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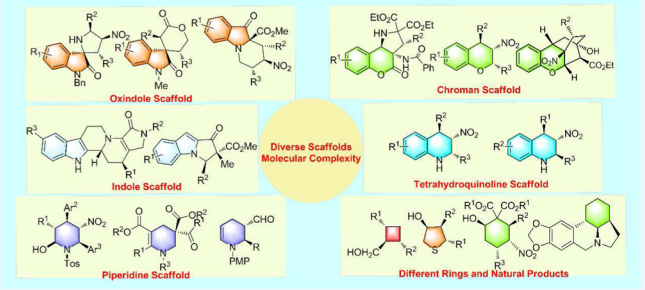
Asymmetric Catalytic Cascade Reactions for Constructing Diverse Scaffolds and Complex Molecules

Yao Wang, Hong Lu, and Peng-Fei Xu*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

CONSPECTUS: With the increasing concerns about chemical pollution and sustainability of resources, among the significant challenges facing synthetic chemists are the development and application of elegant and efficient methods that enable the concise synthesis of natural products, drugs, and related compounds in a step-, atom- and redox-economic manner. One of the most effective ways to reach this goal is to implement reaction cascades that allow multiple bond-forming events to occur in a single vessel. This Account documents our progress on the rational design and strategic application of asymmetric catalytic cascade reactions in constructing diverse scaffolds and synthesizing complex chiral molecules.



Our research is aimed at developing robust cascade reactions for the systematic synthesis of a range of interesting molecules that contain structural motifs prevalent in natural products, pharmaceuticals, and biological probes. The strategies employed to achieve this goal can be classified into three categories: bifunctional base/Brønsted acid catalysis, covalent aminocatalysis/N-heterocyclic carbene catalysis, and asymmetric organocatalytic relay cascades. By the use of rationally designed substrates with properly reactive sites, chiral oxindole, chroman, tetrahydroquinoline, tetrahydrothiophene, and cyclohexane scaffolds were successfully assembled under bifunctional base/Brønsted acid catalysis from simple and readily available substances such as imines and nitroolefins. We found that some of these reactions are highly efficient since catalyst loadings as low as 1 mol % can promote the multistep sequences affording complex architectures with high stereoselectivities and yields. Furthermore, one of the bifunctional base/Brønsted acid-catalyzed cascade reactions for the synthesis of chiral cyclohexanes has been used as a key step in the construction of the tetracyclic core of lycorine-type alkaloids and the formal synthesis of α-lycorane. Guided by the principles of covalent aminocatalysis and N-heterocyclic carbene catalysis, we synthesized chiral piperidine, indole, and cyclobutane derivatives. The synthesis of chiral cyclobutanes and pyrroloindolones showed unprecedented reactivity of substrates and catalysts. The development of the strategy of asymmetric organocatalytic relay cascades has provided a useful tool for the controlled synthesis of specific diastereomers in complex molecules.

This Account gives a panoramic view and the logic of our research on the design, development, and applications of asymmetric catalytic cascade reactions that will potentially provide useful insights into exploring new reactions.

1. INTRODUCTION

Today, chemical synthesis has reached the stage that synthetic chemists can synthesize almost any complex molecule that has been isolated from natural products or artificially designed.[1] A large number of the current synthetic strategies leading to these targets are based on the step-by-step approach, which involves tedious isolation processes, extensive input of effort, and materials associated with reagents and waste disposal. However, in view of the problems of chemical pollution and sustainability of resources, the development and application of efficient methods for the concise synthesis of these valuable molecules in an atom-, step-, and redox-economic manner has attracted a great deal of attention from the synthetic community.[2] As a result, an important challenge facing synthetic chemists is how to develop efficient and elegant strategies for significantly improving the overall efficiency of chemical synthesis.[3] One of the most powerful approaches to reach such a goal is to develop catalytic cascade reactions wherein multiple bond-forming events occur in one pot and only a single reaction solvent, workup procedure, and purification step is required in order to generate a complex product from simple starting materials.[4] Consequently, the development of catalytic cascade reactions has emerged as one of the most effective strategies for the construction of various scaffolds and the synthesis of complex natural products.

Some structural motifs, such as indole, spirooxindole, chroman, piperidine, etc., are widely distributed in pharmaceutical compounds and complex natural products. To this end, we have been actively involved in the design, development, and application of catalytic cascade reactions to collectively construct those privileged scaffolds with multiple stereocenters. Herein we describe how bioactive natural products and drug molecules serve as starting points for the exploration of

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asymmetric catalytic cascade reactions.[5] During this process, the comprehensive investigation of known and specially tailored reagents and catalysts provides valuable insights into understanding reaction mechanisms and designing new cascade reactions. Furthermore, a considerable number of natural products exist as diastereomers, and we also show examples of catalyst- or reagent-controlled diastereomer selection in the synthesis of target molecules with multiple stereocenters. Meanwhile, successful applications of cascade reactions in the synthesis of natural products will also be discussed. This Account highlights these cascade reactions developed in our group.

2. SYNTHESIS OF CHIRAL CYCLOHEXANES AND RELATED NATURAL PRODUCTS

The chiral cyclohexane motif is prevalent in various natural products and drug molecules that usually have pronounced bioactivities (Figure 1).[6] For example, the polysubstituted chiral

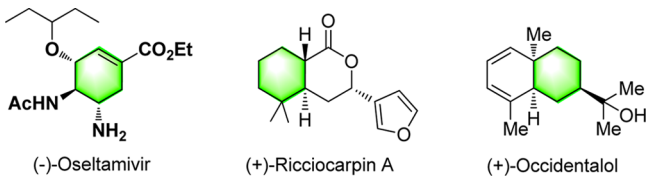
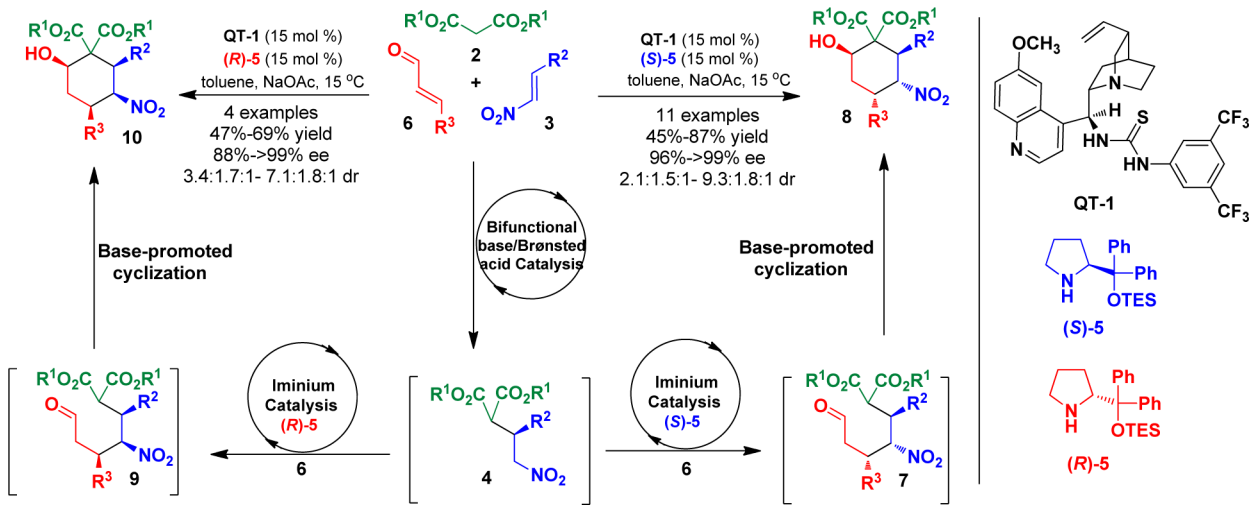


Figure 1. Some drugs and natural products containing the cyclohexane motif.

cyclohexane (−)-oseltamivir is an antiviral medication for the treatment of influenza and postexposure prophylaxis.[7] The development of asymmetric catalytic methods for the synthesis of cyclohexanes has attracted a great deal of attention, and many elegant syntheses have been established. In target-oriented synthesis, the classic approach to construct stereochemical complexity usually involves reliance on the conformational properties of the substrates, which play a crucial role in directing the generation of new stereocenters in a diastereoselective manner (substrate control). To this end, the selective synthesis of a specific diastereomer in complex molecules with multiple chiral centers has often required a considerable level of creativity in synthetic design.[8] In an alternative approach, catalyst-controlled diastereomer selection has been proven to be a particular challenge but holds significant appeal. In this context, we are interested in whether it is possible to produce specific diastereomers of chiral cyclohexanes directed by the stereostructure of the catalyst.

