The Ever-Expanding Role of Asymmetric, Covalent Organocatalysis in Scaleable, Natural Product Synthesis

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HIGHLIGHT

The Ever-Expanding Role of Asymmetric Covalent Organocatalysis in Scalable, Natural Product Synthesis

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Following the turn of the millennium, the role of asymmetric covalent organocatalysis has developed into a scalable, synthetic paradigm galvanizing the synthetic community toward utilization of these methods toward more practical, metal-free syntheses of natural products. A myriad of reports on asymmetric organocatalytic modes of substrate activation relying on small, exclusively organic molecules are delineating what has now become the multifaceted field of organocatalysis. In covalent catalysis, the catalyst and substrate combine to first form a covalent, activated intermediate that enters the catalytic cycle. Following asymmetric bond formation, the chiral catalyst is recycled through hydrolysis or displacement by a pendant group on the newly formed product. Amine- and phosphine-based organocatalysts are the most common examples that have led to a vast array of reaction types. This *Highlight* provides a brief overview of covalent modes of organocatalysis and applications of scalable versions of these methods applied to the total synthesis of natural products including examples from our own laboratory.

1 Introduction

1.1 A Brief Historical Perspective.

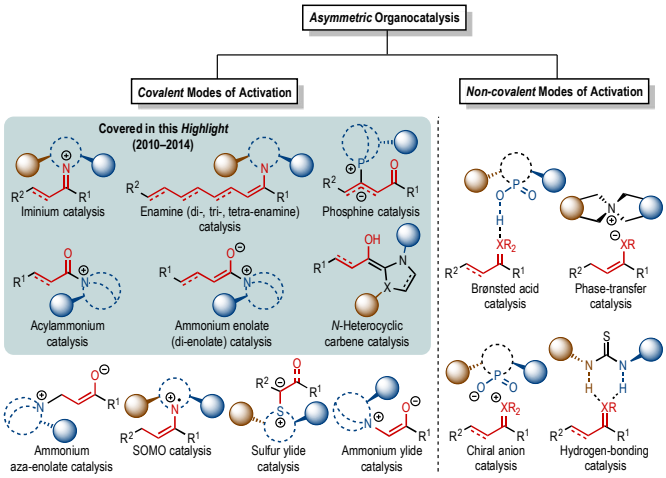
> *"I will therefore call it the 'catalytic force' and I will call 'catalysis' the decomposition of bodies by this force, in the same way that we call by 'analysis' the decomposition of bodies by chemical affinity."*

These famous observations by the Swedish chemist Jöns Jakob Berzelius of the University of Stockholm in 1835 sparked a new era of catalysis.[1a] The first organocatalytic transformation was reported in 1860 by Justus von Liebig in conversion of cyanogen to oxamide in the presence of aqueous acetaldehyde.[1b] The historic roots of the first asymmetric organocatalytic reaction date back to 1912, when two German chemists Bredig and Fiske reported that addition of hydrogen cyanide to benzaldehyde catalyzed by the cinchona alkaloids yields cyanohydrins in ~10% *ee*.[1c] The use of amino acids as catalysts for aldol and condensation reactions of acetaldehyde was first documented in 1931 by Fischer and Marschall.[1d] In 1936, Kuhn[1e] found that ammonium carboxylates of optically active amines effectively catalyze the aldol reaction. The analogies in the catalytic action of enzymes and organic substances were recognized as early as 1928 by the German chemist Wolfgang Langenbeck.[1f] In 1949, Langenbeck revealed the conceptual difference between covalent and non-covalent catalysis, and coined the term "organic catalysis".[1g] Pracejus reported the first enantioselective synthesis of esters in 1960 from phenyl methyl ketene and methanol using 1 mol% *O*-acetylquinine as catalyst in a quite remarkable 93% yield and 74% *ee*.[1h,1i] In 1971, the discovery of *L*-proline as catalyst for the intramolecular asymmetric aldol cyclodehydration was exemplified in the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[1j,1k] Surprisingly, the viability of small organic molecules as organocatalysts in asymmetric reactions remained subcritical and over the next few decades, the area of asymmetric organocatalysis was heavily overlooked with a paucity of isolated reports.[2] However in 2000, two pioneering reports by List, Lerner, Barbas[3] and MacMillan[4] reignited the modern age of organocatalysis triggering the "gold rush" in the last decade. MacMillan coined the term "organocatalysis" which is defined as *the acceleration of a chemical transformation through addition of a substochiometric amount of an organic compound which does not contain a metal atom*.[4] The operational simplicity, robustness, low-cost, availability, chemical efficiency and non-toxicity render organocatalysis advantageous over metal and enzyme catalysis. Organocatalysis remains a vital pillar and popular strand of contemporary asymmetric catalysis research and is now well established in academia and industrial sectors. A myriad of excellent reviews have permeated the chemical community since 2010 in this highly topical field covering many discrete areas of organocatalysis.[5] Regrettably, it is impossible to report every

contribution to this rapidly growing field; therefore, a cross-section of the most recent developments in asymmetric covalent organocatalysis is described in this *Highlight* to provide a flavour of the exciting advances in this area and specifically their growing impact in scalable natural product synthesis.

