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Development of Cascade Reactions for the Concise Construction of Diverse Heterocyclic Architectures

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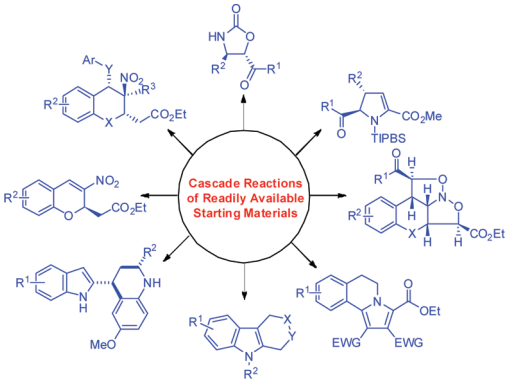

Heterocyclic structural architectures occur in many bioactive natural products and synthetic drugs, and these structural units serve as important intermediates in organic synthesis. This Account documents our recent progress in the development of cascade reactions to construct complex carbocycles and heterocycles. We describe the rational design of cascade reactions and in-depth investigations of their mechanism as well as their applications in the synthesis of drugs, natural products, and related molecular analogs.

Relying on knowledge about the dipole-type reactivity of sulfur ylides, we have developed three different types of cascade reactions: a [4 + 1] annulation/rearrangement cascade, a [4 + 1]/[3 + 2] cycloaddition cascade, and a Michael addition/N-alkylation cascade. Using these processes, we can generate oxazolidinones, fused heterocycles, and pyrrolines starting with simple and readily available substances such as nitroolefins and unsaturated imines. We have also developed corresponding enantioselective reactions, which are guided by axial chirality and asymmetric H-bonding control. In addition, by relying on the reactivity characteristics of newly designed acrylate-linked nitroolefins, we have disclosed an asymmetric Michael/Michael/*retro*-Michael addition cascade using the combination of a protected hydroxylamine and a bifunctional organocatalyst. Using this methodology, we prepared chiral chromenes in good yields and with high enantioselectivities. Moreover, a series of double Michael addition cascade reactions with anilines, thiophenols, and benzotriazoles generated highly functionalized chromanes. Via mechanistically distinct cascade processes that start with vinyl-linked indoles, we have synthesized polycyclic indoles. Intermolecular cross-metathesis/intramolecular Friedel–Crafts alkylation cascades, promoted by either a single ruthenium alkylidene catalyst or a sequence involving Grubbs' ruthenium catalyst and MacMillan's imidazolidinone catalyst, converted ω-indolyl alkenes into tetrahydrocarbazoles, tetrahydropyranoindoles, and tetrahydrocarbolines. In addition, we constructed tetrahydrocarbazoles and tetrahydroquinones using organocatalytic Friedel–Crafts alkylation/Michael addition cascades that used 2-vinyl indoles as common starting materials.

Most green plants carry out photosynthesis to produce organic substances relying on readily available and renewable solar energy. In a related manner, we have also developed two cascade reactions that merge visible light-induced aerobic oxidation with either [3 + 2] cycloaddition/oxidative aromatization or intramolecular cyclization. These processes lead to the formation of pyrrolo[2,1-*a*]isoquinolines and enantiopure tetrahydroimidazoles, respectively.

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1. Introduction

Compared with Nature's biosynthetic processes that have evolved over billions of years, organic synthesis is still in its infancy having started only in the early 1800s. Before that time, Nature was the only source of organic chemicals. For example, ancient Chinese knew how to obtain health-advantaged materials from natural herbs and fungi though in the form of mixtures. Even now, natural feedstocks still serve as important sources of pharmaceuticals.[1] In parallel with efforts focusing on natural product isolation, organic chemists have learned how to mimic the proficiency displayed in Nature's biosynthetic processes. Over the years, chemical efforts have shed light on numerous transformations occurring in cells that proceed in highly selective and efficient ways guided by enzymes as catalysts. The high efficiency of these biosynthetic reactions that often lead to the assembly of complex organic structures is, in part, attributable to Nature's extensive use of cascade reactions. Inspired by natural transformations, synthetic chemists have developed related catalytic strategies[2,3] that utilize metal and organic catalysts and synthetic strategies that employ cascade reactions.[4] In addition, owing to reductions in the availability of fossil fuels and pressures caused by environment concerns, organic chemists have explored green methods that mimic photosynthetic processes in that they utilize the readily available and sustainable energy source found in the sun.[5]

Carbo- and heterocyclic compounds are a diverse class of organic molecules that have received extensive interest owing to their popularity in many natural products and synthetic drugs.[6] Although numerous methods exist to construct various carbo- and heterocyclic systems,[7] new strategies with reduced numbers of transformation steps and purification procedures, lower costs, and minimized chemical waste are still in high demand. This Account describes a rich variety of new synthetic methods that are based on cascade strategies developed in our group (Figure 1). These cascade reactions aimed at the efficient construction of carbo- and heterocyclic systems feature the following issues: (1) new understanding of the known reagents (i.e., sulfur ylides) or design of new reagents based on catalyst character or retrosynthetic analysis of given structures; (2) in-depth investigations of reaction mechanisms and then design of novel cascade reactions; and (3) successful synthetic applications to access valuable synthetic building blocks, natural products, drugs and their analogs. In addition, recently developed, novel cascade reactions that employ visible light-induced aerobic oxidation as the initiation step are also described.

2. Stable Sulfur Ylides as 1,1′-Dipole-Type Reagents

First applied in the 1960s, sulfur ylides, comprised of carbanions with neighboring positively charged sulfur atoms, have been shown to be efficient methylene-transfer reagents.[8a,b] These substances are widely used as key reagents in the three-membered ring-forming reactions and other rearrangement processes. Viewing these reagents as nucleophiles that contain unique leaving groups, Aggarwal, Tang, and others developed a series of novel cascade transformations that act as nontraditional cyclization reactions.[8] Despite the great advances made, relatively reactive sulfur ylides (unstable or semistable sulfur ylides) have been often employed in the processes developed thus far. In contrast, cascade reactions that are mediated by stable sulfur ylides, which contain additional functionality for further diversification, remain challenging owing to the relatively low activity of these reagents.[9] In this context, we

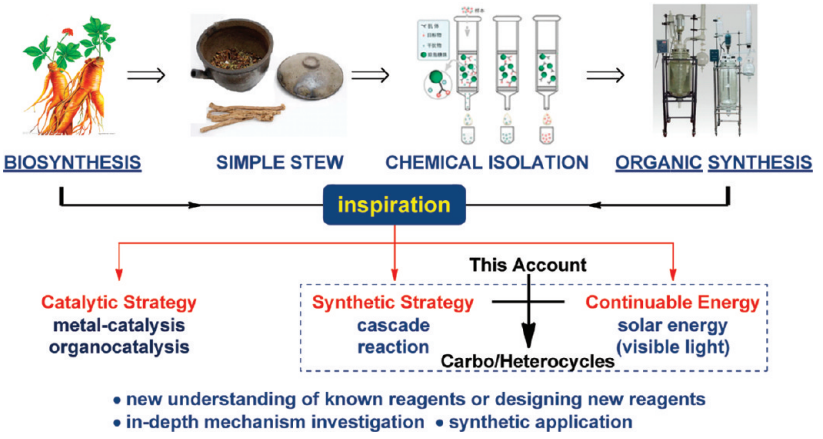


FIGURE 1. Nature-inspired synthetic strategies to construct carbo- or heterocyclic systems.

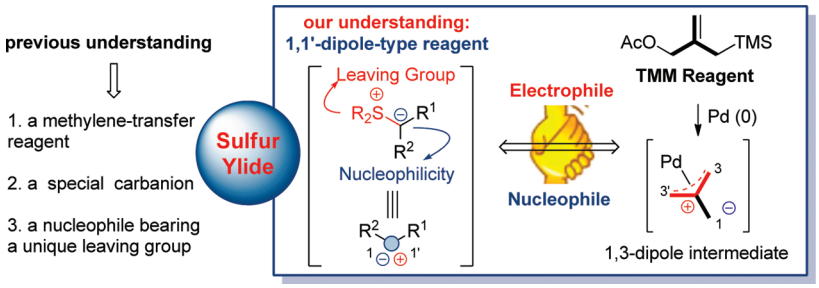
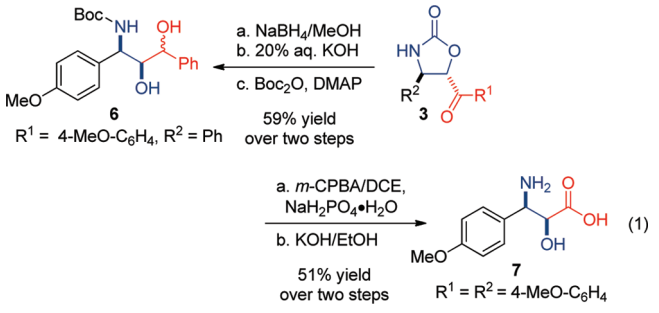


FIGURE 2. New view of sulfur ylides.

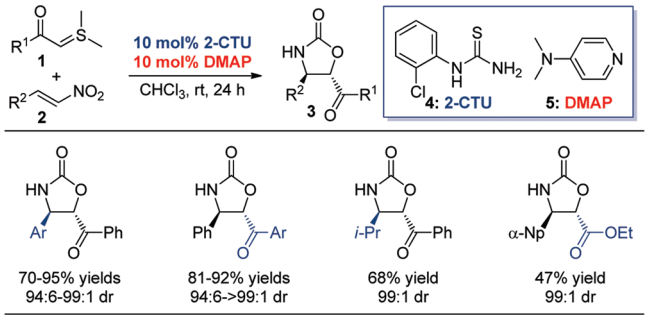
have adopted a distinctly different view of sulfur ylides (Figure 2) that considers them as potential dipole reagents, which can participate in various cascade type cyclization reactions. Considering the reactivity issue associated with the use of stable sulfur ylides, we selected or designed new active electrophiles that would promote the novel cascades.

