Asymmetric organocatalyzed synthesis of coumarin derivatives

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Introduction

Coumarins are important naturally occurring plant constituents and display a wide range of pharmacological and biological activities, such as anticancer [1], antibacterial [2], and antifungal [3]. Moreover, coumarin derivatives have shown activity against neglected diseases as leishmaniasis [4], tuberculosis [5,6] and Chagas’ disease [7]. Examples of coumarin-derived drugs are: methoxsalen, used to treat psoriasis, eczema, vitiligo, and some cutaneous lymphomas; warfarin, an anticoagulant, used to treat blood clots such as deep vein thrombosis and pulmonary embolism, and to prevent stroke; and tioclomarol, also an anticoagulant, that is a long-acting vitamin K antagonist (Figure 1) [8].
This scaffold has also been reported as anti-Alzheimer’s disease [9], such as the natural product decursinol, isolated from Angelica gigas [10]. In this sense, our research group has synthesized and evaluated a library of coumarin derivatives as acetylcholinesterase inhibitors [11-13], being LSPN223 the most potent compound (Figure 2).

Furthermore, coumarin derivatives have been used as fluorescent probes, laser dyes, fluorescent chemosensors, light absorbers for solar cells, optical brighteners, and organic light emitting diodes (OLEDs) [14,15].

From a synthetic perspective, coumarin derivatives have received much attention due to their pivotal role in organic synthesis [16-18]. The development of efficient synthetic processes with eco-friendliness and sustainability that avoid the extensive use of toxic and hazardous reagents and solvents, as well as harsh reaction conditions, has become paramount in the field of organic synthesis in recent years [19]. In this sense, Molnar et al. published a review on green chemistry approaches to the synthesis of coumarin derivatives [20] and Chandrakar et al. reviewed the developments of multicomponent synthesis of biologically relevant coumarins in aqueous medium [21].

Catalysis is one of the fundamental pillars of green chemistry [22], and the transition-metal-catalyzed synthesis of coumarins has been reviewed by Sharma et al. [23]. More recently, Kanchana et al. published an account on the palladium-catalyzed cross-coupling reactions of coumarin derivatives [24].

Coumarins are a promising scaffold for design and development of bioactive agents, however it possesses a flat system [25]. One of the attractive benefits of introducing chirality in a drug candidate is that it leads to increased complexity to a specific target, i.e., it gives access to a greater diversity of compounds to be explored [26]. In this work, a compilation of the enantioselective synthesis of coumarin derivatives using asymmetric organocatalysis is presented, highlighting the proposed mechanism pathways for the formation of the stereogenic centers.

**Review**

A plethora of highly effective small-molecule organocatalysts have enriched the field of organic synthesis [27], including chiral proline derivatives, N-heterocyclic carbenes, chiral thioureas and Brønsted acids as well as phase-transfer catalysts (PTC), such as the quaternary ammonium salts derived from cinchona alkaloids [28]. Therefore, the asymmetric synthesis of coumarin derivatives is herein presented according to the activation mode, i.e., via covalent or non-covalent bonding. Furthermore, the use of bifunctional catalysts and multication are discussed as well.

**Catalysis via covalent bonding**

Organocatalysts made from chiral secondary amines have been widely used in the last years. According to Jørgensen, in general, the carbonyl functionalization employing amine catalysts can be separated in four different types [29]. When aldehydes are employed, both electrophilic and nucleophilic α-functionalizations are possible, whereas with the use of α,β-unsaturated aldehydes the β-position is functionalized with nucleophiles and the γ-position with electrophiles.

In this sense, Jørgensen and colleagues have developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds, including 4-hydroxycoumarins 1, to α,β-unsaturated enones 2 (Scheme 1). This versatile Michael reaction afforded (5)-warfarin (3a) and other Michael adducts 3 in high yields and good enantioemeric excess (ee), using (4S,5S)-4,5-diphenylimidazolidine-2-carboxylic acid (4) as catalyst [30].

