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Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies

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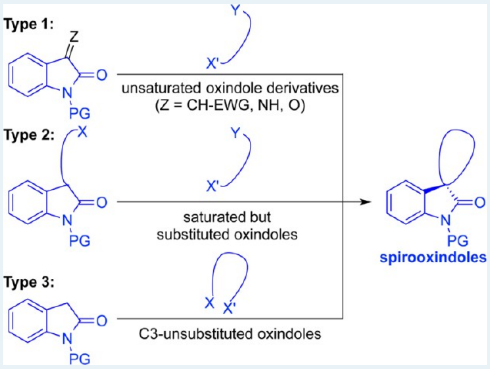
ABSTRACT: Spirooxindoles have become a privileged skeleton given their broad and promising activities in various therapeutic areas. The strategies and catalyst systems described here highlight recent advances in the enantioselective synthesis of spirooxindoles via organocascade strategies. Various organocatalysts with distinct activation modes have found application in constructing these sophisticated compounds. This review focuses on the enantioselective synthesis of spirooxindoles via organocascade strategies and is organized on the basis of three primary starting materials and then further subdivided according to the types of organocatalyst. These methods are of importance for the synthesis of complex natural products and the design of new pharmaceutical compounds. We believe that compounds based on spirooxindole skeletons have the potential to provide novel therapeutic agents and useful biological tools.



KEYWORDS: *spirooxindoles, asymmetric, catalysis, organocascade, strategies*

1. INTRODUCTION

Since our first report of an asymmetric organocatalytic Michael/aldol cascade reaction in the year 2000[1a] and our subsequent early studies in cascade, one-pot, and multicomponent organocatalytic reactions,[1] there has been dramatic growth in the development of organocatalytic synthesis of complex molecules.[2,3] A particular challenge comes with the design of robust and operationally simple approaches to the synthesis of complex molecules containing multiple stereocenters. We have broadly classified reactions of these types as organocatalytic asymmetric assembly reactions because they provide for the asymmetric assembly of multiple substrates into higher-order products with stereochemical complexity. Herein, we review progress toward the synthesis of just one class of molecules, spirooxindoles, which are particularly intriguing with respect to both their structure and biological activities.

Organocatalysis has brought unprecedented progress to the catalytic asymmetric construction of stereochemically complex spirooxindoles. Organocascade or domino stategies[2] are especially attractive because of the general availability and stability of organocatalysts,[3] the mild and simple reaction conditions used, and the powerful ability to construct enantiomerically enriched complex molecules via a cascade process. Spirooxindole motifs are found in many natural products and biologically active molecules (Figure 1).[4] For example, gelsemine is a complex alkaloid that is arguably the most known spirooxindole natural product and one that has been synthesized by numerous groups using various strategies.[4a] Spirotryprostatins A and B have been shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells.[4e] MI-219 is an orally active inhibitor of the interaction between the tumor suppressor p53 and the E3 ubiquitin ligase MDM2.[4h] NITD609 is a very promising drug candidate for the treatment of malaria; it shows pharmacokinetic properties compatible with once-daily oral dosing and has single-dose efficacy in a rodent malaria model.[4i,j] The scope of biological modes of action and the therapeutic promise of spirooxindole-containing molecules are exceptional and have been a major driving force in the development of innovative approaches to their synthesis.

Several challenges are associated with the catalytic asymmetric construction of spirooxindole structures. For example, when starting from a 3-methyleneoxindole, control of the regioselectivity at the double bond is difficult because the reactivity at the two carbon atoms can be influenced by substituents. Moreover, the chiral spirooxindole product features an oxindole core with a spiro ring fused at the 3-position (see oxindole numbering in Figure 2). The substituents on this ring may result in multiple stereocenters, and this steric congestion makes these reactions more challenging than chiral auxiliary-induced cascade reactions. In addition, the actual mechanism of the transformation is not fully understood in many cases. For instance, it is unclear whether chiral organocatalysts activate one substrate to control the stereochemistry or whether interactions with both substrates are required to achieve high asymmetric induction.

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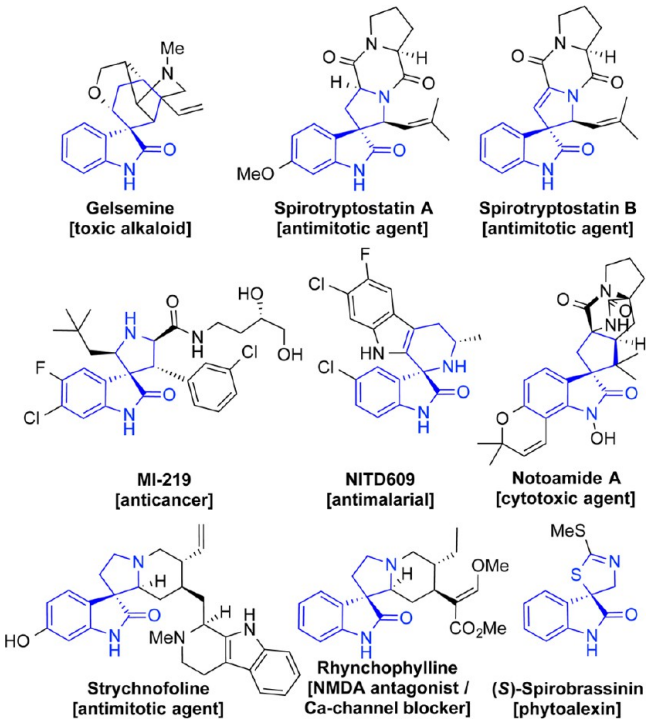

Figure 1. Representative examples of natural products and pharmaceutical molecules containing a spirooxindole core structure.

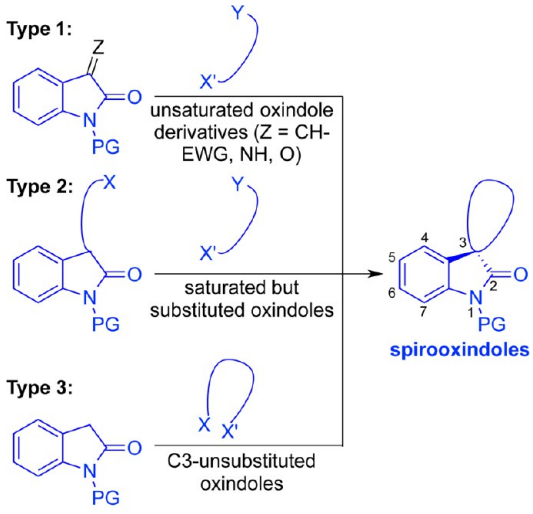

Figure 2. Three types of starting materials for the enantioselective synthesis of spirooxindoles via organocascade strategies.

In the past several years, creative and efficient organocascade strategies have been used to build these sophisticated scaffolds.[5] This review focuses on the enantioselective synthesis of spirooxindoles via organocascade strategies and is organized on the basis of three types of starting materials (Figure 2): First, one can start from unsaturated oxindole derivatives, such as methyleneoxindole, isatin, or isatinimine. These unsaturated derivatives react with designed reaction partners that have both electrophilic and nucleophilic sites through an addition-cyclization sequence to produce spirooxindole motifs. Second, one can couple 3-substituted oxindoles with reaction partners via an addition-annulation process to provide the spirooxindole skeleton. Finally, oxindoles with a formal bis-nucleophilic center at the 3-position may be coupled with two other reaction components or with a single reaction partner with two electrophilic sites.

The three reaction patterns depicted in Figure 2 can then be further subdivided according to the types of catalysis employed, including enamine and iminium catalysis, nucleophilic catalysis, N-heterocyclic carbene (NHC) catalysis, and hydrogen bonding catalysis. All the organocatalysts that are described in this review for the purpose of spirooxindole formation are listed in Figure 3. This list contains proline-derived catalysts **1**, chiral phosphine catalysts **2**, cinchona alkaloid-derived primary (1°) amine catalysts **3**, cinchona alkaloid-derived hydrogen-bonding catalysts **4**, cinchona alkaloid-derived tertiary (3°) amine catalysts **5**, chiral carboxylic acid **6**, thiourea-based catalysts **7**, urea- or thiocarbamate-based catalysts **8**, bifunctional thiourea/phosphine catalyst **9**, binaphthyl phosphate-based catalyst **10**, binaphthyl phosphoric acid-based catalysts **11**, squaramide-based catalysts **12**, and N-heterocyclic carbene (NHC) catalysts **13**.

2. USE OF UNSATURATED OXINDOLE DERIVATIVES

Various organocatalysts promote cascade reactions between methyleneoxindole, isatin, or isatinimine and reacting partners to yield chiral spirooxindoles with different ring systems. These reactions can be classified on the basis of activation mode, and relevant reports on this topic are collected in this section.

2.1. Enamine and Iminium Catalysis. Chiral primary and secondary amine catalysts have been used extensively to activate carbonyl groups. The ability of these catalysts to participate in various enamine- and iminium-mediated processes also makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner. Such reactions can readily access products with multiple stereocenters. Recently, organocascade reactions that proceed through enamine or iminium activation modes have been reviewed.[6] Although a variety of pyrrolidine catalysts, including pyrrolidine ether catalysts, have been described in the early organocatalysis literature, the Hayashi–Jørgensen pyrrolidine organocatalysts **1** (Figure 3) have proven to be versatile and effective in several synthetic strategies to create spirooxindoles with high enantioselectivities.[7]

In 2009, Melchiorre's group developed a triple Michael/Michael/intramolecular aldol and dehydration cascade reaction (Scheme 1).[8] Using chiral amine catalyst (*S*)-**1b**, methyleneoxindoles **14a**, aliphatic aldehydes **15**, and *α*,*β*-unsaturated aldehydes **16** were combined to generate spirooxindoles **17a** in moderate yields, excellent diastereoselectivities (dr) and enantioselectivities (ee). In a related triple cascade strategy, an efficient one-pot, three-component tandem annulation has also been successfully developed by the Chen group to construct various six-membered spirooxindoles **17b**.[9]

On the basis of this strategy, propanal (**15a**) was reacted with electron-deficient methyleneoxindole **14c** in the presence of 2° amine (*S*)-**1b** to give bifunctional intermediate **18**, which was further combined with diverse electrophiles (activated olefins **19a** or **20a** or imine **21a**) either in 1,4- or 1,2-fashion (Scheme 2). The final intramolecular cyclization process yielded the expected six-membered spirooxindole skeleton with molecular diversity, complexity and excellent stereocontrol.

Recently, Ghosh et al. harnessed the reaction between methyleneoxindoles **14** and pentane-1,5-dial (**15b**) to construct substituted spirocyclohexane oxindoles **17** (Scheme 3).[10] This

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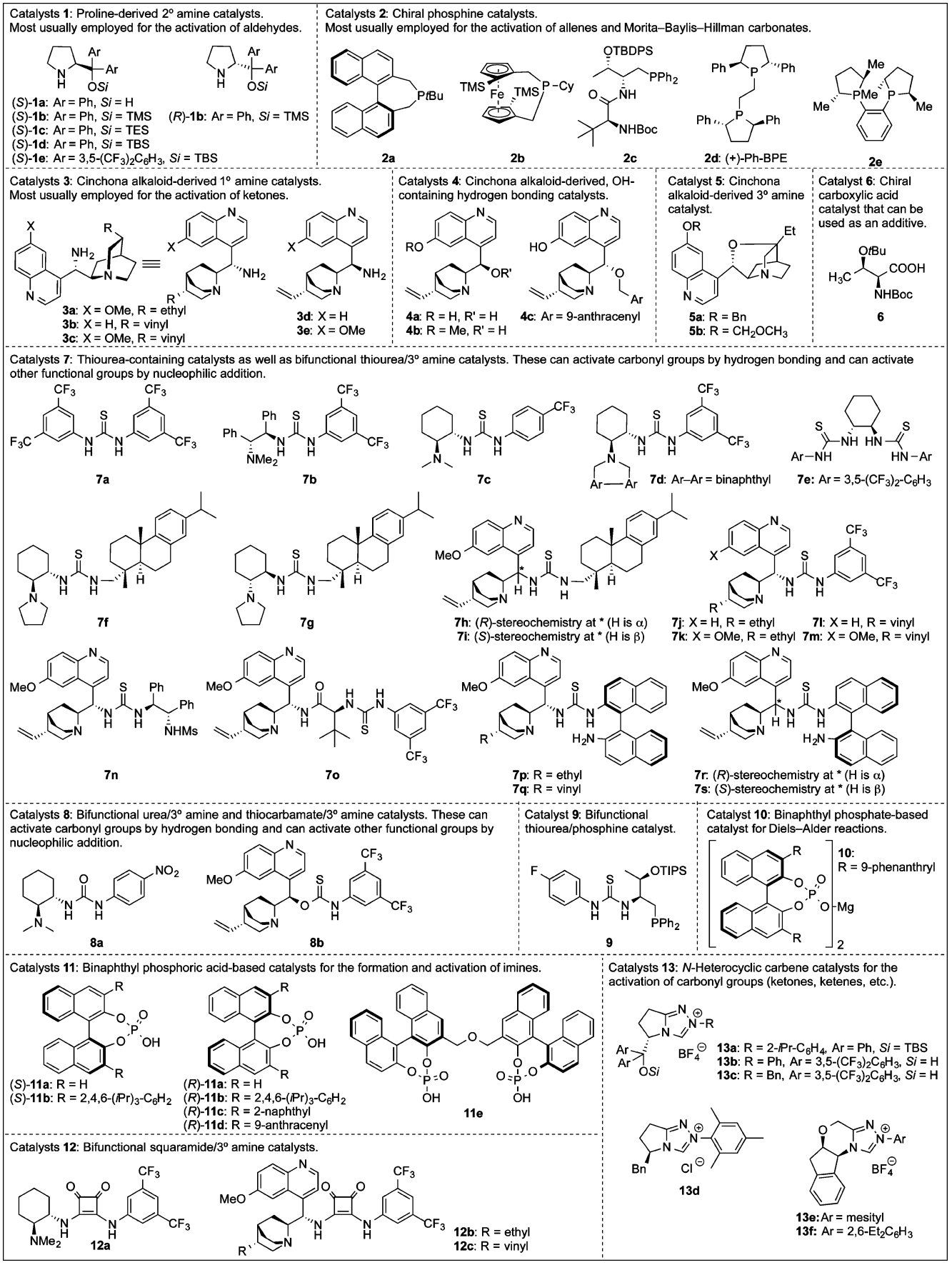

Figure 3. Organocatalysts described in this review for the purpose of spirooxindole formation.