The development of covalent aminocatalysis and bifunctional base/Brønsted acid catalysis has resulted in a rich variety of novel reactions that can provide further opportunities for the design of cascade reactions. We envisaged that the merging of these two fields could result in a powerful method for the expeditious generation of molecular complexity and diversity. Consequently, the strategy of asymmetric organocatalytic relay cascades (AORCs) was successfully developed for the construction of distinct complex molecules that are otherwise difficult to synthesize by traditional methods or using a single catalyst. By employing catalysts with orthogonal but mutually compatible reactant activation modes, we achieved a three-step AORC for the diastereoselective synthesis of polysubstituted cyclohexanes (Scheme 1).[9] Initially, in the presence of bifunctional base/Brønsted acid catalyst **QT-1**, malonate ester **2** and nitroalkene **3** were preferentially activated, leading to a chemoselective and stereoselective Michael addition to generate Michael adduct **4**. Under iminium ion activation with the cyclic secondary amine catalyst (*S*)-**5**, intermediate **4** then served as the donor to participate directly in the second catalytic cycle of regioselective nitro-Michael addition to *α,β*-unsaturated aldehyde **6**. The new Michael adduct **7** with suitably positioned aldehyde and malonate functional groups underwent a base-promoted aldol cyclization to afford the desired cyclohexane **8** in reasonable yield with moderate diastereoselectivity and high enantioselectivity. To our knowledge, this was the first time that covalent aminocatalysis and bifunctional catalysis were merged in a relay cascade reaction to generate distinct complex molecules.[10] To our delight, by variation of the catalyst combinations, in particular the use of (*R*)-**5**, the enantiomer of chiral secondary amine (*S*)-**5**, specific diastereomer **10** could be selectively generated. The catalyst-controlled diastereomer selection can potentially be very useful to achieve full stereochemical complexity, providing a very important complement to the traditional substrate-controlled preference. To date, many other multiple-catalyst-promoted cascade reactions have also been established.[10]

Scheme 1. Catalyst-Controlled Stereoisomer Selection in the Synthesis of Functionalized Cyclohexanes



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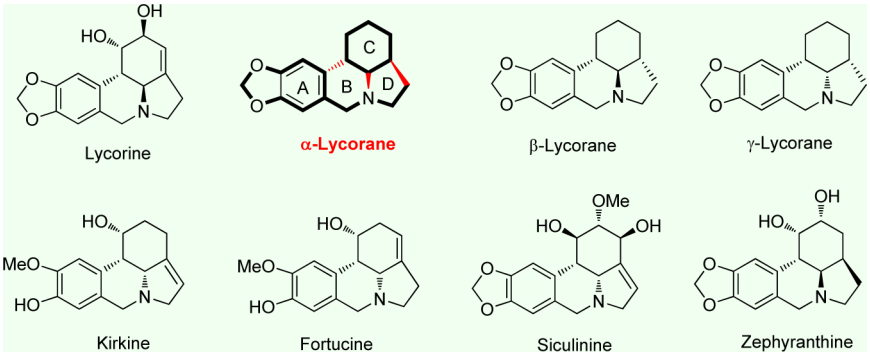
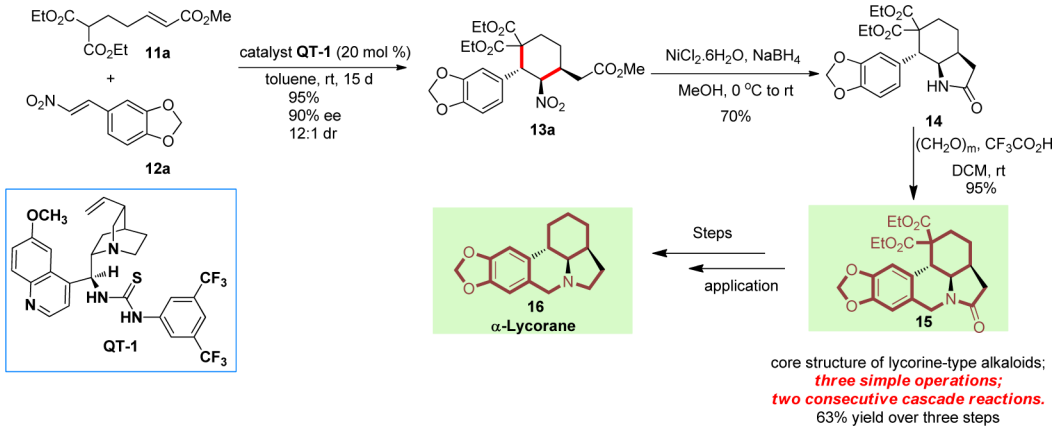
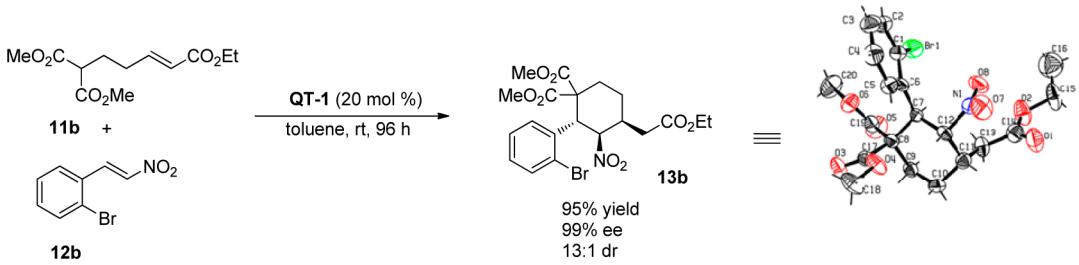


Figure 2. Some lycorine-type alkaloids.

Scheme 2. Construction of the Tetracyclic Core of the Lycorine-Type Alkaloids and Its Application in the Formal Synthesis of *α*-Lycorane



Scheme 3. Synthesis and X-ray Crystal Structure of 13b



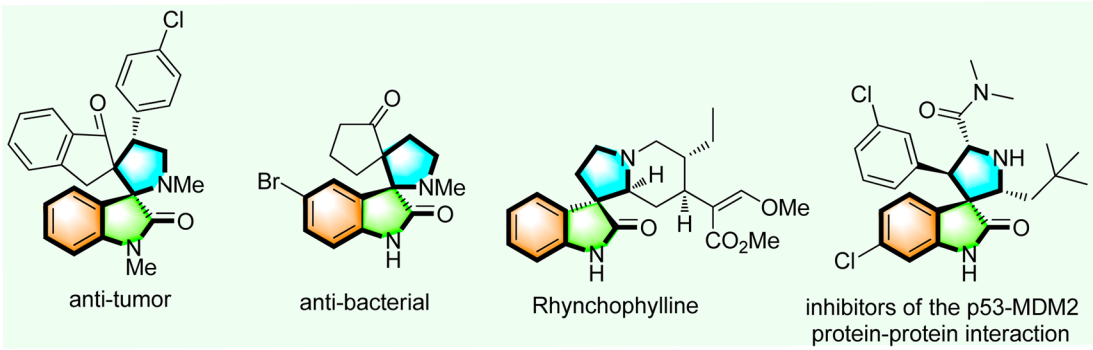


Figure 3. Some biologically important compounds containing the 3,3′-pyrrolidinylspirooxindole motif.