Based on this pioneer work, our research group described an efficient, highly stereoselective, one-pot process comprising an organocatalytic conjugate addition of dimedone or 4-hydroxycoumarin 1 to α,β-unsaturated aldehydes 2 followed by an intramolecular isocyanide-based multicomponent reaction (IMCR) [31]. The enanthoneriched hemiacetals 5 were obtained using the Jørgensen catalyst 7 as previously described by Rueping et al. [32]. This approach enables the rapid assembly of complex natural product hybrids 6 including up to four different molecular fragments, such as hydroquinolinone, chromene, piperidine, peptide, lipid, and glycoside moieties (Scheme 2).

Bojanowski and co-workers developed a methodology to synthesize 3,4-dihydrocoumarins 10 through a decarboxylative and dearomatizative cascade reaction [33]. This reaction was carried out using coumarin-3-carboxylic acids 8, 2-alkyl-3-furfural derivatives 9 and diphenylprolinol trimethylsilyl ether 11 as catalyst, and it was possible to obtain 3,4-dihydrocoumarin derivatives with excellent yields, ee and dr (Scheme 3).
Scheme 1: Michael addition of 4-hydroxycoumarins 1 to \(\alpha,\beta\)-unsaturated enones 2.

Scheme 2: Organocatalytic conjugate addition of 4-hydroxycoumarin 1 to \(\alpha,\beta\)-unsaturated aldehydes 2 followed by an IMCR.
Using a completely different strategy from the above discussed, in which the coumarin core was the starting material in the asymmetric organocatalyzed reaction, the Enders group described the use of (S)-proline as catalyst in an intramolecular aldol reaction, enabling a new strategy to obtain coumarin natural products [34]. As for example, the total synthesis of (+)-smyrindiol (17), a linear dihydrofuranocoumarin isolated from the roots of Smyrniosis aucheri, was developed [35]. The 5-enolendo aldol key step of this synthesis was performed using 40 mol % of (S)-proline and the desired product 14 was obtained in good yield (71%), and high diastereo- and enantioselectivities (Scheme 4). Moreover, the natural product 17 was obtained in 15 steps with 6% overall yield.

**Scheme 3**: Synthesis of 3,4-dihydrocoumarin derivatives 10 through decarboxylative and dearomatizative cascade reaction.

**Scheme 4**: Total synthesis of (+)-smyrindiol (17).
Although chiral secondary amines have proved to be particularly useful catalysts, primary amines as organocatalysts in asymmetric synthesis have also played a significant role [36]. For instance, Kim et al. described the enantioselective Michael addition of 4-hydroxycoumarin (1) by the Re face of the enones 2 through a bifunctional modified binaphthyl organocatalyst 18 with primary amine [37]. The reaction occurs through the activation of the enone substrate by formation of an iminium ion intermediate and, in the presence of an acid additive, provides coumarin derivatives 3 with good to excellent yields and moderate to good enantiomeric excesses (Scheme 5). The authors highlighted that the employed organocatalyst 18 is an alternative to those of squaramide and thiourea commonly used with coumarins.

In 2013, Lee et al. reported the enantioselective Michael addition of ketones 20 to 3-aroylcoumarins 19 [38]. For this transformation, the authors used a cinchona alkaloid-derived primary amine catalyst 22 (Scheme 6a). The study was performed with cyclic and acyclic ketones 20 and various 3-aroylcoumarins 19 and the desired products 21 were obtained with good to excellent yields and enantiomeric excesses. Besides, the one-pot synthesis of coumarins followed by the Michael addition step was proven to be a good alternative, affording the desired product with excellent yield and ee. The applicability of the methodology was also demonstrated by a gram-scale experiment, affording the desired product 21a with excellent yield and ee (Scheme 6b).

Ren et al. reported an enantioselective reaction of cyclopent-2-enone-derived Morita–Baylis–Hillman (MBH) alcohols 24 with 4-hydroxycoumarins 1 catalyzed by a chiral primary amine derived from dihydrocinchonine 26 in combination with trifluoroacetic acid (TFA) as Brønsted acid [39]. The reaction provides pyranocoumarins 25 with three vicinal stereogenic centers in high regio-, diastereo- and enantioselectivities through a tandem allylic alkylation/intramolecular oxa-Michael addition (Scheme 7).
Scheme 6: Michael addition of ketones 20 to 3-arylcoumarins 19 using a cinchona alkaloid-derived primary amine catalyst 22.

