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Digest Paper

Total synthesis of natural and pharmaceutical products powered by organocatalytic reactions

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ABSTRACT

Organocatalysis has emerged as the third pillar of modern asymmetric catalysis in the past two decades. Applying organocatalytic reactions in total synthesis is currently a highly dynamic research area. This Digest focuses on selected recent examples of total synthesis of natural and pharmaceutical products enabled by organocatalytic reactions, highlighting the importance of organocatalytic reactions in fostering structures of biological importance.

Contents

Introduction

Natural products play pivotal roles in drug discovery. Approximately two thirds of all small-molecule drugs approved during 1981–2010 have their origins in natural products.[1] In the process of drug discovery, organic synthesis provides the most transformative power that can build natural or designed molecules of interest. The art and science of organic synthesis have evolved tremendously since its inception.[2] 'Can we synthesize the molecule?' is no longer the question. Nowadays, armed with the strategies and methodologies developed over the past decades, synthetic chemists have been endowed with the capability to

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conquer almost any known natural product if given sufficient resources, efforts, and time. The ideal synthesis is gaining increasing attention from synthetic chemists to confront the demand from interdisciplinary scientific community as well as industry to produce sufficient amount of desired compounds in sustainable ways.[3]

Organocatalysis has emerged as the third pillar of modern asymmetric catalysis, along with metal catalysis and biocatalysis.[4] Organocatalytic reactions usually feature mild reaction conditions, adequate functional group tolerance, insensitivity toward air and moisture, as well as their diverse catalytic mechanisms.[5] The metal-free nature of organocatalytic reactions meets the demands of green chemistry. The ability of organocatalysis to effect cascade reactions and one-pot tandem transformations is of particular importance and has attracted significant attention from the chemical synthesis community. To combine organocatalysis with metal catalysis is a highly dynamic arena. These efforts have culminated in a number of elegant total syntheses of natural products with biological significance. A number of elegant reviews have appeared highlighting respective topics in this research area.[6] This Digest focuses on selected recent examples of total synthesis of natural and pharmaceutical products enabled by organocatalytic reactions. These examples are grouped in terms of the mechanisms of the organocatalytic reactions applied in the total syntheses, including general base catalysis,[5a] enamine catalysis,[5b] iminium catalysis,[5c] and Brønsted acid catalysis.[5d]

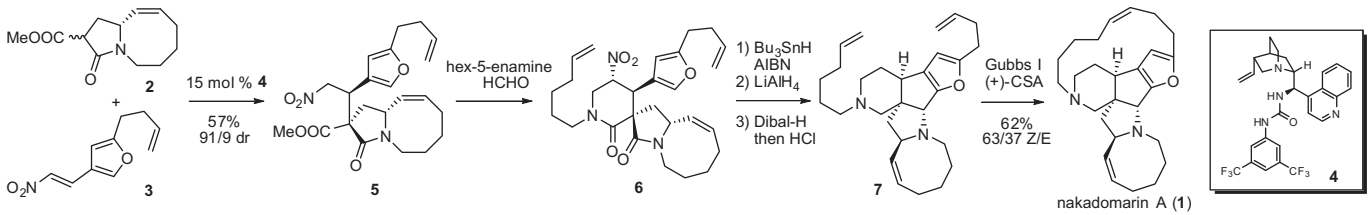
Total syntheses enabled by general base catalysis

Dixon's synthesis of nakadomarin A[7]

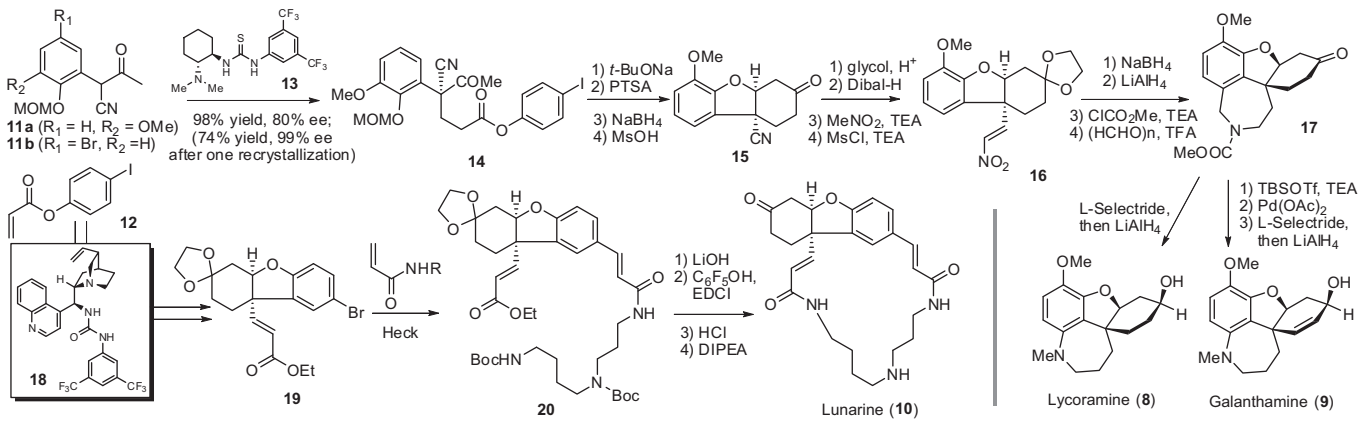
Construction of an all-carbon quaternary center usually constitutes a significant challenge in total synthesis, especially when the quaternary stereogenic carbon is surrounded by ring systems. This is the case in the total synthesis of nakadomarin A (**1**). Nakadomarin A was isolated by Kobayashi and co-workers in 1997 from a sponge collected off the coast of the Kerama Islands, Okinawa, and exhibits significant bioactivities. This molecule contains a synthetically challenging 8/5/5/5/15/6 hexacyclic ring system containing a quaternary carbon. Prior to Dixon's synthesis, the average step count of the three total syntheses of nakadomarin A reached 34. In 2009, Dixon's total synthesis reshaped the landscape. Pivoting on an organocatalytic diastereoselective Michael addition reaction, Dixon and co-workers amazingly telescoped the total synthesis of nakadomarin A into less than fifteen steps (longest linear sequence) (Scheme 1). The Michael reaction between **2** and **3** under the action of 15 mol % of **4** delivered a 91/9 diastereomeric mixture favoring the desired **5** in 57% yield. When LHMDS or KHMDS was employed in the place of the catalyst **4** to promote this reaction, a diastereoselectivity of 1.5/1 was observed. Notably, the configuration of the nascent quaternary carbon was dictated by the strong facial bias of the enolate of the 5/8 bicyclic framework. It was through the hydrogen bonding interactions between the thiourea catalyst **4** and the nitroalkene **3** that the stereochemistry of the newly generated tertiary carbon was effectively controlled. The subsequent nitro-Mannich/lactamization cascade formed the piperidone ring of **6**. Selective reductions transformed **6** to aminol which underwent furan/iminium cyclization to pentacyclic **7**. The camphorsulfonic acid-assisted Z-selective RCM reaction annulated the 16-membered macrocycle and finalized the total synthesis. This synthesis formed the basis of Dixon's second generation route for nakadomarin A, where the geometric selectivity issue in the formation of the macrocycle was addressed by virtue of alkyne metathesis.[8]

