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Non-Covalent Organocatalyzed Domino Reactions Involving Oxindoles: Recent Advances

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Abstract: The ubiquitous presence of spirooxindole architectures with several functionalities and stereogenic centers in bioactive molecules has been appealing for the development of novel methodologies seeking their preparation in high yields and selectivities. Expansion and refinement in the field of asymmetric organocatalysis have made possible the development of straightforward strategies that address these two requisites. In this review, we illustrate the current state-of-the-art in the field of spirooxindole synthesis through the use of non-covalent organocatalysis. We aim to provide a concise overview of very recent methods that allow to the isolation of unique, densely and diversified spirocyclic oxindole derivatives with high structural diversity via the use of cascade, tandem and domino processes.

Keywords: spirooxindole derivatives; non-covalent organocatalysis; hydrogen-bonding; cascade; tandem; domino; enantioselectivity; chiral building blocks

1. Introduction

Heterocyclic compounds are found in a broad range of bioactive molecules, natural products, and drugs. Consequently, several novel efficient strategies based on catalytic methods have been validated to date for the direct assessment of such scaffolds in an enantiopure fashion [1–3]. In this context, spirocyclic oxindole derivatives have appeared as privileged structural motifs being part of a great number of synthetic and natural products displaying remarkable biological activities as well as useful biomedical applications (Figure 1) [4–6]. Asymmetric organocatalysis has appeared as an appealing tool in order to prepare such compounds with rich structural diversity and complexity through cascade, tandem, and domino processes [7–9]. Indeed, since the beginning of the 21st century, the golden-age of organocatalysis, several reports and substantial advances on the field of the synthesis of complex structural entities via the combination of organocatalysis and cascade transformations have been reported so far. The ability to reach for molecular complexity through the conscious choice of substrates and catalysts in a single transformation has inspired a growing number of research groups. Seminal reports that cover this subject have appeared before 2015 [10–13].

The aim of this review is to describe recent advances towards the stereocontrolled synthesis of strained spiro-quaternary stereocenters on the oxindole core through non-covalent organocatalysis [14–16] within the timeframe from 2015 to the middle of 2017. It is the authors’ aim to attract the reader’s attention to the potential of asymmetric non-covalent organocatalysis to mediate one-pot cascade, tandem, and domino processes that, employing an oxindole derivative as starting material, give a facile access to complex molecules featured by several functionalities and various stereogenic centers.
The observed high yields and remarkable stereoinduction, which resemble Nature’s outcomes, mainly rely on H-bond interactions, electrostatic effects, and π-π stacking that are established between the oxindole core, the employed reagent, and the selected catalyst (i.e., dual and cooperative catalysis) [17]. Examples of such connections are depicted in Figure 2.

![Figure 1](image1.png)

**Figure 1.** Examples of bioactive compounds built around the oxindole framework.

Far to be exhaustive and comprehensive, the current review is divided according to the most employed class of catalysts. Specifically, after a quick overview about the Cinchona alkaloids (Section 1), the subsequent synthetic elaborations of these natural-occurring organocatalysts are going to be introduced (Sections 2–5); meanwhile, Section 6 will detail an example of non-covalent activation via Brønsted acids. Finally, we apologize for any omissions.
2. Cinchona Alkaloid Catalysts

Discovered in 1820 for its antimalarial properties, Cinchona alkaloids have found several applications in various and quite different fields ranging from medicine to food and beverage industries, and even including organic chemistry. Besides the initial uses as resolving agents, over the last decades, Cinchona alkaloids have established a primary and outstanding role in asymmetric synthesis as highly efficient organocatalysts capable of promoting a wide range of enantioselective transformations in both homogeneous and heterogeneous environments [18]. The impressive chiral induction mainly relies both on the accessibility of different chiral skeletons and on the facile adaptability to various reaction processes (Figure 3). Specifically, the 1,2-aminoalcohol group summarizes in one molecule:

(i) the basicity and bulkiness of quinuclidine moiety, apt to activate a nucleophile by deprotonation as well as to stabilize the developing positive charge,

(ii) the secondary 9-hydroxy group, which acts as both an acid and a H-bond donor, and is suitable for further chemical modification of the catalyst structure. Additionally, the overall catalytic action is also ascribed to the possible π–π interactions with the aromatic quinoline ring.

Representative examples of widespread used Cinchona alkaloids are depicted in Figure 3. Notably, as fragments of more complex organocatalysts (Sections 3–5) the same structures play a crucial role to induce high levels of diastereo- and enantioselectivity.

Within this context, in 2015, Yuan and co-workers succeeded in the construction of a class of spirocyclic oxindoles through a domino Mannich-cyclization process [19]. Specifically, employing various 3-isothiocyanate oxindoles 1 and imines 2 as substrates, the simplest commercially available quinine (I, 1 mol %) made possible the diastereo- (up to >99:1 d.r.) and enantioselective (up to 97% ee) synthesis of spiro[imidazolidine-2-thione-4,3′-oxindole] derivatives 3 (Scheme 1). Notably, the optimized conditions, i.e., using toluene as solvent at 0 °C with the addition of 4 Å molecular sieves (MS), led, in just 10 min, to the desired products isolated in remarkable yields (up to 95%).

![Figure 3. Representative examples of Cinchona alkaloids.](image-url)
Scheme 1. Synthesis of spiro[imidazolidine-2-thione-4,3′-oxindole] via domino Mannich/Cyclization process and proposed transition states where A and B are the suggested intermediates (Y = Yield).

