(THIO)UREA-CATALYZED FORMATION OF HETEROCYCLIC COMPOUNDS

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Abstract. *The importance of (thio)urea organocatalysts for the efficient construction of N-, O- and S-heterocyclic compounds is briefly disclosed. Thus, in this chapter, representative examples where the heterocyclic ring is formed in the course of the reactions promoted by those chiral catalysts are covered. This compilation excludes examples where there is no new heterocyclic moiety in the final product, with respect to the starting compounds. The use of these methodologies allows the obtainment of a wide variety of heterocyclic structures, such as tetrahydro-β-carbolines, 1,4-dihydropyridines, indolines, pyrrolidines, 2-amino-4H-chromene derivatives, flavanones, chromanones, pyrans, tetrahydrofurans and benzothiopyrans. This kind of structures is present in natural products and biologically active compounds, being of great interest in Pharmacological Chemistry.*

Contents

1. Introduction

In the last years, catalysts acting through hydrogen bonds have fascinated the scientists, becoming the center of research of many groups. This kind of activation represents a significant part of the organocatalysis field.[1] Among the different types of hydrogen bond based catalysts, chiral thiourea/urea derivatives are of great interest and have been focus of intensive studies, resulting to be appropriated catalysts in numerous pivotal processes.[2] In this context, we have centered part of our investigation on the employment of chiral (thio)urea for the development of new organocatalyzed asymmetric methods.[3]

Many of these model thioureas represented in Figure 1, have inspired further investigations and more complex scaffolds have been designed based on these pioneering structures.[4]

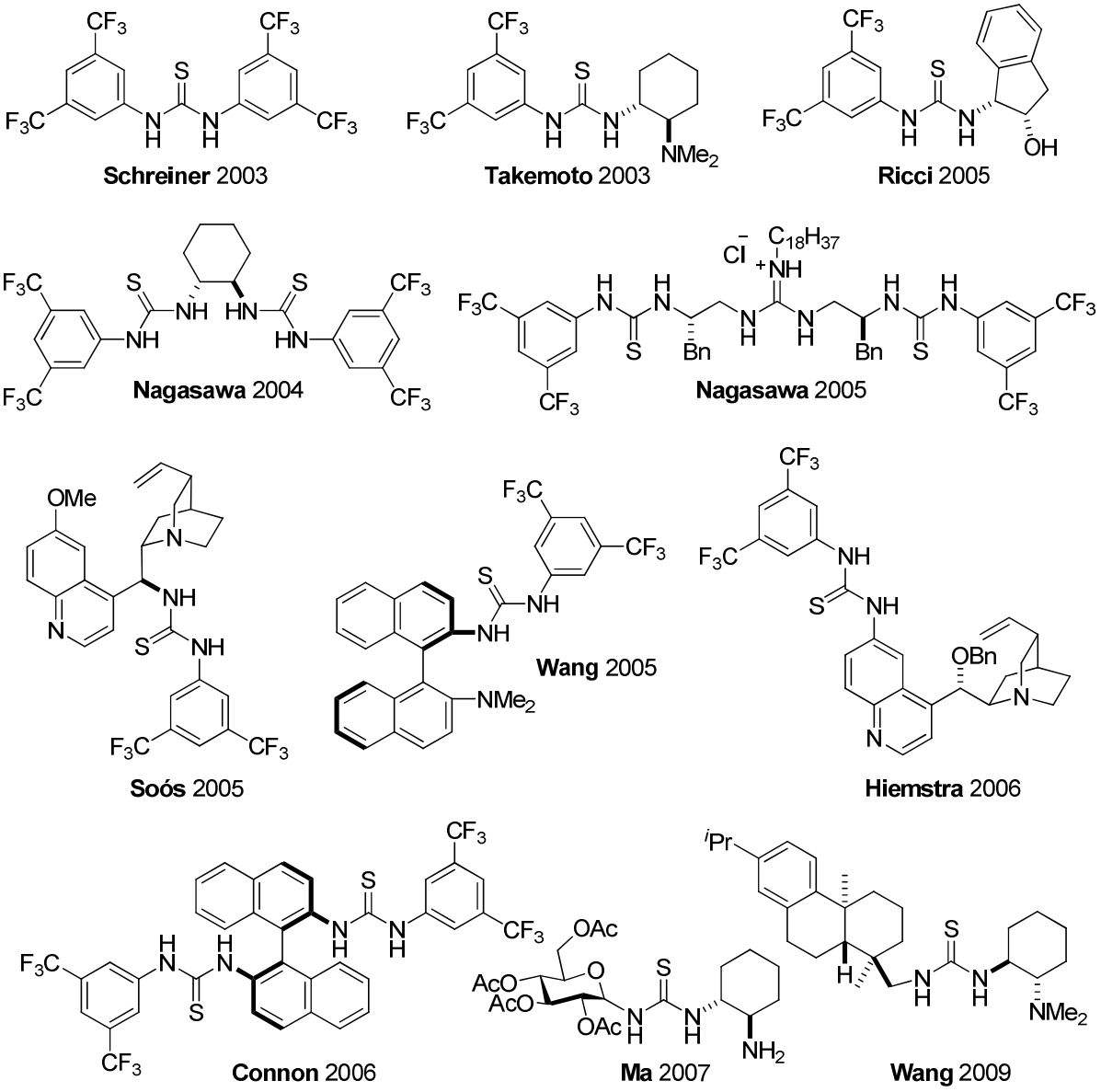


Figure 1

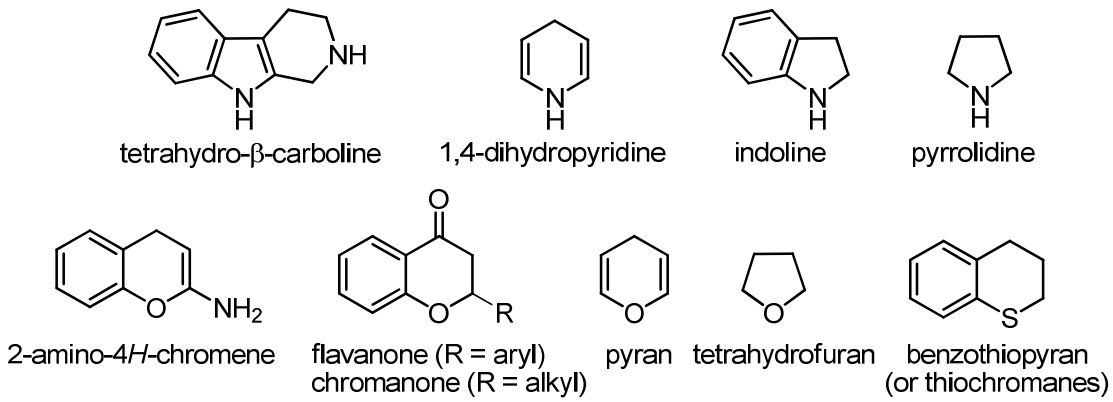


Figure 2

We want to disclose here the importance of thiourea organocatalysts for the efficient construction of heterocyclic compounds. In this chapter, we will cover representative examples where the heterocyclic ring is formed in the course of the reactions. We have selected some pivotal heterocyclic rings which are core structural motifs in many natural products and biologically active compounds (Figure 2). Many other examples that do not appear in this chapter have also successfully contributed to the expansion of Heterocyclic Chemistry.

2. Synthesis of *N*-heterocyclic compounds

2.1. Synthesis of tetrahydro-β-carbolines

Tetrahydro-β-carboline rings are present in many natural and synthetic organic compounds possessing a wide diversity of important biological activities (Figure 3).[5] Pictet-Spengler reaction represents a well-established synthetic approach for the preparation of these systems.[6] In the last decade, the enantioselective version of this reaction has centered many efforts for accessing useful chiral building blocks.

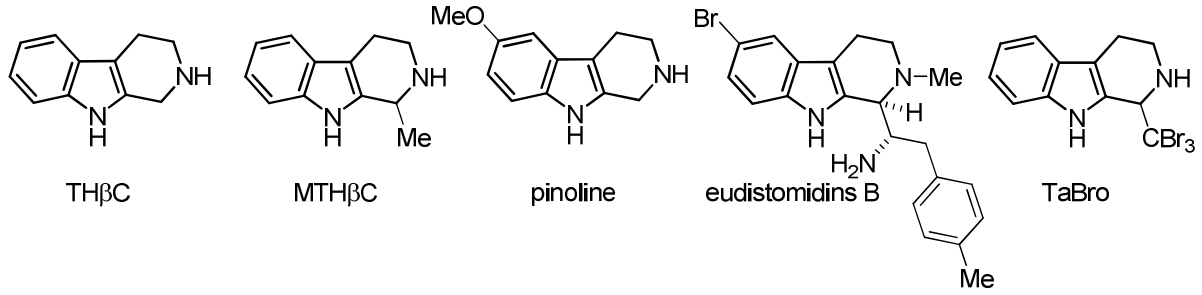
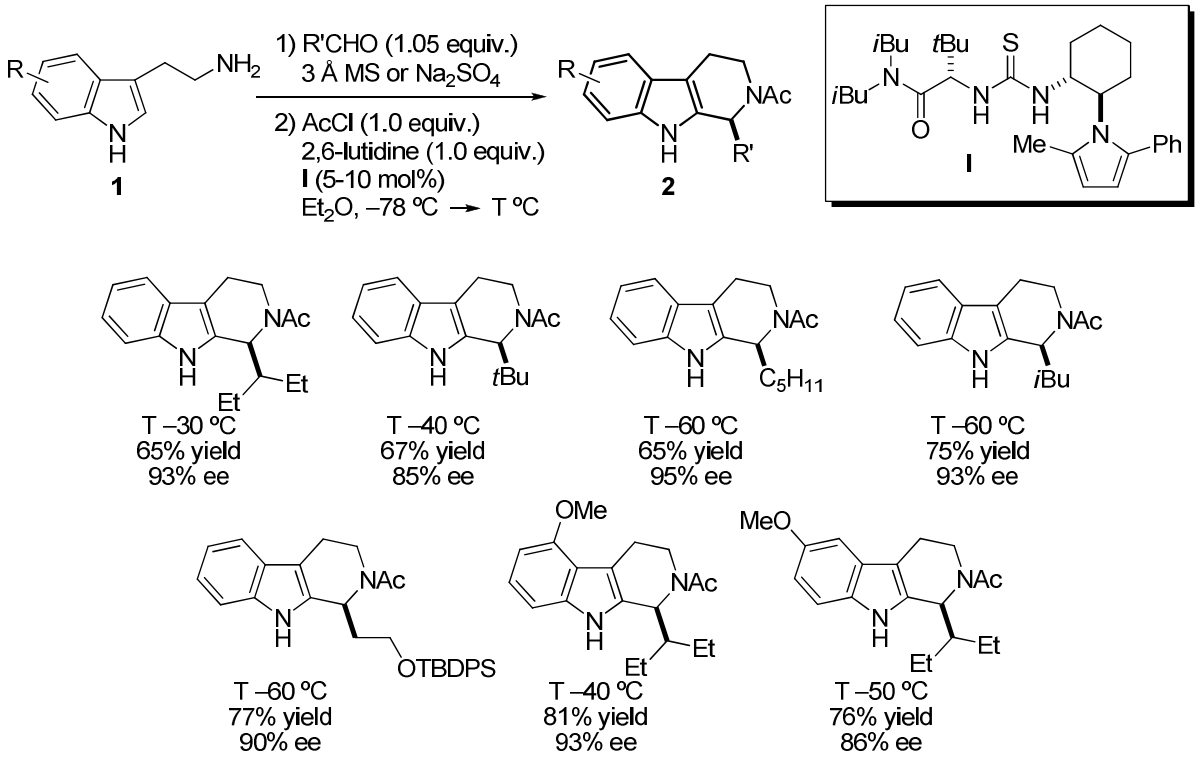
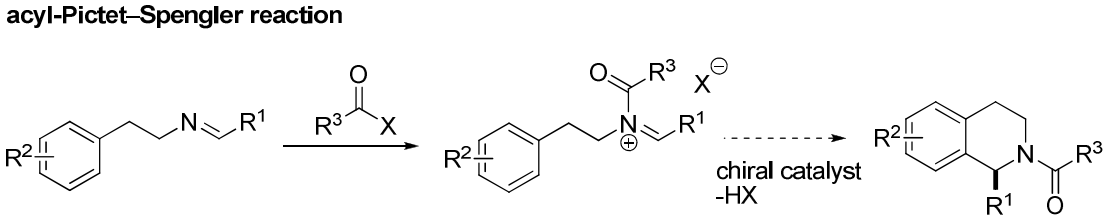


Figure 3



Scheme 1

In this field, Jacobsen and co-workers pioneered in 2004 a thiourea catalyzed example of an acyl-Pictet-Spengler reaction, providing access to different *N*-acetyl β-carbolines **2** in high enantioselectivies (85-95%) and moderate yields (65-81%) (Scheme 1).[7,8] The authors envisioned the possibility of activating this procedure using thiourea catalysts based in the acyl-Pictet-Spengler reaction mechanism (Scheme 2) and in the previously reported ability of chiral thioureas to activate imines for the addition of diverse nucleophiles.