2.1. Formal [4 + 1] Annulation/Rearrangement Cascade with Nitroolefins. Previously, reactions of α-acyl-substituted sulfur ylides with nitroolefins were observed to afford different ratios of nitro- and acyl-substituted cyclopropanes, nitronates and their tautomers.[10] In contrast, we observed that a distinctly different reaction pathway operates in reactions of α-benzoyl sulfur ylide with nitrostyrene in presence of organic bases and thioureas. This process leads to the formation of a synthetically and biologically significant *trans*-oxazolidinones (Chart 1).[11] In addition, we observed that this reaction occurs with a wide range of nitroolefins and sulfur ylides, and that it displays high levels of both chemo- and diastereoselectivity. Further efforts showed that traditional manipulations can be used to convert the products of these reactions to corresponding 1,2-amino alcohols and α-hydroxyl-β-amino acids (eq 1).[11]



As shown in Scheme 1, the new reaction is believed to follow an organocatalytic cascade route involving initial formal [4 + 1] annulation between the sulfur ylides and nitroolefins followed by subsequent rearrangement of the derived nitronates to produce the oxazolidinones. The results of control experiments along with the identification of

CHART 1. A Novel Formal [4 + 1] Annulation/Rearrangement Cascade to Synthesize *trans*-Oxazolidinones



the intermediate cyclic nitronate **10** demonstrated that the two cascade stages are mediated by acid (thiourea) and base (DMAP) catalysis, respectively. This mechanism was further supported by isotope-labeled (D or ^{13}C) experiments and the observation of possible intermediates in the ^{13}C-labeled in situ reaction experiment.

2.2. [4 + 1]/[3 + 2] Cycloaddition Cascade with Acrylate-Linked Nitroolefins. Based on the fact that nitronate **10** could be used as a potential 1,3-dipole,[9,12] a novel [4 + 1]/[3 + 2] cycloaddition cascade was successfully designed and implemented as shown in Figure 3.[13] The success of this process is enhanced by incorporating two different dipolarophiles in a single molecule, which can be prepared from readily available starting materials. Moreover, the [4 + 1]/[3 + 2] cycloaddition cascade is significant in that it leads to a large increase in architectural complexity in a step-economical fashion, because it creates multiple bonds, rings, stereocenters, and a (thio)chromane-embedded fused heterocyclic system in a single operation.

As highlighted by the range of products shown in Chart 2, significant structural variations in both reaction partners of the [4 + 1]/[3 + 2] cycloaddition cascade are possible and the process yields the desired products with high levels of chemo- and stereoselectivity. Moreover, the new reaction can be used to create quaternary carbon-containing adducts, which is often a challenging issue in organic synthesis.

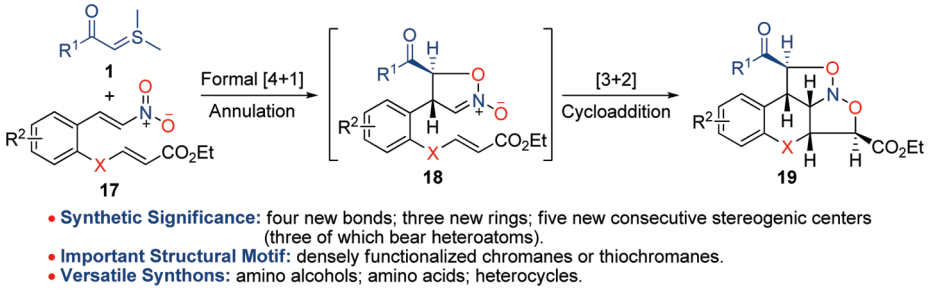


FIGURE 3. Design of [4 + 1]/[3 + 2] cycloaddition cascade to construct fused heterocycles.

SCHEME 1. A Possible Mechanism for the [4 + 1] Annulation/Rearrangement Cascade

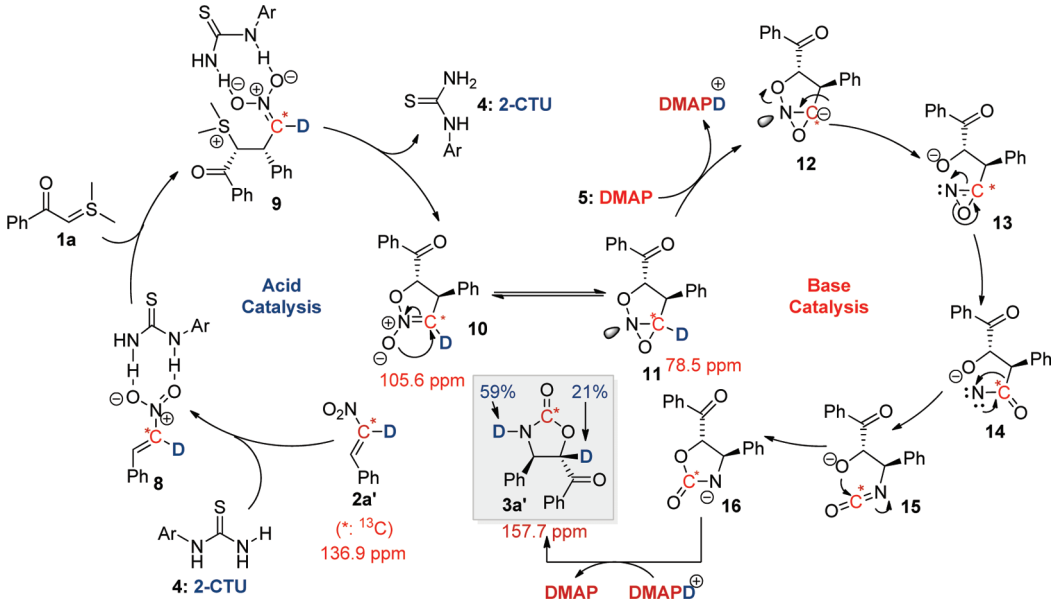
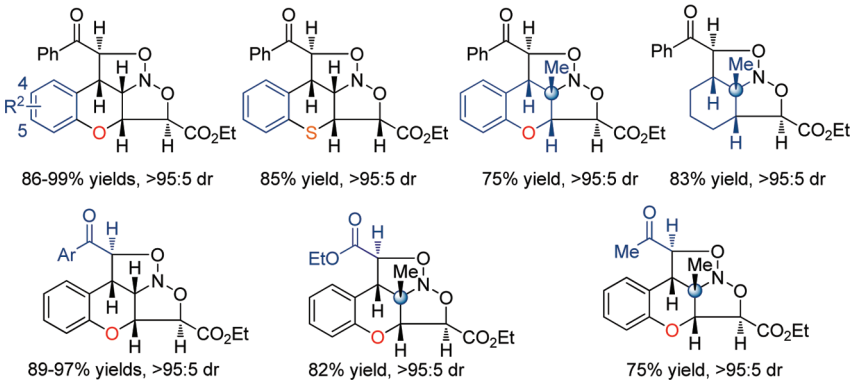


CHART 2. Representative Examples of Products Formed in the [4 + 1]/[3 + 2] Cycloaddition Cascade



Noteworthy is the fact that simple hydrogenolysis reactions assisted by Raney Ni can be utilized to readily cleave N−O bonds in cycloadducts formed in the cascade process to generate chromanes bearing interesting pyrroline rings along with hydroxyl and ester functionality (Scheme 2).

2.3. Michael Addition/N-Alkylation Cascade with Unsaturated Imines. Attracted by the remarkable importance of pyrrolines in pharmaceutical chemistry, the chemical community has devoted a large amount of effort and time into their syntheses.[14] Although the formal [4 + 1] annulation between sulfur ylides and α,β-unsaturated imines was

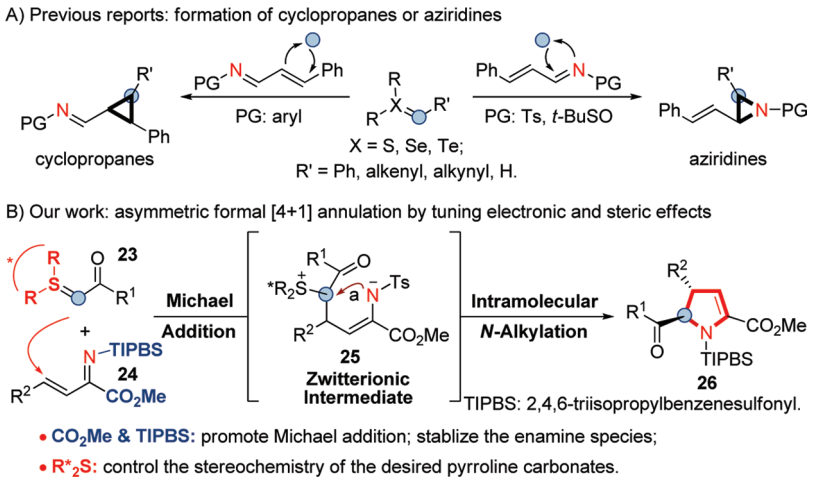
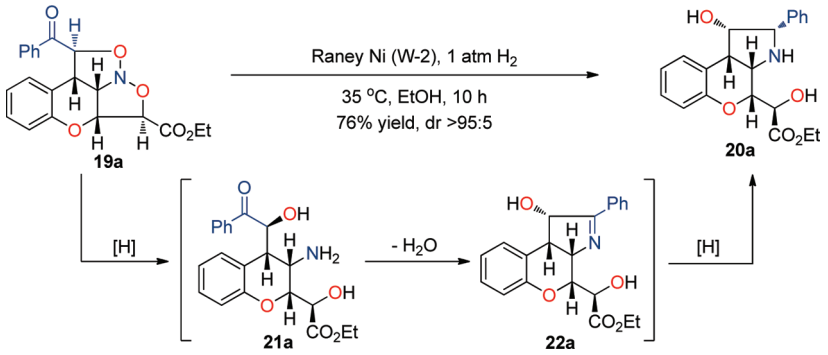


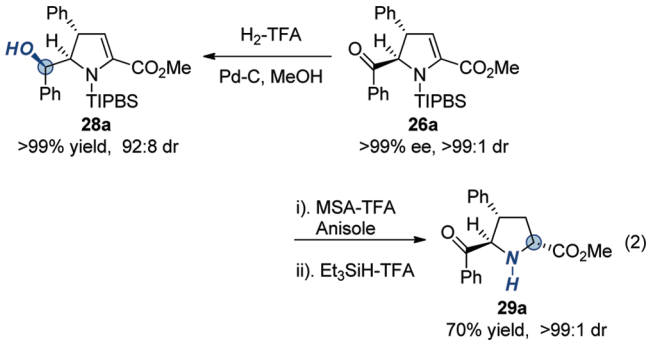
FIGURE 4. Design of Michael addition/N-alkylation cascade to prepare pyrroline carbonates.

