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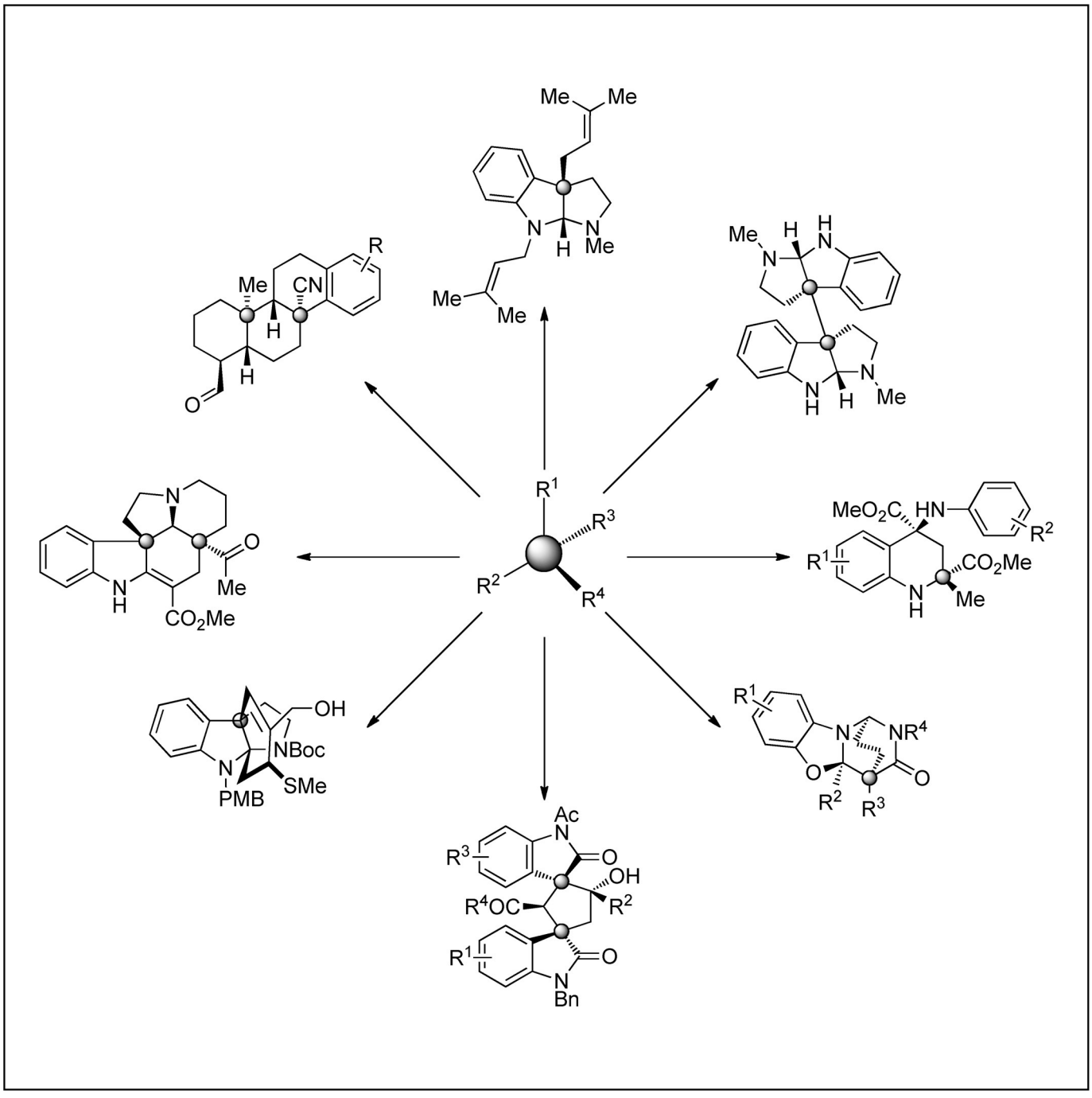
Focus Review

Organocatalytic Cascade Reactions

Recent Developments in the Synthesis of Chiral Compounds with Quaternary Centers by Organocatalytic Cascade Reactions

Li Tian, Yong-Chun Luo, Xiu-Qin Hu, and Peng-Fei Xu*[a]



Abstract: Quaternary carbon stereocenters are present in a wide variety of organic compounds and drug molecules. Highly enantioselective construction of such quaternary carbon stereocenters has received considerable attention owing to the great challenges in their syntheses. With the development of asymmetric organocatalytic cascade reactions, several efficient methods for the construction of optically pure compounds with quaternary carbon centers have been developed. This focused review highlights the asymmetric synthesis of chiral compounds with quaternary centers through organocatalytic cascade reactions.

1. Introduction

Optically pure compounds that play important roles in the fields of chemistry, life sciences, and pharmacology are commonly present in nature as a variety of natural products. Simple and convenient methods for the synthesis of chiral compounds have become a prolonged endeavor of chemists owing to their importance and broad applications. As asymmetric catalysis has the advantages of high stereoselectivity, economical processing, environmental protection, and easy industrialization, it is currently the most effective method for asymmetric synthesis. The field of asymmetric catalysis was originally dominated by metal catalysis and biocatalysis for a long time. In 2000, List et al. first reported the proline-catalyzed direct asymmetric intermolecular aldol reaction, and suggested that the mode of enamine catalysis could be used as a versatile strategy.[1] Then, MacMillan et al. reported an asymmetric Diels–Alder reaction catalyzed by their chiral imidazolidinone catalyst and proposed the mode of imine catalysis.[2] More importantly, they put forward the concept of organocatalysis, which has been developed rapidly and become the third branch of asymmetric catalytic reactions since then.

Organocatalysis, the use of non-metallic small organic molecules to catalyze organic transformations, has enjoyed phenomenal growth as these small organic molecule catalysts are non-toxic, inexpensive, easy to prepare, stable in air and water and so on, compared with metal catalysts. So far, a variety of organocatalytic modes have been developed. As an important field of asymmetric organocatalysis, organocatalytic cascade reactions are characterized by their high efficiencies and biomimetic syntheses of target molecules, which are similar to the biosynthesis of natural products.[3] Through organocatalytic one-pot multistep reactions, complicated chiral products can be obtained through organocatalytic cascade reactions from simple and readily available substrates, under mild reaction conditions, with simple operations without costly protection–deprotection processes, and also without the need to purify the intermediates. Several newly created bonds and stereocenters can be established by these reactions with good stereoselective control. Therefore, it is highly efficient to synthesize natural products and bioactive molecules by asymmetric organocatalytic cascade reactions.

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It is noteworthy that several terminologies have been utilized to describe multistep reactions that take place in one pot, which include "cascade", "domino", and "tandem" reactions. For example, Tietze suggested the use of "domino" rather than "cascade" or "tandem", and defined a domino reaction as a process involving two or more bond-forming transformations that take place under the same reaction conditions without adding additional reagents and catalysts, and in which subsequent reactions result as a consequence of the functionality formed in the previous step.[4] Denmark proposed keeping the all-encompassing definition of "tandem" as reactions that occur one after the other, and use of the modifiers "cascade" (or domino), "consecutive", or "sequential" to specify how the two (or more) reactions will follow.[5] Fogg classified one-pot processes as one-pot reactions, domino (cascade) catalysis, and tandem catalysis, which were further subdivided into orthogonal catalysis, auto-tandem catalysis, and assisted-tandem catalysis.[6] Hayashi utilized the term "one-pot synthesis" in his review, which has a much wider meaning than a cascade, domino, or tandem reaction, to encompass all such reaction types.[7] Nicolaou pointed out that the descriptors "domino", "cascade", and "tandem" were often seemingly interchangeable from one another in the literature.[8] In this review, Nicolaou's viewpoint has been employed and the term "cascade" is mainly employed to encompass all of the above descriptors just to be simple.

Quaternary carbon stereocenters, carbon centers with four different non-hydrogen substituents, are present in a wide variety of natural products and drug molecules. It used to be a great challenge to create quaternary carbon stereocenters with high enantioselectivity in organic synthesis, however, synthetic chemists were and still are very interested in this area.[9] Overman recently summarized some synthetic strategies toward complex natural products with two or more contiguous quaternary carbon atoms in their intricate structures, with emphasis on the methods to create quaternary carton stereocenters.[9d] Clearly, it is both significant and very useful to develop efficient processes to construct quaternary carton stereocenters in a highly enantioselective manner. With the development of asymmetric organocatalytic cascade reactions, several new types of efficient methods for the construction of optically pure compounds with quaternary carbon centers have been developed. Although many reviews about organocatalytic cascade reactions have been reported,[3] it is still highly desirable to summarize the asymmetric synthesis of chiral compounds with quaternary centers through organocatalytic cascade reactions; thus, we will discuss these highly efficient methods for

the highly enantioselective construction of quaternary carbon stereocenters.

This review highlights the asymmetric synthesis of chiral compounds with quaternary centers through organocatalytic cascade reactions, wherein aminocatalysis and hydrogen-bonding catalysis are mainly described. At the end of this paper, ion-pairing catalysis is also briefly discussed.

2. Asymmetric Aminocatalytic Cascade Reactions

Aminocatalysis, which includes iminium and enamine catalysis, has matured in the 15 years since it was first reported in 2000.[10] It is now a well-established and powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds. According to the different types of catalysts, aminocatalysis has been classified into secondary and primary amine catalysis.

Certain chiral pentacyclic amines are mainly used as catalysts for secondary amine catalysis, in particular proline and its derivatives,[11] including diarylprolinol ethers and phenylalanine-derived imidazolidinones. They provide a reliable synthetic platform for the asymmetric functionalization of aldehydes at positions from α to ε. Currently, the most commonly used primary amine catalysts are cinchona-based primary amines, such as 9-amino-9-deoxy-*epi*-cinchona alkaloids, which were developed independently and almost at the same time by Chen et al.,[12] Melchiorre et al.,[13] and Connon et al.[14] in early 2007. A variety of sterically hindered carbonyl compounds that cannot be functionalized by using secondary amines can be stereoselectively functionalized by using primary amines, which greatly expands the potential application of chiral aminocatalysis.

Asymmetric aminocatalyzed cascade reactions are divisible into two classes; (1) iminium-initiated cascade reactions, (2) enamine-activated cascade reactions.

2.1. Iminium-initiated cascade reactions

Cascade reactions induced by iminium catalysis in the first step are defined as iminium-activated cascade reactions. In most cases, the iminium-initiated reactions are followed by enamine-mediated processes in the subsequent step, and various cyclic structures can be obtained by this iminium–enamine catalytic sequence.

The rapid construction of high levels of molecular complexity and stereoselectivity involving multiple catalytic modes are very attractive in organic synthesis. Chen and co-workers have developed a one-pot, three-component cascade Michael–Michael/Michael–aldol process for two different α,β-unsaturated aldehydes with (*E*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoates **1** catalyzed by α,α-diphenylprolinol *O*-TMS ether **3** combined with benzoic acid as the cocatalyst.[15] A series of fused tetracyclic skeletons **2** bearing six contiguous stereocenters were obtained with excellent yields and enantioselectivities. Based on this method, a complex polycyclic framework with up to eight contiguous chiral centers has been established efficiently with α,β-unsaturated aldehydes and nitroolefins. They have also proposed a mechanism of quadruple iminium–enamine–iminium–enamine catalysis to explain this reaction. As shown in Scheme 1, the intermediate **4** was generated after the first cascade Michael–Michael reaction between **1** and one equivalent of the α,β-unsaturated aldehyde, then the second Michael–aldol process occurred with the second equiv-

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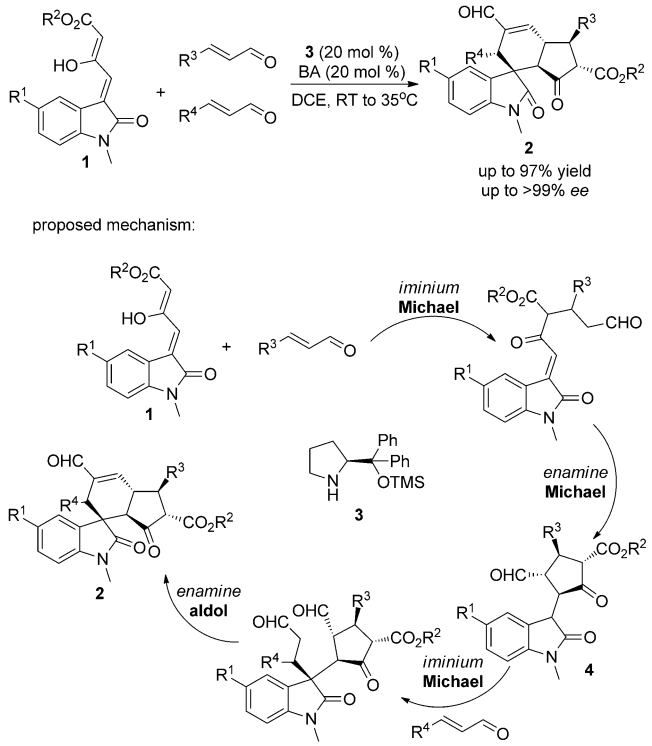
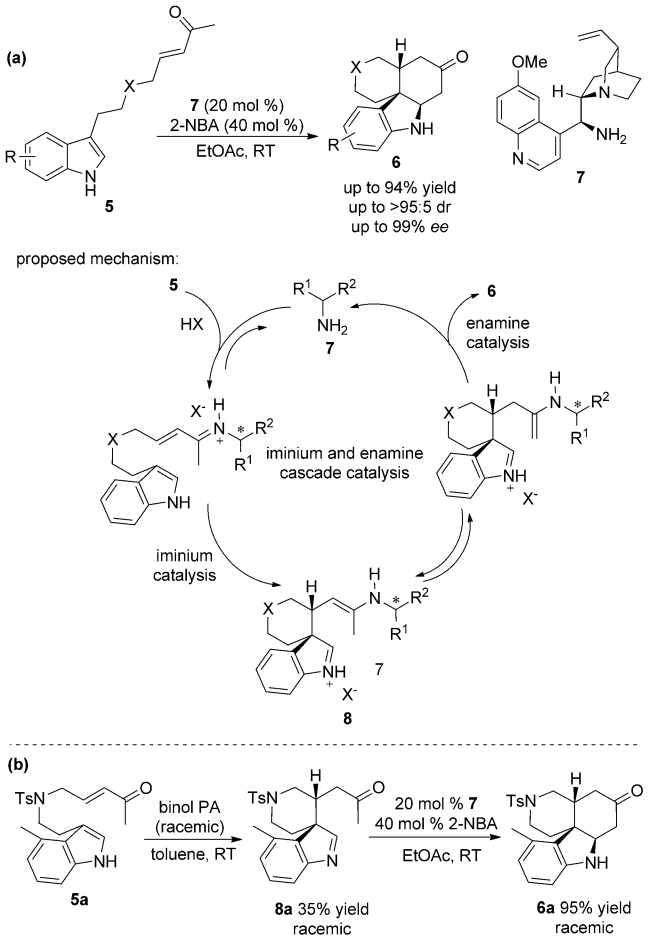


Scheme 1. Synthesis of fused tetracyclic oxindoles by quadruple aminocatalytic cascade reactions.

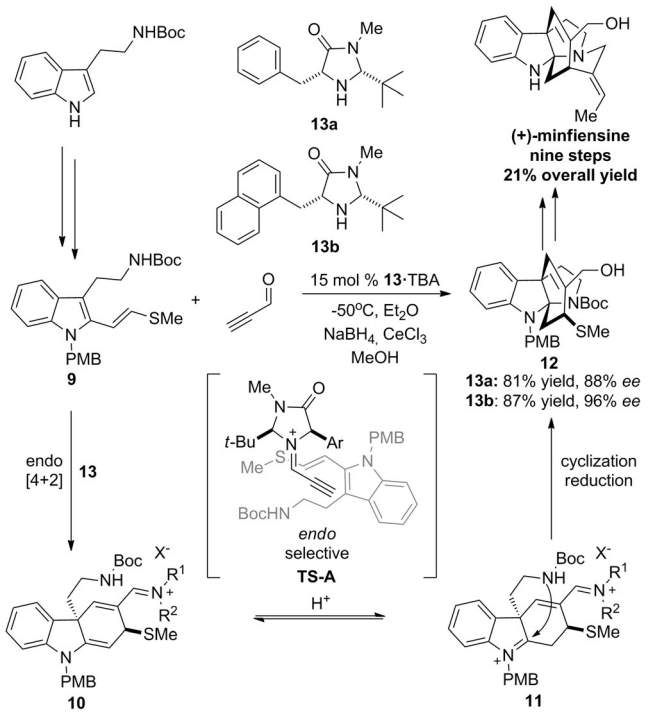
alent of α,β-unsaturated aldehyde and the intermediate **4**, leading to the final products **2**.

Complicated indole derivatives have drawn considerable attention because it was difficult to synthesize them but their structure motif can be frequently found in natural products and pharmaceuticals. Therefore, it is of great interest to develop catalytic enantioselective synthetic methods to construct them. You and co-workers have developed an intramolecular Michael/Mannich cascade reaction of indolyl methyl enones **5** catalyzed by a quinine-derived primary amine **7**, and a series of tetracyclic indole derivatives **6** were synthesized in high yields with good diastereoselectivities and excellent enantioselectivities (Scheme 2a).[16] Under the optimal reaction conditions, the enantiomers of the polycyclic products could also be obtained with excellent enantioselectivities and moderate to high diastereoselectivities by using the pseudoenantiomer of **7**. To shed light on the reaction mechanism, it is desirable to isolate the intermediate. However, the indolenine intermediate **8** is very reactive and inseparable under the optimal reaction conditions. With a BINOL-derived phosphoric acid, **8a** could be obtained in 35% yield from **5a**. In the presence of a catalytic amount of **7** and 2-NBA, **8a** was smoothly converted into product **6a** in 95% yield (Scheme 2b). This result suggested that the cascade reaction very likely proceeded through an iminium-catalyzed nucleophilic Michael addition and a subsequent enamine-catalyzed intramolecular Mannich reaction. To demonstrate the synthetic utility of this methodology, an analog of (+)-kreysiginine was efficiently synthesized in 99% *ee* and the absolute configuration was in accordance with that of the natural product.



Scheme 2. (a) Enantioselective Michael/Mannich polycyclization cascade of indolylenones. (b) Preparation of **8a** and investigations into the mechanism. BINOL = 2,2′-dihydroxy-1,1′-binaphthyl; NBA = nitrobenzoic acid; PA = phosphoric acid.