Scheme 2

2.2. Synthesis of 1,4-dihydropyridines

1,4-Dihydropyridines (1,4-DHP) and their derivatives are important building blocks and versatile synthons in Organic Synthesis owing their biological and broad range of pharmacological properties (Figure 4).[9] However, their enantioselective synthesis has been less explored and the development of new chiral examples still represents an active synthetic challenge.

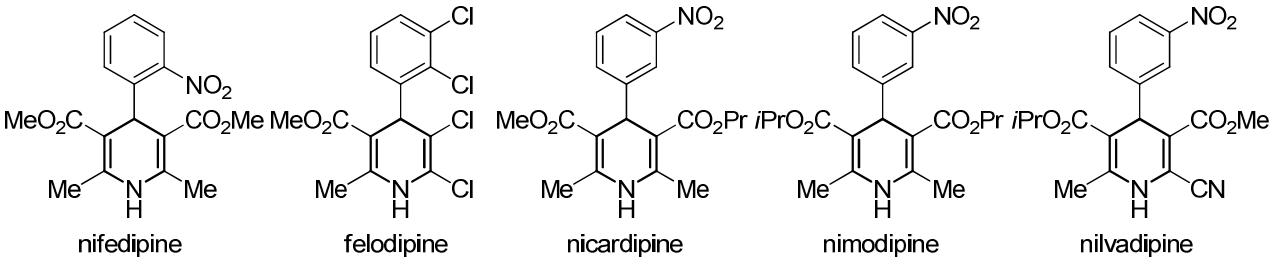
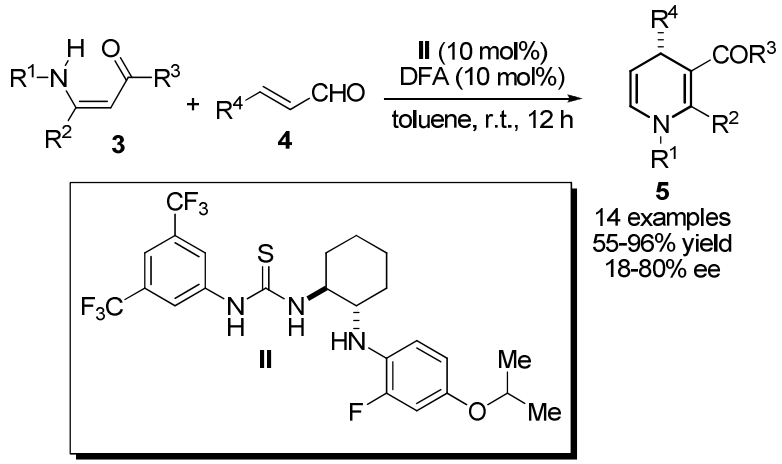
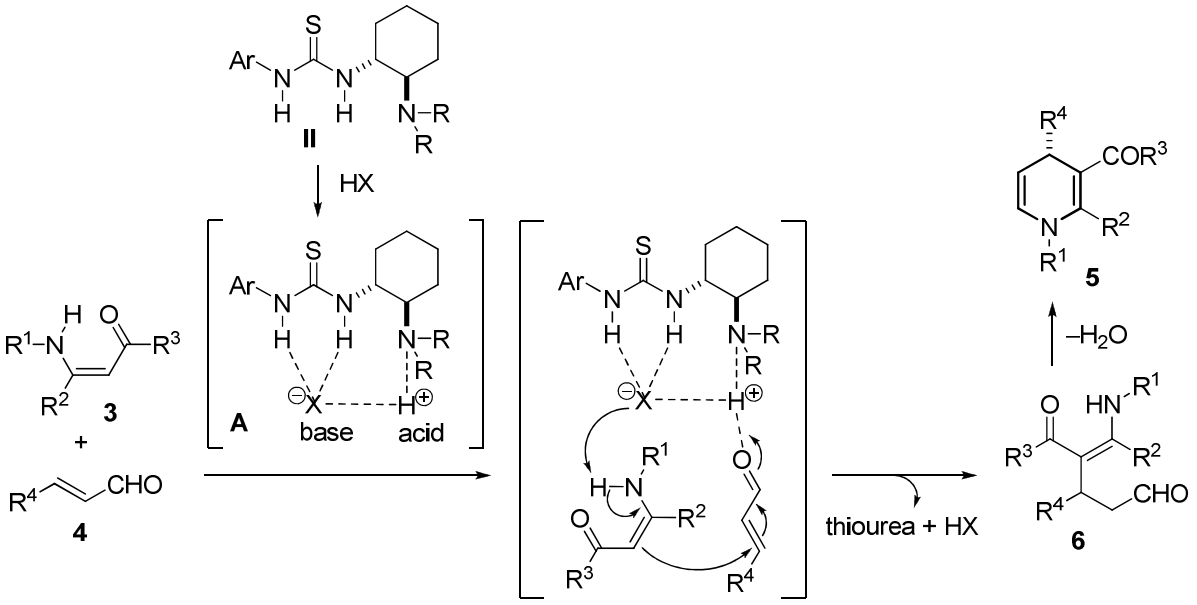


Figure 4

Takemoto's group has developed an interesting synthesis of functionalized 1,4-DHP **5** following a Brønsted acid–thiourea co-catalyzed asymmetric cycloaddition of β-enamino esters **3** and α,β-unsaturated aldehydes **4** using novel thiourea catalyst **II** (Scheme 3).[10] The authors proposed the mechanism depicted in Scheme 4 to explain the role of the catalyst in the course of the reaction.



Scheme 3



Scheme 4

The ammonium salt complex **A** is formed from a mixture of thiourea **II** and a Brønsted acid (HX) (1:1) and it is the new bifunctional catalyst. Thus, enamino ester **3** and α,β-unsaturated aldehyde **4** should be activated by the ammonium proton and the conjugate base (X^-), respectively, leading to the corresponding Michael product **6**. The desired 1,4-DHP **5** is obtained after subsequent intramolecular cyclization and dehydration of **6**. The merit of this strategy is that the acidity and basicity of complex **A** can be tuned by appropriate selection of the acid (HX).

2.3. Synthesis of indolines

The indole core and its derivatives are privilege structural motifs present in many natural products and the construction of this skeleton is nowadays an active area of research in Organic Synthesis.[11] Special interest has received the preparation of chiral scaffolds bearing this core through metal- and organo-catalysis.[12] An important type of molecules belonging to this family is the indoline, which also exhibits interesting biological properties (Figure 5).[13]

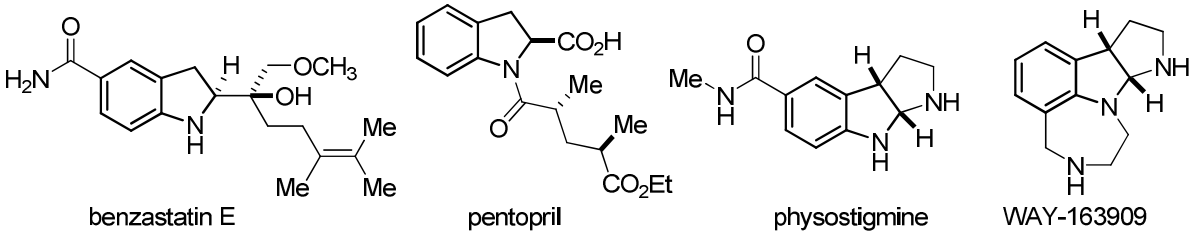
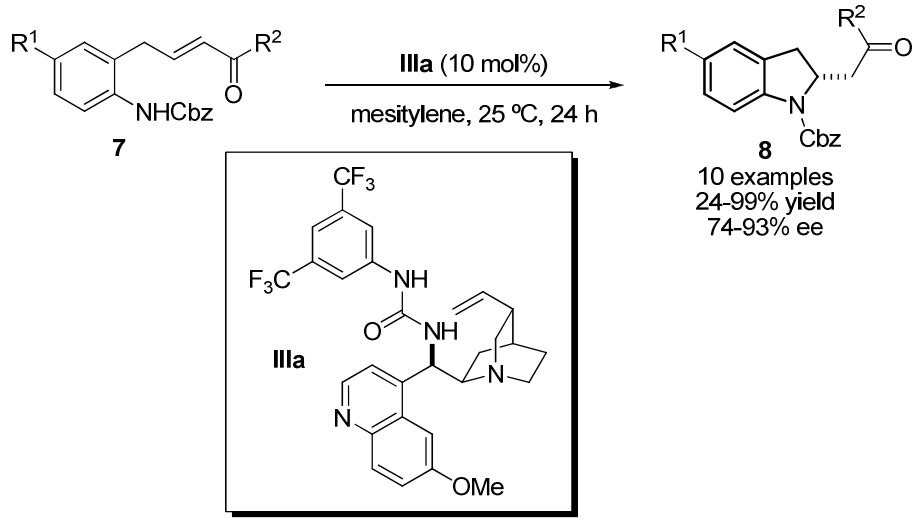


Figure 5

In this field, Asano, Matsumara and co-workers developed a new method for the asymmetric synthesis of 2-substituted indolines **8**, employing bifunctional aminourea **IIIa** as catalyst and α,β-unsaturated carboxylic acid derivatives **7** as starting material (Scheme 5). Final indolines **8** were obtained in moderate to good yields (24-99%) and with high enantioselectivities (74-93%).[14]

The reaction is supposed to proceed *via* an intramolecular aza-Michael addition mediated by hydrogen bond interactions, although the authors did not propose any tentative activation mechanism. The catalytic

process was highly versatile and applicable to a wide range of α,β-unsaturated carboxylic acid derivatives **7**, among them, thioester analogues.