SCHEME 2. Transformation of [4 + 1]/[3 + 2] Cycloadducts to Fused Heterocycles



regarded early as an alternate method to achieve this goal,[8c,15] it has been documented that the reaction of unstable or semistabilized ylides with α,β-unsaturated imines usually preferentially generated the three-membered products such as aziridines or cyclopropanes (Figure 4A).[15]

In our studies, we have devised a procedure to selectively generate pyrroline-type products that relies on tuning of the electronic nature of the unsaturated imine reactant.[16] As the results displayed in Figure 4B demonstrate, incorporation of electron-withdrawing esters and tosyl groups in the unsaturated imines not only increases their reactivity but also promotes generation of thermodynamically more stable five- membered ring products. Furthermore, an asymmetric version of this process was developed that employed the readily available and recoverable atropisomeric sulfide **27** as the stereochemical control element. Excellent levels of chemo-, enantio-, and diastereoselectivity are observed when the sterically bulky 2,4,6-triisopropyl benzenesulfonyl group and low temperature are used for the reaction (Chart 3). In this fashion, β-aryl, -alkenyl, and -alkyl-substituted unsaturated imines are transformed to the corresponding pyrroline carbonates in good to excellent yields and stereoselectivities. Moreover, the enantiopure adducts produced in these processes can be converted to other synthetically useful building blocks, as exemplified by the transformation shown in eq 2.



As shown in Figure 5, a cisoid/quasi-[4 + 2] addition mode for the Michael addition step was proposed based on the possible configuration of chiral stable sulfur ylides, which was established according to the NOE effects of ylides in solution and the absolute configuration of their chiral salt precursors.

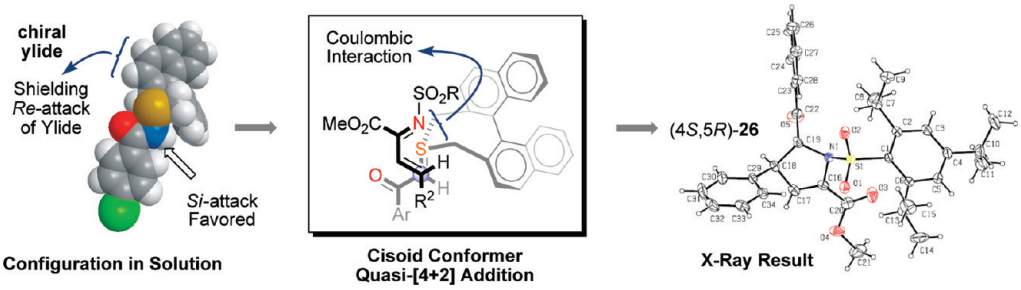
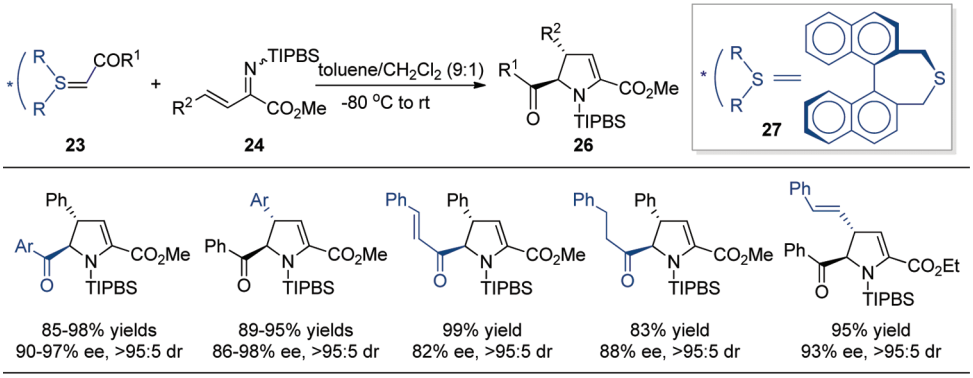


FIGURE 5. Proposed transition state explaining the origin of stereochemistry.

CHART 3. Representative Examples of the Asymmetric Michael Addition/N-Alkylation Cascade



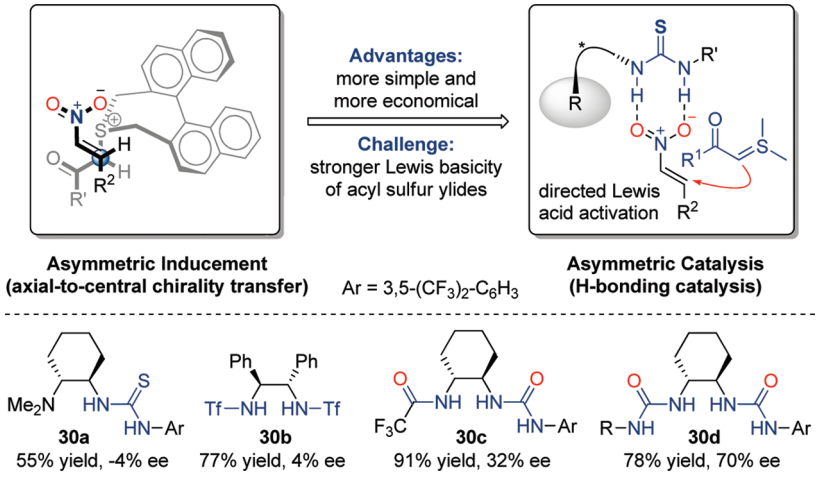
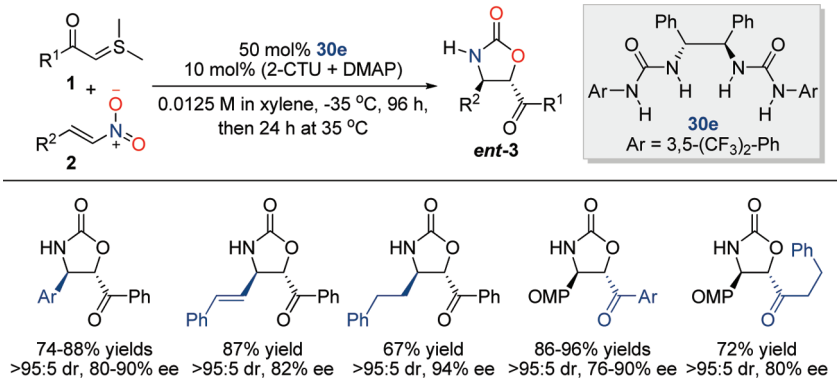


FIGURE 6. Chiral H-bonding controlled asymmetric [4 + 1]/rearrangement cascade.

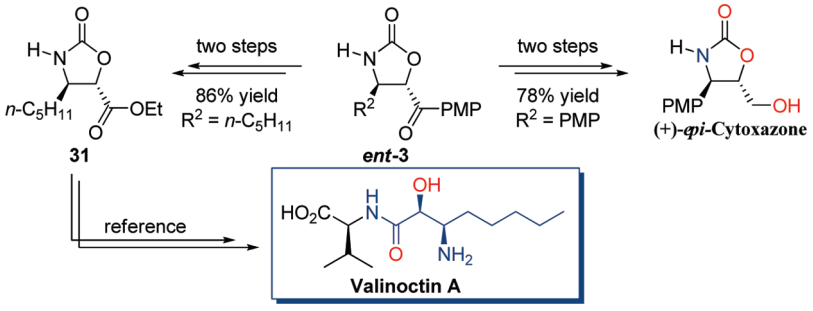
This mode explained the stereoinduction mechanism and rationalized some important effects (i.e., the steric repulsion and Coulombic interaction) responsible for the stereochemical course.

2.4. Enantioselective Cascade Reactions with Nitroolefins. Encouraged by the success encountered in early studies of the asymmetric cascade Michael addition/N-alkylation reactions of imines, we have extended the axial-to-central chirality transfer method to the design of enantioselective cascade reactions of stable sulfur ylides with nitroolefins.[17] We noticed that several potential problems might limit the oxazolidinone forming asymmetric cascade reaction, including the complexity of the process and catalyst system, and the lack of a stereochemical tunable feature like the one present in unsaturated imines. To our delight, the asymmetric cascade reaction of sulfur ylides and nitroolefins was observed to take place in moderate yields and with high levels of enantioselectivity with the use of chiral sulfur ylides (eq 3).

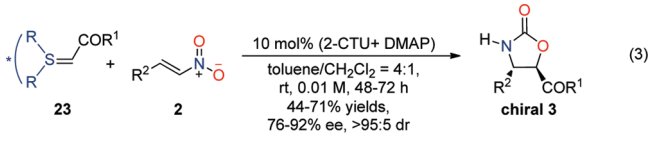
CHART 4. Representative Examples of Chiral H-Bonding Controlled Asymmetric [4 + 1] Annulation/Rearrangement Cascade Reactions

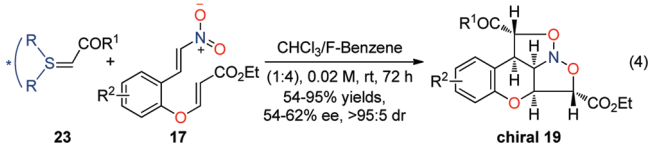


SCHEME 3. Target Directed Synthetic Applications of the Asymmetric Cascade [4 + 1] Annulation/Rearrangement Reaction

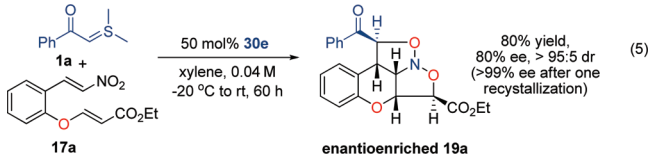


This chirality transfer process also serves as a component of an enantioselective [4 + 1]/[3 + 2] cycloaddition cascade, although the enantioselectivities of these reactions are only moderate (eq 4).