The total synthesis of (+)-minfiensine was completed by MacMillan and co-workers in nine steps with 21% overall yield from commercial available starting materials.[17] One of the prominent features of this synthesis was the amazingly efficient construction of the central tetracyclic pyrroloindoline framework, which involved a novel organocatalytic Diels–Alder/amine cyclization cascade sequence using only an amine catalyst, propynal, and a simple tryptamine derivative **9** (Scheme 3). They proposed that an activated iminium ion with an acetylenic group that was partitioned away from the bulky *tert*-butyl substituent of the catalyst framework should be generated through the condensation of secondary amine catalyst **13** with propynal (**TS-A**). In this conformation, the top face of the reactive alkyne would be shielded by the aryl ring, facilitating an *endo*-selective Diels–Alder cycloaddition with 2-vinylindole **9** to produce the tricyclic diene **10** in a regioselective manner. Protonation of the enamine moiety would then give rise to an iminium ion **11**, which facilitated a 5-*exo* amine cyclization to deliver the tetracyclic pyrroloindoline **12**. A catalyst structure evaluation test has also been investigated, and the 1-naphthyl substituted catalyst **13b** provided superior yield and enantioselectivity, which was presumably due to the extended



Scheme 3. Organocatalytic Diels–Alder/amine cyclization sequence for the construction of the tetracyclic pyrroloindoline framework.

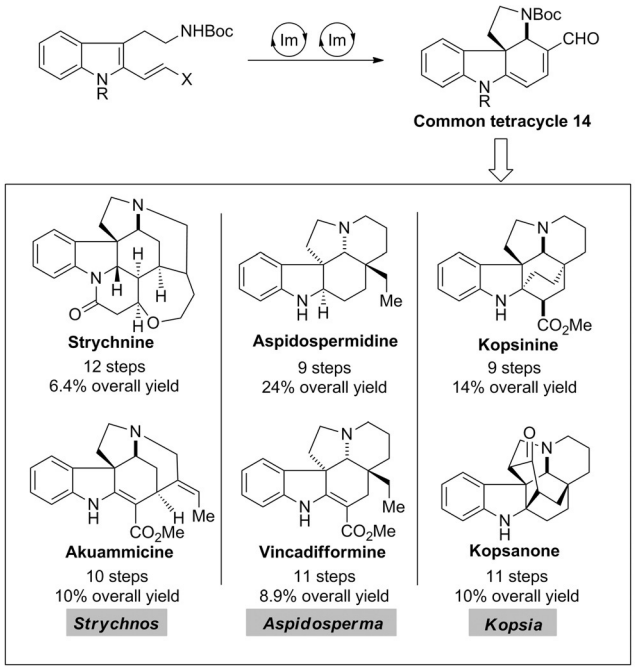
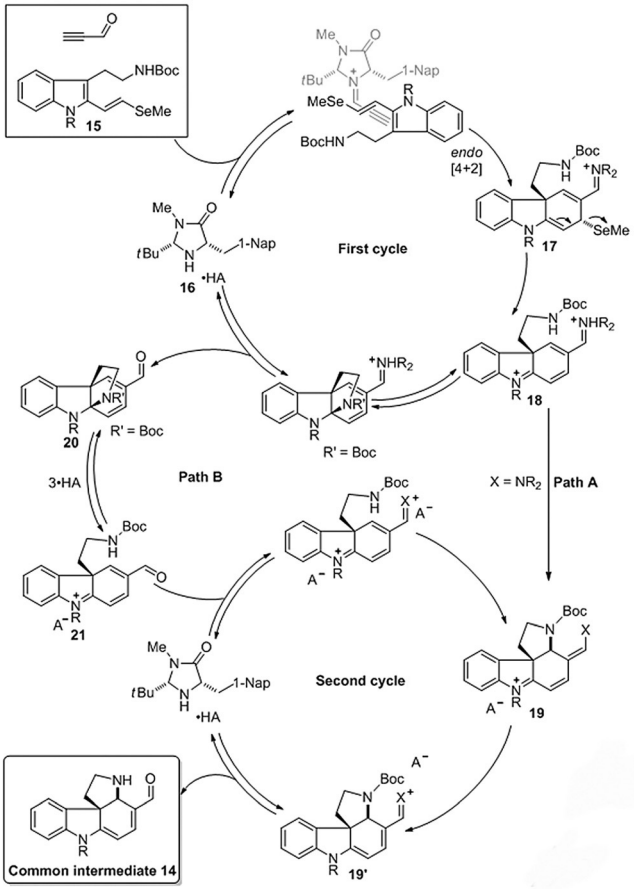


Figure 1. Collective natural product synthesis: nature-inspired applications of cascade catalysis.

shielding effect of the naphthyl ring in the [4+2] transition state. It was also important to note that the high efficiency (80% yield, 94% *ee*) of this cascade could still be maintained even with the catalyst loading as low as 5 mol%.

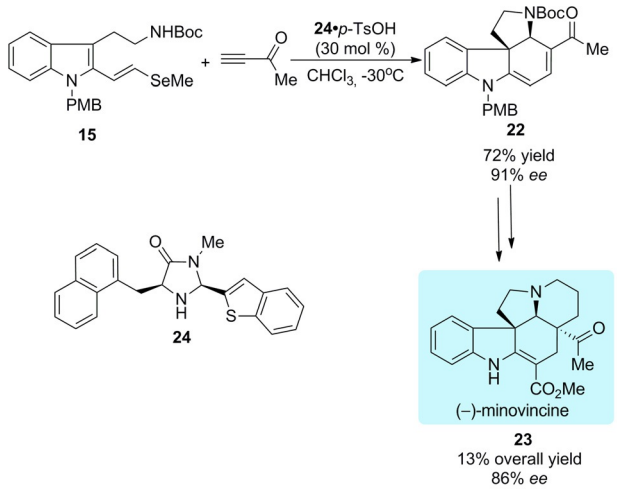
Two years later, MacMillan and co-workers demonstrated the capabilities of collective total synthesis in combination with organocascade catalysis, a synthetic strategy that facilitated the asymmetric total syntheses of six well-known alkaloid natural products: strychnine, aspidospermidine, vincadifformine, akuammicine, kopsanone, and kopsinine from a common tetracyclic intermediate **14** (Figure 1).[18] The key tetracyclic precursor **14** was established through an asymmetric Diels–Alder/β-elimination/conjugate addition organocascade sequence from a simple tryptamine-derived substrate **15**. Similar to their previous studies,[17] they proposed that an *endo*-selective Diels–Alder reaction would initiate this reaction and form the cycloadduct **17**, which would be poised to undergo facile β-elimination of methyl selenide to furnish the unsaturated iminium ion **18**. In the second cycle, iminium-catalyzed 5-*exo*-heterocyclization of the pendant carbamate might occur at the δ-position of the indolinium ion (**18**→**19**; Scheme 4, path A) to deliver the enantioenriched spiroindoline core **14** after hydrolysis. Another possibility that was also considered was that iminium **18** might undergo facile cyclization at the indoline carbon to generate pyrroloindoline **20** transiently (Scheme 4, path B). Amine or Brønsted acid catalysis might thereafter induce the necessary 5-*exo*-heterocyclization of the pendant carbamate to furnish **19**. Notably, they have gathered evidence that path B of the cascade sequence was operational. When this transformation was performed in the presence of a stoichiometric catalyst at



Scheme 4. Proposed mechanism of organocascade cycles for the generation of a common tetracyclic intermediate **14**.

−78 °C and quenched after 10 min with Et_3N, pyrroloindoline **20** (R = *p*-methoxybenzyl (PMB), 84% yield) was obtained. Moreover, both **16**·TBA (TBA = tribromoacetic acid) and *N*-methyl **16**·TBA (incapable of undergoing iminium formation) facilitated the conversion of pyrroloindoline **20** (R = PMB) to the spiroindoline **14** (R = PMB) at comparable rates.

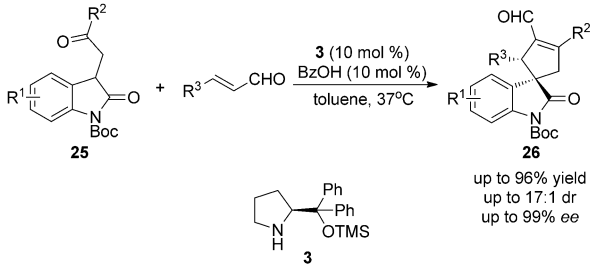
In 2013, MacMillan and co-workers completed the first enantioselective total synthesis of (−)-minovincine **23** in nine steps with 13% overall yield (Scheme 5).[19] Based on previous studies,[18] the tetracyclic core **22**, which could be synthesized from simple tryptamine-derived and ketone substrates, was also the key intermediate of this synthesis. At first, they believed that there would be a significant challenge in the amine-catalyzed Diels–Alder and cascade catalysis reactions owing to the markedly different behaviors of ketones and aldehydes. More specifically, ketones typically exhibit attenuated reactivity towards condensation with secondary amines, which would dramatically impact the overall reaction efficiency, and they are prone to nonselective iminium geometry formation with amine catalysts, leading to diminished enantioselectivity in the critical bond-forming step. Nonetheless, the tetracyclic core **22** was successfully constructed in a highly enantioselective manner with their imidazolidinone catalyst **24**.



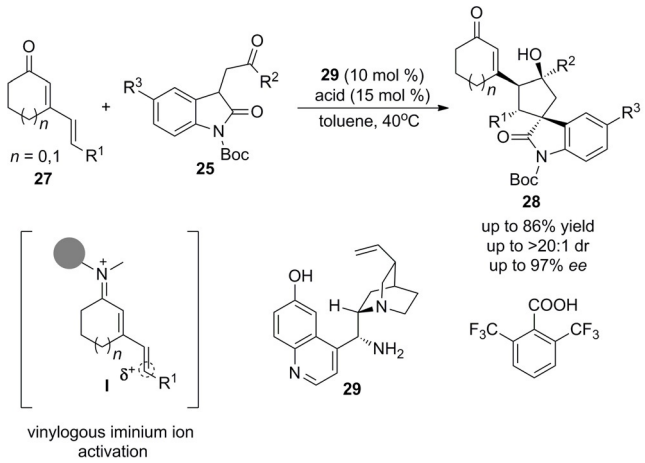
Scheme 5. Enantioselective total synthesis of (−)-minovincine.

Highly substituted chiral spirooxindoles are often found in natural products or synthetic molecules of pharmaceutical interest. Barbas and co-workers reported a highly efficient Michael–aldol cascade reaction catalyzed by commercially available second-generation prolinol ethers **3** by using the simple starting materials of 3-substituted oxindoles **25** and various α,β-unsaturated aldehydes in a single step (Scheme 6).[20] A variety of spirocyclopentaneoxindoles **26** were obtained in high yields with excellent diastereo- and enantioselectivities.

In 2012, Melchiorre and co-workers discovered that the cinchona-based primary amine could condense with β-substituted cyclic dienones **27**, which facilitated the formation of an extended iminium ion intermediate **I**, with an enhanced electrophilic character at the δ-carbon atom through the conjugated



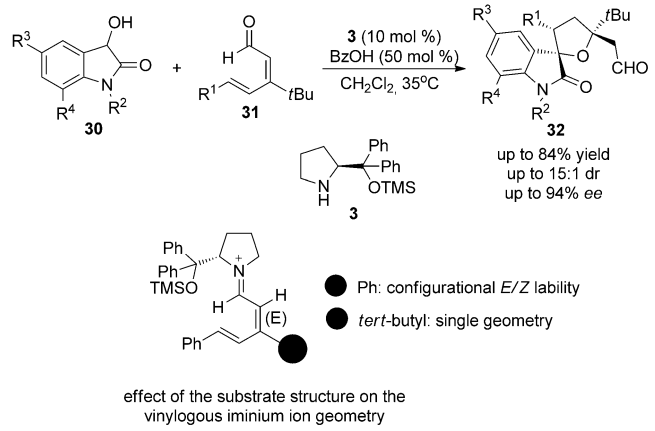
Scheme 6. Synthesis of highly substituted chiral spirocyclopentane oxindoles.



Scheme 7. Synthesis of spirocyclopentane oxindoles using the strategy of vinylogous organocascade catalysis.

π system of cyclic α,β,γ,δ-unsaturated dienones (Scheme 7). The resulting vinylogous iminium ion activation accounted for a highly δ-site- and enantioselective 1,6-addition of alkyl thiols.[21] Then, in 2013, they expanded this activating mode and established the first example of vinylogous organocascade catalysis.[22] Highly enantioenriched spirocyclopentane oxindoles **28** were established through the δ-addition/aldolization sequence from β-substituted cyclic dienones **27** and 3-substituted oxindoles **25** under a cinchona primary amine **29** (Scheme 7). This transformation was initiated by a rare organocatalytic 1,6-addition of a carbon-centered nucleophile and the stereochemical information was transmitted to distant positions. The resulting vinylogous iminium ion/dienamine activation sequence led to highly enantioenriched δ- and γ-functionalized chiral carbonyls with the α,β-unsaturated system preserved.

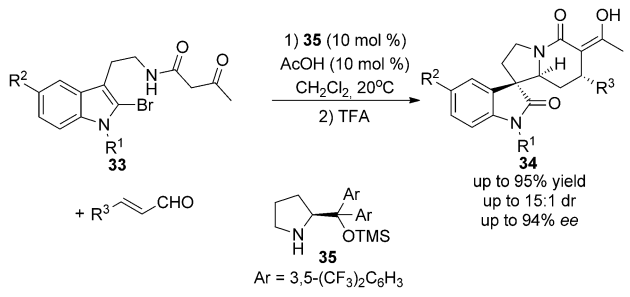
Later, the same group reported another rare example of an asymmetric 1,6-addition cascade reaction, which realized the construction of valuable tetrahydrofuran spirooxindole derivatives **32** from 3-hydroxy-2-oxindoles **30** and linear 2,4-dienals **31** with good yields and high stereoselectivities (Scheme 8).[23] This transformation was based on a δ-addition/oxa-Michael cascade reaction through a vinylogous iminium–iminium activation sequence. The main reason for the success of this reaction was the rational design of the substrates. NMR spectro-



Scheme 8. Asymmetric 1,6-addition to linear 2,4-dienals for the synthesis of tetrahydrofuran spirooxindoles.

scopic studies indicated that the iminium ion intermediate of the dienal with a Ph substituent was not configurationally stable, since a scrambling of the double-bond geometry of the α,β-olefin was observed. Therefore, they attributed the low enantioselectivity observed (46% *ee*) in the cascade reaction to the configurational lability of the substrate. The *tert*-butyl substituted dienal substrate confirmed that the defined *E,E* double-bond geometry was stable under the reaction conditions, as no isomerization was observed in the presence of the catalyst. Therefore, the inherent steric bias of the *tert*-butyl substituted dienal provided a suitable control element for high δ-site and stereoselectivity.

In addition to the cyclization reactions employing the widely used iminium–enamine and iminium–iminium sequences, iminium-activated [3+3] reactions are also common in organocatalytic cascade reactions. In 2012, Zhao and co-workers developed an asymmetric organocatalyzed one-pot, four-step cascade reaction, and highly substituted spiro[indolenine-indolizidine]s and spiro[oxindole-indolizidine]s **34** were established in good to excellent yields and enantioselectivities with moderate diastereoselectivities, and both aromatic and aliphatic α,β-unsaturated aldehydes worked well as substrates (Scheme 9).[24] The iminium-activated [3+3] reaction between masked oxindoles **33** and α,β-unsaturated aldehydes produced six-membered aza-hemiacetals, which was followed by an acid-promoted intramolecular Mannich reaction via an iminium intermedi-



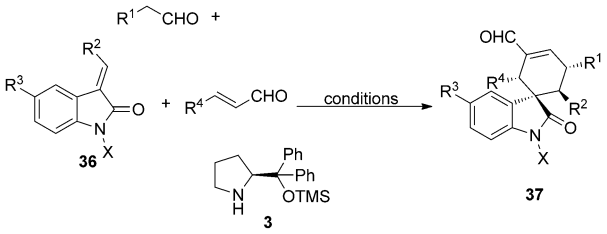
Scheme 9. Synthesis of highly functionalized spirotetracyclic indolenines and oxindoles.

ate to afford the tetracyclic spiral compounds. This methodology is potentially useful in the synthesis of spirooxindole alkaloids and their analogs.

2.2. Enamine-activated cascade reactions

Cascade reactions initiated by enamine catalysis in the initial step are defined as enamine-activated cascade reactions, although the following steps can use iminium, enamine, or other cyclization modes. Besides the iminium and enamine modes, catalytic modes including dienamine catalysis and trienamine catalysis have also been developed.

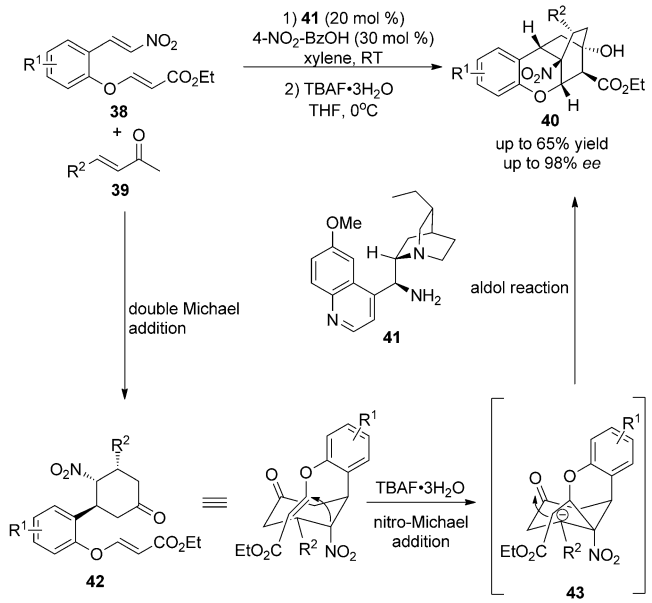
As a versatile strategy, enamine catalysis, which was first introduced by List in 2000, has developed rapidly, especially its extensive application in cascade reactions. Melchiorre[25a] and Chen[25b] et al. independently reported an efficient one-pot, three-component cascade reaction of aliphatic aldehydes, 3-olefinic oxindoles **36**, and α,β-unsaturated aldehydes to deliver spirooxindoles containing a six-membered cyclic moiety **37**



Scheme 10. A formal [2+2+2] annulation or the asymmetric synthesis of spirocyclic oxindoles.

with excellent diastereo- and enantioselectivities (Scheme 10). Both protocols proceeded through a formal [2+2+2] annulation strategy by a sequential amine-based organocatalytic Michael/Michael–aldol cascade. Chen and co-workers have also studied other electrophiles than α,β-unsaturated aldehydes, and a series of carbocyclic and heterocyclic spirooxindoles were synthesized with good results.