The Amaryllidaceae alkaloids are a large family of natural products possessing potential pharmacological and/or biological activities, such as antiviral, analgesic, antineoplastic, and insect antifeedant activities.[11] The lycorine-type alkaloids, which have a common ABCD tetracyclic core structure, are an important subclass of this family (Figure 2). Consequently, an efficient double Michael addition cascade reaction to generate the C ring was conceived.[12] As expected, malonate

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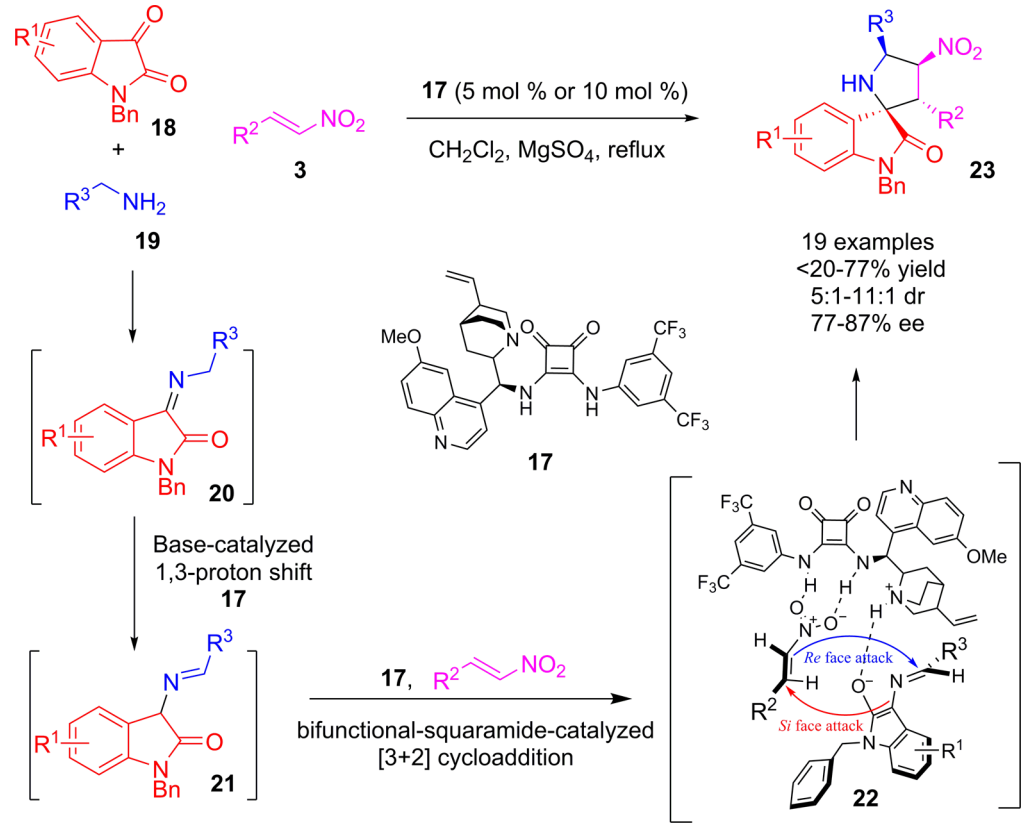
Scheme 4. Catalytic Enantioselective 1,3-Proton Shift/[3 + 2] Cycloaddition for the Synthesis of Spirooxindoles



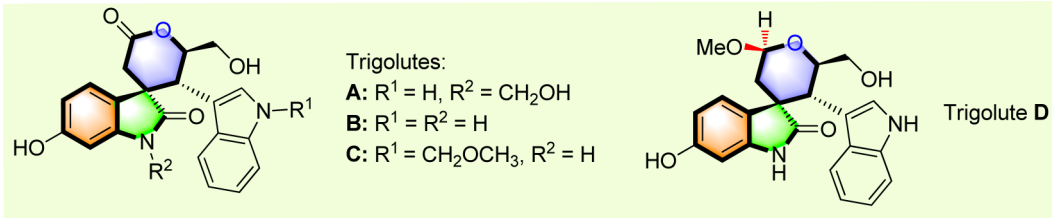
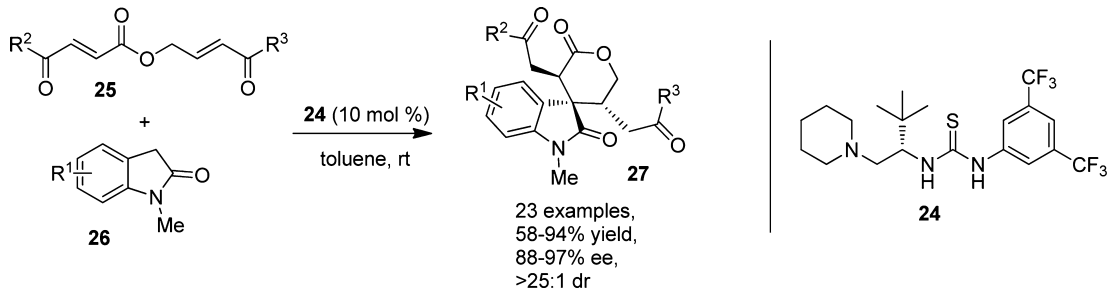


Figure 4. Some trigolute alkaloids.

Scheme 5. Enantioselective Double Michael Addition for the Synthesis of Chiral Spirooxindole δ-Lactones



derivative **11a** successfully reacted with nitroolefin **12a** to afford **13a** containing the C ring in excellent yield and stereoselectivity. The ABCD tetracyclic core skeleton **15** was efficiently constructed via only three simple operations involving two consecutive cascade reactions in a total yield of 63% (Scheme 2). As shown in Scheme 3, the absolute configuration of **13b**, which was synthesized using the same method (95% yield, 99% ee, 13:1 dr), was established by single-crystal X-ray diffraction. For a further application, the tetracyclic core was applied in the formal synthesis of α-lycorane (**16**).

3. SYNTHESIS OF CHIRAL MOLECULES CONTAINING THE OXINDOLE AND INDOLE SCAFFOLDS

The 3,3′-pyrrolidinylspirooxindole scaffold is a privileged structural motif that can be found in a wide range of natural products and pharmaceuticals (Figure 3) that possess various biological activities, such as antitumor, antidiabetic, anti-

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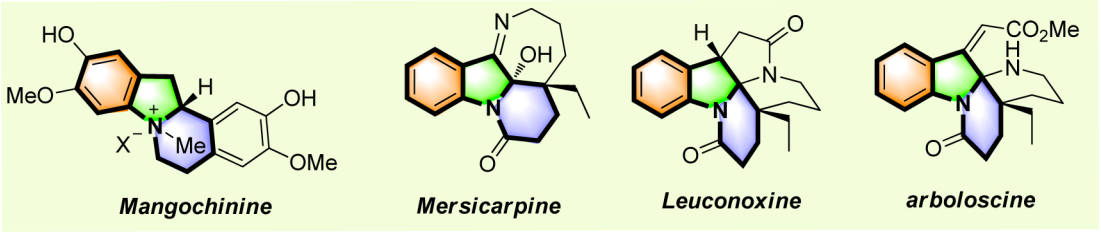
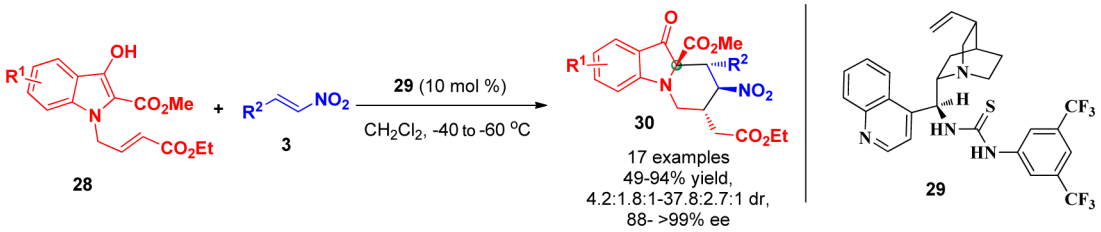


Figure 5. Some natural products containing the piperidino[1,2-*a*]indoline scaffold.