In continuing investigations, we have explored chiral H-bonding-controlled[18] asymmetric cascade [4 + 1] annulation/rearrangement reactions of sulfur ylides and nitroolefins (Figure 6).[19] This process met with difficulties associated with strong binding of stable sulfur ylides with H-bonding catalysts, which results in disappointingly low levels of enantio-induction. However, this problem was resolved by adding multiple H-bonding donor groups to the chiral catalysts. As highlighted by the reactions displayed in Chart 4, this process is general for a range of nitroolefins and stable sulfur ylides, and it can be used to produce structurally diverse chiral oxazolidinones in moderate to excellent yields with high levels of stereoselectivities. In comparison to the axial-to-planar chirality induction method, this process is more favorable in terms of its chemoselectivity and substrate scope as well as availability of the chirality control element. Moreover, the chiral urea catalyst can be quantitatively recovered and the oxazolidinone products serve as versatile intermediates in routes for the preparation of bioactive substances, including (+)-*epi*-cytoxazone and the natural dipeptide valinoctin A (Scheme 3). Significantly, this strategy serves as the foundation of an enantioselective [4 + 1]/[3 + 2] cycloaddition cascade (eq 5), in which enantioenriched fused heterocycles are formed in high efficiency and stereoselectivity.[13]



Two H-bonding interaction modes (modes A and B in Figure 7 where LA is the Lewis acid and LB is the Lewis base) have been used to explain the stereochemistry of these

asymmetric cascade processes. In mode B, the carbonyl oxygen of one urea moiety in the catalyst functions as a Lewis base to activate and direct the addition of the α-acyl sulfur ylide while H-bonding from the other urea unit activates the nitroolefin electrophile. This mechanistic proposal has gained support from the results of NMR experiments and DFT calculations.[18]

3. Acrylate-Linked Nitroolefins as Bis-electrophilic Reagents

In addition to the cascade [4 + 1]/[3 + 2] cycloaddition reaction with stable sulfur ylides previously described, acrylate-linked nitroolefins **17** turned out to be a versatile reagent for additional cascade processes, which enabled the conversion of simple starting materials into structurally complex chromenes or chromanes (Scheme 4).[20] The success of these cascade reactions was undisputedly attributed to the discriminative electrophilicity between the nitroolefin and the acrylate.

3.1. Michael/Michael/*retro*-Michael Addition Cascade Assisted by Protected Hydroxylamine. Rauhut–Currier (RC) and Morita–Baylis–Hillman (MBH) reactions, mechanistically cascade Michael/Michael/*retro*-Michael addition processes, have emerged as unique and valuable carbon–carbon bond-forming protocols.[21a] Whereas remarkable progress has been made in studies of the MBH reaction, the RC transformation remains largely underdeveloped. Until in 2009 an elegant intramolecular crossed RC-type reaction, operating through a dienamine activation strategy, was disclosed by Christmann and co-workers.[21b]

To enrich the substrate diversity of this process, we designed an asymmetric RC version that utilizes acrylate-linked nitroolefins (Scheme 5).[20a] Different from previous reports, phosphines or ternary amines failed here, and only the combination of protected hydroxylamines and organic bases was successful. Chiral amino-H-bonding organocatalysts promoted this asymmetric process in high chemo- and enantioselectively and with complete atom-economy (Chart 5). Additionally, theoretical investigations were implemented via DFT calculations to shed light onto the cascade reaction process and the stereocontrolled modes. The enantioenriched RC adducts can be further transformed into structurally more complex chromanes through stereoselective manipulation (i.e., asymmetric Michael additions and [4 + 2]-type addition reactions).

3.2. Double Michael Addition Cascade with Anilines, Thiophenols, and Benzotriazoles. The chromane architecture is

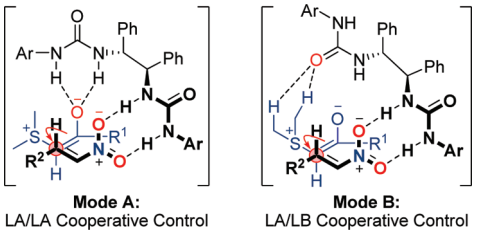
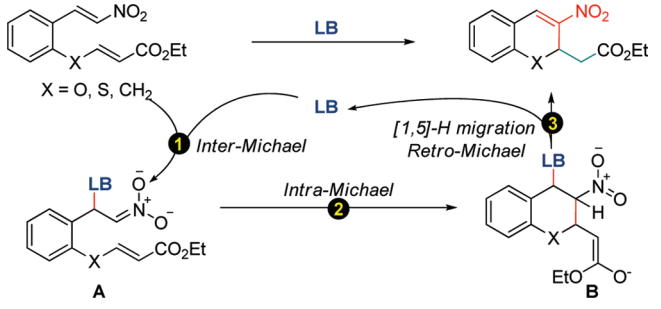


FIGURE 7. Possible modes involved in activation and stereocontrol by the bis-urea catalyst.

SCHEME 5. Design of Michael/Michael/*retro*-Michael Addition Cascade (RC Reaction) To Synthesize Chromenes and Their Analogs



SCHEME 4. Asymmetric Cascade Reactions of Acrylate-Linked Nitroolefins

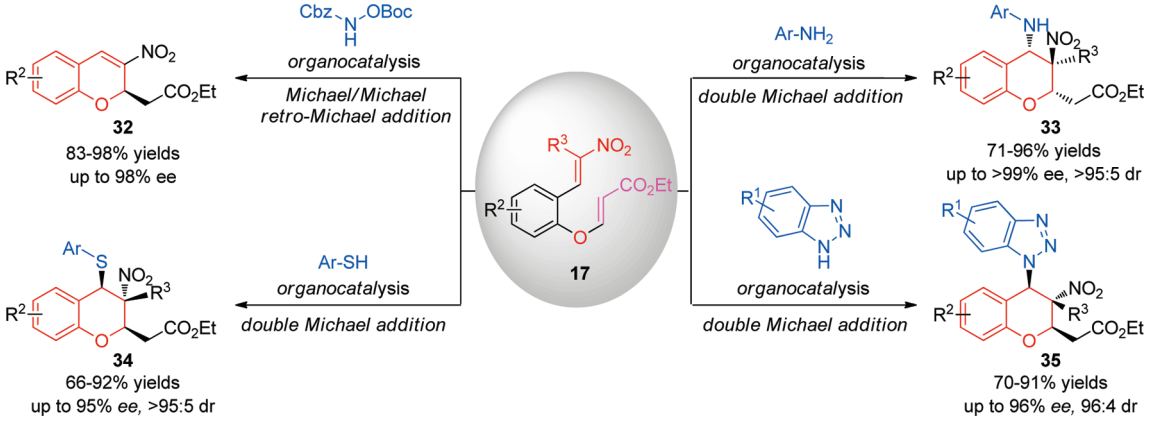
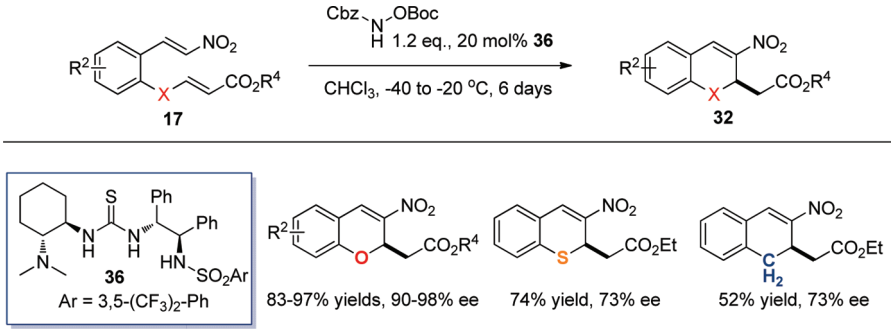


CHART 5. Representative Examples of Michael/Michael/*retro*-Michael Addition Cascade



widely found in numerous natural products and synthetic analogs as a "privileged" structural motif. Consequently, organic chemists have developed a number of Lewis acid or transition metal promoted, asymmetric catalytic methods for their synthesis.[22] Our efforts in this area have led to the development of a new strategy for the construction of this ring system that starts with acrylate-linked nitroolefins, involves a series of double Michael addition cascades, and is promoted by bifunctional organocatalysts (Figure 8). For example, thiophenols,[20b] anilines,[20c] or benzotriazoles[20c] serve as nucleophiles in reactions of acrylate-linked nitroolefins that produce highly substituted chromanes containing three contiguous stereocenters, including a quaternary center, in a highly chemo- and stereoselective manner (Scheme 4).

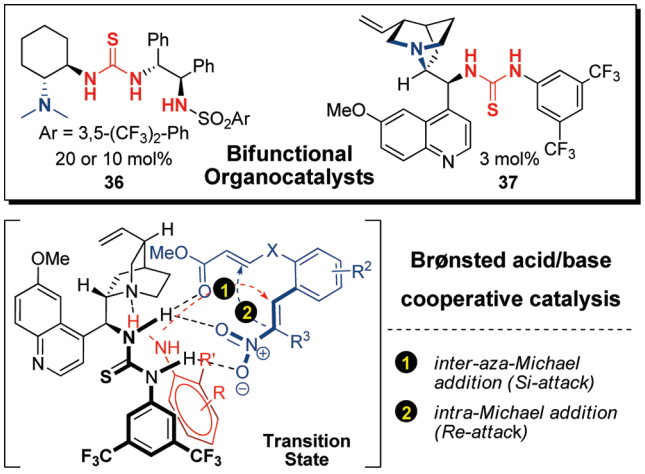


FIGURE 8. Bifunctional organocatalysis of double michael addition cascades.

4. Vinyl-Linked Indoles as Nucleophilic Reagents

Indole-containing molecules represent another important class of alkaloids that are prevalent in drug and natural isolates. Among them, polycyclic indoles possess significant and unique biological activities that have sparked new approaches to exploring new medicinal agents. Owing to their importance, large research efforts have been devoted to the development of efficient synthetic routes into *aza*-heterocyclic systems of this type,[23] including Lewis acid or transition metal catalyzed intramolecular alkylations of indoles and organocatalytic intermolecular Pictet–Spengler reactions. Different from these works, we have developed two distinctly different approaches for the preparation of polycyclic indoles. As the retrosynthetic analysis displayed in Figure 9 shows, readily available ω-indolyl alkenes and vinyl indoles can be exploited as starting materials in routes to the fused indoles that employ appropriate catalytic strategies.