In 2011, our group developed an efficient method for the synthesis of a novel complex tetracyclic ring system **40** containing both chroman and bicyclo[2.2.2]octane structural units through a four-step sequential reaction from nitroolefinenoates **38** and α,β-unsaturated ketones **39** (Scheme 11).[26] Industrially important cyclohexanones **42** were obtained through a Michael/Michael cascade catalyzed by a cinchona primary amine **41**. Then, the intramolecular nitro-Michael addition promoted by tetra-*n*-butylammonium fluoride (TBAF·3 H_2O) afforded intermediates **43**, which underwent a further intramolecular aldol reaction to afford the final products **40** in satisfactory yields with excellent stereoselectivities. Remarkably, this cas-

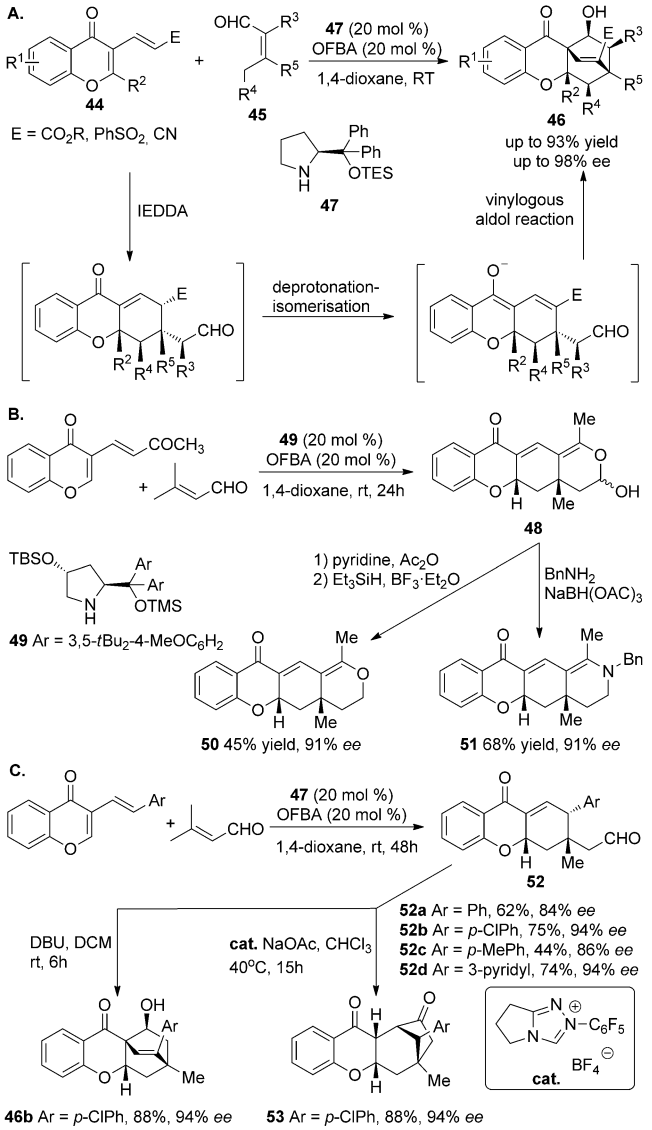


Scheme 11. Synthesis of a novel tetracyclic ring system by a four-step sequential reaction.

cade reaction was highly efficient as six stereogenic centers, including two chiral quaternary stereocenters, were stereospecifically controlled in the construction of this tetracyclic ring.

The strategy of dienamine catalysis was first introduced by Jørgensen et al. in 2006. Since then, highly stereoselective γ-functionalizations of α,β-unsaturated aldehydes have been accomplished by chiral secondary amine catalysis,[27] which has attracted wide attention from chemists. In 2010, Melchiorre et al. developed a dienamine catalysis process by chiral primary amine catalysis, which realized the alkylation of the γ-position of α,β-unsaturated ketones.[28] So far, the dienamine catalysis mode has been broadly applied in asymmetric cascade reactions.

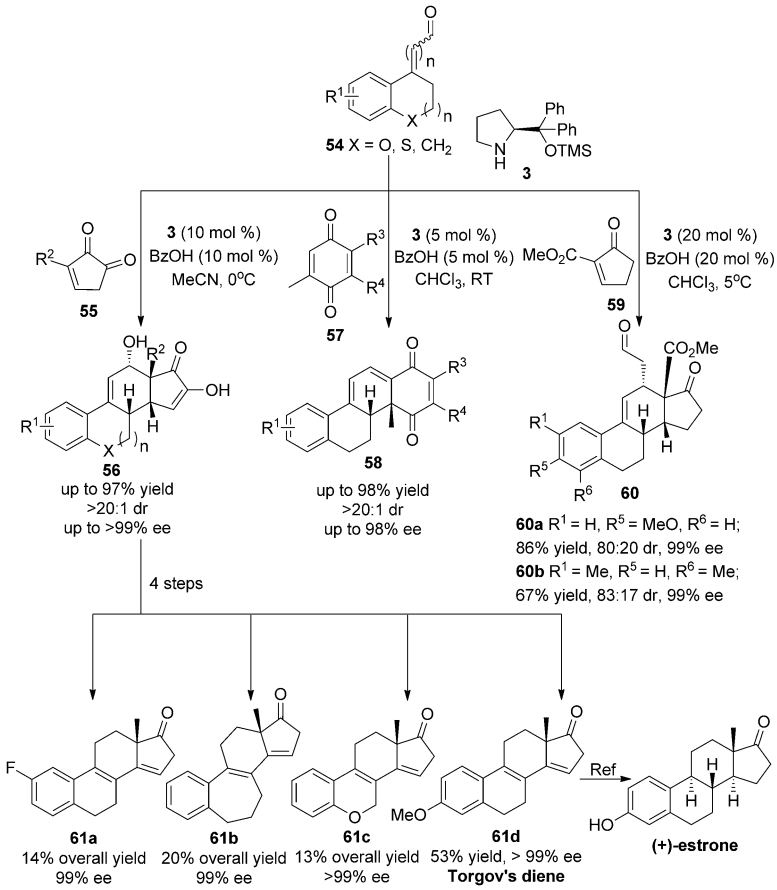
In 2012, Chen's group described an asymmetric cascade reaction of chromone-fused dienes **44** with β,β-disubstituted α,β-unsaturated aldehydes **45** by dienamine catalysis, and tetrahydroxanthone derivatives **46** with up to three quaternary stereocenters were constructed in good yields with excellent stereoselectivities (Scheme 12).[29] By using chiral secondary amine catalyst **47**, the main chiral tetrahydroxanthone scaffold, which has been found in a large number of natural products, was efficiently built through an asymmetric inverse-electron-demand Diels–Alder (IEDDA) reaction, followed by a domino deprotonation/isomerization/vinylogous aldol sequence (Scheme 12 A). Interestingly, a different cascade reaction occurred when a chromone-fused diene containing an acetyl group was applied (Scheme 12 B). A tetracyclic hemiacetal product **48** was obtained as a diastereomeric mixture when a bulky chiral amine **49** was used. After simple transformations, dihydropyran **50** and piperidine derivative **51** were produced as single diastereomers with high enantiocontrol. In addition, 3-styryl-substituted chromones could also be successfully used in the Diels–Alder cycloaddition with 3-methylcrotonaldehyde and the IEDDA products **52 a**–**52 d** were isolated in moderate



Scheme 12. Dienamine-catalyzed inverse-electron-demand Diels–Alder reaction for the synthesis of tetrahydroxanthone derivatives. OFBA = *o*-fluorobenzoic acid.

yields but still with high stereocontrol (Scheme 12 C). The domino cyclization did not occur owing to the decreased acidity of the vinylogous C–H. Nevertheless, the similar caged product **46 b** could be synthesized in high yield by the intramolecular vinylogous aldol reaction by adding 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). Furthermore, an intramolecular Stetter reaction could also be smoothly carried out to obtain bicyclo[3.2.1]octane bridged system **53** with exclusive diastereocontrol.

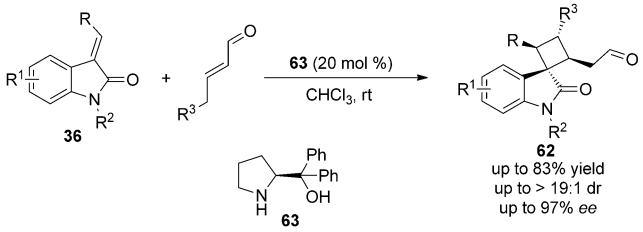
Recently, Jørgensen et al. developed a simple and novel organocatalytic cascade approach to produce a diverse range of 14β-steroids from (di)enals and cyclic dienophiles in the presence of a TMS-protected prolinol catalyst (Scheme 13).[30] A variety of optically active steroids **56** with different substituents at the A ring were constructed by this new reaction in high yields with greater than 99% *ee*. Interesting variations on the B ring were also investigated. A seven-membered ring as well as



Scheme 13. Asymmetric cycloaddition reactions for the synthesis of 14β-steroids.

an oxygen or sulfur atom in the 6-position could be incorporated with excellent stereoselectivities. Further variations of the D ring have also been explored through dienamine catalysis, and quinone-based dienophiles **57** were identified as suitable reaction partners, leading to D-homosteroids **58** with excellent results. To achieve variations on the C ring, a trienamine catalysis strategy was utilized to facilitate the stereoselective incorporation of an alkyl substituent at the 12-position. It was found that the dienals **54** could react with dienophile **59** to afford the products **60a**,**b** in good to excellent yields with good diastereoselectivities and excellent enantioselectivities. Furthermore, analogs of Torgov's diene **61** could be rapidly obtained from the formed products **56**. From these compounds, 14α-steroids such as (+)-estrone and related steroids with variations on the A and B rings were accessible.

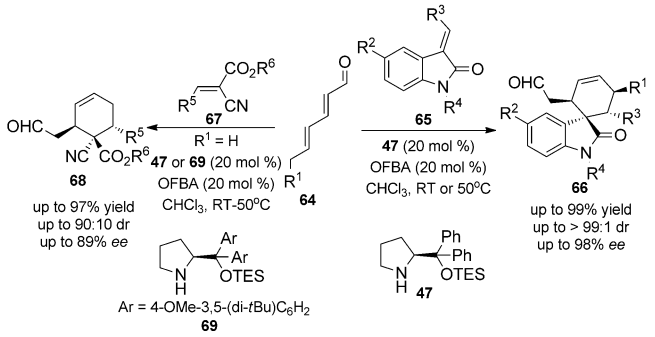
The same year, Wang and co-workers successfully developed the first organocatalytic asymmetric synthesis of a spirooxindole skeleton with a cyclobutane moiety through a formal [2+2] cycloaddition reaction on the basis of hydrogen-bond-directing dienamine activation.[31] Structurally complex spirocyclobutyl oxindoles **62**, which possess four contiguous stereocenters, including one spiro quaternary center, were obtained in good yields with excellent β,γ-regioselectivities and stereocontrol from ethyleneindolinones **36** and α,β-unsaturated aldehydes (Scheme 14). A wide range of methyleneindolinones were investigated and a remarkable substituent effect was observed



Scheme 14. A formal [2+2] cycloaddition reaction for the construction of spirocyclobutyl oxindoles.

on the stereoselectivity. Electron-donating groups on the aromatic ring of methyleneindolinones provided the desired cycloadducts in good yields with excellent diastereoselectivities and enantioselectivities (73–77% yield, 12:1 to >19:1 d.r., 97% *ee*), whereas the corresponding electron-withdrawing counterparts, regardless of the substitution position, gave good yields but moderate diastereoselectivities and slightly decreased enantioselectivities (69–83% yield, 3:1–9:1 d.r., 81–92% *ee*). The steric hindrance of the ester group on methyleneindolinone influenced the diastereocontrol markedly. Interestingly, the reactions could also proceed smoothly with excellent stereocontrol when the ester group was replaced by an acetyl or benzoyl group (70–76% yield, 6:1–10:1 d.r., 92–94% *ee*). However, the reaction did not work well when γ-alkyl-substituted enal was used.

A new activation mode of trienamine catalysis, which achieved perfect chirality relay over a distance of up to eight bonds and the functionalization of the ε-position of 2,4-dienals **64**, was developed by Jørgensen and Chen et al. (Scheme 15).[32] The reactive trienamine intermediate, which



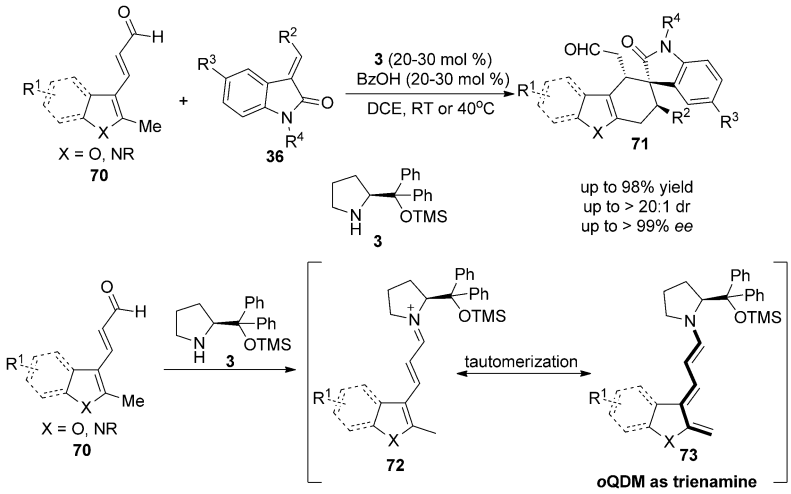
Scheme 15. The application of trienamine catalysis in cascade reactions.

was generated in situ through the combination of the optically active secondary amine and 2,4-hexadienals **64**, was a suitable diene for different electron deficient dienophiles. Spirocyclic oxindoles **66** were obtained with high yields (up to 99%) and selectivities (up to 98% *ee*) from 2,4-hexadienals **64** and 3-olefinic oxindoles **65** by the Diels–Alder reaction in the presence of chiral amine **47**. In a similar fashion, olefinic cyanoacetates **67** also provided multifunctionalized cyclohexenes **68** with high yields (up to 97%) and stereoselectivities (up to 89% *ee*) by using a secondary amine catalyst **69** or **47**. Furthermore, they also presented a trienamine–enamine sequence activated multicomponent cascade reaction that gave good yields with excellent enantioselectivity. Detailed NMR spectroscopic studies and calculations of the reactive trienamine intermediates were performed to rationalize the origin of the stereochemistry. No doubt, these cascade reactions by trienamine catalysis provided an efficient approach for the asymmetric synthesis of some complicated molecules.

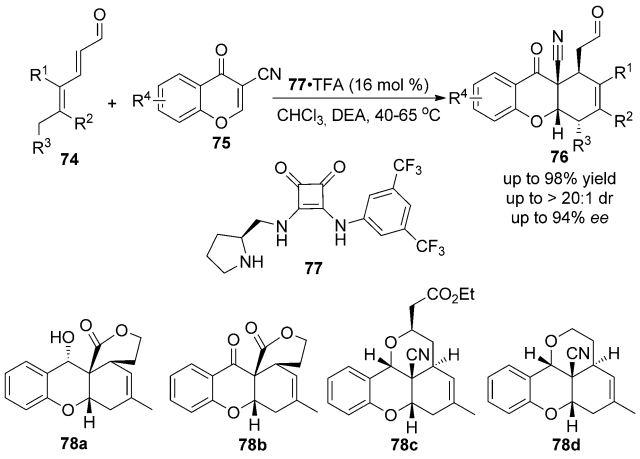
In another context, Melchiorre and co-workers reported the first asymmetric catalytic Diels–Alder reaction of the in situ generated heterocyclic *ortho*-quinodimethanes (*o*QDMs) by trienamine catalysis (Scheme 16).[33] The catalytic reaction was hypothesized to proceed through the condensation of enals **70** and chiral amine catalyst **3** to give the intermediate **72**. Tautomerization with dearomatization of **72** eventually furnished trienamine intermediate **73** as the activated diene. It is worth noting that reactive diene species had never been applied in a catalytic approach before. A series of complicated polycyclic heteroaromatic compounds **71**, which would be difficult to synthesize by other catalytic methods, were obtained in high yields (up to 98%) with excellent selectivities (up to >20:1 d.r. and >99% *ee*).

The first hydrogen-bond-directed trienamine-mediated [4+2] cycloaddition was developed by Jørgensen and co-workers.[34] Tetrahydroxanthone derivatives **76** were smoothly produced from diversely substituted 2,4-dienals **74** and various 3-cyanochromones **75** under optimized conditions in the presence of a squaramide-containing aminocatalyst **77** with high yields (up to 98%) and selectivities (up to 94% *ee*; Scheme 17). Furthermore, they have demonstrated the derivatizations of the obtained cycloadducts, which provided polycyclic products **78a**–**78d** with high molecular and stereochemical complexity and which possess up to five stereogenic centers, in a chemo- and diastereoselective manner. Finally, they also provided a rationalization for the observed unexpected stereochemistry of the transformation.

The new concept of cross-trienamine catalysis was introduced by the same group.[35] Highly enantioselective Diels–Alder reactions proceeded through cross-trienamine intermediate **85** at the γ′ and δ positions instead of the more stabilized linear trienamine intermediate. Based on the computational and experimental results, the cross-trienamine catalyzed reactions proved to be thermodynamically driven to give the more stable [4+2] products **87** rather than the kinetic control products **86**. Utilizing this efficient strategy, functionalized bicyclo[2.2.2]octenes **81** with four stereocenters were obtained



Scheme 16. Asymmetric catalytic Diels–Alder reaction of in situ generated heterocyclic *ortho*-quinodimethanes.

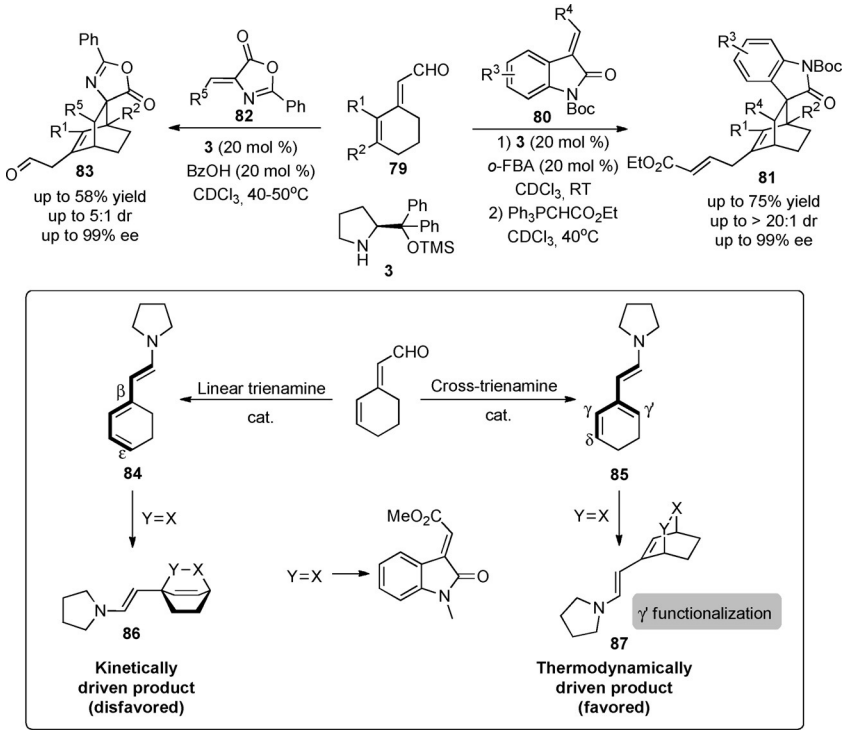


Scheme 17. Hydrogen-bond-directed trienamine-mediated [4+2] cycloaddition for the synthesis of tetrahydroxanthone derivatives. DEA = *N*,*N*-diethylacetamide.