Fan's synthesis of lycoramine, galanthamine, and lunarine[9]

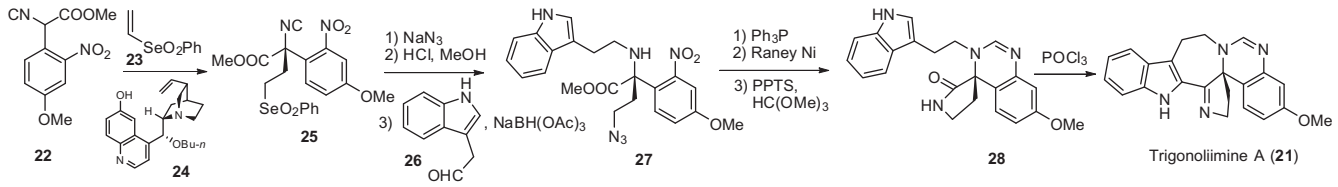
Lycoramine (**8**), galanthamine (**9**) and lunarine (**10**) are hydrodibenzofuran alkaloids with biological significance. In particular, galanthamine possesses acetylcholinesterase inhibitive activity, and is clinically used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments. In 2011, Fan and co-workers reported the collective total synthesis of these three molecules (Scheme 2). The stereochemistry-defining step is the asymmetric Michael addition reaction of **11** and **12**



Scheme 1. Dixon's synthesis of nakadomarin A (**1**).



Scheme 2. Fan's syntheses of lycoramine (**8**), galanthamine (**9**), and lunarine (**10**).



Scheme 3. Zhu's synthesis of trigonoliimine A (**21**).

catalyzed by thiourea **13**. This reaction with **11a** resulted in a nearly quantitative yield of **14** with good enantioselectivity which could be further enhanced to 99% ee after one recrystallization. Compound **14** was converted to **15** by intramolecular condensation and conjugate addition. The nitrile was reduced to aldehyde and condensed with nitromethane to give **16**. By a sequence involving reduction, N-protection and Pictet–Spengler cyclization, nitroalkene **16** was elaborated into the tetracyclic intermediate **17**, which could be readily advanced into lycoramine (**8**) and galanthamine (**9**), respectively, via conventional transformations. In the synthesis of lunarine (**10**), **11b** and **12** was converted to **19** via a similar sequence as for the synthesis of **16**, except that the catalyst **18** was employed in the starting Michael addition reaction and HWE olefination was used to generate the unsaturated ester. A Heck coupling reaction between **19** and acrylamide gave **20**, from which lunarine (**10**) was readily generated.

Zhu's synthesis of trigonoliimine A[10]

Cinchona-alkaloid-based catalysts represent a group of privileged organocatalysts for promoting conjugate addition reactions, including those generating quaternary carbons. These are powerful bifunctional catalysts; usually the quinuclidine moiety in the catalyst activates the nucleophile, while the functional group OH or thiourea at C6′ or C9 activates the electrophile, both via hydrogen bonding interactions. Recently, Zhu and co-workers developed a cinchona alkaloid-catalyzed Michael addition reaction. In this reaction, various α-aryl-α-isocyanoacetates add to vinyl phenylselenone under the action of 6′-OH cinchona alkaloids, providing synthetically useful isocyano-bonding quaternary carbons in good yields and enantioselectivity. By virtue of this new methodology, they nicely demonstrated the total synthesis of trigonoliimine A (**21**) (Scheme 3). The Michael addition reaction of **22** and **23** catalyzed by **24** delivered **25** in 62% yield and 87% ee. This compound was converted to **27** by a sequence involving nucleophilic displacement of the phenylselenone by sodium azide, acidic hydrolysis of the isocyano group, and reductive amination of the resultant amine with aldehyde **26**. The azide and the nitro groups in **27** were successively reduced before being transformed to the aza-spiro compound **28**, which was eventually exposed to $POCl_3$ to effect the Bischler–Napieralski reaction to furnish trigonoliimine A (**21**).