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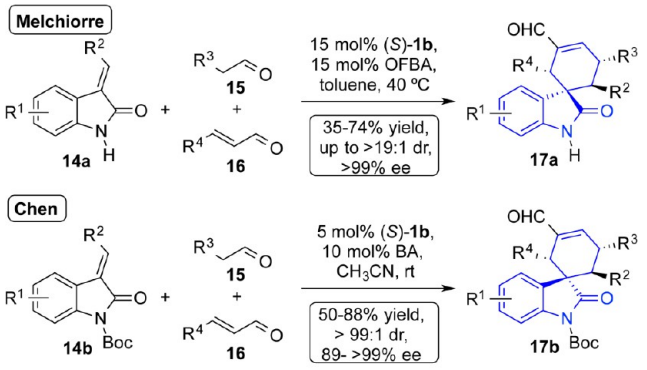
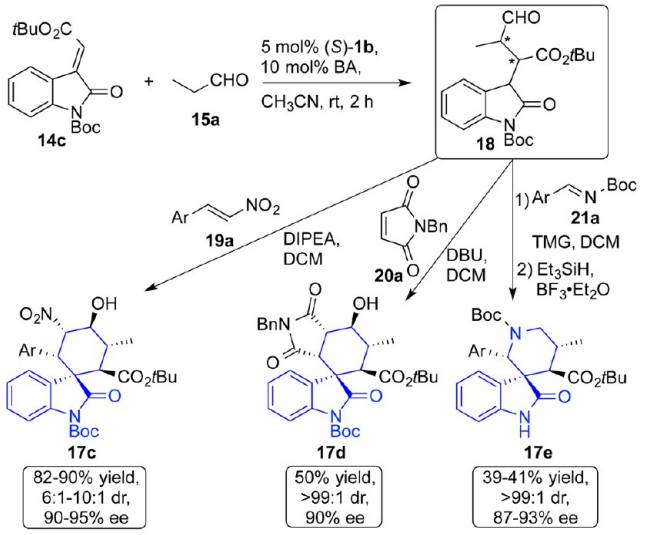
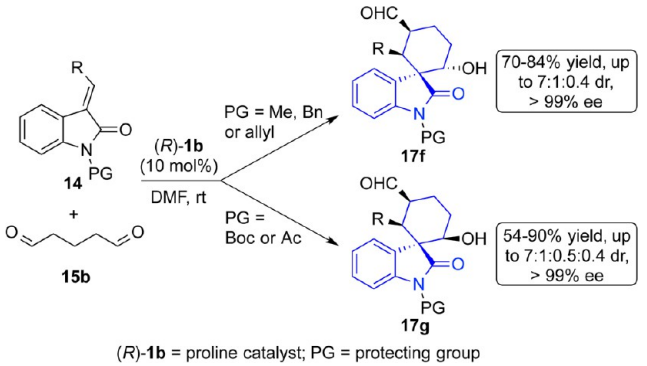
Scheme 1. Cascade Reaction of Methyleneoxindoles 14, Aliphatic Aldehydes 15 and α,β-Unsaturated Aldehydes 16



Scheme 2. Coupling of Chiral Bifunctional Intermediate 18 with Other Electrophiles



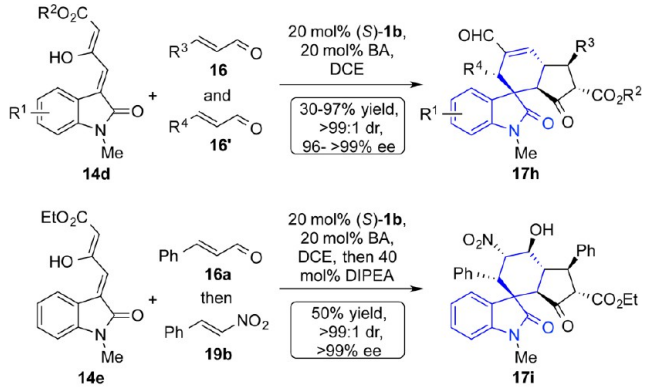
Scheme 3. (*R*)-1b-Catalyzed Michael/Aldol Cascade Reaction between Methyleneoxindoles 14 and Pentane-1,5-dial (15b)



procedure proceeded through a Michael/aldol sequence in the presence of (*R*)-**1b** to afford products with multiple stereocenters in high yields and excellent enantioselectivities. Interestingly, the authors noted that when the N-protecting group on the oxindole was modified from an electron-withdrawing group to an electron-donating group, the absolute configuration of the hydroxyl center also changed to give **17f** and **17g**, respectively, indicating that the N-protecting group on the oxindole has a critical effect on the stereochemistry of aldol ring closure.

In 2010, Chen's group reported a three-component domino reaction of rationally designed methyleneoxindoles **14d** with two molecules of α,β-unsaturated aldehyde **16** and **16′** under quadruple iminium/enamine/iminium/enamine catalysis (Scheme 4).[11] Employing chiral amine (*S*)-**1b** as catalyst, a

Scheme 4. A Three-Component Reaction of Methyleneoxindole 14 with Two Different Molecules of α,β-Unsaturated Aldehyde 16



spectrum of complex spirooxindoles (**17h**) bearing six contiguous stereocenters were obtained via this unique triple-Michael/aldol process. Remarkably, the Michael/Michael intermediate can be trapped by other electrophiles, such as nitroolefins **19b**, further expanding the synthetic utility of this type of reaction.

A trienamine activation method was used by two groups to construct chiral spirooxindoles. In 2011, Chen, Jørgensen, and co-workers found that exposure of polyenals **22** to chiral 2° amines **1** generates reactive trienamine intermediates **23a** that readily undergo Diels–Alder reactions with various classes of dienophiles (Scheme 5).[12] This method offers a facile entry to highly complex molecular frameworks with excellent stereocontrol. For the Diels–Alder reactions between **14** and **24a**, spirooxindoles **17j** were formed in high yields and with excellent enantioselectivities. This activation strategy allowed for excellent chirality "relay" over a distance of up to eight bonds. Examples of trienamine/enamine tandem reactions were also shown. By using NMR spectroscopic studies and calculations of the reactive trienamine intermediates, a mechanistic hypothesis was proposed to rationalize the origin of stereochemistry and the preferred reaction pathway.[12] In the same year, Melchiorre's group documented the first asymmetric catalytic Diels–Alder reaction of heterocyclic *ortho*-quinodimethanes **23b**.[13] In the presence of chiral amine catalyst (*S*)-**1b**, reactive diene species were generated in situ from simple starting materials and cyclizations with nitroolefins (**19**) occurred with high stereocontrol (up to >20:1 dr, >99% ee). For Diels–Alder reactions with methyleneoxindoles **14**, a structurally diverse range of complex spirooxindole-containing tetrahydrocarbazoles **17k** was obtained with high chemical yields and excellent stereoselectivities. This strategy could be extended to pyrrole- and furan-based *ortho*-quinodimethanes,

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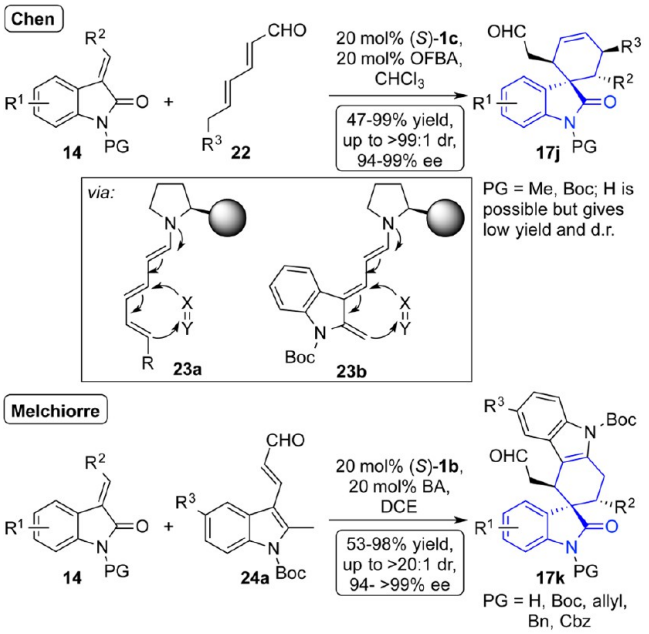
Scheme 5. Trienamine Activation Modes and Their Application to the Synthesis of Chiral Spirooxindoles

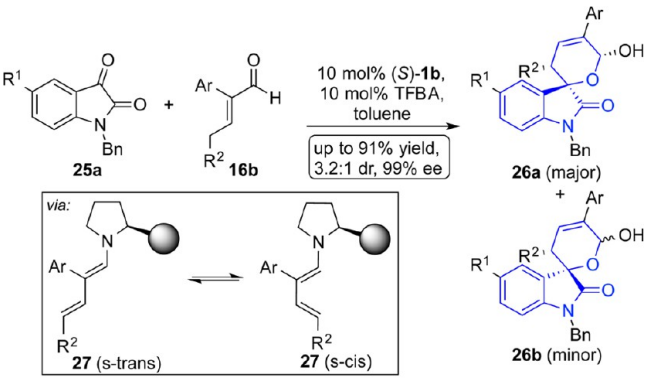


(*S*)-**1b**, (*S*)-**1c** = proline catalyst; BA = benzoic acid; OFBA = *o*-fluorobenzoic acid

which would be beneficial for the application of this methodology in medicinal arenas.

Melchiorre and co-workers have also made use of dienamine activation to synthesize chiral spirooxindoles (Scheme 6).[14]

Scheme 6. Dienamine Activation in the Synthesis of Chiral Spirooxindoles 26 from Isatins 25a and Enals 16b



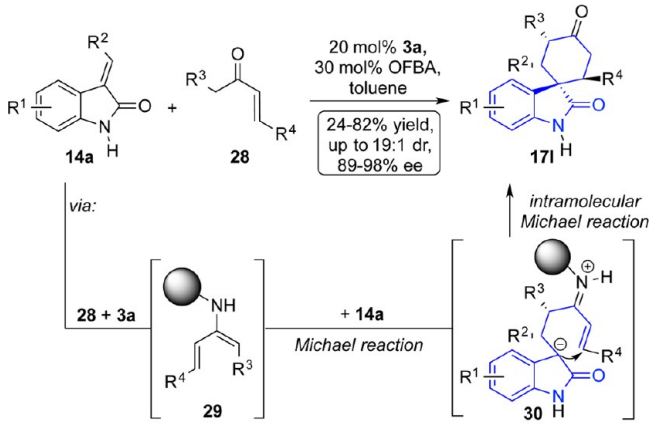
(*S*)-**1b** = proline catalyst; TFBA = 2,6-bis(trifluoromethyl)benzoic acid

Exposure of enal **16b** to the amino catalyst (*S*)-**1b** results in the formation of dienamine intermediate **27**, which reacts with isatin **25a** to generate spirocyclic oxindole scaffold **26**. Their experimental observations were in agreement with a hetero-Diels–Alder (HDA) process for the reaction.

Although aldehyde substrates are often activated using 2° amine catalysts, ketone substrates are typically activated by 1° amine catalysts. Cinchona-based chiral primary amines **3** are recognized as some of the most common catalysts for dienamine intermediate formation (see Figure 3).[15]

In 2009, the Melchiorre group reported Michael/Michael cascade reactions between methyleneoxindoles **14a** and α,β-unsaturated ketones **28** for the synthesis of spiro-4-cyclohexanone oxindole derivatives **17l** (Scheme 7).[8] The authors

Scheme 7. Double Michael Cascade Reactions between Methyleneoxindoles 14a and α,β-Unsaturated Ketones 28 via Dienamine Intermediates

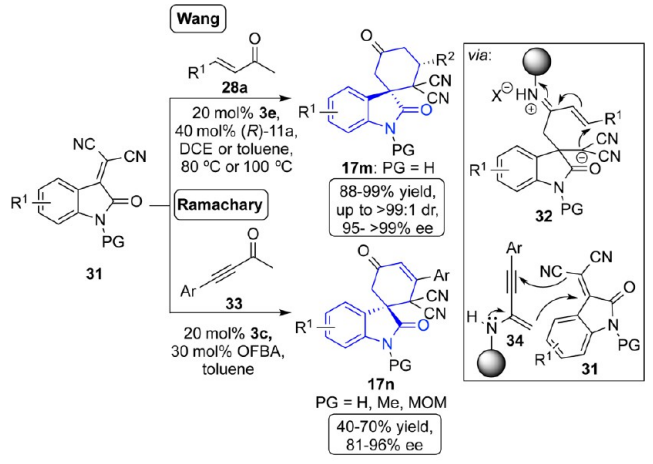


3a = cinchona 1° amine catalyst; OFBA = *o*-fluorobenzoic acid

anticipated that condensation of catalyst **3a** with **28** would generate dienamine intermediate **29**, which could undergo a double Michael addition with methyleneoxindole **14a** acting as both an acceptor and a latent donor to accomplish the sequence. Among the catalysts examined, hydroquinine-derived primary amine **3a** in conjunction with *ortho*-fluorobenzoic acid (OFBA) was found to be most efficacious, giving the desired products **17l** in moderate yields, good diastereoselectivities, and excellent enantioselectivities. This is the first example of a one-step synthesis of multistereogenic spirocyclohexane oxindole derivatives via a tandem iminium and enamine catalytic sequence.

In 2011, Wang's group demonstrated that the combination of a cinchona-based chiral 1° amine **3e** and BINOL-phosphoric acid (*R*)-**11a** is a powerful and synergistic catalyst system for the double Michael addition of isatylidene malononitriles **31** with α,β-unsaturated ketones (**28a**), delivering chiral spiro-[cyclohexane-1,3′-indoline]-2′,3-diones (**17m**) in excellent yields and stereocontrol (Scheme 8).[16] This reaction showed

Scheme 8. Reaction between Isatylidene Malononitriles (31) and α,β-Unsaturated Ketones (28a) or Ynones (33) Catalyzed by Cinchona-Based Chiral Primary Amine Catalysts 3



3c, **3e** = cinchona 1° amine catalysts; (*R*)-**11a** = binaphthyl phosphoric acid; PG = protecting group; OFBA = *o*-fluorobenzoic acid; MOM = methoxymethyl.