To explain the observed outstanding stereocontrol, the authors suggest that in the transition state the quinine simultaneously activates: (i) the tosyl-protected imine via a H-bond interaction of the C9-OH and (ii) the 3-isothiocyanate oxindole moiety via deprotonation and consequent enolization performed by the tertiary amine group. In such a way, the imine $\text{Si}$-face is exposed to the attack of the $\text{Si}$-face nucleophile counterpart (A, Scheme 1). The subsequent ring closure reaction involves the just formed $\text{N}$-nucleophile and the electron-poor carbon of the isocyanate oxindole framework (B, Scheme 1).

More recently the impressive stereoinduction properties of Cinchona alkaloids have been validated even in a kinetic resolution approach. Indeed, Tanaka and co-workers were engaged in the synthesis of spirooxindole polycycles 8 bearing a spiro[4,5]decane system that was remarkably accomplished by a two-step strategy involving a formal $[4 + 1]$ cycloaddition and a subsequent Michael-Henry cascade transformation (Scheme 2) [20].

Scheme 2. Synthesis of spirooxindole polycycles bearing a spiro[4,5]decane system.
While the former reaction was carried under acidic catalysis, the Michael-Henry cascade steps were performed under quinidine (II) catalysis at room temperature. In such conditions, the final polycyclic derivatives 8 featuring seven stereogenic centers were isolated in high optical purity (80–92% ee) despite modest yields (up to 28%) consequence of the racemic mixture used as starting materials. However, the unreacted enantiomer ent-6 was easily recovered in enantioenriched fashion (up to 43% yield, 92–98% ee).

Although initially the simplest naturally available Cinchona alkaloids have been widely exploited, over the years, organic chemists have created more efficient and complex molecules bearing the same scaffold that was implemented with the introduction of further functionality capable of H-bond interactions. In the following sections, we are going to illustrate and compare other privileged organic chirality inducers, most of which could be added to the realm of Cinchona alkaloid derivatives.

3. (DHQD)$_2$ Based Catalysts

Joining together two units of Cinchona derivatives/analogues in a single molecule, creating the so-called bis-Cinchona alkaloids, is the easiest way to enhance the H-bond network inside the catalyst/substrates system. Such structures have mainly shown their efficiency as chiral ligands in the Sharpless dihydroxylation. However, over the years, several research groups have highlighted their potential and effectiveness as simple organocatalysts without the introduction of further metal salt additives. Among others, Wu and co-workers exploited the ability of (DHQD)$_2$PYR (IX) in Michael/cyclization cascade reaction to synthesize different spirocyclic oxindoles starting from isatilidene malonitriles as initial electrophile. Precisely, the employment of acyclic β,γ-unsaturated amides 10 as vinylogous enolates, smoothly provided the titled spirooxindoles 11 in good yields (87–95%) and noteworthy enantioselectivity (77–96% ee) even though the overall outcomes were affected by the steric hindrance introduced on both donor and acceptor reagents (Scheme 3) [21].

![Scheme 3. Michael/cyclization cascade reaction to spirocyclic oxindoles catalyzed by (DHQD)$_2$PYR (IX).](image)

Likewise, the replacement of the Michael donor with suitable pyrazolone 12 furnished the expected spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives 13 by performing the reaction in
analogous conditions (i.e., −20 °C, AcOEt as solvent) and adding only 1 mol % of the chosen organocatalyst IX (Scheme 4) [22]. The whole process was completed in a shorter reaction time (from 10 min to 9 h) with respect the previous vinylogous Michael/cyclization sequence (from 60 min to 7 days) and provided the products in notable yields (96–99%) and good-to-moderate optical purity (47–91% ee).

Scheme 4. Michael/cyclization cascade reaction catalysed by (DHQD)$_2$PYR (IX) when pyrazolone 12 was employed as Michael donor.

Unfortunately, the optimized protocol failed when the one-pot three component reaction of N-trityl isatin (14), malonitrile (15), and pyrazolone 12 (R$^3$ = Me, R$^4$ = Ph) was attempted affording the hypothesized spirocompound 13 (R$^1$ = H, R$^2$ = Tr, R$^3$ = Me, R$^4$ = Ph) in low yield (41%) and poor enantioselectivity (28% ee).

Almost simultaneously, Enders and co-workers designed and realized an organocatalytic Mannich/Boc-deprotection/aza-Michael sequence of N-Boc ketimine 16 and 3-substituted oxindoles 17 that straightforwardly afforded the functionalized 3,3′-pyrrolidinyl derivatives 18 bearing three stereocenters, two of which were contiguous spiro-stereocenters [23]. Therefore, the devised and validated protocol (i.e., room temperature, MTBE as solvent), which relied on the efficiency of (DHQD)$_2$PHAL X (10 mol %) as catalyst, gave access in moderate-to-good yields (41–84%) and high stereoselectivity (up to >20:1 d.r., 90–98% ee) to complex spirocyclic systems 18 (Scheme 5).

Scheme 5. Organocatalytic Mannich/Boc-deprotection/aza-Michael sequence developed by Enders and co-workers.
4. Thiourea-Based Catalysts

Thiourea-based organocatalysts [24–27] have been intensively considered for promoting multiple C-C and C-heteroatom bonds formation via domino reactions through H-bond network between substrates and catalysts. In this section, recent selected cascade reactions involving such organocatalysts (Figure 4) allowing to highly functionalized chiral spirooxindole-bearing compounds are going to be discussed.

Figure 4. Thiourea and thiocarbamate organocatalysts used in this section.