1.2 Classification of Asymmetric Modes of Activation in Organocatalysis.

The classification of asymmetric modes of activation in organocatalytic reactions is challenging. A general distinction can be made between organocatalytic processes that form *covalent* intermediates between catalyst and substrate and processes that rely on *non-covalent* interactions (Scheme 1). Further differentiation within each category can be made on the basis of the mode of substrate activation: highest occupied molecular orbital (HOMO) activation (*e.g.*, enamine, N-heterocyclic carbene catalysis, *etc.*) or lowest unoccupied molecular orbital (LUMO) activation (*e.g.*, iminium, acylammonium, *etc.*). It should be noted that a single organocatalyst can promote reactions by several modes of activation and thus can be classified a multifunctional catalyst.[6]



Scheme 1. Classification of Asymmetric Modes of Activation in Organocatalysis.

An *iminium* activation mode exploits the reversible condensation of a chiral secondary or primary amine catalyst (e.g., *L*-proline, MacMillan's imidazolidinones, cinchona-derived primary amines, *etc.*) with an α,β-unsaturated aldehyde or ketone to form an iminium ion intermediate. This system effectively lowers the LUMO energy of the π-system and thus enhances its reactivity toward nucleophiles. This strategy has been successfully employed in various types of asymmetric transformations.[7]

In the case of saturated carbonyl systems, the LUMO energy lowering induced by the formation of an iminium ion intermediate increases the acidity of the α-proton, enabling facile deprotonation and leads to the generation of the *enamine*. The resultant enolate, with an effectively elevated HOMO energy, augments its reactivity toward electrophiles. This activation mode has led to the development of a vast number of asymmetric α-functionalizations of aldehydes and ketones with carbon- and heteroatom-based electrophiles.[8] This concept has been extended to unsaturated carbonyl systems resulting in the discovery of dienamine,[9] trienamine,[10] and more recently tetraenamine[11] activation modes.

In *phosphine catalysis*, a conjugate addition to an activated carbon-carbon double or triple bond by a chiral tertiary phosphine organocatalyst forms a β-phosphonium enolate, β-phosphonium dienolate, or vinyl phosphonium ylide as reactive intermediates. These zwitterionic species react with a broad array of nucleophiles (LUMO activation mode) and electrophiles (HOMO activation mode) to generate diverse carbo- and heterocyclic molecular architectures.[12]

Acylammonium catalysis is initiated by the nucleophilic attack of a chiral tertiary amine catalyst with an activated carboxylic acid derivative (*e.g.* acid halide, anhydride) to form an acylammonium ion intermediate. This activation mode effectively lowers the LUMO energy of the carbonyl system thus enhancing its reactivity toward nucleophiles. Several acyl-transfer organocatalysts have been developed for asymmetric acylammonium-catalyzed transformations,[13] including transesterifications, kinetic resolutions, desymmetrizations, and Steglich rearrangements. Organocatalysts utilized include Fu's chiral ferrocenyl PPY catalyst,[14] Vedejs' TADMAP catalyst,[15] Okamoto's annulated benzothiazolylidenamine catalysts[16] and Birman's dihydroimidazole CF_3-PIP[17] and isothiourea-based BTM[18] and HBTM[19] catalysts. Furthermore, this activation concept has recently been extended to unsaturated carbonyl systems prompting a diverse array of previously undisclosed complexity-generating organocascades.[20]

In *ammonium enolate catalysis*, the nucleophilic enolate equivalent (HOMO activation mode) is generated either by addition of a chiral tertiary amine catalyst to a ketene or *via* direct α-deprotonation of an acylammonium species. This activation mode has led to the development of numerous asymmetric α-functionalizations with carbon- and heteroatom-based electrophiles[21a] and prompted a spate of elegant, scalable syntheses.[21b,c] Further exploration of this activation concept unveiled yet another reactive intermediate, zwitterionic ammonium dienolate, generated *in situ* by a direct γ-deprotonation of unsaturated acylammonium ions enabling a variety of asymmetric annulations.[22]

In *N-heterocyclic carbene* (NHC) *catalysis*, the nucleophilic attack of the carbene catalyst (*e.g.*, thiazolium, triazolium salts) on the carbonyl carbon (typically aldehydes) forms the initial adduct that leads to the Breslow intermediate through an external base deprotonation of the carbene-aldehyde adduct. This acyl anion equivalent can then react with different electrophiles, including another carbonyl compound as in the benzoin reaction, with Michael acceptors in the Stetter reaction, with activated or unactivated double and triple bonds without electron-withdrawing groups, or with alkyl halides. This unique mode of HOMO activation takes advantage of the inversion of classical reactivity (umpolung) and offers a broad range of unconventional transformations.[23]