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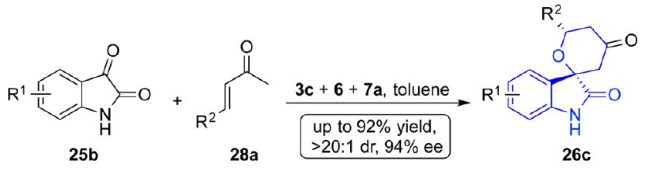
an interesting temperature effect: elevation of the temperature to 100 °C improves reaction efficiency without significant loss of stereoselectivity. It is noteworthy that the regioselectivity of this reaction differs from that of monosubstituted methyleneoxindoles (**14**). This difference might stem from the more electron-withdrawing dicyano groups, making the nucleophilic dienamine intermediate prone to attack the 3-position of the isatylidene moiety to give **32**. The enone is activated by the 1° amine catalyst, and similarly, ynones also have the ability to react with this catalyst to form a reactive intermediate. Thus, Ramachary et al. presented a strategy based on the use of catalytic amino enyne **34** to construct functionalized six-membered spirooxindoles (**17n**) from 2-(2-oxoindolin-3-ylidene) malononitriles (**31**) and ynones (**33**).[17]

In a similar manner, enones (**28a**) can react with isatins (**25b**) through enamine activation of enones (Scheme 9). In

Scheme 9. HDA Reaction between Isatins (25b) and Enones (28a)



3c = cinchona 1° amine catalyst; **6** = chiral carboxylic acid additive; **7a** = thiourea-containing catalyst

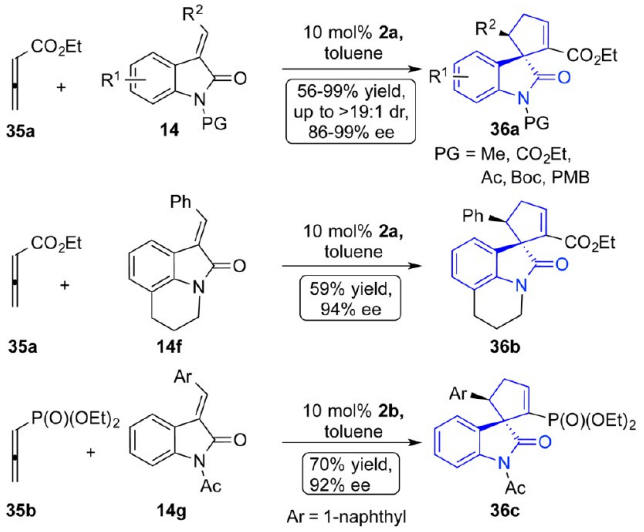
2013, Cui and Tanaka evaluated the feasibility of this kind of HDA reaction.[18] Notably, an amine (**3c**)/acid (**6**)/thiourea (**7a**) combination catalyst system proved optimal. The interaction between thiourea and the two oxygens of isatin was essential for an efficient reaction. Under the published conditions, spirooxindole tetrahydropyranones (**26c**) were synthesized with up to 94% ee. Moreover, the reactions were efficient on gram scale, and various transformations of the product demonstrated the utility of this formal HDA reaction.

2.2. Nucleophilic (Phosphine and Amine) Catalysis. Nucleophilic catalysis remains an active and dynamic area of interest for synthetic chemists. Small-molecule electron-pair donors (Lewis bases) are effective catalysts for a range of synthetic transformations. Nucleophilic phosphine catalysis is firmly established as a reliable platform for a variety of transformations that include activated allenes and Morita–Baylis–Hillman (MBH) carbonates as starting materials.[19]

In 2010, Marinetti's group realized a [3 + 2] cyclization strategy between methyleneoxindoles (**14**) and allenes (**35**) catalyzed by BINOL-derived phosphine catalyst **2a**, resulting in the formation of "γ-adduct" spirocyclopentane oxindoles (**36a**) in excellent yields, regioselectivities, and enantioselectivities (Scheme 10).[20] To further expand this strategy, the group used tricyclic oxindole **14f** as a substrate and obtained the desired product **36b** with 94% ee. Notably, under the catalysis of a ferrocene-derived phosphine catalyst **2b**, allenylphosphonate **35b** also worked well in this spirocyclization to give **36c** with high enantioselectivity.

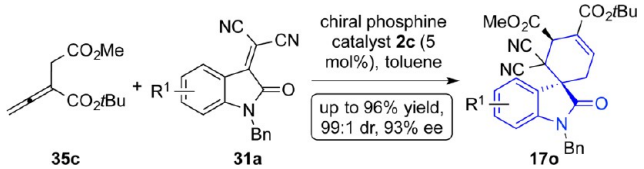
The Lu group successfully used allenes in a [4 + 2] annulation strategy with activated alkenes and α-substituted allenoates (**35c**) catalyzed by amino acid-based bifunctional phosphine **2c** (Scheme 11).[21] Using isatin-derived alkenes (**31a**), the cycloaddition afforded biologically important 3-spirocyclohexene-2-oxindoles (**17o**) with up to 93% ee.

Scheme 10. Chiral Phosphine-Catalyzed [3 + 2] Cyclization between Methyleneoxindoles (14) and Allenes (35)



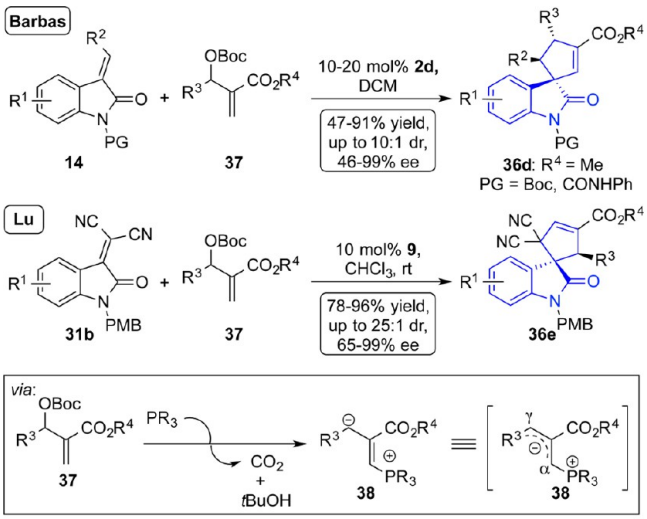
2a, **2b** = chiral phosphine catalysts; PG = protecting group

Scheme 11. [4 + 2] Annulation between 31a and Allenoates 35c Catalyzed by Bifunctional Phosphine 2c



MBH carbonates **37** are readily available and versatile C_3 synthons (Scheme 12).[22] The Barbas[23] and Lu[24] groups independently reported the synthesis of related spirocyclopentane oxindoles from MBH carbonates by [3 + 2] cycloaddition. The Barbas group found that C_2-symmetric phosphine catalyst (+)-Ph-BPE **2d** efficiently catalyzed the [3 + 2] cycloaddition

Scheme 12. Chiral Phosphine-Catalyzed [3 + 2] Cycloaddition between MBH Carbonates (37) and Methyleneoxindoles



2d = chiral phosphine catalyst; **9** = bifunctional thiourea/phosphine catalyst; PG = protecting group; PMB = *p*-methoxybenzyl group

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reaction to give "γ-adduct" spiro cyclopentane oxindoles (**36d**) in excellent yields, regioselectivities, and enantioselectivities.[23a] The authors conducted control experiments that indicated that both the second phosphine of the catalyst **2d** and the carbonyl of methyleneoxindole **14** had a major impact on the stereoselectivity. This reaction likely begins with the activation of MBH carbonate **37** by one of the phosphines, followed by an addition−elimination process in which methyleneoxindole **14** is activated by the second phosphine. Recently, Barbas and co-workers further extended this type of [3 + 2] cycloaddition reaction to 3-substituted methylenebenzofuranone derivatives.[23b] Using (−)-Ph-BPE (*ent*-**2d**) as catalyst, the desired polysubstituted spirocyclopentenebenzofuranone scaffolds were obtained with excellent enantioselectivities. In contrast, the Lu group used a threonine-derived phosphine thiourea **9** to catalyze the stereoselective [3 + 2] cycloaddition process between the MBH carbonates (**37**) and isatin-derived tetrasubstituted alkenes (**31b**), which allowed facile preparation of the "γ-adduct", in this case biologically important 3-spirocyclopentene-2-oxindoles (**36e**), in excellent diastereoselectivities and enantioselectivities.[24] A plausible reaction mechanism was proposed in which the MBH carbonate **37** was activated by the phosphine to generate ylide intermediate **38**, which then underwent γ-addition (or conjugate addition), intramolecular cyclization, and final elimination to give the desired product. Hydrogen-bonding interactions between the thiourea moiety of the catalyst and the isatin may play a crucial role in asymmetric induction (Figure 4).

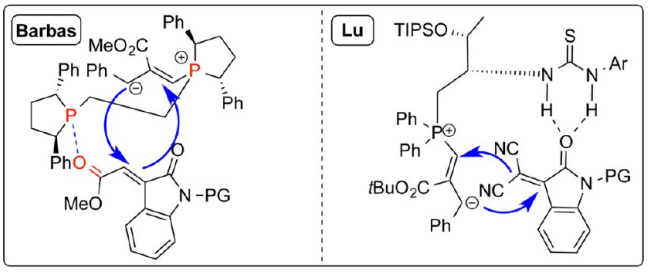
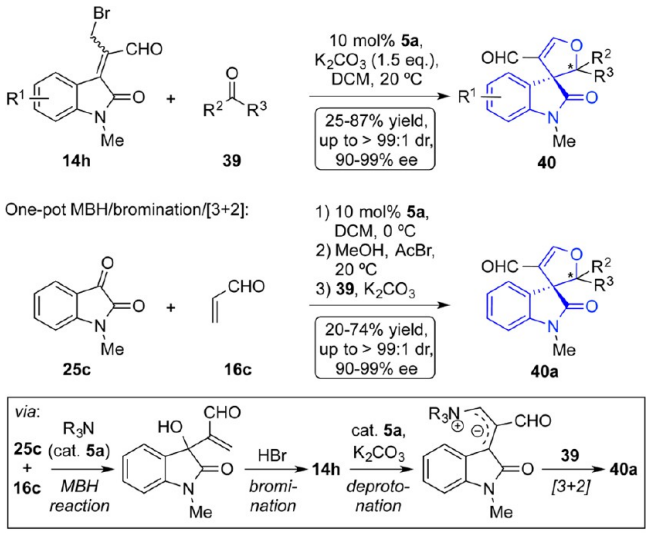


Figure 4. Hydrogen-bonding interactions between the thiourea moiety of the catalyst and the isatin unit, resulting in asymmetric induction.

The MBH reaction can also be employed in the synthesis of spirooxindoles without using MBH carbonates (such as **37** in Scheme 12). Very recently, Zhou and co-workers reported the asymmetric synthesis of spirooxindoles starting from bromomethylated oxindole starting materials, such as **14h** (Scheme 13).[25] With nucleophilic 3° amine catalyst **5a**, **14h** was reacted with ketone **39** in a [3 + 2] cyclization to give spirooxindole **40**, which bears an additional all-carbon quaternary center adjacent to the quaternary center at C3. In an impressive three-step, one-pot transformation, isatin **25c** can be treated with enal **16c** with catalyst **5a**, then HBr, then ketone **39** and base, to yield **40a** in moderate to good yields and excellent ee. This reaction first undergoes an MBH reaction on enal **16c**, then an allylic alcohol displacement with bromide to give **14h**, followed by [3 + 2] cyclization.

2.3. N-Heterocyclic Carbene (NHC) Catalysis. Chiral N-heterocyclic carbenes (NHCs) are a class of Lewis basic (nucleophilic) catalysts used in a number of asymmetric organocatalytic processes. In the past decade, NHC-catalyzed annulation reactions have become powerful methods for the synthesis of various heterocycles.[26] In 2010, the Ye group

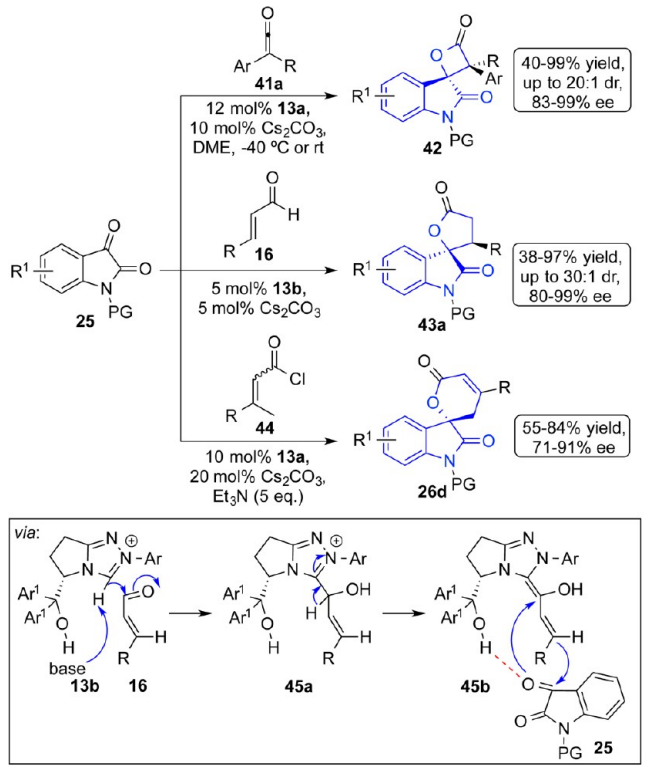
Scheme 13. Chiral Phosphine-Catalyzed, One-Pot MBH/Bromination/[3 + 2] Cyclization Sequence To Give Spirooxindoles 40



5a = 3° amine catalyst; MBH = Morita–Baylis–Hillman

reported the use of NHC **13a** in a formal [2 + 2] cycloaddition of disubstituted ketenes **41a** and isatins **25** to provide the corresponding spirocyclic oxindole-β-lactones **42** in good yields with good diastereoselectivities and excellent enantioselectivities (Scheme 14).[27] The same group also disclosed the first example of NHC-catalyzed [3 + 2] annulation of enals **16** and

Scheme 14. NHC-Catalyzed Cycloaddition Reaction of Isatins (25) with Ketenes (41a), Enals (16), and α,β-Unsaturated β-Methylacyl Chloride 44



13a, **13b** = *N*-heterocyclic carbene (NHC) catalyst; PG = protecting group

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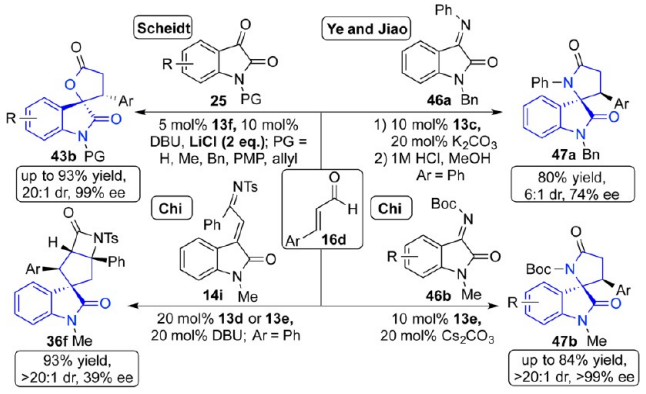
isatins **25** to generate spirocyclic oxindolo-γ-butyrolactones **43a** in good yields with good diastereo- and enantioselectivities.[28] (Thereafter, other examples followed, such as the work of Coquerel in 2013.[29]) Among the catalysts evaluated, **13b** was found to be most efficacious; no reaction occurred when NHCs with a silyl substituent were used. On the basis of the strong influence of the free hydroxyl group on the activity of the catalyst and the stereochemical outcome of the reaction, the authors hypothesized a transition state in which hydrogen bonding between the catalyst **13b** and isatin **25** enhance the reactivity and direct the addition of the dienolate **45b** to the carbonyl group of isatin **25**. Ye's laboratory further extended this strategy to α,β-unsaturated β-methylacyl chloride **44** and found that the silylated NHC catalyst **13a** was optimal in terms of reactivity.[30] The additive triethylamine is essential to generate a ketene intermediate. Under the established conditions, the reaction between α,β-unsaturated β-methylacyl chloride **44** and isatins **25** proceeded smoothly, providing spirocyclic oxindole-dihydropyranones **26d** in good yields with good to high enantioselectivities. The authors further demonstrated that the spirocyclic lactones **26d** could be subjected to aminolysis with pyrrolidine to afford the corresponding 3-hydroxyoxindoles while maintaining its ee. It is noteworthy that unprotected (N−H) isatins are not used in the NHC catalysis literature.