A stereoselective one-pot procedure for the synthesis of five-membered annulated coumarins 28 was described by the group of Enders [40]. Using dual catalysis, with a cinchona primary amine derivative 22 and silver carbonate, a series of functionalized coumarin derivatives 28 were obtained in good yields (up to 91%) and good to excellent enantioselectivities (up to 99% ee) via a Michael addition/hydroalkoxylation reaction (Scheme 8). Interestingly, when alkyl substituted substrates 29 were employed, the corresponding six-membered annulated coumarins 30 were obtained.

The synthesis of (R)-warfarin (3a) was described by Herrera et al. for the first time using primary aromatic diamines 31 as organocatalysts. The application of this class of catalysts for the Michael asymmetric addition of 4-hydroxycoumarins 1 to enones 2 is interesting from the point of view of organocatalysis, since the presence of two primary amines enables both the formation of an imine ion with the enone and activation of the hydroxycoumarin by hydrogen bonding [41]. Despite the long reaction time (3 days), the desired products 3 were obtained with good to excellent yields and moderate enantiomeric excesses (Scheme 9).

A new organocatalyst was synthesized by Kumagai et al. and applied in the Michael addition of 4-hydroxycoumarin 1 with α,β-unsaturated ketones 2 [42]. This chiral primary amino
Scheme 7: Enantioselective reaction of cyclopent-2-enone-derived MBH alcohols 24 with 4-hydroxycoumarins 1.

Scheme 8: Sequential Michael addition/hydroalkoxylation one-pot approach to annulated coumarins 28 and 30.
amide organocatalyst 32 afforded the desired products 3, including warfarin (3a) in 86% yield, although in moderate enantioselectivity (up to 56% ee) (Scheme 10).

A catalytic asymmetric β-C−H functionalization of ketones 33 with 4-hydroxycoumarins 1 was developed by Zhu et al. [43]. The enamine, formed via reaction of the aminocatalyst 35 with
the ketone, is oxidized by IBX resulting in the electrophilic imine, which in turn undergoes a nucleophilic addition of the hydroxycoumarin. The procedure allowed obtaining products 34 with excellent yields and enantiomeric excesses (Scheme 11).

Zhu et al. described the asymmetric Michael addition of substituted 4-hydroxycoumarins (1) to cyclic enones 36, using an in situ formed organocatalyst [44]. The proposed transition state includes activations of the enone via an iminium ion and the coumarin by hydrogen bonding. A series of optically active polycyclic pyranocoumarin derivatives 37 was obtained in high yields with excellent enantioselectivities (up to 97% ee) (Scheme 12).

Kowalczyk and Albrecht described an allylic alkylation reaction between 3-cyano-4-methylcoumarins 39 and Morita–Baylis–Hillman (MBH) carbonates 40 [45]. In this case, the catalyst DHQ$_2$PYR 42 activates the MBH substrate and generates the dienolate in the vinylogous coumarin moiety, acting as a base. After the nucleophilic substitution reaction between the coumarin and the activated MBH substrate, it is possible to obtain functionalized coumarins 41 (Scheme 13). Furthermore, the absolute configuration of the stereogenic center was determined by X-ray crystallography.

The enantioselective synthesis of cyclopropa[c]coumarins 45 was described by Sun et al. [46]. In this method, the catalyst DHQ$_2$PYR 42 reacts with tert-butyl 2-bromoacetate, and then an ylide is formed by the base Cs$_2$CO$_3$. After a conjugated addition of this intermediate to the coumarin 43 followed by nucleophilic substitution, the corresponding cyclopropa[c]coumarins are formed with good to excellent yields and enantioselectivities (Scheme 14).

N-heterocyclic carbenes (NHC) have also been successfully used as organocatalysts, in particular, to obtain coumarin derivatives [47]. In this context, Yetra et al. reported a NHC catalyzed reaction of 2-bromoenals 46 with various heterocyclic C–H acids, resulting in the synthesis of coumarin/quinolinone...
Scheme 12: Enantioselective synthesis of polycyclic coumarin derivatives 37 catalyzed by an primary amine-imine catalyst 38.

