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Perspective

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The Modern Face of Synthetic Heterocyclic Chemistry

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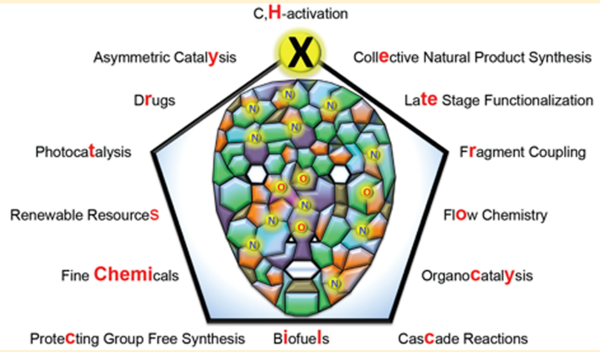
ABSTRACT: The synthesis of heterocycles is arguably one of the oldest and at the same time one of the youngest disciplines of organic chemistry. Groundbreaking principles to form heterocycles, mainly by condensation reactions, were recognized in the beginning of the 19th century, and many of the classical reactions discovered at that time are still of great value today. In the 21st century, the wealth of synthetic methodology toward heterocycles is overwhelming, and catalysis, in particular, as one of the cornerstones of green and sustainable chemistry has contributed in a major way to these developments. This perspective tries the impossible by discussing some recent advances in the construction of heterocycles, focusing on catalytic methodology. We are aware that we do not come close to giving adequate credit to the great creativity of chemists in the field.



■ INTRODUCTION

Heterocyclic chemistry has a rich history with a huge impact on all areas of organic and medicinal chemistry.[1] In particular, natural products, drugs, and renewable resources prominently feature a great variety of heterocyclic moieties that are essential for their manifold properties. Penicillin (antibiotic), cyclosporine (immunosuppressant), azidothymidine (HIV), and sofusbuvir (hepatitis C), to name a few, have changed the world for the better, and it is estimated that antibiotics alone have increased the life expectancy of society up to 10 years.[2] In the aftermath of 9/11, the words "in Cipro [floxacin] we trust" of anchorman Tom Brokaw on Nightly News Monday[3] reassured the US that the threat of bioterrorism can be met by modern developments of heterocyclic chemistry, although this connection was probably not apparent to the lay audience.

Carbohydrates (mainly cellulose, hemicellulose, and lignin), as the most abundant renewable resource on earth, will become in the future the major feedstock for chemical and energy production.[4] Nevertheless, the (ideally catalytic) direct conversion of such renewables into fine chemicals poses a great challenge for heterocyclic chemistry with respect to the selective activation of stable Csp^3–O and Csp^3–H bonds, which will undoubtedly result in the development of many exciting synthetic methods in the future.

Stereoselective synthesis, mediated by auxiliaries or catalysts, would not be possible without the electronic and steric control that can be enacted through heterocycles. Likewise, particularly stable entities such as C,H bonds can be often be activated through the combination of electronic and directing effects a heteroatom in the heterocycle might display, thus opening up versatile and efficient routes for their functionalization. Seminal developments of general synthetic methodology toward heterocycles often discovered decades or even centuries ago have lost none of their importance for heterocyclic chemistry in the 21st century, such as the [3 + 2]-Huisgen cycloaddition, [2 + 2]-Paterno–Büchi reaction, Fischer indole, Friedlander, Bischler–Napieralski isoquinoline, or Paal Knorr syntheses. Nobel prize winning achievements such as asymmetric epoxidation, cross coupling, or metathesis reactions have found spectacular applications in the synthesis and functionalization of heterocycles.

It would be impossible to compose a comprehensive review on all the great achievements that are made in heterocyclic chemistry, even if one would cover only the most recent literature. In this perspective, we will attempt to point out some recent developments geared especially toward the interest of the readership of *The Journal of Organic Chemistry*, highlighting strategic trends in complex total synthesis of natural products in combination with new catalytic methodology for the synthesis or transformation of heterocycles. The latter will focus on privileged heterocyclic scaffolds relevant for drug development that contain only one heteroatom. We feel that this way different synthetic strategies toward common motifs in heterocyclic chemistry can be best illustrated; however, we are clearly aware of the great importance of heterocyclic structures containing several heteroatoms for medicinal chemistry. We hope that this Perspective, being no more than a snapshot of the field, will contribute in creating a sense for the community dedicated to this exciting research area.

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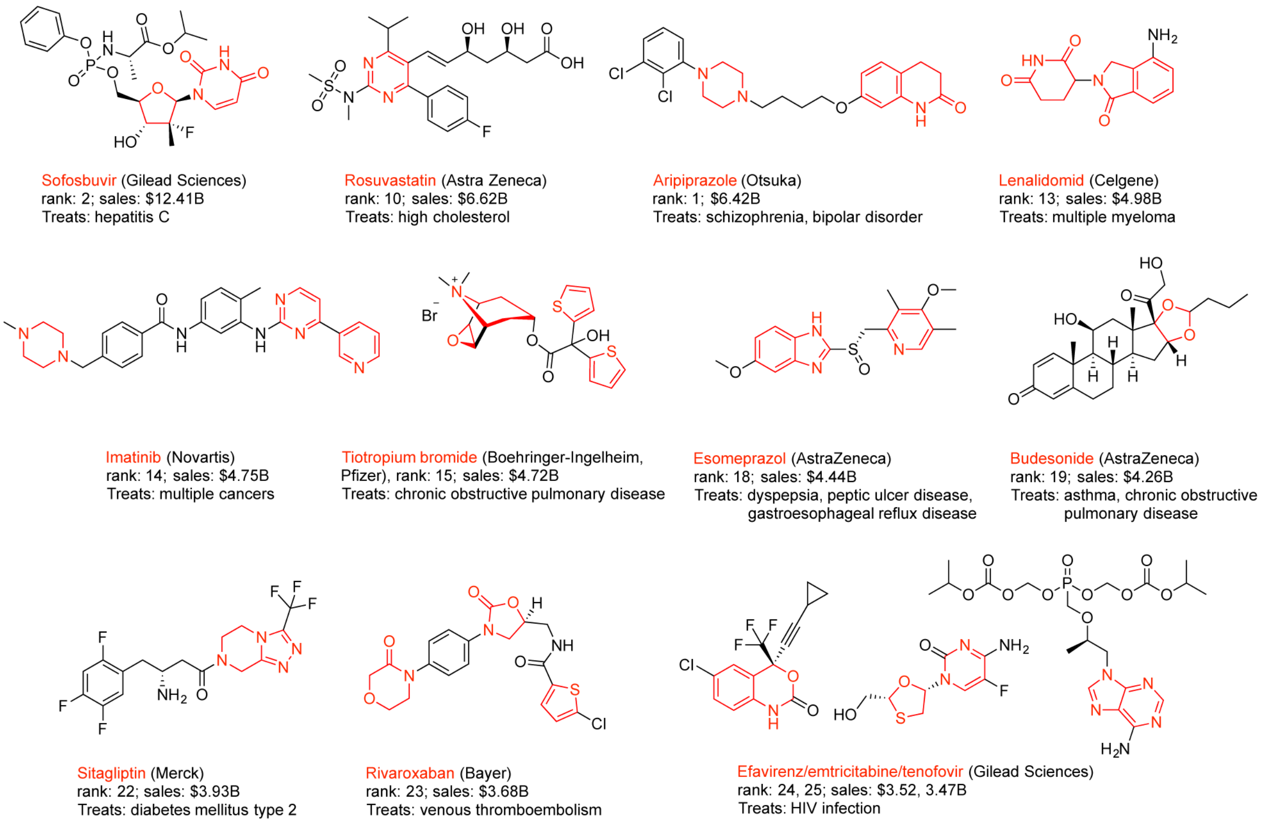


Sofosbuvir (Gilead Sciences)
rank: 2; sales: \$12.41B
Treats: hepatitis C

Rosuvastatin (Astra Zeneca)
rank: 10; sales: \$6.62B
Treats: high cholesterol

Aripiprazole (Otsuka)
rank: 1; \$6.42B
Treats: schizophrenia, bipolar disorder

Lenalidomid (Celgene)
rank: 13; sales: \$4.98B
Treats: multiple myeloma

Imatinib (Novartis)
rank: 14; sales: \$4.75B
Treats: multiple cancers

Tiotropium bromide (Boehringer-Ingelheim, Pfizer), rank: 15; sales: \$4.72B
Treats: chronic obstructive pulmonary disease

Esomeprazol (AstraZeneca)
rank: 18; sales: \$4.44B
Treats: dyspepsia, peptic ulcer disease, gastroesophageal reflux disease