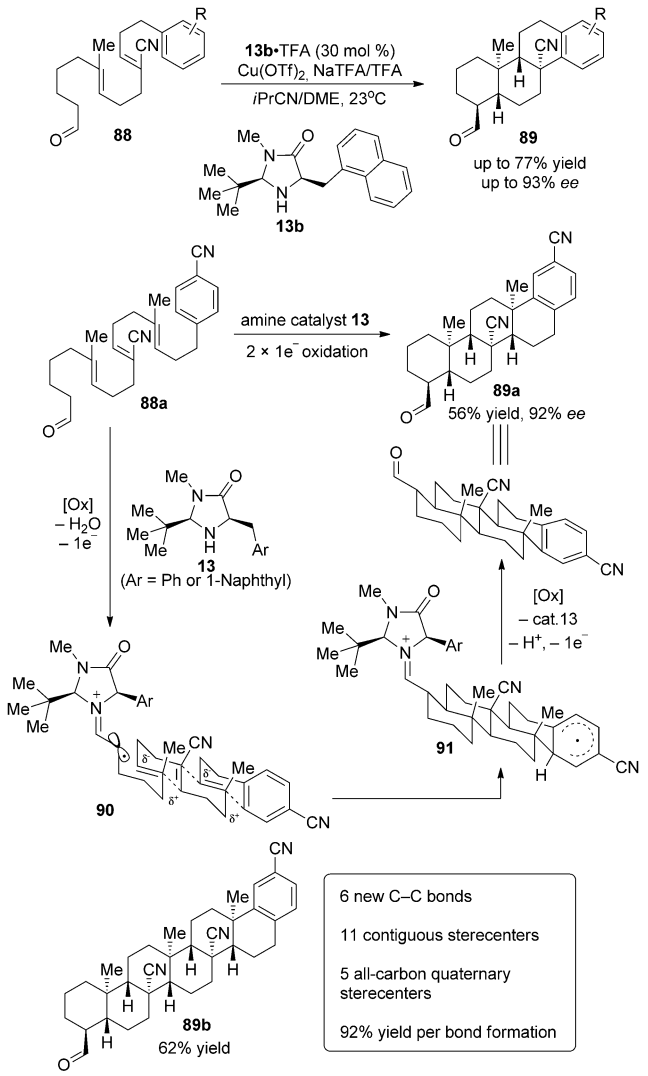
from cyclic 2,4-dienals **79** and 3-olefinic oxindoles **80** in good yields (up to 75%) with high stereoselectivities (up to 99% *ee*). When olefinic azlactones **82** were used as dienophiles, functionalized bicyclic compounds **83** were produced with good results (up to 58% yield, 5:1 d.r., and 99% *ee*; Scheme 18). They also investigated the γ′-addition of cross-trienamines with vinyl bissulfones, which proceeded in a highly enantioselective manner.

2.3. SOMO catalytic cascade reactions

In 2007, MacMillan and co-workers developed a novel activation strategy of SOMO (singly occupied molecular orbital) catalysis and efficiently realized the asymmetric allylation of aldehydes.[36] Later, in 2010, they developed the first catalytic enantioselective cyclization reaction for accessing steroidal and terpenoidal frameworks **89** with this strategy (Scheme 19).[37] A reasonable mechanism has been proposed. They hypothesized that the functionalized aldehyde **88a** with tethered unsaturation would condense with imidazolidinone catalyst **13** to give α-imino radical intermediate **90** upon oxidation with a Cu^{2+} oxidant. At this stage, they expected that cyclohexadienyl radical **91** would be generated through a series of 6-*endo*-*trig* radical cyclizations terminated by a suitable arene from radical cation **90**. A second oxidation step would then furnish the corresponding cyclohexadienyl cation, which would deliver pentacycle **89a** upon rearomatization and liberation of the catalyst. A series of polycyclic cascade products were successfully synthesized in good yields (up to 77%) with high stereoselectivities (up to 93% *ee*). It is important to note that all the products of this survey were obtained as single diastereomers. It is also worth mentioning that the hexacyclization adduct **89b** could be constructed through this new SOMO-polyene cyclization concept as a single diastereomer in 62% yield (corresponding to an average yield of 92% per bond formed). In the course of this cascade bond construction, a total of eleven contiguous stereocenters, of which five are all-carbon quaternary centers, were formed from a simple acyclic starting material under the influence of imidazolidinone **13b**.



Scheme 18. Cross-trienamines in asymmetric organocatalytic Diels–Alder reactions.



Scheme 19. Enantioselective cyclization for accessing steroidal and terpenoidal frameworks by organo-SOMO catalysis.

3. Asymmetric Hydrogen-Bonding Catalytic Cascade Reactions

Hydrogen bonding, one of the most dominant forces for molecular interaction and recognition in biological systems, plays a central role in biocatalysis. In recent years, with the rapid development of organocatalysis, the hydrogen-bonding activation of electrophiles by organocatalysts has attracted great attention from chemists, and the development of a wide range of applications of hydrogen-bonding activation makes it a significant activation mode for organocatalysis. The most common hydrogen-bonding catalysts include chiral ureas, chiral thioureas, chiral squaramides, chiral phosphoric acids, catalysts with aromatic hydroxyl groups, and so on.

3.1. Chiral urea and thiourea catalyzed cascade reactions

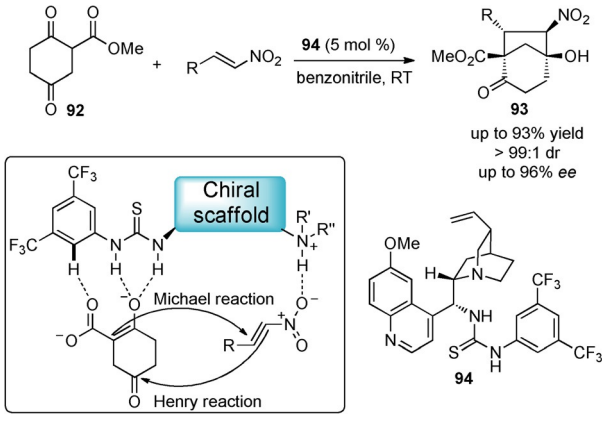
In 1998, the Jacobsen group disclosed a highly enantioselective Strecker reaction of *N*-allyl aldimines promoted by a chiral α-amino acid-derived catalyst.[38] This transformation demonstrated that chiral thioureas could efficiently control the reaction stereoselectivity and opened the door to unprecedented asymmetric catalysis. Since then, several enantioselective nucleophilic additions catalyzed by chiral urea/thiourea derivatives have been reported by the same group.[39]

Although chiral urea/thiourea derivatives can smoothly catalyze various asymmetric approaches, their application to enantioselective reactions was limited in the early stages of organocatalysis owing to their weaker acidities than metallic Lewis acids.

To enhance the catalytic activities of thiourea catalysts, Takemoto and co-workers designed chiral bifunctional thioureas bearing a tertiary amino group and applied them to highly enantioselective Michael additions of dimethylmalonate to nitroalkenes.[40] They demonstrated that thioureas could catalyze the reaction through a bifunctional mechanism, in which the thiourea moiety activated the nitroalkene electrophile by hydrogen bonding while the basic amine deprotonated the pronucleophile. The control experiments showed that in the absence of thiourea or tertiary amino group, the reaction gave poor results under the same conditions.

With the development of this highly active bifunctional thiourea catalyst, asymmetric approaches catalyzed by chiral thioureas attracted even broader attention. Various types of chiral thioureas were synthetized and applied to cascade reactions, which realized the synthesis of many chiral compounds with high stereoselectivities. These reported catalysts were mainly derived from some natural chiral molecules such as cinchona alkaloids, chiral amino acids, chiral diamines, and so on.

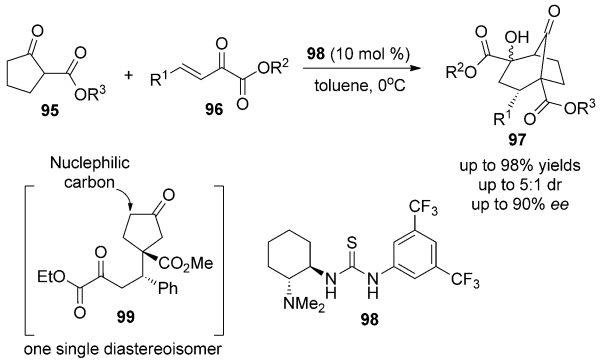
The bicyclo[3.2.1]octane skeleton is an ubiquitous skeleton present in a number of biologically active natural products and pharmaceuticals. Zhong and co-workers reported a highly enantio- and diastereoselective cascade Michael/Henry reaction for the synthesis of medicinally important bicyclo[3.2.1]octane derivatives **93** with four stereogenic centers, including two quaternary stereocenters, under a cinchona-based bifunctional thiourea catalyst **94** (Scheme 20).[41] To rationalize the origin of the excellent stereoselectivities, they proposed a novel dual activation mode from calculations of the transition states, in



Scheme 20. Synthesis of bicyclo[3.2.1]octane derivatives by a Michael/Henry cascade reaction.

which the thiourea group and an acidic proton of the phenyl ring activated the 1,3-dicarbonyl substrates and the tertiary amine activated the nitro group at the same time. A variety of nitroolefin Michael acceptors, which possess neutral, electron-donating, and electron-withdrawing groups on the phenyl ring, have been investigated in this process. It appeared that the electronic and steric nature of the substituents had only minimal impact on efficiencies, enantioselectivities, and diastereoselectivities of the Michael/Henry reactions.

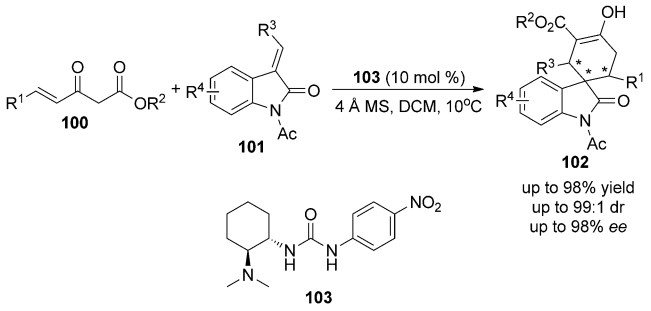
Alexakis's group disclosed another process for the direct preparation of bicyclo[3.2.1]octane derivatives **97** through an enantio- and diastereoselective organocatalytic domino Michael/aldol reaction (Scheme 21).[42] The reaction tolerated



Scheme 21. Synthesis of bicyclo[3.2.1]octane derivatives by a Michael–aldol cascade.

a large variety of substituents on the β,γ-unsaturated 1,2-ketoesters **96** and cyclic 1,3-ketoesters **95**. β,γ-Unsaturated 1,2-ketoesters with *para* and *meta* positioned substituents provided polysubstituted bicyclo[3.2.1]octanes in high yields (up to 97%) with moderate diastereoselectivities (up to 5:1 d.r.) and good enantioselectivities (up to 88:12 e.r.). Interestingly, with the substituents in the *ortho* position, the corresponding bicyclic structures were obtained in lower yields but with higher enantioselectivities (up to 95:5 e.r.). Mechanistic investigations were performed to understand this catalytic system. Product **99**, which was the intermediate formed by the 1,4-addition, was isolated after 1 day at 0 °C with excellent diastereoselectivity (>20:1 d.r.) and good enantioselectivity (90:10 e.r.). As the nucleophilic carbon of the intramolecular aldol reaction was on the same rigid five-membered cycle as the stereogenic center previously formed after 1,4-addition, its stereochemistry was affected by and depended on that of the newly formed stereogenic center. Only the configuration of the alkoxy ester was determined according to the attack face of the dicarbonyl group. Therefore, they concluded that the second step determined the diastereoselectivity of the domino process, with the first step being totally diastereoselective.

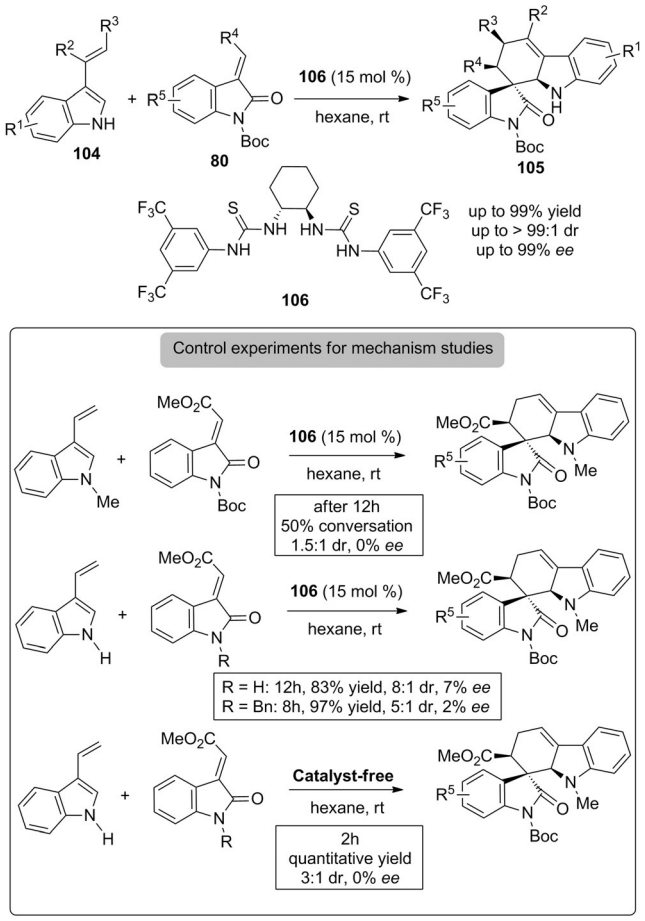
Spirooxindole skeletons can be found in a large number of natural products and bioactive molecules, however, some asymmetric synthetic challenges still exist for the construction of the quaternary carbon stereocenter. Therefore, it is a research hotspot to synthesize this type of compound by asymmetric organocatalytic cascade reactions. Gong and co-workers reported an efficient formal [4+2] cycloaddition reaction between methyleneindolinones **101** and Nazarov reagents **100** catalyzed by a bifunctional chiral urea **103**, providing a series of diverse biologically active spiro[cyclohexane-1,3′-indoline]-2′,4-dione derivatives **102** with excellent stereoselectivities (Scheme 22).[43] This transformation involved a sequential Mi-



Scheme 22. Asymmetric formal [4+2] cycloaddition for the synthesis of spiro[4-cyclohexanone-1,3′-oxindoline] derivatives.

chael–Michael process in which two substrates were activated synergistically by the bifunctional chiral catalyst through hydrogen-bonding interactions. The derivatization of the obtained products has also been investigated and the medicinally important spiro[cyclohexane-1,3′-indoline]-2′,4-dione derivative was obtained in three steps and with good results (71% yield, 95% *ee*).

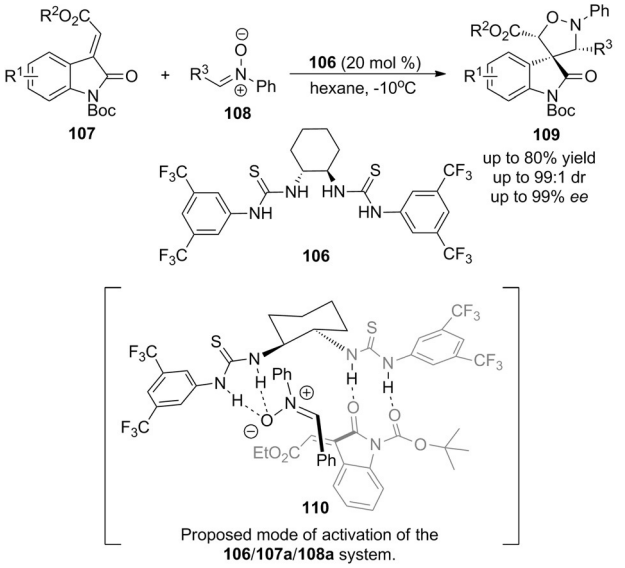
Barbas and co-workers have developed a very rapid and efficient organocatalytic Diels–Alder reaction with a simple bisthiourea **106** from 3-vinylindoles **104** and methyleneindolinones **80**.[44] Under very mild reaction conditions, carbazoles-pirooxindole derivatives **105** were constructed in almost quantitative yields with excellent stereoselectivities (>99:1 d.r., up to 99% *ee*; Scheme 23). There was no change in reactivity or stereoselectivity when the reaction was carried out on a gram scale. In addition, the catalyst and solvent could be readily recycled by simple operations. Based on those two features, this method should be suitable for large-scale chemical production. Mechanistic studies have also been performed. In ^{1}H and ^{13}C NMR experiments, no evidence for an interaction between the catalyst and 3-vinylindole was found, whereas a strong interaction between the catalyst and methyleneindolinone was observed in NMR experiments. The poor stereocontrol obtained with 1-methyl-3-vinylindole indicated that the N–H group of the vinylindole is essential, which suggested that the stereoselectivity should be related to additional interactions between the oxindole and vinylindole reagents. Furthermore, the effects of the N-methyleneoxindole protecting group on the *ee* were striking. A bulky electron-acceptor group at the 3-position was necessary, as only Boc-protected 3-methyleneoxindole derivatives provided stereocontrolled products. In the absence of the catalyst, the reaction was significantly slower and required several hours to complete. On the basis of these data, the authors hypothesized that vinylindole might be directed or oriented by



Scheme 23. Enantioselective Diels–Alder reaction catalyzed by a bisthiourea for the construction of carbazolespirooxindole derivatives.

the interactions between the N–H group of the diene and the Boc group of the dienophile through π–π and weak hydrogen-bonding interactions prior to C–C bond formation. This would provide a well-organized environment for asymmetric induction as well as a pocket to enable this reaction to proceed smoothly.

