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Review

Enantioselective Organocatalyzed Synthesis of 2-Amino-3-cyano-4*H*-chromene Derivatives

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Abstract: The structural motif that results from the fusion of a benzene ring to a heterocyclic pyran ring, known as chromene, is broadly found in nature and it has been reported to be associated with a wide range of biological activity. Moreover, asymmetric organocatalysis is a discipline in expansion that is already recognized as a well-established tool for obtaining enantiomerically enriched compounds. This review covers the particular case of the asymmetric synthesis of 2-amino-3-cyano-4*H*-chromenes using organocatalysis. Herein, we show the most illustrative examples of the methods developed by diverse research groups, following a classification based on these five different approaches: (1) addition of naphthol compounds to substituted α,α-dicyanoolefins; (2) addition of malononitrile to substituted *o*-vinylphenols; (3) addition of malononitrile to *N*-protected *o*-iminophenols; (4) Michael addition of nucleophiles to 2-iminochromene derivatives; and (5) organocatalyzed formal [4+2] cycloaddition reaction. In most cases, chiral thioureas have been found to be effective catalysts to promote the synthetic processes, and generally a bifunctional mode of action has been envisioned for them. In addition, squaramides and cinchona derivatives have been occasionally used as suitable catalysts for the substrates activation.

Keywords: chromene; benzopyran; 2-amino-3-cyano-4*H*-chromene; malononitrile; enantioselective; organocatalysis; synthesis; thiourea; squaramide; cinchona derivatives

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1. Introduction

Chromene analogues can be frequently found as structural core motif in a great number of natural and synthetic compounds exhibiting interesting medicinal and pharmacological properties [1,2]. Among these, anticancer activity [3] and their potential use as cognitive enhancers for the treatment of schizophrenia, myoclonus and different neurodegenerative diseases [4,5] are the most significant ones. Among the different types of chromenes, we want to focus on 2-amino-3-cyano-4*H*-chromene scaffolds. They have received increasing attention in the last years due to the interesting biological activities that this specific family of heterocycles exhibits, such as antimicrobial [6–8] and antioxidant [9] activities as well as pro-apoptotic activity [10–15], conferring potential use as promising anticancer therapeutic drugs among others applications (Figure 1).

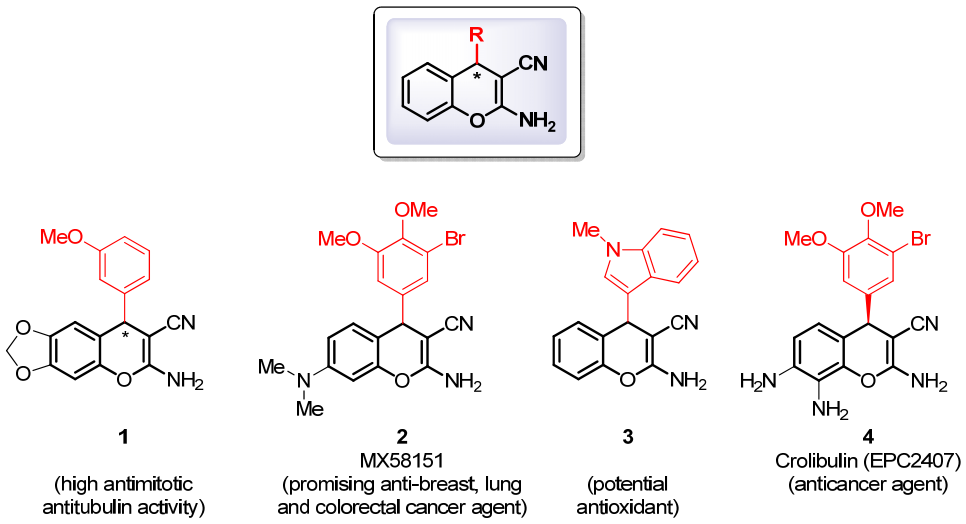
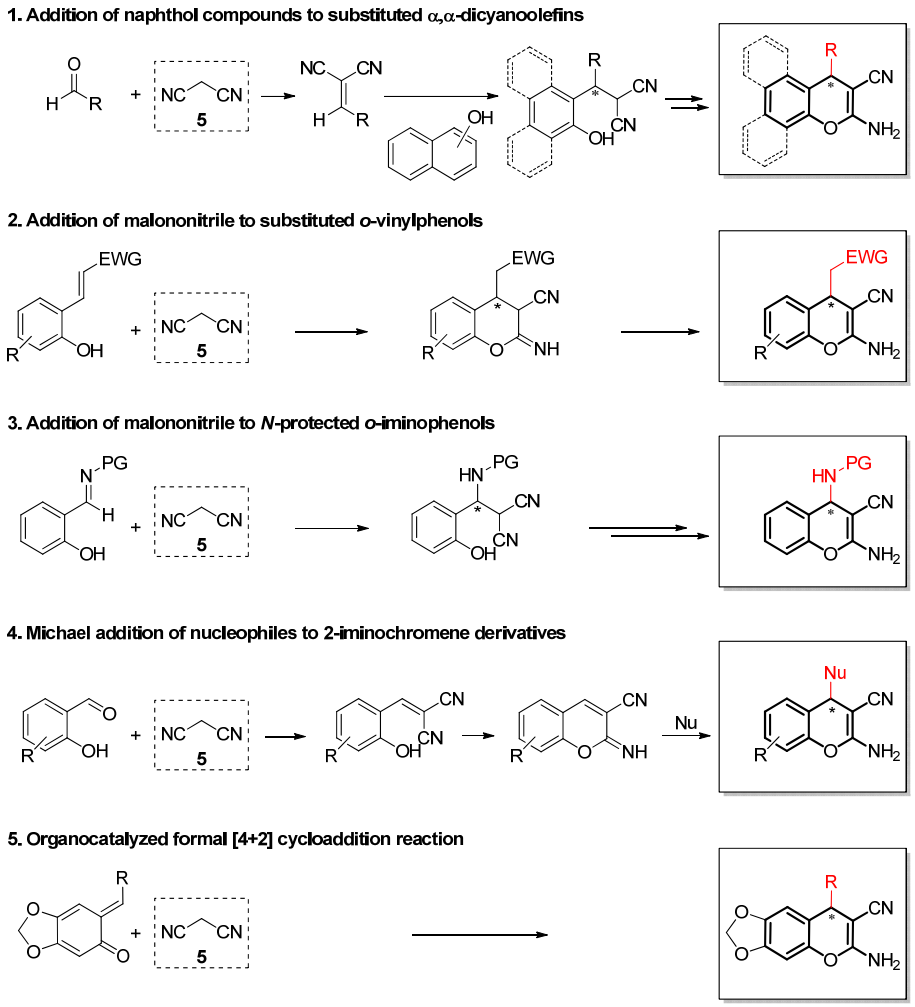


