Strategies to Bypass the Taxol Problem. Enantioselective Cascade Catalysis, a New Approach for the Efficient Construction of Molecular Complexity

Abbas M. Walji, David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Washington Rd, Princeton, NJ 08544, USA
E-mail: dmacmill@princeton.edu

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Abstract: Millions of years of evolution have allowed Nature to develop ingenious synthetic strategies and reaction pathways for the construction of architectural complexity. In contrast, the field of chemical synthesis is young with its beginnings dating back to the early 1800's. Remarkably, however, the field of chemical synthesis appears capable of building almost any known natural isolate in small quantities, yet we appear to be many years away from operational strategies or technologies that will allow access to complexity on a scale suitable for society's consumption. This essay attempts to define some of the issues that currently hamper our ability to efficiently produce complex molecules via large-scale total synthesis. In particular, issues such as 'regime of scale' and 'stop-and-go synthesis' are discussed in terms of a specific example (the taxol problem) and more broadly as they apply to the large-scale production of complex targets. As part of this essay we discuss the use of enantioselective cascade catalysis as a modern conceptual strategy to bypass many of the underlying features that generally prevent total synthesis being utilized on a manufacturing scale. Last we provide a brief review of the state of the art with respect to complex molecule production via enantioselective cascade catalysis.

Key words: cascade catalysis, organocatalysis, stop-and-go synthesis, natural product synthesis, enantioselective catalysis

1 Introduction

The proficiency with which Nature constructs intricate molecular architectures, arranged in complex structural environments continues to intrigue and inspire the field of chemical synthesis. Over four billion years of evolution have allowed Nature to reach a systematic and highly efficient approach to the construction of architectural complexity. Nature's biosynthetic machines rapidly convert simple raw materials into intricate molecular systems, generating a seemingly unlimited library of natural products with expansive diversities in structural sophistication and biological properties. In comparison, the field of chemical synthesis is young with its beginnings dating back to the early 1800's. Over the past century, the practice of total synthesis has gradually evolved into a dynamic scientific discipline, providing its practitioners with powerful tools to assemble even the most complex molecular systems. This is clearly evident by the increasing molecular complexity of targets chosen for total synthesis, such as vitamin B_{12} (Woodward–Eschenmoser 1973),[1] ginkgolide (Corey 1988),[2] palytoxin (Kishi 1994),[3] taxol (Holton and Nicolaou 1994),[4,5] brevetoxin A (Nicolaou 1998),[6] and many others.

Among the innumerable complex natural products isolated from Nature, there exist a selection that have had a lasting impact on synthetic chemistry, biology, medicine, and the society at large. These privileged natural isolates have potent biological properties, unique mechanisms of action, and most importantly, significant therapeutic value. In many cases, this therapeutic success is associated with highly complex molecular architectures and although Nature might assemble these molecular systems with remarkable ease, they still present a formidable challenge for modern synthetic chemistry. Indeed, while the field of chemical synthesis appears now capable of building almost any known natural isolate in small quantities, we remain perhaps many years away from operational strategies or technologies that will allow access to such complexity on a scale suitable for society's consumption. As such, the utility of chemical synthesis currently remains a function of operational scale, a fact that clearly highlights (i) the limitations of known chemical reactions with respect to capacity for rapid development of molecular complexity, and (ii) the limitations of 'stop-and-go' synthesis, the operational strategy that is employed on a worldwide basis for the de novo construction of organic molecules. We shall illustrate the dichotomy of scale between biosynthesis and chemical synthesis, using the story of taxol (**1**) as a representative example.

1.1 Taxol

Taxol (**1**, Figure 1) has probably spawned more interest within the scientific communities and the general public than any other natural product drug candidate over the last

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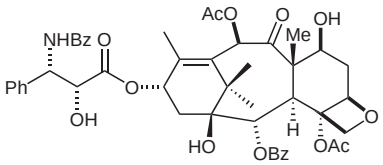


taxol (**1**)

- Potent anticancer activity
- Exponential medical demand
- Major supply crisis
- Challenging chemical synthesis

Figure 1

40 years.[7,8] Isolated in 1966 from the bark of the Pacific yew tree (*Taxus brevifolia*), the rapid disclosure of taxol's important biological properties was delayed because of difficulties in proving its molecular structure.[8] In 1971, Wall, Wani and co-workers reported the isolation and structure elucidation of taxol as a new antileukemic and antitumor agent.[9] Promising cytotoxicity studies against a variety of cell lines[10] and the discovery of taxol's novel mechanism of action fueled tremendous interest to initiate clinical trials on taxol.[11] After almost two decades, hampered by severe supply issues and formulation problems, taxol entered the drug market as an anticancer agent.[7,8]

1.2 Benefits and Therapy

Since its discovery, taxol has been regarded as one of the most significant advances in cancer therapy.[7,8] The United States Food and Drug Administration (U.S. FDA) initially approved its use for the treatment of refractory ovarian cancer[10c] and metastatic breast cancer.[10d] Currently, taxol is also prescribed to treat non-small-cell lung cancer and AIDS-related Kaposi's sarcoma,[12] and is being tested for the treatment of numerous cancer types in combination therapies with other antineoplastic agents.[13] The global demand for taxol has multiplied exponentially reaching 1 metric ton, making it a preeminent anticancer drug, with estimated annual sales exceeding $3 billion worldwide.[14]

1.3 Commercialization Problems and Ultimate Production Route

Although taxol's biological activity profile initially attracted the interest of the National Cancer Institute (NCI),[15] further evaluation and even clinical trials were

Biographical Sketches

Dave MacMillan received his undergraduate degree in chemistry at the University of Glasgow, where he worked with Dr. Ernie Colvin. In 1990, he left the UK to begin his doctoral studies under the direction of Professor Larry Overman at the University of California, Irvine. In 1996, he moved to a postdoctoral position with Professor Dave Evans at Harvard University where his studies centered on enantioselective catalysis. He began his independent career at University of California, Berkeley in July of 1998 before moving to the California Institute of Technology in June of 2000. In 2003, he was promoted to Full Professor at Caltech, before being appointed the Earle C. Anthony Chair of Organic Chemistry in 2004. In 2006, MacMillan moved to the east coast of the US to take up a position at Princeton University as the A. Barton Hepburn Chair of Chemistry and Director of the Merck Center for Catalysis at Princeton University. Professor MacMillan's research program is centered on chemical synthesis with specific interests in new reaction development, enantioselective organocatalysis and the rapid construction of molecular complexity. He has received several awards including the Mukaiyama Award (2007), ISHC Award in Heterocyclic Chemistry (2007), ACS Cope Scholar Award (2007), Thieme–IUPAC Prize in Organic Synthesis (2006), Elias J. Corey Award for Outstanding Original Contribution in Organic Synthesis by a Young Investigator (2005), the Tetrahedron Young Investigator Award (2005), the Corday-Morgan Medal (2005), Henry Dreyfus Teacher-Scholar Award (2003), a Sloan Fellowship (2002), and a Woodward Scholarship Award from Harvard University (2001). Dave is currently a member of the Chemical Communications, Tetrahedron, Tetrahedron Letters and Chemistry – An Asian Journal editorial advisory boards as well as a member of the scientific advisory boards of Lexicon pharmaceuticals and Materia. He is also a scientific consultant with Merck (worldwide), Amgen (worldwide), Schering-Plough, Abbott Research Laboratories, Johnson & Johnson Pharmaceuticals, Bayer Pharmaceuticals and Gilead Research Laboratories.