4.1. Michael Addition/Cyclization Sequence

Electrophilic isatilydene malonitrile derivatives 9 are substrates of choice to promote Michael addition/cyclization transformations through reaction with nucleophiles. In 2015, Kesavan and co-workers have indeed devised a sequential vinylogous Michael addition/cyclization in the presence of vinyl malononitriles 19 and 20 as vinylogous nucleophiles [28]. The reaction, conducted in the presence of L-proline derived bifunctional thiourea catalyst XI (10 mol %) in toluene at 0 °C, demonstrated a wide scope with both substrates (Scheme 6, compounds 21 and 22). In addition, an enantioselective three-component reaction could also be proposed via in situ formation of isatylidene malonitrile derivatives. The authors have also highlighted the ability of XI to afford high levels of enantioselectivity without the need for N-protected oxindoles. Indeed, enantioselective transformations involving oxindoles usually require the prior N-protection in order to avoid unsought substrate interactions with the catalyst.
were obtained in a racemic manner. Is crucial to afford enantioenriched spiro compounds XVII.

In this case, the domino transformation also takes place in shorter reaction times and the catalytic system proved to be suitable to a series of 2-substituted thiazol-4-ones. 

R Herrera and co-workers reported the combination of enamines 23 and isatylidene malonitrile 9 to propose a promising asymmetric synthesis of few 2-oxospiro-[indole-3,4'-1',4'-dihydropyridine] 24 in moderate yields and enantioselectivities (Scheme 6, compound 24) [29]. The domino process is believed to follow a mechanism that involves a Michael addition, an intramolecular cyclization and then, a tautomerization and is catalyzed by Takemoto’s catalyst [30] XIII (30 mol %) in acetonitrile at 15 °C. The synthesis of several spiro[4H-pyrano-oxindole] derivatives was proposed by Wu and co-workers by using α-cyano ketones 25 as nucleophiles (Scheme 6) [31]. In the presence of very low loadings of quinidine-derived thiourea organocatalyst XVII (2 mol %) and morpholine (1 mol %) in dichloromethane at 0 or −10 °C, the cascade process takes place within less than two hours and accommodates a broad range of substrates affording the expected products in excellent yields and high enantioselectivities. The authors have shown that the chiral tertiary amine moiety in catalyst XVII is crucial to afford enantioenriched spiro compounds 26 as in its absence, the expected products were obtained in a racemic manner.

Novel thiazole-fuzed spirooxindoles 28 were synthesized in high yields and enantioselectivities by using (1R,2R)-1,2-diphenylethane-1,2-diamine derived thiourea catalyst XII (2 mol %) (Scheme 6) [32]. In this case, the domino transformation also takes place in shorter reaction times and the catalytic system proved to be suitable to a series of 2-substituted thiazol-4-ones 27 as nucleophiles and 2-(1-methyl-2-oxoindolin-3-ylidene)malonitrile as electrophile. Concerning the mechanism, the authors reasoned that the observed stereochemistry of this domino reaction can be explained via a first Michael addition of thiazolones 27 to 9 to afford the Michael addition intermediate followed by its

![Scheme 6](image-url)
subsequent intramolecular Thorpe-Ziegler-type cyclization. Both steps operate through dual activation of substrates in the presence of the bifunctional thiourea catalyst XII.

The combination of naphthoquinone and chromenone derivatives with oxindole ketoesters as Michael acceptors has paved the way to the preparation of versatile heterocyclic compounds. The group of Kesavan has, once again, underscored proline-based catalyst XI (5 mol %) as powerful catalyst to carry on tandem Michael addition/hemiketalization of ketoester 29 with 2-hydroxy-1,4-naphthoquinone 30 in dichloromethane at room temperature (Scheme 7) [33]. The expected hybrid spirooxindole-naphthoquinone compounds 31 were obtained in excellent yields and enantioselectivities and displayed good functional tolerance concerning the oxindole ketoester scaffold including different N-protecting groups. However, unprotected (i.e., N-H) oxindole substrates gave lower yields and enantioselectivities probably due to the additional H-bond binding site that might be in competition either with the organocatalyst or with the substrates. Independently and shortly after, the group of Wang proposed a similar transformation in the presence of catalyst XX (10 mol %). In this work, a broader scope has been proposed with respect of both substrates [34]. Additionally, the synthesis of several optically active spiro[oxindole-benzo[g]chromene-dione] derivates was also described via cascade reaction between 2-hydroxy-1,4-naphthoquinone as nucleophile and oxindole ketoesters.

![Scheme 7. Synthesis of hybrid spirooxindole-naphthoquinones through catalysis with proline-based catalyst XI.](image)

In 2016, Enders and co-workers developed a highly selective domino oxa-Michael/1,6-addition sequence to synthesize functionalized chromans with an oxindole moiety [35]. The success of the transformation relies on the use of unprecedented ortho-hydroxyphenyl-substituted para-quinone methide 33 as donor-Michael acceptor substrates in combination with isatin-derived enoate 32 (Scheme 8). The mild reaction conditions [i.e., catalyst XVIII (5 mol %) in toluene at room temperature] showed significantly wide substrate scope and functional group tolerance.