4.1. Cross-Metathesis/Intramolecular Friedel–Crafts Alkylation Cascade of ω-Indolyl Alkenes. Grubbs' ruthenium alkylidenes have been shown to be valuable catalysts for carbon–carbon bond formation reactions.[24a] More significantly, the ability of these catalysts to participate in cascade processes has also been demonstrated on numerous occasions.[24b] Critical to the success of these cascade protocols is the use of additional catalysts (such as a Lewis acid) or reagents to carry out the sequential processes. In contrast, the use of a single species to catalyze a tandem process is rare.

In a study of Lewis acid assisted ring-closing metathesis reactions of diallylamines, we encountered an example of the Lewis acidity of ruthenium alkylidenes (Scheme 6).[25] Inspired by this effort, we designed an efficient cross-metathesis/intramolecular Friedel–Crafts alkylation cascade that takes advantage of two distinct characteristics of ruthenium alkylidenes found in their ability to catalyze intermolecular cross metathesis reactions and to serve as Lewis acids to induce intramolecular Friedel–Crafts alkylations (Chart 6).[26] For example, cascade reactions starting with various ω-indolyl alkenes and a wide range of electron-deficient alkenes take place to form diverse polycyclic indoles, such as tetrahydrocarbazoles, tetrahydropyranoindoles,

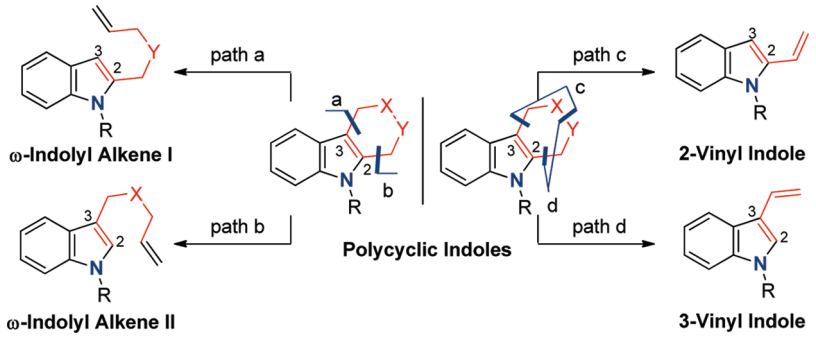
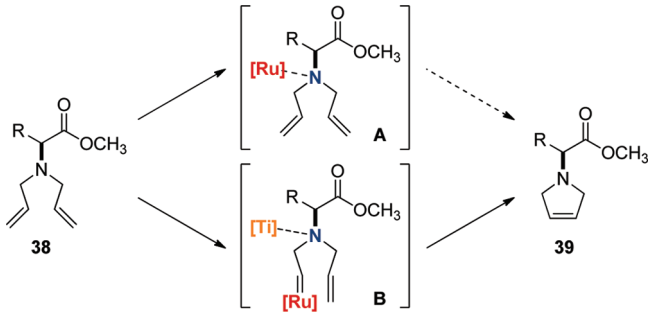
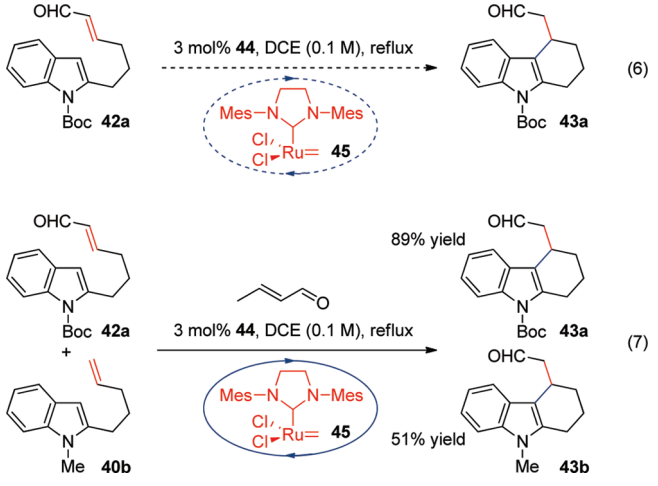


FIGURE 9. ω-Indolyl alkenes and vinyl indoles applied to the construction of polycyclic indoles.

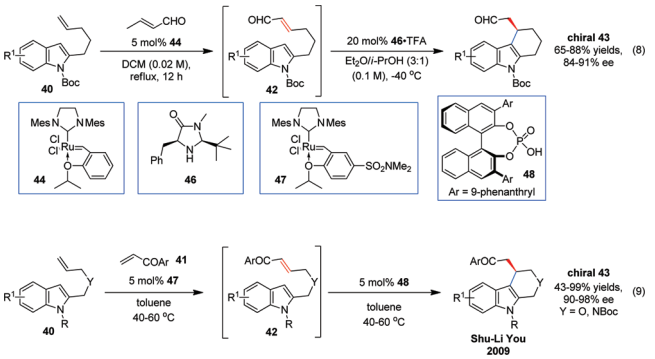
SCHEME 6. Lewis Acid Assisted Ring-Closing Metathesis of Diallylamines



and tetrahydrocarbolines in good to excellent yields. The combination of two mechanistically distinct transformations relying on a single catalyst precursor makes this cascade reaction particularly useful. The bifunctional nature of the ruthenium species **45** was confirmed by using the control experiments outlined in eqs 6 and 7.

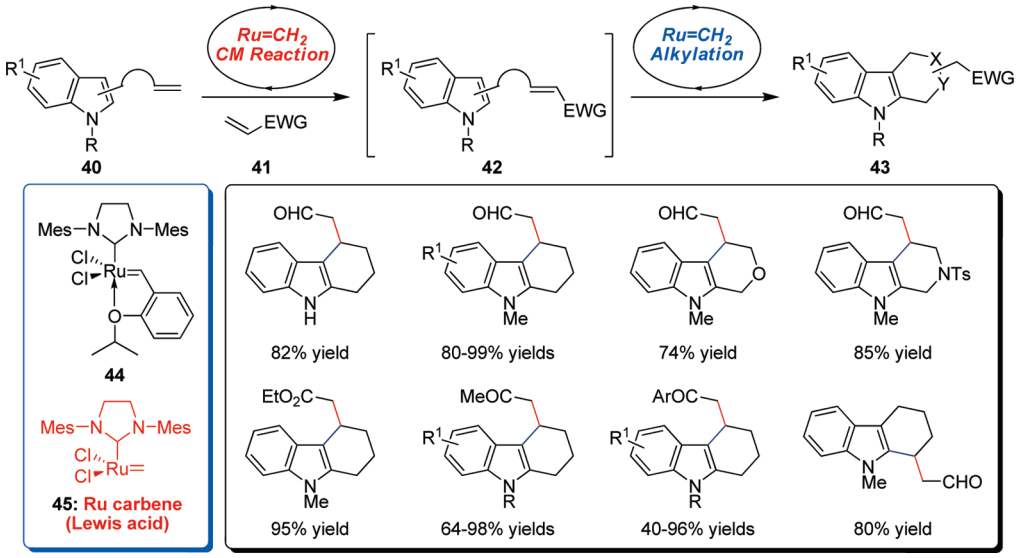


Following the success of this work, we further investigated incorporating enantioselectivity into a cascade reaction sequence by combining the two distinct catalytic entities, including ruthenium catalysis and iminium catalysis.[27] As the process outlined in eq 8 shows, this sequential catalytic system promotes efficient reactions of various ω-indolyl alkenes and crotonaldehyde to afford the corresponding fused indoles in moderate to good overall yields and with high enantioselectivities.[26b] Elegantly, You and co-workers also developed an efficient asymmetric cascade, which merges ruthenium and Brønsted acid catalysis, to generate chiral polycyclic indoles with excellent levels of chemo- and enantioselectivity (eq 9).[28]

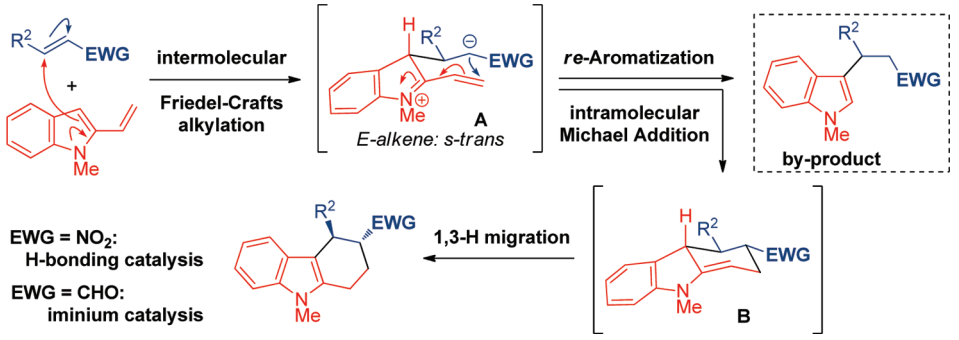


4.2. Friedel–Crafts Alkylation/Michael Addition/Aromatization Cascade with Nitroolefins, Unsaturated Aldehydes, and Imines. 2-Vinyl and 3-vinyl indoles represent a versatile nucleophilic reagent that allows a facile entry into polycyclic indoles with enriched functionality through [4 + 2]-type cycloaddition.[29] Several triple cascade reactions of vinyl indoles were developed to construct the stereoenriched polycyclic indoles following the work of cross-metathesis/intramolecular Friedel–Crafts alkylation cascade reactions.[30] As described in Scheme 7, this sequence contained intermolecular Friedel–Crafts alkylation of vinyl indoles with electron-deficient alkenes, intramolecular Michael addition of a transient intermediate **A**, and a rapid [1,3]-H migration process driven by the aromaticity of indole ring. Challenges in this design included the chemoselectivity between the intramolecular Michael addition, fast *re*-aromatization of intermediate **A**, and the stereocontrol during the cascade process.