Scheme 5

2.4. Synthesis of pyrrolidines

Pyrrolidines are common cores in many natural products and pharmacologically active scaffolds, such as L-proline,[15] (–)-kainic acid,[16] swainsone,[17] (–)-mesembrine,[18] (–)-slaframine,[19] and lepadiformine[20] (Figure 6).[21] Many efforts have been devoted to the enantioselective synthesis of these functionalized structures due to their great importance, and the development of new catalytic approaches is currently of interest.[22]

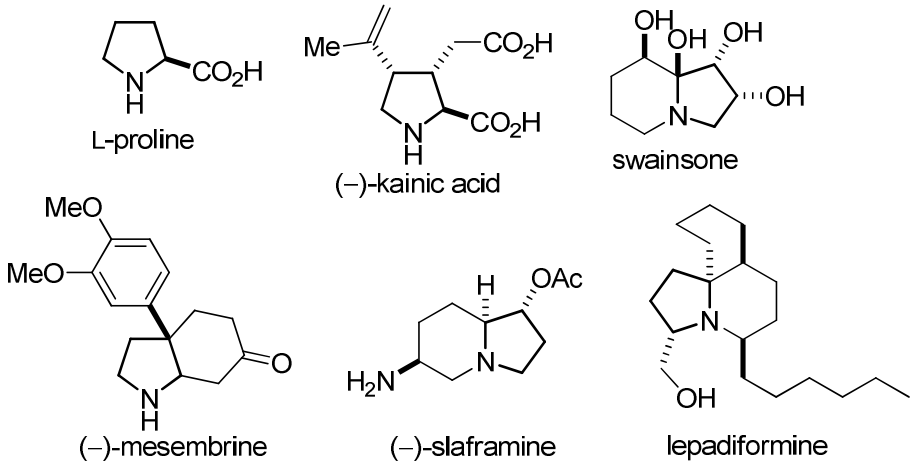
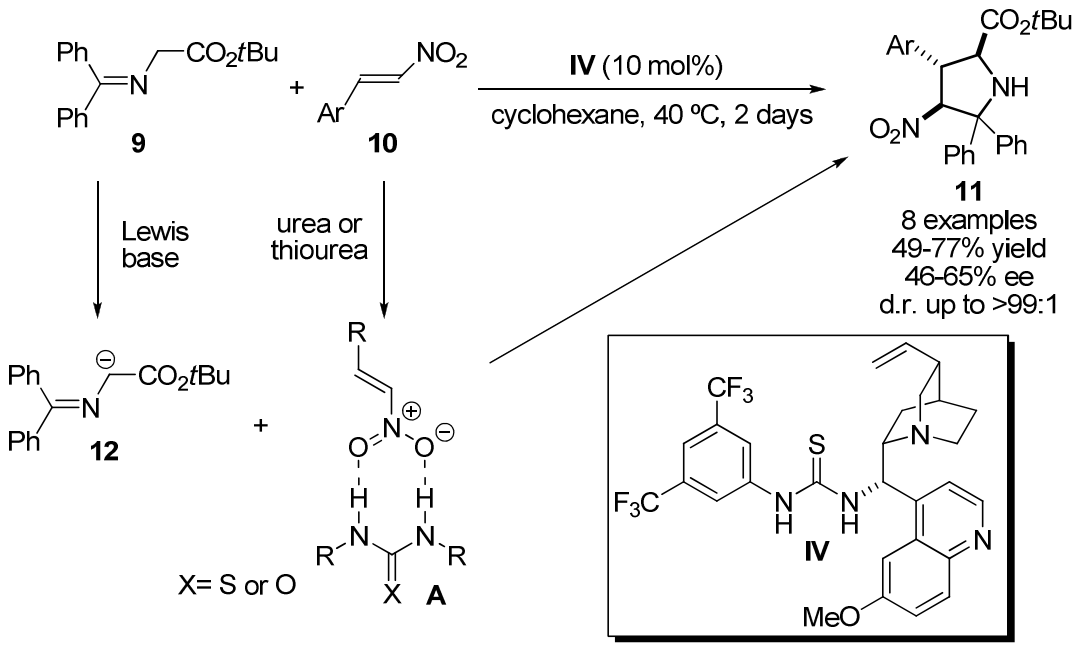


Figure 6

Zhang and co-workers reported the first asymmetric 1,3-dipolar cycloaddition of azomethineylides[23] **12** with nitroalkenes **10** for the preparation of highly functionalized pyrrolidines **11** in good yields (49-77%), high diastereoselectivities (up to >99:1) and moderate enantioselectivities (46-65%) (Scheme 6).[24]

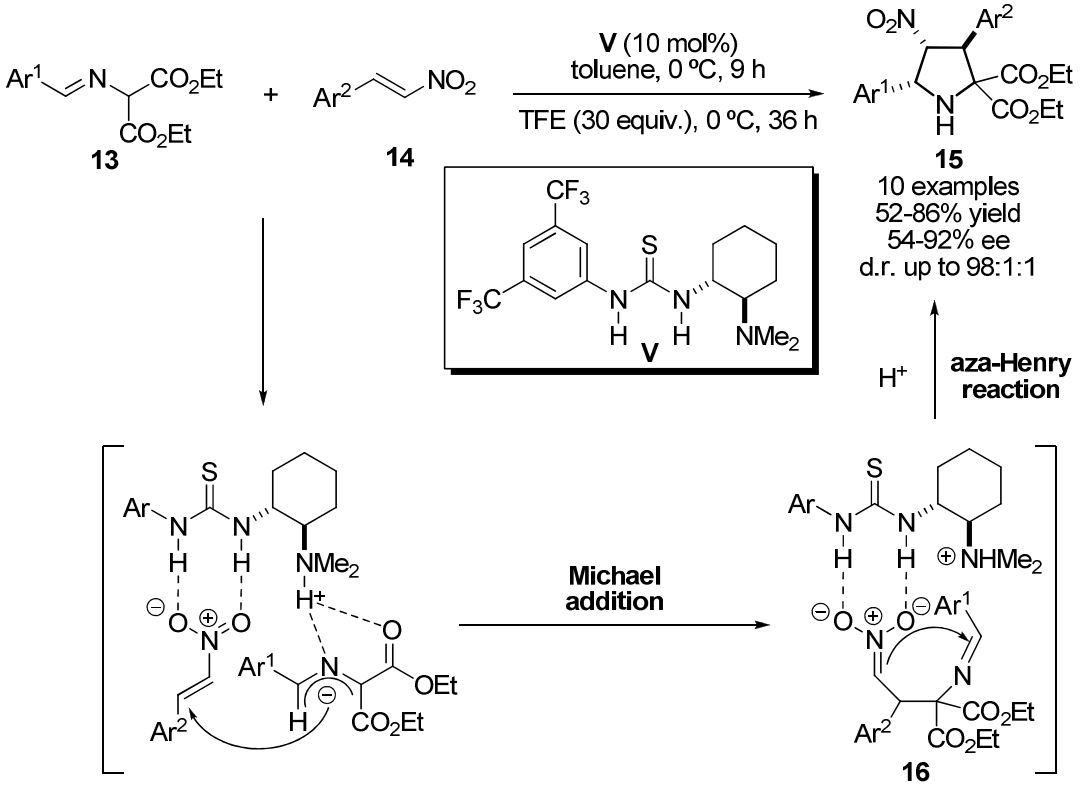
The authors envisioned that the enolate **12**, which can be formed by treatment of **9** with a Lewis base, would attack the nitroalkenes **10**, activated at the same time through hydrogen-bonds between the nitro

group of **10** and the NH protons of the thiourea catalyst **IV** (complex **A**), favoring the subsequent apparent 1,3-dipolar cycloaddition reaction (Scheme 6).



Scheme 6

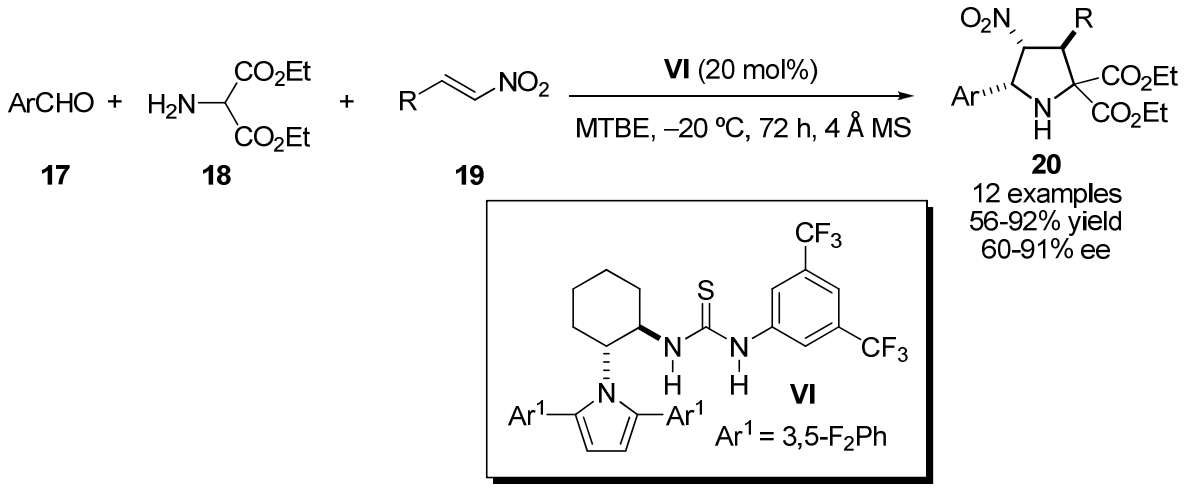
Contemporaneously, Takemoto's group reported a similar 1,3-dipolar cycloaddition process catalyzed by chiral thiourea **V** (Scheme 7).[25] The authors proposed that the possible stepwise mechanism could proceed *via* a first Michael addition and a successive intramolecular aza-Henry reaction, as depicted in Scheme 7.



Scheme 7

In this mechanism, the formal azomethineylide would be formed by initial deprotonation of imine **13** and successive anchorage to the thiourea catalyst **V** through hydrogen bonds as shown in Scheme 7. The addition of an external proton donor 2,2,2-trifluoroethanol (TFE) is believed to activate the imine moiety of compounds **13** and it would stabilize the transition state by the hydrogen bonds.

Interestingly, Chen and co-workers reported the first asymmetric multicomponent version of this 1,3-dipolar cycloaddition reaction using aldehydes **17**, α-aminomalonates **18** and nitroalkenes **19**, catalyzed by chiral thiourea-pyrrol structure **VI**. They obtained the corresponding pyrrolidine compounds **20** in good yield (56-92%) and good enantioselectivities (60-91%) (Scheme 8).[26]



Scheme 8

Based on the absolute configuration of final pyrrolidine adducts, the authors invoked the concerted 1,3-dipolar cycloaddition shown in Figure 7. This process proceeds with the initial formation of an imine **21** from the aldehyde **17** and α-aminomalonate **18**. The formal azomethineylide **21** stabilized by a hydrogen bond, would react with the *re*-face of nitroalkenes **19** activated by the thiourea group of the catalyst **VI** through a double hydrogen bonding interaction, in a formal [3+2] cycloaddition reaction in an *endo*-attack (Figure 7). β-Phenyl group of compound **19** directed away from the catalyst, avoiding the steric hindrance, would allow the formation of the aforementioned double hydrogen-bonding interaction between the thiourea moiety and nitrostyrene.

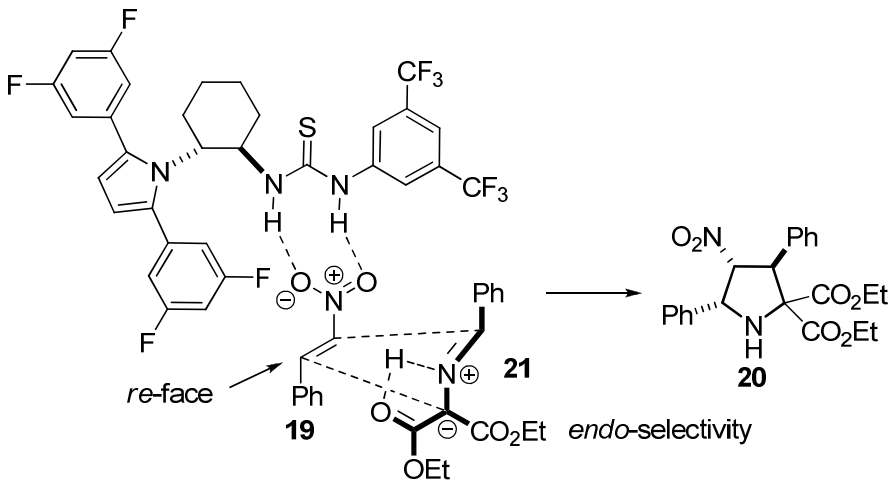


Figure 7

It is worth noting that in these three mechanisms (Schemes 6-8) the dipole is believed to be formed through deprotonation of the corresponding imine and subsequent activation by hydrogen bonds with the thiourea catalyst or with an additional proton donor, giving rise to the formal azomethineylide involved in the final step of the process.