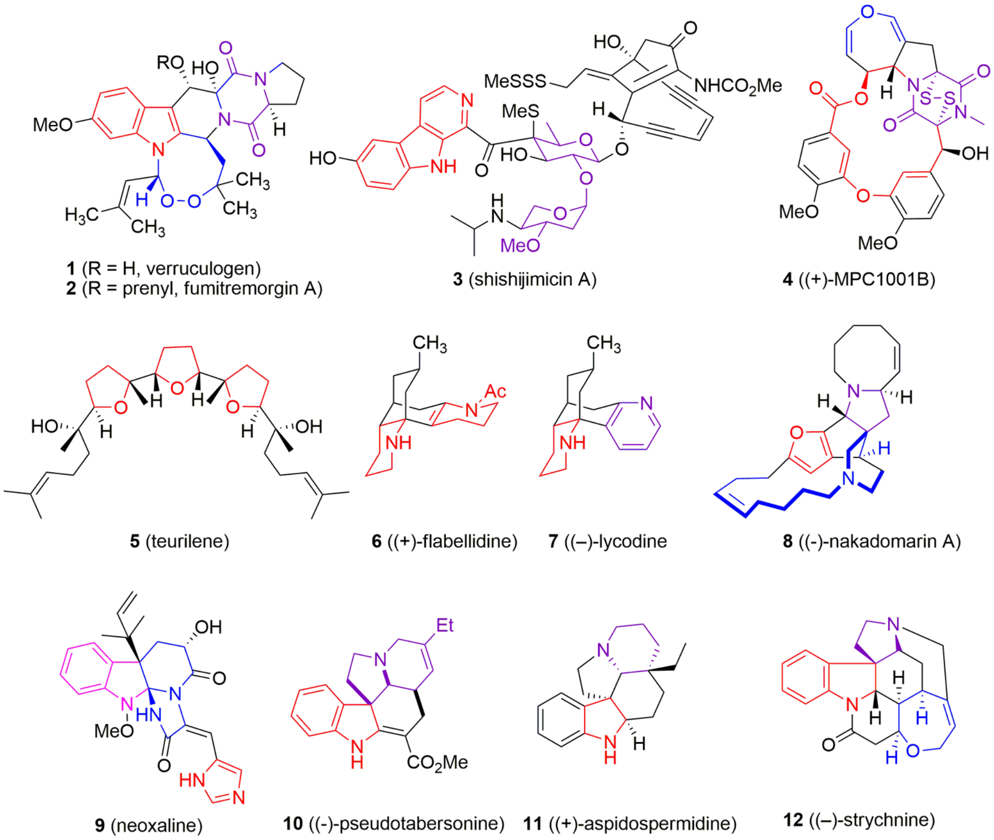
Budesonide (AstraZeneca)
rank: 19; sales: \$4.26B
Treats: asthma, chronic obstructive pulmonary disease

Sitagliptin (Merck)
rank: 22; sales: \$3.93B
Treats: diabetes mellitus type 2

Rivaroxaban (Bayer)
rank: 23; sales: \$3.68B
Treats: venous thromboembolism

Efavirenz/emtricitabine/tenofovir (Gilead Sciences)
rank: 24, 25; sales: \$3.52, 3.47B
Treats: HIV infection

Figure 1. Top grossing pharmaceuticals (2014) containing heterocyclic moieties.



1 (R = H, verruculogen)
2 (R = prenyl, fumitremorgin A)

3 (shishijimicin A)

4 ((+)-MPC1001B)

5 (teurilene)

6 ((+)-flabellidine)

7 ((−)-lycodine

8 ((-)-nakadomarin A)

9 (neoxaline)

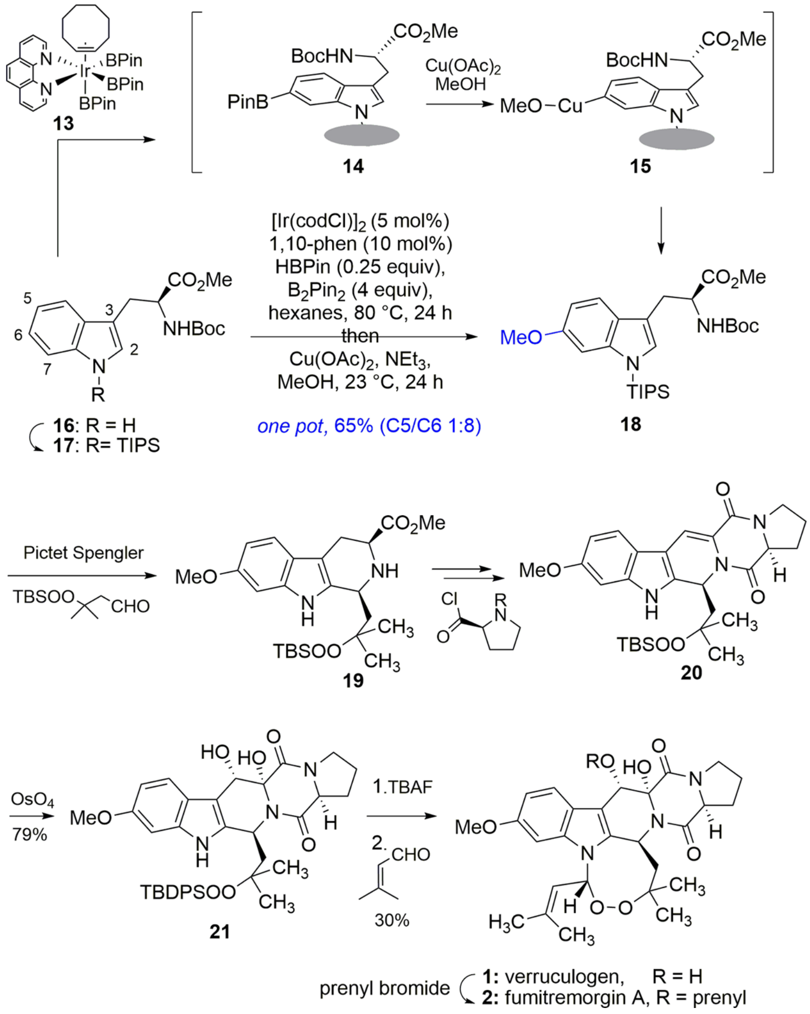
10 ((-)-pseudotabersonine)

11 ((+)-aspidospermidine)

12 ((−)-strychnine)

Figure 2. Selection of natural products featuring common scaffolds relevant in medicinal chemistry.

Scheme 1. Total Synthesis of Verrucologen (1) and Fumitremorgin A (2)[6]



■ DRUGS AND NATURAL PRODUCTS CONTAINING PRIVILEGED SCAFFOLDS

Heterocycles continue to play an overwhelming role in the development of new drugs. Among the top 25 best-selling pharmaceuticals from the year 2014, there have been 12 small molecules with heterocyclic moieties, by and large nitrogen-containing ones, accounting for more than 50 billion USD in annual revenue (Figure 1).[5]

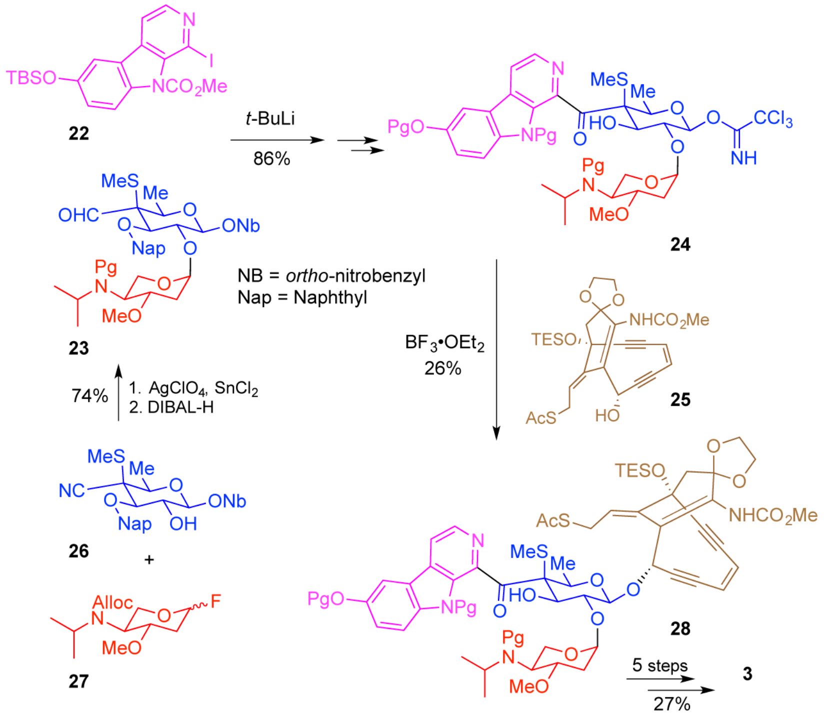
Life-threatening diseases like hepatitis C or AIDS have become treatable with high success rates, having saved millions of lives but at the same time revealing the ethical dilemma caused by the high costs being in part due to long development times mandated by strong safety concerns of society and short patent protection times counteracting the necessity to distribute such drugs to economically weak regions in Africa or Asia at low cost.

Natural products continue to be the greatest inspiration in the search for new lead compounds for drugs. Utilizing many common heterocycles that have been recognized as privileged scaffolds in medicinal chemistry, a seemingly infinite diversity to incorporate those into complex structures is displayed by Nature: some examples are shown in Figure 2, which are chosen to illustrate some modern trends in total synthesis in the following sections (see Schemes 3−10).