limited due to a major supply crisis.[7,8] Isolation of taxol from its natural source was impractical since it gave low yields and led to ecological destruction of the limited distribution of *T. brevifolia* in old-growth forests (Pacific Northwest, USA).[7,8] Each tree yielded only about 2 kg of bark and approximately 10 kg of dried bark were required to obtain 1 g of taxol.[7,8] As a result, extensive research efforts were initiated to find alternative sources of taxol, which included semisynthesis,[16] cellular fermentation,[17] and chemical synthesis.[18] Fortunately for society, the large-scale demand for taxol was first satisfied by a renewable biochemical source of baccatin III, a semisynthetic precursor (found in needles of various *Taxus* species[19]), that could be translated to taxol in 7 chemical steps. This process has recently been supplanted by biological methods of production, where direct extraction from the Chinese yew tree (*Taxus chinensis* or *Taxus yunnanensis*) and plant cell-culture fermentation processes, provide industrial quantities of taxol without the need for synthetic intervention.[17,20]

1.4 Chemical Synthesis of Taxol

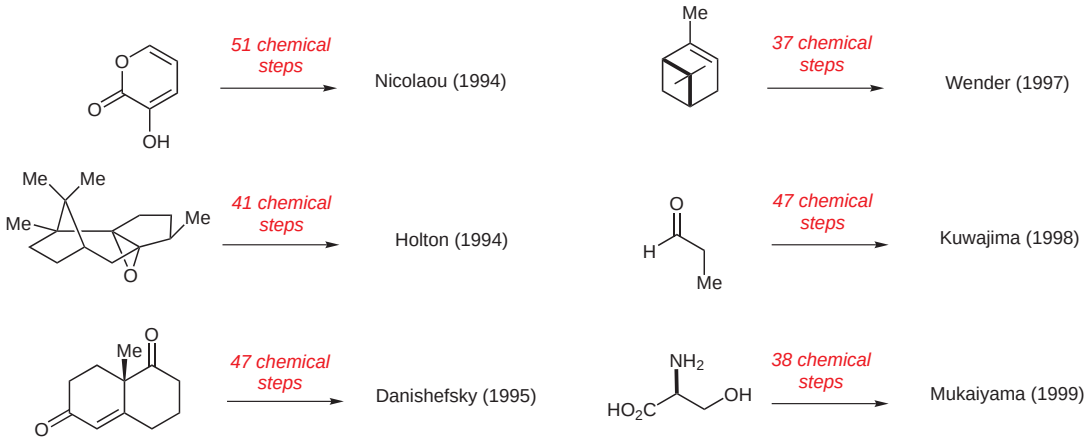
The molecular complexity of taxol has captivated synthetic chemists since the report of its structure elucidation in 1971.[18] Belonging to the diterpene class of natural products, taxol is distinguished by a highly oxygenated 6-8-6 tricyclic ring system with a distinctive ester side chain. Of the total 11 chiral centers present in taxol's molecular skeleton, the six-membered ring bearing a sensitive oxetane functional group contains five contiguous chiral centers. With the combination of the central eight-membered carbocycle and intricate arrangement of oxygen bearing stereocenters, taxol presents itself as one of the premier challenges to synthetic chemists and to the discipline of natural product synthesis.

Six independent total syntheses of taxol have been achieved.[18] The first two syntheses, published concurrently in 1994, were from the Nicolaou[5] and Holton[4] laboratories. Shortly after in 1995, the Danishefsky group reported their synthesis,[21] followed by the Wender group in 1997,[22] Kuwajima group in 1998,[23] and Mukaiyama group in 1999.[24] Scheme 1 shows the number of steps required to the natural product from the respective starting materials chosen by each group. To date, Wender's synthesis of taxol is the shortest and most efficient at 37 steps and 0.4% overall yield starting from verbenone.[22]

It is a true testament to the field of chemical synthesis and the perseverance, dedication and innovation of the researchers that undertook this Herculean endeavor, that taxol could be forged by total synthesis. Perhaps most importantly, the studies outlined above describe in several ways both the frontiers of chemical synthesis and the current limitations of the field. Indeed, it is remarkable to consider that a molecule of taxol's complexity might be furnished in as few as 37 chemical steps (a feat that likely would have been impossible only fifteen years earlier). Moreover, it might be argued that there are but only a handful of laboratories around the globe that have the resources, capacity, and synthetic ability to accomplish this goal. However, we must also concede that the most efficient synthesis that has been accomplished to date could not be employed to furnish quantities of taxol on a scale suitable to provide a global therapy (0.4% overall yield would be prohibitive with respect to cost of goods and manufacturing). Moreover, taxol is by no way unique in this regard. Indeed, to the best of our knowledge, the total number of natural isolate medicinal agents (across all therapeutic areas) that have been produced on large scale by total synthesis is ≤4,[25] a striking statistic that appears to strongly contradict the widespread notion of total synthesis being a 'mature field.' With this in mind, the question that is raised is why is chemical synthesis able to make complexity on a small scale but not a large scale? To begin to answer such a question we must consider two fundamental components of the practice of total synthesis, (a) the regime of scale that is traditionally employed, and (b) the global use of 'stop-and-go' synthesis as an operational strategy for complex target synthesis.