Other interesting substrates used in cascade transformations to afford highly substituted and poly-functionalized spirooxindoles through Michael addition/cyclization process are 3-isothiocyanate oxindoles (Scheme 9, compound 35). Indeed, their ambiphilic character (e.g., bearing both electrophilic and nucleophilic sites) allows for the synthesis of several functionalized spirooxindoles via reaction with diversified suitable substrates such as electron-poor olefins. Chowdhury, Ghosh, and co-workers proposed the use of quinine-derived thiourea catalyst XIX (20 mol %) in toluene at 0 °C in order
to synthesize a broad range of 3,2'-pyrrolidinyl spirooxindoles 37 in high yields and excellent diastereo- and enantioselectivities by using quite unreactive $\pi$-electrophiles such as diethyl benzylidene malonate 36 [36]. Moreover, Jing, Qin, and co-workers reported an asymmetric synthesis of trans-configured trispirooxindoles by combining 35 and cyclic methyleneindolinones 38 in the presence of Takemoto’s catalyst XIII (15 mol %) [37]. Interestingly, less than 60 min is enough to the cascade reaction to reach completion and the expected spiro compounds that bear three quaternary stereocenters are isolated in good yield and selectivities.

Scheme 8. Synthesis of chromans 34 with an oxindole moiety catalyzed by XVIII.

Remarkably, the use of chiral amino-thiocarbamate catalyst XXII (10 mol %) gave rise to several polycyclic spirooxindoles 41 containing three contiguous chiral centers, with two of them having quaternary stereocenters, in the presence of 35 and 3-nitroindoles 40 (Scheme 10) [38]. Excellent yields and selectivities were obtained when the N1-position of 35 was blocked with a methyl group while slight erosion of the diastereo- and enantioselectivities were observed for more hindered N1-protecting groups.

Scheme 10. Asymmetric synthesis of polycyclic spirooxindoles in the presence of amino-thiocarbamate catalyst XXII.
4.2. Michael Addition/Mannich/Cyclization Sequence

Recyclable fluorous bifunctional Cinchona alkaloid catalyst XV [39] has proved its efficiency to catalyze cascade reaction in the presence of electron-deficient olefinic oxindole 42 and nucleophiles. The syntheses of spirooxindoles containing 2-piperidinone 44 and tetrahydropyridine 46 rings were successfully accomplished in 2015 by Zhang and co-workers through a four-component cascade transformation in the presence of diethyl malonate 43 or 1,3-diketone 45 respectively (Scheme 11) [40]. Under the optimal conditions [i.e., catalyst XV (10 mol %) in toluene] high yields and levels of selectivity were reached affording polycyclic molecules densely functionalized that were prone to either further derivatization or scale-up. Although the authors have mainly proposed the use of oxindoles bearing a methyl group at the N1-position, one single example using free-N1 has been described affording slightly lower yields and comparable selectivities.

![Scheme 11. Synthesis of piperidone and tetrahydropyridine rings bearing spirooxindoles in the presence of recyclable catalyst XV.](image)

Shortly after, the same group has used catalyst XV (10 mol %) during a similar cascade reaction for the synthesis of spiro-γ-lactam oxindoles via a thiol-Michael/Mannich/lactamization cascade reaction in good yields and enantioselectivities and moderate diastereoselectivities [41]. The method goes through a four-component/one-pot synthesis and paves the way to novel compounds 48 containing three contiguous stereocenters including a quaternary one (Scheme 12). As for the previous example, N-Me indoles were exclusively used as substrates and only one example with N-H was reported. In both cases, catalyst recovery has been realized through first (i) loading onto a fluorous silica gel cartridge for solid-phase extraction (F-SPE) [42] followed by (ii) elution with 80:20 MeOH/H2O for products and other non-fluorous components and 100% MeOH for the catalyst XV. Overall, catalyst is recovered in more than 91% yield and >97% of optical purity.
Recently, Enders and co-workers have described the asymmetric preparation of trifluromethylated 3,3′-pyrrolidinyl-dispirooxindole derivatives bearing four contiguous stereogenic centers among which two are vicinal [43]. The Michael-Mannich [3 + 2] cycloaddition takes place in the presence of oxindoles 42 and 49 through thiourea-based derivative XXI catalysis (Scheme 13). Concerning the scope, several olefinic oxindoles 42 (containing electron-neutral, electron-donating or electron-withdrawing groups in the benzene ring) as well as trifluoroethyl isatin ketimines 49 (bearing electron-donating or a 5-F groups in the benzene moiety) are well tolerated. To replace the Boc protecting group by a Me group on the nitrogen of substrate 42 did not hamper the enantioselectivities. Under the optimized conditions (i.e., XXI (10 mol %) in CCl₄ at 4 °C for 12 h) the authors described 17 novel 3,3′-pyrrolidinyl-dispirooxindoles 50 in good yields (60–92%), moderate-to-good diastereoselectivities (4:1 to >20:1 d.r.) and enantioselectivities (72–93% ee). In addition, scale up on a gram scale of the reaction was realized conserving high yields and keeping the same levels of selectivities.

![Scheme 12](image_url)

**Scheme 12.** Synthesis of spiro-γ-lactam oxindoles via cascade reaction catalyzed by catalyst XV.

4.3. **Double Michael Addition Sequence**

A double Michael cascade reaction sequence, that allowed for a stereoselective [3+2] and [4+2] spiroannulation process, gave rise to both five- and six-membered β-nitro spirocarbocyclic oxindoles respectively [44]. After the screening of several thiourea-based organocatalysts, Quintavalla and co-workers have identified Takemoto’s catalyst XIII (10 mol %) as the most effective in terms of yields and selectivities. By combining 2-(2-oxindolin-3-ylidene)-acetic esters 32 and nitroenoates 51 as donor/acceptor compounds, novel spirooxindoles densely functionalized were isolated via this Michael-Michael cascade process (Schemes 14 and 15). Noteworthy to mention, the authors foreground that upon varying the double bond geometry (E or Z) of nitroesters 51, the configuration of the spiro quaternary stereocenter is inverted affording C3-epimers. This observation is valid for both five-membered and six-membered spirooxindoles. If the absolute configuration of the spiro center was determined accordingly to the E/Z geometry of nitroesters double-bonds, the remaining stereocenters were forged under the catalyst XIII control.
Scheme 14. Synthesis of β-nitro spirocyclopentane indolinones 52 via double Michael cascade in the presence of Takemoto’s catalyst XIII.