Total syntheses powered by enamine catalysis

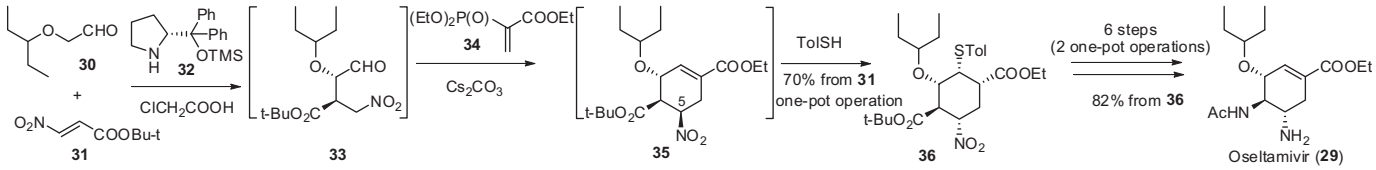
Hayashi's and Ma's syntheses of oseltamivir[11,12]

Influenza strikes the world in seasonal epidemics, leading to hundreds of thousands of annual deaths. The influenza viruses have glycoproteins on their surfaces that bind to sialic acids found on the surface of human erythrocytes and on the cell membranes of the upper respiratory tract. Widely used anti-influenza drugs are sialic acid analogs that inhibit the viral enzyme neuraminidase, thereby interfering with the proliferation of viruses. Oseltamivir (**29**) is the first orally active neuraminidase inhibitor commercially developed for the fight against both influenza A and influenza B viruses. Efficient synthesis of this molecule containing three contiguous stereocenters in short steps with a good overall yield is highly desirable, and challenging. In 2009, Hayashi and co-workers achieved this goal by realizing the synthesis of oseltamivir in three one-pot operations with an amazingly high overall yield (Scheme 4).[11] This efficient synthesis relied heavily on the Michael addition reaction of **30** and **31** catalyzed by 5 mol % of **32**-$ClCH_2COOH$ via an enamine mechanism, which generated the multi-functional **33** in quantitative yield with 96% ee. The subsequent domino reaction of **33** with vinylphosphonate **34** delivered cyclohexenecarboxylate **35** with an undesired configuration at C5. *p*-Toluenethiol was then employed to give the conjugate addition product **36** with the C5 configuration rectified. These three steps were integrated into the one-pot operation which supplied **36** in 70% overall yield. After another two well executed one-pot operations, the total synthesis of oseltamivir was eventually accomplished with 57% overall yield from nitroolefin **31**.

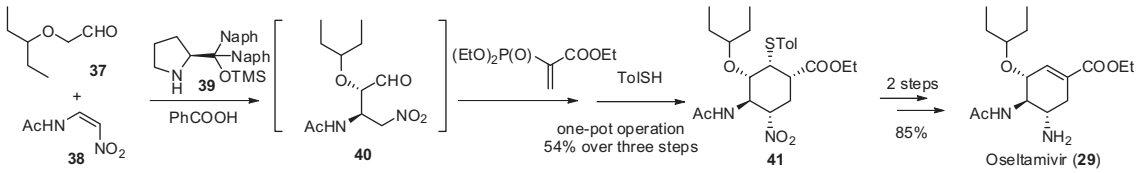
In 2010, Ma and co-workers demonstrated their total synthesis of oseltamivir based on a similar strategy (Scheme 5).[12] Notably, Ma and co-workers introduced nitroenamides as useful Michael acceptors. By applying **38** in their total synthesis of oseltamivir, they significantly improved the step economy of the synthetic route. Their efforts have laid the basis for development of a practical industrial process for the production of oseltamivir.

Ma's synthesis of zanamivir, laninamivir, and CS-8958[13]

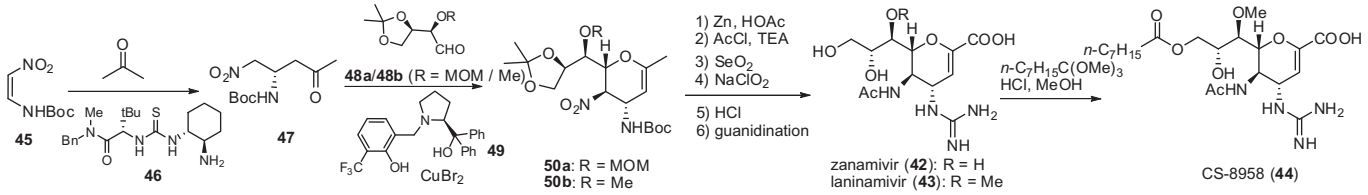
Recently, Ma's group reported the total synthesis of three relevant neuraminidase inhibitors, zanamivir (**42**), laninamivir (**43**), and CS-8958 (**44**) (Scheme 6). This organocatalytic and scalable synthesis relied on a Michael addition reaction involving nitroenamide **45**. With 5 mol % of thiourea **46**, the Michael addition of acetone to nitroenamide **45** proceeded smoothly, providing **47** in 72% yield and 98% ee after recrystallization. The subsequent *anti*-selective Henry reaction of **47** with **48** was realized with $CuBr_2$ in the presence of ligand **49**. Products **50a** and **50b** were then elaborated into zanamivir (**42**) and laninamivir (**43**), respectively, through the same sequence involving functional group transformations. CS-8958 (**44**) was obtained by esterification of **43**.



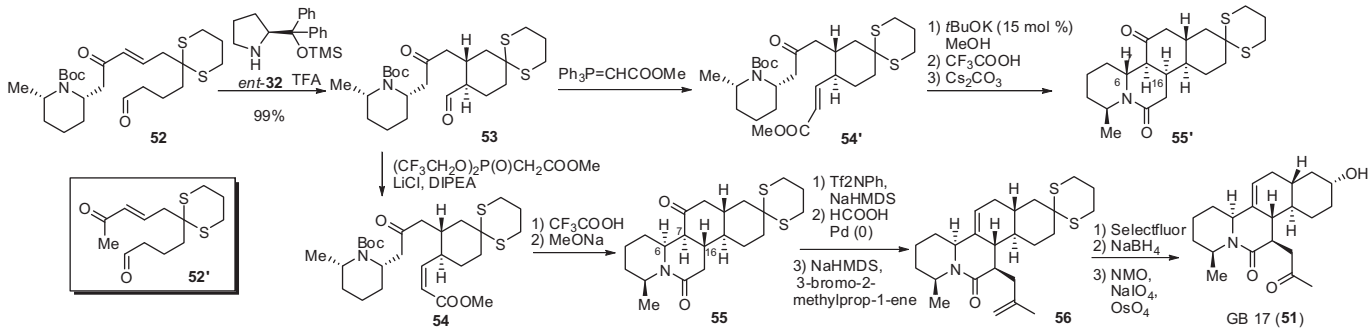
Scheme 4. Hayashi's synthesis of oseltamivir (**29**).