Figure 1. Biologically active 2-amino-3-cyano-4*H*-chromene scaffolds: **1** [16], **2** [10,13], **3** [9] and **4** [17].

It is noteworthy that distinct enantiomers often show different biological activity, such as one enantiomer of the anticancer agent **1**, which is about 50 times more active than the other enantiomer [16]. All these aspects make necessary the development of new chemical protocols for the obtainment of such an interesting class of compounds in an enantioselective manner to further explore the correlation enantioselectivity-pharmacological activity.

In the last years, organocatalysis has appeared as an efficient alternative tool to yield enantiopure compounds, through different kind of activation [18–21]. In this respect, although numerous organocatalyzed racemic syntheses of this family of compounds can be found in the literature [22–33], only scarce examples following an enantioselective approach have been reported to date [34].

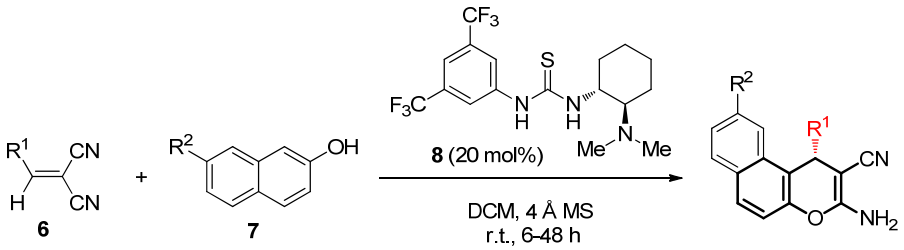
In this review, an overview of enantioselective organocatalyzed procedures for the synthesis of chiral 2-amino-3-cyano-4*H*-chromene derivatives is provided. In the center of the synthetic paradigm, malononitrile (**5**) usually appears as the key piece in these strategies. The different synthetic approaches used for the preparation of these potentially pharmacological compounds can be classified into the five strategies depicted in Scheme 1 and, consequently, this work has been divided into the same sections where the most significant examples are covered.



Scheme 1. Synthetic strategies for the building of 2-amino-3-cyano-4*H*-chromene skeleton.

2. Addition of Naphthol Compounds to Substituted α,α-dicyanoolefins

The first enantioselective organocatalytic example for the synthesis of 2-amino-3-cyano-4*H*-cromene derivatives was reported by Yang and Zhao's group in 2008 (Scheme 2) [35]. In this work, catalyzed addition/intramolecular cyclization reaction between different substituted α,α-dicyanoolefins **6** with β-naphthol **7** in the presence of efficient bifunctional thiourea catalyst **8**, led to adducts **9** with good yields and moderate to high enantioselectivities (up to 99% yield and up to 90% ee).

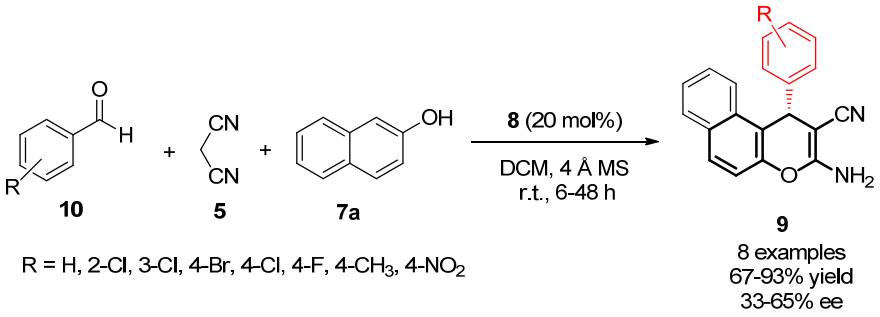


R^1 = C_6H_5, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-ClC_6H_4, 3-FC_6H_4, 3-$CH_3OC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 2-Furyl, *n*-Hexyl
R^2 = H, CH_3O

15 examples
19-99% yield
56-90% ee

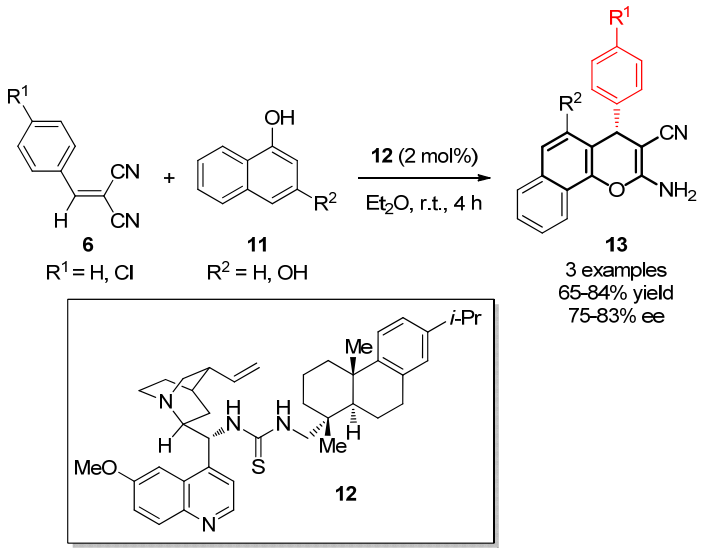
Scheme 2. Asymmetric synthesis of benzochromene derivatives **9**.