2 Iminium/Enamine Catalysis

2.1 Recent Developments in the Iminium/Enamine Catalysis: Synopses of Examples including Formal Syntheses.

Jørgensen[9a] recently introduced a new dual activation mode of α,β-unsaturated aldehydes **1**, *via* dienamine formation, and activation of nitro-olefins **2**, *via* hydrogen-bonding, affording fully substituted cyclobutanes **4** by an organocatalytic formal [2 + 2]-cycloaddition catalyzed by a computationally designed

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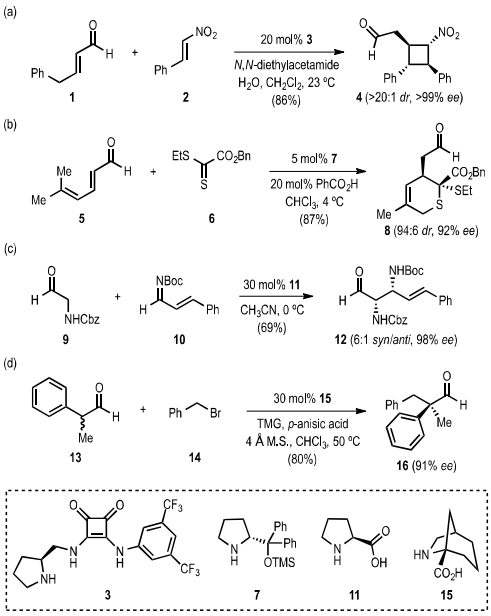
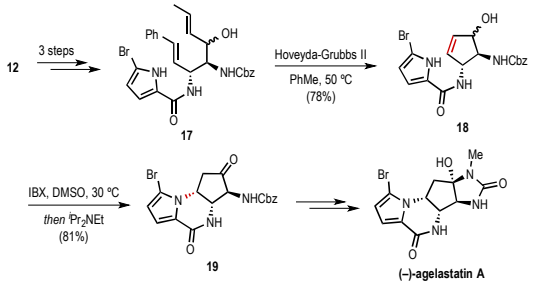
catalyst **3** (Scheme 2a). In other work, Jørgensen[10c] utilized trienamine-activated dienes, generated *in situ* from α,β,γ,δ,-dienyl aldehydes **5** and chiral aminocatalyst **7**, in thio-Diels-Alder reactions with thiocarbonyls **6** to access highly enantioenriched dihydrothiopyrans **8** (Scheme 2b). In 2012, Maruoka and co-workers[24] developed the first diastereo- and enantioselective direct Mannich reaction (Scheme 2c) of *N*-protected α-aminoacetaldehydes **9** with *N*-protected imines **10** catalyzed by *L*-proline (**11**). This organocatalytic process delivers optically active vicinal diamines **12**, motifs present in a number of natural products and useful chiral catalysts. More recently, List[25] disclosed the first aminocatalyzed α-alkylation of racemic α-branched aldehydes **13** with benzyl bromide (**14**) as alkylating agent *via* enamine catalysis (Scheme 2d). Using a sterically demanding proline-derived catalyst **15**, enantiomerically enriched α-alkylated aldehydes with quaternary stereogenic centers were obtained in good yields and high enantioselectivities.



Scheme 2. Recent examples of asymmetric iminium/enamine catalysis.

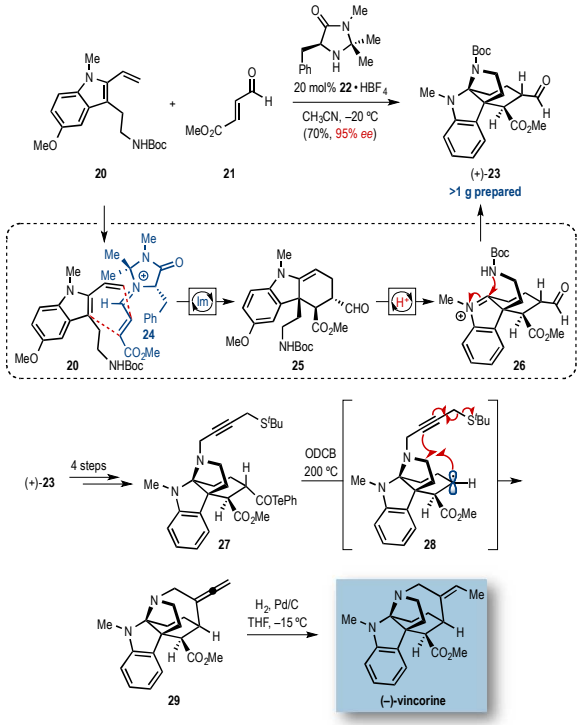
Maruoka successfully demonstrated the synthetic utility of the developed Mannich reaction in the formal synthesis of (–)-agelastatin A, a potent antitumor marine alkaloid (Scheme 3). Mannich product, diamine **12**, was converted to diene **17** in 3 steps. Treatment of **17** with Hoveyda-Grubbs second-generation catalyst afforded cyclopentene **18**, which was converted in one pot to cyclopentanone **19**, an intermediate previously used in the synthesis of (–)-agelastatin A.