3. Synthesis of *O*-heterocyclic compounds

3.1. Synthesis of 2-amino-4*H*-chromene derivatives

Chromene scaffolds are a class of benzopyran derivatives commonly present in natural products and biologically active compounds. In particular, the synthesis of 2-amino-4*H*-chromenes has attracted much attention due to their pharmacological properties (HA14-1,[27] MX58151,[28] HFI-437,[29] and inhibitor of MK-2[30]) (Figure 8). However, although many procedures have been reported for the racemic version of these compounds,[31] asymmetric methodologies have been scarcely explored and they are of great interest.[32] Some groups have performed pivotal contributions in this field using chiral thiourea catalysts as efficient tool for the construction of these molecular architectures and they are represented and discussed in Schemes 9-11.

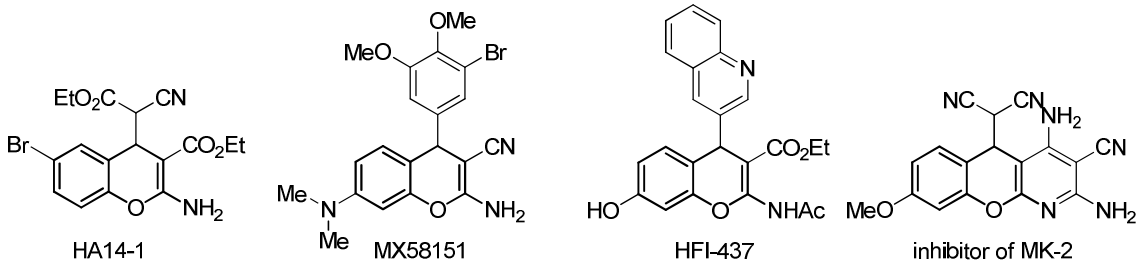
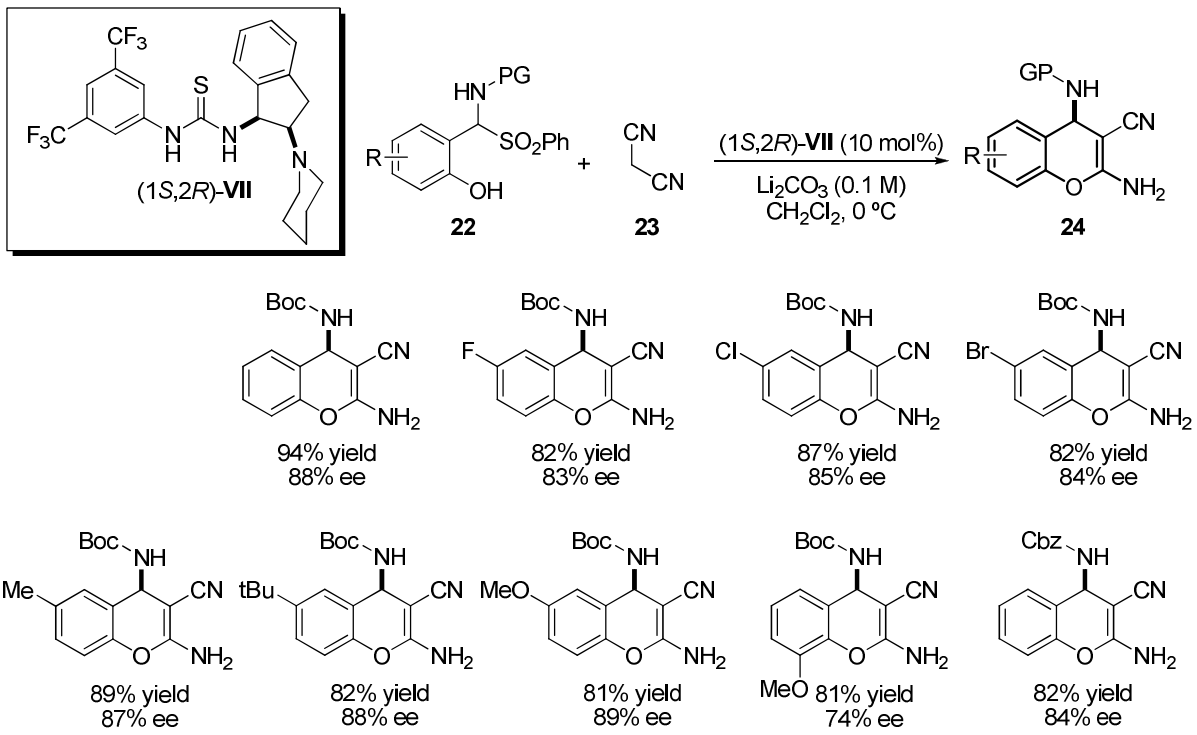


Figure 8

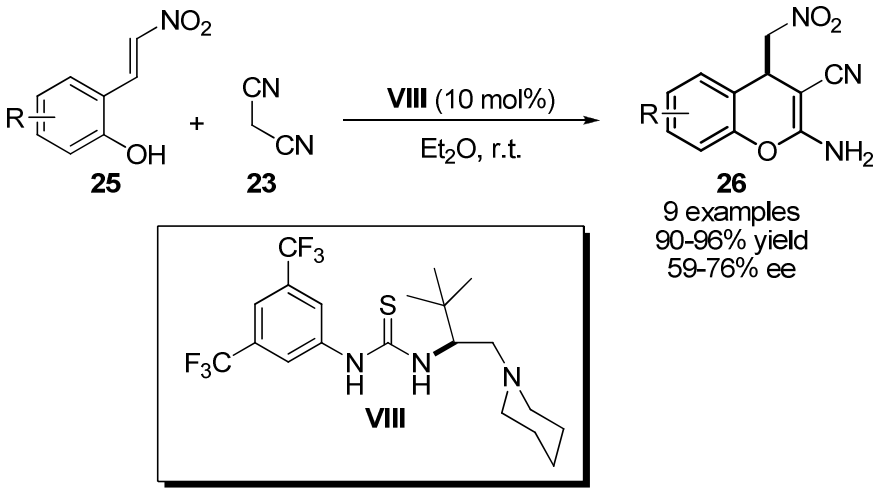


Scheme 9

Wang and co-workers reported an interesting Mannich cyclization–tautomerization cascade procedure for the synthesis of **24** in high yields (81-94%) and good enantioselectivities (74-89%), promoted by catalyst

(1*S*,2*R*)-**VII**. The method was also applicable to different protecting groups in the α-amidosulfone reagent **22** (Scheme 9).[33]

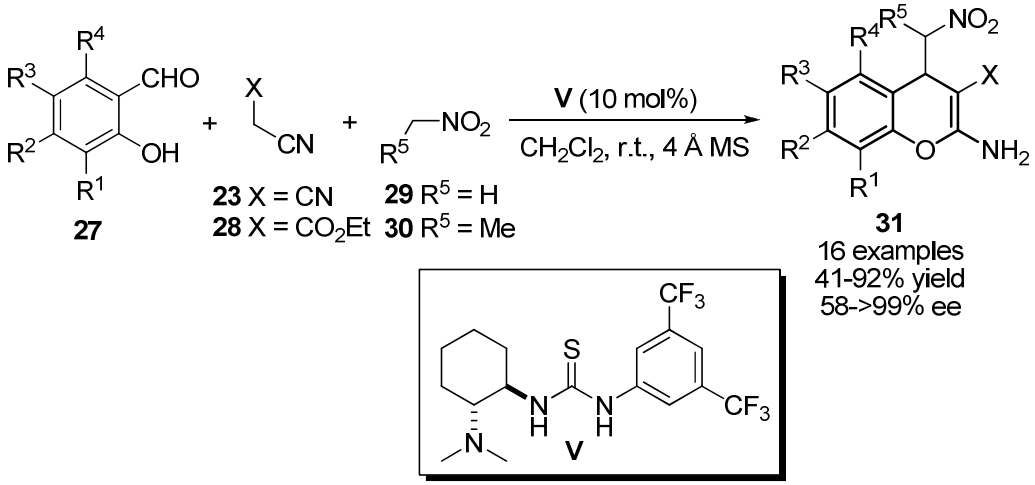
The same research group reported an interesting cascade approach for the obtainment of 2-amino-4*H*-chromene derivatives **26** in high yields (90-96%) and high ee values (59-76%), using a new bifunctional thiourea **VIII** (Scheme 10).[34]



Scheme 10

In both mechanisms the thioureas **VII** and **VIII** are envisioned to play a bifunctional role activating at the same time the nucleophile and the electrophile of these reactions through the basic function and the thiourea moiety of both catalysts.

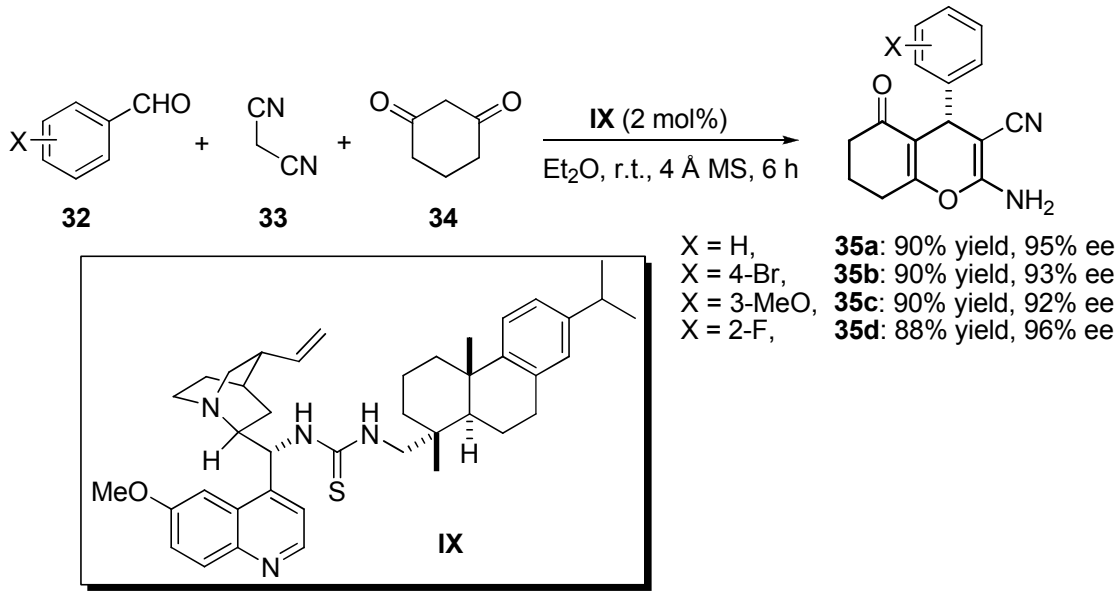
Later, Yang, Liu and co-workers developed an interesting multicomponent reaction for the straightforward synthesis of similar functionalized chromenes **31** starting from salicylaldehyde **27**, malononitrile (**23**)/cyanoacetate (**28**) and nitroalkane **29**-**30** using a simple tertiary amino-thiourea **V** (Scheme 11).[35]