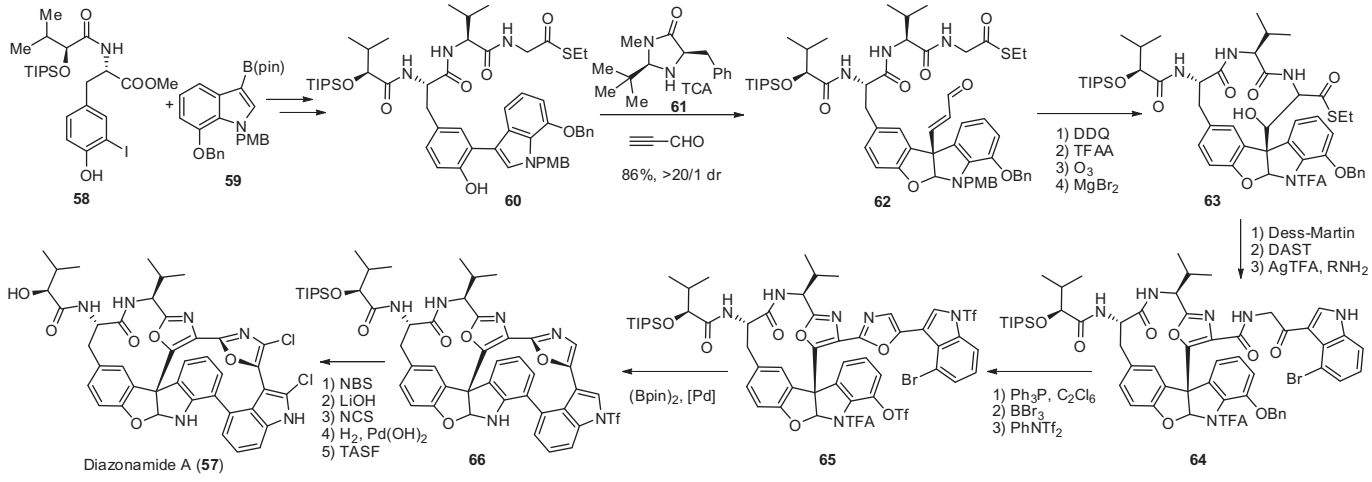
Scheme 5. Ma's synthesis of oseltamivir (**29**).



Scheme 6. Ma's syntheses of zanamivir (**42**), laninamivir (**43**), and CS-8958 (**44**).



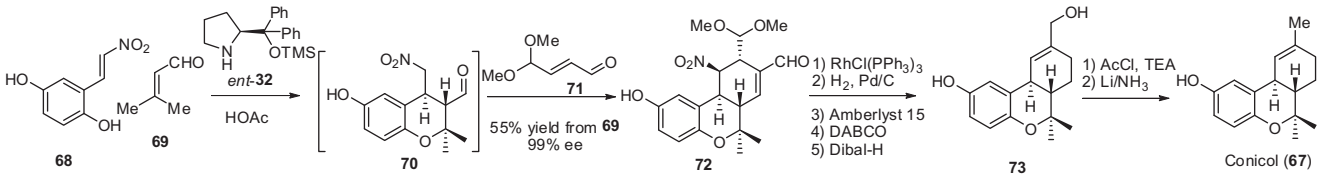
Scheme 7. Thomson's synthesis of GB17 (**51**).



Scheme 8. MacMillan's synthesis of diazonamide A (**57**).

Thomson's synthesis of GB 17[14]

Organocatalytic intramolecular Michael addition reactions can be powerful tools for construction of cyclic compounds with two contiguous stereogenic centers. Thomson and co-workers demonstrated this strategy in their total synthesis of GB 17 (**51**) (Scheme 7). In the presence of 5 mol % *ent*-**32**-TFA, **52** underwent an annulating Michael addition reaction, affording **53** in a nearly quantitative yield. This highly effective stereocontrol was exerted by the catalyst, not the substrate, as evidenced by the similar result obtained with **52′**. Through the intramolecular Michael addition reaction of (*Z*)-olefin **54**, compound **53** could be elaborated into **55** and 7-*epi*-**55** as a 1/1 mixture diastereomeric at C7. The geometry of the olefin played a critical role in determining the stereochemistry of the addition product; with the (*E*)-olefin **54′** as the substrate, the Michael addition proceeded with the undesired sense of stereochemistry at C16 and the C6 stereocenter epimerized under the conditions, leading to formation of **55′**. 7-*epi*-**55** could be equilibrated upon exposure to base to give a 3/2 mixture



Scheme 9. Hong's synthesis of conical (**67**).

of **55** and 7-*epi*-**55** and recycled. Compound **55** was transformed to **56** by conversion of the carbonyl to the olefin and the subsequent allylation, before being further advanced into GB 17 (**51**).