Scheme 3. Application of diamine **12** towards the formal synthesis of (–)-agelastatin A.

2.2 MacMillan's Total Synthesis of (–)-Vincorine.

In 2013, Horning and MacMillan[26a] reported a concise, enantioselective total synthesis of (–)-vincorine, an akuammiline alkaloid containing a tetracyclic cage-like core with a strained seven-membered azepanyl ring system. Various members of this alkaloid family are known to exhibit anti-cancer activity and glycine receptor antagonism. A prominent feature of the synthesis is a scalable, organocatalytic Diels-Alder/iminium cyclization cascade, the general synthetic strategy for representative polycyclic indole alkaloids,[26b] initiated by a highly enantioselective *endo* Diels-Alder reaction between diene **20** and *in situ* generated α,β-unsaturated iminium dienophile **24** delivering cycloadduct **25** (Scheme 4). Subsequent, Brønsted acid-mediated conversion of **25** to iminium **26** prompted intramolecular 5-*exo* cyclization by the pendant carbamate group to generate the tetracyclic adduct **23**, on gram scale (>1 g), bearing three of four stereocenters found in vincorine including the all-carbon quaternary center. Final seven-membered azepanyl ring annulation was accomplished by 7-*exo-dig* radical cyclization initiated with an unusual acyl telluride precursor **27** under thermal conditions providing allene **29**. The authors postulate C–Te bond homolysis and loss of carbon monoxide to generate alkyl radical **28**. Selective terminal hydrogenation from the less hindered face of the allene functionality furnished (–)-vincorine as a single olefin isomer in nine total steps and 9% overall yield.

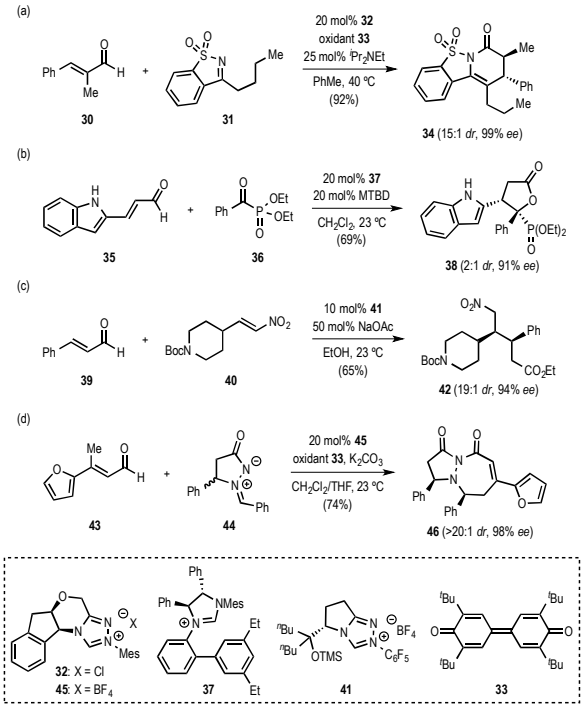


Scheme 4. MacMillan's total synthesis of (–)-vincorine.

3 N-Heterocyclic Carbene Catalysis

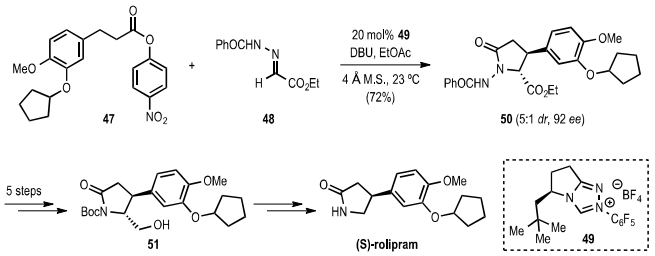
3.1 Recent Developments in N-Heterocyclic Carbene Catalysis: Synopses of Examples including Formal Syntheses.