CHART 6. Cross-Metathesis/Intramolecular Friedel–Crafts Alkylation Cascade Catalyzed by Grubbs' Ruthenium Alkylidenes



SCHEME 7. Design of Friedel–Crafts Alkylation/Michael Addition/Aromatization Cascade To Prepare Chiral Tetrahydrocarbazoles



In 2007, we launched a program to explore cascade reactions of vinyl indoles with various electron-deficient components.[31] Based on the 2009 studies of Brønsted acid mediated tandem Diels–Alder/aromatization reactions of 2-vinyl indoles,[30a] we described a hydrogen bonding-catalyzed, asymmetric Friedel–Crafts alkylation/Michael addition/aromatization cascade of 2-propenyl-indoles and nitroolefins (Chart 7).[30b] The cascade process was found to have substantial generality with respect to both nitroolefins and vinyl indole components and to produce a range of structurally diverse and complex tetrahydrocarbazoles in good to excellent enantio- and diastereoselectivities.

In continuing studies, we extended the iminium-catalyzed asymmetric Friedel–Crafts alkylation/Michael addition/aromatization cascade by applying it to reactions of vinyl indoles and unsaturated aldehydes (Chart 8).[30d] This protocol also served as an efficient route to produce highly functional tetrahydrocarbazoles with good chemoselectivities and excellent stereoselectivities. It is important to note that the more complex product **56** was formed in moderate yield and in a completely stereoselective manner via a quadruple cascade reaction, which possibly proceeds through a cascade double Michael addition/aromatization mechanism rather than the alternative Diels–Alder cycloaddition route.

In studies of a one-pot multicomponent cascade reaction of aldehydes, anilines, and 2-vinyl indoles, we accidentally uncovered a protocol for the controlled synthesis of two structurally different products.[30e] As shown in Scheme 8, changing substituents on the indole nitrogen led to a switch in chemo- and regioselectivity and generation of either a tetrahydro-γ-carboline or an indolyl tetrahydroquinoline product under otherwise identical reaction conditions. For example, unprotected 2-vinyl indoles react to form tetrahydroquinolines in good yields and with excellent diastereoselectivities. However, when *N*-benzyl, *N*-methyl, allyl-, or *N*-tosyl-protected 2-vinyl indoles are used as starting

CHART 7. Representative Examples of the Asymmetric Cascade with Nitroolefins

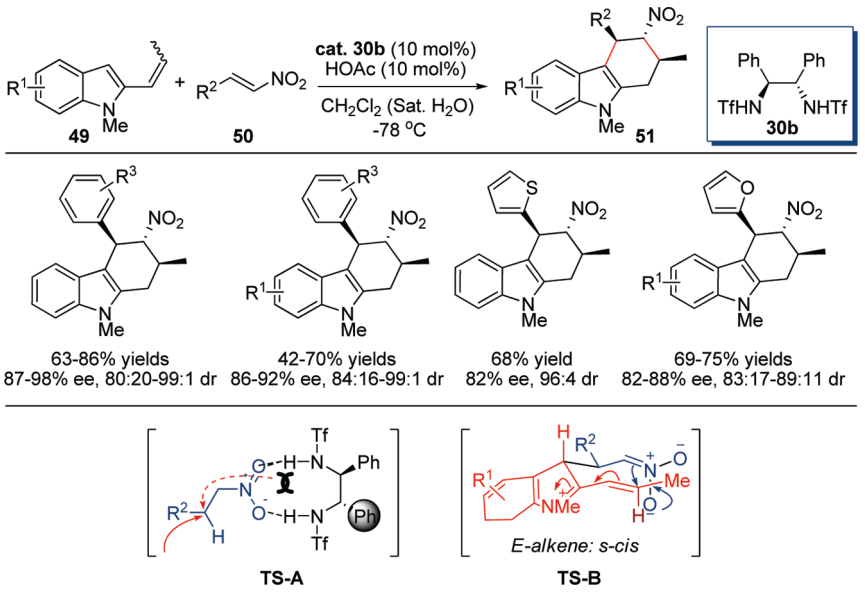
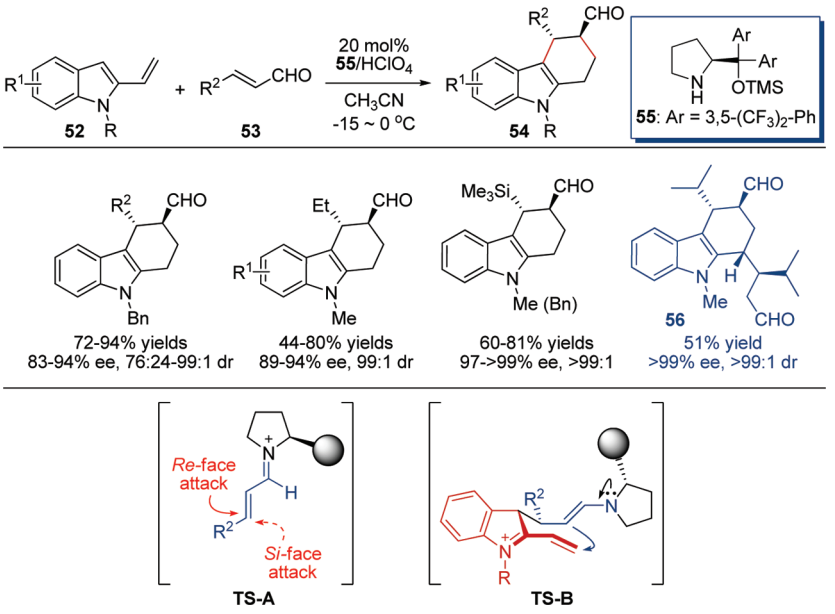


CHART 8. Representative Examples of the Asymmetric Cascade with Unsaturated Aldehydes



materials, tetrahydro-γ-carbolines are obtained in good yields. Although a complete understanding of these unexpected observations awaits the results of additional experimentation, we believe that the chemo- and regioselectivity switch is the result of cooperative interaction between Brønsted acid and N−H of unprotected vinyl indoles (Scheme 8).

5. Visible Light as a Renewable Energy Source

Cascade reactions have been proven to be an extremely efficient method in the construction of complex carbo- and heterocycles. Though highly efficient, atom-economic, and operationally simple, it would be interesting to convert traditional thermochemical processes into visible light-induced photochemical processes. The visible light-induced photochemical process would use clean and renewable solar energy, thereby replacing the nonrenewable fossil fuel energy.[5] Notably, the availability of photosensitive catalysts, which can be activated by the irradiation of visible light (the main component of sunshine), paved the way for us to develop novel cascade reactions.

SCHEME 8. Tunable One-Pot Multicomponent Cascade Reaction

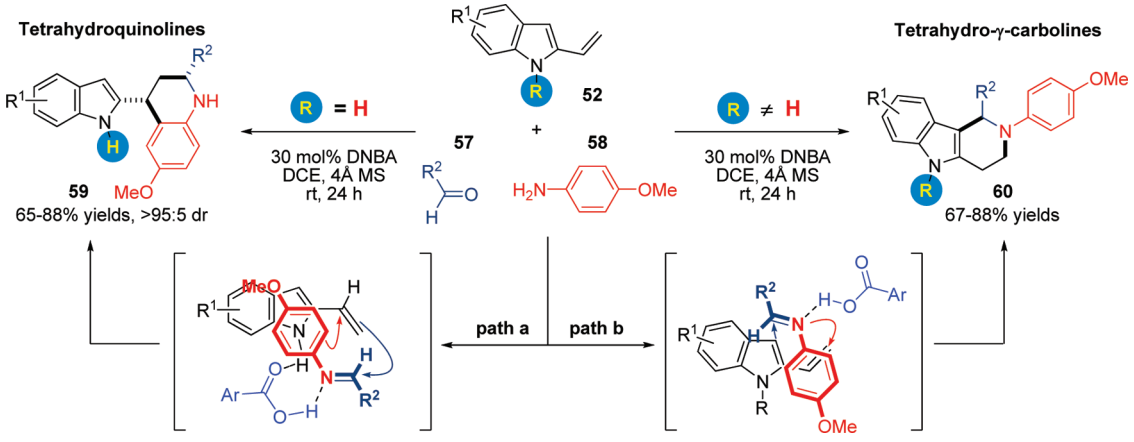
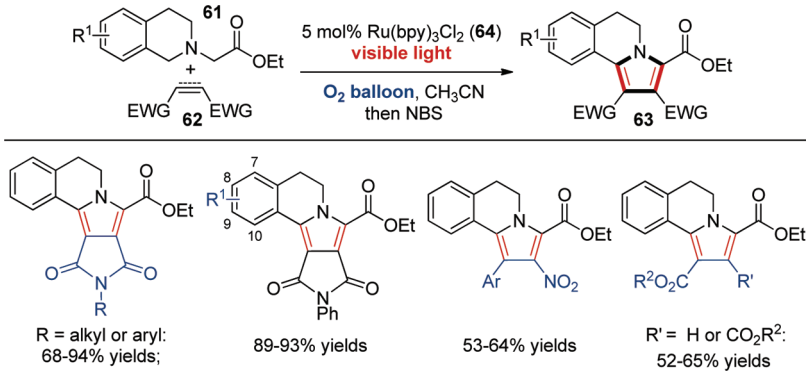


CHART 9. Photocatalytic Cascade Strategy To Construct Pyrrolo[2,1-*a*]isoquinolines



5.1. Visible-Light-Induced Oxidation/[3 + 2] Cycloaddition/Oxidative Aromatization Cascade. Pyrrolo[2,1-*a*]-isoquinolines belong to a family of nitrogen-containing heterocycles that possess important biological activities. As such, this ring system is the core unit in many pharmaceuticals and the naturally occurring lamellarin alkaloids.[32] Prior to our work in this area, several methods had been developed to construct this ring system, including those that employ the intramolecular Pd-catalyzed decarboxylative Heck reaction, direct arylation of pyrroles, and intermolecular cycloaddition reactions.[32] Our recent studies[33] have led to the development of a photoredox strategy to produce pyrrolo[2,1-*a*]isoquinolines.[33a] As the examples given in Chart 9 demonstrate, the new reaction appears to be general with respect to both dipolarophile and dipole components, and it produces the desired adducts in moderate to excellent yields. Importantly, oxygen serves as the green oxidant, and the photocatalytic cascade is still efficient when oxygen is replaced by air.