1.5 Regime of Scale

The exercise of total synthesis is typically performed within a highly specific regime of scale that spans the



Scheme 1 Chemical syntheses of taxol: the frontiers of 'stop-and-go' chemical synthesis

range of 10^3 to 10^{-4} grams. This realm of scale has evolved naturally as it borders the limits of laboratory operational convenience at the upper level and the limits of analytical detection on the lower end. Perhaps most important to this discussion, laboratory chemists generally traverse this entire molecular range in the pursuit of a complex target, a strategy that employs seven orders of scale to reach fruition (10^3 to 10^{-4}). Unfortunately, this latitude of scale cannot be afforded to chemists that operate at much higher batch quantities. For example, the bench chemist might think it reasonable to begin with a kilogram of starting material to generate a milligram of natural product, yet it would be inconceivable that a million tons of reagents be used to prepare 1 ton of taxol. Indeed, batch-scale chemists typically traverse less than three orders of scale in the production of multiton quantities of any given therapeutic agent. As such, we can appreciate that laboratory chemists' work within an extremely broad yet highly specific regime of scale that allows synthetic accomplishments that are often impossible outside of this operational range. Surprisingly, however, the field of total synthesis has not focused great attention on this issue of 'scale-specific utility' in the evaluation of natural-product strategies, a philosophical deficiency that should be addressed if we are to realize the true potential of chemical synthesis and its application to complex targets. Indeed, a valuable component in the evaluation of any natural product synthesis might be an assessment of the latitude of scale that is employed (≤ 3 orders of scale being considered optimal). Such an evaluation might standardize synthetic accomplishments against the capacity for large-scale application (a measure that in many ways reflects the potential of total synthesis to benefit society). Moreover, the establishment of such a calibration point would continue to push the field of total synthesis towards its ultimate objective: to continually improve the efficiency and selectivity with which we construct any given molecule (a.k.a. step-economy or the Wender principle).[26] With all of this in mind, a second fundamental question becomes why do bench chemists typically employ six to seven orders of scale in the production of complex natural products? One possible answer lies in the practice of 'stop-and-go' synthesis.

1.6 The Practice of 'Stop-and-Go' Synthesis

The chemical synthesis of taxol and similarly complex natural products can certainly be achieved on small scale. However, extending the traditional 'stop-and-go' approach for the chemical synthesis of these natural products typically cannot produce them on industrial scale. The taxol problem reflects this underlying limitation with the current practice of 'stop-and-go' synthesis. Laboratory chemical syntheses are designed on sequences of individual chemical transformations that are operated as stepwise processes. After each chemical transformation, the sequence is stopped for necessary purification and isolation prior to continuation of the chemical process. To enhance chemical efficiency, several such sequences are operated concurrently to construct equally complex fragments of the target molecule. Further chemical manipulation conjoins these fragments uniting the sequences and completing the total synthesis.

With this strategy, synthetic sequences on the order of 10 to 12 steps are manageable and can produce complexity on a large scale. However, when the number of steps required to synthesize the target molecule increases, chemical efficiency can easily be compromised exponentially at every operation. The compounding loss at each chemical step ultimately impacts the overall yield of the sequence and thus the isolated mass of the final product. This decrease in chemical efficiency can be paralleled to the exponential increase of rice grains placed on the chessboard in the old parable: 'second half of the chessboard'.[27] Here a single grain of rice is placed on the first square of the chessboard, two grains on the second, four grains on the third, eight on the fourth and so on – a doubling of rice grains across all 64 squares (Figure 2). The first half of the chessboard would have to hold a total of exactly $2^{32} - 1 = 4{,}294{,}967{,}295$ grains of rice, which corresponds to approximately 100,000 kg of rice. On the second half of the chessboard, approximately $2^{64} = 18{,}446{,}744{,}073{,}709{,}551{,}614$ grains of rice would be placed, which is about 460 billion tons, or 6 times the entire weight of the Earth's biomass.

In the realm of total synthesis this mathematical phenomenon affects chemical efficiency as an inverse relationship (Figure 3). Synthetic sequences routinely start with large

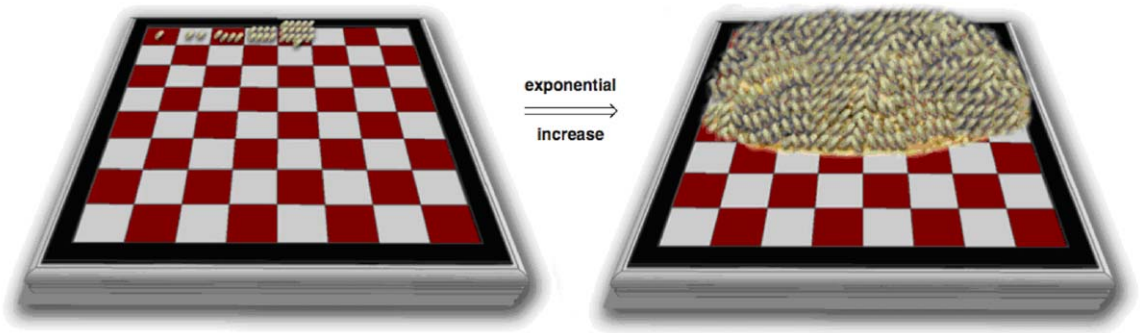


Figure 2

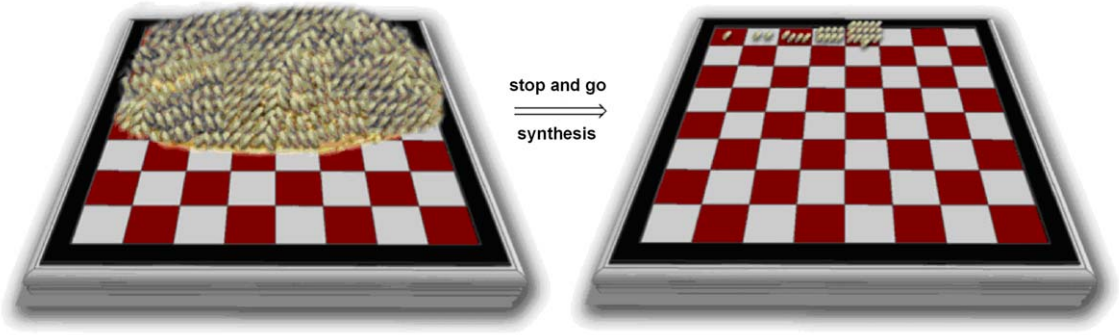


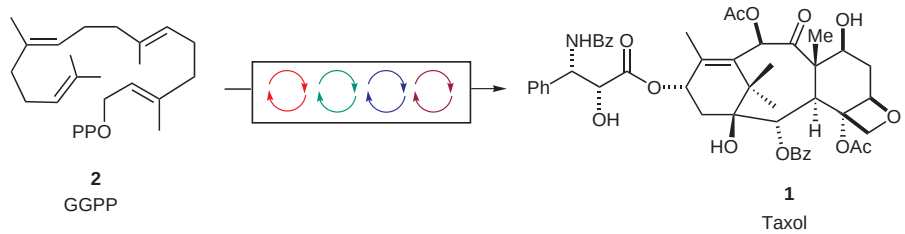
Figure 3

quantities of starting materials to end with a few precious milligrams of the final product. For example, if the longest linear sequence in a total synthesis requires 25 steps, with 25 purifications (a total of 50 operations) with an average of 80% efficiency being obtained for each operation, the sequence would have to start with approximately 1 kg of starting material to obtain 14 mg of the final product. This is indeed an accepted consequence of the current approach to laboratory chemical synthesis. However, if this effect were to be translated to meet taxol's yearly 1 ton pharmaceutical demand, it would require 71 thousand tons of starting material based on a 25-step synthesis and 1.7 million tons of starting material based on a 37-step synthesis, clearly an impractical approach for large-scale commercialization. With this simple arithmetical analysis in hand it is clear that the discovery of new chemical strategies that allow increasingly rapid access to molecular complexity is necessary for the discipline of total synthesis to be more broadly applied in the context of pharmaceutical production. In this light, it is intriguing to consider the 'synthetic strategy' that nature has evolved for the biochemical production of complex architectures.