Total syntheses powered by iminium catalysis

MacMillan's synthesis of diazonamide A[15]

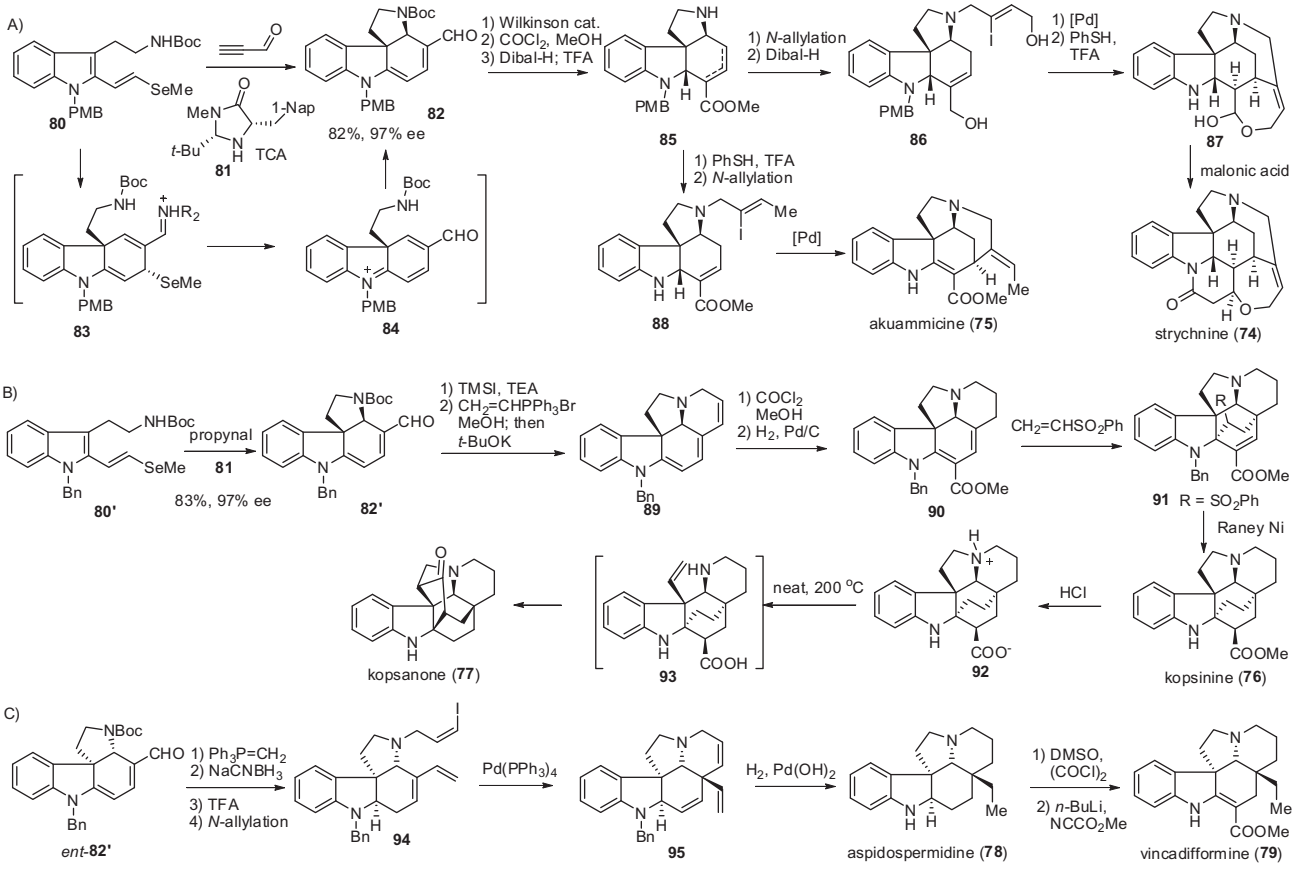
Diazonamides are a structurally unique family of marine natural products isolated by Fenical and co-workers. Among these, diazonamide A (**57**) was identified to be a potent antimitotic agent, exhibiting cytotoxicity toward a variety of human cancer cell lines through interaction with ornithine δ-amino-transferase, a mitochondrial matrix protein. Total synthesis of this molecule has been intensely explored in the past two decades, with the original structure being corrected by Harren and co-workers through synthetic studies. One of the major synthetic challenges lies in the construction of the C10 quaternary carbon. In 2011, MacMillan's group contributed the total synthesis of **57** covering twenty steps from commercial materials (Scheme 8). Thus, segments **58** and **59** were assembled via Suzuki coupling and further converted to **60**. Under the action of **61**-TCA, the Michael addition reaction of **60** and propynal went on efficiently, providing **62** with a diastereoselectivity of over 20/1. This reaction established the C10 quaternary center and the complete benzofuranoindoline core. Notably, when *rac*-**61** was tested for this reaction, 1/1 dr was resulted, indicating the formation of the C10 stereocenter was dominated by the catalyst. Compound **62** was subjected to protecting group manipulations, oxidative cleavage, and macrocyclization by intramolecular aldol reaction, furnishing **63**, which was further advanced into **64** via oxidative aromatization and Ag^+ promoted amidation. Formation of the second oxazole ring followed by debenzylation and triflation generated **65**, which was subjected to a tandem borylation/annulation to yield **66**. After initial bromination of the activated indoline *E*-ring and hydrolysis of the indolyl triflate, a sequence involving chlorination/debromination/desilylation was then carried out to furnish diazonamide A (**57**). This synthesis elegantly blended organocatalysis and transition-metal catalysis to attain unprecedented synthetic efficiency.