Scheme 6. Catalytic Asymmetric Michael–Michael Cascade for the Construction of Highly Functionalized N-Fused Piperidinoindoline Derivatives



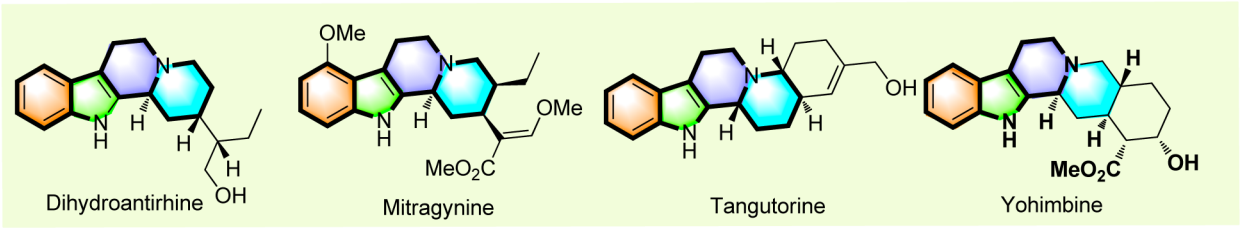


Figure 6. Some natural products containing the indoloquinolizidine core.

inflammatory, and antitubercular activities, among others.[13] Because of these significant bioactivities, 3,3′-pyrrolidinylspirooxindole has emerged as an attractive target, and many elegant strategies have been established to construct this scaffold.[14] We developed an enantioselective approach to assemble this heterocycle involving a three-component reaction of isatins **18**, amines **19**, and nitroalkenes **3** catalyzed by chiral bifunctional squaramide **17** (Scheme 4).[15] Initially, a base-catalyzed 1,3-proton shift occurred from in situ-generated ketimine **20** to form aldimine **21**. A 1,3-dipolar cycloaddition reaction occurred subsequently through synergistic activation of aldimine **21** and nitroalkene **3** by bifunctional catalyst **17**. As a result, the [3 + 2] cycloaddition successfully afforded the desired 3,3′-pyrrolidinylspirooxindole products **23** bearing four contiguous stereogenic centers from simple and readily available starting materials in generally good yields and stereoselctivities.

The trigolute alkaloids, which possess an intriguing spirooxindole skeleton, were recently isolated from genus *Trigonostemon* (Figure 4).[16] Inspired by the previous achievements in the construction of spirooxindoles through the addition of oxindoles and various Michael acceptors,[17] we established a new method for the construction of the core of these alkaloids (Scheme 5). In the presence of a suitable bifunctional catalyst **24**, ester-linked bisenones **25** serving as a new partner reacted with oxindoles **26** to afford spirooxindole *δ*-lactones **27** in generally good yields with excellent stereoselectivities.[18]

The piperidino[1,2-*a*]indoline framework can frequently be found in a wide range of bioactive natural products (Figure 5). For example, mangochinine is a key component of the traditional Chinese medicine plant *Manglietia chingii* Dandy, which has muscle relaxant, antiulcer, and antibacterial effects. Some interesting indole alkaloids such as mersicarpine, arboloscine, and leuconoxine also have a common piperidino-[1,2-*a*]indoline core structure. Because of the intriguing structure and promising activity, the piperidino[1,2-*a*]indoline scaffold has been the subject of extensive study. To date, metal-catalyzed racemic synthesis has been the main theme of the synthetic approaches to this framework, and direct access to chiral piperidino[1,2-*a*]indolines by catalytic asymmetric transformations is scarce.[19] It is noteworthy that the application of 2-oxindole derivatives in cascade reactions has been demonstrated to be a very reliable method for the construction of a large number of complex molecular scaffolds and natural products.[17,20] Surprisingly, however, compared with the significant advances in the exploration of 2-oxindole chemistry, 3-indolinone-related compounds have received only very little attention, and the application of this class of substrates in cascade reactions, which is potentially useful for the design of a diverse array of novel reactions, remains an underdeveloped research field.[20] In this context, a double Michael addition of **28** with nitroalkenes **3** catalyzed by **29** was developed for the construction of the piperidino[1,2-*a*]indoline scaffold **30** (Scheme 6).[21] The desired products were generally obtained in good yields with moderate diastereoselectivities and excellent enantioselectivities.

Indoloquinolizidine represents a key structural backbone that can be found in natural indole alkaloids such as corynentheol, dihydroantirhine, mitragynine, tangutorine, and so on (Figure

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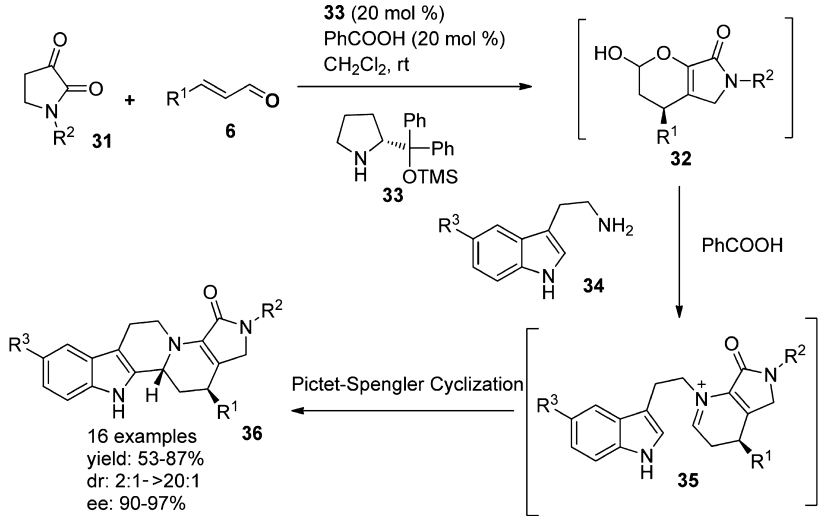
Scheme 7. One-Pot Michael/Pictet–Spengler Sequence To Construct the Indoloquinolizidine Scaffold



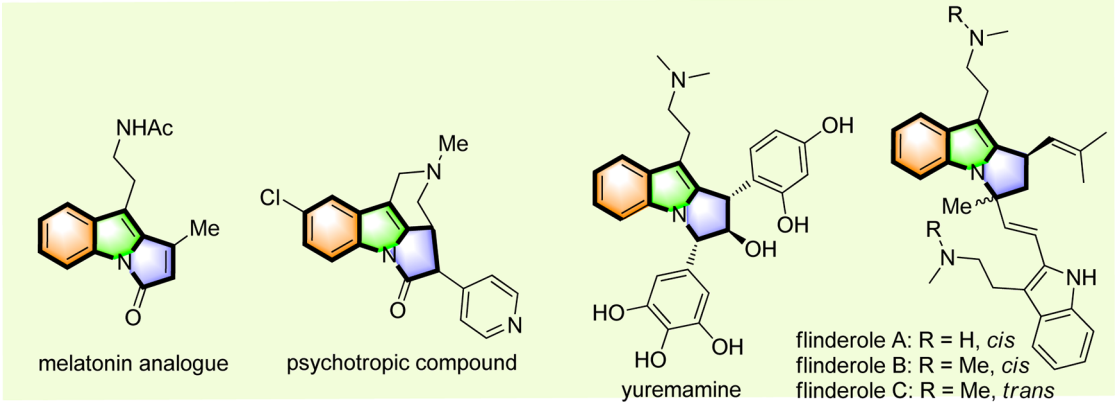
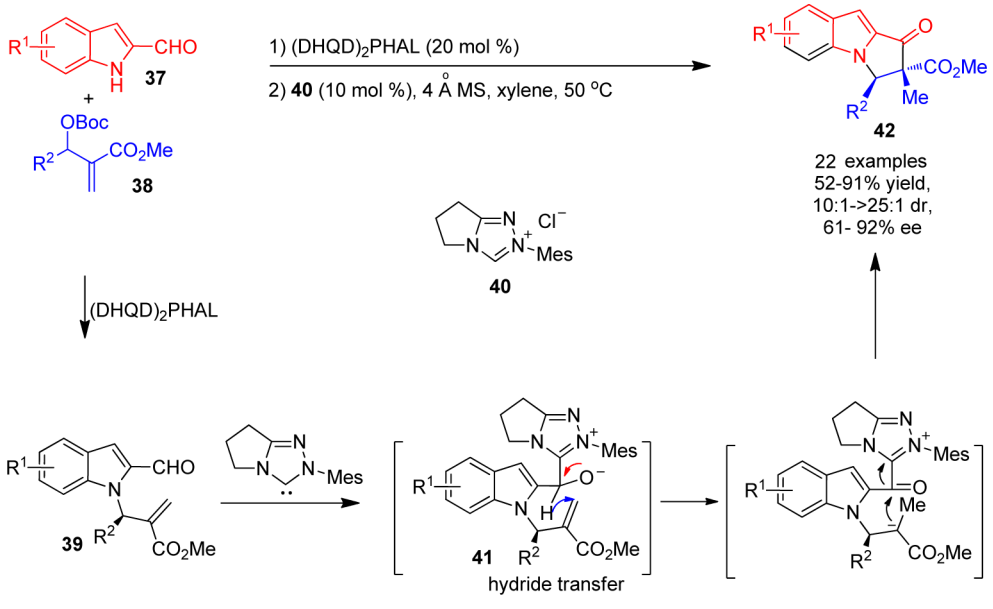


Figure 7. Some natural products containing the pyrroloindolone core.