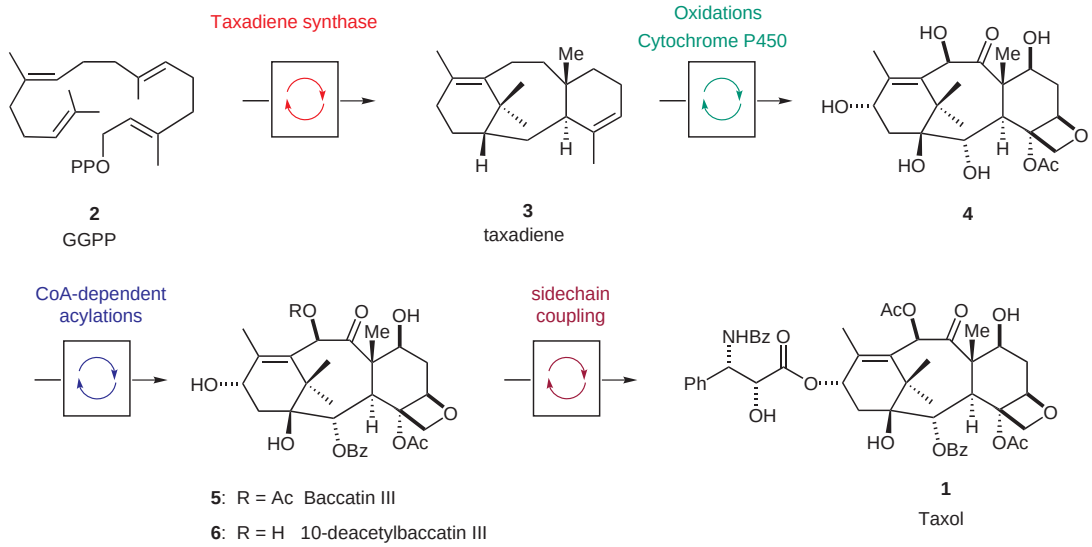
1.7 Nature's Approach to the Synthesis of Complexity

In contrast to laboratory synthesis, Nature does not use the practice of 'stop-and-go' synthesis for the production of complexity. Instead, Nature's biological systems construct complex molecules such as taxol using continuous processes driven by transform specific enzymes. These enzymatic transformations are combined in highly regulated catalytic cascades, which can easily convert simple raw materials into complex molecular systems, a sophisticated chemical pathway that in laboratory language we would term cascade catalysis.[28] For example, the biosynthesis of taxol uses a continuous series of 4 cascade sequences starting from the universal diterpene precursor geranylgeranyl diphosphate (GGPP, **2**, Scheme 2).[14a,29] The initiating sequence is catalyzed by taxadiene synthase and converts GGPP (**2**) to taxadiene (**3**, Scheme 3). This remarkable single sequence assembles the polycyclic taxane carbon skeleton with perfect stereochemical fidelity, and is entirely controlled by the conformational constraints of the substrate in the active catalytic site of the enzyme. The next cascade sequences involve chemoselective oxidations followed by acyl coenzyme A catalyzed esterifications en route to baccatin III (**5**, Scheme 3). Side-chain synthesis and coupling with **5** completes the biosynthesis of taxol (**1**).

This continuous catalysis approach ensures that high levels of chemoselectivity and chemical efficiency are achieved. Membrane-transport proteins and other transport systems precisely maintain the concentration of starting materials, reaction intermediates, and products within each sequence. Nature's reagents in the form of activating groups are preserved in situ, through recyclable energy and redox carriers (ATP, NADPH, etc.). Notably, one reason for the ultimate success of these biocatalytic 'assembly lines' is attributed to the capacity of the enzymes to coexist in the same reaction medium without any deleterious interactions.



Scheme 2 Enzymatic cascade catalysis applied in the biosynthesis of taxol



Scheme 3 Cascade sequences in the biosynthesis of taxol

2 Cascade Catalysis as a Key Strategy for Laboratory Complex Target Synthesis

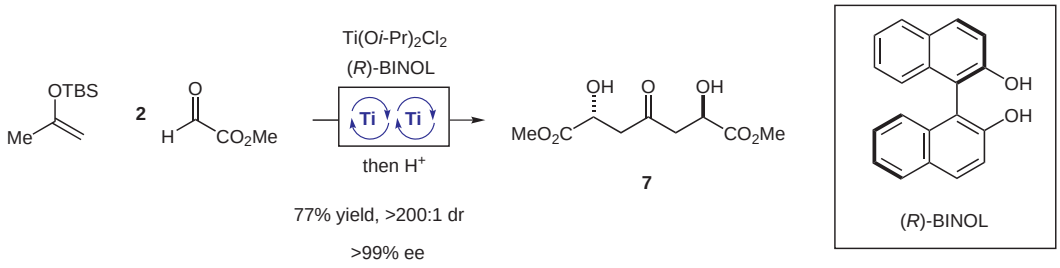
Nature's cascade-catalysis pathways represent a powerful strategy for the construction of intricate molecular architectures, without the inherent limitations of 'stop-and-go' synthesis.[30] As such, an interesting question becomes is it possible for laboratory synthesis to adopt the blueprints of biosynthesis and employ cascade catalysis to overcome many of the efficiency issues that plague natural product synthesis? It certainly appears logical that the successful execution of practical laboratory approaches to cascade catalysis should provide an alternative chemical strategy for increasingly rapid access to molecular complexity. In addition to benefits in efficiency, the combination of multiple enantioselective transformations in a predesigned cascade sequence provides the opportunity to transform simple achiral starting materials into essentially single enantiomer complex cascade products (≥99% ee) with multiple chiral centers (employing catalysts that do not provide 99% ee for each specific step). Furthermore, the discovery of chiral transform specific catalyst systems should allow complete control of the diastereo- and enantioselective outcome based on the choice of the enantiomeric series of the chiral catalyst. With this question in mind, it is important to recognize that a number of metal and organic catalyst based cascade protocols (asymmetric and nonasymmetric) have been developed in this last decade in the context of methodological studies. The capacity to translate these processes to the realm of natural product synthesis will constitute one of the first steps towards realizing the potential of cascade catalysis for the generation of complex molecules for society's consumption.