The creativity Nature displays for heterocyclic architecture allows chemists to devise imaginative ways for the synthesis of such complex structures. Such targets often require challenging transformations that appear impossible to achieve, which has been a major driving force for the development of synthetic methodology that subsequently became of great value in general. Moreover, the aim is not only to conquer a natural product by its total synthesis but at the same time to include sustainable and green principles such as atom and step economy, convergent and cascade strategies, fragment coupling with high functional group tolerance, selective C,H-bond activations with minimal involvement of protecting groups, or catalytic transformations with environmentally benign and cost-economic reagents.

Illustrating such principles, the bioactive alkaloids verruculogen (**1**) and fumitremorgin A (**2**) were synthesized from commercially available Boc-L-Trp-OMe **16** in only 11 and 12 steps, respectively, by Baran and co-workers (Scheme 1).[6] In a carefully orchestrated sequence of events that were expertly carried out, the hexacyclic structure of the targets was efficiently assembled, capitalizing on proven transformations such as Pictet−Spengler cyclization onto an indole moiety, α-amino acid condensation to install a diketopiperazine, or hydroperoxide/hemiaminal cyclization to install the unusual eight-membered endoperoxide.

Scheme 2. Highly Convergent Fragment Coupling Approach for the Synthesis of Shishijimicin A (3)[10]



In this total synthesis, an important piece of the puzzle for regioselective indole functionalization has been found in the synthesis of the rather inconspicuous-appearing 6-methoxy indole **18**. In contrast to known transformations to functionalize indoles at C2, C3, and C7,[7] methods for C6 functionalization were elusive. A convincing solution for this problem was found with the one-pot protocol featuring an iridium-catalyzed C,H-borylation[8] followed by Chan−Lam−Evans[9] coupling with methanol. Protecting indole (**16**) with the sterically demanding TIPS group shields C2 and C7 and employing 1,10-phenanthroline (phen) as a ligand for iridium are required for high C6/C5 regioselectivity, and the regioselective methoxylation of **17** in the 6-position was achieved on gram scale. Catalytic amounts of HBPin had to be employed as co-catalyst to $[\mathrm{Ir(cod)Cl}]_2$, which might serve as a hydrogen donor to generate the active cyclooctene-coordinated catalyst **13**, which has been proposed by Ishiyama, Miyaura, and Hartwig in their groundbreaking work of this type of transformation.[8]

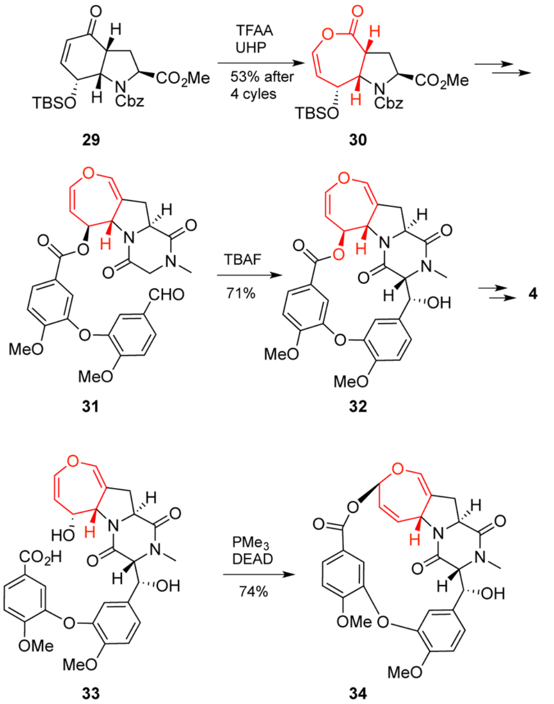
The marine natural product shishijimicin A (**3**) (Figure 2), having sub-picomolar antitumor properties, features a carboline system as part of its DNA binding domain, differing from other well-known enediyne natural products such as calicheamicin $\gamma 1$. In a highly convergent approach, Nicolaou and co-workers succeeded in the first total synthesis of the densely functionalized **3**, in which the interplay of the full range of orthogonal protecting group strategies and several fragment couplings were instrumental for its successful assembly (Scheme 2).[10]

A macrolactone, as the characteristic structural element in many natural products, is ingeniously combined with a dithioketopiperazine and a seven-membered dihydrooxepine in the MPC1001 family. Such compounds show a broad biological profile, especially against human prostate cell lines. Tokuyama and co-workers recently disclosed a total synthesis of MPC1001B (**4**, Figure 2), demonstrating the successful dihydrooxepine construction via regioselective Bayer−Villiger oxidation of a cyclohexanone moiety with trifluoroacetic anhydride/urea hydrogen peroxide (TFAA/UHP). The surprises often encountered with the formation of macrocycles were seen in the final stage of the synthesis: attempting to cyclize **33** by a macrolactonization strategy gave rise to the 17-membered **34** rather than the desired 15-membered **32** as shown by Tokuyama and co-workers.[11] However, the fluoride-induced, intramolecular aldol reaction of **31** proved to be highly efficient giving rise to **32**, which could be further elaborated to the target compound **4** in a few more steps (Scheme 3).

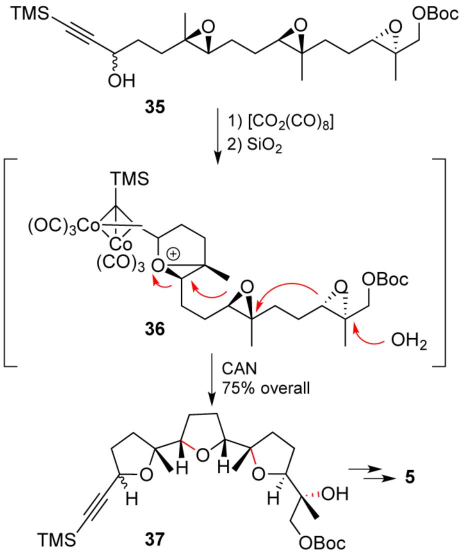
Cascade reactions are especially powerful for the rapid construction of complex architectures and have found many spectacular examples in natural product synthesis.[12] Inspired by the biomimetic pathway, a very successful approach toward polycyclic ether natural products, being of great interest as ionophores, are cascade cyclizations of a polyepoxide backbone.[13] One principle difficulty encountered with such a strategy is the necessity to selectively activate one epoxide to initiate the cyclization. A convincing solution to this problem was disclosed by Martín, Martín, and co-workers in the synthesis of teurilene (**5**)[14] (Scheme 4, cf. Figure 2).[15] Precursor **35** was converted to the corresponding dicobalthexacarbonyl complex, which set the stage for an intramolecular Nicholas reaction. Activation with silica was sufficient to displace the propargylic hydroxyl group, which triggered the cascade via intermediate **36**. Upon oxidative decomplexation with CAN, **37** was obtained in high yield, which could be converted to teurilene (**5**) in three more high-yielding steps.

Owing to the monumental work and insightful analysis of Heathcock and co-workers, spectacular reactions cascades toward daphniphyllum alkaloids with great diversity have been unraveled.[16a] In a recent example of this strategy by Takayama et al.,[16b] a compelling interplay of enamine/iminium intermediates and chair-type transition states controlled by the pseudoequatorial preference of the methyl group as the sole stereogenic center has been demonstrated, allowing the

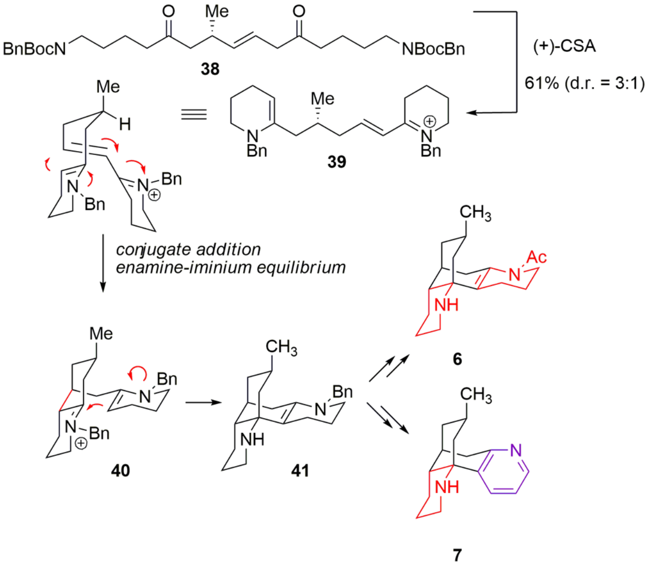
Scheme 3. Dihydrooxepine Construction and Macrocyclization Strategies in the Synthesis of MPC1001B (4, Figure 2)[11]



Scheme 4. Regioselective Cascade Cyclization in the Synthesis of Teurilene (5, cf. Figure 2)[15]



Scheme 5. Cascade Cyclization of 38 to 41 in the Synthesis of Lycopodium Alkaloids

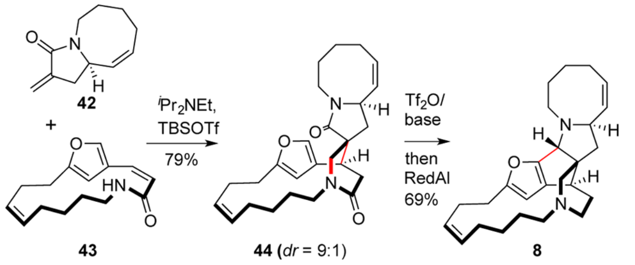


cyclization of the acyclic precursor **38** in a single step to the tetracycle **41** (Scheme 5).