Based on the idea that compounds **6** are synthetized via Knoevenagel condensation, the authors also explored the multicomponent approach between various substituted benzaldehyde derivatives **10**, malononitrile (**5**) and β-naphtol (**7a**). Under the same optimized conditions, the corresponding 4-aryl derivatives **9** were obtained with moderate to high yields although with lower enantiomeric excesses (up to 93% yield and up to 65% ee) (Scheme 3).



Scheme 3. Multicomponent enantioselective synthesis of benzochromene derivatives **9**.

In 2012, a new enantioselective synthesis of 4-aryl derivatives **13** was reported by Wang's group [36]. In this case, bencylidenemalonitrile derivatives **6** reacted with α-naphthols **11** to afford the corresponding product **13** with moderate to high yields and high selectivities after short reaction times (up to 84% yield and up to 83% ee) (Scheme 4). This process works through a catalyzed tandem Michael addition/intramolecular cyclization reaction in the presence of a catalytic amount of abietic acid-cinchona-thiourea compound **12** in diethyl ether and at room temperature.

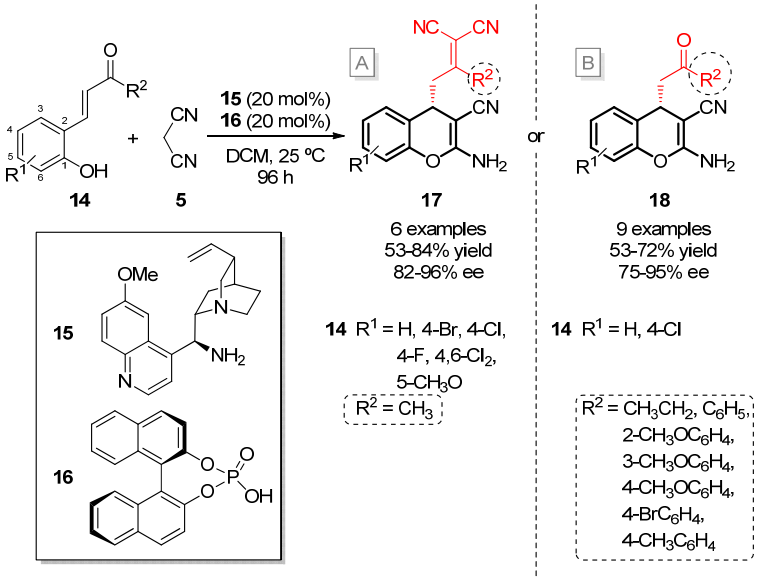


Scheme 4. Organocatalytic asymmetric synthesis of 4-aryl derivatives **13**.

3. Addition of Malononitrile to Substituted *o*-vinylphenols

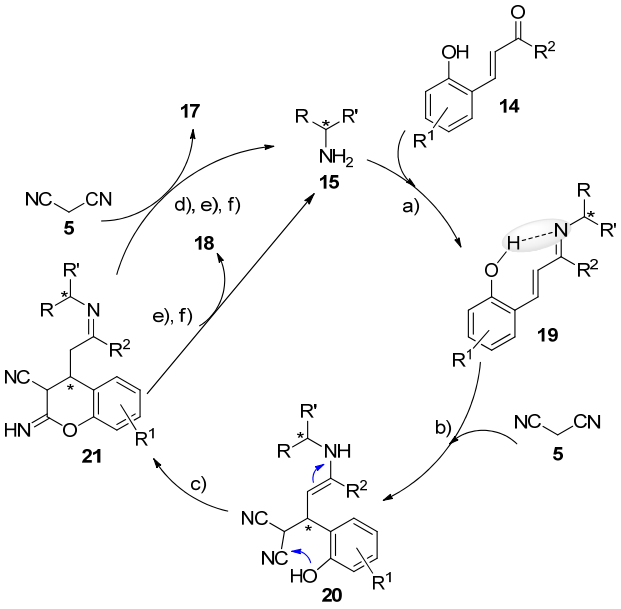
Xie and coworkers reported in 2009 the first asymmetric synthesis of highly functionalized 4-ethylidenemalononitrile derivatives **17** from α,β-unsaturated ketones **14** ($R^2 = CH_3$) and malononitrile (**5**), employing an equimolecular mixture of 9-amino-9-deoxy-epiquinine (**15**) as catalyst, and (*R*)-1,1′-binaphth-2,2′-diyl hydrogen phosphate (**16**) as additive (Scheme 5, A) [37]. Products **17** were

reached with moderate to high yields and high enantioselectivities (up to 84% yield and up to 96% ee). The same group employed diverse bulkier alkyl/aryl enones **14** under the same reaction conditions leading to 4-β-ketoalkyl/aryl derivatives **18**, with moderate yields and from moderate to high enantioselectivities (up to 72% yield and up to 95% ee) (Scheme 5, B).



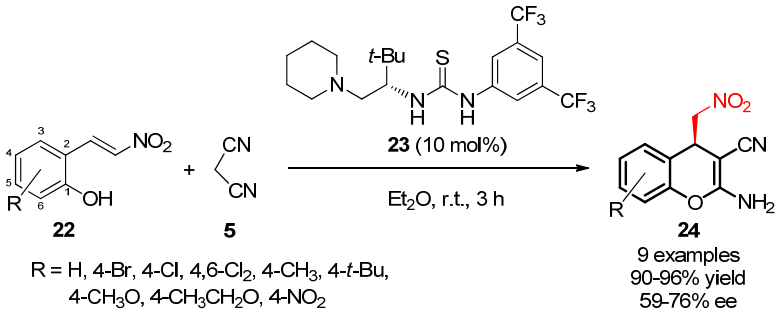
Scheme 5. Tandem synthesis of chromene derivatives **17** and **18**.