The proposed mechanism of this cascade reaction is shown in Scheme 9. Initially, ethyl 2-(3,4-dihydro-isoquinolin-2(1*H*)-yl)acetate **61a** was oxidized to iminium ion **B** through a photoredox process in the presence of $Ru(bpy)_3Cl_2$ catalyst (**64**), oxygen, and visible light. Then iminium intermediate **B** was transformed into 1,3-dipolar azomethine **C** through a hydrogen peroxide anion-promoted deprotonation process. Following the 1,3-dipolar azomethine ylide **C** undergoing a [3 + 2] cycloaddition reaction with various dipolarophiles, the adduct was sequentially oxidized to pyrrolo[2,1-*a*]isoquinoline. The kinetic isotopic effect experiment suggested that the abstraction of hydrogen in the α-position of the radical cation **A** by the superoxide radical anion might be the rate-determining step for this visible light-induced cascade reaction.

5.2. Visible Light-Induced Oxidation/Intramolecular Cyclization Cascade of Chiral Diamines. Following the successful development of the visible light-induced cascade described above, we conducted studies aimed at extending the same oxidation strategy to other asymmetric cascade

SCHEME 9. Possible Mechanism of the Photocatalytic Cascade

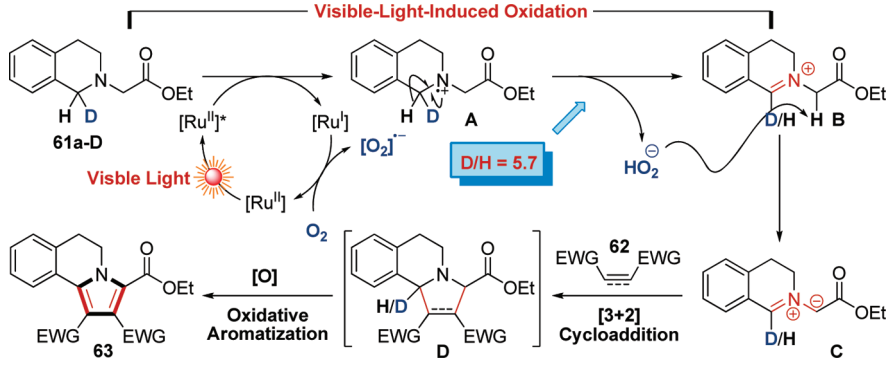
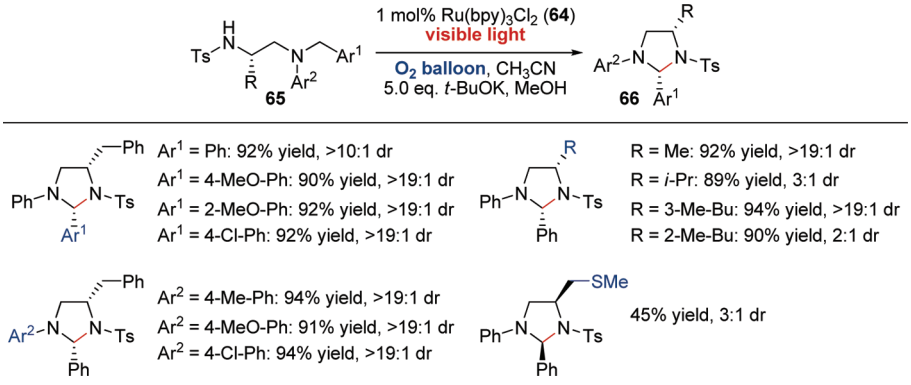
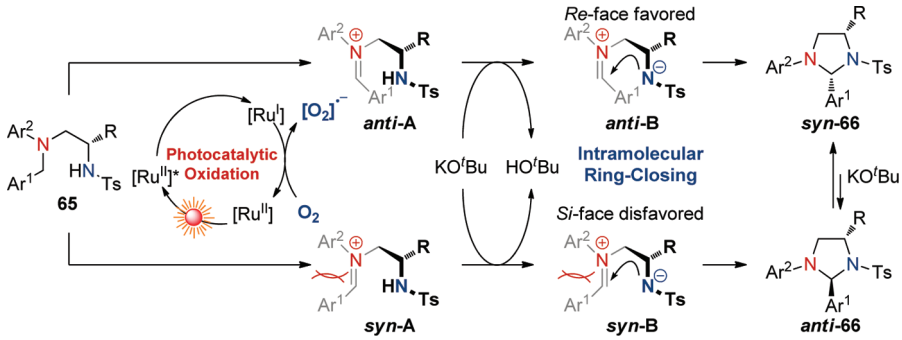


CHART 10. Photocatalytic Cascade Strategy to Enantiopure Tetrahydroimidazoles



SCHEME 10. Possible Explanations for the Stereochemical Course of the Photocatalytic Cascade



reactions. This effort led to the discovery of a visible light driven process that transforms natural amino acid derived chiral diamines into products containing the tetrahydroimidazole ring system (Chart 10), a common structural feature of many biologically active natural products.[33b]

Two pathways appear plausible to explain the high stereoselectivity observed in this chirality-induced asymmetric process (Scheme 10). Under photoredox conditions, the diamines are oxidized to iminium ion intermediates, which are transformed to chiral tetrahydroimidazole products through an *aza*-nucleophilic addition pathway. The control experiments have shown that high *syn*-selectivity can be attributed to either the methanol and the ruthenium catalyst assisted isomerization or the *t*-BuOK-promoted deprotonation/diastereoselective protonation sequence (the latter believed to be more favored).

6. Conclusion

In this Account, we have summarized the results of recent studies aimed at developing new cascade-based methods

for the efficient construction of complex carbo- and heterocycles. First, a renewed understanding of the reactive character of sulfur ylides led to the design of three different kinds of cascade reactions that could stereoselectively afford oxazolidinones, fused heterocycles, and pyrrolines. Second, by utilizing the reactivity profiles of acrylate-linked nitroolefins, we have developed a series of cascade protocols to obtain highly functional chromanes and chromenes. Third, using alkene-linked indoles as versatile substrates, we uncovered procedures to prepare polycyclic indoles, such as tetrahydrocarbazoles, tetrahydropyranoindoles, and tetrahydrocarbolines, which are based on mechanistically distinct cascade processes. Last, two recent examples of cascade reactions that allowed the synthesis of pyrrolo-[2,1-*a*]isoquinolines and enantiopure tetrahydroimidazoles were disclosed by virtue of visible light-promoted photoredox technologies. Notably, many of these unprecedented cascade reaction mechanisms were investigated in-depth. Also these synthetic applications will be appealing in drug, natural products, and related analogs, which will attract the interest of the organic, bioorganic, and medicinal community. In the future, the endeavor to develop more novel cascade reactions to construct biologically and synthetically significant cyclic systems will continue, especially the fascinating reactions involving visible light photocatalysis. In addition, the bioactivities of these structurally diverse carbo- and heterocyclic compounds will be evaluated with the aim to find novel lead compounds of drugs or drug candidates.

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BIOGRAPHICAL INFORMATION

Liang-Qiu Lu was born in Zhejiang, P. R. China. He received his B.Sc. in Applied Chemistry at Central China Normal University (CCNU) in 2005 and obtained his Ph.D. degree in 2011 under the guidance of Professor Wen-Jing Xiao at the same University. Then, he joined the College of Chemistry at CCNU as a Lecturer. Dr. Lu is now a Humboldt postdoctoral fellow with Prof. Matthias Beller at the Leibniz-Institut für Katalyse e.V., Germany (2011–2013). His current research interests focus on iron-catalyzed reduction reactions.

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FOOTNOTES

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The authors declare no competing financial interest.

REFERENCES

1 (a) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Last 25 Years. *J. Nat. Prod.* **2007**, *70*, 461–477. (b) Li, J. W.-H.; Vederas, J. C. Drug Discovery and Natural Products: End of an Era or an Endless Frontier? *Science* **2009**, *325*, 161–165.

2 (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999; Vols. I—III. (b) Beller, M., Bolm, C., Eds. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

3 (a) Berkessel, A.; Groeger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Special Issue: List, B. Organocatalysis. *Chem. Rev.* **2007**, *107*, 5413–5883. (c) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308. (d) Barbas, C. F., III Organocatalysis Lost: Modern Chemistry, Ancient Chemistry, and an Unseen Biosynthetic Apparatus. *Angew. Chem., Int. Ed.* **2008**, *47*, 42–47.

4 (a) Muller, T. J. J., Ed. *Metal Catalyzed Cascade Reactions*; Topics in Organometallic Chemistry, Vol. 19; Springer: New York, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (d) Yu, X.-H.; Wang, W. Organocatalysis: Asymmetric Cascade Reactions Catalysed by Chiral Secondary Amines. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046. (e) Nicolaou, K. C.; Chen, J. S. The Art of Total Synthesis through Cascade Reactions. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (f) Grondal, C.; Jeanty, M.; Enders, D.; Hüttl, M. R. M. Organocatalytic Cascade Reactions as a New Tool in Total Synthesis. *Nature Chem.* **2010**, *2*, 167–178.

5 (a) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (b) Yoon, T. P.; Ischay, M. A.; Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. *Nat. Chem.* **2010**, *2*, 527–532.

6 (a) Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2011. (b) Dua, R.; Shrivastava, S.; Sonwane., S. K.; Srivastava, S. K. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review. *Adv. Biol. Res.* **2011**, *5*, 120–144.

7 (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: Chichester, U.K., 2010.

8 (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination, Olefination, and Rearrangement. *Chem. Rev.* **1997**, *97*, 2341–2372. (b) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. Chalcogenides as Organocatalysts. *Chem. Rev.* **2007**, *107*, 5841–5883. (c) Sun, X.-L.; Tang, Y. Ylide-Initiated Michael Addition-Cyclization Reactions beyond Cyclopropanes. *Acc. Chem. Res.* **2008**, *41*, 937–948.

9 Appel, R.; Hartmann, N.; Mayr, H. Scope and Limitations of Cyclopropanations with Sulfur Ylides. *J. Am. Chem. Soc.* **2010**, *132*, 17894–17900.

10 Feuer, H., Ed. *Nitrile, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Wiley-VCH, Hoboken, NJ, 2007.

11 Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. A New Entry to Cascade Organocatalysis: Reactions of Stable Sulfur Ylides and Nitroolefins Sequentially Catalyzed by Thiourea and DMAP. *J. Am. Chem. Soc.* **2008**, *47*, 2489–2492.