N-Aryl isatinimines (**46**) also serve as substrates in NHC-catalyzed conjugate umpolung reactions (Scheme 15).[31] The

Scheme 15. NHC-Catalyzed Cycloaddition Reaction of Enals 16d with Isatinimines 46, Vinyligous Isatinimines 14i, or Isatins 25



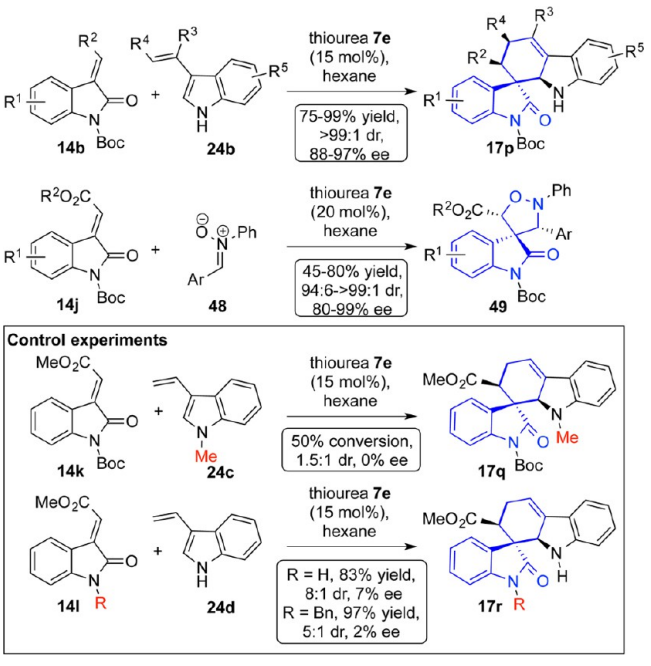
13c, **13d**, **13e**, **13f** = *N*-heterocyclic carbene (NHC) catalyst; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; PG = protecting group; PMP = *p*-methoxyphenyl

NHC-catalyzed addition of enals (**16d**) to isatinimines (**46**) proceeds efficiently in one pot to yield spirocyclic γ-lactam oxindoles (**47**). An enantioselective variant of this methodology using **13c** as the catalyst resulted in moderate enantioselectivity. The Chi group carried out an NHC-catalyzed annulation reaction of **16d** and **46b** for the rapid construction of spirooxindole-γ-lactams **47b** with excellent diastereo- and enantioselectivities.[32] In 2012, another NHC-catalyzed cascade reaction between challenging β,β-disubstituted, α,β-unsaturated imines **14h** and enals **16d** was disclosed by Chi and co-workers, providing diastereoselective access to β-lactam-fused spirocyclic oxindoles **36f**.[33] In the group's attempt to realize an asymmetric version of this reaction using NHC catalysts **13d** or **13e**, only moderate enantioselectivities were obtained. In addition, in the same year, Scheidt's group employed an NHC/Lewis acid cooperative catalysis strategy to carry out the annulation reaction between enals **16d** and isatins **25**.[34] The addition of lithium chloride as a Lewis acid to β-aryl substituted enals **16d** generated lactone products with good enantioselectivity, whereas lithium chloride was detrimental to the reaction of enals bearing β-alkyl substituents. The authors proposed that the enantioselectivity for β-aryl substituted enals **16d** might stem from the generation of an organized transition state by lithium cations through coordination of the enol oxygen atom of the NHC-bound homoenolate and the 1,2-dicarbonyl of the isatin **25**. The utility of this method was highlighted by a concise total synthesis of maremycin B.

2.4. Hydrogen Bonding Catalysis. Hydrogen bonding (H-bonding) catalysts are designed on the basis of the assumption that small organic molecules are able to increase the electrophilic character of a substrate via H-bonding interactions with oxygen or nitrogen lone pair electrons in the reagent, making the reaction more likely to take place and under stereocontrol.[35] Recently, H-bond donors such as ureas and thioureas have been recognized as efficient organocatalysts. Novel urea and thiourea derivatives act as general Brønsted acids in various transformations that yield chiral spirooxindoles.[36] The most common bifunctional catalysts contain a urea or a thiourea and a tertiary amine group, which also serves as an H-bonding catalyst.

In 2011, Barbas and co-workers utilized a C_2-symmetric bisthiourea organocatalyst **7e** to promote the Diels−Alder reaction of 3-vinylindoles **24b** and methyleneoxindoles **14b** to yield optically active and structurally diverse carbazolespirooxindole derivatives **17p** in almost quantitative yield and with high enantiopurity (Scheme 16).[37] Mild reaction conditions, simple starting materials, scalability, and ability to recycle the catalyst and solvent make this strategy appealing. Although the mechanism of this reaction has not been completely elucidated, it was shown that both the N−H group of vinylindole **24b** and the protecting group in methyleneoxindole **14b** had a

Scheme 16. Diels−Alder Reaction and [3 + 2] Cycloaddition Catalyzed by Bisthiourea Organocatalyst 7e



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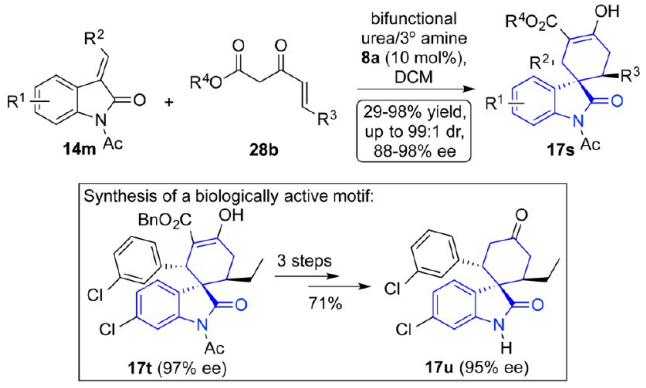
significant effect on stereoselectivity. No evidence of catalyst interactions with 3-vinylindole **24b** alone was found by ^{1}H or ^{13}C NMR experiments, but strong interactions with the methyleneoxindole **14b** were observed in the ^{13}C NMR spectra. The H-bonding induced a downfield shift of up to 0.98 ppm. The authors hypothesized that, prior to C−C bond formation, the bisthiourea **7e** activated methyleneoxindole **14b** through H-bonding interactions and that the vinylindole **24b** was oriented by interactions between the N−H group of the diene and the Boc group of the dienophile via $\pi-\pi$ stacking and weak H-bonding interactions. The effects of the N-protecting group of methyleneoxindole **14** on the enantioselectivity are striking. A bulky electron-acceptor group at the 3-position is necessary; N-Boc-protected 3-methyleneoxindole derivatives **14k**, but not the unprotected derivative or the Bn-protected derivative (**14l**), provided stereocontrolled product.

Using the same bisthiourea **7e** as a multiple H-bonding donor catalyst, a novel [3 + 2] annulation of methyleneoxindole **14j** with nitrones **48** was disclosed by the Cheng group.[38] Their protocol provides a convenient approach to enantioenriched spiro[isoxazolidine-3,3′-oxindole] derivatives (**49**) in good yields with excellent enantio- and diastereoselectivities. Again, the N-protecting group plays a significant role in the stereocontrol. On the basis of NMR and mass spectrometry experiments, this process is directed by multiple H-bonding interactions between the bisthiourea catalyst and the two substrates.

Using urea catalyst **8a**, which has Brønsted acidic and Lewis basic functionalities, sequential double Michael addition reactions of Nazarov substrates **28b** with methyleneoxindoles **14m** proceeded smoothly, providing spirocyclohexanoneoxindole derivatives **17s** with excellent enantioselectivities (Scheme 17).[39] The high level of stereocontrol results from

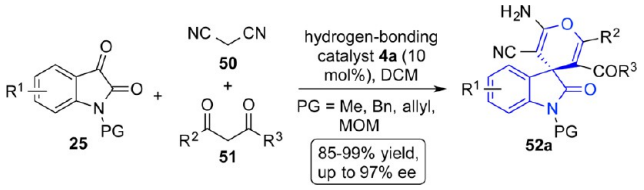
Scheme 17. [4 + 2] Cycloaddition Reaction of Nazarov Substrates (28b) and Methyleneoxindoles (14m)



the simultaneous activation of each reaction component by the catalyst. Remarkably, use of urea **8a** rather than thioureas for the catalyst enhanced stereoselectivity. This protocol has the potential to synthesize biologically active spiro[cyclohexane-1,3′-indoline]-2′,4-dione derivatives (e.g., **17u**) in high enantiomeric purity.

Cupreine (**4a**) is also an efficient catalyst for organocatalytic reactions between isatylidene malononitrile derivatives (formed from **25** and **50**) and 1,3-diones (**51**), as shown by Yuan's group (Scheme 18).[40] This catalytic process involves a domino Knoevenagel/Michael/cyclization sequence with **4a** serving as the catalyst, leading to optically active spiro[4*H*-pyran-3,3′-

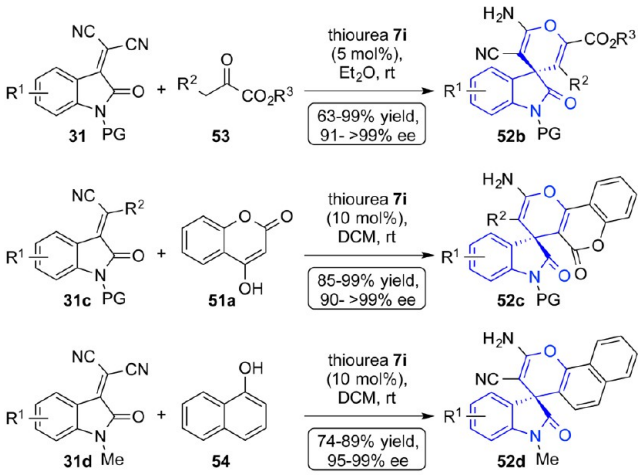
Scheme 18. Cupreine (4a)-Catalyzed One-Pot Reaction of Isatin 25, Malononitrile (50), and 1,3-Diketone 51



oxindoles] (**52a**) in excellent yields with good to excellent enantioselectivities. In this one-pot procedure, no loss of yield or selectivity for the organocatalytic reaction is observed.

An alternative strategy for the construction of chiral spiropyranooxindoles **52** was developed through an asymmetric Michael/cyclization sequence by the Wang group (Scheme 19).[41] The group employed a rosin-derived bifunctional catalyst

Scheme 19. Michael/Cyclization Sequence of Isatylidene Malononitriles 31 with α-Keto Esters 53, 4-Hydroxycoumarin (51a) or Naphthol (54)



7i = bifunctional thiourea/3° amine catalyst; PG = protecting group

7i. They extended the reaction to isatylidene malononitriles **31** with α-keto esters **53**, 4-hydroxycoumarin (**51a**), and naphthol (**54**) to afford spiropyranoxindoles **52b**, **52c**, and **52d** with excellent results. It is noteworthy that several of these novel spirocyclic alkaloids significantly inhibit the proliferation of cancer cells in a preliminary biological evaluation, showing promise as chemotherapeutic agents.

α-Isothiocyanato derivatives were recently used as nucleophiles for organocatalytic asymmetric aldol and Mannich reactions, proving to be useful synthons for the synthesis of chiral spirooxindoles.[42] In 2010, Wang's group reported an aldol/cyclization reaction of isatins (**25**) with α-isothiocyanato imides (**55a**; Scheme 20).[43] By screening various catalysts, the authors found that bifunctional thiourea catalyst **7f** promoted the reaction efficiently, leading to optically active spiro-[thiocarbamate-3,3′-oxindole]s (**56a**) in excellent yields, diastereoselectivities, and enantioselectivities. The products were readily transformed into biologically active chiral spirooxazolines **56b**. It is likely that the electron-deficient N-protected isatin (**25**) is activated by the two thiourea hydrogen atoms, while the α-isothiocyanato imide (**55a**) is enolized by the tertiary amine of the catalyst. Using thiourea organocatalyst **7l** derived from a cinchona alkaloid, Zhao and co-workers

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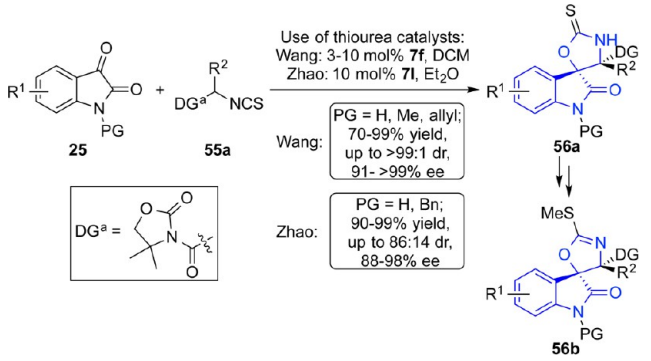
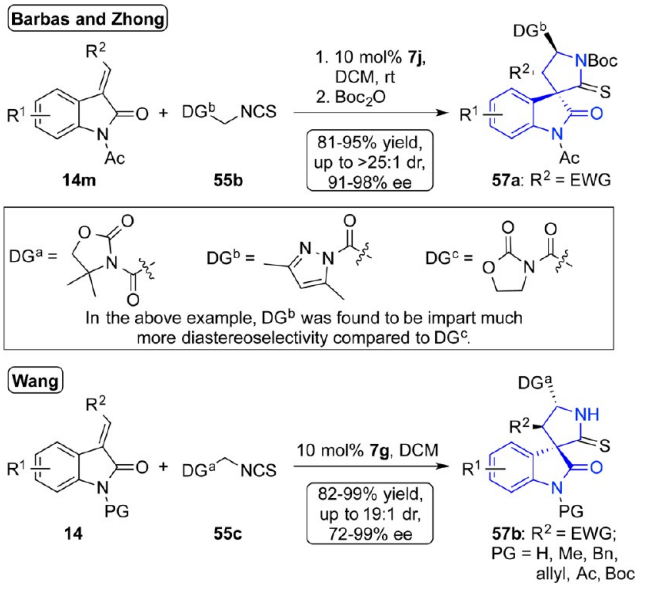
Scheme 20. Aldol/Cyclization Reaction of Isatins 25 with α-Isothiocyanato Imides 55a Catalyzed by Bifunctional Thiourea Catalysts 7



described a similar process that results in the desired products in high yields with excellent stereocontrol.[44]

The Barbas[45] and Wang[46] groups independently developed a highly enantioselective synthesis of thiopyrrolidonyl spirooxindole derivatives **57** from methyleneoxindoles **14** and α-isothiocyanatoimides **55** (Scheme 21). The [3 + 2] cycloaddition reaction of rationally designed dimethylpyrazole isothiocyanato amides **55b** with methyleneoxindoles **14** led to the formation of 3,3′-thiopyrrolidonyl spirooxindoles **57a**.[45] Initial studies of this reaction using oxazolidinone **DG^c** as the directing group gave poor diastereoselectivities. Inspired by a report by Sibi and Itoh,[47] the Barbas group utilized dimethylpyrazole directing group **DG^b**, expecting that such substrates would have an extra H-bond acceptor site for the thiourea catalyst. Experimental results showed that, in the presence of catalyst **7j**, this new methodology provides access to multisubstituted spirooxindole derivatives **57a** in excellent enantioselectivities (up to 98% ee) and almost complete diastereoselectivities (>25:1 dr in all cases), regardless of the stereoelectronic nature of the substituents. One important feature of this strategy is that the pyrazole moiety can be easily converted into other functional groups, such as alcohols. In contrast, Wang and co-workers employed rosin-derived bifunctional catalyst **7g** with oxazolidinone isothiocyanatoimides **55c** to access thiopyrrolidonyl spirooxindoles **57b**, which bears three contiguous stereocenters.[46] In this procedure, both substrates are activated by the bifunctional catalyst (Figure 5). Barbas and co-workers proposed a [3 + 2] cycloaddition process for the reaction in which the methyleneoxindole is activated by the tertiary amine, and the α-isothiocyanato imide is enolized by deprotonation at its α-carbon atom by double H-bonding. Wang's group proposed that the methyleneoxindole is activated by double H-bonding and that the α-isothiocyanato imide is enolized by the tertiary amine of the catalyst.

