derived catalysts **XI** or **XIII**, followed by the addition of tryptamine derivatives **56** (Scheme 16a).<sup>[36]</sup> the overall Michael addition-iminium ion formation-Pictet-Spengler cyclization sequence delivered the 1,4,5,6-THPs **57** as single diastereomers in good yields and moderate to high enantioselectivities. Shortly after, the same authors prepared similar products **57** lacking the substituent  $\text{R}^1$  via a two-step sequence involving an aza-Michael addition of **56** to propionate **59** followed by the organocatalyzed sequence with the resulting enaminoester and  $\beta$ -alkylenals **58** (Scheme 16b).<sup>[37]</sup> The former reactivity pattern could also then be extended to cyclic  $\beta$ -diketones as illustrated by the same group and Rueping and co-workers.<sup>[38]</sup> To finish with, attempts to introduce a chiral phosphoric acid as the catalyst in the Michael addition-Pictet-Spengler sequence with tryptamine was less successful, with only 49% ee.<sup>[39]</sup>



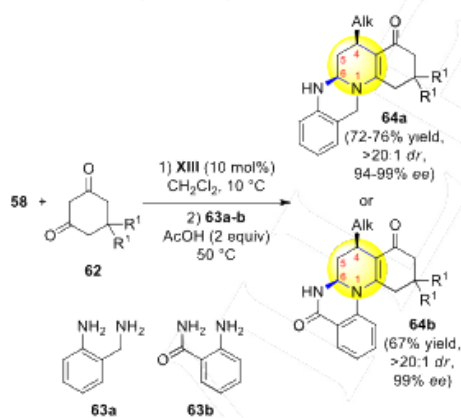
**Scheme 16.** Synthesis of functionalized 1,4,5,6-THPs **57** through secondary-amine catalyzed Michael addition and Pictet-Spengler cyclization.<sup>[36,37]</sup>

In 2014, our group showed that it is possible to replace the indole moiety by a pyrrole ring as the nucleophile in the Pictet-Spengler cyclization (Scheme 17).<sup>[40]</sup> *N*-(2-aminoethyl)pyrroles **60** delivered the expected 1,4,5,6-THPs **61** in moderate yields without diastereocontrol. However, the two diastereomers could generally be separated and were formed with high enantiomeric excesses. It is worth noting that the reaction could be carried out in a multicomponent fashion and that the higher nucleophilicity of the pyrrole ring compared to the indole obviated the use of an acid to achieve the Pictet-Spengler cyclization.



**Scheme 17.** Synthesis of functionalized 1,4,5,6-THPs **61** through secondary-amine catalyzed Michael addition and Pictet-Spengler cyclization with a pyrrole ring as the nucleophile.<sup>[40]</sup>

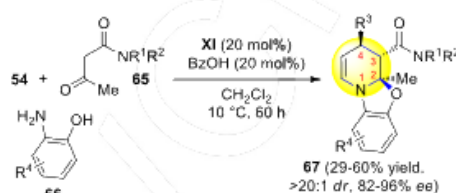
In addition to electron-rich aromatic rings, the iminium ion formed after the initial Michael addition of pronucleophiles such as  $\beta$ -cyclohexadiones **62** could also be trapped by heteroatoms. A few examples were reported by Rueping and co-workers using 2-aminomethylaniline **63a** and anthranilic acid **63b** to deliver the tetracyclic 1,4,5,6-THPs **64a-b** with good yields and nearly perfect stereoselectivities (Scheme 18).<sup>[33c]</sup>



**Scheme 18.** Synthesis of **64a-b** through secondary-amine catalyzed Michael addition and followed by iminium ion trapping with a heteroatomic nucleophile.<sup>[33c]</sup>

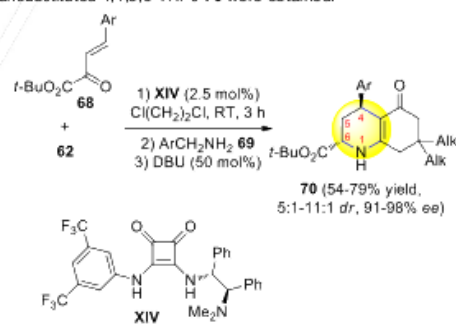
All the reactions discussed in this sub-section afforded the same regioisomer with the intracyclic enamine being conjugated with a carbonyl function. In 2015, our group tried to reverse the

regioselectivity by using tertiary  $\beta$ -ketoamides **65** as pronucleophiles in the Michael addition to destabilize the conjugated enamine because of the added steric interaction brought about by the amide function (Scheme 19).<sup>[41]</sup> With aromatic enals **54** as electrophiles and 2-aminophenols **66** as the third reaction partner, 1,2,3,4-THPs **67** were formed in moderate yields, notably better with more activated Weinreb  $\beta$ -ketoamides,<sup>[42]</sup> but with very high stereoselectivities.