Remarkably, in the route to give **17**, a second molecule of malononitrile (**5**) is added in the carbonyl moiety of final expected adducts **18**. To explain the formation of the observed products, the authors propose an addition/intramolecular cyclization mechanism, followed by a final Knoevenagel condensation in case of products **17**, catalyzed via iminium activation by condensation of enone systems **14** with the chiral primary amine **15**, in which the additive **16** might activate the formed imine derivative **19** (Scheme 6).

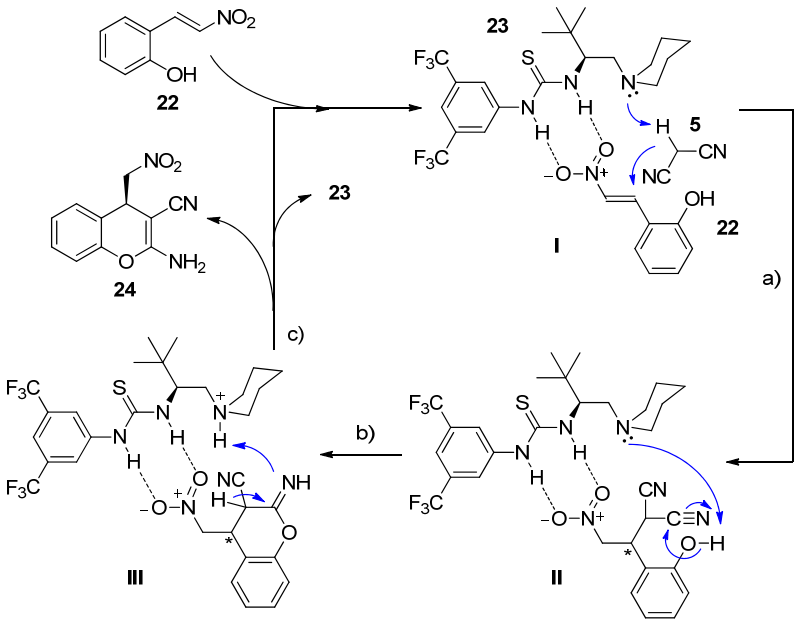


Scheme 6. Proposed mechanism for the enantioselective synthesis of compounds **17** and **18**.

The enantioselective synthesis of highly substituted 4-nitromethyl derivatives **24** was developed for the first time by Wang's group in 2011 [38]. In the presence of thiourea-based catalyst **23**, different (*E*)-2-(2-nitrovinyl)phenol compounds **22** reacted with malononitrile (**5**) in diethyl ether at room temperature to give the corresponding product **24** with moderate enantiomeric excesses and excellent yields after short reaction times (up to 96% yield and up to 76% ee) (Scheme 7). In the proposed catalytic cycle, a concomitant coordination of the malononitrile (**5**) activated by the amino group of thiourea **23** and the nitroalkene **22** anchored to the catalyst via hydrogen bonding (Scheme 8, **I**), is invoked to firstly give a stereo-controlled Michael adduct (Scheme 8, **II**). A subsequent cascade starting by the attack of alkoxide to the cyano group to form a cyclic intermediate (Scheme 8, **III**) and final tautomerization afforded the desired product **24** with the release of thiourea catalyst **23**.

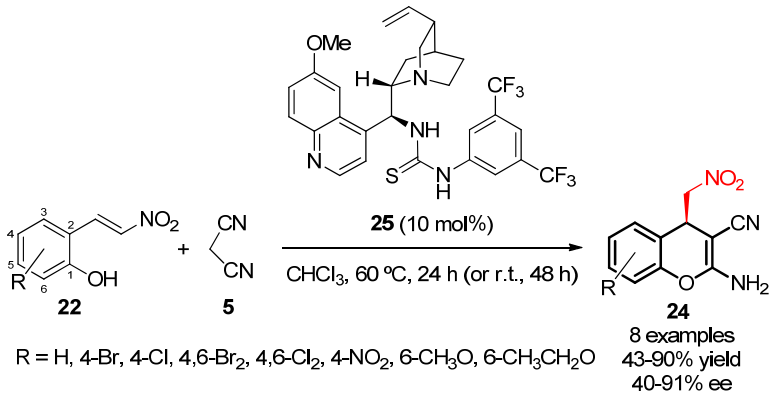


Scheme 7. Asymmetric synthesis of chromenes **24**.



Scheme 8. Proposed mechanism in the asymmetric synthesis of adducts **24**, catalyzed by thiourea **23**.

Later, Du and coworkers reported a new enantioselective organocatalytic version of this reaction, using the cinchona-thiourea catalyst **25** (Scheme 9) [39]. Final 4-nitromethyl chromene **24** were obtained with slightly better results of selectivity in some cases and lower yields after longer times even when the reaction mixture was heated at 60 °C (up to 90% yield and up to 91% ee).



Scheme 9. Enantioselective synthesis of 4-nitroalkyl derivatives **24**.

In order to explain the formation of the final products, a bifunctional mode of activation is hypothesized by the authors, where both reagents would be activated and coordinated to the catalyst through hydrogen bonds, as depicted in Figure 2. The course of the reaction would be identical to the abovementioned mechanism described in Scheme 8.