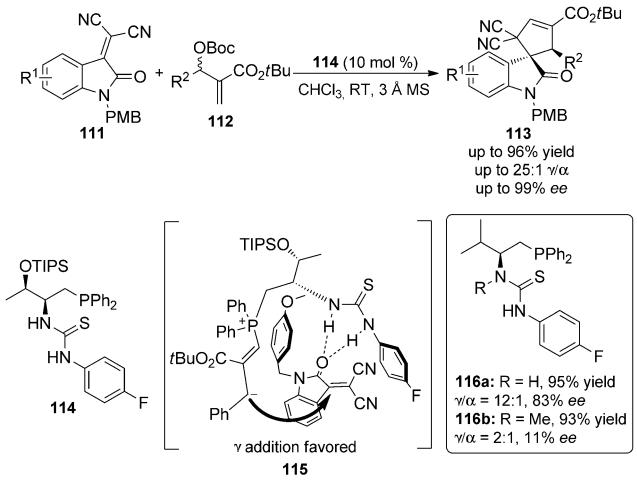
With the same bisthiourea catalyst **106**, Zhu and Cheng et al. disclosed a [3+2] annulation of methyleneindolinones **107** with nitrones **108** to construct enantioenriched spiro[isoxazolidine-3,3′-oxindole] derivatives **109** in good yields with excellent enantio- and diastereoselectivities (Scheme 24).[45] Interestingly, only Boc-protected 3-methyleneoxindole derivatives **107** could provide the product stereoselectively, whereas the corresponding benzyl- or methyl-protected products were not detected. Mechanistic studies were performed based on MS and NMR spectroscopy analysis. When catalyst **106** was mixed with methyleneindolinone **107a** (R^1 = H, R^2 = Et) and 1,3-dipolar nitrone **108a** (R^3 = Ph), a new species characterized by a base peak at m/z = 1171.08 was detected and assigned to be **106** + **107a** + **108a**. In the NMR experiments, the spectra gave strong evidence for interactions between the catalyst and both substrates. They proposed that this highly convenient and practical approach was realized through synergistic multiple hydrogen-bonding interactions between the bisthiourea cata-



Scheme 24. Enantioselective [3+2] annulation catalyzed by a bisthiourea as a multiple hydrogen-bond donor.

lyst **106** and the two substrates (**110**). A gram-scale experiment was also carried out and gave the desired product with good results (75% yield, 98:2 d.r., 95% *ee*).

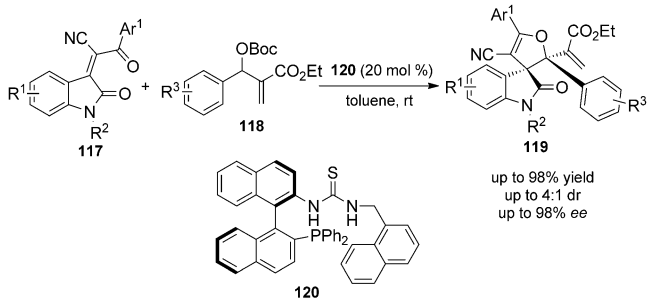
In 2011, Lu and co-workers developed a threonine-derived thiourea–phosphine **114** catalyzed stereoselective [3+2] cycloaddition process between Morita–Baylis–Hillman (MBH) carbonates **112** and isatin-derived tetrasubstituted alkenes **111**, which produced a series of biologically important 3-spirocyclopentene-2-oxindoles **113** with two contiguous quaternary centers (Scheme 25).[46] It is worth noting that this was the first example of MBH carbonates as C_3 synthons in asymmetric [3+2] annulation reactions. Excellent yields (up to 96%) and selectivities (up to 25:1 γ/α, up to 99% *ee*) were attainable for all the examples examined. Notably, the presence of *ortho*-substituted aryls in **112** resulted in reduced regioselectivity and enantioselectivity (4:1 γ/α, 87% *ee*). In addition, the MBH carbonate



Scheme 25. Asymmetric [3+2] annulation reactions of MBH carbonates catalyzed by threonine-derived thiourea–phosphine catalyst.

bearing an alkyl group has also been tested, although only a modest *ee* value (65%) was observed. A dual activation mode was proposed, with nucleophilic phosphine attack on the MBH carbonate to yield the phosphonium salt and the isatin-derived electrophile being activated by the thiourea through hydrogen bonding at the same time. The observed γ selectivity might be attributed to the steric hindrance induced by the *N*-PMB group of **111** in the key cycloaddition step, but potential aromatic interactions could not be excluded at this stage. The control experiment disclosed the crucial role of the hydrogen-bonding interactions between the thiourea moiety of the catalyst and the isatins in asymmetric induction. Compared with the normal catalyst, the methylated phosphine thiourea would give the [3+2] annulation product with poor selectivity (**116a** vs **116b**).

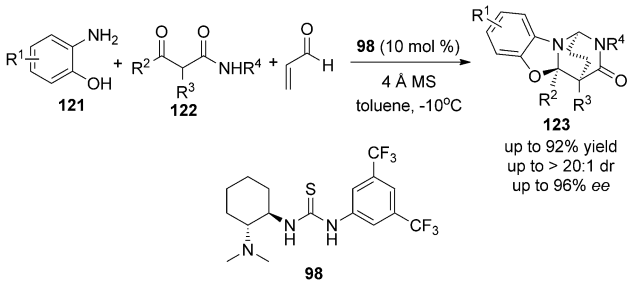
In 2014, Shi and co-workers developed another axially chiral binaphthyl scaffold derived bifunctional thiourea–phosphine **120** catalyzed asymmetric cascade reaction.[47] The [4+1] annulation of activated α,β-unsaturated ketones **117** with MBH carbonates **118** was successfully realized. A series of spirooxindoles **119** with two adjacent quaternary stereocenters were obtained in good yields with high enantioselectivities and moderate diastereoselectivities (Scheme 26). Interestingly,



Scheme 26. Asymmetric [4+1] annulation reactions of MBH carbonates catalyzed by binaphthyl-derived thiourea–phosphine catalyst.

when *N*-unprotected α,β-unsaturated ketones were used, the corresponding [4+1] annulation products were obtained with lower yields (up to 65% yield) but with excellent enantioselectivities (90–96% *ee*) and moderate d.r. values (up to 3:1 d.r.). Moreover, when a methyl group was introduced into the aromatic ring of the MBH carbonate, the reactivity decreased remarkably with no desired product formed.

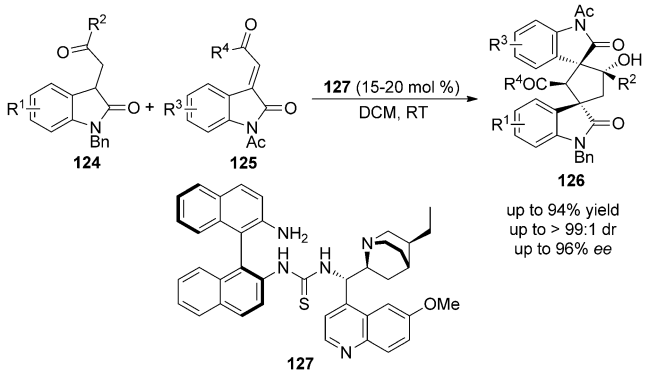
Bugaut and Constantieux described an one-pot multicomponent organocatalytic cascade reaction with β-ketoamides **122**, aminophenols **121**, and acrolein, which afforded chiral functionalized 2,6-diazabicyclo-[2.2.2]octanones (2,6-DABCO) **123** in high yields with good stereoselectivities (Scheme 27).[48] This transformation involved a Michael addition/double iminium trapping sequence and established five new bonds and three stereocenters under the Takemoto catalyst **98**. Various β-ketoamides and aminophenols were studied by using this approach and a diverse range of complex 2,6-DABCO scaffolds were ob-



Scheme 27. Multicomponent cascade reaction for the synthesis of 2,6-diazabicyclo[2.2.2]octanones.

tained. A strongly electron-withdrawing group on the nitrogen atom of the amide in **122** was necessary to allow the formation of the 2,6-DABCO unit. This transformation is one of the examples that employed the Michael addition of a 1,3-dicarbonyl as the enantiodetermining step in multicomponent sequences.

Barbas and co-workers have developed a novel organocatalytic cascade Michael–aldol approach between 3-substituted oxindoles **124** and methyleneindolinones **125** for the highly efficient construction of bispirocyclic oxindole derivatives **126** under mild conditions (Scheme 28).[49] A newly designed multi-

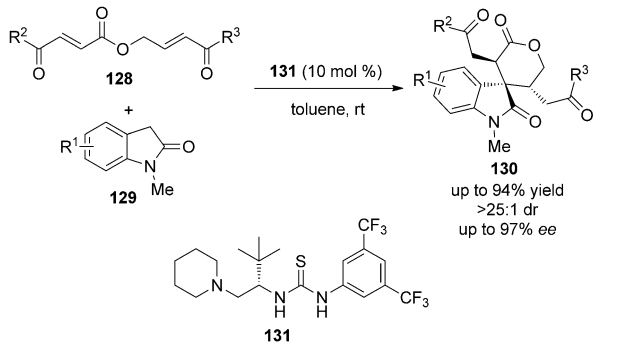


Scheme 28. Construction of bispirooxindoles by using a single multifunctional organocatalyst.

functional cinchona alkaloid **127**, which contains tertiary and primary amines and a thiourea moiety to activate substrates simultaneously, was used in this transformation, and four chiral centers including three quaternary carbon chiral centers were established with excellent stereocontrol (up to 99:1 d.r., up to 98:2 e.r.). Notably, it was observed that the electronic nature, bulkiness, and the positions of the substituents only had minimal impact on the reaction efficiencies, enantioselectivities, and diastereoselectivities. Interestingly, the opposite enantiomer was also obtained by changing the organocatalyst. This new methodology provided an efficient synthesis method for a range of complicated bispirocyclooxindole derivatives that are useful in medicinal chemistry.

The trigolute alkaloids, which possess an intriguing spirooxindole δ-lactone skeleton, were recently isolated from genus

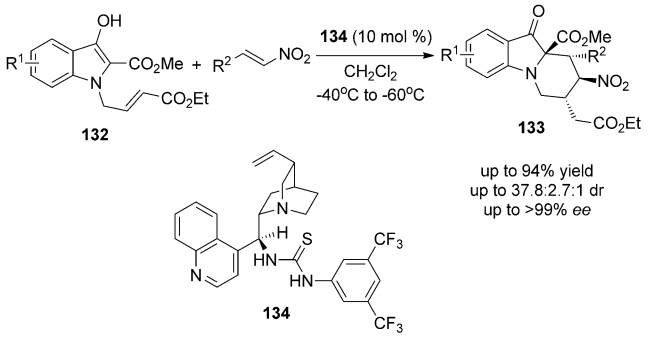
Trigonostemon. In 2014, our group developed a novel formal [5+1] cyclization for the construction of the core structure of these alkaloids.[50] In the presence of a suitable bifunctional catalyst **131**, the spirooxindole δ-lactones **130** with three contiguous stereocenters, including an all-carbon quaternary center, were obtained in generally good yields with excellent stereoselectivities through a Michael–Michael cascade from oxindoles **129** and ester-linked bisenones **128** (Scheme 29). The position



Scheme 29. A novel formal [5+1] cyclization for the construction of the spirooxindole δ-lactones.

and electronic nature of the substituents on the aromatic rings of the dienone substrates had only a slight influence on the results, probably because of the long distance between the aromatic rings and the reaction sites. However, it should be pointed out that N-substituents of the oxindoles had a remarkable effect on the reactivity and selectivity of this transformation.

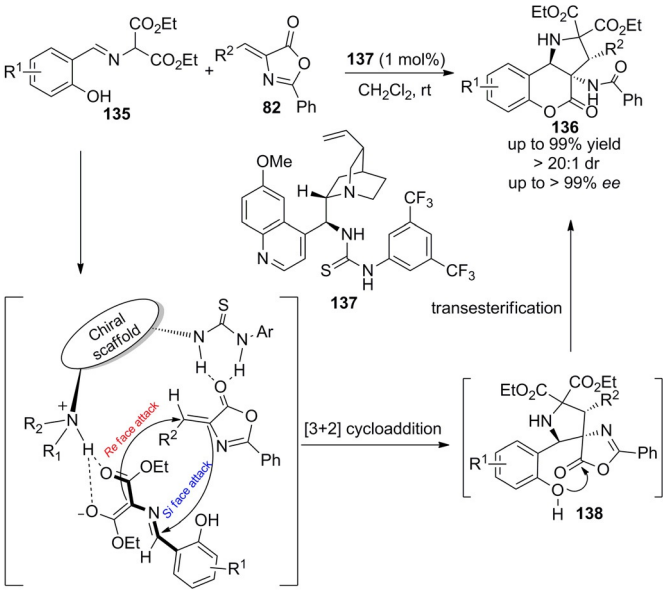
Later, we developed another efficient Michael–Michael cascade reaction for the construction of piperidino[1,2-*a*]-indolines **133**, the core skeleton of which can be frequently found in a wide range of bioactive natural products, between indolin-3-one derivatives **132** and nitroolefins (Scheme 30).[51] Contrary



Scheme 30. Synthesis of piperidino[1,2-*a*]-indolines by a Michael–Michael cascade reaction.

to the significant advances in the development of 2-oxindole chemistry, indolin-3-one derivatives have received very little attention from synthetic chemists, and the application of this type of substrate in cascade reactions is still an underdeveloped research field. From the cascade reaction, the desired products containing four contiguous stereocenters, including one tetrasubstituted carbon center, were readily obtained with good yields and excellent enantioselectivities by using a bifunctional catalyst **134**. Interestingly, the diastereoselectivities were significantly improved when *ortho*-substituted nitroolefins were employed, probably as a result of the steric effect. Moreover, an aliphatic substituted nitroalkene was tested; the reaction successfully gave the desired product, albeit with lower selectivities (4.2:1.8 d.r., 88% and 59% *ee*).

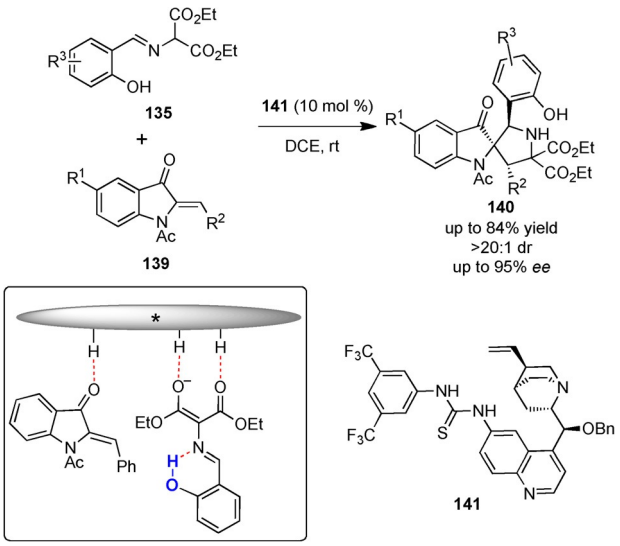
In the same year, our group developed another efficient strategy for the synthesis of biologically important chromeno[4,3-*b*]pyrrolidine derivatives **136** catalyzed by a cinchona-based bifunctional thiourea **137** (Scheme 31).[52] Through proposed synergistic activation of both of the rationally designed



Scheme 31. Synthesis of chromeno[4,3-*b*]pyrrolidine derivatives with a bifunctional thiourea.

o-hydroxy aromatic aldimines **135** and alkylideneazlactones **82** by bifunctional thiourea, a [3+2] cycloaddition reaction occurred smoothly to generate intermediates **138**. An intramolecular transesterification reaction then afforded the ring-fused products **136**. With low catalyst loading (1 mol%) and short reaction time, three new bonds and three contiguous stereogenic centers, including one quaternary stereocenter, were established in excellent yields (up to 99% yield) with nearly absolute stereocontrol (>20:1 d.r., up to >99% *ee*) under mild conditions. A gram-scale synthesis was also performed with excellent results (97% yield, >20:1 d.r., >99% *ee*), which demonstrated the potential application of this methodology.

The enantioselective construction of a spirocyclic quaternary stereogenic carbon center at the C2 position of indoles has long been an elusive problem in organic synthesis. Recently, we developed a reasonable hydrogen-bonding network promoted [3+2] cycloaddition for the direct asymmetric synthesis of 2,2′-pyrrolidinyl-spirooxindoles **140** from *o*-hydroxy aromatic



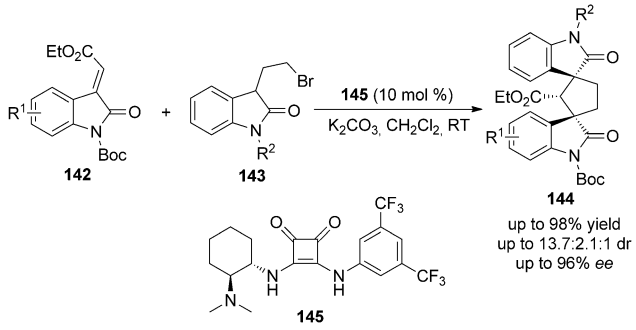
Scheme 32. Construction of spiro-pseudoindoxyl derivatives by hydrogen-bonding network promoted [3+2] cycloaddition.

aldimines **135** and azaaurones **139** (Scheme 32).[53] Three stereocenters, including one spiro quaternary chiral center at the C2 position of the indole, were constructed with excellent stereoselectivities under the bifunctional catalyst **141**. It is worth noting that the reaction of the azomethine ylide substrate without a phenol group did not occur, even with long reaction times, which indicated that the phenol group was critical to the success of this transformation. We proposed that a hydrogen-bonding network might be assembled when a phenol group is introduced in the substrate, which would significantly activate the whole catalytic system.

3.2. Chiral squaramide catalyzed cascade reactions

Compared with chiral urea/thiourea catalysts, chiral squaramides as catalysts in asymmetric synthesis were developed lately and the first example was reported by Xie et al. in 2005.[54] They investigated an asymmetric reduction of prochiral ketones with borane dimethyl sulfide by using a catalytic amount of chiral squaric amino alcohol. Although the squaric derivative was used as a ligand instead of a bifunctional catalyst, this work represented the first example of the use of this structure in asymmetric synthesis. In 2008, Rawal and co-workers first reported a cinchona-based bifunctional squaramide catalyzed addition of dicarbonyl compounds to nitroalkenes.[55] The Michael addition products were obtained with high yields and enantioselectivities with very low catalyst loading. From then on, more bifunctional squaramides have been developed and applied to lots of asymmetric transformations.