Scheme 21. Michael/Cyclization Reaction of Methyleneoxindoles 14 and α-Isothiocyanatoimides 55



7g, **7j** = bifunctional thiourea/3° amine catalyst; DG = directing group; EWG = electron-withdrawing group; PG = protecting group

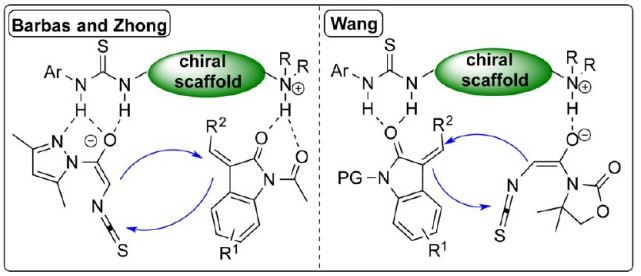
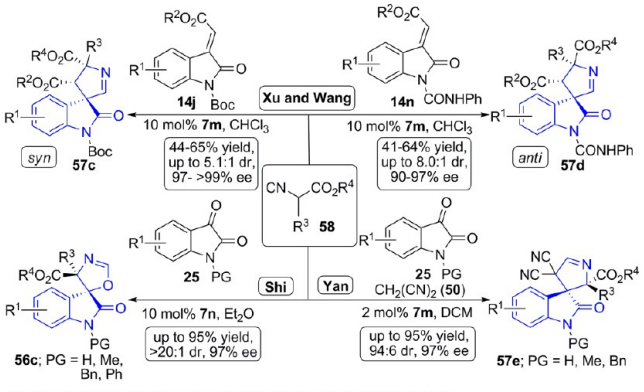


Figure 5. Proposed activation modes for the synthesis of pyrrolidonyl spirooxindole derivatives from methyleneoxindoles and α-isothiocyanatoimides.

Isocyanides are irreplaceable building blocks for the synthesis of a number of important classes of nitrogen heterocycles. The unique divalent features of the isocyano group enable isocyanides to react with both electrophiles and nucleophiles. Isocyanoacetates (**58**) possess several potential reaction centers (an isocyano group, an acidic C−H, and a protected carboxylic acid) and show exceptional reaction diversity. The following examples in Scheme 22 describe elegant work utilizing isocyanoacetates to construct chiral spirooxindoles via cascade strategies.

A novel [3 + 2] cycloaddition of isocyanoesters **58** and methyleneoxindoles **14** in the presence of quinine-based thiourea tertiary amine catalyst **7m** was adopted by Wang et al. in 2012 to access optically active 3,3′-pyrrolidinyl spirooxindoles **57d** with multiple contiguous stereocenters.[48] It is noteworthy that the N-protecting groups of the

Scheme 22. Catalytic Asymmetric Synthesis of Spirooxindoles from Isocyanoesters (58)



7m, **7n** = bifunctional thiourea/3° amine catalyst; PG = protecting group

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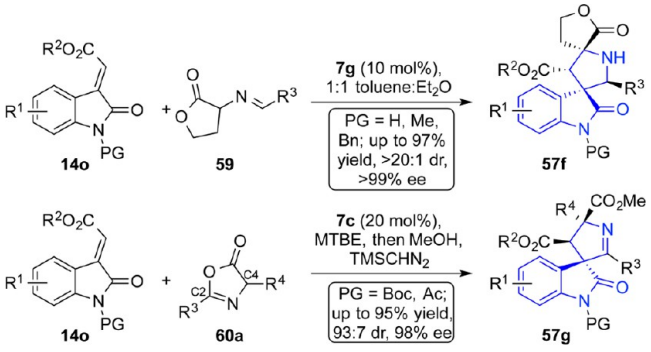
methyleneoxindoles had a significant effect on diastereoselectivity. Syn products (**57c**) were obtained when the N-protecting group was *N*-*tert*-butoxycarbonyl, and anti products (**57d**) when it was *N*-(phenylamido)carbonyl.

Yan's group reported a three-component reaction of isatins **25**, malononitrile (**50**), and isocyanoacetates **58** catalyzed by tertiary amine-thiourea **7m**.[49] A number of 3,3′-dihydropyrryl-spirooxindoles (**57e**) were prepared in excellent yields and enantioselectivities. The products were transformed into valuable 3,3′-pyrrolidinyl-spirooxindoles simply by selective reduction of the imine group.

For a further application of isocyanides, Shi's group successfully executed a [3 + 2] cycloaddition strategy for the construction of optically active spirooxindole oxazolines (**56c**).[50] The reaction between α-aryl isocyanoacetates **58** and isatins **25** was accomplished using a quinine-derived bifunctional amine−thiourea catalyst, **7n**, which contains a sulfonamide unit as an H-bonding donor. The desired products were obtained in good yields, high diastereoselectivities, and good to excellent enantioselectivities.

The Wang group reported two additional examples of the 1,3-dipolar cycloaddition strategy for the preparation of chiral spirooxindoles in 2013 (Scheme 23).[51,52] For the first, a 1,3-

Scheme 23. Catalytic Asymmetric 1,3-Dipolar Cycloaddition Strategies for the Synthesis of Spirooxindoles

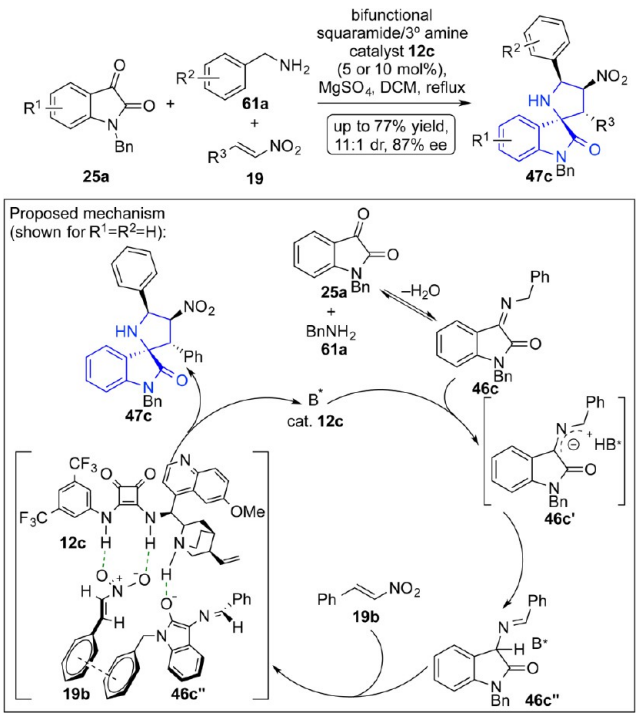


7c, **7g** = bifunctional thiourea/3° amine catalyst; PG = protecting group; MTBE = methyl *t*-butyl ether

dipolar cycloaddition reaction of homoserine lactone-derived cyclic imino esters **59** with methyleneoxindoles **14o** was used to construct spiro[γ-butyrolactone-pyrrolidin-3,3′-oxindole] tricyclic skeletons **57f**.[51] Using bifunctional organocatalyst **7g**, the desired products were obtained with excellent levels of stereocontrol over four contiguous stereocenters. In the second example, the group took advantage of the nucleophilic C4 and electrophilic C2 atoms of azlactone **60a** in an organocatalytic enantioselective 1,3-dipolar cycloaddition reaction between **60a** and **14o** to construct spirooxindole derivatives **57g**.[52] The bifunctional thiourea catalyst **7c** deprotonated the azlactone to generate a cyclic mesoionic azomethine ylide and provide products with excellent enantioselectivity.

Recently, motivated by successful transamination strategies, an enantioselective route to the biologically important spiro[pyrrolidin-3,2′-oxindole] scaffolds (**47c**) from very simple and readily available starting materials was developed (Scheme 24).[53] Cinchona-based squaramide **12c** catalyzed both 1,3-proton shift and [3 + 2] cycloaddition among isatins **25a**, benzylamines **61a**, and nitroalkenes **19**, providing the desired products in moderate yields and good diastereo- and

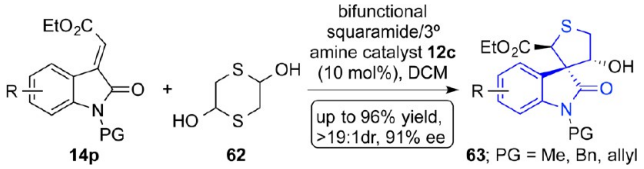
Scheme 24. [3 + 2] Cycloaddition Involving Transamination Catalyzed by Squaramide 12c



enantioselectivities. The authors proposed a plausible catalytic cycle in which the synergistic activation of both reaction partners by the catalyst as well as $\pi-\pi$ interaction could rationalize the stereocontrol. In this example, squaramide **12c** recognizes the nitro group and directs the stereoselectivity via H-bonding.

Xiao's group found that squaramide **12c** is also able to activate methyleneoxindoles efficiently (Scheme 25).[54] The

Scheme 25. Michael/Aldol Cascade between Methyleneoxindoles 14p and 1,4-Dithiane-2,5-diol (62)



simple and commercially available 1,4-dithiane-2,5-diol (**62**; the dimer of mercaptoacetaldehyde) was used for the construction of spirooxindole derivatives fused with tetrahydrothiophenes (**63**). In this case, a Michael/aldol cascade between methyleneoxindoles **14p** and 1,4-dithiane-2,5-diol (**62**) resulted in the desired products **63** in a highly stereoselective fashion.

Pesciaioli et al. reported an efficient asymmetric strategy for the construction of spirocyclopropyloxindoles with three contiguous stereogenic centers via an organocatalytic Michael/alkylation cascade sequence of methyleneoxindoles **14b** and halonitroalkanes **64** (Scheme 26).[55] Use of a low loading of bifunctional thiourea organocatalyst **7k** yielded the desired products **65a** in good yields, diastereoselectivities, and enantioselectivities. The base additive had a very strong effect on the reactivity and selectivity. The addition of one equivalent of Na_2CO_3 provided excellent enantiocontrol and an increase in

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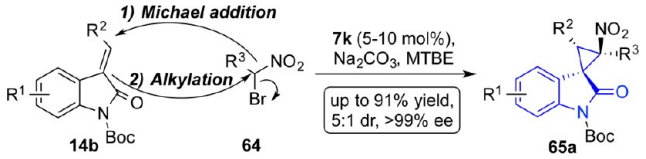
Scheme 26. Michael/Alkylation Cascade between Methyleneoxindoles 14b and Halonitroalkanes 64

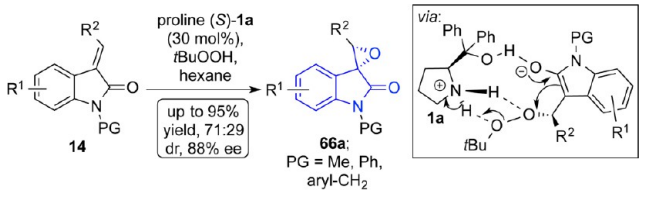


7k = bifunctional thiourea/3° amine catalyst; MTBE = methyl *t*-butyl ether

conversion and diastereoselectivity relative to the reaction without base additives.

In addition to urea, thiourea, and squaramide, (*S*)-α,α-diphenylprolinol (**1a**) can also activate methyleneoxindoles by creating a complex H-bond network between substrate and oxidant (Scheme 27). Nucleophilic epoxidation of methyl-

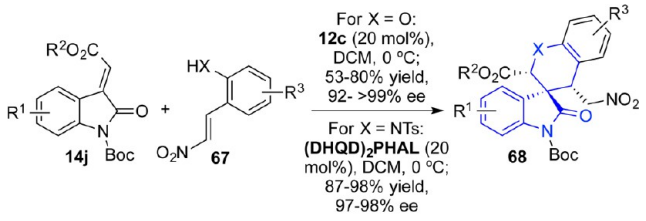
Scheme 27. Epoxidation for the Construction of Enantioenriched Spiroepoxyoxindoles 66a



eneoxindoles **14** has been used to construct enantioenriched spiroepoxyoxindoles **66a**.[56] Although this route did not provide high yields or stereoselectivities, it provided a novel asymmetric approach to the organocatalytic epoxidation of α,β-unsaturated carboxylic acid derivatives and a valuable alternative to the electrophilic procedure developed by Shi's group.[57]

Finally, a unified approach was taken by Zhu and co-workers for the construction of spiro[chroman/tetrahydroquinoline-3,3′-oxindole] motifs (Scheme 28).[58] Starting from methyl-

Scheme 28. Oxa/aza-Michael/Michael Cascade Strategy for the Synthesis of Spiro[chroman/tetrahydroquinoline-3,3′-oxindoles] 68



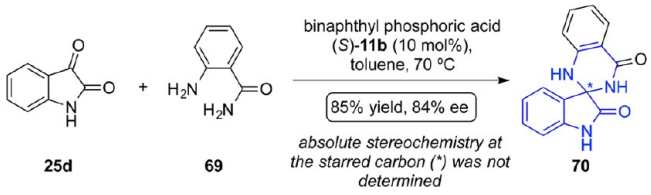
12c = bifunctional squaramide/3° amine catalyst; $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether

eneoxindole **14j** and a phenol or a protected aniline derivative **67**, an oxa/aza-Michael/Michael cascade strategy was employed to generate spirocyclic products **68** in good yields and excellent enantioselectivities.