In 2012, Bode[27a] disclosed a new class of NHC-catalyzed annulations of trisubstituted α,β-unsaturated aldehydes **30** and cyclic *N*-sulfonylimines **31** (Scheme 5a) operating through the catalytic generation of α,β-unsaturated acyl azoliums in the presence of catalyst **32** and oxidant **33**. Scheidt and co-workers[27b] developed a highly selective synthesis of γ-butyrolactones through a formal [3+2] annulation (Scheme 5b) of α,β-unsaturated aldehydes **35** and acyl phosphonates **36** catalyzed by a computationally designed, C_1-symmetric biaryl-saturated imidazolium catalysts **37**. Rovis[27c] recently developed a novel chiral N-heterocyclic carbene catalyst **41** that favors a homoenolate pathway over the established acyl anion (Stetter) pathway. This enabled a novel coupling between α,β-unsaturated aldehydes **39** and nitroalkenes **40** to access a diverse array of *syn*-δ-nitroesters **42** (Scheme 5c). More recently, Chi and co-workers[27d] disclosed the first N-heterocyclic carbene catalyzed [3+4] cycloaddition of α,β-unsaturated aldehydes **43** and azomethine imines **44** to generate dinitrogen-fused seven-membered heterocycles **46** (Scheme 5d). In this process, NHC catalyst **45** also enables a highly effective kinetic resolution of racemic azomethine imines **44**.



Scheme 5. Recent examples of asymmetric N-heterocyclic carbene catalysis.

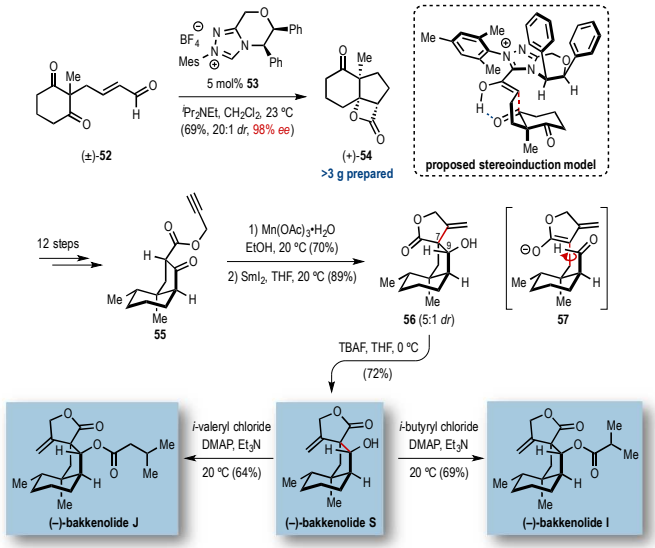
Activation of the otherwise inert β-sp^3 carbon of saturated esters as nucleophiles has recently been achieved by Chi and co-workers[28] utilizing NHC catalyst **49**. This methodology delivers a diverse set of optically active substrates including cyclopentenes, γ-butyrolactones and γ-lactams (*e.g.* **50**, Scheme 6). Chi then established the utility of this methodology employing saturated ester **47** and hydrazone **48** to provide a concise, formal asymmetric synthesis of (*S*)-rolipram, a potent phosphodiesterase inhibitor (Scheme 6). The synthesis of **51**, a key intermediate previously employed in the synthesis of (*S*)-rolipram, was achieved in 5 steps from γ-lactam **50**.



Scheme 6. Application of γ-lactam **50** towards the formal synthesis of (*S*)-rolipram.

3.2 Scheidt's Total Syntheses of (–)-Bakkenolides I, J, and S.

Scheidt has recently described the utility of the tricyclic β-lactone (+)-**54**, obtained by desymmetrization through an aldol-lactonization reaction of readily accessible 1,3-diketone **52** catalyzed by N-heterocyclic carbene **53**,[29a] as a key intermediate in the enantioselective total syntheses of (–)-bakkenolides I, J, and S (Scheme 7).[29b] The tricyclic β-lactone (+)-**54** was prepared on gram scale (>3 g) in 69% yield with 98% ee as a single diastereomer.



Scheme 7. Scheidt's total syntheses of (–)-bakkenolides I, J, and S.

The stereochemical outcome of the reaction was rationalized through the transition state model depicted in Scheme 7. A 12-step elaboration of the fused 6,5-bicyclic ring system (+)-**54**, led to the β-keto propargyl ester **55** and set the stage for the formation of the key γ-spirobutyrolactone. Thus, in the presence of $Mn(OAc)_3$, the β-keto propargyl ester **55** cyclized, forming the γ-spirobutyrolactone **56** as a 5:1 mixture of diastereomers, following reduction of the resulting ketone using SmI_2. However, this route produced the undesired epimer at the C7 position. Fortunately, exposure of **56** to TBAF promoted an intriguing retro-aldol/aldol sequence (*via* formation of transient aldehyde **57**) to afford the desired diastereomer, (–)-bakkenolide S. The authors hypothesized that this thermodynamically favoured process is driven by hydrogen bonding between the C9 secondary alcohol and the γ-spirobutyrolactone carbonyl oxygen. Finally, conversion to (–)-bakkenolides I and J was accomplished by direct acylation of (–)-bakkenolide S with isobutyryl and isovaleryl chlorides,