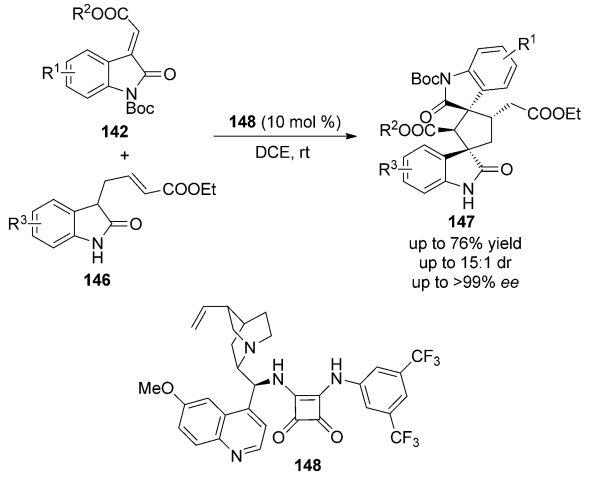
Wang and co-workers developed a rapid and highly efficient asymmetric cascade Michael/alkylation reaction between methyleneindolinones **142** and 3-substituted oxindoles **143** catalyzed by a chiral squaramide **145** in the presence of a base.[56] A range of biologically important bispirocyclic oxindole derivatives **144** were obtained by this powerful approach in high



Scheme 33. Synthesis of bispirocyclic oxindole derivatives by a cascade Michael/alkylation reaction.

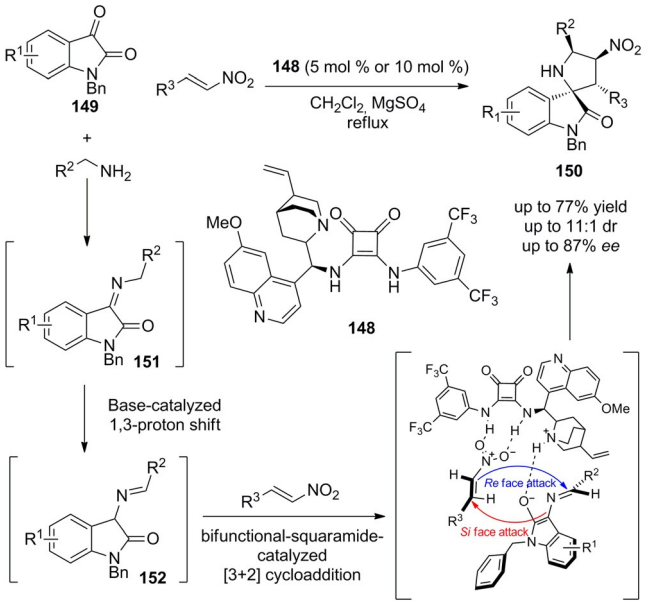
yields and enantioselectivities albeit with moderate diastereoselectivities (Scheme 33). Two new C–C bonds and three contiguous stereocenters, including two spiro quaternary centers, were established efficiently in one single operation. It is worth noting that the electronic nature, bulkiness, and positions of the substituents on methyleneindolinone **142** had very little effect on the reaction efficiencies, enantioselectivities, and diastereoselectivities. They also investigated the possible mechanism of this transformation with MS and NMR experiments by mixing catalyst **145** with methyleneindolinone **142a** ($R^1 = H$) and 3-substituted oxindole **143a** ($R^2 = Bn$). The MS experiment detected a new species, which was characterized by a base peak at $m/z = 767.2833$ and assigned as **145** + **142a**. This observation demonstrated that there was a strong interaction between methyleneindolinone **142** and the catalyst. Furthermore, strong interactions between the catalyst **145** and the 3-substituted oxindole **143a** were observed in the ^1H and ^{13}C NMR spectra, and a new structure (the enol form of **143a**) was formed. The same phenomenon was observed when mixing **143a** with Et_3N, which indicated that the tertiary amine of the catalyst would activate the substrate **143** by its enolization. These findings suggested that the two substrates of this reaction were activated simultaneously by the same catalyst.

Further studies by the same authors have revealed that the bispirocyclic oxindole derivatives **147** could also be successfully constructed through an efficient asymmetric organocatalytic Michael–Michael cascade process by using a bifunctional chiral squaramide catalyst **148**.[57] Four contiguous chiral centers, including two quaternary carbon chiral centers, were established with good diastereoselectivities and excellent enantioselectivities (Scheme 34). Various methyleneindolinones **142** with different substitution patterns, in terms of electronic properties, steric hindrances, and substitution positions, could participate in the cascade reaction to afford the products in moderate to good yields (59–76%) with good to excellent selectivities (4:1–15:1 d.r. and 88 to >99% *ee*). In general, electron-deficient groups substituted on **142** afforded the desired products with slightly lower diastereo- and enantioselectivities. Moreover, 3-substituted oxindoles were also investigated and gave the desired bispirooxindoles in good yields (69–76%) and diastereoselectivities (10:1–15:1) with excellent enantioselectivities (98 to >99%).



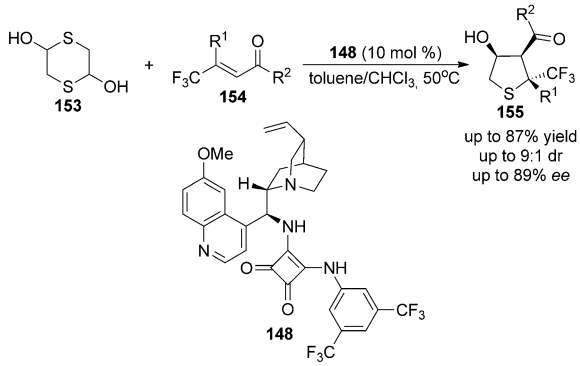
Scheme 34. Synthesis of bispirocyclic oxindole derivatives by a cascade Michael–Michael reaction.

The spiro[pyrrolidin-3,2′-oxindole] scaffold is a privileged structural motif that can be found in a wide range of natural products and pharmaceuticals. Although biomimetic 1,3-proton shift reactions have been widely used in the synthesis of various chiral amines, their application in cascade reactions was rare. In 2013, our group successfully established an efficient enantioselective route to the synthesis of biologically important spiro[pyrrolidin-3,2′-oxindoles] **150** involving a three-component reaction of isatins **149**, amines, and nitroalkenes catalyzed by chiral bifunctional squaramide **148** (Scheme 35).[58] A plausible catalytic mechanism has been proposed. Initially, a base-catalyzed 1,3-proton shift occurred from the in situ generated ketimine **151** to form aldimine **152**. A [3+2] cycloaddition reaction occurred subsequently through synergistic activation of aldimine **152** and nitroalkene by bifunctional catalyst **148** to deliver the desired product. Interestingly, variation of the N-protecting group of the isatin had a significant effect on the enantioselectivity and benzyl-protected isatin was proven to be an optimal selection. Three C–C bonds and four contiguous stereogenic centers were established in a single operation with reasonable yields and good stereoselectivities. It is noteworthy that the aliphatic nitroalkene was also investigated and gave the desired product albeit with lower yield.



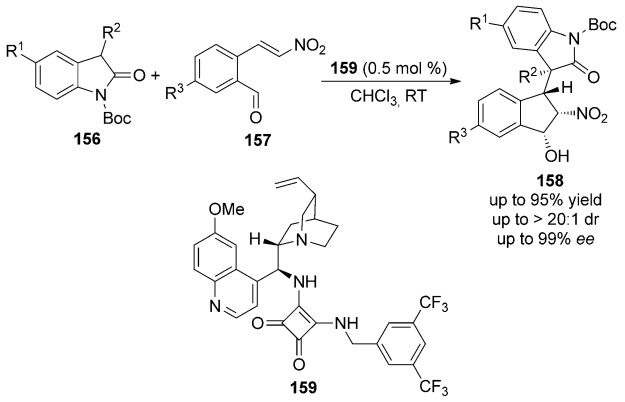
Scheme 35. The application of a 1,3-proton shift in the synthesis of spiro-[pyrrolidin-3,2′-oxindoles].

Our group reported another chiral bifunctional squaramide **148** promoted asymmetric sulfa-Michael/aldol cascade reaction between β-aryl-β-trifluoromethylated enones **154** and 1,4-dithiane-2,5-diol **153** for the synthesis of tetrahydrothiophene derivatives **155** with a trifluoromethylated quaternary stereocenter in generally good yields with high enantioselectivities (Scheme 36).[59] The challenge of this transformation was the construction of the chiral trifluoromethylated quaternary carbon in the first step of the sulfa-Michael addition. A diverse range of β-aryl-β-trifluoromethylated enones were investigated, it was found that the nature and the position of the substituents on the aromatic ring had no significant influence on the enantioselectivity. However, β-alkyl-β-trifluoromethylated enone gave the desired product with low yield (37% yield) and moderate enantioselectivity (66% *ee*). The aliphatic enone showed very low reactivity and could only provide a trace amount of product.



Scheme 36. Cascade reaction of β,β-disubstituted enones for the synthesis of tetrahydrothiophenes.

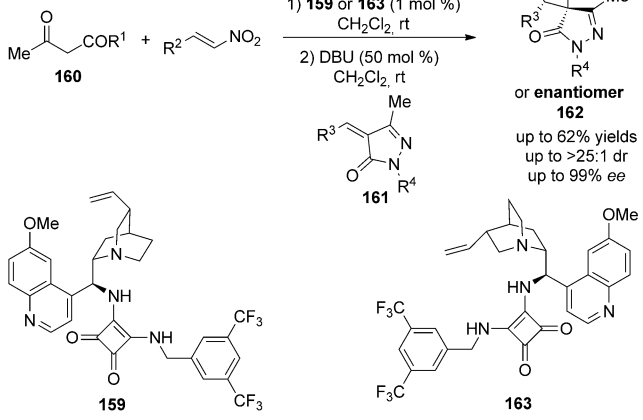
In 2013, Enders and co-workers developed an efficient asymmetric organocatalytic Michael/Henry cascade reaction for the synthesis of polyfunctionalized indanes **158** with four contiguous stereogenic centers under a cinchona-based bifunctional squaramide **159** with 0.5 mol% catalyst loading (Scheme 37).[60] This transformation was activated through the hydrogen bonding of the squaramide and created a maximum of two stereogenic centers per bond formation in generally very short reaction times. One limitation of this methodology was that R^2 should be a phenyl or a phenyl derivative. When a methyl substituent or a hydrogen substituent was tested, both the yields and enantioselectivities decreased (R^2 = Me, 39% yield, 39% *ee*; R^2 = H, 44% yield, 73% *ee*). When a thiophene substituent was used as R^2, decomposition was ob-



Scheme 37. Synthesis of polyfunctionalized indanes with a sub-mol% amount of bifunctional squaramide.

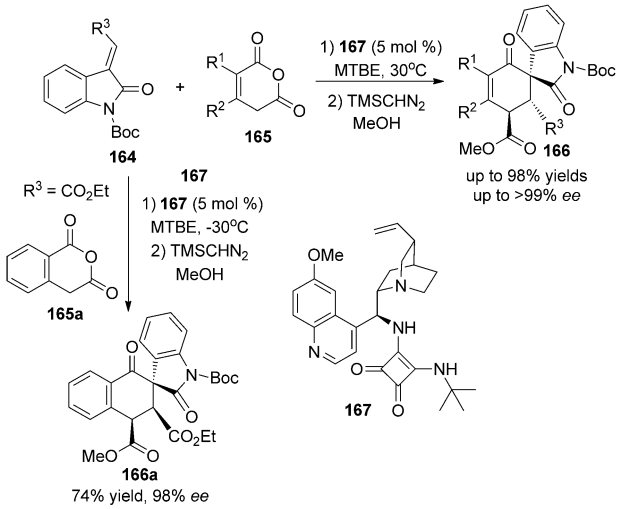
served and the cascade product could not be isolated. They explained that the presence of a phenyl group on R^2 could stabilize the carbanion formed at C3 of the oxindole. A gram-scale synthesis was investigated, which proceeded much faster to afford the cascade product with excellent yield (91%) and very good selectivity (17:1 d.r., 89% *ee*).

The same group disclosed another highly stereoselective one-pot procedure facilitated by a low loading of a cinchona-derived bifunctional squaramide **159** and a readily available achiral base.[61] A new series of potentially biologically important spirocyclohexanepyrazolone derivatives **162** bearing six stereocenters, including two vicinal tetrasubstituted carbons, were obtained by sequential organocatalytic Michael/Michael/1,2-addition reactions (Scheme 38). Various pyrazolone-derived olefins **161** and different nitroalkenes bearing electron-withdrawing as well as electron-donating substituents at the different aromatic positions reacted efficiently to afford the desired spiropyrazolones in good yields (52–62% yield) and excellent enantio- and diastereoselectivities (>25:1 d.r., 98–99% *ee*). Furthermore, they tried to create three consecutive tetrasubstituted carbons by employing a trisubstituted β-ketoester, which provided the corresponding spiropyrazolone bearing three contiguous tertiary and three tetrasubstituted stereogenic centers in excellent stereoselectivity (>25:1 d.r. and 95% *ee*), albeit with a low yield of 16%. This one-pot cascade sequence could be scaled up without losing the reaction efficiency in terms of product yield and stereoselectivity. In addition, the opposite enantiomer of the spiropyrazolones could also be synthesized in good yield (50–61% yield) and excellent stereoselectivity (97–99% *ee*) by employing a pseudoenantiomeric catalyst **163**.



Scheme 38. Construction of spirocyclohexanepyrazolone derivatives by Michael/Michael/1,2-addition reactions.

Connon and co-workers reported the first catalytic asymmetric Tamura cycloaddition reaction between alkylidene oxindoles **164** and a variety of stable, enolizable anhydrides **165** to afford one-step, base-free access to more densely functionalized 3,3-spirooxindoles **166** (Scheme 39).[62] Two new C–C



Scheme 39. Synthesis of 3,3-spirooxindoles by an asymmetric Tamura cycloaddition reaction. MTBE = methyl *tert*-butyl ether.

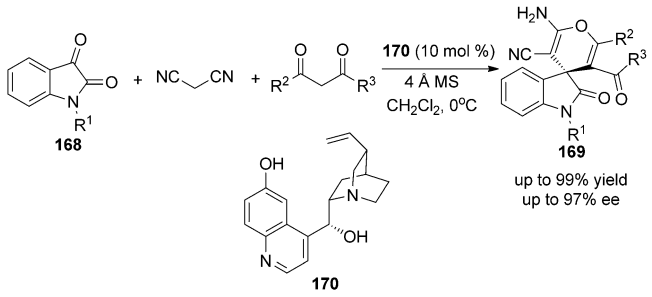
bonds and three new contiguous stereocenters, including one quaternary center, were formed with excellent stereocontrol with the promotion of a novel, *tert*-butyl-substituted squaramide-based catalyst **167**. It is worth noting that the scope of the methodology was not confined to homophthalic anhydride derivatives. Glutaconic anhydride derivatives such as phenyl glutaconic anhydride (R^1 = H, R^2 = Ph) and its methyl variant (R^1 = H, R^2 = Me) underwent smooth cycloaddition to afford the highly substituted cyclohexenones in excellent yields (94%, 95%) and with perfect optical purity (99% *ee*, >98% *ee*). Besides the ester-substituted alkylidene oxindoles, Michael acceptors with a phenyl ring are well tolerated by the catalyst (65–98% yield, 89 to >99% *ee*). Interestingly, an unusually high temperature dependence of diastereocontrol was observed and the epimeric diastereomer **166a** could be isolated in high yield (74%) with excellent enantioselectivity (98%) at a lower temperature.

3.3. Other asymmetric hydrogen-bonding catalytic cascade reactions

In addition to chiral ureas/thioureas and squaramides, other hydrogen-bonding catalysts have also been broadly applied in a range of asymmetric cascade reactions, such as cinchona alkaloid derivatives with aromatic hydroxyl, chiral phosphoric acids, and their derivatives.

In 1999, Hatakeyama and co-workers reported the first application of 6′-OH cinchona alkaloid in organocatalytic asymmetric transformation.[63] According to their research findings, the asymmetric MBH reaction between hexatrifluoroisopropyl acrylate and various aromatic and aliphatic aldehydes could be catalyzed with their β-isocupreidine (β-ICPD) catalyst with high enantioselectivity, which was the first example of the highly enantioselective MBH reaction. Since then, a series of 6′-OH cinchona alkaloids such as cupreines, cupreidines, β-isocupreidine, and their derivatives have been developed and widely used.

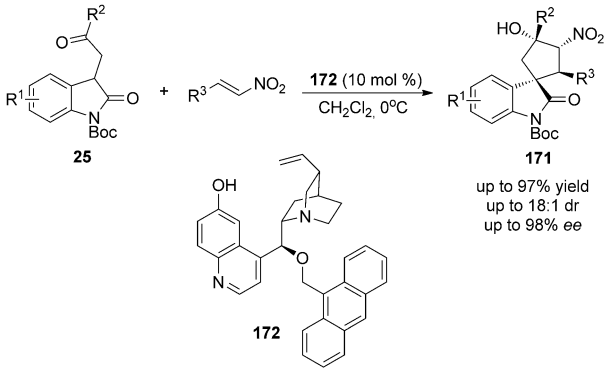
Yuan and co-workers developed an efficient cascade approach for the first enantioselective synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives **169** catalyzed by a cupreine **170** from simple and readily available substrates (Scheme 40).[64] This catalytic system was applied for the two-



Scheme 40. Construction of spiro[4*H*-pyran-3,3′-oxindoles] catalyzed by cupreine.

component reaction, which synthesized optically active heterocyclic spirooxindoles in very high yields and enantioselectivities. Furthermore, they have successfully developed the one-pot, three-component organocatalytic asymmetric reaction involving a cascade Knoevenagel/Michael/cyclization sequence for efficient construction of spiro[4*H*-pyran-3,3′-oxindole] derivatives. A dual activation mode for both substrates by the bifunctional organocatalyst was suggested. This type of heterocyclic spirooxindoles will also provide potential compounds for chemical biology and drug discovery.