2.5. Chiral Phosphoric Acid or Chiral Metal Phosphate Catalysis. Since the pioneering independent studies from the laboratories of Akiyama and Terada in 2004 on the design and application of chiral BINOL-derived phosphoric acids,[59] chiral phosphoric acids and derivatives have been shown to be powerful Brønsted acid catalysts and bifunctional catalysts in numerous highly enantioselective transformations. Initially, the activation was restricted to reactive imine substrates, but recent reports have established the versatility of phosphoric acid catalysts in the activation of other functional groups in a stereocontrolled fashion.

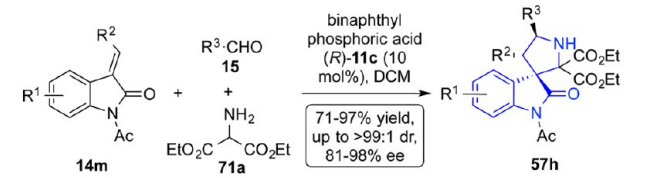
In 2008, List and co-workers utilized isatin (**25d**) as an electrophile in a reaction with 2-aminobenzamide (**69**) to give spirocyclic aminal **70** in 85% yield with 84% enantioselectivity by using (*S*)-TRIP **11b** as the catalyst (Scheme 29).[60] This is the first example of an asymmetric organocatalytic synthesis of spirooxindole aminals.

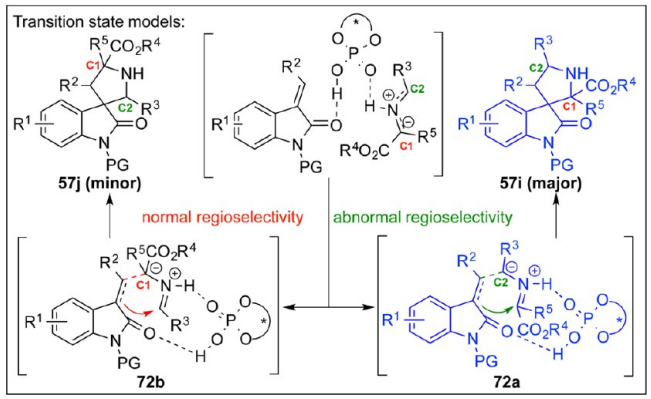
Scheme 29. (*S*)-TRIP-Catalyzed Cyclization Reaction of Isatin (25d) with 2-Aminobenzamide (69)



Certain spiro[pyrrolidin-3,3-oxindole] derivatives exhibit important biological activities. The first enantioselective organocatalytic approach to the rapid synthesis of spiro-[pyrrolidin-3,3-oxindole] derivatives with high enantiopurity and structural diversity was described by Gong's group in 2009 (Scheme 30).[61] The asymmetric catalytic three-component 1,3-

Scheme 30. 1,3-Dipolar Cycloaddition of Methyleneoxindoles 14m with Aldehydes 15 and Amino Esters 71a Catalyzed by Chiral Phosphoric Acid 11c





dipolar cycloaddition of a broad range of methyleneoxindoles (**14m**) with aldehydes (**15**) and amino esters (**71a**) in the presence of chiral phosphoric acid **11c** provided spirooxindole derivatives **57h** in high yields with unusual regiochemistry and excellent stereoselectivities (up to 98% ee). This straightforward construction of spirooxindole skeletons with high stereo- and regioselectivity suggested a new avenue to medicinal chemists for diversity-oriented synthesis. Theoretical calculations revealed that both the azomethine ylide and the methyleneoxindole are H-bonded with the phosphoric acid, accounting for the high enantio- and regioselectivity, and that

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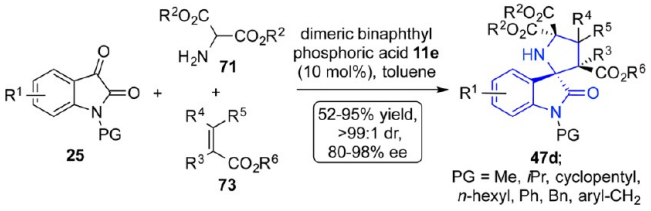
the unusual regioselectivity results from $\pi-\pi$ stacking interactions between the oxindole and the conjugated esters. On the basis of density functional theory calculations, the authors hypothesized that the unique regioselectivity arises from the energetically favored transition state **72a** rather than **72b**. It is worth mentioning that in 2010, Waldmann and co-workers disclosed an asymmetric Lewis acid-catalyzed 1,3-dipolar cycloaddition of an azomethine ylide to a substituted 3-methylene-2-oxindole.[62] Using a chiral catalyst formed from a *N*,*P*-ferrocenyl ligand and $CuPF_6(CH_3CN)_4$, the "normal" regioselective products were obtained with excellent results.

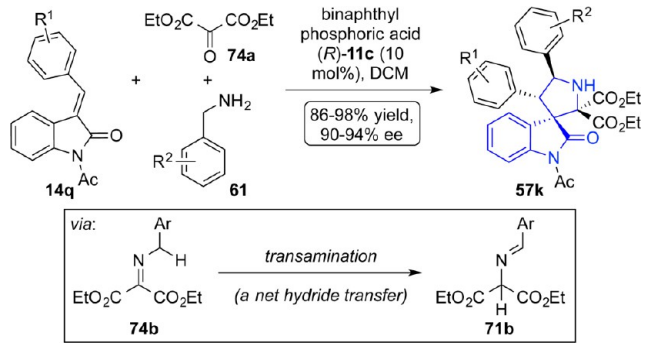
The Gong laboratory extended this catalytic asymmetric 1,3-dipolar cycloaddition reaction and established a strategy for the synthesis of biologically important spiro[pyrrolidin-3,2′-oxindole] scaffolds (**47d**) from azomethine ylides generated in situ from isatins **25** and various electron-deficient olefins (Scheme 31).[63] Biphosphoric acid **11e** was the most efficient catalyst of those evaluated. Theoretical calculations performed on the transition state explained the observed stereochemistry.

Scheme 31. 1,3-Dipolar Cycloaddition Reaction of Various Electron-Deficient Olefins Catalyzed by Chiral Phosphoric Acid 11e



Inspired by biomimetic transamination, Gong's group reported the asymmetric, three-component, 1,3-dipolar cycloaddition of α-keto esters **74a** and benzylamine **61** with electron-deficient olefins (Scheme 32).[64] The most important

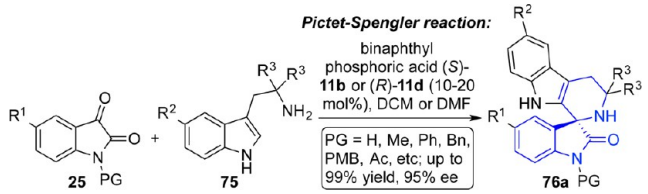
Scheme 32. 1,3-Dipolar Cycloaddition of α-Ketoesters 74a and Benzylamines 61 with Methyleneoxindoles 14q



feature of this study was the strategic use of phosphoric acid derivative **11c** to catalyze the transamination of ketimines **74b** formed from α-keto esters and amines to generate azomethine ylides **71b** in situ. These ylides readily participate in a 1,3-dipolar cycloaddition with a structurally diverse range of dipolarophiles. The authors also showed that methyleneoxindoles **14q** served as suitable substrates and generated a collection of spiro[pyrrolidin-3,3′-oxindole] derivatives (**57k**) with excellent results in the presence of phosphoric acid catalyst **11c**.

NITD609 is a very promising drug candidate for the treatment of malaria because it has single-dose efficacy in a mouse model with one enantiomer demonstrating greater potency than the other.[4j] To synthesize its spirooxindole core structure in an enantioselective manner, both the Bencivenni[65] and Franz[66] groups reported the enantioselective synthesis of spirooxindoles **76a** using catalytic asymmetric Pictet–Spengler reactions of isatins **25** with tryptamine derivatives **75** (Scheme 33). The Bencivenni laboratory identified (*S*)-TRIP **11b** as the

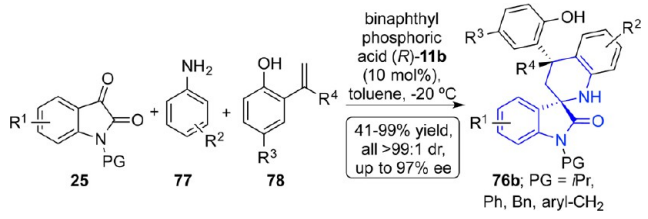
Scheme 33. Pictet–Spengler Reactions of Isatins 25 for the Synthesis of Spirooxindoles 76a



optimal catalyst for this reaction.[65] Franz's group found that both (*S*)-TRIP **11b** and (*R*)-**11d** promote this reaction with good yields and enantioselectivities. Interestingly, the same absolute configuration of product was accessed by using both (*S*)- and (*R*)-BINOL-containing phosphoric acids; this indicated that the substitution on the binaphthyl system is crucial in directing the enantioselection.[66]

Using a similar strategy, the Tu group developed a catalytic asymmetric Povarov reaction that provides a straightforward approach to enantioenriched spiro[indolin-3,2′-quinoline] scaffolds (**76b**) in high yields and excellent stereoselectivities (Scheme 34).[67] The authors proposed that the reaction

Scheme 34. Asymmetric Povarov Reaction for the Construction of Spirooxindole 76b



sequence begins with the vinyligous Mannich reaction of ketimine generated from isatin **25** and aniline **77**, followed by an intramolecular Friedel–Crafts reaction. Both steps were conducted under the catalysis of chiral phosphoric acid (***R***)-**11b**.

Recently, Antilla and co-workers reported a direct asymmetric Diels–Alder reaction between oxindole dienophile **14b** and Danishefsky-type diene **79**, giving 2,6-*cis*, six-membered spirooxindoles **17v** (Scheme 35).[68] Chiral phosphate magnesium complex **10** was used as the catalyst to induce stereocontrol. This reaction displays broad substrate scope and provides excellent results. The protecting group on oxindole **14b** had a significant effect on reaction efficiency: when the protecting group was carbonyl-based, enantioselectivity was higher than when the protecting group was a benzyl. Notably, molecular sieves (MS) were necessary for high enantioselectivity. The MS likely removed water that, when coordinated to magnesium, would decrease the Lewis acidity of the magnesium cations and change the conformation of the

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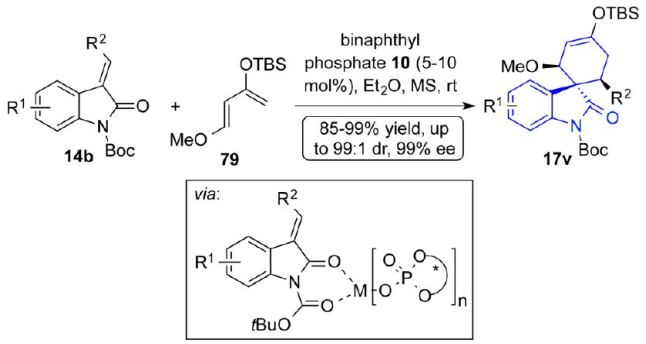
Scheme 35. Asymmetric Diels–Alder Reaction between Oxindole Dienophile 14b and Danishefsky-Type Diene 79, Catalyzed by Chiral Phosphate Magnesium Complex 10

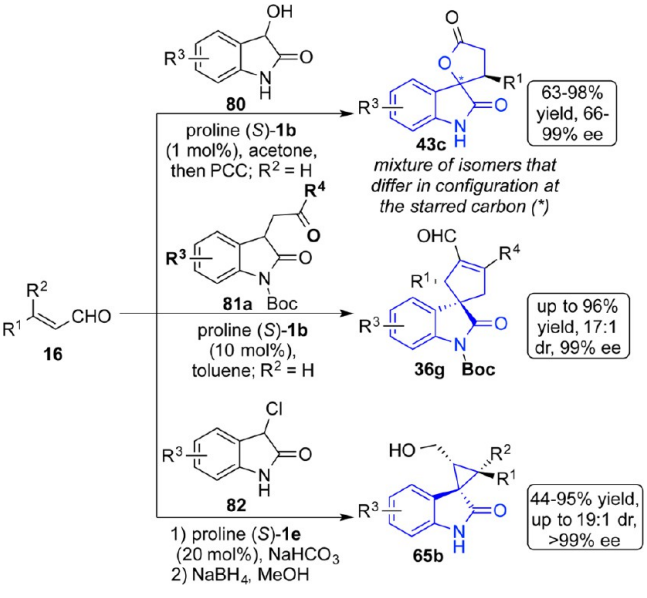


Mg^{2+} intermediate. The authors suggested that the imide group of the oxindole coordinates with Mg^{2+} to form a tetrahedral intermediate that is important for stereocontrol.

3. USE OF SATURATED SUBSTRATES

3.1. Enamine and Iminium Catalysis. In 2011, Bergonzini and Melchiorre disclosed a strategy for the synthesis of spirooxindole γ-butyrolactones **43c** from dioxindoles **80** and α,β-unsaturated aldehydes **16** (Scheme 36).[69] An important

Scheme 36. Cascade Reactions of α,β-Unsaturated Aldehydes 16 with Various 3-Substituted Oxindoles



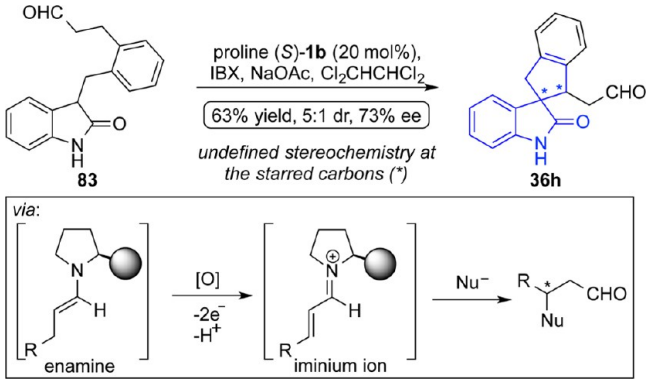
outcome of this study was an improved understanding of the reactivity of dioxindole (**80**) under different reaction conditions, which allowed the careful choosing of conditions to harness its inherently high nucleophilicity. In the presence of chiral secondary amine catalyst (*S*)-**1b**, the desired products could be achieved with good yields and enantioselectivities but with a poor diastereomeric distribution (ranging from 1.5:1 to 1:1).

Using rationally selected 3-substituted oxindoles **81a** and the same catalyst (*S*)-**1b**, the Barbas group developed a strategy for the synthesis of spirocyclopentaneoxindoles (**36g**) from various α,β-unsaturated aldehydes **16**.[70] The organocatalytic iminium/enamine cascade process was accomplished smoothly and provided the desired products **36g** in high yields with excellent levels of stereoselectivity in a single step.