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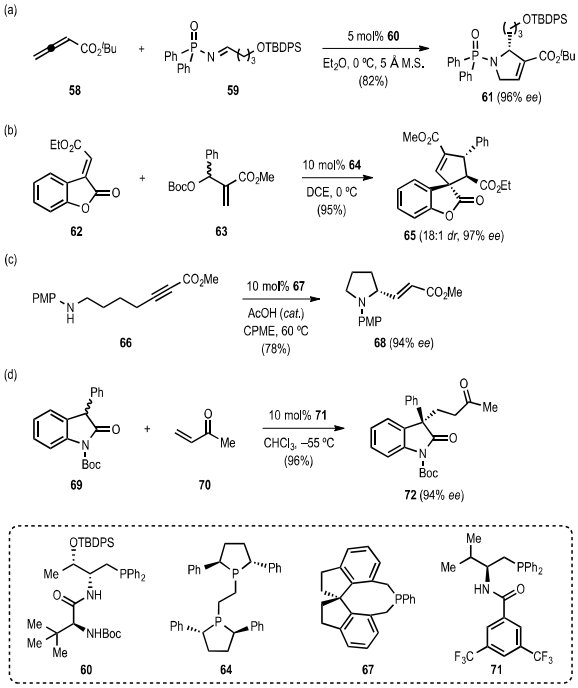
respectively. These natural products possess a wide spectrum of biological activity including antifeedant effects, platelet aggregation inhibition, and potent inhibitory activity against a variety of tumor cell lines.

4 Phosphine Catalysis

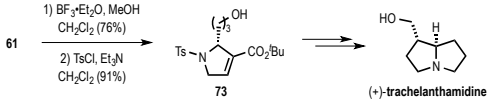
4.1 Recent Developments in Phosphine Catalysis: Synopses of Examples including Formal Syntheses.

The Lu group[30a] broadened the potential of chiral peptide-based phosphines **60** for catalysis of allene-alkylimine [3+2] annulations (Scheme 8a) leading to synthetically valuable optically pure five-membered N-heterocycles (*e.g.*, **61**). Recently, Barbas[30b] utilized C_2-symmetric phospholane **64** to promote an expeditious assembly of complex polysubstituted spirocyclopentenebenzo-furanones **65** (Scheme 8b) consisting of three contiguous stereocenters, including an all-carbon quaternary carbon. In their recent studies, Fu and co-workers[30c] reported the first examples of intra- and intermolecular γ-umpolung additions of nitrogen nucleophiles to allenoates and alkynoates (Scheme 8c) with spirophosphepine **67** found to be the optimal catalyst. More recently, Lu[30d] disclosed the first asymmetric phosphine-catalyzed Michael addition (Scheme 8d) mediated by a chiral phosphine **71** that was presumed to promote additional catalyst-substrate interactions through hydrogen bonding.



Scheme 8. Recent examples of asymmetric phosphine catalysis.

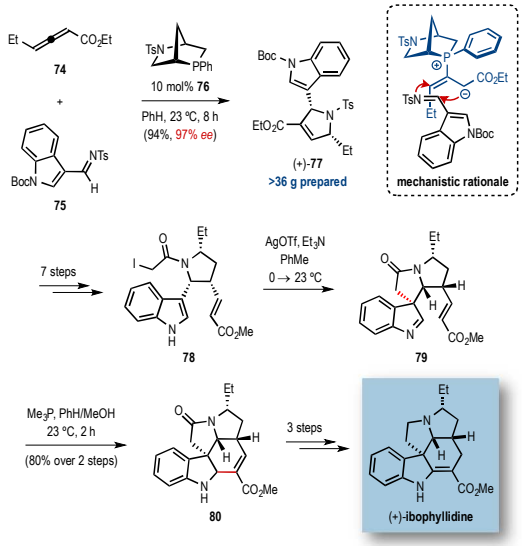
Lu and co-workers demonstrated the utility of the asymmetric allene-alkylimine [3+2] methodology by a concise formal asymmetric synthesis of (+)-trachelanthamidine (Scheme 9). The synthesis of **73**, a key intermediate previously employed in the synthesis of (+)-trachelanthamidine, a pyrrolizidine alkaloid possessing a wide range of pharmacologically relevant activities, was secured from dihydropyrroline **61** following removal of protecting groups.



Scheme 9. Application of dihydropyrroline **61** towards the formal synthesis of (+)-trachelanthamidine.

4.2 Kwon's Total Synthesis of (+)-Ibophyllidine.

Recently, Andrews and Kwon reported the first example of asymmetric phosphine-catalyzed [3+2] annulation employed in the total synthesis of (+)-ibophyllidine[31] (Scheme 10), a member of the terpene indole alkaloids possessing intriguing biological activities. The practical procedure allowed the preparation of the optically pure pyrroline (+)-**77** as a single *syn*-diastereomer on 30 g scale in excellent yield with high enantiocontrol employing the readily accessible allenoate **74** and imine **75** with the chiral [2.2.1] bicyclic phosphine catalyst **76**. Following a 7-step elaboration of the pyrroline (+)-**77** to the cyclization precursor **78**, AgOTf-mediated intramolecular spiroalkylation delivered the desired indolenine **79**. The final six-membered E-ring of (+)-ibophyllidine was formed *via* an intramolecular aza-Morita-Baylis-Hillman reaction, again through phosphine catalysis, yielding the desired pentacyclic framework **80** in 80% yield over two steps. Overall, the first enantioselective synthesis of (+)-ibophyllidine was accomplished in 15 steps and 13% overall yield through enantioselective phosphine-based catalysis.