Scheme 15. Synthesis of β-nitro spirocyclohexane indolinones 53 via double Michael cascade in the presence of Takemoto’s catalyst XIII.

4.4. Aldol/Lactonization/Elimination Sequence

An enantioselective domino reaction involving an unprecedented one-pot aldol/lactonization/elimination sequence has been developed, in 2016, yielding a broad range of 3-spiro-α-alkyldiene-γ-butyrolactone oxindoles 58 (Scheme 16) [45]. The reaction is performed in the presence of β-nitro indolin-2-ones 54 and paraformaldehyde 55 as starting materials and it is catalysed by bifunctional Cinchona-derived thiourea XVI (10 mol %) in dichloromethane at 0 °C or room temperature. While 54 was used as a 1:1 mixture of C3 epimers, where both the Cα and Cβ absolute configuration were fixed and known [46], the expected products were isolated with well-established C3 quaternary spirocenter. Even though the two well defined Cα and Cβ stereocenters are destroyed during the domino process, it is interesting to mention that the only stereolabile C3 center of 54 became the unique controlled and defined one present on the final products. It was postulated that the reaction might proceed through an aldol reaction between 54 and 55 to afford the acyclic intermediate 56 which bears three stereodefined centers including the fixed C3 quaternary one. Then, lactonization affords the cyclic lactone 57 which in turn loses its nitro group through HNO₂ extrusion to afford the expected compounds 58 (Scheme 16).
4.5. Friedel-Crafts/Hemiketalization Sequence

The Kesavan group has published a straightforward synthesis of several oxindole-fused naphthopyran derivatives 60 by combining oxindole α-ketoester 29 and 2-naphthol 59 and using a sequence of Friedel-Crafts-hemiketalization reactions [47]. Under the optimized conditions (i.e., XI (5 mol %), in 1,1,1-trifluoromethyl benzene at room temperature) N1-protected oxindoles afforded the expected products in good yields and enantioselectivities. However, unprotected N-H oxindoles conducted to lower yields and selectivities probably due to competitive binding of the N-H site with the catalyst that might partially hamper the catalytic activity (Scheme 17).

Scheme 17. Synthesis of spirooxindole-naphthopyrans 60 in the presence of Cinchona-derived thiourea catalyst XVI. α 86% ee after recrystallization.

4.6. Miscellaneous

The synthesis of spiro-3,4-dihydropyran 62 bearing three stereocenters with vicinal quaternary ones has been reported by Kesavan and co-workers through the use of catalyst XI (5 mol %) in toluene at room temperature (Scheme 18a) [48]. Supported by the obtained syn configuration of the secondary alcohol and the cyclopentanone moiety, the authors defend an inverse-electron-demand hetero-Diels-Alder reaction pathway of oxindole α-ketoester 29 with cyclic β-oxoaldehyde 61 rather than a cascade transformation via Michael addition/hemiketalization. An efficient enantioselective [3+2] cyclization of 3-isothiocyanate oxindoles 63 and trifluoromethylated 2-butenedioic acid diester 64 or 65 paved the way to the synthesis of spirooxindoles with a CF₃-containing all-carbon stereogenic center 66 (Scheme 18b) [49]. Interestingly, the authors highlighted the possibility to obtain either isomers (i.e., epimers at C4 position) in the presence of the same catalyst XIV (20 mol %) at different temperatures. This observation relies on the ability of isomerization of dimethyl maleate 64 into dimethyl fumarate 65 through azomethine ylide intermediate in the presence of the amine moiety of aminals [50].
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Scheme 17. Synthesis of spirooxindole-naphthopyrans in the presence of catalyst XI. a 86% ee after recrystallization.

4.6. Miscellaneous

The synthesis of spiro-3,4-dihydropyrans bearing three stereocenters with vicinal quaternary ones has been reported by Kesavan and co-workers through the use of catalyst XI (5 mol %) in toluene at room temperature (Scheme 18a) [48]. Supported by the obtained syn configuration of the secondary alcohol and the cyclopentanone moiety, the authors defend an inverse-electron-demand hetero-Diels-Alder reaction pathway of oxindole α-ketoester 29 with cyclic β-oxoaldehyde 61 rather than a cascade transformation via Michael addition/hemiketalization. An efficient enantioselective [3+2] cyclization of 3-isothiocyanate oxindoles 63 and trifluoromethylated 2-butenedioic acid diester 64 or 65 paved the way to the synthesis of spirooxindoles with a CF$_3$-containing all-carbon stereogenic center (Scheme 18b) [49]. Interestingly, the authors highlighted the possibility to obtain either isomers (i.e., epimers at C4 position) in the presence of the same catalyst XIV (20 mol %) at different temperatures. This observation relies on the ability of isomerization of dimethyl maleate 64 into dimethyl fumarate 65 through azomethine ylide intermediate in the presence of the amine moiety of aminals [50].

Scheme 18. (a) Synthesis of spiro-3,4-dihydropyrans 62 and (b) synthesis of trifluoromethylated spirooxindoles derivatives 66.