Hong's synthesis of conicol[16]

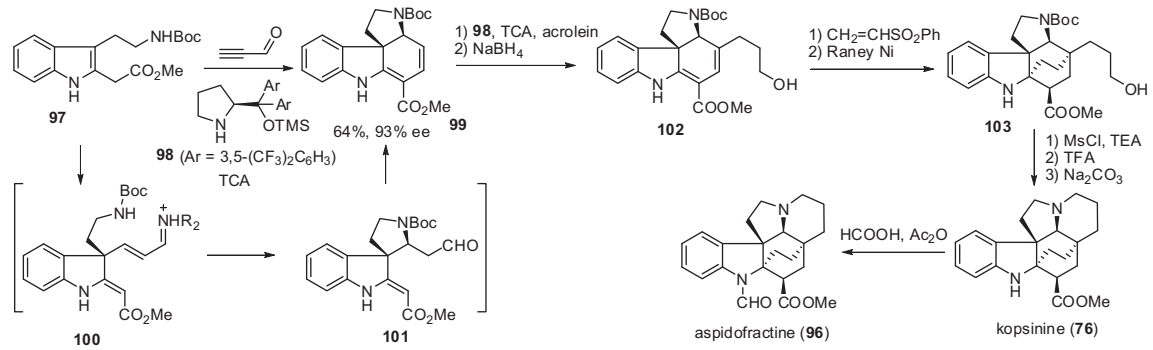
In the past century, total synthesis has been playing an indispensible role in determining the structure of natural products. In 2010, Hong and co-workers accomplished the catalytic enantioselective total synthesis of conicol (**67**) and settled the stereochemical issue of this molecule (Scheme 9). Hong's approach to this molecule features a domino oxa-Michael–Michael–Michael-aldol reaction sequence. By employing *ent*-**32**-AcOH as the catalyst, the first stage of this one-pot sequence involved the oxa-Michael addition of **68** and **69** and the ensuing intramolecular Michael addition, furnishing compound **70**. In the second stage, enal **71** was introduced and the Michael-aldol cascade reaction proceeded to give tricyclic **72**. This one-pot sequence delivered **72** in 55% overall yield with 99% ee. The stereochemistry of this tandem reaction was established unambiguously through X-ray crystallographic analysis of relevant products, thus certifying the stereochemistry of the target molecule. By trimming off the undesired functionalities, compound **72** was transformed to **73**, which was further subjected to acylation and deacetoxylation to give (+)-conicol (**67**). This asymmetric total synthesis determined the absolute configuration of (+)-conicol, which had previously been a mystery due to the lack of an efficient analytical method.

MacMillan's synthesis of strychnine, akuammicine, kopsinine, kopsanone, aspidospermidine, and vincadifformine[17]

In nature, simple building blocks could be assembled rapidly to form highly complex and diverse molecular architectures via enzyme-catalyzed cascade reactions, as exemplified by the biosynthesis of terpenoids. These biological pathways are distinctive from general chemical synthesis where 'stop-and-go' protocols are prevailing with significantly lower efficiency. Therefore, to mimic nature's strategies has been a constant attraction for synthetic chemists. In 2011, MacMillan and co-workers marked a milestone in this arena. By realizing an organocatalytic cascade reaction, they achieved the collective synthesis of six structurally complex terpene indole alkaloids, strychnine (**74**), akuammicine (**75**), kopsinine (**76**), kopsanone (**77**), aspidospermidine (**78**) and vincadifformine (**79**), each with high step economy (Scheme 10). In particular, they accomplished the shortest asymmetric synthesis of strychnine (**74**), the best-known *strychnos* alkaloid (Scheme 10A). This collective total synthesis was centered on a one-flask, asymmetric Diels–Alder/elimination/conjugate addition organocascade reaction that coined the key tetracyclic core of the targets. In this reaction, by forming the corresponding iminium species with catalyst **81**, propynal was activated toward the Diels–Alder [4+2] cycloaddition with 2-vinyl indole **80**, engendering iminium **83**. The ensuing elimination and hydrolysis provided **84**, which underwent intramolecular conjugate addition to deliver **82** in 82% yield and 97% ee. Employment of the selenide-substituted 2-vinyl indole, such as **80**, as the diene component was critical for the success. Use of the corresponding methyl-sulfide-substituted 2-vinyl indole as the diene component would lead to a different product due to the mitigated propensity of the sulfide to undergo elimination. Treatment of **82** with Wilkinson's catalyst to effect decarbonylation followed by introduction of a carbomethoxy group with $COCl_2$/MeOH and reduction with Dibal-H resulted in **85** as an inconsequential mixture of olefin isomers. N-alkylation and ester reduction gave **86** as a proper Heck substrate. The Heck cyclization-lactol formation and the subsequent debenzylation gave the Wieland–Gumlich aldehyde, which was converted to strychnine (**74**) following the know procedure. This total synthesis delivered strychnine in 12 steps and 6.4% overall yield from commercially available materials, constituting the shortest route to enantioenriched strychnine to date. Notably, in the Heck cyclization, the PMB protecting group was believed critical in facilitating regioselective β-hydride elimination away from the indoline ring methine since formation of the *N*-PMB-substituted enamine would accompany destabilizing allylic strain. This destabilizing factor was envisioned in the synthesis of akuammicine (**75**). Thus, compound **85** was subjected to cleavage of the PMB group with concomitant isomerization of the alkene in conjugation with the ester group. After installation of the iodoallyl



Scheme 10. MacMillan's syntheses of indole alkaloids **74**–**79**.



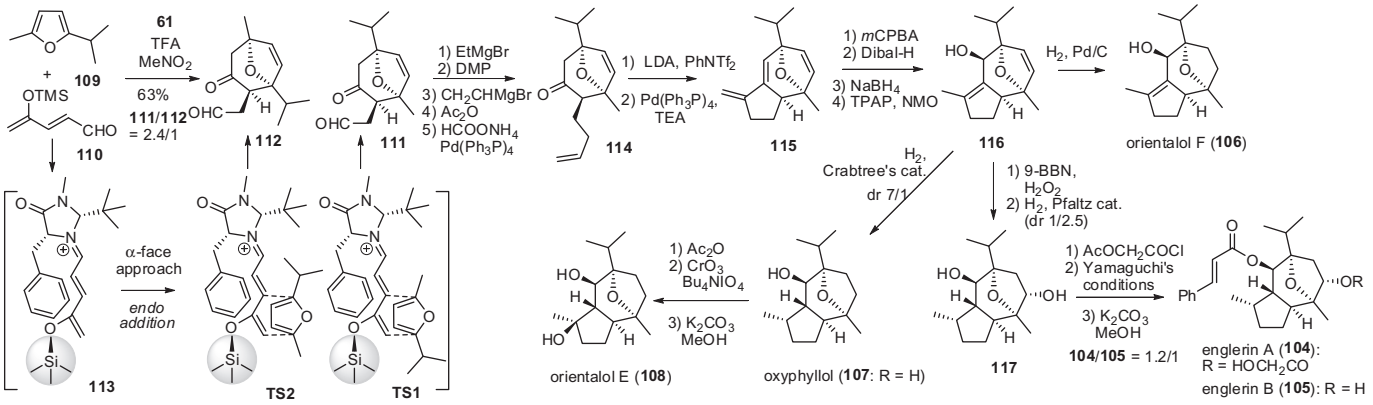
Scheme 11. Wu's synthesis of kopsinine (**76**) and aspidofractine (**96**).