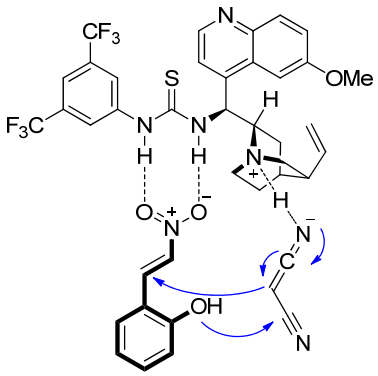
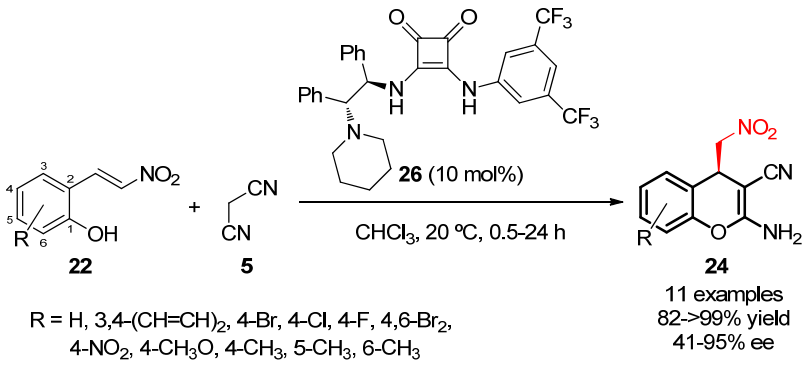


Figure 2. Bifunctional mode of activation for the tandem Michael addition-cyclization catalyzed by chiral thiourea **25**.

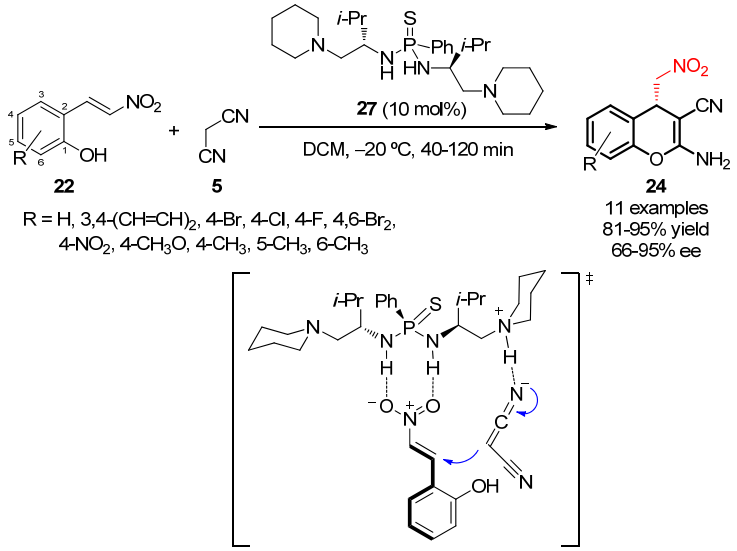
More recently, Wang, Zhou and coworkers disclosed a new catalytic strategy to reach the same products **24** using, in this case, the chiral bifunctional squaramide **26** via tandem Michael addition/cyclization-tautomerization reaction [40]. The corresponding products **24** were isolated with high yields and moderate to high enantioselectivies after short times (up to >99% yield and up to 95% ee) (Scheme 10). In this case, the authors do not propose any mechanistic hypothesis.



Scheme 10. Squaramide catalyzed asymmetric synthesis of 4-nitroalkyl derivatives **24**.

The use of functionalized nitroolefins bearing both electron-withdrawing and electron-donating substituents was possible in this transformation.

The same research group reported the last example of this catalytic strategy using a chiral hydrogen-bond based organocatalyst, thiophosphonodiamide **27** (Scheme 11) [41]. Chromenes **24** were obtained at low temperatures, with high yields and moderate to high selectivities and really short reaction time (up to 95% yield and up to 95% ee).



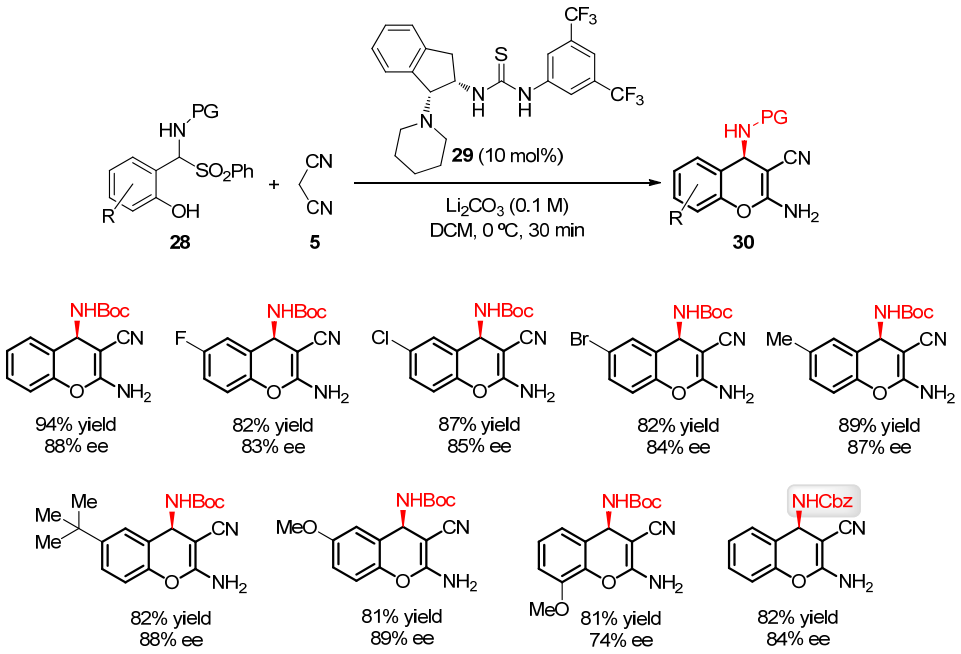
Scheme 11. Asymmetric synthesis of 4-nitroalkyl derivatives **24** employing organocatalyst **27**.

A ternary complex consisting of the deprotonated malononitrile, the nitroalkene and thiophosphonodiamide **27** was envisioned as plausible transition state to explain the enantioselectivity of the process, where both reagents are simultaneously anchored to the catalyst and activated via hydrogen bond interactions (Scheme 11).