5. Squaramide Catalysts

Inspired by the ability of urea/thiourea derivatives to promote high stereoselective organocatalytic reactions, several research groups have been engaged in the construction of alternative and complementary catalysts that involve in their architecture less explored H-bond donor motifs. Among others, in 2008 Rawal and co-workers postulated the potential of squaramide catalophores [51]. Specifically, over the years, several thorough studies have recognized that secondary squaramides featured by two H-bond donors (NH) and two H-bond carbonyl acceptors (C=O) should easily establish a strong hydrogen bond network with acceptors and donors as well as with mixed acceptor-donor systems (Figure 5a).

Additionally: (i) the conformational restriction due to the aromaticity enhancement of the cyclobutendione core upon the delocalization of nitrogen lone pairs, which make the two N-H bonds coplanar with the rigid “squara structure” and (ii) the distance between the two N-H that is of 0.6 Å broader than in thioureas, make squaramide derivatives not only a valuable alternative to the urea/thiourea counterpart but also a class of more wide-range applicable organocatalysts (Figure 5b).

Herein we are going to depict selected recent examples that demonstrate their remarkable ability in various cascade reactions involving an oxindole derivative as substrate and the catalophores depicted below (Figure 6).
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(a) H-Bond Interactions

(b) Resonance forms of the aromatic system

Figure 5. (a) H-Bond donor ability of squaramide and thiourea; (b) Lone pairs conjugation and resonance forms of the aromatic system.

Figure 6. Squaramide based organocatalysts reported in the present section.
5.1. Double Michael Addition Sequence

As stated before, oxindole derivatives have been a privileged substrate in organocatalysis. Specifically, as consequence of its unique electron-demand, α-alkylidene oxindoles have been often involved in cascade reactions mainly relying on Michael addition promoted by both C-nucleophiles and hetero atoms. In such a scenario, squaramide derivatives clearly have ever played a predominant role since their undisputed ability as bifunctional catalysts [52]. Notably in this field Zhao and Du devoted their efforts not only to the design and synthesis of novel more efficient squaramide organocatalysts but also to the preparation of uncommon cascade reagents that should be suitable to build quite complex and densely functionalized carbocycles. Thus, in 2015, their group reported the first squaramide asymmetric protocol for the synthesis of chiral spiro[pyrrolidine-3,3'-oxindoles] 67 (Scheme 19). The optimized cascade aza-Michael/Michael addition sequence, distinguished for its yield or stereoselectivity. The authors reasoned that such an outstanding stereocontrol should be ascribed to the squaramide moiety that contemporarily activates and orients the (Scheme 20). In the aza-Michael addition, the settled H-bond network (A) drives the nitrogen attack only from the Si face of the substrate to furnish the intermediate B where the enone group undergoes an intramolecular Michael addition on the Si face via the transition state C, which rapidly provides the product 67 and restores the catalyst XXIII.

Remarkably, the reaction could be repeated even on gram scale without any loss in both yield or stereoselectivity. The authors reasoned that such an outstanding stereocontrol should be ascribed to the squaramide moiety that contemporarily activates and orients the (E)-tert-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate 32 as well as the hydroquinine framework and enhances the nucleophilicity of the tosylaminomethyl enone 68 (Scheme 20). In the aza-Michael addition, the settled H-bond network (A) drives the nitrogen attack only from the Si face of the substrate to furnish the intermediate B where the enone group undergoes an intramolecular Michael addition on the Si face via the transition state C, which rapidly provides the product 67 and restores the catalyst XXIII.

The just disclosed reaction mechanism and the consequent stereochemical outcomes prompted the authors to replace the α,β-unsaturated esters with α-alkylidene succinimides 69 structurally similar to the oxindole counterpart [53]. The previously developed squaramide-catalysed approach in even milder conditions (i.e., room temperature and THF as solvent) guaranteed the formation of highly functionalized spirooxindoles 70 in elevated yield and stereocontrol (up to 97:3 d.r., up to 98% ee). In Scheme 21 it is reported the most representative examples of the produced library, which was also synthesized in gram scale without any loss in term of stereinduction.

\[ \text{Scheme 19. Asymmetric cascade aza-Michael/Michael addition for spiro[pyrrolidine-3,3'-oxindoles] 67.} \]

\[ ^{a} \text{The reaction was carried out on gram scale.} \]
Scheme 20. Proposed reaction mechanism for the aza-Michael/Michael cascade reaction developed by Zhao and Du. A–D are hypothesized intermediates on the catalytic proposed cycle.

Scheme 21. Organocatalytic cascade Michael/Michael addition for spirooxindoles containing five contiguous stereocenter. a The reaction was carried out on gram scale.

Once validated the efficiency of their squaramide XXIV as catalyst, in 2016 Zhao and Du designed the new cascade reagent 72 featured by both an active nucleophile center and an electrophile site (Scheme 22) [54]. The authors demonstrated their hypothesis fruitfully employing the developed donor Michael acceptor reagent 72 in a tandem Michael/Michael reaction which smoothly furnished highly functionalized bispirooxindole-tetrahydrofuran scaffolds 73 bearing four contiguous stereocenters. Despite the number of different substituents introduced on each oxindole framework, the overall
process never failed to give the expected products 73 in very high levels of optical purity (>20:1 d.r., up to >99% ee) and moderate-to-high yields (58–96% yield).

Scheme 22. Asymmetric enantioselective tandem Michael/Michael reaction to bispirooxindoles 73.