In the remainder of this article we provide a short review of the use of laboratory cascade catalysis for the construction of enantioenriched molecules involving multiple catalytic stereoinduction events (as is commonly found in biosynthetic processes).[31] For the sake of perspective we will compartmentalize this review section into three categories of increasing complexity: (i) Cascade catalysis with one catalyst and one iterative reaction type, (ii) cascade catalysis with one catalyst and multiple reaction types, and (iii) cascade catalysis with multiple catalysts and multiple reaction types (cycle specific catalysis).

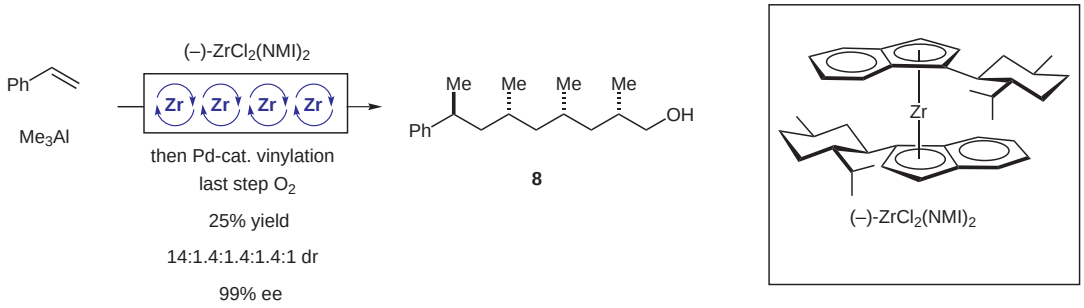
2.1 Iterative Cascade Catalysis

In 1997, Mikami and co-workers reported one of the earliest and most notable examples of enantioselective cascade catalysis, which demonstrated the concept of chiral amplification.[32] They designed a double Mukaiyama aldol cascade sequence using the binaphthol-based titanium complex (BINOL-Ti)[33] as catalyst. Addition of the acetone-derived silyl enol ether to two equivalents of methyl glyoxylate gave the cascade product **7** essentially as a single isomer (>99% de, >99% ee) in 77% yield (Scheme 4). This methodology was successfully used to access analogues of L-700,417, a potent HIV protease inhibitor.[32]

Recently in 2005, Negishi and co-workers successfully combined their previously developed Zr-catalyzed asymmetric carboalumination of olefins (ZACA reaction)[34] with a Pd-catalyzed vinylation of the intermediate isoalkylalanes. This reaction sequence generates a new olefin, which is subjected to a second ZACA reaction. The methodology was showcased in the preparation of the polypropionate subunit of borrelidin, using styrene as the bulk starting material.[35] The cascade sequence of four ZACA/three Pd-catalyzed vinylation reactions was terminated by oxidation with O_2 and formed alcohol **8** in 25% yield with excellent control of diastereoselectivity and enantioselectivity (99% ee, Scheme 5).[35]



Scheme 4 Enantioselective titanium-catalyzed iterative Mukaiyama aldol reaction



Scheme 5 Zirconium-catalyzed asymmetric carboalumination

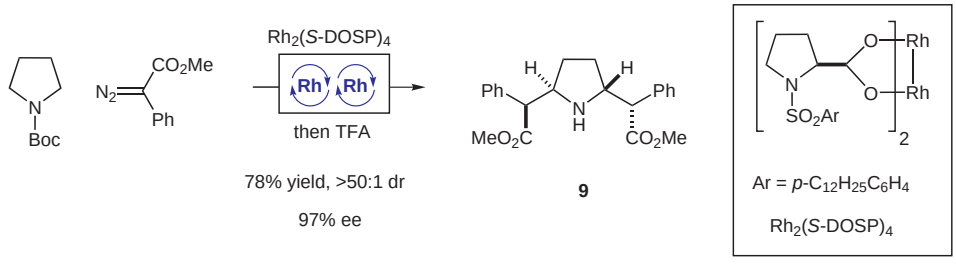
Research efforts within the realms of metal-catalyzed carbenoid chemistry have provided several powerful, stereoselective C–C bond-forming transformations for organic synthesis.[36] Namely, the direct enantioselective C–H activation chemistry of rhodium carbenoids represents a practical catalytic asymmetric method for selective C–H functionalization.[37] In 1999, Davies and co-workers reported a double C–H activation cascade sequence where *N*-Boc pyrrolidine was functionalized using 2 equivalents the of Rh_2(*S*-DOSP)$_4$-derived carbenoid from methyl phenyldiazoacetate. This reaction forms the C_2-symmetric bisfunctionalized pyrrolidine **9** in 78% yield, as a single diastereomer in 97% ee (Scheme 6). Related double C–H functionalization reactions of *N*,*N*-dimethylanilines and dihydronaphthalenes using the Rh_2(*S*-DOSP)$_4$ catalyst system have also been reported.[38]

Gillingham and Hoveyda have reported one of the most recent examples of metal-cascade catalysis and its applications to natural product synthesis.[39] For the synthesis of the symmetrical diketone fragment of (+)-baconipyrone C, they devised a double asymmetric allylic alkylation cascade sequence catalyzed by a Ag–Cu-based N-heterocyclic carbene complex. The bisallylic phosphate starting material undergoes two sequential Cu-catalyzed asymmetric conjugate additions with Me_3Al and forms the symmetric triene product essentially as a single isomer (>98% de, >98% ee) in 61% yield (Scheme 7).