4. Addition of Malononitrile to *N*-protected *o*-iminophenols

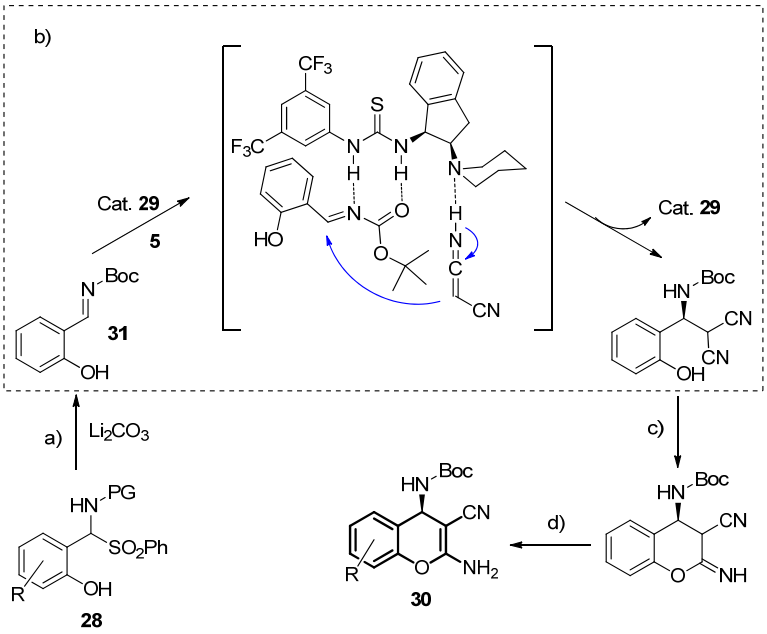
Wang's group reported the first reaction between *N*-Boc α-amido sulfones **28** and malononitrile (**5**) using the indane amine-thiourea derivative **29** as catalyst and lithium carbonate as base to *in situ* generate an imine intermediate [38,42]. The strategy led to the formation of the corresponding *N*-protected

4-amine-chromene derivative **30** with high yields and enantioselectivities after short reaction times (up to 94% yield and up to 89% ee) (Scheme 12).



Scheme 12. Catalyzed enantioselective synthesis of compounds **30**.

A reasonable mechanism through enantioselective Mannich-intramolecular ring cyclization-tautomerization cascade sequence is proposed to explain the final products. The catalyst is believed to act in a bifunctional way activating both reagents via hydrogen bondings (Scheme 13).

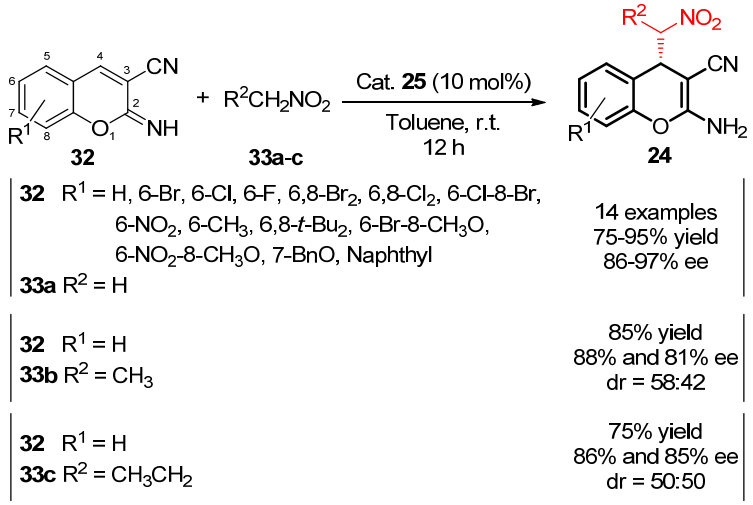


a) elimination step; b) enantioselective organocatalyzed Mannich reaction; c) intramolecular oxa-nucleophilic addition; d) tautomerization step.

Scheme 13. Mechanism for the asymmetric synthesis of compound **30**.

5. Michael Addition of Nucleophiles to 2-iminochromene Derivatives

In 2012, Jiang, Wang and coworkers [43] obtained excellent results of reactivity and selectivity employing a new enantioselective organocatalytic approach for the synthesis of 4-nitroalkyl derivatives **24**, via catalyzed conjugate addition of nitroalkanes **33a–c** to 2-iminochromene compounds **32** (Scheme 14). A bifunctional-type catalytic mechanism is proposed, where 2-iminochromene **32** and the tautomeric form of corresponding nitroalkane **33** are activated via hydrogen bonding, and thus, affording a stereo-controlled Michael addition (Figure 3).



Scheme 14. Enantioselective conjugate addition of nitroalkanes **33** to electrophilic 2-iminochromenes **32**.