Scheme 11

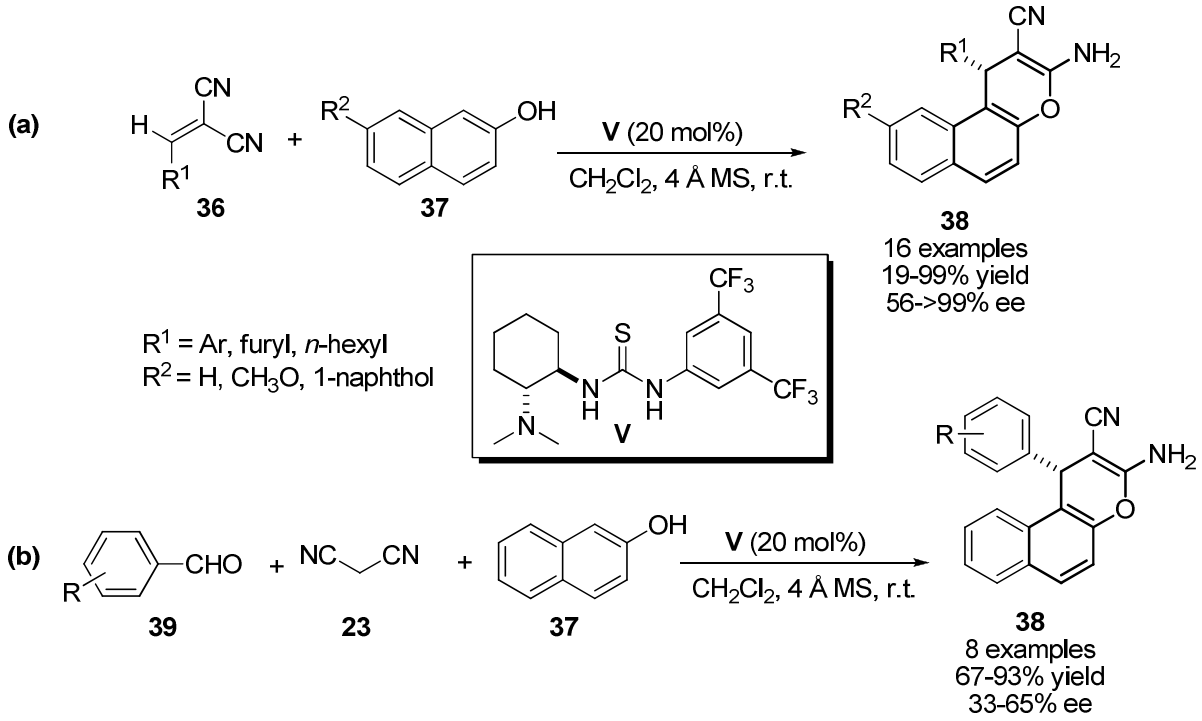
This protocol represents a straightforward approach for the construction of chiral highly functionalized 2-amino-4*H*-chromenes **31** in good yields (41-92%) and with good enantioselectivities (58->99% ee) from simple starting materials.

At the same time, Wang and co-workers developed a different multicomponent reaction using diketone **34**, which allows the preparation of adducts **35a-d** (Scheme 12). The authors use a terpene-derived bifunctional chiral thiourea catalyst **IX** employing a low catalytic charge (2 mol%).[36,37]



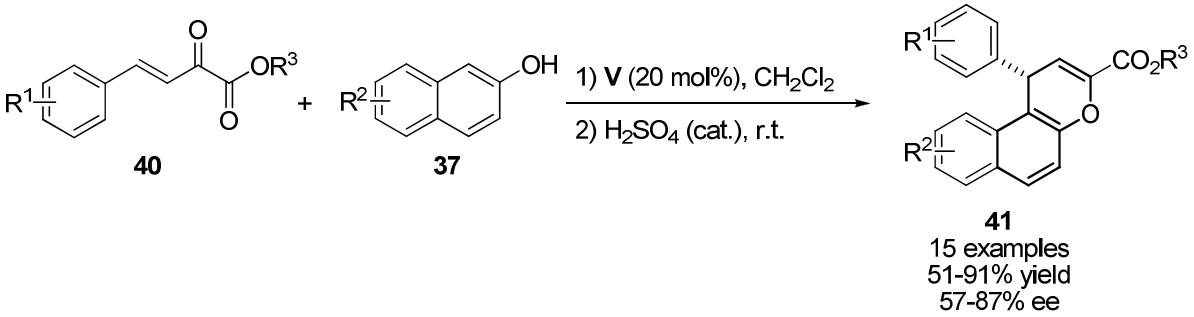
Scheme 12

Yang, Zhao and co-workers have reported the first synthesis of chiral naphthopyran derivatives[38] (a class of 2-amino-4*H*-chromene derivatives) using an efficient bifunctional thiourea **V** to promote the addition–cyclization reaction of 2-naphthol **37** with α,α-dicyanoolefins **36** under mild conditions (Scheme 13, a). The final adducts **38** were obtained in moderate to high yields (19-99%) and moderate to good enantioselectivities (56->99%).[39]



Scheme 13

Interestingly, the authors also explored the viability of the asymmetric three-component one-pot version, affording final products **38** with good results (67-93% yield and 33-65% ee), although slightly lower that employing the preformed malononitrile **36** (Scheme 13, b). The same group extended this reaction to a range of β,γ-unsaturated α-keto ester **40** instead of α,α-dicyanoolefins **36** (Schemes 14).[40] In this case, the corresponding final chromene derivatives **41** were also obtained with good results (51-91% yield and 57-87% ee).

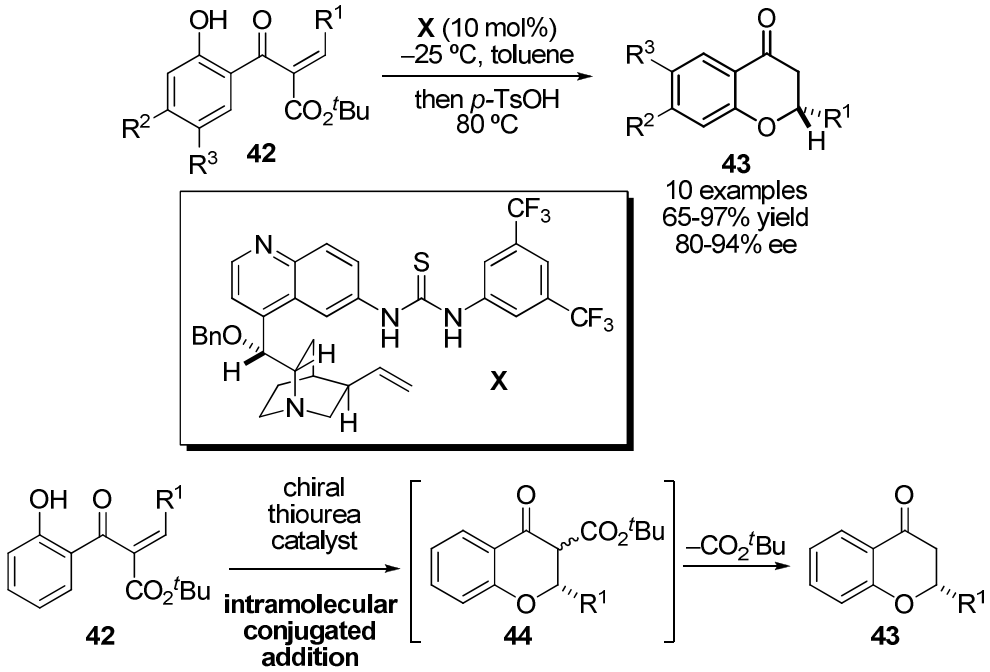


Scheme 14

3.2. Synthesis of flavanones and chromanones

Flavanone moiety is present in many biologically active products[41] that exhibit anti-tumor and anti-inflammatory properties, among others.[42] However, methods which allow their asymmetric synthesis are very scarce in the literature.[43]

Scheidt's group has reported an enantioselective method for the synthesis of chromanones **43** starting from β-ketoester alkylidene substrates **42**. Concerning the mechanism, the authors envisaged that bifunctional quinine-derived thiourea catalyst **X** would promote an intramolecular conjugate addition of a deprotonated phenol over the activated β-ketoesteralkylidene to deliver the desired flavanones (R^1 = Ar) and chromanones **43** (R^1 = alkyl) (Scheme 15).[44]



Scheme 15

It is worth noting that after the cyclization step, the 3-carboxylate group (X) can be removed by treatment with acid in toluene without affecting the integrity of the newly formed stereocenter at C2. This decarboxylation process allows formation of enantioenriched flavanones in high yields since the 3-carboxy flavanone products **44** are firstly formed as mixtures of *cis* and *trans* diastereomers.

3.3. Synthesis of pyrans and their fused derivatives

Pyran derivatives are a significant class of heterocyclic compounds which can exhibit biological and pharmacological activities (YCM1008A,[45] melicobisquinolinone B,[46] zhantosimuline,[47,48] huajiaoisimuline,[47] and cytotoxic fusaricide[49]) (Figure 9).[50]