The latter was readily transformed to flabellidine (**6**) and lycodine[17] (**7**), which belong to the family of *Lycopodium* alkaloids that are being evaluated for treatment of Alzheimer's disease.

There have been most impressive synthetic approaches developed toward highly congested natural products, often further complicated by quaternary stereocenters and strained medium-sized rings. In an exciting finish, Evans and co-workers[18] completed the synthesis of (−)-nakadomarin A[19] (**8**), an alkaloid that belongs to the manzamine family with a fascinating assembly of differently sized heterocycles (Scheme 6).

Scheme 6. Final Stages in the Synthesis of (−)-Nakadomarin A (8)[18]

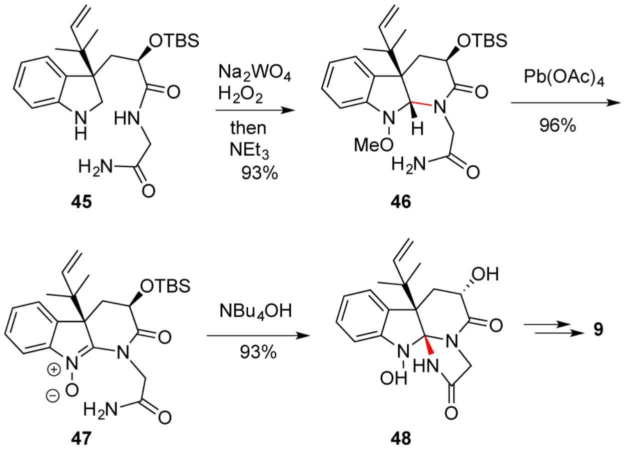


When lactams **42** and **43** in the presence of Hünig's base and TBSOTf were combined, a cascade conjugate addition gave rise to **44** with high yield. The diastereoselectivity was governed by convex/concave differentiation of the bicyclic ring structure through the single stereocenter present in **42** and dipole minimization by orienting the carbonyl moieties *anti* to each other. In **44**, the furan and lactam moiety are ideally oriented for the final bond construction by an electrophilic substitution to complete (−)-nakadomarin A (**8**), which was achieved by activation with triflic acid anhydride followed by RedAl reduction in a one-pot protocol.

Neoxaline (**9**, Figure 2), which was found to inhibit cell proliferation and arrest the cell cycle during the M phase, features an unusual indoline spiroaminal framework with two contiguous quaternary stereocenters. Omura, Sunazuka, and co-workers were able to build up this core by a high-yielding series of oxidations, demonstrating that the sophistication in the development of chemoselective transformations of functional groups with similar reactivity is constantly increasing (Scheme 7). Starting with the oxidative ring closure of **45** to **46** mediated by sodium tungstate followed by lead tetraacetate oxidation set the stage for the second ring closure to **48**.[20]

The great advances that have been made in the development of chemoselective transformations compatible with a wide

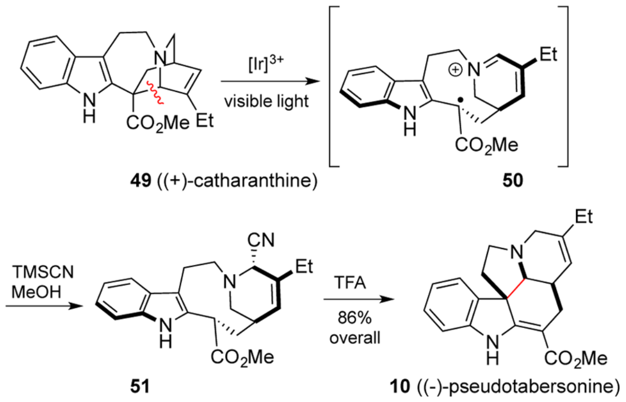
Scheme 7. Construction of the Indoline Spiroaminal Core in the Synthesis of Neoxaline (9, Figure 2)[20]



range of functional groups is increasingly recognized for the late-stage functionalization (LSF) of natural products, which has a major impact on drug development. LSF not only speeds up the discovery of new chemical entities but also turns around the logic of chemical synthesis, achieving protecting group free introductions of functional groups into complex chemical structures.

Using such a strategy, Stephenson and co-workers developed the iridium(III)-mediated photooxidation of commercially available (+)-catharanthine (**49**) to the radical cation intermediate **50**, which could be trapped by TMSCN and MeOH to give rise to **51** in excellent yield (Scheme 8).

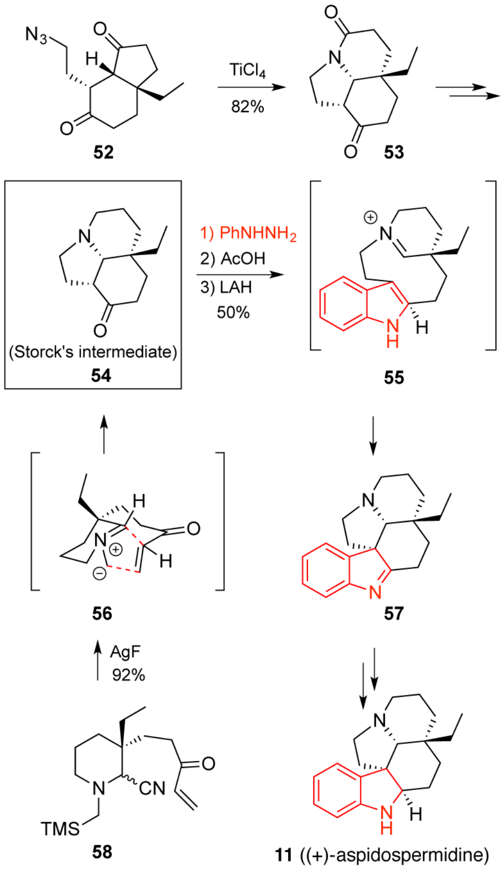
Scheme 8. Synthesis of (−)-Pseudotabersonine (10) by Photooxidative Fragmentation of (+)-Catharanthine (49)[21]



Compound **51** served as the starting point to rapidly construct several alkaloids, among them (−)-pseudotabersonine (**10**), which was obtained in a single step upon treatment with trifluoroacetic acid.[21]

Spanning more than 130 years of development, the synthesis of the pentacyclic alkaloid aspidospermidine (**11**) nicely illustrates modern developments of asymmetric synthesis and catalysis along with a shift in synthetic logic to tackle complex synthetic targets (Scheme 9, 10). In 1963, Dolfini and Stork[22] disclosed that a stereoisomeric mixture of ketone **54** can be efficiently converted to the targeted pentacyclic alkaloids via the classic Fischer indole synthesis (discovered in 1883) in diastereomerically pure form (Scheme 9). The stereoconvergent course of this transformation was rationalized by the

Scheme 9. Huisgen [3 + 2]-Cycloaddition, Fischer Indole Synthesis, and Aubé−Schmidt Reaction as Key Steps in the Synthesis of Aspidospermidine (11)



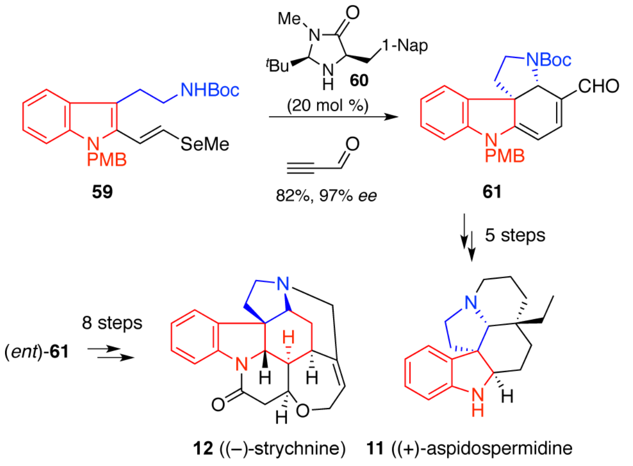
formation of intermediate **55**, in which the single remaining stereogenic center dictates the outcome of the reaction by forming the most stable isomer **57**. Consequently, the tricycle **54** has become a key target for the synthesis of aspidospermidine (**11**) and related alkaloids.

Aubé and co-workers[23] disclosed the first enantioselective synthesis of **54** and in this course developed the intramolecular variant of the Schmidt reaction, yet another classic transformation dating back to 1924, with the cyclization of azide **52** to the tricycle **53**. This type of transformation is now widely recognized to be of great value in natural product synthesis (Aubé−Schmidt reaction). In 2016, Pandey and co-workers[24] disclosed in a complex setting a modern variant of the Huisgen 1,3-dipolar [3 + 2]-cycloaddition: azomethineylide **56** could be generated under mild conditions from **58**, being readily available on gram scale, which underwent a highly efficient and stereoselective cycloaddition to give rise to **54** in excellent yield.