**Scheme 19.** Use of tertiary  $\beta$ -ketoamides **65** as pronucleophiles to reverse the regioselectivity in the synthesis of THPs.<sup>[38b, 41]</sup>

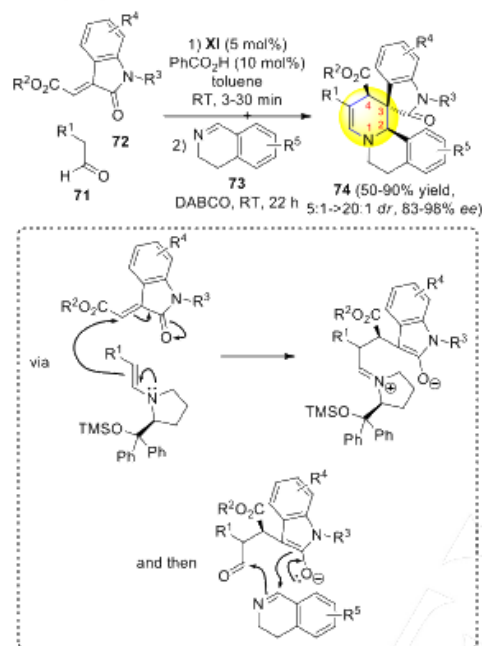
Other modes of activation have been more sporadically used for the preparation of enantioenriched THPs from  $\alpha,\beta$ -unsaturated compounds. When enals are replaced by activated enones, iminium ion activation is outcompeted by hydrogen-bonding activation. The group of Shi could combine cyclic diketones **62**,  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **68** and substituted benzylamines **69** in the presence of bifunctional squaramide catalyst **XIV** (Scheme 20).<sup>[43]</sup> This species can activate at the same time the diketone by deprotonation and the Michael acceptor by hydrogen-bonding. The addition of DBU was able to promote a transamination-hydrolysis sequence, explaining why the *N*-unsubstituted 1,4,5,6-THPs **70** were obtained.



**Scheme 20.** Synthesis of 1,4,5,6-THPs **70** under bifunctional squaramide catalysis.<sup>[43]</sup>

The last reaction that can be placed in this sub-section consists in the addition of enolizable aldehydes **71** to alkylideneindolinones **72** in the presence of catalyst **XI** to deliver an open chain synthetic intermediate (Scheme 21).<sup>[52]</sup> Subsequent introduction of 3,4-dihydroisoquinoline **73** and

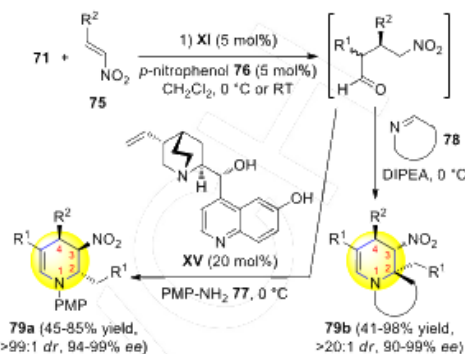
DABCO could promote a cascade Mannich-enamine formation to afford spirocyclic 1,2,3,4-THP **74**.



**Scheme 21.** Sequential synthesis of spirocyclic 1,2,3,4-THPs **74** through aminocatalysis.<sup>[44]</sup>

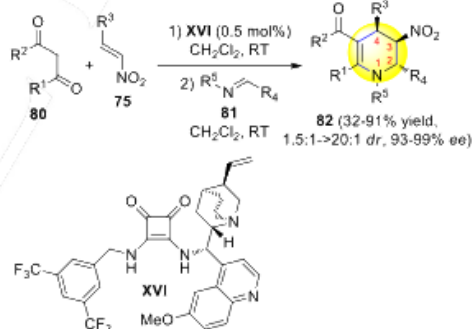
### 3.3. Additions to nitroolefins

Nitroolefins are exceptionally efficient Michael acceptors for enantioselective organocatalysis and these transformations can serve as the starting point to prepare enantioenriched THPs. The group of Sun and Lin published a couple of studies where nitroolefins **75** were at first combined with enolizable aldehydes **71** in the presence of secondary amine **XI** and 4-nitrophenol **76** as co-catalyst (Scheme 22).<sup>[45]</sup> In a second time, an aza-Henry reaction followed by cyclization delivered the 1,2,3,4-THPs **79a,b**. In the first case, the imine engaged in the aza-Henry reaction catalyzed by **XV** was produced in situ by adding an amine **77** that combines with the excess aldehyde. In the second case, an external cyclic ketimine **78** was added together with a stoichiometric amount of DIPEA. In both transformations, the products were obtained in excellent diastereo- and enantioselectivities.