12 Denmark, S. E.; Thorarensen, A. Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. *Chem. Rev.* **1996**, *96*, 137–166.

13 Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. Construction of Fused Heterocyclic Architectures by Formal [4 + 1]/[3 + 2] Cycloaddition Cascade of Sulfur Ylides and Nitroolefins. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542–9545.

14 Pandey, G.; Banerjee, P.; Gadre, S. R. Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3 + 2]-Cycloaddition of Azomethine Ylides. *Chem. Rev.* **2006**, *106*, 4484–4517.

15 A recent representative example, see: Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Dai, L.-X. The Michael Addition−Elimination of Ylides to α,β-Unsaturated Imines. Highly Stereoselective Synthesis of Vinylcyclopropane-carbaldehydes and Vinylcyclopropylaziridines. *J. Am. Chem. Soc.* **2005**, *127*, 12222–12223, and also please see other related references in ref 16.

16 Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. Tuning Electronic and Steric Effects: Highly Enantioselective [4 + 1] Pyrroline Annulation of Sulfur Ylides with α,β-Unsaturated Imines. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495–4498.

17 Lu, L.-Q.; Ming, Z.-H.; An, J.; Li, C.; Chen, J.-R.; Xiao, W.-J. Enantioselective Cascade Reactions of Stable Sulfur Ylides and Nitroolefins through an Axial-to-Central Chirality Transfer Strategy. *J. Org. Chem.* **2012**, *77*, 1072–1080.

18 Cheng, Y.; An, J.; Lu, L.-Q.; Luo, L.; Wang, Z.-Y.; Chen, J.-R.; Xiao, W.-J. Asymmetric Cyclopropanation of β,γ-Unsaturated α-Ketoesters with Stabilized Sulfur Ylides Catalyzed by C_2-Symmetric Ureas. *J. Org. Chem.* **2011**, *76*, 281–284.

19 Lu, L.-Q.; Li, F.; An, J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. Hydrogen-Bond-Mediated Asymmetric Cascade Reaction of Stable Sulfur Ylides with Nitroolefins: Scope, Application and Mechanism. *Chem.—Eur. J.* **2012**, *18*, 4073–4079.

20 (a) Wang, X.-F.; Peng, L.; An, J.; Li, C.; Yang, Q.-Q.; Lu, L.-Q.; Gu, F.-L.; Xiao, W.-J. Enantioselective Intramolecular Crossed Rauhut-Currier Reactions through Cooperative Nucleophilic Activation and Hydrogen-Bonding Catalysis: Scope and Mechanistic Insight. *Chem.—Eur. J.* **2011**, *17*, 6484–6491. (b) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. Organocatalytic Asymmetric Sulfa-Michael/Michael Addition Reactions: A Strategy for the Synthesis of Highly Substituted Chromans with a Quaternary Stereocenter. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379–8383. (c) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. Catalytic Asymmetric Aza-Michael-Michael Addition Cascade: Enantioselective Synthesis of Polysubstituted 4-Amino-benzopyrans. *Org. Lett.* **2011**, *13*, 808–811.

21 (a) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084. (b) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. Crossed Intramolecular Rauhut-Currier-Type Reactions via Dienamine Activation. *Org. Lett.* **2009**, *11*, 4116–4119.

22 Shen, H. C. Asymmetric Synthesis of Chiral Chromans. *Tetrahedron* **2009**, *65*, 3931–3952.

23 (a) Bandini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel-Crafts Alkylations*; Wiley-VCH: Weinheim, Germany, 2009. (b) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644.

24 (a) Samojłowicz, C.; Bieniek, M.; Grela, K. Ruthenium-Based Olefin Metathesis Catalysts Bearing N-Heterocyclic Carbene Ligands. *Chem. Rev.* **2009**, *109*, 3708–3742. (b) Alcaide, B.; Almendros, P.; Luna, A. Grubbs' Ruthenium-Carbenes beyond the Metathesis Reaction: Less Conventional Non-Metathetic Utility. *Chem. Rev.* **2009**, *109*, 3817–3858.

25 Yang, Q.; Xiao, W.-J.; Yu, Z.-K. Lewis Acid Assisted Ring-Closing Metathesis of Chiral Diallylamines: An Efficient Approach to Enantiopure Pyrrolidine Derivatives. *Org. Lett.* **2005**, *7*, 871–874.

26 (a) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. Ru-Catalyzed Tandem Cross-Metathesis/Intramolecular Hydroarylation Sequence. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492. (b) An, X.-L.; Li, C.-F.; Zhang, F.-G.; Zou, Y.-Q.; Guo, Y.-C.; Chen, J.-R.; Xiao, W.-J. Highly Efficient Route to Functionalized Tetrahydrocarbazoles Using a Tandem Cross-Metathesis/Intramolecular-Hydroarylation Sequence. *Chem.—Asian J.* **2010**, *5*, 2258–2265.

27 (a) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. Enantioselective Organocatalytic Intramolecular Ring-Closing Friedel-Crafts-Type Alkylation of Indoles. *Org. Lett.* **2007**, *9*, 1847–1850. (b) Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. Catalytic Asymmetric Intramolecular Hydroarylations of ω-Aryloxy- and Arylamino Tethered α,β-Unsaturated Aldehydes. *Chem.—Eur. J.* **2009**, *15*, 2742–2746. (c) Zhu, X.-Y.; An, X.-L.; Li, C.-F.; Zhang, F.-G.; Hua, Q.-L.; Chen, J.-R.; Xiao, W.-J. A Practical and Enantioselective Approach to Tetrahydrocarbazoles by Asymmetric Organocatalysis. *ChemCatChem* **2011**, *3*, 679–683.

28 Cai, Q.; Zhao, Z.-A.; You, S.-L. Asymmetric Construction of Polycyclic Indoles through Olefin Cross-Metathesis/Intramolecular Friedel-Crafts Alkylation under Sequential Catalysis. *Angew. Chem., Int. Ed.* **2009**, *48*, 7428–7431.

29 (a) Ziegler, F. E.; Spitzner, E. B.; Wilkins, C. K. The Dimerization of 2-Vinylindoles and Their Alcohol Precursors. *J. Org. Chem.* **1971**, *36*, 1759–1964. (b) Pindur, U.; Eitel, M. New Regio- and Stereocontrolled Reactions of 2-Vinylindoles with CC-Dienophiles: Diels-Alder Reactions, Ene Reactions, and Michael Additions. *Heterocycles* **1988**, *27*, 2353–2362.

30 (a) Chen, C.-B.; Wang, X.-F.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. Brønsted Acid Mediated Tandem Diels−Alder/Aromatization Reactions of Vinylindoles. *J. Org. Chem.* **2009**, *74*, 3532–3535. (b) Wang, X.-F.; Cao, Y.-J.; Cheng, H.-G.; Chen, J.-R.; Xiao, W.-J. An Enantioselective Approach to Highly Substituted Tetrahydrocarbazoles through Hydrogen Bonding-Catalyzed Cascade Reactions. *Org. Lett.* **2010**, *12*, 1140–1143. (c) Tan, F.; Li, F.; Zhang, X.-X.; Wang, X.-F.; Cheng, H.-G.; Chen, J.-R.; Xiao, W.-J. Brønsted Acid Catalyzed Diels-Alder Reactions of 2-Vinylindoles and 3-Nitrocoumarins: An Expedient Synthesis of Coumarin-Fused Tetrahydrocarbazoles. *Tetrahedron* **2011**, *67*, 446–451. (d) Cao, Y.-J.; Cheng, H.-G.; Lu, L.-Q.; Zhang, J.-J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. Organocatalytic Multiple Cascade Reactions: A New Strategy for the Construction of Enantioenriched Tetrahydrocarbazoles. *Adv. Synth. Catal.* **2011**, *353*, 617–623. (e) Cheng, H.-G.; Chen, C.-B.; Tan, F.; Chang, N.-J.; Chen, J.-R.; Xiao, W.-J. Convenient Synthesis of Tetrahydro-γ-carbolines and Tetrahydroquinolines through a Chemo- and Regioselectivity Switch by a Brønsted Acid Catalyzed, One-Pot, Multicomponent Reaction. *Eur. J. Org. Chem.* **2010**, *26*, 4976–4980.

31 During our study on this project, several other groups also implemented related investigations: (a) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. Organocatalytic Asymmetric Diels-Alder Reactions of 3-Vinylindoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236–9239. (b) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. Nine-Step Enantioselective Total Synthesis of (+)-Minfiensine. *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607. (c) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. The Enantioselective, Organocatalyzed Diels-Alder Reaction of 2-Vinylindoles with α,β-Unsaturated Aldehydes: An Efficient Route to Functionalized Tetrahydrocarbazoles. *Chem.—Eur. J.* **2010**, *16*, 5853–5857. (d) Tan, B.; Hernandez-Torres, G.; Barbas, C. F., III Highly Efficient Hydrogen-Bonding Catalysis of the Diels-Alder Reaction of 3-Vinylindoles and Methyleneindolinones Provides Carbazo-lespirooxindole Skeletons. *J. Am. Chem. Soc.* **2011**, *133*, 12354–12357.

32 (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev.* **2008**, *108*, 264–287. (b) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. Cu(II) Catalyzed Oxidation-[3 + 2] Cycloaddition-Aromatization Cascade: Efficient Synthesis of Pyrrolo[2,1-a]isoquinolines. *Chem. Commun.* **2011**, *47*, 1036–1038.

33 (a) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. Visible-Light-Induced Oxidation/[3 + 2] Cycloaddition/OxidativeAromatization Sequence: A Photocatalytic Strategy To Construct Pyrrolo[2,1-a]isoquinolines. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171–7175. (b) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. Visible Light-Induced Intramolecular Cyclization Reactions of Diamines: A New Strategy to Construct Tetrahydroimidazoles. *Chem. Commun.* **2011**, *47*, 8337–8339. (c) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. Highly Efficient Aerobic Oxidative Hydroxylation of Arylboronic Acids: Photoredox Catalysis Using Visible Light. *Angew. Chem., Int. Ed.* **2012**, *51*, 784–788.