Contrasting the approach described above, MacMillan and co-workers identified **61** as a key intermediate that would allow not only the synthesis of (+)-aspidospermidine (**11**) but a whole series of structurally diverse alkaloids, namely (−)-strychnine (**12**), vincadifformine, akuammicine, kopsanone, and kopsinine (Scheme 10).[25]

Compound **61** was assembled with high enantiocontrol by an organocatalytic Diels−Alder/β-elimination/amine conjugate addition sequence. Imidazolinone catalysts of type **60**, introduced by MacMillan as a general solution for asymmetric organocatalyzed cycloadditions, are available in either enantio-

Scheme 10. Collective Alkaloid Synthesis Making Use of the Common Precursor 61, from which (+)-Aspidospermidine (11) and (−)-Strychnine (12) among Others Can Be Accessed in a Few Steps



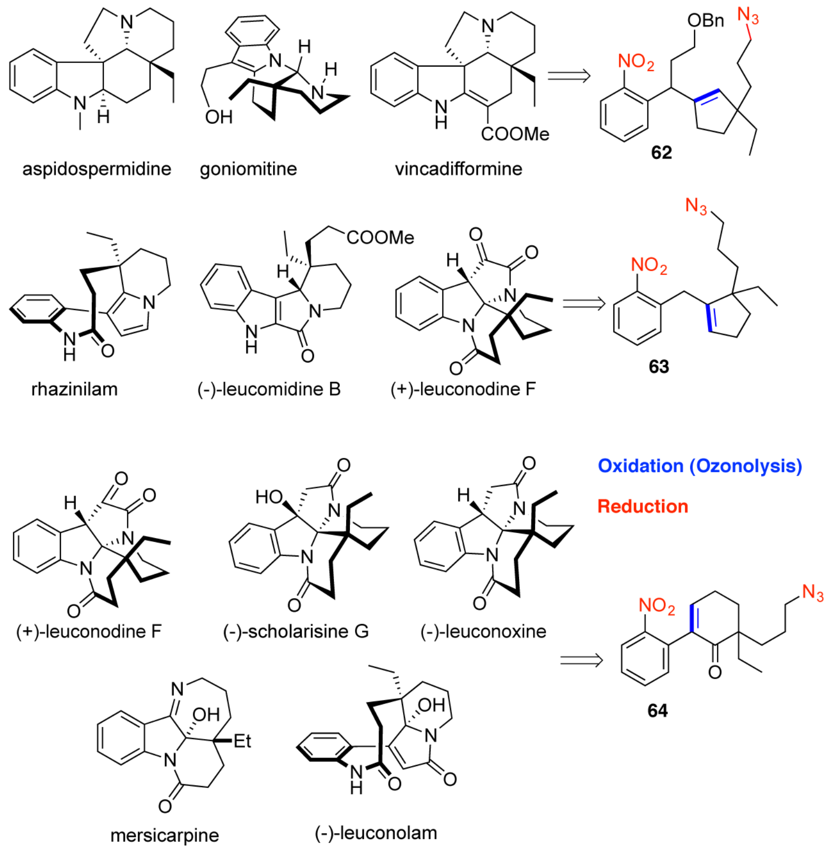
meric form, and consequently, both chiral domains of the alkaloids, which are indeed created by Nature, can be readily synthesized. Thus, *ent*-**61** provided a very efficient access to (−)-strychnine (**12**) in a total of nine steps, rivaling the record synthesis of Vanderwal and co-workers, which was achieved at the same time by a longest linear sequence of six steps.[26]

Taking this concept in a different direction, Zhu and co-workers disclosed the three building blocks **62**−**64** for which they could devise a one-pot integrated oxidation/reduction/cyclization that made the synthesis of a large number of structurally diverse alkaloids possible (Scheme 11).[27]

■ NEW METHODOLOGY FOR THE CONSTRUCTION OF PRIVILEGED HETEROCYCLIC SCAFFOLDS

The development of novel synthetic methods toward heterocyclic structures, especially for those that are prominently present in a large number of biologically active compounds, continues to be a highly active area. Catalytic methods that do not require elaborate prefunctionalization or protecting group manipulations and starting from readily available precursors are especially sought after, meeting the requirements of sustainable synthesis to a high extent. Noble metal catalysts still play a dominant role, but today there is also a strong focus on applying 3d metals such as iron, cobalt, or nickel, or on organocatalysts, even though in many cases the performance of those with respect to turnover cycles and rates have not reached the level that noble metal catalysts can provide. In particular, asymmetric metal or organocatalysis was greatly advanced by the aid of appropriate heterocyclic moieties, serving either as ligands or as the catalyst themselves. There is now a myriad of heterocyclic ligands and organocatalysts available; nevertheless, common motifs have been recognized that have proven to be applicable for a wide range of reaction types (Figure 3).[28]

Scheme 11. Total Synthesis of Structurally Diverse Alkaloids from Common Precursors 62−64 by a One-Pot Integrated Oxidation/Reduction/Cyclization



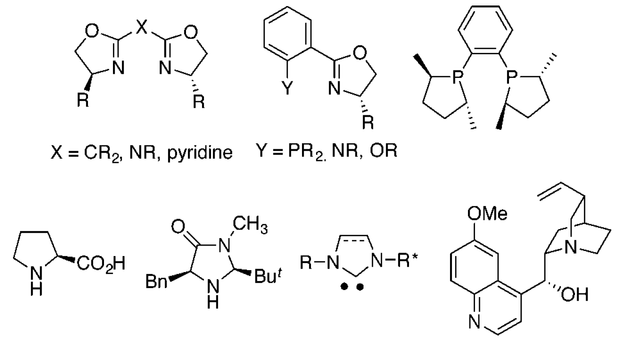


Figure 3. Privileged classes of heterocyclic ligands for metal and organocatalysts widely applied in asymmetric catalysis.

■ *β*-LACTAMS

Ever since the discovery of penicillin, *β*-lactams remain an important lead structure in medicinal chemistry. Expanding from the classical approach of [2 + 2]-cycloadditions utilizing isocyanates or ketenes, catalytic methodology to synthesize this scaffold from widely available precursors has been developed in great diversity.

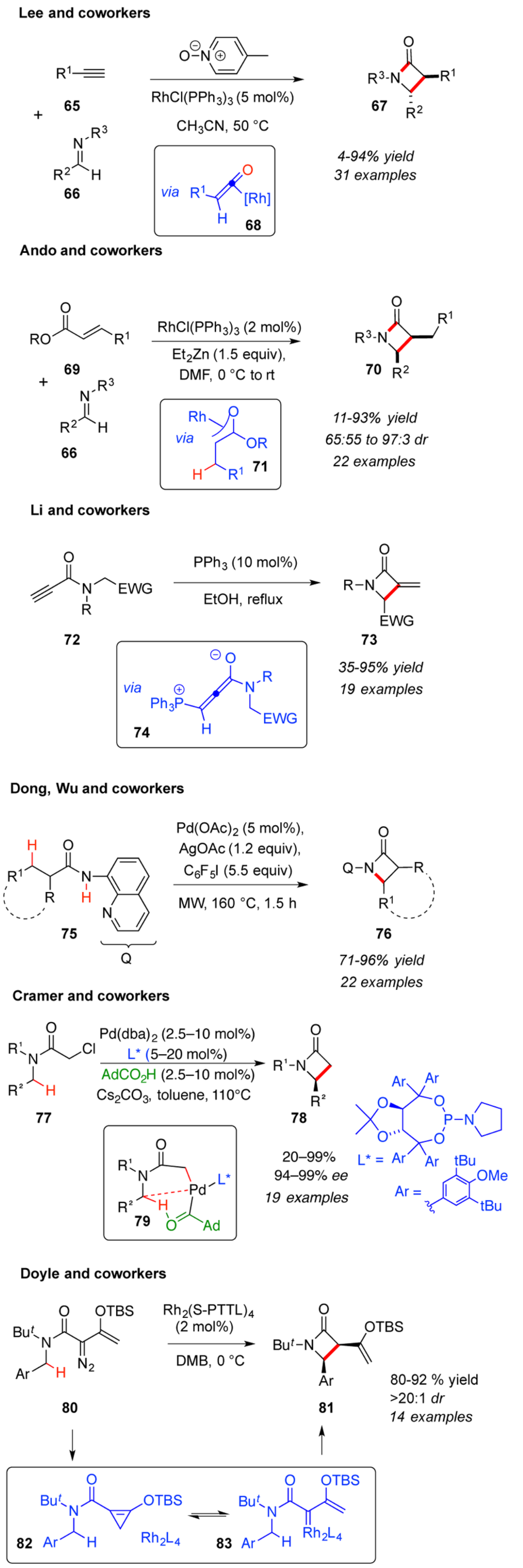
Lee and co-workers disclosed the oxidative generation of a rhodium–ketene species **68** (Scheme 12) from terminal alkynes, which underwent facile [2 + 2]-cycloaddition with imines to give rise to *β*-lactams **67** with high *trans* diastereoselectivity.[29] Complementary to this approach, Ando and co-workers were able to develop an approach in which the reductive formation of a Rh(I) enolate **71** was achieved that was also amenable to the reaction with imines **66**, arriving at *cis*-substituted *β*-lactams **70**.[30] An organocatalyzed Umpolung approach was successfully demonstrated by Li and co-workers by the addition of triphenylphosphine to propioamido acetates or ketones **72**, efficiently resulting in the formation of *β*-lactams **73** via the intermediate **74**.[31]

The Csp^3–H activation in *β*-position of carboxyamides **75** in the presence of catalytic amounts of Pd(OAc)$_2$ was achieved by Dong, Wu, and co-workers, which allowed an intramolecular amination to yield the title structure **76**.[32] High temperatures were needed; nevertheless, the products were obtained in excellent yields, demonstrating the thermal robustness under which many metal catalysts can be employed.