Scheme 13: Allylic alkylation reaction between 3-cyano-4-methylcoumarins 39 and MBH carbonates 40.
fused dihydropyranones and dihydropyridinones 47. The reaction optimization and the scope and limitations study were carried out using an achiral NHC, but the enantioselective version was also performed using 4-hydroxycoumarin (1) with the chiral catalyst 48, as shown in Scheme 15 [48].

The enantioselective synthesis of dihydrocoumarins 51 from an inverse demand [4 + 2] cycloaddition of ketenes 50 with o-quinone methides 49 using carbene catalyst (NHC) 52 was described by Ye and co-workers [49]. This transformation resulted in products with moderate to excellent yields and enantiomeric excesses as shown in Scheme 16.

Enders et al. developed the enantioselective synthesis of cyclopenta[c]-fused chromenones 54 starting from hydroxylated malonate 53 with enals 2 [50]. The reaction stands out for its good to excellent yields and enantioselectivities when subjected to four sequential reactions mediated by a cooperative catalysis of a NHC organocatalyst with LiCl in the presence of DPQ as an oxidant, as shown in Scheme 17.

Recently, Chen et al. used a NHC catalyst 59 in γ,δ-difunctionalization of coumarins 56 through an oxidative [4 + 2] cycloaddition with unsaturated aldehydes 57 [51]. The methodology draws attention for the wide variety of products 58 obtained with moderate to excellent yields and enantiomeric excesses (Scheme 18).

**Activation via noncovalent bonding**

Besides the activation mode via a covalent bond, as discussed above, the organocatalysts may also proceed by noncovalent activation, in which a hydrogen bond or an ion pair is formed. A
Scheme 15: NHC-catalyzed lactonization of 2-bromoenals 46 with 4-hydroxycoumarin (1).

Scheme 16: NHC-catalyzed enantioselective synthesis of dihydrocoumarins 51.
broad variety of mono- and bifunctional chiral hydrogen-bonding organocatalysts has been developed, in special using cinchona alkaloid derivatives [52]. In this sense, Lin and colleagues proposed an asymmetric [3 + 2] cycloaddition employing a coumarin dipolarophile 43 with azomethine ylides 60 organocatalyzed by quinidine (62) for the formation of fused pyrrolidine compounds through activation of the coumarin substrate by hydrogen bonding [53]. The methodology enabled a high diastereoisomeric control and in most cases with good enantioselectivity of the products. It becomes even more attractive, since it allows an in situ rearrangement of the acyl group that can be used in other functionalization methodologies. However, it presents a limitation relative to the presence of a carbonyl group in the coumarin, since it makes a hydrogen bond with the organocatalyst and when it is replaced by other electron-withdrawing groups, the hydrogen bond formation is blocked, consequently there is no product formation (Scheme 19).

Lin et al. described an organocatalyzed Mannich reaction between 4-hydroxycoumarins 1 and aromatic imines 63 for the synthesis of α-benzylaminocoumarins 64 [54]. Among the cinchona alkaloid derivatives evaluated in this reaction, cupreine (65) was found to be the best option in terms of yields and enantioselectivities (Scheme 20). Both electron-withdrawing and electron-donating substituents were well tolerated in either coumarin or imine portion, and electron-withdrawing
Scheme 18: Oxidative [4 + 2] cycloaddition of enals 57 to coumarins 56 catalyzed by NHC 59.

Scheme 19: Asymmetric [3 + 2] cycloaddition of coumarins 43 to azomethine ylides 60 organocatalyzed by quinidine 62.
substituents at ortho-position of the imine phenyl ring afforded the corresponding products with excellent yields and moderated to good ee.