side chain, the Heck cyclization of **88** was set in motion to produce akuammicine (**75**).

The total synthesis of kopsinine (**76**) and kopsanone (**77**) employed a slightly modified precursor **82′** obtained from **80′** via the organocascade reaction (Scheme 10B). Conjugate addition of the revealed amine to the vinylphosphonium bromide produced the corresponding ylide that underwent olefination with the vicinal aldehyde to furnish **89**. Compound **89** was converted via conventional procedures to **90**, and the latter was further subjected to [4+2] cycloaddition reaction with vinylsulfone to access **91** with a [2.2.2] bicyclic framework. After desulfurization with Raney nickel, the total synthesis of kopsinine (**76**) was accomplished in 14% overall yield spanning 9 steps from commercial materials. Further, kopsinine was demethylated to give **92**, which was converted to kopsanone (**77**) simply by heating without solvent. Heck cyclization was also featured in the synthesis of the last two natural products (Scheme 10C). From *ent*-**82′**, **94** was obtained via a sequence involving Wittig reactin, enamine saturation, *N*-Boc deprotection and N-allylation. The subsequent Heck cyclization provided **95**, the precursor for both aspidospermidine (**78**) and vincadifformine (**79**). This accomplishment of the collective syntheses of six complex natural products in 6.4–24% yields with 9–12 steps have highlighted the capability of organocatalysis, which combined with metal catalysis may provide rapid access to complex molecular architectures.

Wu's synthesis of kopsinine and aspidofractine[18]

Indole alkaloids comprise a rich source of appealing targets that form a test base for new synthetic methodologies. Recently, Wu selected kopsinine (**76**) and aspidofractine (**96**) as the synthetic



Scheme 12. Sun and Lin's syntheses of 7,10-epoxy guaianoids **104**–**108**.

targets to demonstrate their organocatalytic method (Scheme 11). In this exquisite Michael addition/aza-Michael addition/cyclization cascade reaction, **97** reacted with propynal under the catalysis of **98** to deliver the key tetracyclic **99** directly, presumably via the intermediacy of **100** and **101**. In the second catalysis by **98**, the conjugate addition of compound **99** to acrolein proceeded to furnish, after reduction, dienamine **102**, which underwent the [4+2] cycloaddition/desulfurization sequence to give **103**. After formation of the last ring by nucleophilic substitution, the total synthesis of kopsinine (**76**) was accomplished in a concise manner. The endgame N-formylation of kopsinine provided aspidofractine (**96**).

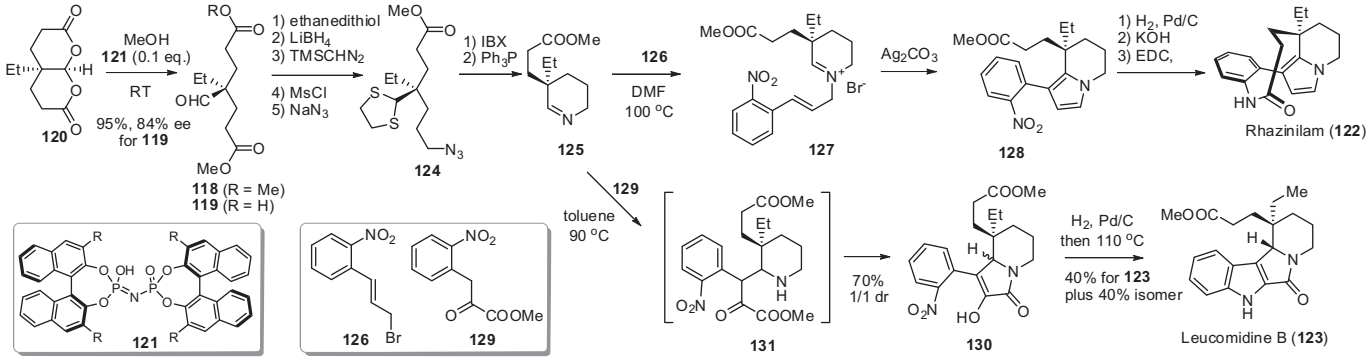
Sun and Lin's synthesis of englerin A/B, orientalol E/F, and oxyphyllol[19]