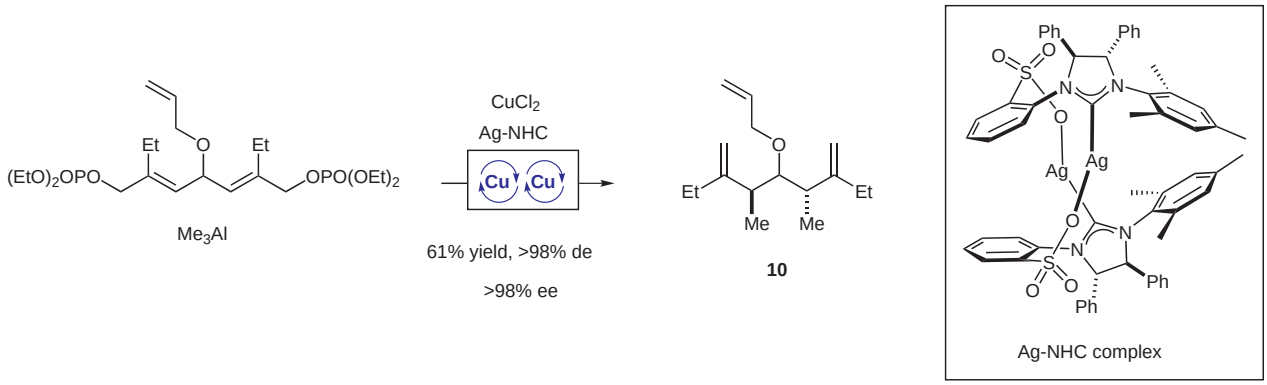
Lastly, in 1999, our group introduced an imidazolidinone-based chiral amine as an enantioselective LUMO-lowering catalyst, and demonstrated its applicability for a broad range of synthetic transformations that previously required Lewis acid catalysts.[40] In 2001, we reported the first enantioselective organocatalytic Friedel–Crafts alkylation and illustrated its utility in the bisalkylation of *N*-methylpyrrole with either the same or two discrete α,β-unsaturated aldehydes (Scheme 8).[41] This cascade sequence forms the 2,5-disubstituted pyrroles **11** and **12** with excellent enantioselectivities (≥98% ee) and in 83–72% yield.

2.2 Cascade Catalysis Based on Multiple Reaction Types

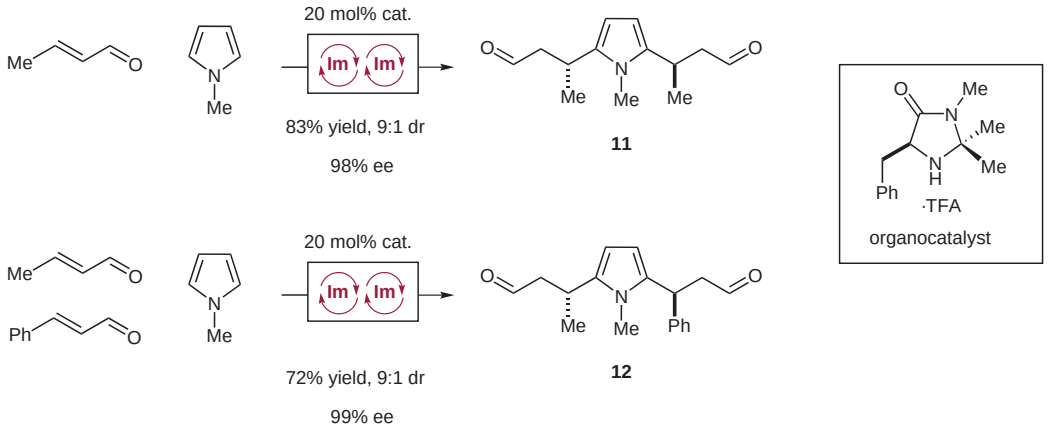
Studies on the aldol-Tishchenko reaction by Nord and coworkers in the 1940's represent one of the early examples of a cascade protocol with a single catalyst and multiple reaction types.[42] Almost 60 years later, Morken and co-



Scheme 6 Enantioselective rhodium-catalyzed C–H functionalization



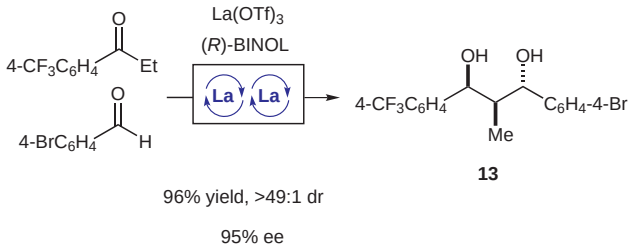
Scheme 7 Copper-catalyzed asymmetric allylic alkylation



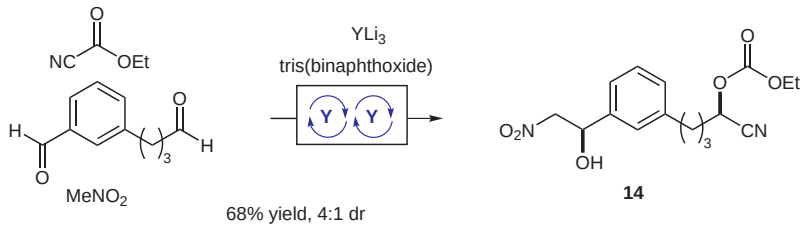
Scheme 8 Enantioselective organocatalyzed Friedel–Crafts alkylation

workers reported the first example of a catalytic asymmetric aldol-Tishchenko reaction using a yttrium–salen catalyst system.[43] More recently, Shibasaki and coworkers have developed a highly stereoselective aldol-Tishchenko procedure using the lanthanide–BINOL catalyst system,[44] previously effective in their seminal studies on the direct asymmetric aldol reaction.[45] Although the substrate scope was limited to electron-deficient aryl ethyl ketones and aryl/heteroaryl aldehydes, excellent levels of diastereoselectivity and enantioselectivity were observed for the isolated diols (of type **13**, Equation 1). Another notable example of a stereoselective cascade sequence from the Shibasaki laboratories was the incorporation of their enantioselective cyanation and nitroaldol methodologies into a cascade sequence (Equation 2).[46] The process was optimized using a YLi_3[tris(binaphthoxide)] (YLB) catalyst which only provided modest diastereocontrol. Addition of catalytic amounts of $LiBF_4$ was necessary for maintaining structural integrity of the chiral catalyst and allowed high enantioselectivities for the overall sequence.