The asymmetric addition of malonic acid half-thioesters 67 to coumarins 66 using a sulphonamide organocatalyst 69 was reported by Nakamura et al. [55]. The hydrogen bond between the secondary amine and the coumarin carboxyl provides a nucleophilic addition on the Re face, and therefore resulting in products 68 with R absolute configuration, with moderate to excellent enantioselectivity followed by two decarboxylations (Scheme 21).
Huang’s group has used azadienes to perform an enantioselective 1,4-addition to afford benzofuran-fused six-membered heterocycles with a squaramide catalyst [56]. Based on their previous work, the authors reported an enantioselective 1,4-addition of azadienes 71 to 3-homoacyl coumarins 70 to achieve benzofuran coumarin derivatives 72 [57]. It was possible to obtain good to excellent diastereo- and enantioselectivities by using a low amount of the catalyst, besides the high yield of the reaction. The best results were obtained using a squaramide cinchona alkaloid catalyst 73 in only 1 mol % loading. In addition, the reaction was also very efficient in a gram-scale experiment, which demonstrates the applicability of the method (Scheme 22).

More recently, Yuan et al. developed a methodology for the synthesis of spiroonxindole-cyclopropa[c]coumarins 75 through the cyclopropanation of 3-acylcoumarins 43 and 3-haloxxindoles 74 [58]. The authors chose a quinine-derived squaramide catalyst 73 to perform the [2 + 1] cycloaddition. This catalyst reacts with 3-haloxxindole, generating an ammonium salt which is deprotonated by a base, affording an ammonium ylide/enolate. Meanwhile, the Re-face attack is favored after interaction of squaramide portion of the catalyst with coumarin. Then, a Michael addition followed by intramolecular cyclization affords the desired product 75, as shown in Scheme 23.

An enantioselective cascade synthesis of hydrocoumarin 78 mediated by squaramide catalyst with 9-amino-9-deoxy-epiquinine moiety 73 was reported by Albrecht et al. [59]. In this transformation, the authors developed a Michael addition of azlactones to 2-hydroxychalcones 76 followed by the opening of the azlactone 77 ring to form the product of interest, which

Scheme 22: Enantioselective 1,4-addition of azadienes 71 to 3-homoacyl coumarins 70.
could be obtained with moderate to excellent yields and enantioselectivities. The protocol used allowed obtaining hydrocoumarins with a wide structural variety and with a diastereoselective control, as shown in Scheme 24.

In 2016, Albrecht et al. [60] published the synthesis of 3,4-dihydrocoumarins 80 bearing a cyclohexene ring, through [4 + 2] cycloaddition between 2,4-dienals 79 and 3-coumarincarboxylates 43. This stereoselective transformation was performed using a squaramide 81 derivative catalyst, which activates the aldehyde with the formation of an enamine intermediate and the coumarin through hydrogen bonding, as shown in Scheme 25.

An enantioselective one-pot synthesis of spiro[dihydrofurocoumarin/pyrazolone] 83 mediated by quinine and squaramide catalyst 84 was reported by Xu et al. [61]. The work draws attention for the wide range of compounds obtained with high diastereo- and enantioselectivity and moderate to excellent yields. The authors highlighted that the catalyst also contributes to cyclization, since subjecting the isolated Michael adduct to the second conditions with iodine and K$_2$CO$_3$ there is a decrease in yield and enantiomeric excess when compared to the one-pot procedure. The obtained products possess a (R)-configuration, determined by X-ray crystallography (Scheme 26).

Sebesta and colleagues described an enantioselective Michael/hemiketalization addition of hydroxycoumarins 1 to enones 2 and ketoesters 86 using squaramide 85 [62]. The methodology developed made it possible to obtain a mixture of open and closed forms of (R)-warfarin (3a) from a bifunctional catalyst of squaramide by the formation of an iminium ion intermediate with enone and hydrogen bonding with hydroxycoumarin.
Scheme 24: Enantioselective synthesis of 3,4-dihydrocoumarins 78 catalyzed by squaramide 73.

Scheme 25: Organocatalyzed [4 + 2] cycloaddition between 2,4-dienals 79 and 3-coumarincarboxylates 43.
Scheme 26: Enantioselective one-pot Michael addition/intramolecular cyclization for the synthesis of spiro[dihydrofurocoumarin/pyrazolone] 83.