Scheme 8. Asymmetric Synthesis of Pyrroloindolones through a Multicatalytic N-Allylation/Hydroacylation Sequence



6).[22] Therefore, the efficient construction of this scaffold has attracted a considerable amount of attention from the synthetic community. As a result, over the past several years, many elegant strategies have been established for the fast and efficient construction of indoloquinolizidine scaffold from simple starting materials.[23] Inspired by these achievements, we

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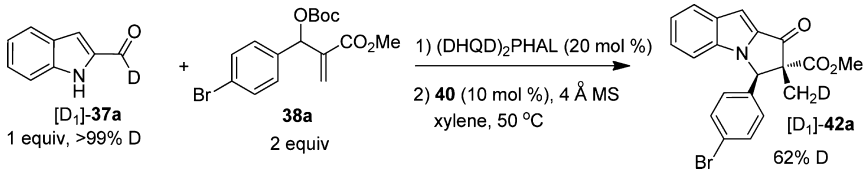
Acc. Chem. Res. 2015, 48, 1832–1844

Scheme 9. Deuterium-Labeling Experiment



developed a cascade reaction employing α-oxo-γ-butyrolactam **31** as a new N-containing pronucleophile for the synthesis of the butyrolactam-fused indoloquinolizidine scaffold (Scheme 7).[24] Initially, Michael addition of **31** to **6** generated chiral hemiacetal **32** in the presence of secondary amine **33** through iminium activation. Then under Brønsted acid catalysis, hemiacetal **32** reacted with tryptamine **34** to form iminium ion **35**, which subsequently underwent a diastereoselective Pictet−Spengler cyclization to afford the desired indoloquinolizidine scaffold **36** in generally good yields with good diastereoselectivities and excellent enantioselectivities.

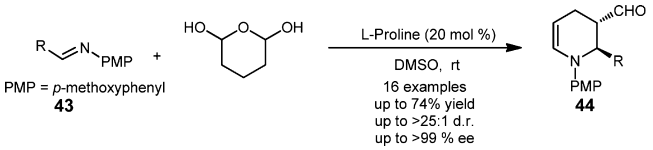
The pyrroloindolone scaffold belongs to an important class of heterocycles that are prevalent in natural products exhibiting a wide range of biological activities (Figure 7). We have developed a unique approach to construct this core structure (Scheme 8).[25] In the presence of the catalyst $(DHQD)_2PHAL$, the reaction between indole-2-carbaldehydes **37** and carbonates **38** smoothly afforded reactive N-allylation intermediates **39**. To our delight, an unprecedented intramolecular hydroacylation of α-substituted acrylates occurred under catalysis of an N-heterocyclic carbene (NHC). It was proposed that an intramolecular hydride transfer in intermediate **41** followed by nucleophilic attack to release catalyst occurred in this catalytic process. The hydroacylation of ketones under NHC catalysis was reported by Chan and Scheidt.[26] As a result, pyrroloindolone products **42** were obtained in generally good yields and stereoselectivities. To gain mechanistic insights into this unexpected hydroacylation reaction, a deuterium-labeling experiment was then carried out (Scheme 9). When deuterated indole-2-carbaldehyde $[D_1]$-**37a** and **38a** were employed as the substrates, the experimental results showed that the deuterium atom was incorporated exclusively into the methyl group to afford product $[D_1]$-**42a**. The unusual intramolecular hydroacylation discovered in this reaction nicely complements the current research in NHC catalysis.[27]

4. SYNTHESIS OF CHIRAL MOLECULES CONTAINING THE TETRAHYDROPYRIDINE AND PIPERIDINE SCAFFOLDS

The tetrahydropyridine and piperidine ring systems are distributed in numerous natural products and drug molecules possessing various pharmaceutical properties. Furthermore, they have also been used as fundamental building blocks in various transformations.[28] On the basis of previous achievements in proline-catalyzed Mannich reactions, we developed a Mannich/intramolecular cyclization cascade reaction for the synthesis of chiral tetrahydropyridines from imines **43** and aqueous tetrahydro-2*H*-pyran-2,6-diol (Scheme 10).[29] The desired products were obtained in reasonable yields with excellent stereoselectivities.

Later, we developed a relay catalytic three-component cascade reaction comprising aldehydes **45**, nitroalkenes **3**, and imines **46** for the efficient synthesis of fully substituted piperidines in the presence of two catalysts, (*S*)-**5** and **48**

Scheme 10. Proline-Catalyzed Enantioselective Construction of Tetrahydropyridines



(Scheme 11).[30] Initially, activation of aldehydes **45** by catalyst (*S*)-**5** (enamine activation) led to a selective and expeditious addition to nitroalkenes in a Michael-type reaction. In the presence of bifunctional catalyst **48**, a nitro-Mannich reaction of intermediates **47** with imines **46** then generated persubstituted *N*-Tos-protected amino aldehydes **49**, which underwent cyclization to give the final hemiaminals **50** in moderate yields with excellent stereoselectivities. Later, similar reactions for the synthesis of fully substituted piperidines were developed by the groups of Hayashi and Barbas.[31]

In connection with our interest in the construction of piperidine derivatives, we further developed an enantioselective multicomponent cascade reaction for facile access to this framework (Scheme 12).[32] Initially, β-keto ester **51** reacted with formaldehyde to form reactive Michael acceptor intermediate **53** via a Knoevenagel condensation. Then in the presence of an amine base, another β-keto ester attacked intermediate **53** to form intermediate **54**, which then participated in the next Mannich reaction with the in situ-generated imine catalyzed by L-proline to give intermediate **55**. As expected, an intramolecular cyclization/dehydration cascade of intermediate **55** occurred subsequently to afford the final product, tetrahydropyridine **56**, in generally moderate yields and enantioselectivities. This cascade reaction is very efficient since three C−C bonds, two C−N bonds, and an all-carbon quaternary stereocenter are formed in a single operation from very simple starting materials.

5. SYNTHESIS OF THE CHIRAL CHROMAN SCAFFOLD

The chiral chroman scaffold can frequently be found in natural products and pharmacologically active compounds (Figure 8).[33] For example, α-tocopherol is a natural product that belongs to the vitamin E family and possesses remarkable biological activities. 4-Dehydroxydiversonol is a member of a family of compounds produced by the fungal species *Penicillium diversum*. (+)-Catechin, often found in land plants such as the traditional Chinese medicine plant green alga *Myriophyllum spicatum* and *Uncaria rhynchophylla*, displays modest antioxidant and antitumor activity. The chroman moiety is also embedded in many other bioactive natural products such as sauchinone A, (−)-siccanin, and bisabosqual A. Because of the biological properties of the chiral chroman scaffold and its wide occurrence in nature, the development of new and efficient approaches to this class of compounds has become an active research field. As a result, many elegant asymmetric catalytic cascade reactions have been established for the concise