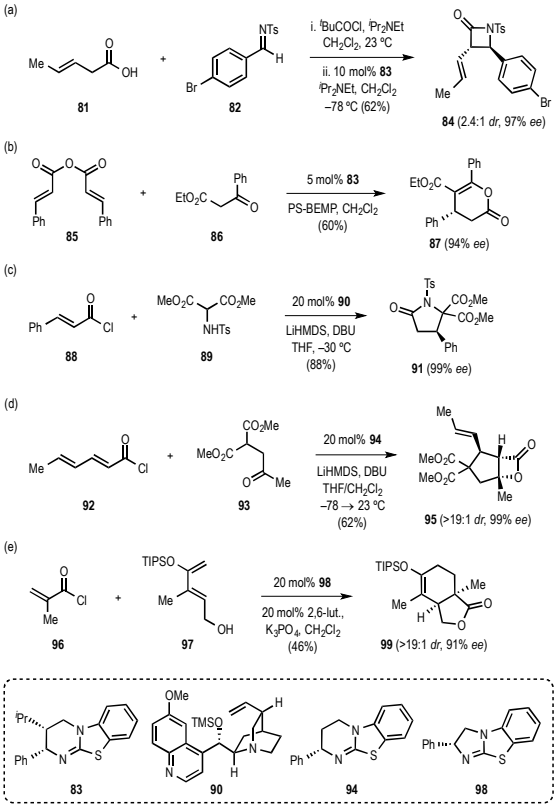
Scheme 10. Kwon's total synthesis of (+)-ibophyllidine.

5 Acylammonium/Ammonium Enolate Catalysis

5.1 Recent Developments in Acylammonium/ Ammonium Enolate Catalysis: Synopses of Examples including Formal Syntheses.

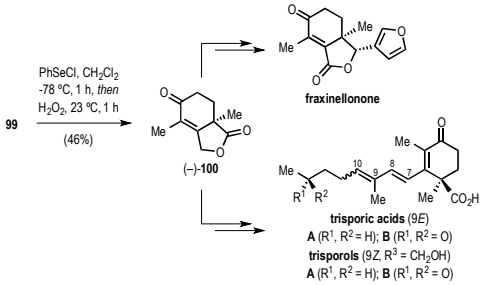
The Smith[22b] group recently utilized *in situ* activated β,γ-unsaturated alkenoic acids **81** through mixed anhydride formation, as ammonium dienolate precursors in an enantioselective formal [2+2] cycloaddition with *N*-tosyl aldimines **82** promoted by a chiral isothiourea HBTM-2.1 (**83**) catalyst (Scheme 11a). Building on early work by Fu, who demonstrated the potential of acid fluorides and unsaturated

aclylammonium catalysis for a tandem allylsilane/ene reaction,[20a] Smith recently demonstrated the utility of mixed anhydrides and unsaturated acylammoniums for the enantioselective synthesis of enol lactones **87** (Scheme 11b).[20b] In our own studies in this area, the full potential of the latent, triply reactive, α,β-unsaturated acylammonium catalysis was realized employing acid chlorides (*e.g.*, **88**, **92**) and carboxylic acids in a rapid assembly of complex cyclopentanes[20d] **95** (Scheme 11d) and in a further extension, N-heterocycles[20c] **91** (Scheme 11c). Furthermore, we very recently demonstrated the utility of these chiral α,β-unsaturated acylammonium salts as competent chiral dienophiles in a Diels-Alder-lactonization (DAL) organocascade[20e] (Scheme 11e).



Scheme 11. Recent examples of asymmetric acylammonium/ammonium enolate catalysis.

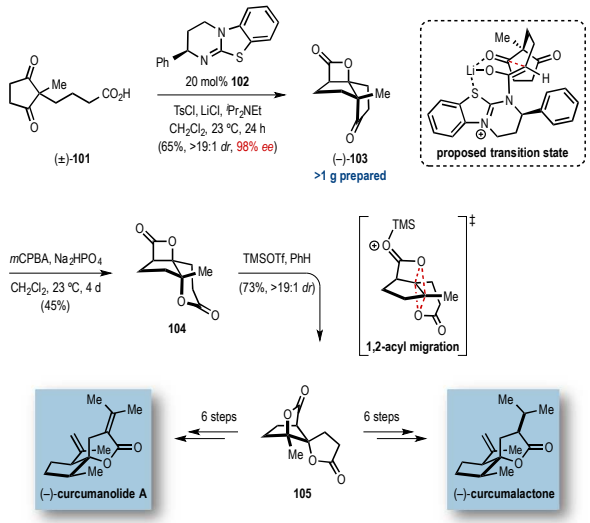
The utility of the DAL methodology was validated through a short, enantioselective synthesis of cyclohexenone (–)-**100** from cycloadduct **99**. Bicyclic lactone **100** was previously employed in racemic form for the synthesis of (±)-fraxinellonone, a degraded limonoid that displays moderate antifeedant and ichthyotoxicity activity, in addition to (±)-trisporic acid and (±)-trisporols, naturally occurring fungal pheromones derived from β-carotene (Scheme 12).