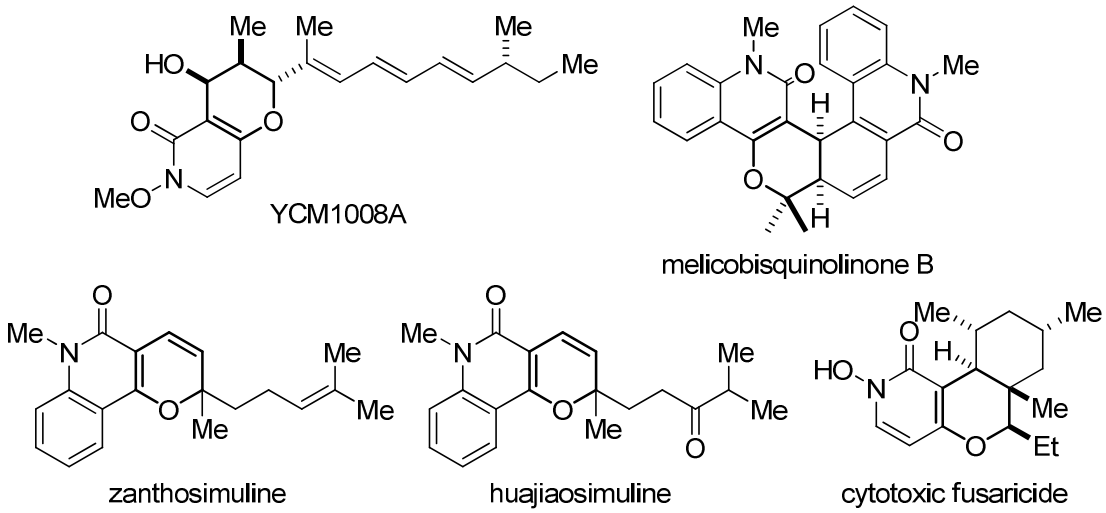


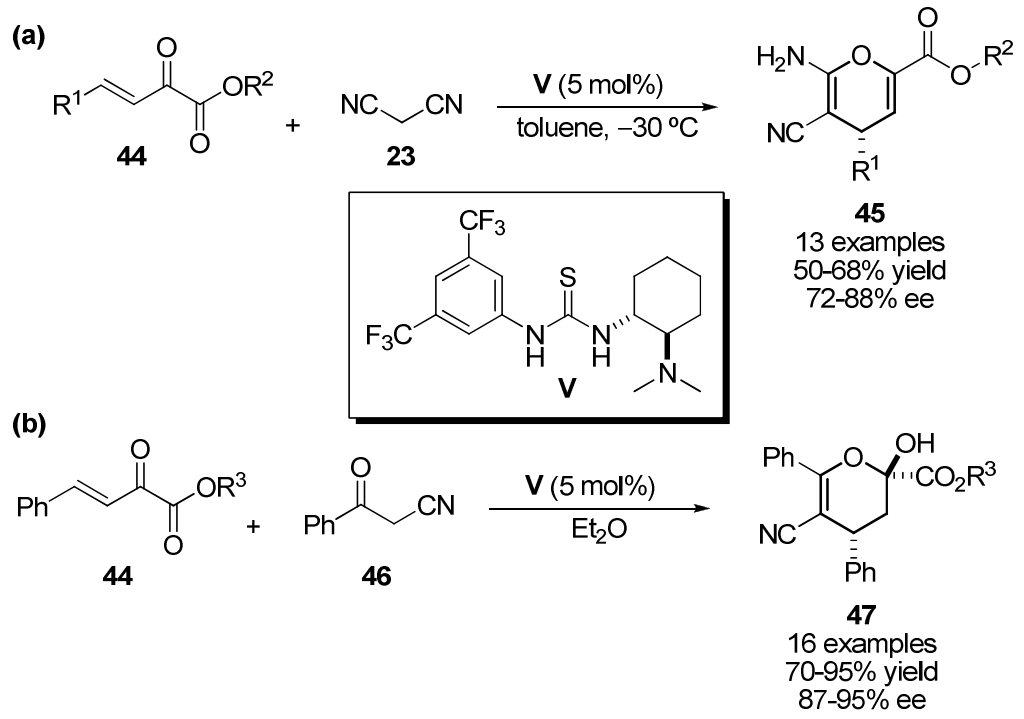
Figure 9

Many of them could also be synthetic intermediate for the preparation of more complex scaffolds.[51] Consequently, the development of new synthetic approaches giving access to such compounds has attracted the interest of many research groups.[52]

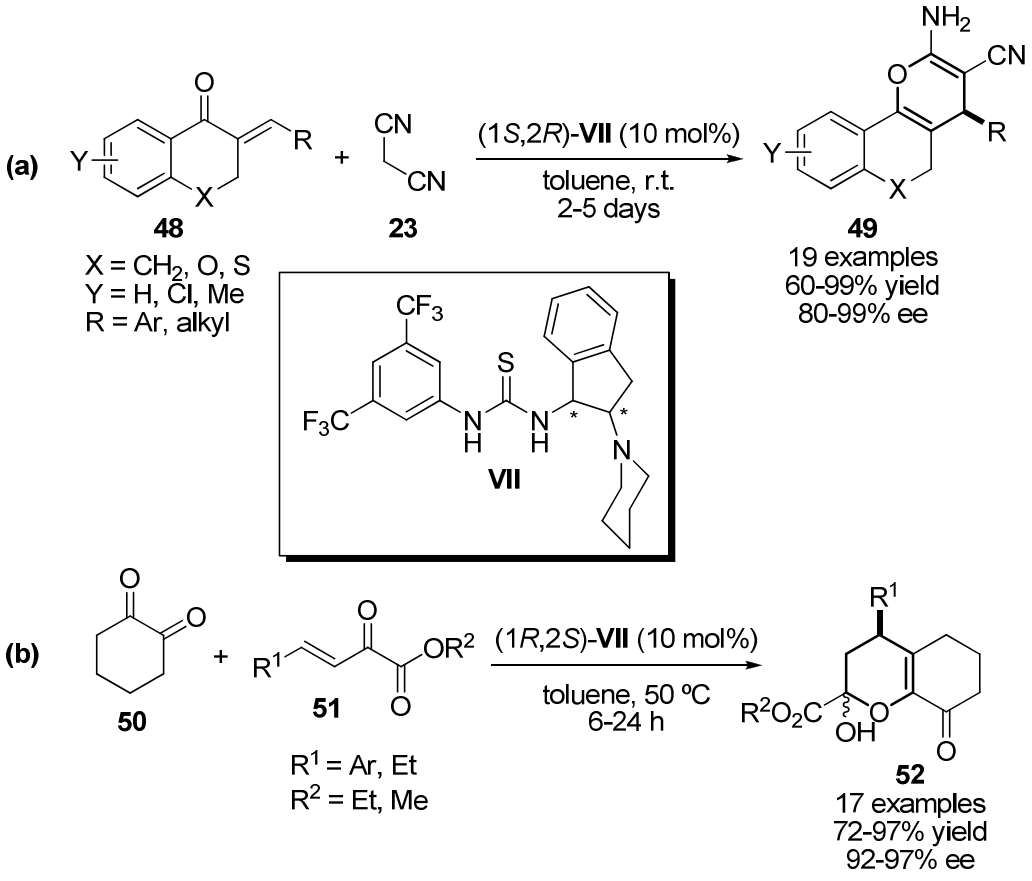
In this field, Zhao's group has developed two interesting and straightforward methodologies using different nucleophiles for the chiral addition over β,γ-unsaturated α-ketoester **44**. Malononitrile **23**[53] and 3-oxo-3-phenylpropanenitrile **46**[54] were used in each case to afford the corresponding pyrans **45** and **47**, respectively (Scheme 16).

Other remarkable examples were developed by Wang and co-workers using (*E*)-3-benzylidene-chroman-4-one **48**[55] and 1,2-diones **50**[56] as key substrates to access the target compounds, pyranochromenes **49** and 3,4-dihydro-2*H*-pyrans **52**, respectively (Scheme 17, a and b).

Based on the experimental results, the first process is believed to proceed through an enantioselective cascade Michael-oxa-Michael-tautomerization sequence (Scheme 17, a) and the second one, through an enantioselective cascade Michael-enolation-cyclization process (Scheme 17, b). Both catalysts **VII** seem to play a bifunctional role in the activation of the reagents. In the second case, the catalyst **VII** would activate simultaneously the 1,2-cyclohexadione **50** and the β,γ-unsaturated α-keto ester **51** *via* its amine and thiourea functional groups, respectively, as represented in Scheme 18. After formation of Michael adducts **53**, enolization and subsequent *oxa*-nucleophilic attack would complete the cyclization step. Finally, two possible diastereoisomers would be in equilibrium in the final adduct **52**.



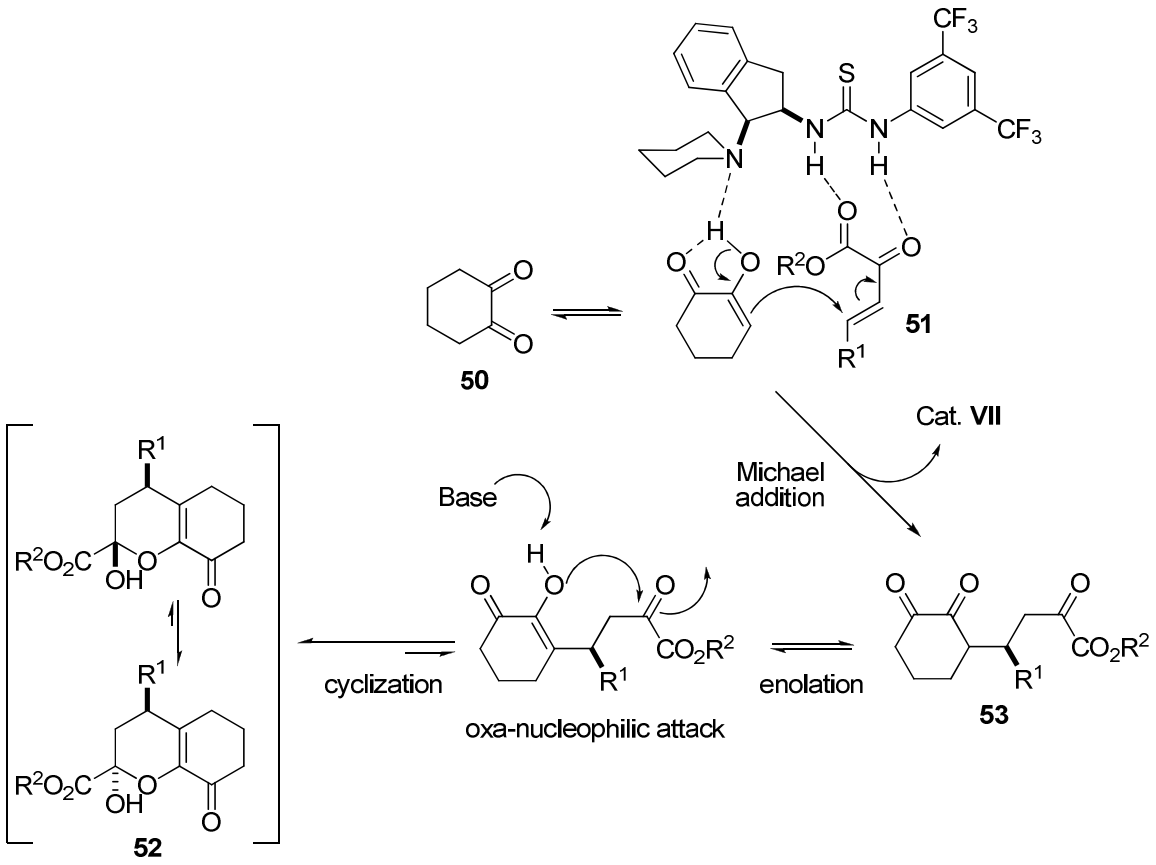
Scheme 16



Scheme 17

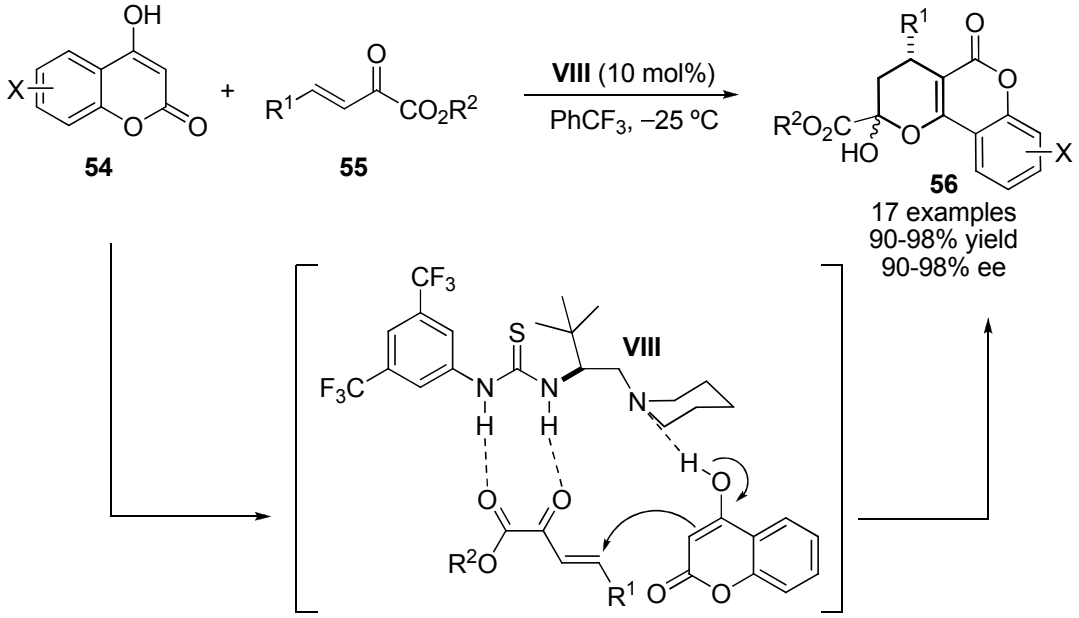
The coumarin structural core is present in a large number of natural products and biologically active molecules.[57] Many natural coumarin derivatives are precursors and synthetic intermediates in the construction of more complex structure and target compounds with interesting activities.[58] We have

considered these examples in this section because a pyran ring is generated in the course of the process,[36] since in all selected cases the authors use a coumarin derivative as starting material.