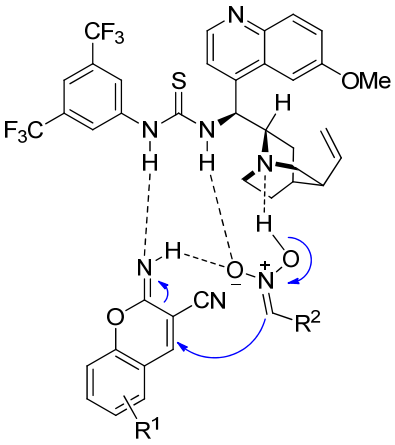
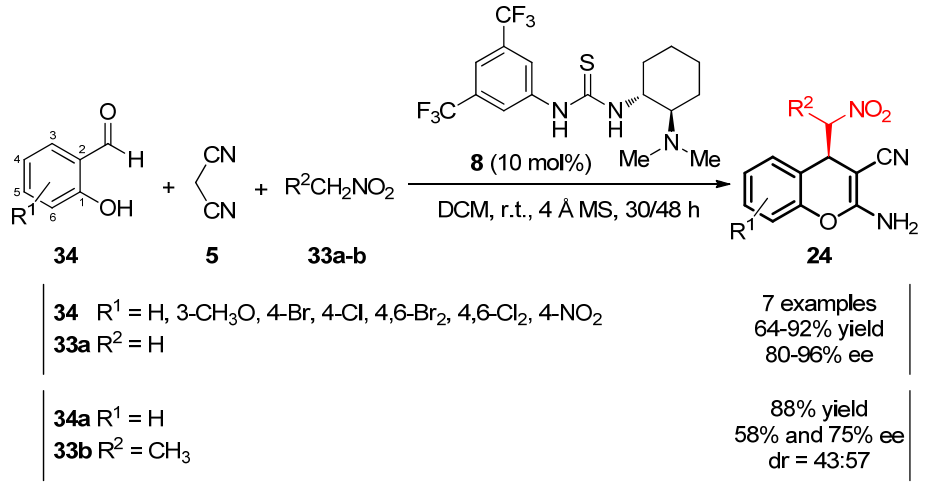


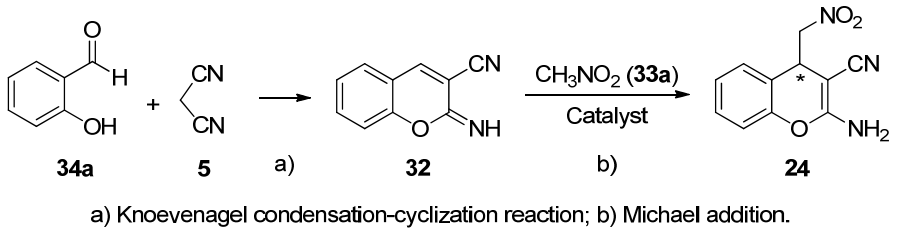
Figure 3. Proposed activation mode for the addition of nitroalkanes **33** to 2-iminochromenes **32** catalyzed by chiral thiourea **25**.

The multicomponent version of the abovementioned reaction was previously reported by Yang and Liu's group [44]. In the presence of chiral tertiary amine-thiourea **8**, different salicylaldehyde derivatives **34** reacted with malononitrile (**5**) and nitroalkanes **33a**,**b** to provide the 4-nitroalkyl product **24** with moderate to excellent yields and selectivities under mild conditions (up to 92% yield and up to 96% ee) (Scheme 15).



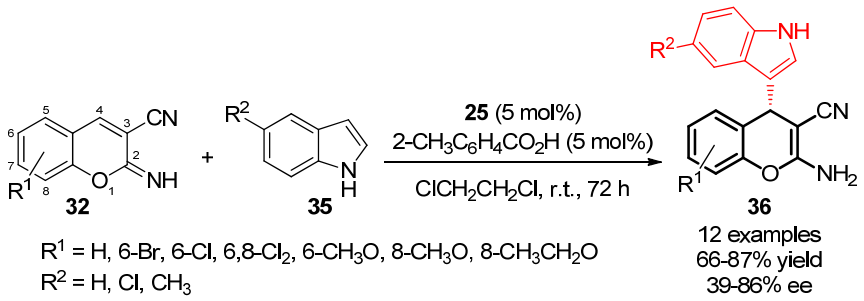
Scheme 15. Multicomponent enantioselective synthesis of 4-nitroalkyl derivatives **24**.

On the base of the experimental results, a plausible reaction mechanism involving a tandem Knoevenagel condensation-cyclization reaction followed by a stereo-controlled conjugate addition is proposed in order to explain this multicomponent approach (Scheme 16).



Scheme 16. Multicomponent mechanistic proposal to obtain compound **24**.

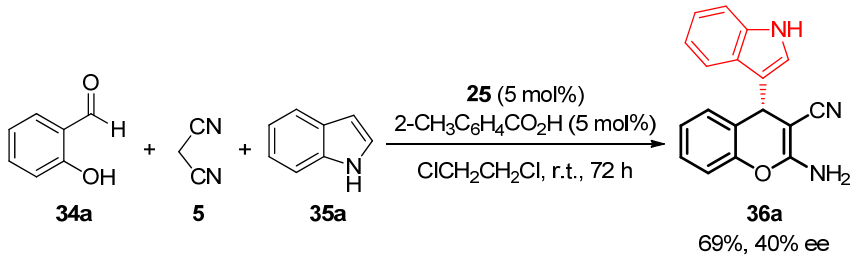
Other efficient example of this approach is the enantioselective organocatalytic synthesis of potentially active 4-(indol-3-yl) derivatives **36** [45]. In the presence of an equimolecular mixture of the cinchona-thiourea-based organocatalyst **25** and 2-methylbenzoic acid as additive, indole compounds **35** reacted with 2-iminochromene derivatives **32** via Friedel-Crafts alkylation to give the product **36** under mild conditions with good yields and moderate enantioselectivities (up to 87% yield and up to 86% ee) (Scheme 17).



Scheme 17. Enantioselective synthesis of 4-(indol-3-yl) derivatives **36**.

The same authors also reported an example of the multicomponent version of this reaction involving salicylaldehyde (**34a**), malononitrile (**5**) and indole (**35a**), under the same reaction conditions, to provide

the corresponding product **36a**, although with lower enantioselectivity (69% yield, 40% ee *vs.* 72% yield, 62% ee) (Scheme 18).



Scheme 18. Enantioselective multicomponent approach to synthesize compound **36a**.

A similar bifunctional mode of activation as the one showed in Figure 3 is envisioned in this strategy for the same catalyst, where cinchona derivative **25** would activate the indole and the 2-iminochromene via hydrogen bonding affording the stereo-controlled addition (Figure 4). The authors do not explain the role of the 2-methylbenzoic acid employed as cocatalyst.