7,10-Epoxy guaianoids represent a small group of sesquiterpene natural products. These structurally exquisite natural products have aroused significant attention from the synthesis community since englerin A and englerin B were disclosed by Beutler and co-workers to possess potent cytotoxicity toward renal cell carcinoma. In early 2013, Sun, Lin, and co-workers demonstrated how an organocatalytic [4+3] cycloaddition reaction could be tamed for the production of a collection of natural products including englerin A (**104**), englerin B (**105**), orientalol F (**106**), oxyphyllol (**107**), and orientalol E (**108**) (Scheme 12). The [4+3] cycloaddition reaction catalyzed by **61**-TFA involved the unsymmetrically substituted furan **109** and dienal **110**, affording two regioisomers in a ratio of 2.4/1 favoring the desirable **111**. The TMS group was deemed to play a critical role in the stereochemical guidance: the benzyl group and *t*-butyl group of catalyst **61** occupy the α face of iminium **113**, while the even bulkier TMS group blocks its β face, forcing **109** to approach from the α face through the *endo* orientation. The regioselectivity could be rationalized by the preference of the postulated transition state **TS1** over **TS2**. Compound **111** was subjected to a sequence to give **114**, which was triflated before undergoing Heck cyclization to furnish guaiane triene **115**. Selective epoxidation of the trisubstituted olefin followed by S_N2'-type hydride delivery provided allylic alcohol **116**, which after hydrogenation with Pd/C gave orientalol F (**106**). Formal hydration of the disubstituted olefin via the hydroboration/oxidation procedure generated diol **117**, which was readily converted into englerin A (**104**) and englerin B (**105**) by esterification and saponification. The directed hydrogenation of **116** with Crabtree's catalyst resulted in oxyphyllol (**107**). Eventually, a three-step sequence involving acylation, chemoselective and stereospecific C–H oxidation, and saponification produced orientalol E (**108**).

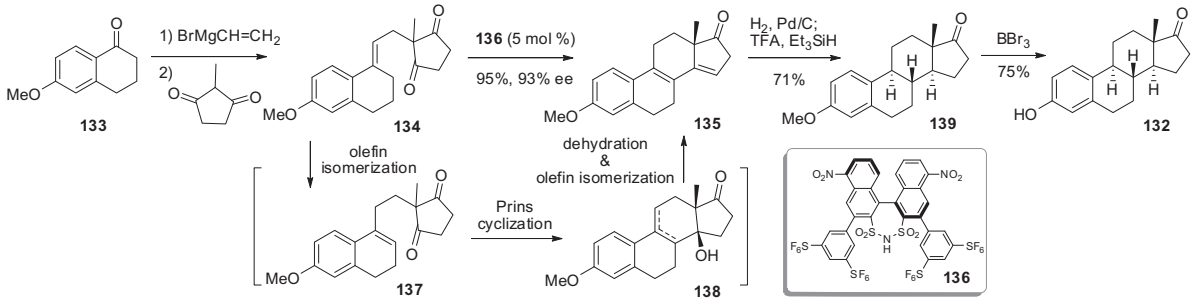
Total syntheses featuring Brønsted acid catalysis

Zhu's synthesis of rhazinilam and leucomidine B[20]

Desymmetrization represents an effective strategy for generating chiral all-carbon quaternary centers. The desymmetrization of prochiral diesters via enzymatic hydrolysis has been a powerful method. Nevertheless, it is less efficient for long-chain-bridged diesters, such as dimethyl **118** (Scheme 13), which is the key precursor in several indole alkaloid syntheses accomplished by Kuehne. Recently, Zhu and co-workers developed a catalytic desymmetrization method to access **119** enantioselectively (Scheme 13). This desymmetrization was realized by the alcoholysis of bicyclic bislactone **120** catalyzed by the chiral Brønsted acid **121**. Aldehyde **119** was secured in 95% yield and 84% ee, and was utilized for the total synthesis of rhazinilam (**122**) and leucomidine



Scheme 13. Zhu's synthesis of rhazinilam (**122**) and leucomidine B (**123**).



Scheme 14. List's synthesis of estrone (**132**).

B (**123**). Compound **119** was converted to **124** before being elaborated into tetrahydropyridine **125**, the common precursor to the two natural products. The N-allylation of **125** by **126** produced iminium salt **127**, which upon heating in toluene in the presence of Ag_2CO_3 under an inert atmosphere delivered **128**. Reduction of the nitro group and lactamization engendered rhazinilam (**122**). On the other hand, heating the mixture of **125** and **129** resulted in **130** as a 1/1 diastereomeric mixture, probably via the intermediacy of **131**, before further proceeding to leucomidine B (**123**).

List's synthesis of estrone[21]

Steroids have captured the imagination of synthetic chemists for decades owing to their appealing molecular architecture as well as their biological significance. While the female sex hormone estrone (**132**) has been the target of numerous syntheses, the synthesis developed by Torgov in 1963, albeit racemic, appeared particularly efficient. Recently, List and co-workers achieved the asymmetric synthesis of **132** by virtue of a catalytic enantioselective Torgov cyclization (Scheme 14). The substrate **134** was readily prepared from **133** via a two-step procedure. Torgov cyclization entails strong acidic conditions. In List's work, a highly Brønsted acidic disulfonimide was selected out as the catalyst. Thus, in the presence of only 5 mol % of **136** at low temperature for 4 days, the Torgov cyclization of **134** went on smoothly to deliver **135** in 95% yield and 93% ee. After one recrystallization, **135** could be isolated in 88% yield with 99.8% ee. The Torgov cyclization of **134** presumably involves these consecutive reactions: (1) isomerization of **134**–**137**; (2) Prins reaction of **137** that ends in deprotonation furnishing **138** as an olefin mixture; and (3) dehydration and olefin isomerization. The strong acidic conditions are necessary that ensure the final product as the desired thermodynamically most stabilized one. Torgov diene was then hydrogenated to give **139**, which furnished estrone (**132**) after demethylation.

Conclusions and perspectives

Organocatalytic reactions generally involve convenient, mild, and metal-free conditions, and are amenable to the construction of molecular architectures with complexity and diversity in enantioselective manner. These virtues bestow them an edge in synthesis of natural and pharmaceutical products. Selected contributions summarized in this Digest highlight the importance of organocatalytic reactions in fostering structures of interest, particularly quaternary stereogenic carbons and polycyclic systems embedded in complex molecules with biological significance. We hope this Digest will inspire more efforts in applying organocatalytic transformations in total synthesis of complex natural products. On the other hand, organocatalytic reactions are still underdeveloped, and some of the organocatalytic reactions are far from being satisfactory. Therefore, further development of organocatalytic reactions in both breadth and depth is anticipated.

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