Scheme 18

In this field, Wang's group developed an efficient enantioselective synthesis of coumarin analogues with high yields (90-98%) and excellent enantioselectivities (90-98%) using a simple amine-thiourea **VIII** as bifunctional catalyst, which promotes the conjugated addition strategy (Scheme 19).[59]



Scheme 19

Zhao, Cao and co-workers also developed a similar approach using β,γ-unsaturated α-keto esters and a different thiourea catalyst **XI** with a low catalytic charge (5 mol%) (Figure 10).[60] Final chiral coumarin derivatives were synthesized in excellent yields (up to 99%) and excellent enantioselectivities (up to 96%) under very mild conditions (room temperature) within short reaction time (2 h).

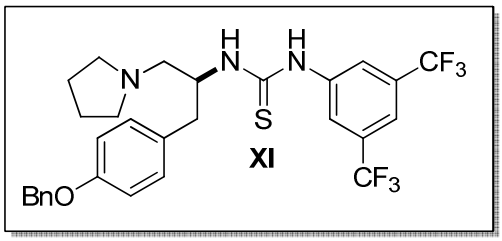
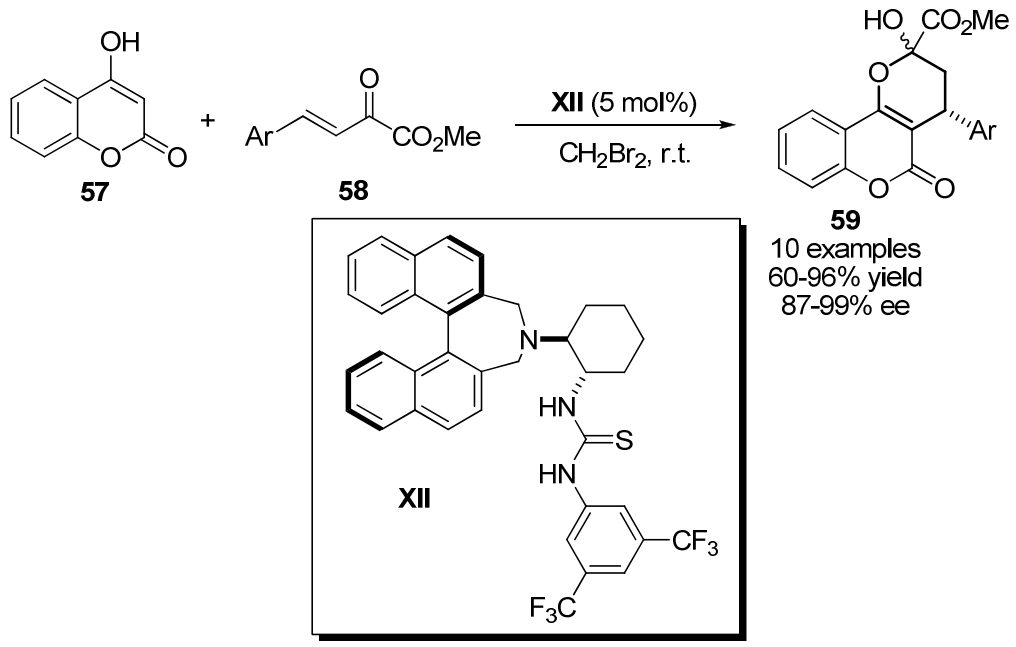


Figure 10

Kim and co-workers reported an appealing example of the use of thiourea catalyst **XII**, employing 4-hydroxycoumarin **57** and β,γ-unsaturated α-keto esters **58**, giving access to biologically valuable warfarin analogues **59** (Scheme 20).[61]



Scheme 20

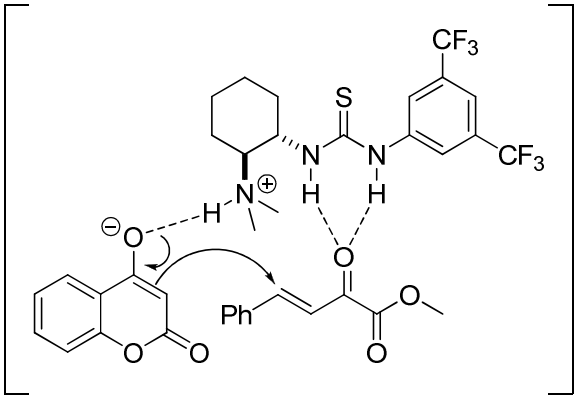


Figure 11

Final adducts **59** are obtained with good yields (60-96%) and high enantioselectivities (87-99%) under mild reaction conditions. Similar results were achieved by Yan's group using Takemoto's catalyst (**V**) and also a bifunctional mechanism is proposed to explain the dual role of the catalyst (Figure 11).[62]

3.4. Synthesis of tetrahydrofurans

The presence of tetrahydrofuran ring cores in natural products and biologically active agents,[63] such as fosamprenavir (pro-drug of the protease inhibitor and antiretroviral drug amprenavir[64]),[65] MK-287[66] and caribenolide I[67] (Figure 12), has promoted the development of numerous synthetic methods for their stereoselective preparation.[68] Among these methods, cycloetherification allows the obtainment of 2-substituted oxacyclic compounds in a straight way. Nevertheless, the enantioselective version of this reaction has not been intensively explored so far, and only few protocols have been developed. Some relevant examples catalized by thiourea are described below.

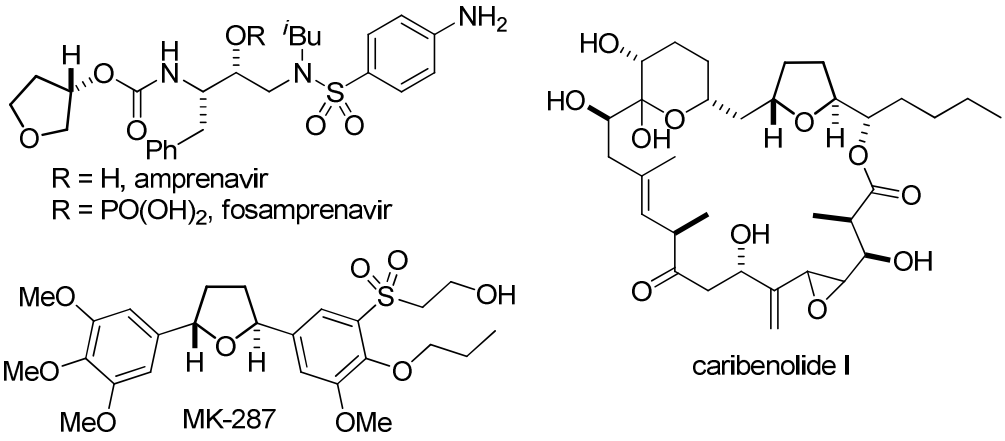


Figure 12

Matsubara's group envisioned the possibility of using a bifunctional thiourea for the construction of tetrahydrofuran rings following the dual mode of activation displayed in Figure 13.[69]

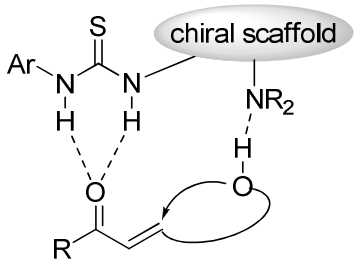
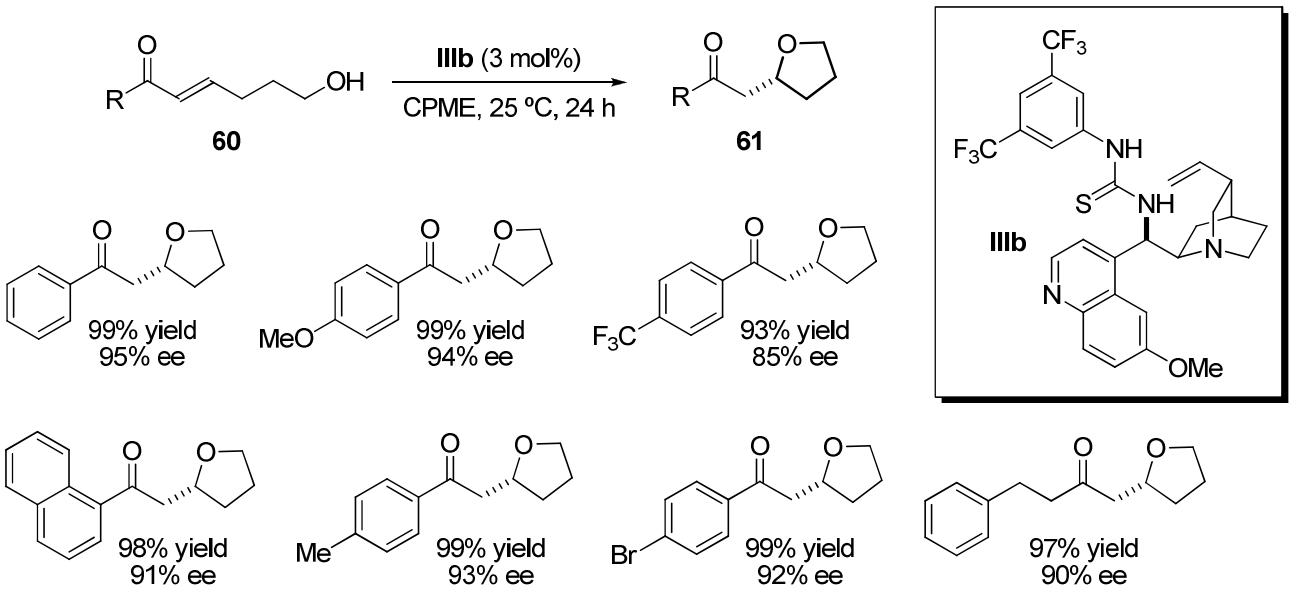


Figure 13

Based on this idea, they developed a highly enantioselective catalytic cycloetherification method for the synthesis of 2-substituted tetrahydrofurans using ε-hydroxy-α,β-unsaturated ketones **60** and thiourea cinchona derivative **IIIb**, as efficient catalyst (Scheme 21).

This method represents an interesting and straightforward synthetic approach for the preparation of new heterocyclic cores with a low catalyst loading and at room temperature.



Scheme 21

Additionally, Matsubara and co-workers have also applied the use of chiral (thio)ureas as catalysts for the efficient obtainment of a wide variety of heterocycles, such as 1,3-dioxolanes,[70] tetrahydro-2*H*-pyran,[71] 1,3-oxazolidines,[72] 2-oxazolidinone,[73] β-mercaptolactones[74] and chromanes[75] (Figure 14).