Barbas and co-workers reported a simple and highly efficient organocatalytic asymmetric Michael/Henry cascade reaction between simple and readily available 3-substituted oxindoles **25** and nitrostyrenes, providing a variety of bioactive highly substituted spirocyclopentaneoxindoles **171** in high yields with excellent enantioselectivities (Scheme 41).[65] Two C–C bonds and four consecutive stereogenic centers, including an all-carbon spiro quaternary center, were established in a single

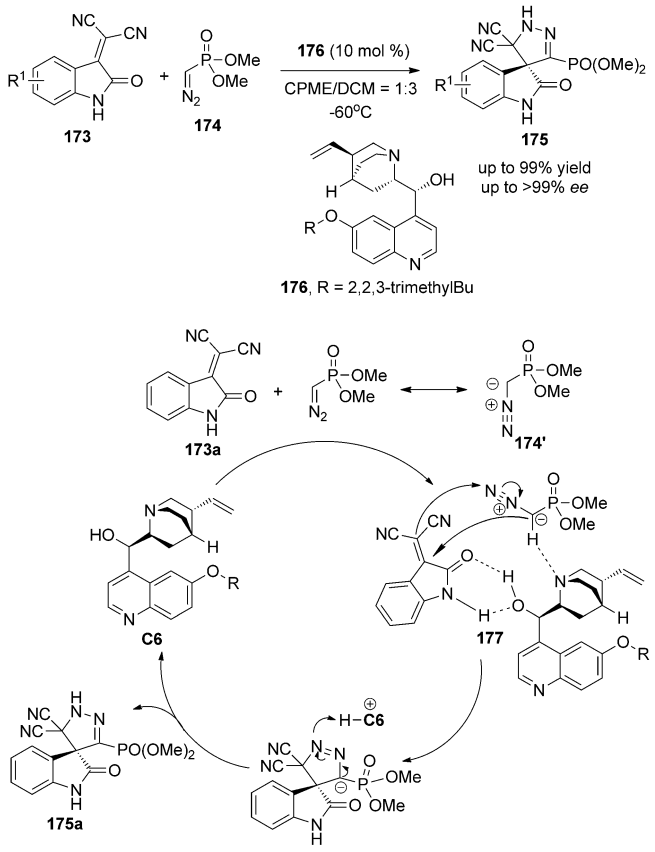


Scheme 41. Formation of highly substituted spirocyclopentane oxindoles.

step through the promotion of a new bifunctional 6′-OH cinchona alkaloid-derived catalyst **172**. In general, a range of substituted nitrostyrenes and oxindole derivatives were successfully tested and provided reaction products in high chemical and optical yields (85–97% yield, 6:1–18:1 d.r., 90–98% *ee*). Enantiomeric excesses with electron-donating substituted nitrostyrenes were slightly lower (91–92%) and strongly electron-withdrawing substituents such as nitro groups provided the product in excellent enantioselectivity (98% *ee*).

Peng and co-workers first reported the catalytic asymmetric 1,3-dipolar cycloaddition of the Seyferth–Gilbert reagent (SGR) **174** with isatylidene malononitriles **173** using cinchona alkaloid derivative **176** as the catalyst.[66] A series of corresponding chiral spiro-phosphonylpyrazoline-oxindoles **175** were smoothly synthesized in good yields with excellent enantioselectivities (Scheme 42). The electronic properties of the substituents on the aryl ring of the isatylidene malononitriles had no discernible impact on the enantioselectivity of the reaction, although substrates bearing electron-donating groups generally afforded the corresponding products in lower yields. The position of the substituent had a slight impact on the enantioselectivity of the reaction. They have also conducted a three-component reaction between isatin, malononitrile, and the SGR, which was efficiently catalyzed by the same cinchona alkaloid derivative through a domino Knoevenagel condensation/1,3-dipolar cycloaddition sequence. They proposed that the hydroxyl group of cinchona alkaloid catalyst could act as a Brønsted acid to activate the isatylidene malononitrile through hydrogen bonding and the amine moiety could activate the SGR as a base to attack the C3 position of the isatylidene malononitrile from its *Si* face (**177**). The intramolecular hydrogen transfer would then take place to form the final chiral spiro-pyrazoline-oxindole.

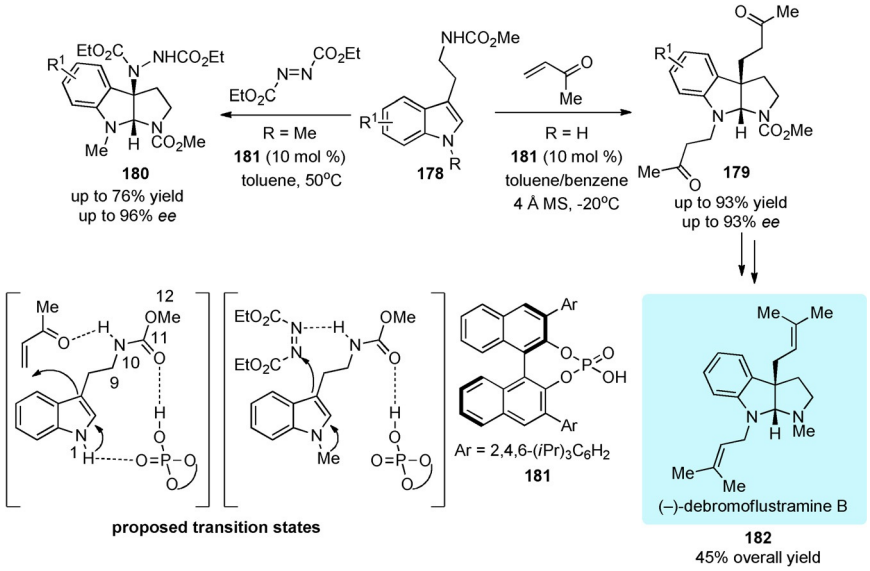
Chiral phosphoric acid catalysts, which possess strong acidic functionalities were first developed by Akiyama[67] and co-workers and Terada[68] and co-workers independently in 2004, and highly enantioselective Mannich reactions of nucleophiles with imines were successfully achieved by using 1,1′-bi-2-naphthol (BINOL)-derived monophosphoric acids as chiral Brønsted acid catalysts. So far, various chiral phosphoric acids and their derivatives have been developed and applied to many asymmetric organic transformations. Owing to their relatively strong yet appropriate acidities, chiral phosphoric acid catalysts can



Scheme 42. Formation of spiro-phosphonylpyrazoline-oxindoles by the 1,3-dipolar cycloaddition between the SGR and isatylidene malononitriles. CPME = cyclopentyl methyl ether.

easily activate the electrophiles through hydrogen-bonding interactions. Moreover, the nucleophiles can be activated by the Brønsted basic site of phosphoryl oxygen, therefore they are also bifunctional catalysts. Axially chiral biaryls with C_2 symmetry are mainly employed as chiral sources for the asymmetry introduction, the C_2 symmetry is crucial because the same catalyst molecule can be generated when the acidic proton migrates to the phosphoryl oxygen. A variety of substituents can be introduced to the 3,3′-positions of the biaryl backbones to provide a chiral environment for enantioselective transformations.

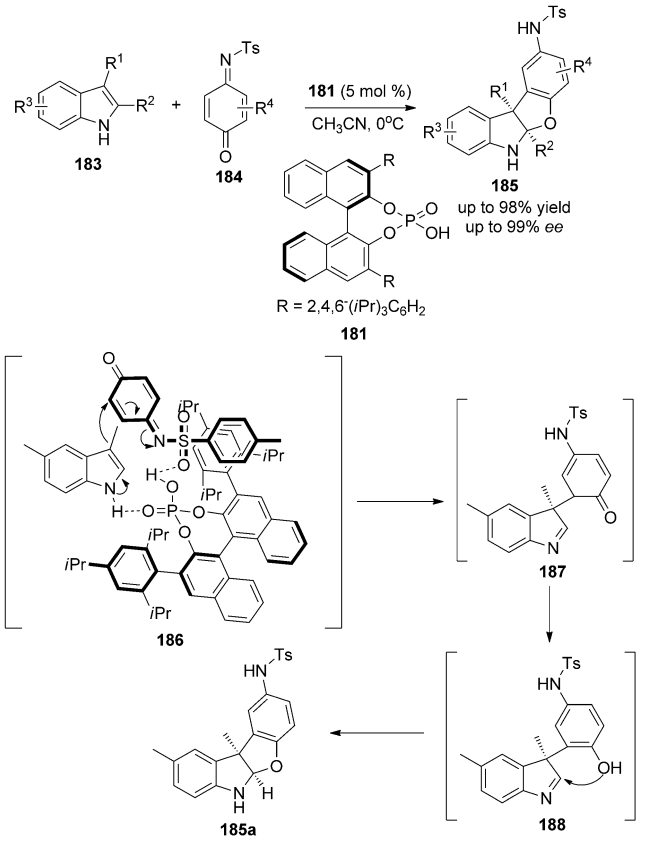
Antilla and co-workers developed a novel method for the synthesis of pyrroloindolines, whose structural motif can be found in an array of natural products, with high enantioselectivities catalyzed by a chiral phosphoric acid **181**.[69] The transformation was accomplished through the cascade of Michael addition and amination of tryptamine **178**, providing two important kinds of pyrroloindolines **179** and **180** with either carbon–carbon or carbon–nitrogen linkage (Scheme 43). They proposed two important transition states based on the following experimental results: 1) when 10-carbomethoxy-1-methyltryptamine was used in the reaction with methyl vinyl ketone (MVK), the product was given with 36% *ee* (93% *ee* for 10-carbomethoxytryptamine), which indicated a hydrogen bond between the catalyst and the N–H of the indole ring. 2) NMR studies were carried out to understand the mechanism. When an equal amount of 10-carbomethoxytryptamine (**178a**) was added to **181** in [D_6]benzene, the chiral proton on **181** shifted upfield from 6.9 ppm to 6.5 ppm and the ^{13}C NMR spectrum of **178a** showed two peaks for C9, C11, and C12, which proposed a hydrogen bond between the chiral proton on **181** and the carbonyl group on **178a**. Moreover, ^{1}H NMR studies of a mixture of MVK and **178a** showed the downfield shift of N1–H and N10–H, which indicated a hydrogen bond between MVK and **178a**. Also, NMR studies showed no shift for the mixture of MVK and **181**. For the amination reaction, the same experiment was studied and similar changes were observed. 3) The reaction of tryptophol with MVK provided the product with 12% *ee*, which might be due to the lack of a hydrogen bond between the catalyst and the carbomethoxy group. The asym-



Scheme 43. Construction of pyrroloindolines and the total synthesis of (–)-debromoflustramine B catalyzed by a chiral phosphoric acid.

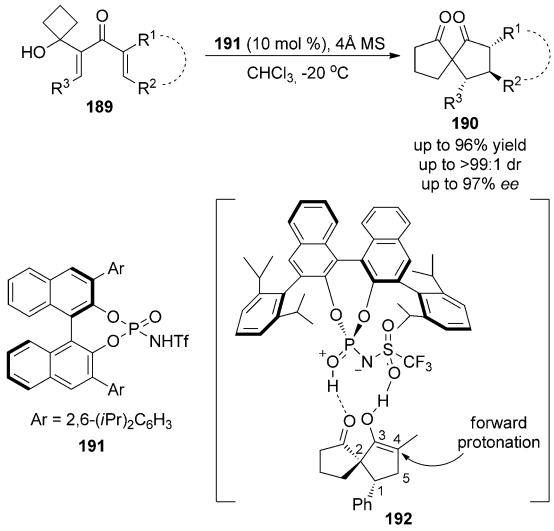
metric total synthesis of (−)-debromoflustramine B **182** was achieved through a concise three-step transformation from the obtained product.

The benzofuroindoline core is a unique motif found in some important natural alkaloids. In 2014, Zhang et al. reported a highly enantioselective [3+2] coupling of 3-substituted indoles **183** with quinone monoimines **184** promoted by a chiral phosphoric acid **181** (Scheme 44).[70] A variety of benzofuroindolines **185** were synthesized through this transformation. Various electron-donating and electron-withdrawing groups on the benzene part of the indoles were tested and afforded the corresponding benzofuroindolines in moderate to good yields with high *ee* values, except for 3-phenyl indole, which exhibited lower enantioselection (80% *ee*). A better *ee* value (86% *ee*) was achieved by employing 10 mol% of the catalyst. Lower yields were obtained even after a prolonged reaction time when indoles with bulkier substituents were used. It is worth noting that the reaction did not occur when the *ortho*-methyl substituted quinone monoamine was employed, which might be caused by the decreased electrophilicity of this quinone monoamine. According to the absolute configuration of the product **185a**, the authors proposed a plausible reaction mechanism: under the bifunctional activation mode of the phosphoric acid catalyst (**186**), 3-methylindole attacked the quinone monoimine to give the intermediate **187**, which underwent aromatization immediately to give the phenol intermediate **188**. Finally, spontaneous cyclization generated (2*R*,3*S*)-**185a**.



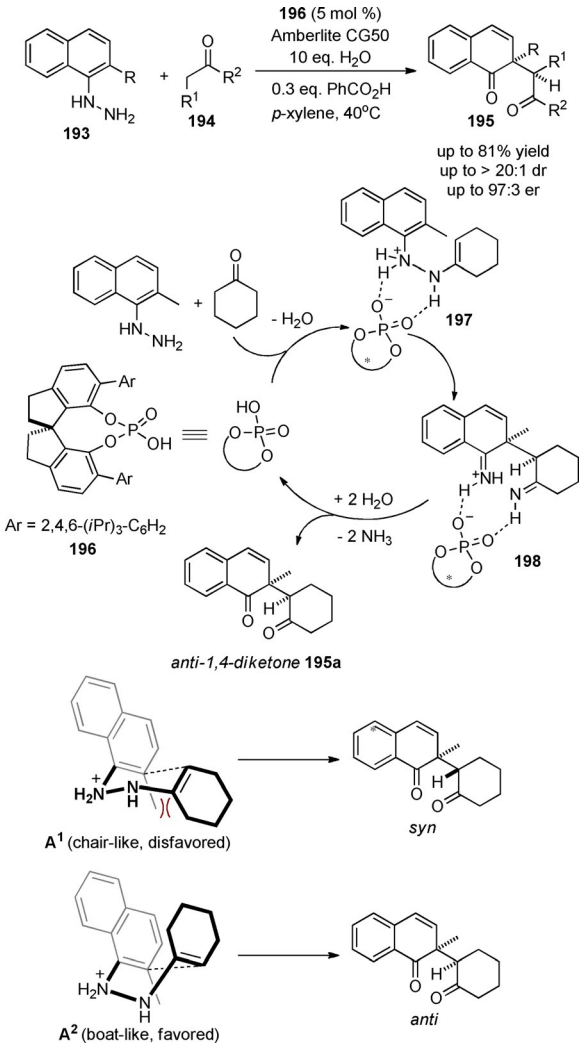
Scheme 44. Highly enantioselective [3+2] coupling of 3-substituted indoles with quinone monoimines to build benzofuroindolines.

Generally, most asymmetric Nazarov cyclizations are achieved by the use of "activated" substrates (that is, substituted by an α-carboxy or α-ether group, or both) to improve the reactivity and enantioselectivity, which limits the substrate scope. Tu and co-workers developed a novel organocatalytic asymmetric tandem Nazarov cyclization/semipinacol rearrangement process with "unactivated" substrates **189** to yield a series of chiral spiro[4.4]-nonane-1,6-diones **190** by using chiral *N*-triflylphosphoramide **191** as the catalyst (Scheme 45).[71] Up to four consecutive stereocenters, including one quaternary stereogenic center, were successfully constructed with excellent enantioselectivity by this transformation. A series of substrates containing different R^1, R^2, and R^3 groups were investigated and gave the desired products with good to excellent diastereo- and enantioselectivities (93:7 to >99:1 d.r., 84–97% *ee*). DFT calculations indicated that the Nazarov cyclization was the most difficult step in the process, and the stereochemistry at C1 was determined by the catalyst's stereochemistry at the cyclization step, which then influenced the stereochemistry at C2 in the ring expansion step. Finally, the chiral catalyst environment influenced the protonation from the forward face of **192** and built the chiral center at the C4 atom. Significantly, this was the first direct example to synthesize asymmetric cyclopentanones with four stereocenters by using the Nazarov cyclization.



Scheme 45. Synthesis of chiral spiro[4.4]-nonane-1,6-diones by a cascade Nazarov cyclization/semipinacol rearrangement process.

Recently, List's group disclosed a mild and efficient catalytic asymmetric dearomatizing redox cross-coupling reaction of arylhydrazines **193** and ketones **194**, furnishing enantioenriched 1,4-diketones **195** with an all-carbon quaternary stereocenter in high enantiopurity (Scheme 46).[72] They investigated the scope of this transformation by testing different hydrazines and ketones. Cyclic ketones such as thio-substituted ketones, nitrogen-containing ketones, and cyclohexanones gave the de-



Scheme 46. Dearomatizing redox cross-coupling reaction to furnish enantioenriched 1,4-diketones.

sired products in good yields (61–75%) with high stereoselectivities (10:1 to >20:1 d.r., 90.9:9.1–99:1 e.r.). The change from cyclohexanone to cyclopentanone led to a diminished reactivity and stereocontrol (29% yield, 2.5:1 d.r., 78.4:21.6 e.r.), whereas the use of alternative hydrazines delivered the desired products in good yields (37–81%) and enantioselectivities (89.5:10.5–96.4:3.6 e.r.). One phenyl hydrazine, (2,6-dimethylphenyl)hydrazine, was also tested but only gave moderate enantioselectivity (77.6:22.4 e.r.) and poor yield (<5%). They proposed that this reaction proceeded through a Fischer-type [3,3]-sigmatropic diaza-Cope rearrangement of the protonated ene hydrazine intermediate **197** to give diimine **198**, then the corresponding product **195a** was obtained after hydrolysis. The diaza-Cope rearrangement would reasonably proceed either via a chair-like (**A1**) or a boat-like (**A2**) conformation of the protonated ene hydrazine intermediate. Apparently, the axial substituent in **A1** caused steric repulsion with the cyclohexene ring, leading to a less favored conformation. In contrast, the [3,3]-sigmatropic rearrangement from the boat-like conformation **A2** would proceed smoothly to generate the observed *anti*-1,4-diketone.

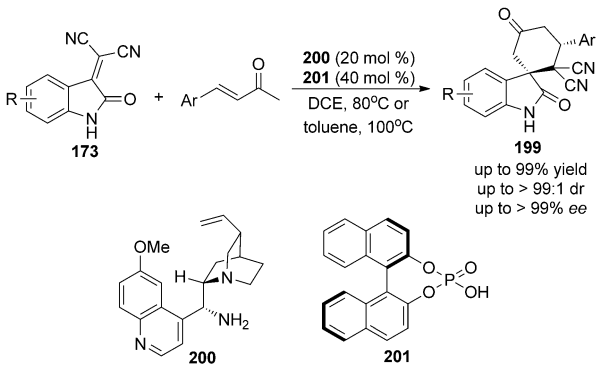
4. Asymmetric Ion-Pairing Catalytic Cascade Reactions

Charged reagents and intermediates are very common in organic synthesis. Although covalent Lewis acid and hydrogen-bond donor catalysts cannot promote the reactions of charged intermediates straightforwardly, ion-pairing catalysis has emerged as a most attractive strategy.[73] Ion-pairing catalysis is realized through the interaction between two ions of opposite charges; these types of interactions are inherently less directional than covalent or hydrogen-bonding interactions, which increases the challenge of the stereoselective control. Therefore, the designing of efficient chiral ion-pairing catalysts to induce high stereoselectivity is the long-term targets of chemists. Phase-transfer catalysis with chiral cationic or cation-binding catalysts has a relatively long history,[74] whereas asymmetric ion-pairing catalysis with chiral anionic and anion-binding catalysts, which will be briefly described in this section, is a relatively new field that has developed rapidly in the past few years.[75]

4.1. Chiral anion-directed catalytic cascade reactions

Chiral anion-directed catalysis relies on chiral anionic catalyst activated transformations through electrostatic interactions with cationic intermediates or intermediates that utilize cationic reagents or catalysts to realize the selective control. Strong chiral Brønsted acids such as chiral phosphoric acid derivatives have been mainly used as this kind of catalyst over the past few years.