**Scheme 22.** Synthesis of 1,2,3,4-THPs **79a,b** initiated by a Michael addition to nitroolefins catalyzed by a secondary amine.<sup>[45]</sup>

A similar strategy has been exploited by the group of Enders, but with 1,3-dicarbonyl compounds **80** as pronucleophiles and 0.5 mol% of Rawal's squaramide **XVI** as catalyst (Scheme 23).<sup>[46]</sup> After the addition of aldimines **81**, 1,2,4,3-THPs **82** were obtained with variable diastereoselectivities but uniformly high enantioselectivities.



**Scheme 23.** Synthesis of 1,2,3,4-THPs **82** initiated by a Michael addition to nitroolefins catalyzed by a bifunctional squaramide.<sup>[46]</sup>

## 4. Conclusion and Perspective

In summary, we have presented a general overview of the organocatalytic synthetic methods that allow the preparation of diversely functionalized regioisomers of enantioenriched tetrahydropyridines. Both 1,2- and 1,4-additions are equally represented as the key enantioselective step, in combination with all the most common activation modes of organocatalysis. Many

of those transformations allowed to reach high levels of regio- and stereocontrol.

However, compared to the diversity of functions that could potentially be installed on the different positions of the THP ring, we feel like there is still a rather large unexploited potential of innovative development and we can expect that this review could help to draw the attention of more research groups to this inspiring family of synthetic targets.