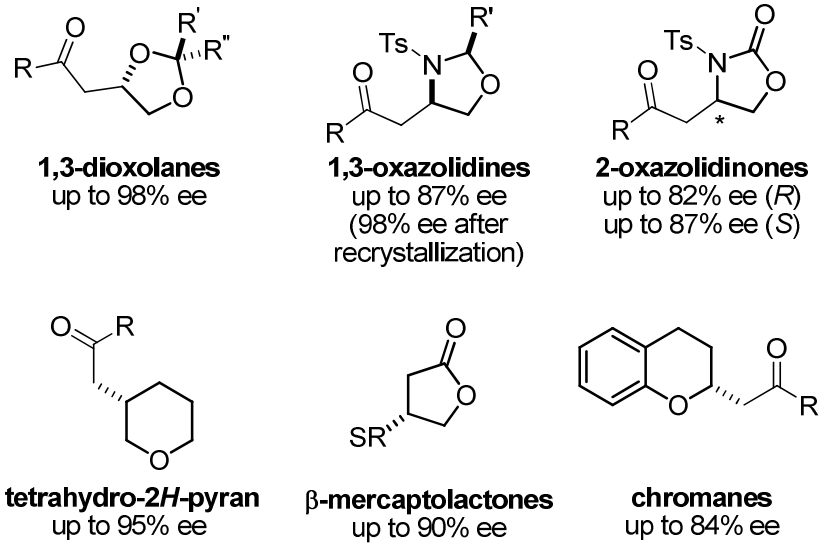


Figure 14

4. Synthesis of *S*-heterocyclic compounds

4.1. Synthesis of benzothiopyrans (or thiochromanes)

The presence of benzothio pyrans the structural core of more complex skeletons with biological activity, such as tertatolol,[76] 7-thia-DCK,[77] among others,[78] has encouraged the study of synthetic protocols, which allows their obtainment (Figure 15).[79]

Thus, Wang and co-workers have developed different works for the preparation of benzothiopyrans. The authors have employed for this purpose 2-mercaptobenzaldehydes **62** with maleimides **63** (Scheme 22),[80] or with α,β-unsaturated oxazolidinones **65** (Scheme 23),[81] and in both cases they envisioned the same bifunctional mode of action by the catalyst in a Michael-aldol cascade process.

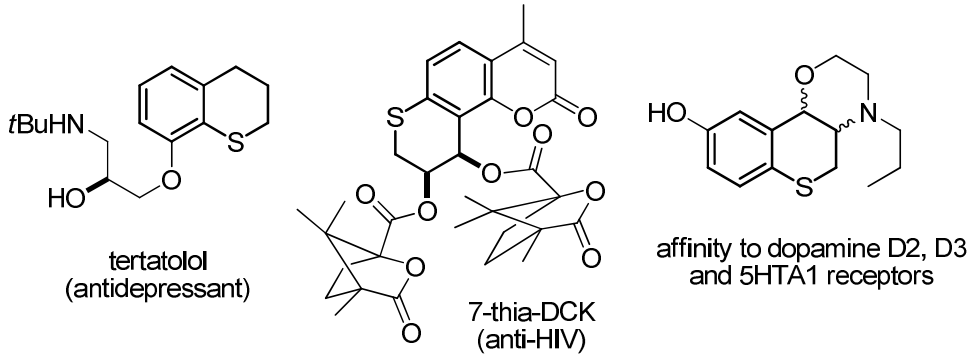
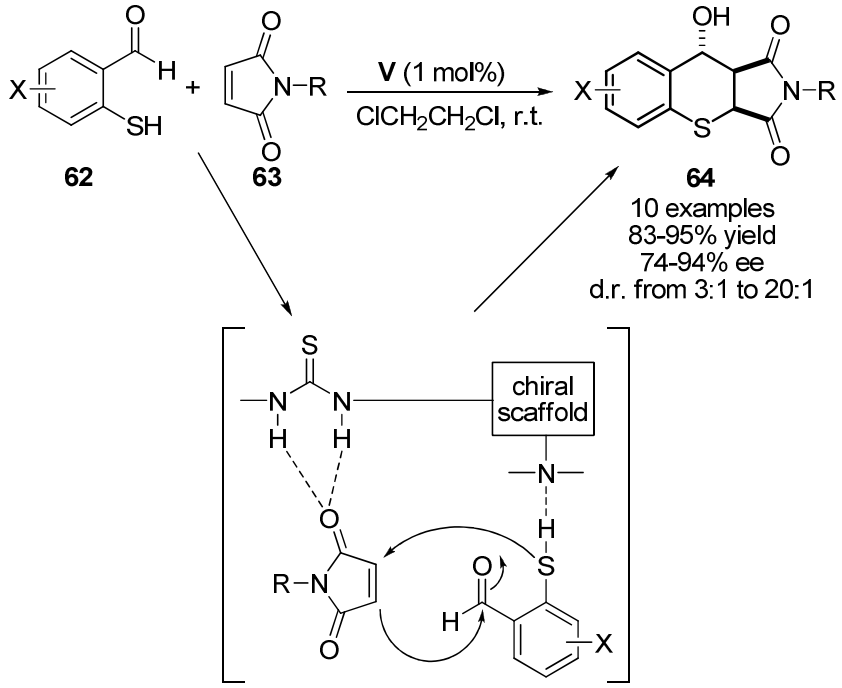
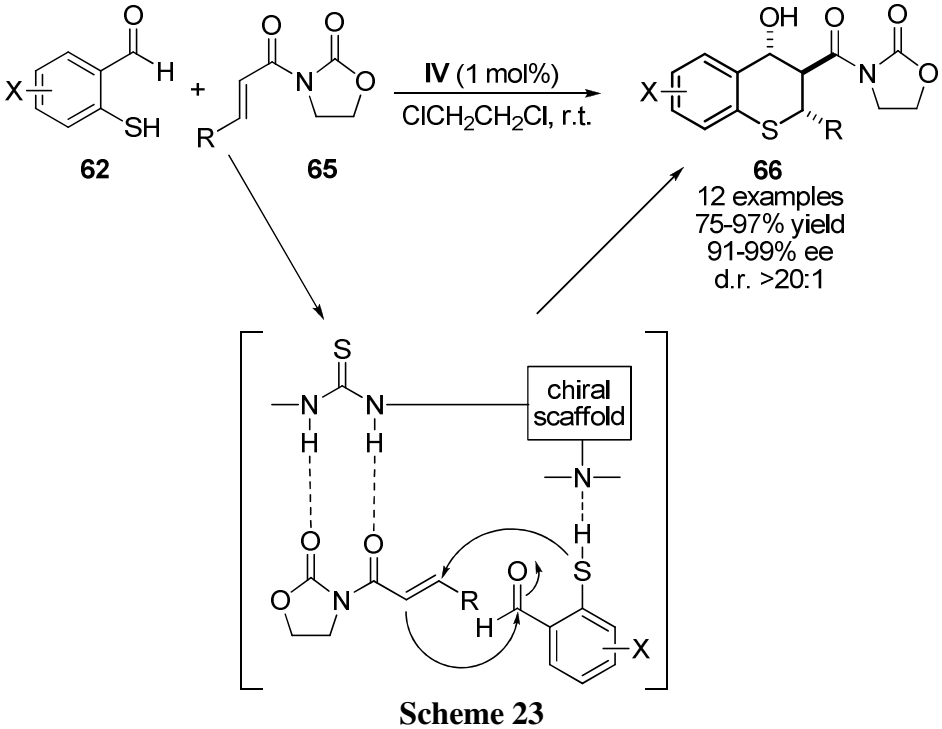


Figure 15

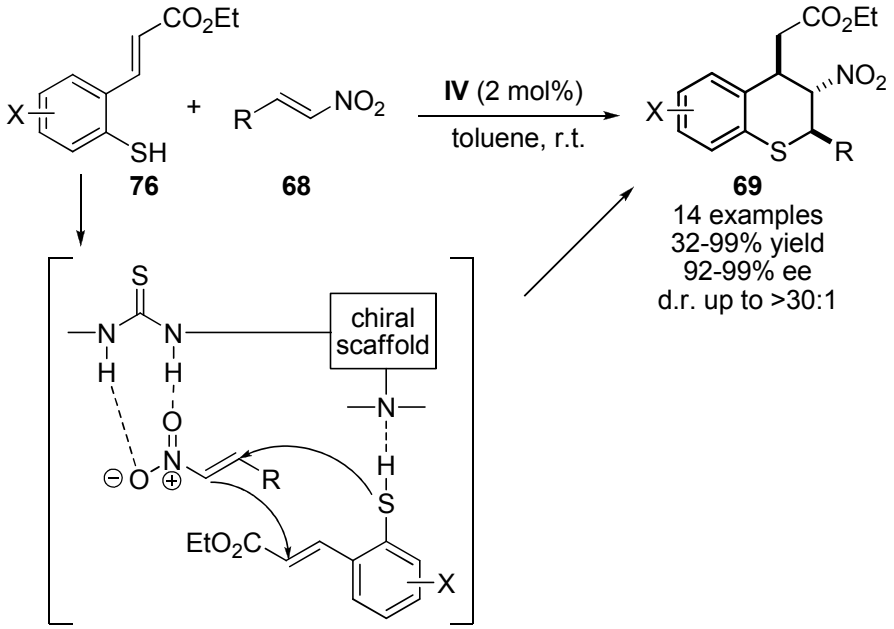


Scheme 22

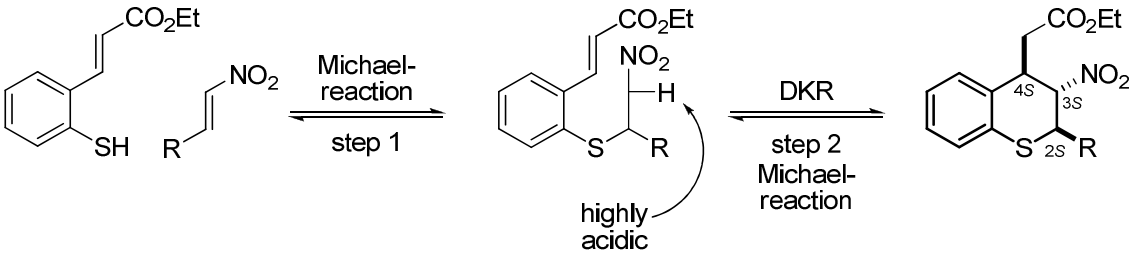


Scheme 23

More recently, the same group envisioned a Michael-Michael cascade reaction to obtain enantio-enriched tiochromanes **69** through a dynamic kinetic resolution (DKR), as a new mode of activation of this kind of organocatalysts (Scheme 24).[82] To explain the high enantioselection, the authors proposed an alternative pathway because low enantioselectivity was observed when they performed the reaction between thiophenol and *trans*-β-nitrostyrene under the same reaction conditions. In this case, based on the experimental results, they proposed a DKR-mediated Michael–retro-Michael–Michael–Michael cascade pathway, as represented in Scheme 25.

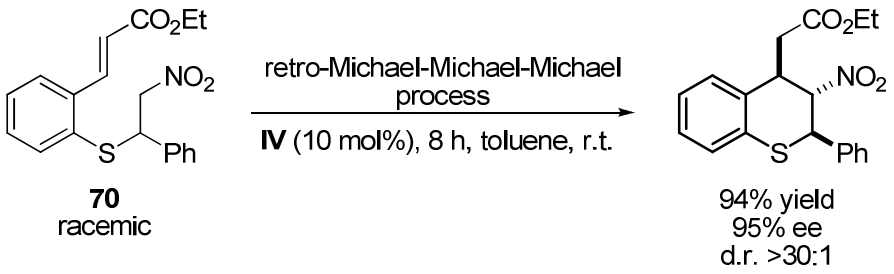


Scheme 24



Scheme 25

This interesting hypothesis was confirmed carrying out the reaction above described but starting from racemic compound **70** (Scheme 26).



Scheme 26

5. Conclusions

Organocatalysis is a research area in expansion, and (thio)urea organocatalysts in particular, have been intensively investigated in the last years. Some key (thio)urea-catalyzed synthesis of heterocyclic compounds have been disclosed and commented in this report. All these examples, together with many other interesting cases that have not been shown here, have strongly contributed to the development of Heterocyclic Chemistry. It is remarkable the importance of bifunctional thioureas as efficient catalysts in numerous processes of the abovementioned ones, since the dual role played by these molecules seems to be crucial for their success.[83] The better knowledge about the mode of action of the (thio)ureas and the design of new molecules of this type will necessarily continue contributing in the near future to Heterocyclic Chemistry by the development of new efficient organocatalytic methods, which will allow the obtainment of many others and more complex heterocyclic structural cores.

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