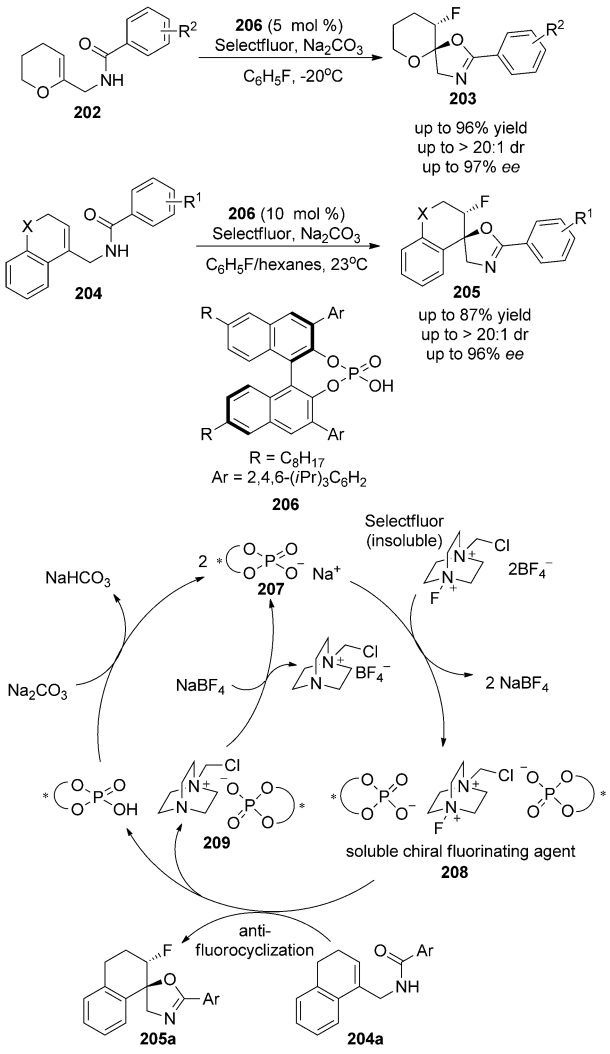
In 2011, Wang and Tao et al. developed an asymmetric ion-pairing catalytic double Michael cascade reaction between isatylidene malononitriles **173** and α,β-unsaturated ketones to provide a series of novel chiral spiro[cyclohexane-1,3′-indoline]-2′,3-diones **199** in high yields with excellent diastereo- and enantioselectivities (Scheme 47).[76] A cinchona-based chiral primary amine **200** and a BINOL-phosphoric acid **201** were combined as a powerful and synergistic catalyst system, in which the optimal ratio of catalysts was proven to be 1:2 for this transformation. The reaction led to the corresponding products in high yields (88–99%) with excellent selectivities (96:4–99:1



Scheme 47. Construction of spiro[cyclohexanone-oxindoles] through chiral counteranion synergistic organocatalysis.

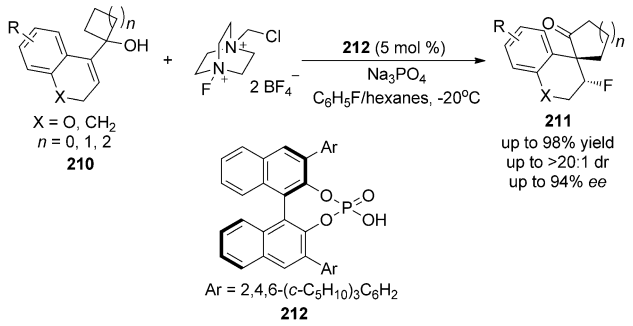
d.r., 97–99% *ee*), variations in electronic and steric properties of the substituents of isatylidene malononitriles had very little effect on the results. Enone substrates bearing electron-donating, electron-withdrawing, and heteroaromatic substituents on the β-phenyl group also gave the desired adducts with excellent results (90–99% yield, 94:6–99:1 d.r., 97–99% *ee*). It is worth noting that the stereoselectivities of this reaction were still excellent (95:5 to >99:1 d.r., 95% to >99% *ee*) even at relatively high temperature (100 °C).

Although chiral cation phase-transfer catalysis (PTC) was developed more than 25 years ago, the first example of chiral anion PTC was not reported until 2008 by Toste and co-workers, which provided a series of β-alkoxy amines via *meso*-aziridinium ion intermediates.[77] In 2011, they developed the second application of chiral anion PTC, which successfully realized an asymmetric electrophilic fluorination by using an achiral insoluble cationic fluorinating agent and a chiral phosphate catalyst (Scheme 48).[78] A series of fluorinated heterocycles **203** and **205** were smoothly constructed from dihydropyran-derived substrates **202** and dihydronaphthalenes or chromenes **204** with excellent results. They have also proposed the mechanism of this transformation. Two equivalents of lipophilic chiral phosphate **207** underwent salt metathesis with dicationic Selectfluor to generate a more soluble, chiral electrophilic fluorinating agent **208**, which was available to mediate the asymmetric fluorocyclization to provide the spiro product **205a**. Upon reaction, one equivalent of phosphoric acid **206** was generated along with one equivalent of the defluorinated monocationic ion pair **209**. The anionic phosphate **207** could then be regenerated by deprotonation and ion exchange. Unlike the majority of enantioselective electrophilic fluorination methodologies, this method allowed for catalytic generation of the chiral fluorinating reagent.



Scheme 48. Asymmetric electrophilic fluorocyclization by chiral anion phase-transfer catalysis.

In 2013, Alexakis and co-workers described the first highly enantioselective organocatalytic Wagner–Meerwein rearrangement of strained allylic alcohols **210** by utilizing the strategy of chiral anion PTC (Scheme 49).[79] With the catalytic generation of the chiral fluorinating reagent, a wide range of chiral fluoro

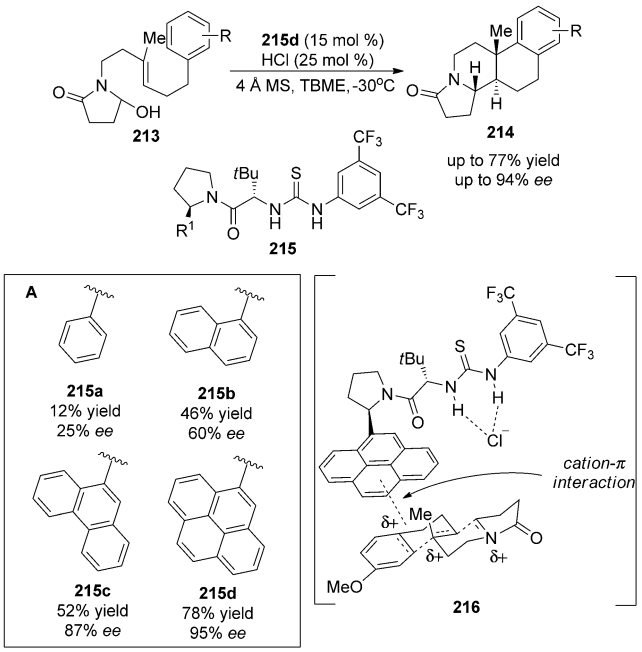


Scheme 49. Organocatalytic Wagner–Meerwein rearrangement initiated by an electrophilic fluorination.

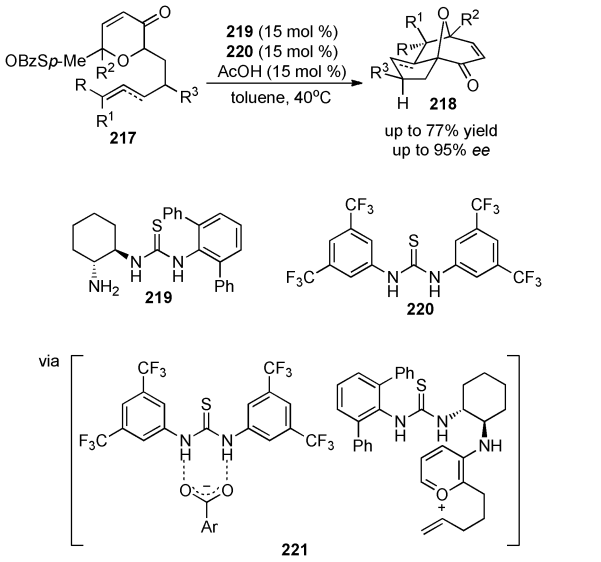
spiroketones **211** were smoothly constructed with excellent stereoselectivities through the ring expansion of strained allylic alcohols. The substrate scope encompassed both allylic cyclobutanols and allylic cyclopropanols based on the tetralone as well as the chromanone scaffolds, with electron-releasing, electron-neutral, and moderately electron-withdrawing substituents at C5 and C6. The aromatic ring of the substrates was essential to the results. For example, substrates based on dihydropyran or cyclohexene scaffolds furnished the desired β-fluoro spiroketones in good yields but with only moderate stereoselectivities. They have also tested the derivatization of the obtained product and the fluoro spirolactone compound was obtained with good results through a stereospecific Baeyer–Villiger oxidation.

4.2. Anion-binding catalytic cascade reactions

Anion-binding catalysis relies on the binding of neutral hydrogen-bond donor catalysts to unreactive or reactive counterions of cationic intermediates in the enantiodetermining transition-state structures. To date, only (thio)urea catalysts have been successfully applied for the anion-binding approaches as neutral hydrogen-bond donor catalysts.



Scheme 50. Enantioselective thiourea-catalyzed cationic polycyclizations. TBME = *tert*-Butyl methyl ether.

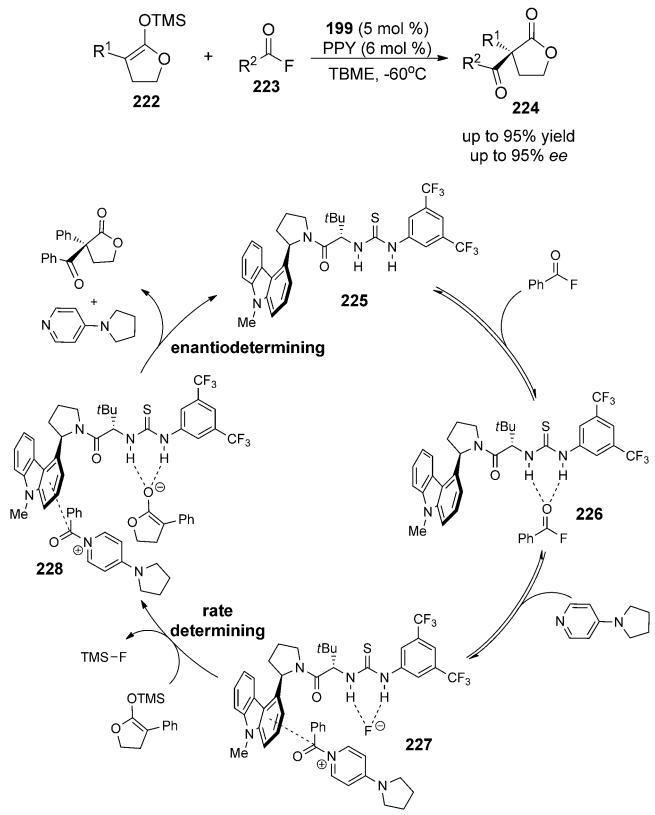


Scheme 51. Dual thiourea catalyst system in the enantioselective intramolecular oxidopyrylium [5+2] cycloadditions.

Jacobsen and co-workers developed a new thiourea catalyst **215** for the enantioselective cationic polycyclization reactions of hydroxylactams **213** (Scheme 50).[80] The proposed mechanism was that the dehydration of hydroxylactam first took place under the acidic conditions to provide the *N*-acyliminium ion intermediate, then the important transition state **216** was formed through the binding of chiral thiourea to the counterion of the cationic intermediate, which induced the polycyclization to afford the final product **214**. Interestingly, there was a clear correlation between the size of the aromatic group of 2-arylpyrrolidine thiourea catalysts and catalytic performance, with larger arenes providing improved reactivity and selectivity (Scheme 50 A, R = 4-OMe). Then, pyrenyl-substituted thiourea **215 d** was used to catalyze this transformation with various aromatic terminating nucleophiles in excellent enantioselectivities (89–95% *ee*). Finally, based on the experimental data, they proposed that the stabilizing cation–π interactions in the transition state played the key role in asymmetric induction.

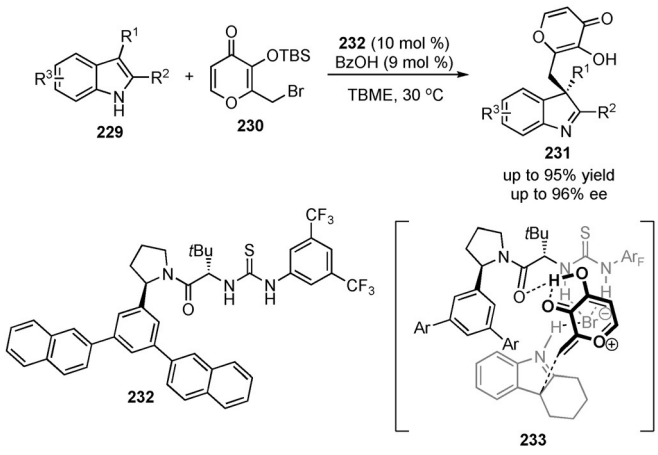
Later, the same group developed a dual thiourea catalyst system consisting of a chiral primary aminothiourea **219** and an achiral thiourea **220** for intramolecular oxidopyrylium [5+2] cycloadditions, which provided a wide range of enantioselective 8-oxabicyclo[3.2.1]octane architectures **218** (Scheme 51).[81] The achiral thiourea had a remarkable effect on this reaction and both the reactivity and enantioselectivity were improved in the presence of this catalyst. To elucidate the roles of the different components in this dual thiourea catalyst system, they performed a series of catalyst structure–activity relationship studies in the presence and absence of **220**. The chiral primary amino catalyst lacking the thiourea moiety could also promote this reaction in good yield and enantioselectivity (85% *ee*), but only in the presence of thiourea **220**. Tertiary aminothiourea was unreactive in both of the presence and absence of **220**, which indicated the necessity of a primary amine for the catalytic activity. Based on the experiments, a mechanism was proposed that involved condensation of the primary aminothiourea with the ketone of the pyranone substrate to form a dienamine intermediate, followed by benzoate abstraction by achiral thiourea and the formation of the key ion-pairing transition state **221**, which finally underwent the cycloaddition to provide the target products.

In 2011, they reported another asymmetric anion-binding/nucleophilic co-catalysis to generate α,α-disubstituted butyrolactone products **224** through the enantioselective acylation of silyl ketene acetals **222** by using a chiral thiourea catalyst **225** in combination with 4-pyrrolidinopyridine (Scheme 52).[82] The nature of the acylating agent had a great influence on the results and benzoyl fluoride proved to be more reactive and selective than benzoic anhydride. It is worth noting that the outstanding hydrogen-bond accepting ability and silicon affinity of the fluoride anion likely played important roles in enabling this transformation. They observed that the size of the silyl group had a measurable influence on the rate of the reaction, but it did not affect the enantioselectivity. A mechanism was proposed involving the formation of a thiourea-bound acylpyridinium·fluoride ion pair **227**, in which the thiourea was associated with the fluoride anion and the catalyst arene substituent was engaged in a stabilizing interaction with the acylpyridinium cation. Intermediate **228** was formed by desilylation of the silyl ketene acetal, which was proposed to be rate determining on the basis of the observed dependence of the overall rate on the identity of the silyl group. Then, enantiodetermining acylation occurred to generate the target product. This was the first example of anion-binding catalysis with fluoride, and the gram-scale synthesis was also realized by using only 0.5 mol% thiourea catalyst.



Scheme 52. Acylation of silyl ketene acetals through asymmetric fluoride anion-binding catalysis. PPY = pyrrolidinopyridine.

Recently, Jacobsen et al. developed a catalytic method for the addition of 3-substituted indoles **229** to pyrone-derived electrophiles **230** to provide a series of simplified pleiomaltinine analogs **231** bearing a defined quaternary stereocenter (Scheme 53).[83] Arylpyrrolidino-derived thiourea **232** catalyzed this reaction with high stereoselectivity in the presence of catalytic quantities of an achiral Brønsted acid. Both electron-withdrawing and electron-donating substituents on the indole ring were well tolerated and gave the desired products in good yields with excellent selectivities. Several experiments were carried out to investigate the mechanism of this indole–pyrone addition reaction. Variation of the leaving group on the pyrone precursor was found to impact the enantioselectivity. Furthermore, the *N*-methylated analog of tetrahydrocarbazole gave only racemic cycloaddition products, which indicated a crucial role of the indole N–H in the catalytic mechanism. Variation of the identity or the amount of the Brønsted acid cocatalyst had very little effect on the reaction outcome, suggesting that the acid does not participate directly in the enantiodetermining step. Based on those findings, they believed that specific interactions between the catalyst and both the pyrone leaving group and the indole N–H moiety would be involved in the enantiodetermining step. Finally, ion-pairing intermediate **233** was proposed to elucidate the mechanism and stereoinduction.



Scheme 53. Synthesis of simplified pleiomaltinine analogs by the addition of indoles to pyrone-derived electrophiles.

5. Summary and Outlook

Since the concept of "organocatalysis" was introduced in 2000, all kinds of new activation modes, new catalysts, and catalytic systems have been rapidly developed over the past 15 years. These research findings provide a good theoretical basis for the development of asymmetric organocatalytic cascade reactions, which greatly enrich the asymmetric synthesis of complicated chiral compounds. Asymmetric organocatalysis has already reached the maturity stage, however, there are still some limitations, which should not be neglected. For example, the loading of organocatalysts is generally much higher, the reaction time is relatively longer, and large-scale reactions cannot always be accomplished with good results. These existing problems limit the further developments and applications of organocatalysis. Therefore, it is still necessary to develop more efficient catalysts and transformations. As it is such an important research area to synthesize natural products and bioactive molecules through novel asymmetric organocatalytic cascade reactions, more exciting progress can be expected in the near future.

Acknowledgments

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Keywords: aminocatalysis · catalytic cascade reactions · hydrogen-bonding catalysis · ion-pairing catalysis · quaternary centers

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