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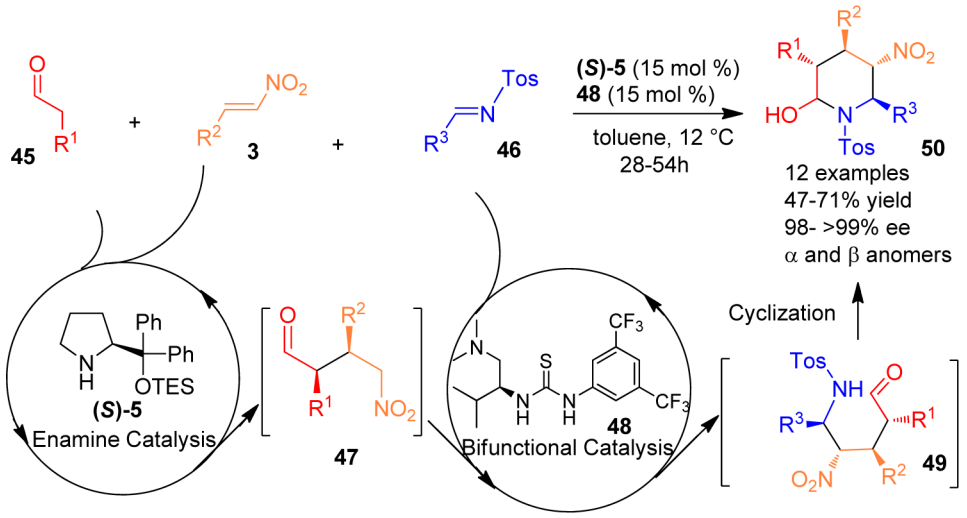
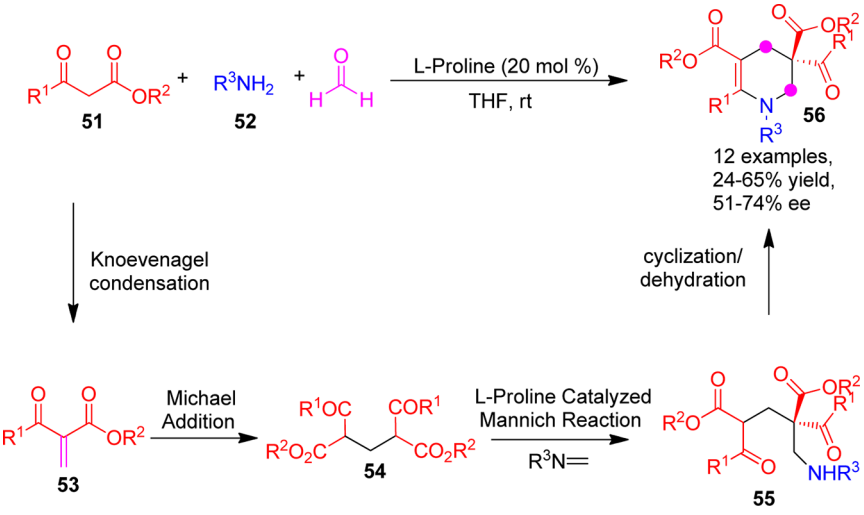
Scheme 11. Enantioselective Catalytic Synthesis of Fully Substituted Piperidines



Scheme 12. Enantioselective Multicomponent Cascade Reaction for the Synthesis of Tetrahydropyridines



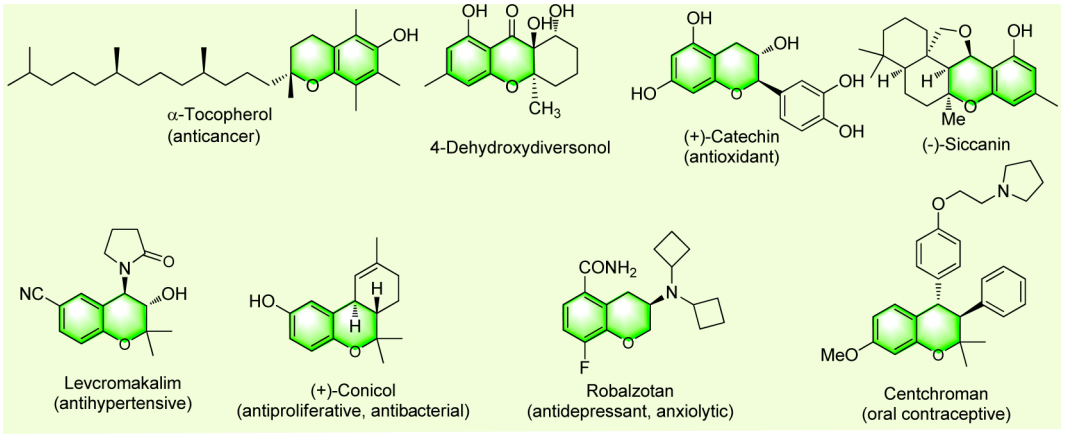


Figure 8. Some natural products containing the chroman core.

construction of this scaffold and the total synthesis of related natural products.

As an initial attempt, we developed a new approach to chiral polysubstituted chromans **59** from nitromethane and chalcone enolates **57** via a cascade Michael–Michael reaction in the presence of chiral bifunctional catalyst **DHQT-58** (Scheme 13).[34] This cascade reaction showed broad substrate scope and efficiently afforded the desired products with three consecutive stereocenters in generally good yields with high stereoselectivities. We further expanded the method to the

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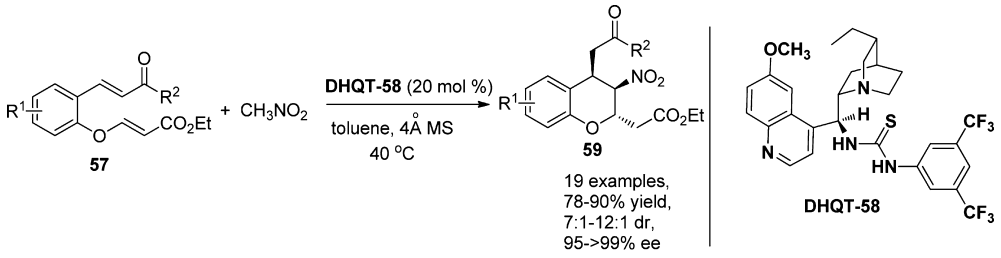
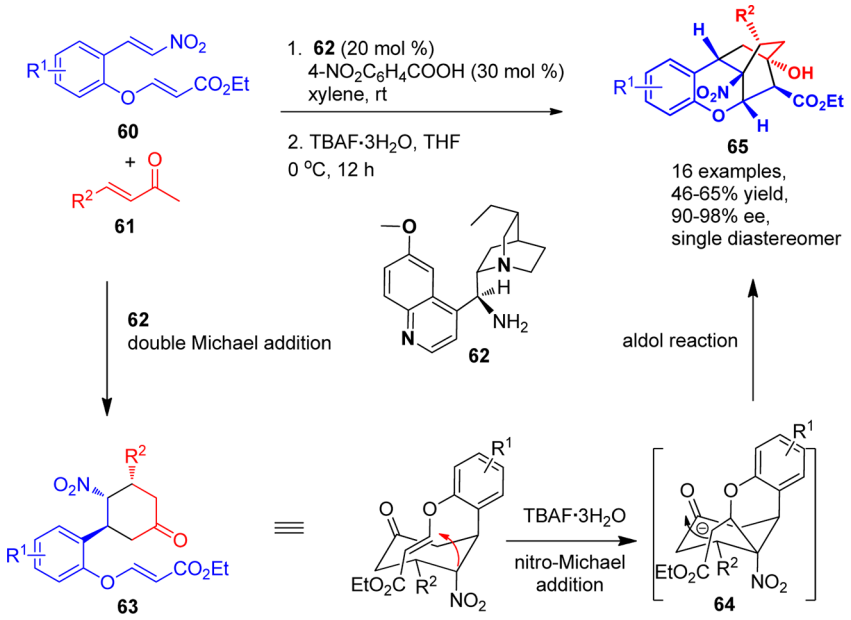
Acc. Chem. Res. 2015, 48, 1832–1844