Scheme 12. Application of bicyclic γ-lactone **99** towards the formal syntheses of fraxinellonone, trisporic acids, and trisporols.

5.2 Romo's Total Synthesis of (–)-Curcumanolide A and (–)-Curcumalactone.

A recent example of scalable, ammonium enolate catalysis can be found in the asymmetric, divergent route to the spirocyclic sesquiterpene natural products (–)-curcumanolide A and (–)-curcumalactone from common spirocycle **105** (Scheme 13).[32a] These spirolactone-containing sesquiterpenoids are present in the crude drug Zedoary, have been used as remedies for cervical cancer, and were reported to exhibit anti-inflammatory activity. The synthesis of these natural products demonstrated the gram-scale utility of the organocatalytic, asymmetric nucleophile-catalyzed aldol-lactonization (NCAL) desymmetrization process[32b] of dione acid (±)-**101** leading to a tricyclic β-lactone (–)-**103** *via* a proposed bicyclic boat-like transition-state arrangement (as depicted in Scheme 13). Furthermore, the ability to perform a Baeyer-Villiger oxidation in the presence of a β-lactone (–)-**103** led to the ring-expanded δ-lactone **104** and set the stage for a key dyotropic rearrangement. This rare dyotropic process, involving a fused bis-lactone **104** possessing both β- and δ-lactone moieties, enabled rapid access to the core structure **105** of curcumanolide A and curcumalactone. Our current mechanistic understanding of the transition state for this transformation, based on computational studies by the Tantillo group, involves a nearly concerted, stereospecific, "double S_N2" 1,2-bis-acyl migration process (as shown in Scheme 13) delivering the bridged, spiro-γ-butyrolactone **105**.[32c] The described enantioselective total synthesis of curcumanolide A and curcumalactone was accomplished in 11 and 12 steps, respectively, and employed scalable, ammonium enolate organocatalysis.



Scheme 13. Romo's total synthesis of (–)-curcumanolide A and (–)-curcumalactone.

Although racemic, a recent application of the NCAL methodology by Weinreb deserves mention given that it was performed on >2 g scale and utilized as a key step for constructing the *cis*-2-azadecalin found in the indole alkaloids, (±)-alstilobanine A and E, and (±)-angustilodine.[33]

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6 Conclusions and Perspective

In the past decade, the field of asymmetric covalent organocatalysis has seen tremendous progress. This *Highlight* has briefly illustrated the power of these organocatalytic reactions, which have become a prevalent and highly efficient tool in organic chemistry. The discovery and implementation of new reactivities and organocatalysts led to a considerable surge in reaction efficiency and selectivity. Indeed, the discovery of novel activation modes for substrates employing secondary amine catalysis, N-heterocyclic carbine catalysis, phosphine catalysis, and tertiary amine catalysis has enabled rapid construction of molecular complexity with excellent levels of stereocontrol and simple operational procedures employing non-heavy metal catalysts. These advances have led to many successful and imaginative applications of asymmetric covalent organocatalysis in the field of scalable natural product synthesis. Despite significant innovations in this highly topical area, there still remain many challenges and opportunities ahead. Certainly, the relatively high catalyst loading (*e.g.*, 10 and 20 mol%) in many cases leaves room for future improvement. Furthermore, the discovery of novel modes of substrate activation, especially of commodity chemicals, will drive further advances in the area of organocatalysis enabling unusual disconnections and more practical procedures. Based on the diversity of recently developed activation modes involving covalent organocatalysis, numerous organocascade sequences can be envisaged and will undoubtedly be applied to more ambitious synthetic targets. Given these advances, we further anticipate powerful strategies for the scalable synthesis of biologically relevant molecules including bioactive natural products and pharmaceuticals, providing invaluable tools for continued advances in biology. However, realizing these goals in earnest, necessitates not only the discovery but also invention of new modes of reactivity, that either exposes or amplifies both the innate and sometimes hidden reactivity of organic substrates, which in turn contributes to further developments in chemical synthesis logic. This principle finds its full expression in the words of the epitome of the artist-scientist, Leonardo da Vinci:

> *"Where nature finishes producing its own species, man begins, using natural things and with the help of this nature, to create an infinity of species."*

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