5.2. Michael Addition/Cyclization Reaction Sequence

A second highly exploited reaction sequence that straightforwardly furnishes complex spiro compounds involves a Michael addition followed by a fast cyclization reaction (see also Section 4.1). Among all the possible substrate/reagent systems largely reported in literature, Yuan and co-workers chose the previously investigated 3-hydroxyoxindoles 75 and 3-aminooxindoles 76 as initial Michael donor and the α,β-unsaturated acylphosphonates as Michael acceptor [55]. Such an uncommon electron poor counterpart was mainly selected due to the lability of the C-P bond that simplifies the phosphonate group removal. Relying on the efficiency of squaramide organocatalyst XXV...
together with the designed starting molecules, the authors developed a highly stereoselective Michael/cyclization cascade sequence able to afford a broad spectrum of spirocyclic oxindoles 78 and 79. Indeed, applying the initial optimized conditions (i.e., CH$_3$CN or CH$_2$Cl$_2$ as solvent, room temperature), the overall reaction proceeded without any loss in stereoselectivity (up to >99:1 d.r.; 71–97% ee) and yield (up to 98%) when (i) the Michael donor was either a 3-hydroxy or a 3-amino-oxindoles (75 and 76 respectively), which afford to the spiro γ-lactones (78 for X = O) and γ-lactams (79 for X = N), as well as (ii) substituents quite different in terms of electron demand and steric hindrance were introduced on both nitrogen and aromatic ring.

A slight drop in the stereoinduction was observed when the β position of the α,β-unsaturated acylphosphonate 74 was decorated with excessively bulky groups (Scheme 23). The observed efficiency should be due to the dual activation of the catalyst that (i) promotes the enolization of the 3-hydroxyoxindoles and (ii) exposes the Re face of the α,β-unsaturated acylphosphonate to the attack from the Si-face of the just generated nucleophile.

More recently, the similar squaramide-quinine based catalyst XXVI (10 mol %) was effective when α,β-unsaturated N-acylated succinimides 80 were chosen as the initial Michael acceptor and 3-hydroxyoxindoles 75 as the nucleophilic counterpart (Scheme 24). [56] Specifically, after having carefully optimized the reaction conditions (i.e., CH$_2$Cl$_2$ as solvent, −10 °C as best temperature), Du and co-workers validated their protocol by performing the proposed asymmetric cascade Michael/cyclization reaction on various Michael donor/acceptor systems obtaining the corresponding spirooxindoles lactones 78 in good yields (75–89%). Although the stereochemical outcomes were always excellent in term of enantioselectivity (96–99% ee), the diastereomeric ratios seemed to be more easily affected by various substituents introduced both on the enone system and on the oxindole moiety (from 75:25 to >95:25 d.r.). Afterwards, once assigned the correct configuration to the generated stereocenter, the authors provided a mechanistic study that pointed out how the quinine-derived squaramide XXVI should act as bifunctional catalyst. As depicted in Scheme 24, the tertiary amine unit deprotonates the 3-hydroxyoxindole while the squaramide moiety binds the resulting nucleophile (A) which in turn, attacks the electrophile already activated by the protonated amine (B). The Michael

![Scheme 23. Organocatalysed Michael/cyclization cascade reaction for the construction of spirocyclic oxindole-γ-lactones/lactams.](image-url)
adduct C undergoes an intramolecular cyclization which removes the succinimide auxiliary and generates the expected spirooxindole 78.

Exploiting the well-known reactivity of 3-isothiocyanato oxindoles conferred by the strongly electron withdrawing NCS group, Du and co-workers reported also the preparation of more complex pyrrolidinyl spirooxindoles employing either chalcones 82 [57] or maleimides 84 [58] as acceptor counterpart (Scheme 25). In both cases the extremely similar quinine-derived squaramide XXVII (10 mol %) and XXVIII (5 mol %) resulted to be the best catalysts in the same reaction condition (i.e., CH₂Cl₂, 0 °C). The desired spirocyclic products 83 and 85 were achieved in high yields (87-99%) and excellent diastereo- (up to >99:1 d.r.) and enantioselectivities (up to 99% ee) triggered by a complex H-bond network where the organocatalyst enable the stereocontrolled attack of the oxindole donors toward either the electron-poor chalcones 82 or maleimides 84.

Scheme 24. Asymmetric cascade Michael/cyclization reaction performed on 3-hydroxyoxindoles/N-acylated succinimides as donor/acceptor system. A–C are hypothesized intermediates on the catalytic cycle proposed.
and stereocontrol (85–98% ee) were accomplished only when the squaramide catalyst XXIX was substituted with the (1R, 2R)-diphenyl-1,2-diamine derived bifunctional thiourea XII.

The just depicted results, one more time, confirm the complementary use of thiourea-based and squarate derived organocatalyst for the stereoselective preparation of complex bioactive products.
and stereocontrol (85–98% ee) were accomplished only when the squaramide catalyst XXIX was substituted with the (1R, 2R)-diphenyl-1,2-diamine derived bifunctional thiourea XII.

Scheme 25. Du’s research toward the preparation of pyrrolidinyl spirooxindoles 83 and 85 employing respectively chalcones 82 and maleimides 84.

Scheme 26. Synthesis of dihydropyranoindole derivatives, a comparison between squaramide-based and thiourea catalyst.