Recently, Kanger and colleagues demonstrated that 3-chlorooxindoles **82**, which have both nucleophilic and electrophilic character at the carbon bearing the Cl atom, are versatile precursors for the synthesis of spirocyclopropyl oxindoles (**65b**).[71] For example, the chiral secondary amine catalyst (*S*)-**1e** promotes the Michael/cyclization cascade reaction between 3-chlorooxoindoles **82** and α,β-unsaturated aldehydes **16**, leading to the formation of spirooxindoles (**65b**) in good yields and stereoselectivities.

In 2011, a new cascade strategy for the enantioselective β-functionalization of aldehydes via oxidative conversion of enamines to iminium species was developed by Wang's group (Scheme 37).[72] Employing (*S*)-**1b** as the catalyst and 2-

Scheme 37. Intramolecular Oxidative Annulation Cascade of Oxindole 83 To Yield Spirooxindole 36h



iodoxybenzoic acid (IBX) as the oxidant in conjunction with the essential additive NaOAc, oxindole **83** smoothly underwent intramolecular oxidation/cyclization to yield annulation product spirooxindole **36h** with moderate selectivity. Although only one example has been provided, this is a promising avenue for the construction of spirooxindole frameworks.

In 2010, Wang's group disclosed an efficient Michael/ketone aldol/dehydration domino reaction to access spirocyclohexanoneoxindoles **17w** in the presence of chiral cinchona-based primary amine **3d** in combination with trifluoroacetic acid (Scheme 38).[73] The designed substrate **84a**, which has both nucleophilic and electrophilic characters, undergoes an enamine/iminium cascade reaction with enones **28a** to afford the desired products with high yields and excellent diastereoselectivities and enantioselectivities. Using a similar stereocontrol strategy, Zhang's group utilized chiral amine **3b** to catalyze the Michael/aldol/dehydration reaction from simple 3-acyloxindole **84b**.[74] The desired cyclohexanone spirooxindoles **17x** were obtained with excellent diastereo- and enantioselectivities.

3.2. Nucleophilic (Phosphine and Amine) Catalysis. Liu designed MBH carbonates **85a** derived from isatins for use in a Me-DuPhos (**2e**)-catalyzed, efficient, asymmetric [3 + 2] cycloaddition reaction involving *N*-phenylmaleimide (**20b**) as the dipolarophile (Scheme 39).[75] Various spirocyclopentaneoxindoles **36i** were obtained in good yields with excellent diastereo- and enantioselectivities. In a further application, a chemoselective asymmetric [3 + 2] annulation of MBH carbonates **85a** with propargyl sulfones **35d** was achieved by Chen's group.[76] The reaction proceeds with very high fidelity in

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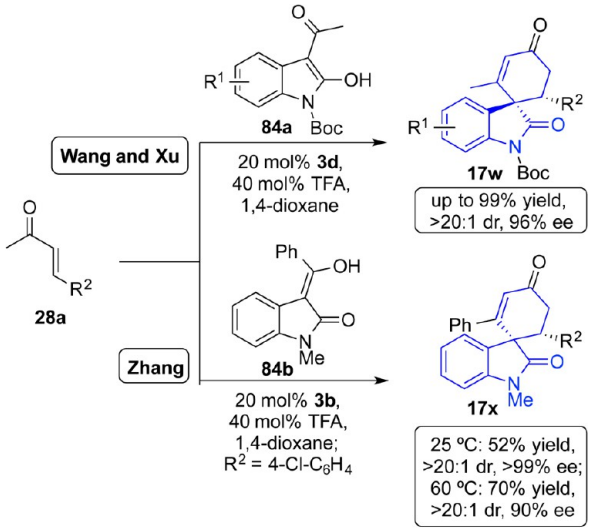
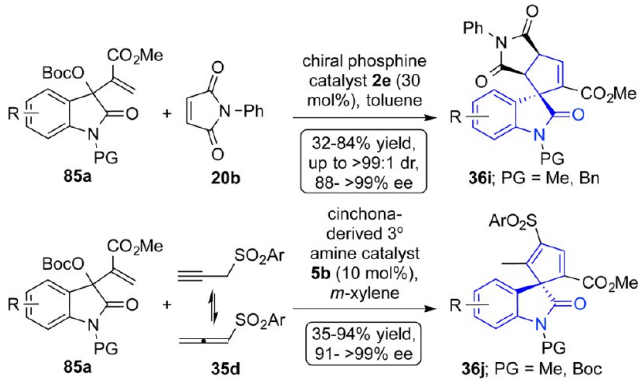
Scheme 38. Cascade Reaction between 3-Acyloxindole 84 and Enone 28a Catalyzed by 1° Amine Catalysts 3



3b, 3d = cinchona-derived 1° amine catalyst; TFA = trifluoroacetic acid

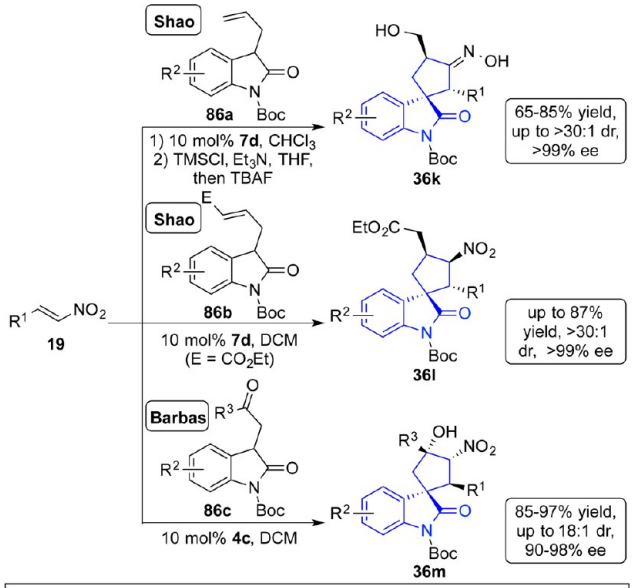
Scheme 39. [3 + 2] Cycloaddition between MBH Carbonates 85a and Dipolarophiles

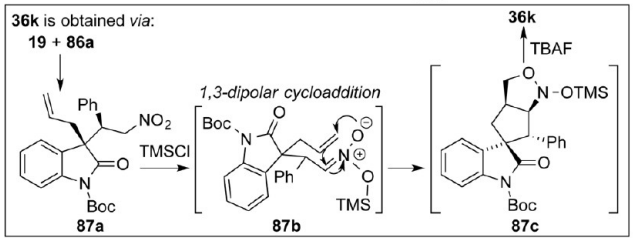


the presence of β-isocupreidine ether **5b** as the catalyst, resulting in the formation of enantioenriched spirocyclopentadiene oxindoles **36j**. The reaction involves a formal dipolar cycloaddition of in situ-generated allylic *N*-ylide and allenyl sulfone, followed by a C═C bond isomerization sequence.

3.3. Hydrogen Bonding Catalysis. In 2011, Shao and co-workers developed a highly diastereo- and enantioselective organocatalytic protocol for the synthesis of spirocyclopentaneoxindoles **36k** containing an oxime functional group from easily accessible 3-allyl-substituted oxindoles **86a** and nitroolefins **19** (Scheme 40).[77] This one-pot Michael addition/intramolecular silyl nitronate−olefin cycloaddition/fragmentation sequence is catalyzed by a novel bifunctional thiourea organocatalyst **7d** with central and axial chiral elements (see boxed reaction mechanism in Scheme 40). Using the same bifunctional thiourea organocatalyst **7d** in combination with Ru-catalyzed cross-metathesis and organocatalytic asymmetric double-Michael addition, the same group constructed spirocyclopentaneoxindoles **36l** with four contiguous stereocenters, including one spiroquaternary stereocenter, with excellent enantioselectivity.[78] Using an oxindole ketone rather than an unsaturated ester, Barbas and co-workers performed a Michael/Henry cascade reaction with quinidine derivative **4c** as the

Scheme 40. Cascade Reactions of Nitroolefins with Various 3-Substituted Oxindoles



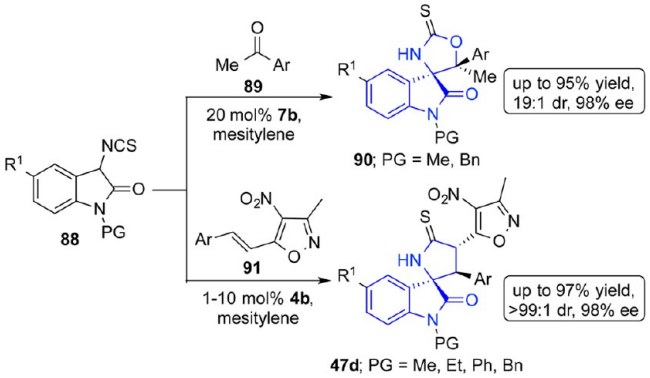


4c = cinchona-derived hydrogen bonding catalyst; 7d = bifunctional thiourea/3° amine catalyst; TBAF = tetrabutylammonium fluoride

catalyst to yield highly substituted spirocyclopentaneoxindoles **36m** with excellent enantioselectivities.[79]

In 2011, Yuan's group was the first to use 3-isothiocyanato oxindoles **88** for the selective construction of spirooxindoles (Scheme 41).[80] They installed an isothiocyanato group onto the 3-position of oxindoles to react as a nucleophile with simple ketones (**89**), to give structurally complex spirooxindoles **90** in good yields and selectivities. Bifunctional thiourea−tertiary amine **7b** was the optimal catalyst for this intermolecular aldol/cyclization reaction. On a gram scale, the protocol yielded excellent results. A Michael/cyclization reaction was also

Scheme 41. Reactions of 3-Isothiocyanato Oxindoles with Ketones or 3-Methyl-4-nitro-5-alkenyl Isoxazoles



4b = cinchona-derived hydrogen-bonding catalyst; 7b = bifunctional thiourea/3° amine catalyst; PG = protecting group

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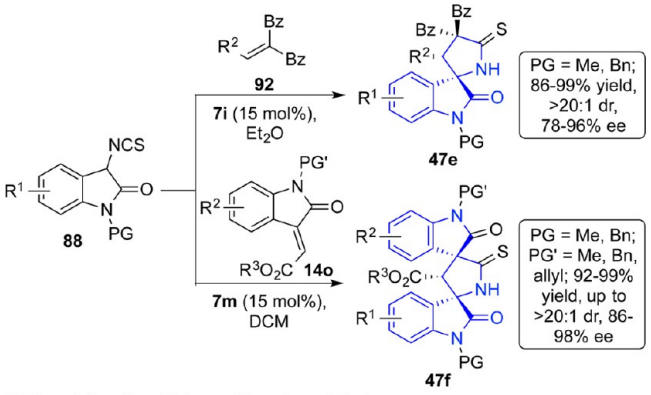
reported by Yuan's laboratory for the synthesis of 3,3′-thiopyrrolidonyl spirooxindoles **47d**.[81] Commercially available quinine **4b** was used to catalyze the domino reaction between 3-isothiocyanato oxindoles **88** and 3-methyl-4-nitro-5-alkenyl isoxazoles **91**. The utility of the protocol was demonstrated in a gram-scale reaction and in a versatile conversion of cycloadducts **47d** into other 3,3′-spirocyclic oxindoles. Thus, 3-isothiocyanato oxindoles **88** have become powerful and versatile precursors to structurally diverse chiral spirooxindoles.

In 2013, Wang and co-workers found that asymmetric Michael addition/cyclization reactions between isothiocyanato oxindoles **88** and electron-poor alkenes such as **92** and methyleneoxindoles **14o** result in an efficient synthesis of enantioenriched spirooxindoles **47e** and bispirooxindoles **47f**, respectively (Scheme 42).[82]

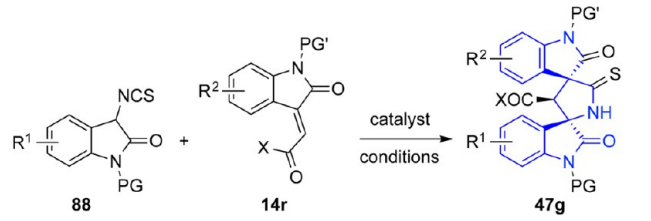
Scheme 42. Michael Addition/Cyclization Reactions between Isothiocyanato Oxindoles 88 and Electron-Poor Alkenes



7i, **7m** = bifunctional thiourea/3° amine catalyst

Also in 2013, Huang, Wang, and co-workers reported a cascade Michael/cyclization reaction between isothiocyanato oxindoles **88** and methyleneoxindoles **14r** to construct bispirooxindole derivatives **47g**, as shown in Scheme 43.[83] Bifunctional organocatalyst **7m** developed by the Barbas group was the most efficient in catalyzing the reactions of

Scheme 43. Synthesis of Bispirooxindoles 47g



Huang and Wang

For X = OEt: bifunctional thiourea/3° amine catalyst **7m** (15 mol%); PG = Me, Bn; PG' = Me, Bn, Ac; 98% yield, >20:1 dr, 92% ee
For X = (hetero)aryl: bifunctional thiourea/3° amine catalyst **7s** (15 mol%), PG = Me, Bn; PG' = Me, Ac; up to 99% yield, >20:1 dr, 99% ee

Chen and Xiao

For X = O-alkyl: bifunctional squaramide/3° amine catalyst **12c** (1 mol%); PG = Me, Bn; PG' = H, Me, Bn, PMB, allyl, Ac; up to 99% yield, >95:5 dr, 99% ee

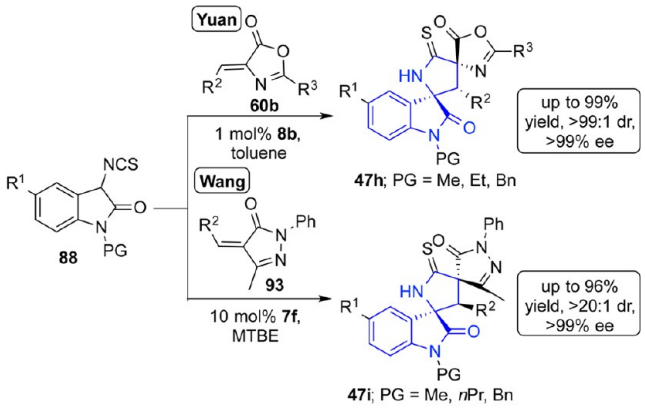
Yuan

For X = OEt: bifunctional thiocarbamate/3° amine **8b** (1 mol%); PG = Me, Et, Bn; PG' = Boc; 98% yield, >99:1 dr, 98% ee
(the -COX group can be replaced by aryl or heteroaryl as well)

methyleneoxindoles bearing different ester substituents, whereas for methyleneoxindoles bearing ketone moieties, **7s** was optimal. Notably, all of the reactions were completed under mild conditions in less than 1 min and afforded bispirooxindole derivatives **47g** in almost quantitative yields with excellent enantiomeric and diastereomeric purities. The authors demonstrated that the reaction occurs through dual activation. Chen's group also reported this type of formal [3 + 2] cycloaddition utilizing a cinchona-derived squaramide **12c** as the catalyst, producing the desired bispirooxindole products **47g** in almost quantitative yields with extremely high enantio- and diastereoselectivities.[84] Furthermore, quinine-derived thiocarbamate **8b** efficiently catalyzed the asymmetric cascade Michael/cyclization reaction between **88** and **14r**.[85] Under optimal reaction conditions, a spectrum of densely functionalized thiopyrrolidineoxindoles **47g** were synthesized with excellent diastereo- and enantioselectivity as well as good functional group compatibility. The ready transformation of the cycloadducts into other functionalized spirocyclic compounds bode well for the potential biomedical applications of this route.