A complementary approach was followed by Cramer and co-workers, demonstrating the Csp^3–Csp^3 of *α*-chlorocaboxyamides **77**. Using chiral phosphonamide ligands, this transformation could be rendered asymmetric to yield lactams **78** with excellent enantioselectivities.[33] Featuring the same bond disconnections, Doyle and co-workers reported the rhodium(II)-catalyzed cyclization of **80** to lactams **81**. Notably, the authors identified that cyclopropenes **82** are initially formed in equilibrium with the carbenoid **83**, which eventually undergoes C,H-insertion to the final product **81**. These findings suggest that cyclopropenes can be activated by rhodium(II) catalysts for C,H-insertion processes as well, which might be an alternative to more commonly employed diazo compounds.[34]

These last examples impressively demonstrate innovative strategies to highly strained *β*-lactam structures; however, most of the methods discussed here are reported to generate only monocyclic structures. While there are a number of examples for biologically active monocyclic *β*-lactams such as the plasma cholesterol-lowering ezetimibe,[35] novel catalytic methodology

Scheme 12. Recent Developments for Catalytic Processes toward *β*-Lactams

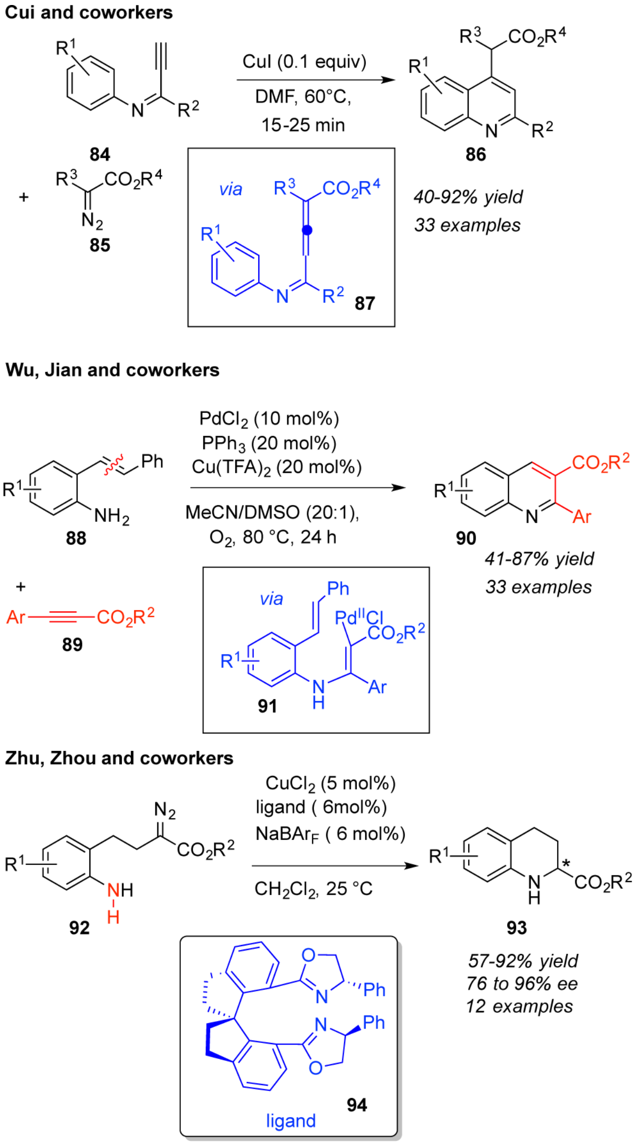


toward bicyclic structures that are in high demand as antibiotics would be especially desirable.

QUINOLINES

Quinolines display manifold biological activities, being important leads toward new antimalarial, anti-inflammatory, or antibacterial compounds. With the Friedländer, Camps, or Skraup quinolone synthesis, classic and reliable strategies based on condensation reactions are available toward these scaffolds. Catalytic methodology has led to new approaches to these structures, and a few recent developments are shown in Scheme 13.

Scheme 13. Recent Developments of Catalytic Processes toward Quinolines



In an intriguing application of copper(I)-catalyzed carbenoids derived from diazoesters **85**, Cui and co-workers demonstrated that those can be efficiently trapped by alkynylimines **84** to give rise to allene intermediate **87**, which undergoes facile 6π-electrocyclization to form quinolines **86**.[36] Wu, Jiang, and co-workers reported and unusual, but nevertheless broadly applicable palladium catalyzed oxidative cyclization of *ortho*-vinylanilines **88** and alkynes **89** with molecular oxygen, in which ultimately a carbon−carbon bond fission of the stilbene unit occurs.[37]

A plausible intermediate in this sequence is **91**, which subsequently undergoes carbopalladation to complete the quinoline ring structure. The resulting Pd(II) intermediate is then oxidized with concurrent elimination of an aromatic aldehyde.[37] A tetrahydroquinoline synthesis by Zhu, Zhou and co-workers by intramolecular cyclization of **92** marks the first highly enantioselective N−H insertion of carbenes. The ligand **94** was key for high enantiocontrol; other bis(oxazoline) ligands with a dimethylmethylene or pyridine backbone (cf. Figure 3), that are generally highly successful in asymmetric catalysis, failed to give appreciable enantioselectivities.[38]

INDOLES

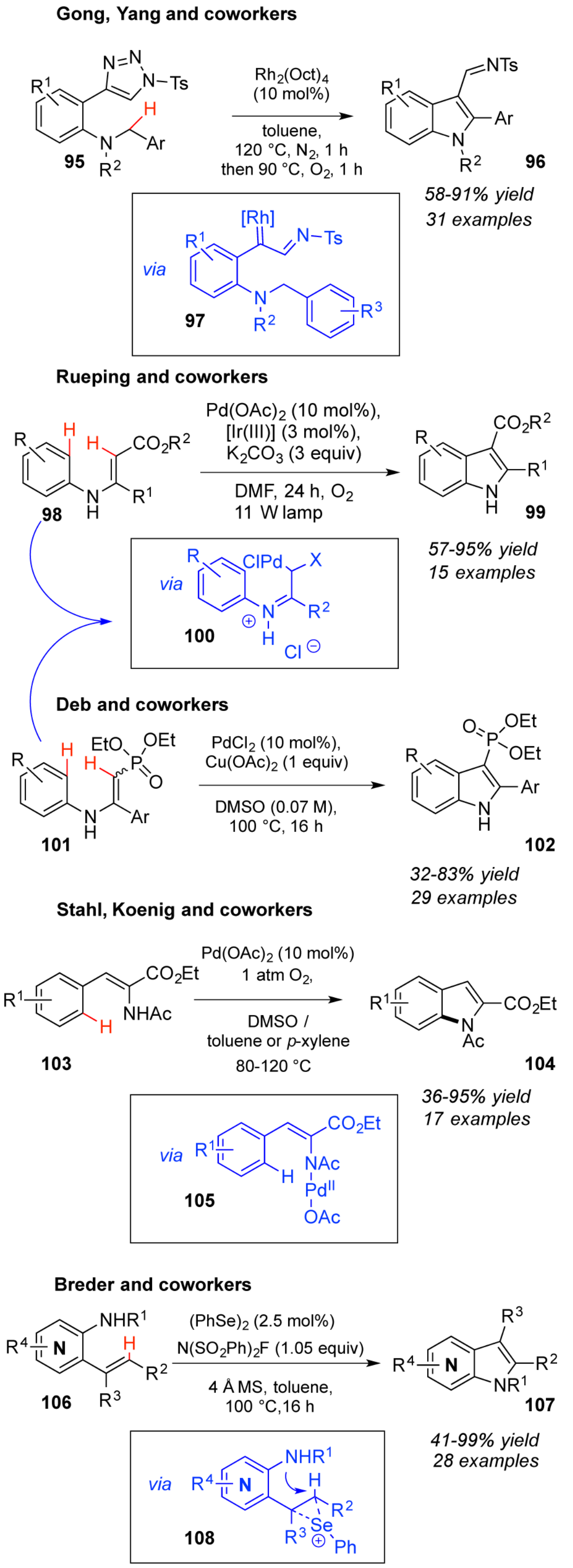
More than 130 years after Fischer devised the synthesis of indoles, the indole scaffold has become one of the most important lead structures for medicinal chemistry.[39] Notably, catalytic methodology involving C,H-activation has been devised, allowing the efficient cyclization of the five-membered pyrrole moiety at various positions (Scheme 14). Gong, Yang, and co-workers generated a rhodium(II)-carbenoid **97** by ring-opening of *N*-tosyltriazole **95**, which was amenable to C,H-insertion into *N*-alkylated anilines.[40] The resulting dihydroindoles were subsequently dehydrogenated to indoles **96** with molecular oxygen. Rueping and co-workers demonstrated a C,H-activation of enamines in β-position, utilizing the electrophilic nature of palladium(II)acetate that allows addition of electron rich alkenes.[41] Generating an intermediate of type **100**, a second C,H-activation with the arene moiety takes place, forming after reductive elimination of Pd(0) the indole core **99**. In order to close the catalytic cycle, reoxidation of Pd(0) to Pd(II) is necessary, which is accomplished by visible light photoredox catalysis with an Ir(III) catalyst and oxygen as terminal oxidant. Following the same concept, Deb and co-workers achieved the palladium(II)-catalyzed cyclization of **101**, using $Cu(OAc)_2$ as the terminal oxidant.[42] A C,H-activation by palladium(II) was also demonstrated by Stahl and Koenig, who exploited the directing/activating effect of an acetyl-protected amino group in **103** that allows ring closure with an adjacent arene. After formation of indoles **104** accompanied by palladium(0), the direct reoxidation to palladium(II) by oxygen was possible.[43]