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- [1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
- [2] For a review on the synthesis of THPs using multicomponent reactions (mostly achiral or in the racemic series), including a comprehensive listing of their biological activities, see: M. M. Khan, S. Khan, Saigal, S. K. Bal, *RSC Adv.* **2016**, *6*, 42045.
- [3] (a) T. Hofmann, P. Schieberle, *J. Agric. Food. Chem.* **1998**, *46*, 2721. (b) I. Blank, S. p. Devaud, W. Matthey-Doret, F. Robert, *J. Agric. Food. Chem.* **2003**, *51*, 3643.
- [4] R. A. Harmer, *Food Chem.* **1980**, *5*, 81.
- [5] Y.-C. Tsai, M.-L. Yu, M. El-Shazly, L. Beerhuys, Y.-B. Cheng, L.-C. Chen, T.-L. Hwang, H.-F. Chen, Y.-M. Chung, M.-F. Hou, Y.-C. Wu, F.-R. Chang, *J. Nat. Prod.* **2015**, *78*, 2346.
- [6] W.-S. Yap, C.-Y. Gan, K.-S. Sim, S.-H. Lim, Y.-Y. Low, T.-S. Kam, *J. Nat. Prod.* **2016**, *79*, 230.
- [7] A. Nakao, N. Ohkawa, T. Nagasaki, T. Kagari, H. Doi, T. Shimozato, S. Ushiyama, K. Aoki, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4607.
- [8] G. Zheng, A. M. Smith, X. Huang, K. L. Subramanian, K. B. Sripurapu, A. Deadiu, C.-G. Zhan, L. P. Dworkin, *J. Med. Chem.* **2013**, *56*, 1693.
- [9] J. W. Chang, A. M. Zuhl, A. E. Speers, S. Niessen, S. J. Brown, M. M. Mulvihill, Y. C. Fan, T. P. Spicer, M. Southern, L. Scampavia, V. Fernandez-Vega, M. M. Dix, M. D. Cameron, P. S. Hodder, H. Rosen, D. K. Nomura, O. Kwon, K.-L. Hsu, B. F. Cavall, *ACS Chem. Biol.* **2015**, *10*, 925.
- [10] (a) W. Langenbeck, *Justus Liebig's Ann. Chem.* **1929**, *469*, 16. (b) B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
- [11] For selected general review, books and special issues, see: (a) B. List, *Chem. Rev.* **2007**, *107*, 5413. (b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304. (c) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178. (d) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167. (e) B. List, K. Maruoka, *Asymmetric Organocatalysis* Thieme, Stuttgart, **2012**. (f) P. I. Dalko, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Wiley-VCH, Weinheim, **2013**. (g) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774. (h) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41.
- [12] (a) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156. (b) H. Thu Pham, I. Chataigner, J.-L. Renaud, *Curr. Org. Chem.* **2012**, *16*, 1754.
- [13] F. Auria-Luna, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2017**, *359*, 2161.
- [14] For leading references, see: (a) J. Franzén, A. Fisher, *Angew. Chem.* **2009**, *121*, 801; *Angew. Chem. Int. Ed.* **2009**, *48*, 787. (b) H. Fang, X. Wu, L. Nie, X. Dai, J. Chen, W. Cao, G. Zhao, *Org. Lett.* **2010**, *12*, 5366. (c) B.-C. Hong, W.-K. Liao, N. S. Dange, J.-H. Liao, *Org. Lett.* **2013**, *15*, 468. (d) Y. Tan, H.-L. Luan, H. Lin, X.-W. Sun, X.-D. Yang, H.-Q. Dong, G.-Q. Lin, *Chem. Commun.* **2014**, *50*, 10027. (e) L. Li, P. Alibabula, Q. Jia, Y. Jia, *Org. Lett.* **2017**, *19*, 2642.
- [15] For leading references and reviews, see: (a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086. (c) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070. (d) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598. (e) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804. (f) J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem.* **2011**, *123*, 8692; *Angew. Chem. Int. Ed.* **2011**, *50*, 8538. (g) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157. (h) M. E. Muratore, L. Shi, A. W. Pilling, R. I. Storer, D. J. Dixon, *Chem. Commun.* **2012**, *48*, 6351. (i) I. Aillaud, D. M. Barber, A. L. Thompson, D. J. Dixon, *Org. Lett.* **2013**, *15*, 2946. (j) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515. (k) C. Luo, Y. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 8193. (l) C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem.* **2013**, *125*, 14334; *Angew. Chem. Int. Ed.* **2013**, *52*, 14084. (m) H. Xu, H. Zhang, E. N. Jacobsen, *Nat. Protoc.* **2014**, *9*, 1860. (n) N. Mittal, D. X. Sun, D. Seidel, *Org. Lett.* **2014**, *16*, 1012. (o) J. Brioché, T. Courant, L. Alcaraz, M. Stocks, M. Furber, J. Zhu, G. Masson, *Adv. Synth. Catal.* **2014**, *356*, 1719. (p) E. Mons, M. J. Wanner, S. Ingemann, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2014**, *79*, 7380. (q) W. Dai, X.-L. Jiang, J.-Y. Tao, F. Shi, *J. Org. Chem.* **2016**, *81*, 185. (r) R. S. Klausen, C. R. Kennedy, A. M. Hyde, E. N. Jacobsen, *J. Am. Chem. Soc.* **2017**, *139*, 12239 and references included therein. (s) D. Slevanović, G. Bertuzzi, A. Mazzanti, M. Fochi, L. Bernardi, *Adv. Synth. Catal.* **2018**, *360*, 893.
- [16] (a) J. M. M. Verkade, L. J. C. v. Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Ruijs, *Chem. Soc. Rev.* **2008**, *37*, 29. (b) S. Hoekman, J. M. M. Verkade, F. P. J. T. Ruijs, in *Enantioselective Organocatalyzed Reactions II: Asymmetric C-C Bond Formation Processes* (Ed.: R. Mahrwald), Springer Netherlands, Dordrecht, **2011**, pp. 343.
- [17] R.-G. Han, Y. Wang, Y.-Y. Li, P.-F. Xu, *Adv. Synth. Catal.* **2008**, *350*, 1474.
- [18] E. Veverková, L. Liptáková, M. Veverka, R. Šebesta, *Tetrahedron: Asymmetry* **2013**, *24*, 548.
- [19] P. Ramaraju, N. A. Mir, D. Singh, I. Kumar, *RSC Adv.* **2016**, *6*, 60422.
- [20] For reviews on the use of multicomponent reactions to prepare heterocycles, see: B. Jiang, T. Rajale, W. Wever, S.-J. Tu, G. Li, *Chem. Asian J.* **2010**, *5*, 2318. (b) I. A. Isara, A. Islas-Jacome, E. González-Zamora, *Org. Biomol. Chem.* **2018**, *16*, 1402.
- [21] D.-F. Yu, Y. Wang, P.-F. Xu, *Tetrahedron* **2011**, *67*, 3273.
- [22] (a) X. Li, Y. Zhao, H. Ou, Z. Mao, X. Lin, *Chem. Commun.* **2013**, *49*, 1401. (b) F. Shi, W. Tan, R.-Y. Zhu, G.-J. Xing, S.-J. Tu, *Adv. Synth. Catal.* **2013**, *355*, 1605.
- [23] See for example: M. M. Sanchez Duque, O. Baslé, Y. Génésion, J.-C. Plaquevent, X. Bugaut, T. Constantieux, J. Rodriguez, *Angew. Chem.* **2013**, *14393*, *Angew. Chem. Int. Ed.* **2013**, *52*, 14143.
- [24] V. Dederck, J. Martínez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1.
- [25] S. Takizawa, N. Inoue, H. Sasaki, *Tetrahedron Lett.* **2011**, *52*, 377.
- [26] S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasaki, *Asian J. Org. Chem.* **2014**, *3*, 412.
- [27] D. M. Barber, H. J. Sanganee, D. J. Dixon, *Org. Lett.* **2012**, *14*, 5290.
- [28] C. Beato, T. Krappitz, G. Raabe, D. Enders, *Synthesis* **2015**, *47*, 3813.
- [29] (a) S.-G. Wang, Z.-L. Xia, R.-Q. Xu, X.-J. Liu, C. Zheng, S.-L. You, *Angew. Chem.* **2017**, *129*, 7548; *Angew. Chem. Int. Ed.* **2017**, *56*, 7440. (b) Z.-L. Xia, C. Zheng, S.-G. Wang, S.-L. You, *Angew. Chem.* **2018**, *130*, 2683; *Angew. Chem. Int. Ed.* **2018**, *57*, 2653.
- [30] M. Rueping, A. P. Antonchick, *Angew. Chem.* **2008**, *120*, 5920; *Angew. Chem. Int. Ed.* **2008**, *47*, 5836.