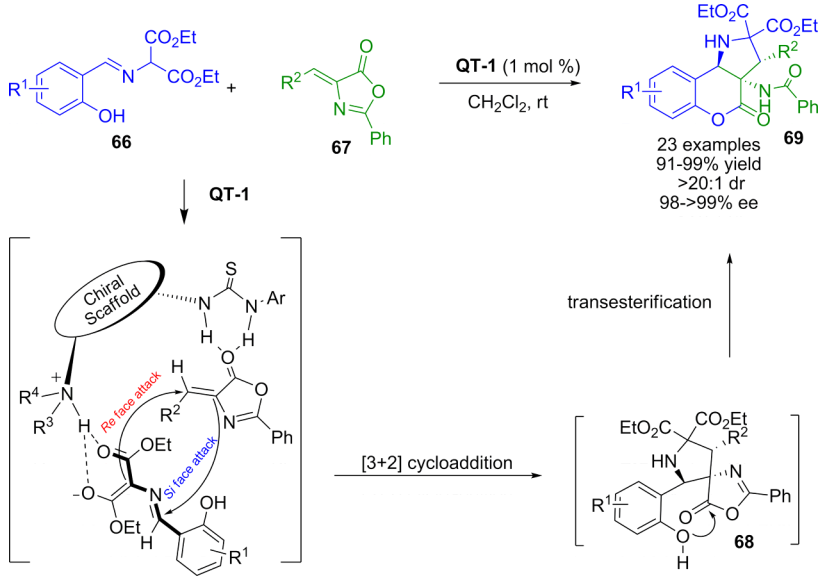
Scheme 13. Enantioselective Double Michael Cascade Reaction for the Synthesis of Chroman Derivatives



Scheme 14. Diastereo- and Enantioselective Synthesis of a Tetracyclic Ring System Containing the Chroman Scaffold



Scheme 15. Asymmetric Synthesis of Polysubstituted Chromeno[4,3-*b*]pyrrolidine Derivatives



construction of a more complex tetracyclic ring system incorporating both chroman and bicyclo[2.2.2]octane structural units (Scheme 14).[35] On the basis of the previous success of double Michael addition of nitroolefins with α,β-unsaturated ketones, we designed new substrates with multiple functional groups, nitroolefinenoates **60**, for the synthesis of complex chroman derivatives. Initially, under catalysis by 9-amino-9-deoxy-*epi*-hydroquinine **62**, nitroolefinenoates **60** reacted smoothly with α,β-unsaturated ketones **61** through a double Michael addition approach to afford cyclohexanones **63**. Then an intramolecular nitro-Michael addition promoted by TBAF·$3H_2O$ afforded intermediates **64**, which underwent a further

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Acc. Chem. Res. 2015, 48, 1832−1844

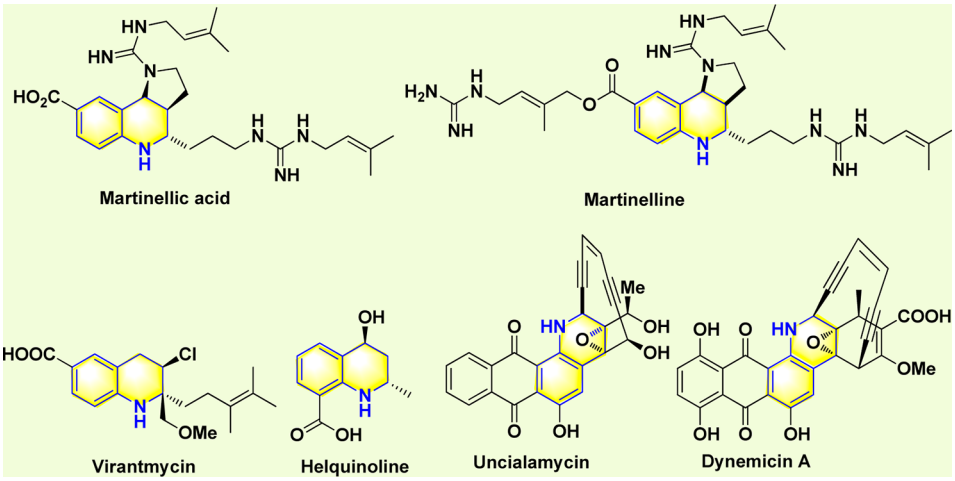
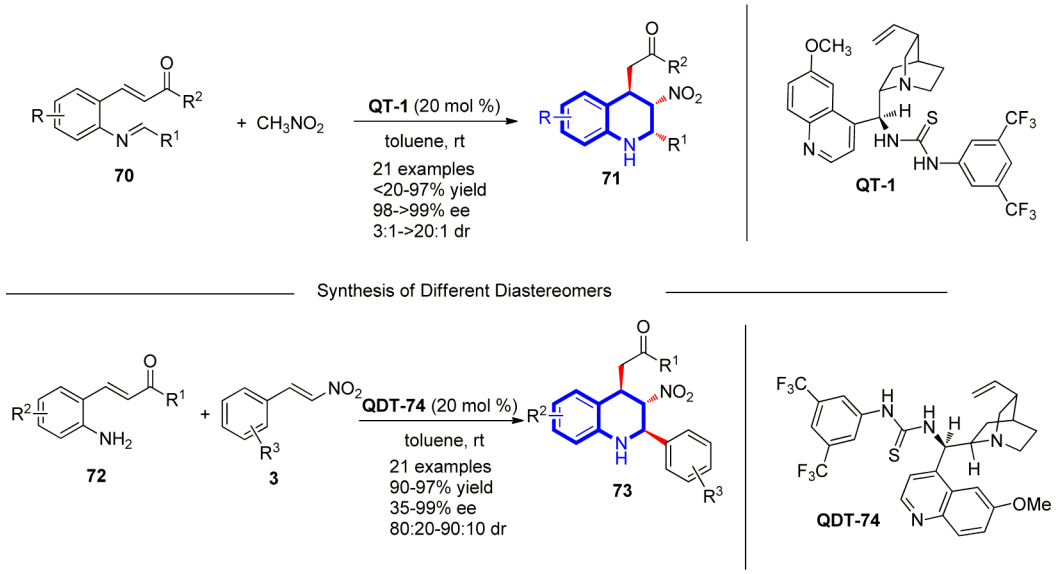


Figure 9. Some natural products containing the tetrahydroquinoline core.

Scheme 16. Controlled Access to Specific Diastereoisomers of Tetrahydroquinoline Derivatives



intramolecular aldol reaction to afford the final products **65** in satisfactory yields with excellent stereoselectivities. Remarkably, this cascade reaction is very efficient since six stereogenic centers, including two chiral quaternary stereocenters, can be stereospecifically controlled in the construction of this tetracyclic ring.

Recently, we further developed a new strategy for fast and concise access to the ring-fused chroman framework.[36] As shown in Scheme 15, through synergistic activation of both the rationally designed *o*-hydroxy aromatic aldimines **66** and alkylideneazlactones **67** by bifunctional thiourea **QT-1**, a [3 + 2] cycloaddition reaction occurred smoothly to generate intermediates **68**. An intramolecular transesterification reaction then afforded the ring-fused products **69**. Remarkably, this cascade reaction is highly efficient since three new bonds and three contiguous stereogenic centers, including one quaternary stereocenter, are generated in excellent yields with nearly absolute stereocontrol in a short reaction time under mild conditions with a low catalyst loading (1 mol %).

6. DIASTEREOMER-CONTROLLED SYNTHESIS OF TETRAHYDROQUINOLINES

The tetrahydroquinoline structural unit is an important heterocycle that is widely distributed in natural products and pharmaceuticals (Figure 9).[37] Numerous natural or designed molecules containing the tetrahydroquinoline moiety are pharmacologically active compounds that can be used as antioxidants, pesticides, corrosion inhibitors, etc. Therefore, there is significant interest in developing synthetic methodologies for the stereoselective construction of the tetrahydroquinoline motif.[37] As discussed in the section on catalyst-controlled synthesis of specific diastereomers of chiral cyclohexanes, the exploration of new approaches to access specific diastereomers is one of the important topics in contemporary organic synthesis. We are interested in the controlled synthesis of diastereoisomers of tetrahydroquinoline derivatives.