Metal-mediated conjugate addition of nucleophiles to electron-deficient π-systems has long been established as a powerful strategy for C–C bond formation.[47] Recent advances in copper- and rhodium-based chiral catalysts have provided highly enantioselective reactions with broad substrate scope.[47d,e] Based on this strategy, Krische and co-workers have developed intramolecular cascade sequences initiated by an asymmetric Rh–BINAP-catalyzed conjugate addition followed by an aldol cyclization event.[48] This methodology was very successful in the construction of five- and six-membered rings with up to three contiguous stereocenters in excellent diastereo- and enantioselectivity (Equation 3).[48a] The cascade protocol has also been extended to a spectacular desymmetrization sequence where now the formation of up to four contiguous stereocenters can be controlled (Equation 4).[48b]



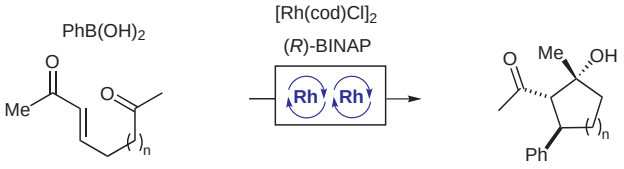
Equation 1



68% yield, 4:1 dr

98% ee

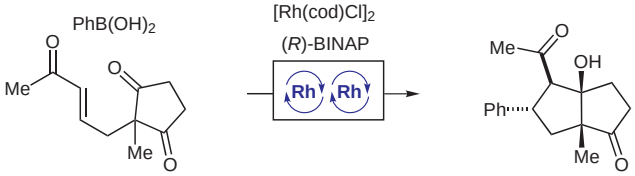
Equation 2



88–69% yield, >99% de

94–95% ee

Equation 3



88% yield, >99% de

90% ee

Equation 4

In February of 2004, and in several subsequent lectures, we presented the successful accomplishment of a new practical laboratory approach to cascade catalysis.[49] Based on the possibility that our previously developed secondary amine catalysts[40] could co-exist in the same reaction medium without deleterious interactions, we questioned whether the conceptual blueprints of biosynthesis might be translated to a laboratory 'cascade-catalysis' sequence using organocatalysis. Based on this bioinspired catalysis platform, we were able to merge orthogonal modes of substrate activation, namely LUMO-lowering iminium activation and HOMO-raising enamine activation, where a single imidazolidinone catalyst could enable both activation cycles. We also envisioned that the iminium and enamine steps might be discretely controlled by cycle-specific catalysts. Within this mechanistic scenario, modular control of enantio- and diastereoinduction (e.g. *R* vs. *S*, *syn* vs. *anti*), could be achieved via the judicious selection of the amine enantiomer involved in each catalytic cycle.

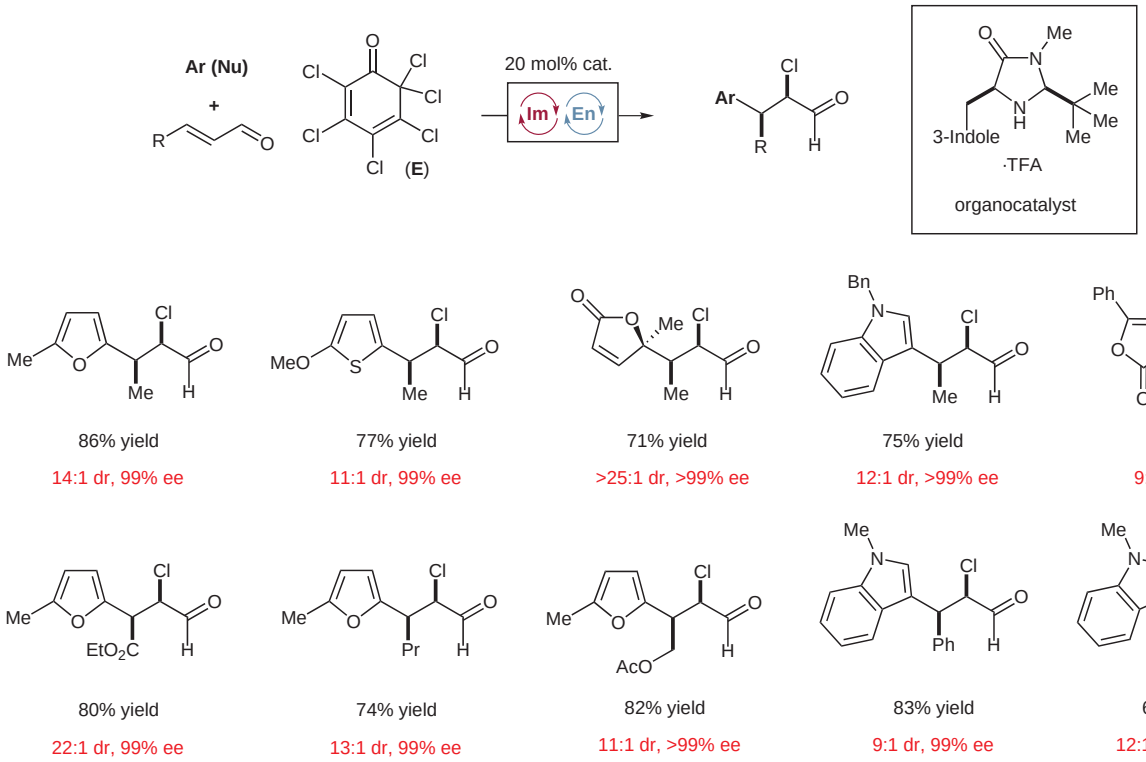
Starting from simple α,β-unsaturated aldehydes (R = Me, CO_2Et, *i*-Pr, CH_2OAc, Ph), a diverse range of nucleophiles (furans, thiophenes, indoles, siloxyfurans, siloxyoxazoles) were shown to participate in the conjugate addition–chlorination cascade sequence to provide the cascade products with spectacular levels of diastereoselectivity and enantioselectivity (Scheme 9). A remarkable benefit of combining multiple asymmetric catalytic events into one sequence is the mathematical requirement for enantioenrichment in the second cycle, as was demonstrated by the enantioselectivities obtained throughout this study (≥99% ee in all cases). For example, if two catalytic cycles, each 86% ee selective, were combined, the resulting cascade would furnish a 7:1 mixture of diastereomers, with the major diastereomer being formed in 99% ee.

In 2005, Jørgensen and co-workers reported a similar organo-cascade protocol using the proline-derived organocatalyst to accomplish the first enantioselective thiol-addition–amination reaction.[50] The organo-cascade reaction provides thio/hydrazine-substituted aldehydes with high diastereoselectivity and exquisite level of enantioselectivity (≥ 99% ee, Scheme 10). After the cascade sequence the product aldehydes were cyclized to provide functionalized oxazolidinones (of type **17**).