In 2013, Yuan's group disclosed an asymmetric approach for the synthesis of chiral polycyclic spirooxindoles **47h** using (*Z*)-alkylidene azlactone **60b**,[85] and Wang's group made a similar motif (**47i**) from unsaturated pyrazolones **93**, both from isothiocyanato oxindoles **88** (Scheme 44).[86] In the latter, rosin-

Scheme 44. Syntheses Using Isothiocyanato Oxindoles 88



7f = bifunctional thiourea/3° amine catalyst; **8b** = bifunctional thiocarbamate/3° amine catalyst; PG = protecting group; MTBE = methyl *t*-butyl ether

derived tertiary amine thiourea **7f** promoted this Michael/cyclization sequence most effectively, leading to multicyclic core structures **47i** in high yields and excellent diastereo- and enantioselectivities.

Single-step constructions of molecules with multiple quaternary carbon stereocenters, such as bispirooxindoles, are challenging. In 2011, Barbas's group described an organocatalytic asymmetric domino Michael/aldol reaction between 3-substituted oxindoles **81b** and methyleneoxindoles **14m** that afforded complex bispirooxindoles **36n** (Scheme 45).[87] This reaction was catalyzed by a novel multifunctional organocatalyst (**7p**) that contains tertiary and primary amines as well as a thiourea to activate the substrate simultaneously. The catalyst provides extraordinary levels of stereocontrol over four stereocenters, three of which are quaternary carbons. Notably, methyleneoxindole **14m** that is directly connected to a phenyl group does not give any product (i.e., in **36n**, R^4 must be a ketone or ester, not phenyl). The group proposed that the two substrates involved in the reaction are activated simultaneously

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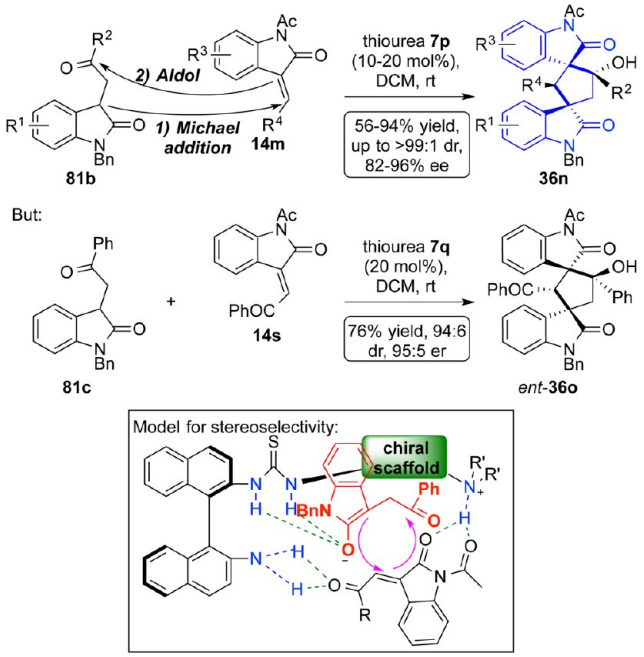
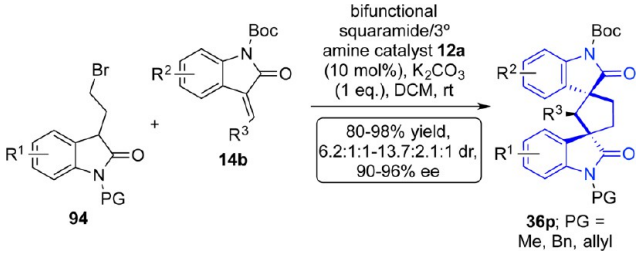
Scheme 45. Domino Michael/Aldol Reaction between 3-Substituted Oxindoles 81 and Methyleneoxindoles 14 for the Construction of Bispirooxindoles 36 with Three Quaternary Centers



by the catalyst **7p**, as illustrated in Scheme 45. The Barbas laboratory also prepared and characterized catalyst **7q**, which retains the (*S*)-diamine component but has a tertiary amine and different thiourea configurations compared with catalyst **7p**. This novel catalyst provided the opposite enantiomer (*ent*-**36o**) with good stereocontrol. This methodology provides facile access to a range of multisubstituted bispirocyclooxindole derivatives and should be useful in medicinal chemistry and diversity-oriented synthesis.

Following Barbas's work, some elegant organocascade strategies have been explored to construct chiral bispirooxindoles. In 2012, Wang and colleagues successfully made use of the Michael/alkylation cascade sequence to construct spirocyclopentane bioxindoles **36p** from rationally selected methyleneoxindoles **14b** and bromooxindoles **94** (Scheme 46).[88] This

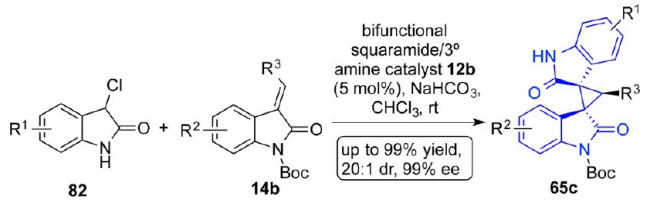
Scheme 46. Michael/Alkylation Cascade to Construct Spirocyclopentane Bioxindoles 36p



process was efficiently catalyzed by chiral squaramide **12a** in the presence of a base, K_2CO_3, affording the desired products in good yields (80−98%) and enantioselectivities (90−96%), but with moderate diastereoselectivities. The cascade process was fueled by the high efficiency in the production of two new C−C bonds and three contiguous stereocenters, including two quaternary centers, which are difficult to achieve by traditional strategies. On the basis of experimental data, the authors suggested that the two substrates involved in the reaction are activated simultaneously by the catalyst.

Kanger's group evaluated catalysts of the reaction between 3-chlorooxoindoles **82** and methyleneoxindoles **14b**, as shown in Scheme 47.[71] Squaramide **12b** proved to be the best H-bonding

Scheme 47. Cascade Reactions between 3-Chlorooxoindoles 82 and Methyleneoxindoles 14b for the Construction of Bispirooxindoles 65c

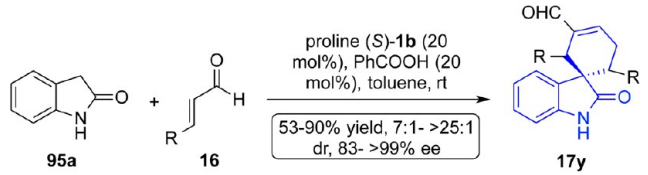


bifunctional catalyst out of those tested. Under optimized reaction conditions, the Michael/intramolecular nucleophilic substitution cascade reaction delivered bispirooxindoles derivatives **65c** in good yields and selectivities.

4. USE OF NONSUBSTITUTED OXINDOLE AS REACTANTS

4.1. Enamine and Iminium Catalysis. Nonsubstituted oxindoles have double nucleophilic centers (after a formal double deprotonation) that make the domino process possible. The Rios group's strategy was to simply combine oxindole (**95a**) with two molecules of α,β-unsaturated aldehydes **16** in the presence of chiral secondary amine catalyst (*S*)-**1b** (Scheme 48).[89] The desired products **17y** were obtained in good yields and with excellent stereocontrol in most cases.

Scheme 48. Cascade Michael/Michael/Aldol Reaction among Oxindoles and Two Molecules of α,β-Unsaturated Aldehydes



On the basis of this successful example, Xu and Wang's group demonstrated a Michael reaction of 3-unsubstituted oxindoles **95** with dienones **96** promoted by primary amine catalyst **3d** in combination with (*S*)-BINOL-phosphoric acid (**11a**), leading to spirooxindoles **17z** in good yields and excellent selectivities (Scheme 49).[90] Protecting groups had a significant influence on the reactivity: only *N*-CO_2Et-substituted oxindoles performed smoothly. Wang and Ji then reported a [5 + 1] Michael/Michael addition process for the construction of enantiomerically enriched spiro[cyclohexanone-oxindoles] **17z**.[91] In this case, *unprotected* oxindoles **95** reacted with divinyl ketones **96** to yield the desired products. A cinchona-based chiral primary amine **3c** and an α-amino acid derivative were used as cocatalysts.

4.2. Hydrogen Bonding Catalysis. Dou and Lu envisioned that employment of oxindoles containing a 3-unsubstituted carbon atom as a C_1 unit in combination with

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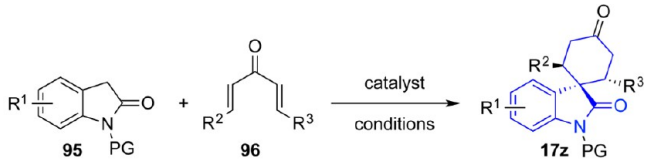
Scheme 49. Double Michael Addition of Oxindoles 95 with Dienones 96



Xu and Wang

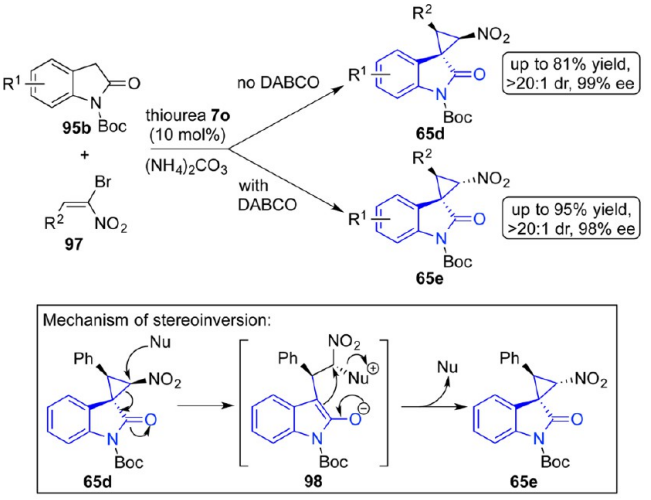
cinchona-derived 1° amine catalyst **3d** (20 mol%), binaphthyl phosphoric acid (*S*)-**11a** (40 mol%); PG = CO_2Et; up to 98% yield, 98% ee

Wang and Ji

cinchona-derived 1° amine catalyst **3c** (20 mol%), *N*-Boc-D-phenylglycine (40 mol%); PG = H; up to 98% yield, 99% ee

halogenated nitroolefins **97** would result in an enantioselective cyclopropanation of oxindoles (Scheme 50).[92] By fine-tuning

Scheme 50. Cascade Reaction of Oxindoles 95b with Halo-Nitroolefins 97 To Give Spirocyclopropyl Oxindoles 65

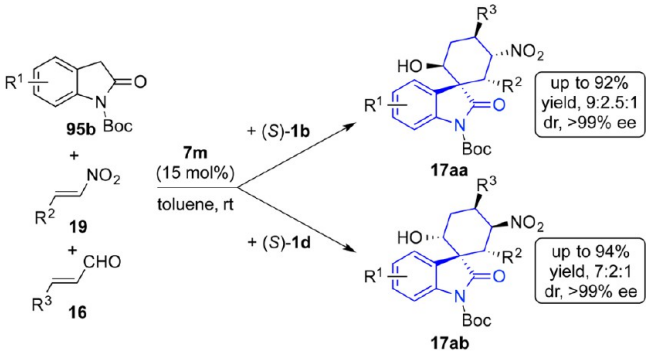


7o = bifunctional thiourea/3° amine catalyst; DABCO = 1,4-diazabicyclo[2.2.2]octane

the catalyst structures, the tertiary amine−thiourea **7o** containing an amino acid moiety was optimized to catalyze this cascade reaction. Notably, a stoichiometric amount of $(NH_4)_2CO_3$ was added to serve as an HBr scavenger. The process begins with the addition of an oxindole to a nitroolefin; followed by an intramolecular proton transfer; and finally, an S_N2 substitution, resulting in 3-spirocyclopropyl-2-oxindoles (**65d**). In the presence of DABCO as a nucleophilic catalyst, a stereochemical inversion through a cyclopropane opening-closing process (i.e., via **98**) was demonstrated to give **65e**.

4.3. Synergistic Catalysis. The combinations of two organocatalysts or of a metal and an organocatalyst have been elegantly employed in one-pot reactions. In this synergistic catalysis, the two substrates are simultaneously activated, each by a different catalyst, to afford a single chemical transformation. Zhou et al. made use of the combination of diphenylprolinol silyl ether **1b** and bifunctional quinine thiourea **7m** to promote the one-pot, relay Michael/Michael/aldol addition reactions of N-substituted oxindoles **95b**, nitrostyrenes **19**, and α,β-unsaturated aldehydes **16** to assemble highly substituted spirooxindoles **17aa** in high yields and with excellent enantioselectivities (Scheme 51).[93] Through judicious choice of the organocatalyst **1d**, the reaction course was modified to predominantly afford an alternative diastereomer, giving product **17ab**.

Scheme 51. Relay Michael/Michael/Aldol Addition Reaction of N-Substituted Oxindoles 95b, Nitrostyrenes 19 and α,β-Unsaturated Aldehydes 16 by Synergistic Catalysis



7m = bifunctional thiourea/3° amine catalyst

5. CONCLUSIONS AND OUTLOOK

Asymmetric organocatalysis is a powerful and versatile tool for the rapid construction of spirooxindole motifs. Over the past few years, we have witnessed the significant development of organocascade strategies for the enantioselective synthesis of optically active spirooxindoles in high yields and excellent enantioselectivities under mild conditions. The strategies and catalyst systems described here highlight recent advances in the enantioselective synthesis of spirooxindoles via organocascade strategies. Various organocatalysts with distinct activation modes have found application in constructing these sophisticated compounds. There is still room for improvement with regard to the catalyst loadings as well as to the substrate scopes. The ongoing interest in the development of methods for the synthesis of these targets stems in large part from their potential as pharmaceutical compounds. We believe that it is likely that novel compounds based on bispirocyclic oxindole skeletons, such as those reported here, will provide novel therapeutic agents and useful biological tools.

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Notes

The authors declare no competing financial interest.

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