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.

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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
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, 7 enamine catalysis, 8 iminium catalysis, 9 and Brønsted acid catalysis. 10

**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 aminal which underwent furan/iminium cyclization to pentacyclic 7. The camphorsulfonic acid-assisted Z-selective RCM reaction anchored 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.

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

**Scheme 2. Fan’s syntheses of lycoramine (8), galanthamine (9), and lunarine (10).**
catalyzed by thiourea 13. This reaction with 11a resulted in a nearly quantitative yield of 14 with good enantioselective yield 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

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-isocyanocetates add to vinyl phenylselenone to give 21, 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.

Total syntheses powered by enamine catalysis

Hayashi’s and Ma’s syntheses of oseltamivir

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). This efficient synthesis relied heavily on the Michael addition reaction of 30 and 31 catalyzed by 5 mol % of 32-CIC4H9COOH 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 Cs. 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). 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

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 CuBr2 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).
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 (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 stereocenters 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 stereocenters at C16 and the C6 stereocenters 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.
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 alllylation, before being further advanced into GB 17 (51).

Total syntheses powered by iminium catalysis

MacMillan’s synthesis of diazonamide A

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 Ï€-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 benzo[â]furano[â]indoline 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 aldon 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

In the past century, total synthesis has been playing an indispensable 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 oxo-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

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 terpeno 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 coiled 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 carboxymethoxy group with COCl2/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 entantioenriched strychnine to date. Notably, in the Heck cyclization, the PMB protecting group was believed critical in facilitating regioselective 4-b-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
Heck cyclization was also featured in the synthesis of the last two natural products (Scheme 10C). From enter, 94 was obtained via a sequence involving Wittig reactin, enamine saturation, N-Boc protection and N-allylation. The subsequent Heck cyclization yielded 95, the precursor for both aspidospermidine (78) and vincadiffrinone (79). This accomplishment of the collective syntheses of six natural products is 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**

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
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

7,10-Epoxo 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 tuned 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 trifiedlated before undergoing Heck cyclization to furnish guaiane triene 115. Selective epoxidation of the trisubstituted olefin followed by 5α,6γ-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, chemo- 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

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).
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 Ag2CO3 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**

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 98% 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 demethylolation.

**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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**References and notes**