A distinctively different, but remarkably efficient catalytic system for indole cyclization and related heterocycles was reported by Breder and Ortgies. Electrophilic $PhSe^{II}X$ is generated from diphenyl diselenide upon treatment with *N*-fluorobenzenesulfonimide serving as the terminal oxidant, which sufficiently activates alkenes **106** via **108** to allow nucleophilic ring closure that ultimately leads to **107**.[44]

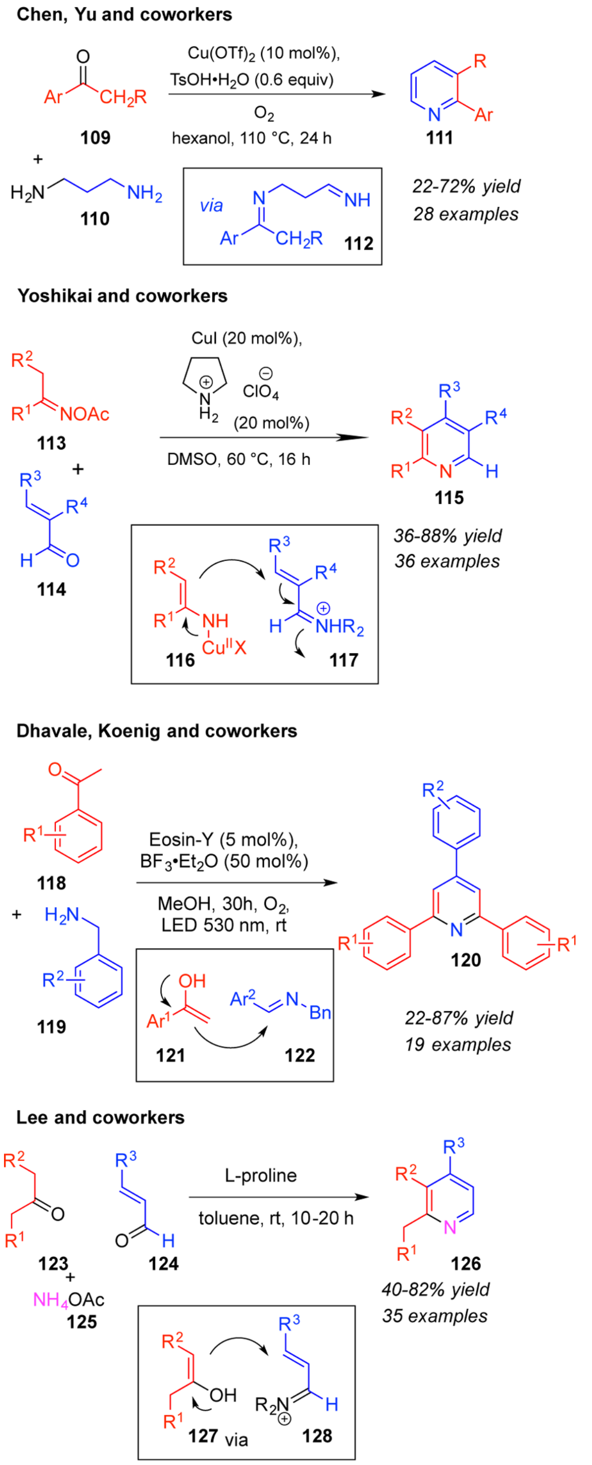
PYRIDINES

The pyridine synthesis according to Hantzsch can be regarded as a milestone in heterocyclic synthesis, and 130 years after its inception, the basic concept calling for condensation of an aldehyde with 2 equiv of a β-ketoester in the presence of ammonia can still be recognized in recent developments (Scheme 15). Chen, Yu, and co-workers demonstrated that 1,3-diaminopropane (**110**) can be efficiently coupled with acetophenones **109**, giving rise to 2-arylpyridines **111**. The role of the copper(II) catalyst is assumed to facilitate the amine

Scheme 14. Recent Developments of Catalytic Processes toward Indoles



Scheme 15. Recent Developments for Catalytic Processes toward Pyridines



oxidation to imine, giving rise to an intermediate like **112**, which then can further be cyclized followed by dehydrogenation to give rise to pyridines **111**.[45] The formal [3 + 3]-cycloaddition between oximes **113** and *α*,*β*-unsaturated carbonyl compounds **114** giving rise to pyridines **115** was accomplished by catalytic dual activation: The role of Cu(I) was proposed to reduce **113** to the nucleophilic enamine **116**, while the secondary amine activates **114** via the iminium cation **117**, acting as electrophile.[46]

Dhavale and Koenig demonstrated the coupling of acetophenones **118** and benzylamines **119**. Again, the key step in this process was the oxidation of the latter to imine **122**, which was achieved by eosin-Y as photocatalyst and oxygen as the stoichiometric oxidant.[47] The three-component condensation between ketones **123**, α,β-unsaturated aldehydes **124**, and ammonium acetate (**125**) is efficiently possible when L-proline is used as a dual catalyst. The latter activates the α,β-unsaturated carbonyl compound **124** as an electrophile **128** and the ketone **123** as a nucleophile **127**. After hydrolysis and final condensation with ammonia and oxidative aromatization, pyridines **126** are obtained in good yield and variety.[48]

■ PYRROLES AND FURANS

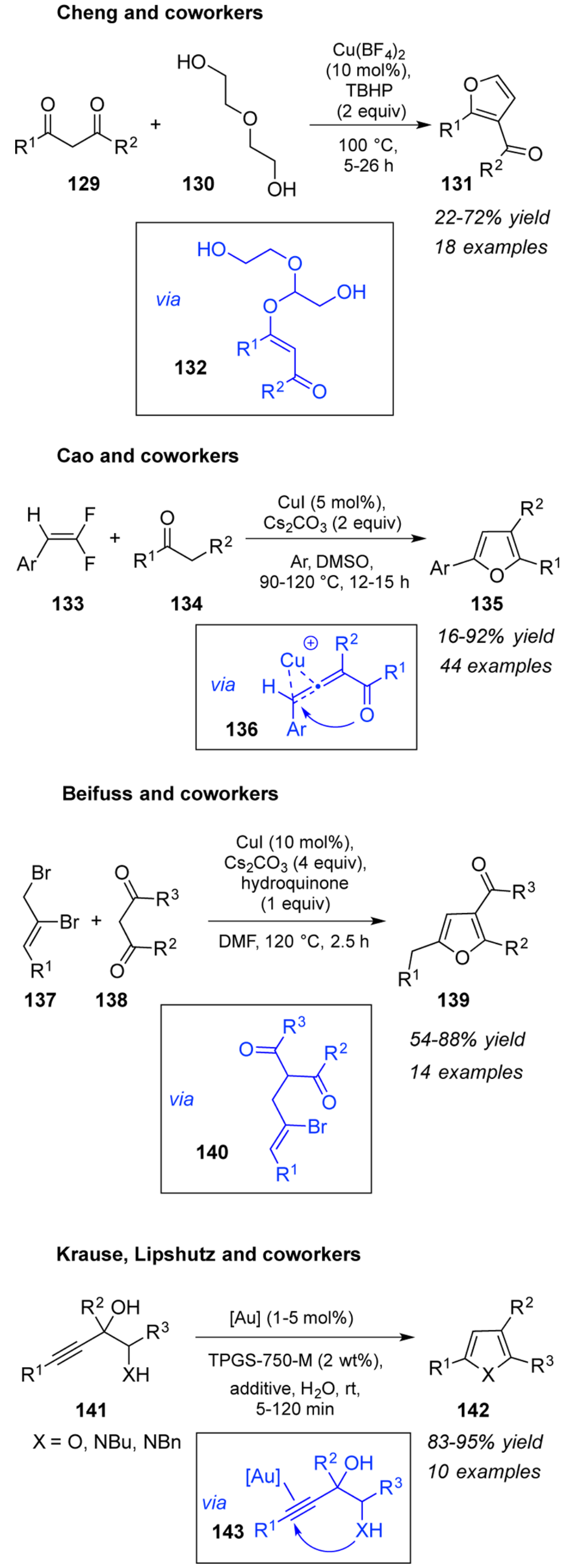
Classic methods for the synthesis of pyrroles and furans make use of the condensation of dicarbonyl compounds. The Paal−Knorr furan synthesis (acid-catalyzed cyclization of 1,4-dicarbonyl compounds) or the Feist−Benary synthesis (condensation of 1,3-dicarbonyl compounds with α-halogen ketones) are two examples that have been successfully utilized for a great variety of furans for more than 100 years. Looking at nitrogen, the Paal−Knorr pyrrole synthesis (cyclization of 1,4-dicarbonyl compounds with amines) or the Hantzsch pyrrole synthesis (reaction of β-ketoesters and α-halogen ketones with amines or ammonia) provide a reliable access to substituted pyrroles. Nevertheless, new variants of these classic themes are continuously being developed, and again, catalytic methods play a prominent role in these endeavors that often allow nonclassical bond constructions (Scheme 16).