We developed two different reactions that could be used to construct specific diastereomers of tetrahydroquinolines (Scheme 16).[38,39] Initially, under the catalysis of bifunctional catalyst **QT-1**, nitromethane selectively attacked unsaturated ketones **70** from the *Si* face. Then an intramolecular

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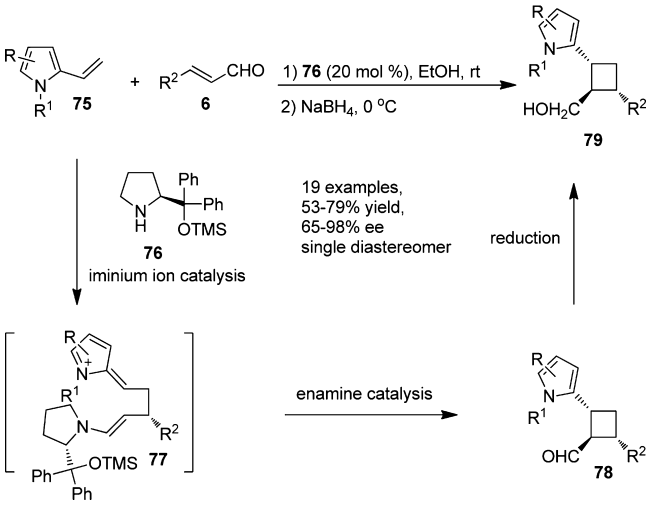
Acc. Chem. Res. 2015, 48, 1832−1844

nucleophilic nitro-Mannich reaction afforded the desired products **71** in generally excellent yields with high stereoselectivities. This cascade reaction yielded the 2,3-*cis* isomers.[38] In our effort to further explore the synthesis of tetrahydroquinolines with diverse stereochemical features, we developed a different cascade reaction to produce the 2,3-*trans* isomers.[39] Catalyzed by **QDT-74**, an aza-Michael−Michael cascade process employing a variety of unsaturated ketones **72** and nitroalkenes **3** smoothly afforded the desired products **73** in generally excellent yields with good diastereoselectivities and high enantioselectivities.

7. SYNTHESIS OF CHIRAL CYCLOBUTANES AND TETRAHYDROTHIOPHENES

Cyclobutanes represent a fundamental molecular scaffold and constitute the framework of many natural products and biologically attractive molecules. Furthermore, cyclobutanes often serve as useful intermediates for further synthetic operations. Consequently, considerable effort has been directed toward the construction of these privileged building blocks. Among these reports, the [2 + 2] cycloaddition reaction has proven to be the most versatile and powerful approach to this ring system. We recently developed a cascade reaction that provides unique access to chiral cyclobutanes (Scheme 17).[40]

Scheme 17. Unique Approach to Chiral Cyclobutanes



Initially, under iminium ion activation, a vinylogous Michael addition reaction between 2-vinylpyrroles **75** and unsaturated aldehydes **6** generated intermediates **77**, which underwent a unusual 1,6-addition to form the strained four-membered rings **78** rather than 1,4-addition to produce six-membered rings. The final products **79** were obtained in moderate to high yields with excellent enantioselectivities. The unique reactivity discovered in this reaction should provide insights into the design of new reactions for the synthesis of other intriguing chiral molecules.

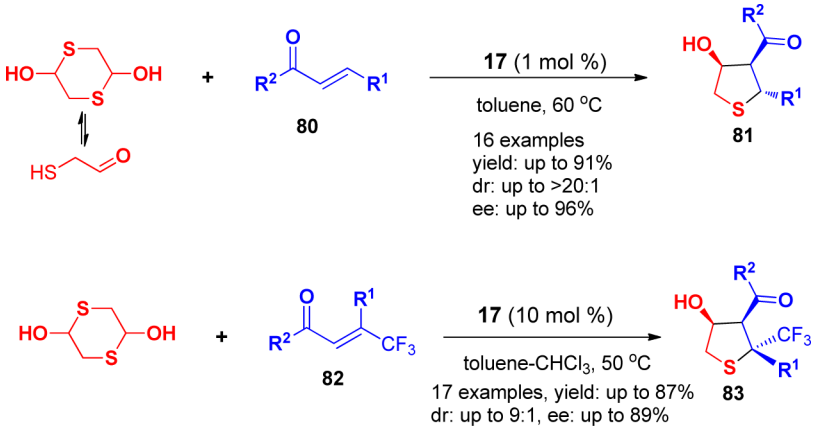
The tetrahydrothiophene moiety is also an important structural unit that is found in a number of bioactive natural products such as oral hypocholesterolemic agents (breynins A and B and epibreynin B), α-glucosidase inhibitors (salacinol, kotalanol, and salaprinol), brain-type cholecystokinin (CCK) receptor antagonists (tetronothiodin), and many others. Furthermore, tetrahydrothiophenes have also been frequently utilized as chiral ligands or templates for various enantioselective transformations. In this regard, tetrahydrothiophenes are of particular value as targets for synthetic and biological elaboration.

We developed a sulfa-Michael/aldol cascade reaction for the synthesis of this class of heterocyclic compounds (Scheme 18).[41] Through synergistic activation of both mercaptoacetaldehyde and enones **80** by bifunctional squaramide **17**, a selective sulfa-Michael addition occurred smoothly, and a subsequent intramolecular aldol reaction closed the catalytic cycle, thus delivering the desired products **81** with three contiguous chiral centers in generally good yields with high stereoselectivities. This cascade reaction is highlighted by its efficiency, since only 1 mol % catalyst is needed to produce these chiral polysubstituted tetrahydrothiophenes. The incorporation of a trifluoromethyl group into organic compounds often leads to remarkable changes in their physicochemical and biological properties. To this end, we further expanded this methodology to the enantioselective synthesis of functionalized tetrahydrothiophenes **83** containing a trifluoromethylated quaternary carbon (Scheme 18).[42] These products were obtained in generally moderate to good yields with high enantioselectivities.

8. CONCLUSION

In this Account, we have endeavored to present our contributions to the design, development, and application of asymmetric catalytic cascade reactions in constructing diverse

Scheme 18. Catalytic Asymmetric Synthesis of Polysubstituted Tetrahydrothiophenes



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scaffolds and building molecular complexity. A range of cascade reactions have been developed for the collective synthesis of some structurally interesting chiral scaffolds, including spirooxindoles, indole alkaloids, piperidines, chromans, tetrahydroquinolines, tetrahydrothiophenes, cyclobutanes, and cyclohexanes. During the process, we have also tried to show the identification and application of new reactivities of substrates and catalysts in designing novel cascade reactions. Meanwhile, we have described different strategies for efficient access to specific diastereomers. Some of these cascade reactions are very powerful because catalyst loadings as low as 1 mol % are sufficient to produce complex architectures with very good results. Furthermore, some other cascade reactions show unusual reactivities of substrates and catalysts, such as the synthesis of chiral cyclobutanes and pyrroloindolones. These new findings provide insights into the development of more robust reactions. In the future, the endeavor to develop more powerful and novel cascade reactions for the construction of some privileged scaffolds will continue. In particular, it is exciting to observe the development of more and better cascade sequences that can be directly applied to natural product synthesis and drug discovery.

AUTHOR INFORMATION

Corresponding Author

*E-mail: xupf@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

Biographies

Yao Wang was born in Gansu, China, in 1984. He received his B.S. and Ph.D. degrees from Lanzhou University in 2006 and 2012, respectively, under the supervision of Professor Peng-Fei Xu. He is currently working as an Alexander von Humboldt Postdoctoral Fellow in the Department of Chemical Biology at the Max Planck Institute of Molecular Physiology, Dortmund.

Hong Lu was born in Gansu, China, in 1987. He received his B.S. degree from Lanzhou University in 2010 and currently is pursuing his Ph.D. studies under the supervision of Professor Xu.

Professor Peng-Fei Xu was born in Shannxi, China, in 1964. He received his Ph.D. degree from Lanzhou University in 1998 and conducted postdoctoral studies at National Chung-Hsing University in Taiwan (hosted by Prof. Ta-Jung Lu) for 2 years. In 2002 he became a full professor at the State Key Laboratory of Applied Organic Chemistry at Lanzhou University. In 2003−2004, he worked as a visiting professor at Nagoya University (hosted by Prof. Kazuyuki Tatsumi) for 18 months. He currently serves as the Dean of Cuiying Honors School of Lanzhou University and an advisory board member of the Chinese Chemical Community. His research interests focus on the design, development, and application of new strategies in asymmetric catalysis and total synthesis of natural products.

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