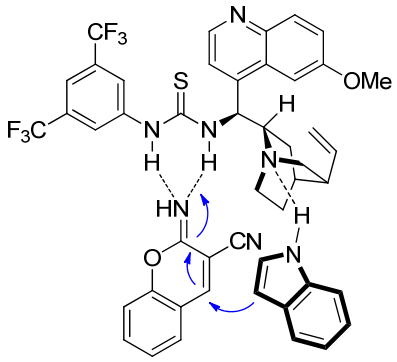
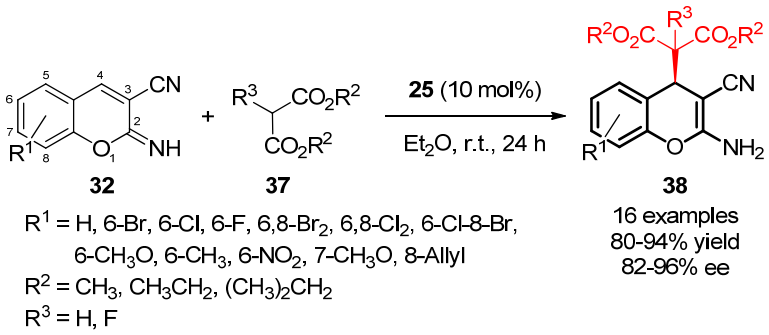


Figure 4. Activation hypothesis of indole and 2-iminochromenes by catalyst **25**.

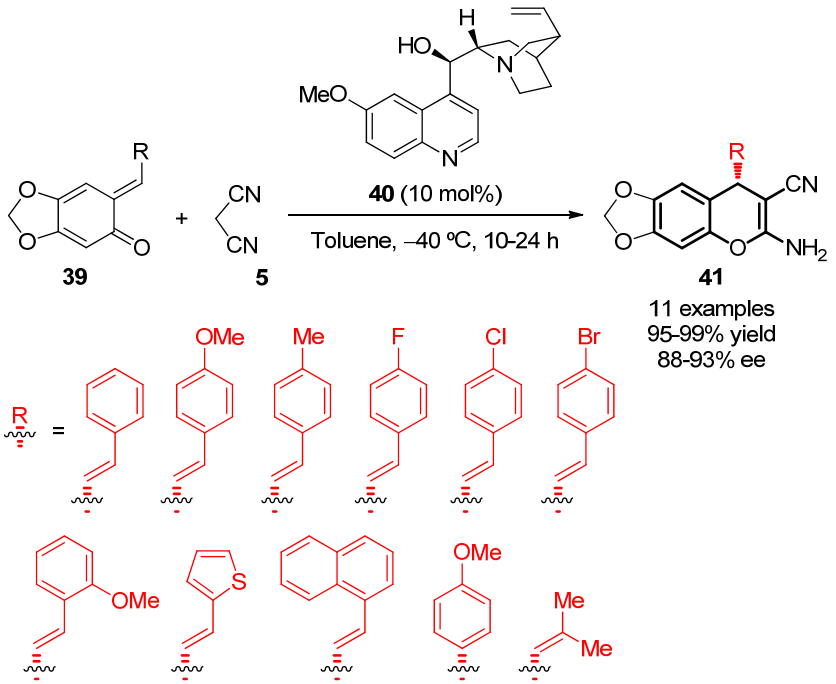
More recently, the enantioselective organocatalytic synthesis of 4-dialkylmalonate derivatives **38** via conjugate addition promoted by multi-hydrogen-bond cooperation was reported by Wang's group [46]. In the presence of a catalytic amount of cinchona-thiourea **25**, 2-iminochromene compounds **32** reacted with dialkylmalonate **37**, under mild conditions, to give the product **38** with high to excellent yields and high enantiomeric excesses (up to 94% yield and up to 96% ee) (Scheme 19).



Scheme 19. Enantioselective synthesis of 4-dialkylmalonate derivatives **38**.

6. Organocatalyzed Formal [4+2] Cycloaddition Reaction

Han and coworkers disclosed a new approach based on the enantioselective cycloannulation of ortho-quinone methides **39** with malononitrile (**5**) in the presence of quinine (**40**), to give the corresponding dioxolane-fused 4-vinyl/aryl derivatives **41** with excellent results of reactivity and selectivity (up to 99% yield and up to 93% ee) (Scheme 20) [47].



Scheme 20. Enantioselective [4+2] cycloaddition affords dioxolane-fused 4-vinyl/aryl derivatives **41**.

The authors envisioned that these two reagents, as 2π partners or dipoles, would act through a formal [4+2] cycloaddition with a bifunctional organocatalyst, as previously reported by other authors [48].

7. Conclusions

2-Amino-4*H*-chromene-3-carbonitrile is a structural core motif present in a great number of natural and synthetic compounds exhibiting interesting medicinal and pharmacological properties. In this review, we have disclosed the most significant examples concerning the organocatalytic enantioselective synthesis of these scaffolds through five different approaches: (1) addition of naphthol compounds to substituted α,α-dicyanoolefins; (2) addition of malononitrile to substituted *o*-vinylphenols; (3) addition of malononitrile to *N*-protected *o*-iminophenols; (4) Michael addition of nucleophiles to 2-iminochromene derivatives; and (5) organocatalyzed formal [4+2] cycloaddition reaction. To successfully perform these protocols, bifunctional thiourea organocatalysts [49,50] have been found to be crucial to efficiently promote the most of the abovementioned reactions, where the dual role played by these molecules has been found pivotal for the reactivity and enantioselective induction in all cases. These synthetic strategies are remarkable because they lead to enantiomerically enriched 2-amino-3-cyano-4*H*-chromene scaffolds, which have received increasing attention in the last years due to their interesting biological activities. However,

because of its importance, more investigation focused on this key scaffold is still needed, and we expect the development of more efficient and complex enantioselective examples in the future.

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Author Contributions

All authors reviewed the concerning literature, wrote the paper, read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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