5.3. Miscellaneous

In 2012 Casiraghi and co-workers illustrated how 3-alkylidene oxindoles could also react as vinylogous nucleophile in order to functionalize the γ-position in the presence of a suitable electrophile [60,61]. Inspired by this evidence as well as by subsequent Casiraghi’s researches concerning the Mukaiyama type aldol reactions [62], Han and Chang postulated the creation of biologically relevant 3-hydroxyoxindole framework relying on the nucleophilicity of 3-alkylidenes 90 and the undeniable electrophilicity of isatins 91 [63]. Surprisingly, instead of obtaining the expected aldol adduct, the spirooxindole dihydropyranones 93 were isolated by using the chiral Cinchona alkaloid-squaramide bifunctional organocatalyst system XXVIII (Scheme 27). The stereochemical outcome of the overall reaction was not influenced by the introduction of different substituents (i.e., in terms of either electron demand or steric hindrance) on both substrates (87–99% ee). A slight drop down was observed in the yield only when a NO2 group decorated the electrophilic aromatic ring (R3 = NO2). Without going in fine details, the authors suggested two models for explaining the dual activation of both nucleophile and electrophile (Scheme 27, B and C) which could account for the Si face addition of the s cis-enolate in the initial aldol reaction. Once obtained the intermediate A, the surprising replacement of the lactam C-N bond with a lactone C-O bond occurs delivering the product 93 after protonation and catalyst regeneration.

Such an uncommon behaviour of amide C-N bond was also recently detected by Zhao and co-workers during their studies concerning the organocatalytic Friedel-Crafts/lactonization domino reaction (Scheme 28) [64]. Actually, the authors reported a remarkable example of the employment of squaramide catalophore XXX in the asymmetric synthesis of dihydrocoumarins, a ubiquitous scaffold in bioactive natural products. Specifically, the formal [3+3] protocol involved an initial Friedel-Crafts alkylation of naphthols at the Cβ position of the 3-ylidene oxindoles 94 (A, Scheme 28) followed by an unexpected intramolecular cyclization with a C-N bond cleavage of the lactam moiety by the phenolic hydroxyl group (B, Scheme 28).
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Scheme 27. Asymmetric aldol/lactonization sequence for the synthesis of spirooxindole dihydropyranones 93. A is the hypothesized intermediate on the reaction pathway, while B and C are proposed alternative models for explaining the dual activation of nucleophile and electrophile.

Scheme 28. Friedel-Crafts/lactonization domino reaction developed by Zhao and co-workers and suggested reaction pathway.
Although the lactonization occurred to disadvantage of the chemically inert oxindole unit, the overall process proceeded under very mild conditions (i.e., CH$_2$Cl$_2$ at low temperature) and affording attractive outcomes in term of yields (60–99%) and stereoselectivity (>20:1 d.r., 80–98% ee) when both α- and β-naphthols (95 and 97) were alternatively used as nucleophiles (Scheme 28).

*Cinchona*-derived squaramides have shown their potential as organocatalysts even when they are involved in more complex domino reactions. An interesting example was reported by Lu and co-workers in 2015 who initially optimize a simple Diels-Alder/aromatization sequence and then, by adding an excess of oxindole moiety, observed a Diels-Alder/Michael/aromatization domino process (Scheme 29) [65]. The reactions always proceeded smoothly under very mild conditions (i.e., CH$_2$Cl$_2$ at room temperature) and with quite low catalyst loading (10 mol % of XXVI) providing the expected carbazolespirooxindole derivatives 101 in moderate-to-good yields (48–90%) and interesting stereoinduction (from 4:1 to >20:1 d.r., 60–99% ee). Unfortunately, for the product 102 with six contiguous stereocenters furnished by the triple domino reaction, it was not possible to define the stereochemical outcome mainly due to the arduous separation of the complex diastereomeric mixture.

![Tandem DA/aromatization reaction](image1)

![Tandem DA/Michael/aromatization reaction](image2)

**Scheme 29.** Diels-Alder (DA)/aromatization sequence and triple DA/Michael/aromatization domino process.

### 6. Miscellaneous

The impressive reactivity of oxindole derivatives has found several notable applications even when phosphoric acids, a less explored class of catalophores are employed as Brønsted acid organocatalyst. Among the very few reported examples, Shi and co-workers rationally designed a chiral phosphoric acid (CPA)-catalyzed Michael addition/intramolecular Friedel-Crafts cascade reaction toward the construction of cyclopenta[b]indole and spirooxindole frameworks [66]. Specifically, the authors supposed that, in order to promote the initial vinylogous Michael addition, the CPA XXXI could simultaneously activate throughout a complex H-bond network both the 7-vinylindoles 103 as nucleophile and the electrophilic vinyliminium C, which should be generated in situ form the 3-indolylmethanols 104. Subsequently the transient adduct B should undergo, always assisted by the dual H-bond activation of CPA XXXI, the intramolecular Friedel-Crafts reaction to
restore the initial aromatic indolic structure and furnish the expected complex spirooxindole systems 105 (Scheme 30).

The authors demonstrated their hypothesis successfully performing the diastereo- and enantioselective synthesis of several cyclopenta[b]indole derivatives 105 starting from a series of 7-vinylindoles 103 and various isatin-derived 3-indolylmethanols 104. Comparing the obtained results, it was clear that the stereoinduction was essentially not affected by the different nature of the substituents on both acceptor and donor partners. Conversely, they dramatically influenced the overall reactivity. Particularly, electron-donating groups on C7-functionalised indoles gave much higher yields than the electron-withdrawing groups, while it was less explainable the electronic effect due to substituents on the isatin units.

7. Conclusions

As shown by the examples depicted here, when newly developed organocatalysts meet oxindole derivatives, one of the most widespread frameworks in Nature, it is possible to achieve impressive levels of molecular complexity featured by the formation of multiple stereogenic centers upon multiple cascade reactions. Such outstanding results and all the future predictable improvements not only are going to constantly provide easier and easier access to a broad spectrum of highly valuable complex
compounds, but also to furnish a better understanding of Nature’s modes of action and ultimately even reach an almost similar degree of perfection.

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