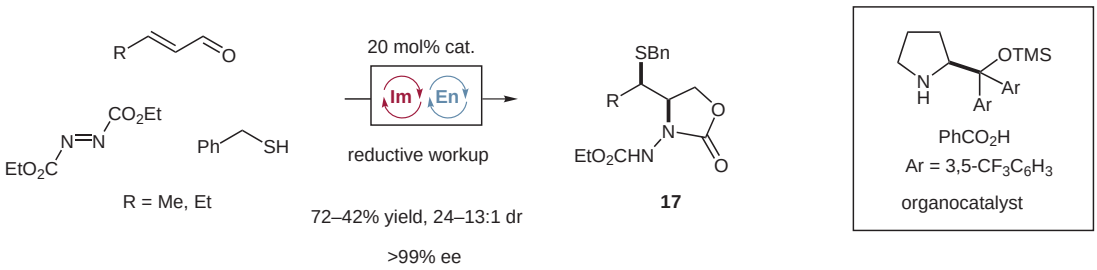
Later in 2006, Enders and co-workers reported a spectacular example of an enantioselective triple organo-cascade sequence.[51] The design of this cascade reaction involved the use of a single catalyst system and was initiated by an enamine-catalyzed Michael addition, followed by an iminium-catalyzed conjugate-addition step, and finally an intramolecular enamine-catalyzed aldolization–cyclization event which terminated the sequence. The intermediates from this cascade reaction underwent elimination forming cyclohexene aldehydes as the products with high diastereoselectivity, exquisite levels of enantioselectivity (≥ 99% ee) and reasonable synthetic yield (Scheme 11).

2.3 Cycle-Specific Cascade Catalysis

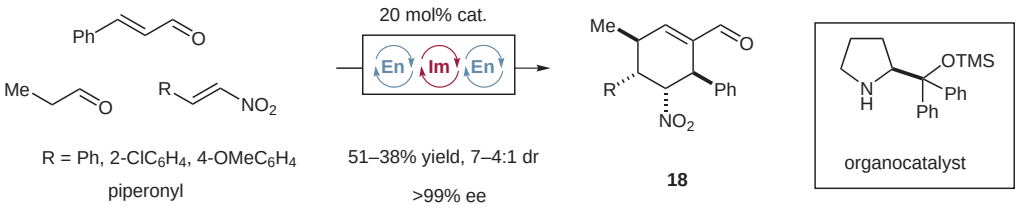
Our new organo-cascade catalysis strategy has allowed the invention of enantioselective transformations that, to our knowledge, have no precedent in asymmetric synthesis. We have shown that our transfer-hydrogenation process[52] using Hantzsch esters in conjunction with our direct α-fluorination methodology[53] effectively adds the elements of HF across a trisubstituted olefin (Scheme 12). We devised this cascade sequence with cycle-specific amine catalysts, which can easily be modulated to provide a required diastereo- and enantioselective outcome via the judicious choice of the enantiomeric series of the amine



Scheme 9 Enantioselective organo-cascade catalysis



Scheme 10 Enantioselective organo-cascade thiol addition–amination

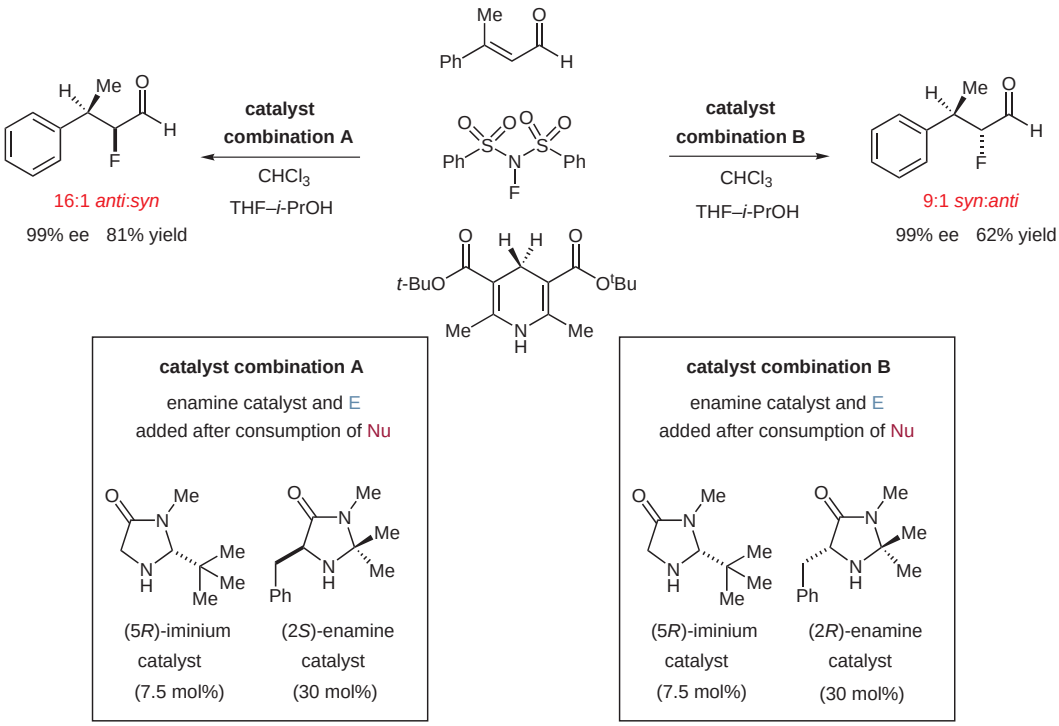


Scheme 11 Enantioselective triple organo-cascade catalysis

catalysts. Using catalyst combination A, with the 2*S*-enamine catalyst, we access the *anti*-diastereomer in 16:1 dr and 99%ee. Catalyst combination B provides direct entry to *syn*-diastereomer in 9:1 dr maintaining 99% ee. We believe this type of cycle-specific cascade catalysis will be of great benefit to practitioners of syntheses that require rapid access to structural diversity while maintaining predictable control of stereoselectivity.

3 Summary

The taxol problem, as we have introduced it, describes the operational deficiencies of the traditional ‘stop-and-go’ approach to total synthesis. For natural products with taxol’s molecular complexity and medicinal importance, this approach clearly does not provide a practical solution for large-scale production. Inspired by Nature’s synthetic proficiency, the development of laboratory approaches to



Scheme 12 Enantioselective cycle-specific organo-cascade catalysis

cascade catalysis has been identified as a new paradigm for target-oriented synthesis. The sequencing of multiple catalytic transformations performed on a given substrate provides a powerful chemical strategy for the rapid construction of molecular complexity with exquisite levels of enantiocontrol. Based on this concept, several enantioselective metal-cascade catalysis sequences, using single-metal- and multiple-metal-catalyzed transformations, have been validated and elegantly applied to natural product synthesis. Recently, our group introduced an enantioselective organocatalytic approach to cascade catalysis, using simple imidazolidinone catalysts that participate in orthogonal substrate-activation modes. Most notably, our work has inspired the development of other enantioselective cascade sequences, including a remarkable triple organocatalytic cascade sequence,[51] and this research area has also been recently reviewed.[54] Future directions will focus on the design of cascade sequences based on new modes of substrate activation, directly applicable to natural products synthesis and the discovery of synthetic transforms previously unknown within the realms of asymmetric catalysis.

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