(Scheme 27a). By using the squaramide catalyst with tertiary amine (S)-warfarin analogues 3 could be obtained with moderate to excellent enantiomeric excesses (Scheme 27b).

In 2018, Modrocká et al. described the synthesis of 2,3-dihydrofurocoumarins 89 through an enantioselective Michael addition of 4-hydroxycoumarins 1 to β-nitrostyrenes 88, followed by an intramolecular cyclization [63]. For this transformation, the authors use a squaramide catalyst 90 to perform the enantioselective Michael addition in 1,4-dioxane at room temperature, as shown in Scheme 28a. Moreover, the group tried a reusable immobilised squaramide catalyst 91, which gave the desired product with high ee in the two first cycles, although the yield of the product in the first cycle was lower (Scheme 28b). Finally, the absolute configuration of the products was determined by ECD analysis.

Zheng et al. described an asymmetric organocatalyzed domino reaction between 4-hydroxycoumarins 1 and substituted methylene malononitriles 92, affording a variety of pyrano[3,2-
Scheme 27: Michael/hemiketalization addition enantioselective of hydroxycoumarins (1) to: (a) enones 2 and (b) α-ketoesters 86.
Scheme 28: Synthesis of 2,3-dihydrofurocoumarins 89 through Michael addition of 4-hydroxycoumarins 1 to \( \alpha,\beta \)-unsaturated ketones 2 promoted by chiral primary amine thiourea bifunctional catalyst. An asymmetric Michael addition of 4-hydroxycoumarin (1) to \( \alpha,\beta \)-unsaturated ketones 2 promoted by chiral primary amine thiourea bifunctional catalyst 97 was reported by Mei et al. [66]. Using the optimized conditions, a series of Michael adducts 3 were obtained in excellent yields (up to 97%) and enantiomeric excesses (up to 95% ee) (Scheme 31). As a highlight, optically pure (S)-warfarin (3a) was obtained in 99% ee after simple and single recrystallization.

Wang’s group developed a bifunctional thiourea and abietic acid catalyst for enantioselective synthesis. In this context, they applied this catalyst in a domino reaction of pyranocoumarins 99 [67]. The procedure proved to be efficient for obtaining products with good to excellent yields and enantiomeric excesses, and in some cases starting from three components in a one-pot procedure (Scheme 32). The chiral catalyst 100 allows the addition in the least hindered Re face, consequently result-
Scheme 29: Synthesis of pyrano[3,2-c]chromene derivatives 93 via domino reaction between 4-hydroxycoumarins (1) and substituted methylene malononitriles 92.

Scheme 30: Conjugated addition of 4-hydroxycoumarins 1 to nitroolefins 95.
**Scheme 31:** Michael addition of 4-hydroxycoumarin 1 to α,β-unsaturated ketones 2 promoted by primary amine thiourea bifunctional catalyst 97.

**Scheme 32:** Enantioselective synthesis of functionalized pyranocoumarins 99.
ing in products of (R)-configurations, which were determined via X-ray crystallography.

A stereoselective [3 + 2] cycloaddition with indandione alkylidenes 103 and 3-homoacylcoumarin 70 as the 1,3-dipole precursor, to generate a series of coumarin/indandione-fused spirocyclopentanes 104 bearing four contiguous stereogenic centers, was described by Chen et al. [68]. This transformation was catalyzed by a cinchona-thiourea derivative 105 furnishing the spiro compounds with good to high yield and enantioselectivity (Scheme 33). In this method two mechanisms occur in parallel, which results in the formation of the Michael adduct as a by-product and the desired spirocyclopentanes 104. It is noteworthy that the mechanistic studies showed that the product is formed through a concerted mechanism and therefore is not part of an intermediate adduct.

A conjugate addition of 4-hydroxycoumarin (1) to β,y-unsaturated α-ketoesters 106 was reported the Kim’s group [69]. In this case, a bifunctional binaphthyl-modified thiourea organocatalyst 108 was used, and among the solvents probed (such as CH$_2$Cl$_2$, CH$_3$CN and toluene), the best results were achieved when the reaction was conducted in dibromomethane at room temperature. The use of only 5 mol % of the catalyst afforded the desired products with excellent yields and enantioselectivities (Scheme 34).