- [31] B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5582, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474.
- [32] S.-L. Zhou, J.-L. Li, L. Dong, Y.-C. Chen, *Org. Lett.* **2011**, *13*, 5874.
- [33] L. He, G. Laurent, P. Retailleau, B. Folléas, J.-L. Brayer, G. Masson, *Angew. Chem.* **2013**, *125*, 11294, *Angew. Chem. Int. Ed.* **2013**, *52*, 11088.
- [34] L. Zu, H. Xie, H. Li, J. Wang, X. Yu, W. Wang, *Chem. Eur. J.* **2008**, *14*, 8333.
- [35] J.-P. Wan, C. C. J. Loh, F. Pan, D. Enders, *Chem. Commun.* **2012**, *48*, 10049.
- [36] X. Wu, X. Dai, L. Nie, H. Fang, J. Chen, Z. Ren, W. Cao, G. Zhao, *Chem. Commun.* **2010**, *46*, 2733.
- [37] X. Wu, X. Dai, H. Fang, L. Nie, J. Chen, W. Cao, G. Zhao, *Chem. Eur. J.* **2011**, *17*, 10510.
- [38] (a) X. Wu, H. Fang, Q. Liu, L. Nie, J. Chen, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 7251. (b) M. Rueping, C. M. R. Volla, M. Bolte, G. Raabe, *Adv. Synth. Catal.* **2011**, *353*, 2853.
- [39] M. Rueping, C. M. R. Volla, *RSC Adv.* **2011**, *1*, 79.
- [40] H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Adv. Synth. Catal.* **2014**, *356*, 851.
- [41] (a) Y. Dudognon, H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Chem. Commun.* **2015**, *51*, 1980. (b) H. Du, Y. Dudognon, M. d. M. Sanchez Duque, S. Goudedranche, D. Bonne, J. Rodriguez, X. Bugaut, T. Constantieux, *Synthesis* **2016**, *48*, 3479.
- [42] H. Du, Y. Dudognon, J. Rodriguez, T. Constantieux, X. Bugaut, *Synthesis* **2018**, DOI: 10.1055/s-0036-1597870.
- [43] C. Rong, H. Pan, M. Liu, H. Tian, Y. Shi, *Chem. Eur. J.* **2016**, *22*, 2887.
- [44] Y. Tan, E.-L. Feng, Q.-S. Sun, H. Lin, X. Sun, G.-Q. Lin, X.-W. Sun, *Org. Biomol. Chem.* **2017**, *15*, 778.
- [45] (a) H. Lin, Y. Tan, W.-J. Liu, Z.-C. Zhang, X.-W. Sun, G.-Q. Lin, *Chem. Commun.* **2013**, *49*, 4024. (b) Y. Tan, Y.-J. Chen, H. Lin, H.-L. Luan, X.-W. Sun, X.-D. Yang, G.-Q. Lin, *Chem. Commun.* **2014**, *50*, 15913.
- [46] M. Bümel, P. Chauhan, R. Hahn, G. Raabe, D. Enders, *Org. Lett.* **2014**, *16*, 6012.