The use of multicatalytic systems have become a useful strategy for the case where it is not possible to achieve the desired transformation by using only one catalyst [70]. In this sense, an efficient asymmetric organocatalytic reaction was reported by Zhang et al. for the synthesis of 2,8-dioxabicyclo[3.3.1]nonanes [71]. A combination of catalysts 7 and 110, involving iminium

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**Scheme 33:** 3-Homoacylcoumarin 70 as 1,3-dipole for enantioselective concerted [3 + 2] cycloaddition.
Scheme 34: Synthesis of warfarin derivatives 107 through addition of 4-hydroxycoumarins 1 to β,γ-unsaturated α-ketoesters 106.

and anion-binding catalysis, respectively, has proved to be the most effective for the promotion of the conjugate addition of 4-hydroxycoumarins 1 to 2-hydroxycinnamaldehydes 109, leading to chiral bridged bicyclic acetal products 110 with high ee (Scheme 35). The mechanistic study performed showed that possibly the phenolic hydroxy group of 2-hydroxycinnamaldehydes is important for the success of the employed catalytic system.

Finally, but not least, the phase-transfer chiral organocatalysts have also been highly explored [72,73]. Most of the PTCs are based on the skeletons of cinchona alkaloids and chiral binaphthyls, though, more recently, the strategy via introducing secondary interactions for the design of the bifunctional catalysts achieved wide application in asymmetric reactions [74].

Wu et al. described a Mannich asymmetric addition of cyanocoumarins 39 to isatin imines 112 catalyzed by an amide-phosphonium salt 114. This catalyst provides the formation of an ionic pair with coumarin enolate and activation of the imine by hydrogen bonding with the secondary amine, resulting in products 113 with excellent yields and high enantioselectivity [75]. This transformation draws attention because it uses only 0.1 mol % of catalyst, tolerates electron-donating and -withdrawing groups and maintains its performance in gram scale (Scheme 36).

Page et al. developed a total synthesis of the natural product (+)-scuteflorin A (119), being the key step an asymmetric epoxidation of xanthyletin (115) employing biphenylazepinium 120 as PTC together with tetraphenylphosphonium monopersulfate (TPPP) as the stoichiometric oxidant [76]. The authors mentioned that this epoxidation had been previously reported using Jacoben’s (S,S)-(S)-salen-Mn(III) catalyst with 78–83% yield and 95% ee, and via organocatalysis they obtained 98% yield and ≥99% ee (Scheme 37). Furthermore, the natural product was synthesized in seven steps with 14% overall yield.

Conclusion
Coumarin derivatives are important scaffolds for synthetic and medicinal chemistry. These structures have an interesting reactivity and can be used in diverse organic reactions, for example
Scheme 35: Asymmetric multicatalytic reaction sequence of 2-hydroxycinnamaldehydes 109 with 4-hydroxycoumarins 1.

Scheme 36: Mannich asymmetric addition of cyanocoumarins 39 to isatin imines 112 catalyzed by the amide-phosphonium salt 114.
enantioselective organocatalyzed reactions, as presented in this review. Furthermore, coumarin derivatives are known for their wide variety of biological activities.

As can be noticed in this literature review, a wide variety of new catalysts were applied in the synthesis of coumarin derivatives and the methodologies were found to be good choices to achieve functionalized coumarins, such as the use of immobilized squaramide catalyst, which allowed the catalyst to be recycled twice with high ee. Moreover, the squaramide catalyst could also be used with low catalyst loading (1–2 mol %) providing excellent results, besides the use of only 0.1 mol % of amide-phosphonium salt for the synthesis of coumarin derivatives. Some methodologies have also proven to be highly efficient in one-pot and gram-scale procedures, which turns to be more environmentally benign.

Nevertheless, studies are still needed to accomplish procedures that allow recycling and lower catalyst loading, intertwined with the use of green solvents, in order to provide efficient and sustainable synthesis of these important pharmacologically active compounds.

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