The direct condensation between 1,3-dicarbonyl compounds **129** with diethylene glycol (**130**) to furans **131** was achieved by Cheng and co-workers.[49] Under oxidative conditions and catalyzed by Cu(II), sequential O- and C-functionalization of β-ketoester **129** by diethylene glycol (**130**) occurs, the latter serving as an equivalent for ethyne. Only water and alcohol are released, providing a sustainable process that has potential for the catalytic conversion of biomass into fine chemicals. An unusual condensation between 1,1-difluoroalkenes **133** and ketones **134** was discovered by Cao and co-workers, in which the formation of allene **136** is proposed as decisive intermediate that subsequently undergoes cyclization to furans **135**.[50] A conceptually interesting approach to furans **139** was reported by Beifuss and co-workers, in which ultimately a copper-catalyzed Ullmann-type coupling between an enol and a vinyl bromide is occurring via the initial substitution product **140**.[51] Alkyne activation by gold catalysts makes the synthesis of both furans and pyrrols of type **142** from propargyl alcohols **141** possible, featuring high yields and very short reaction times.[52]

■ PYRROLIDINES AND PIPERIDINES

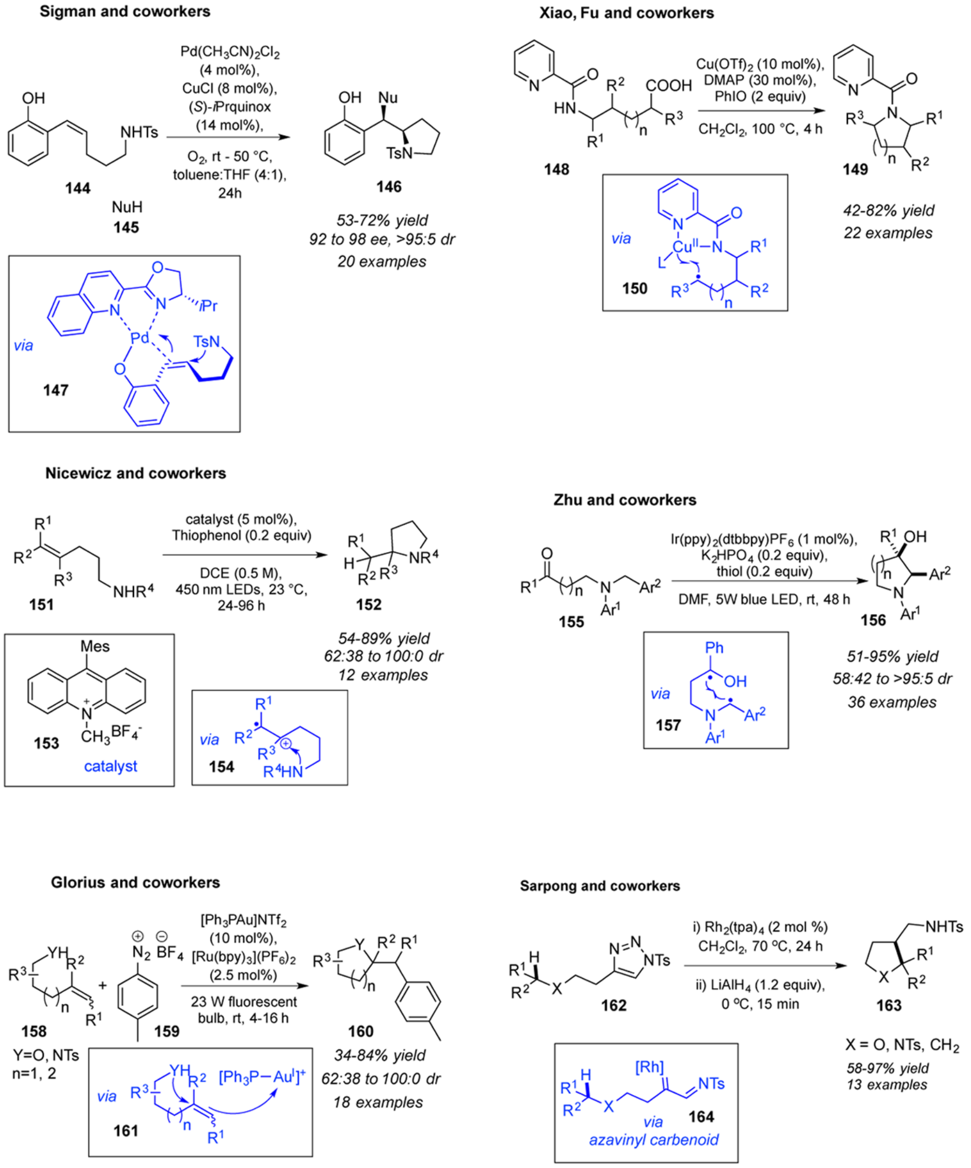
Acid-catalyzed, intramolecular addition of alcohols to alkenes offers a general synthetic route to tetrahydrofurans and dihydropyrans. The analogous cyclization toward pyrrolidines or piperidines as nucleophiles is less straightforward due to the deactivation of the amine rather than activation of the alkene by protonation. In recent years, a number of groundbreaking discoveries have been made to overcome this problem, and the underlying concepts are finding now fascinating applications in the synthesis of saturated nitrogen heterocycles (Scheme 17). Sigman and co-workers demonstrated the enantioselective hydroamination of alkenes **144** via their activation with a chiral palladium complex. After cyclization via intermediate **147**, the reaction is terminated by an external nucleophile (alcohols, indoles) giving rise to **146** with outstanding diastereo- and enantiocontrol.[53]

Scheme 16. Recent Developments of Catalytic Processes toward Furans and Pyrroles



Carbon-centered radicals have also been recognized as efficient coupling partners for amines. Xiao, Fu, and co-workers succeeded in the copper(II)-catalyzed decarboxylative amida-

Scheme 17. Recent Developments for Catalytic Processes toward Pyrrolidines and Piperidines



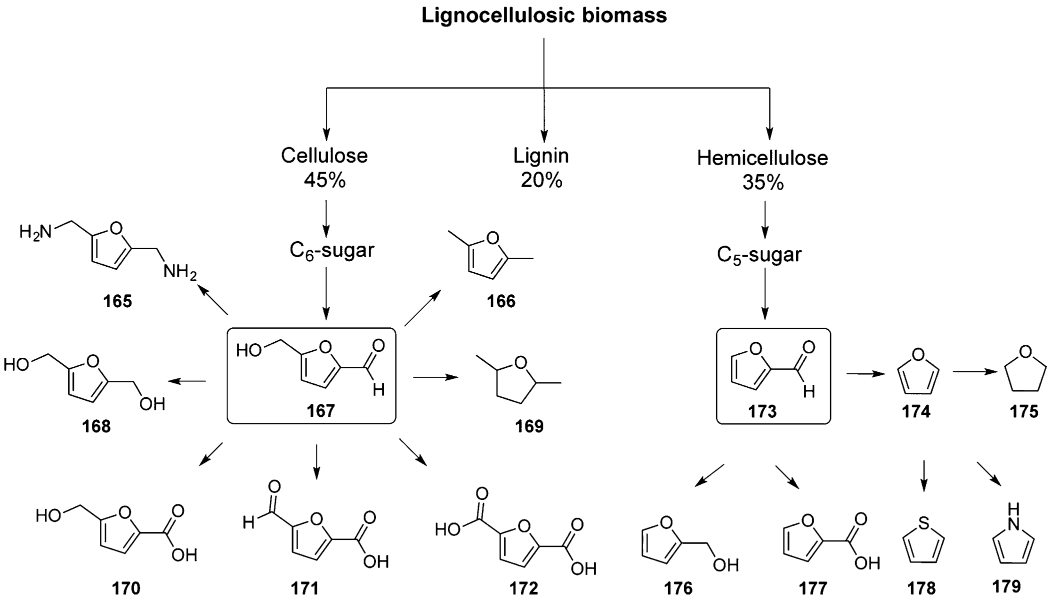
tion from unactivated carboxylic acids **148**, allowing the efficient synthesis of both pyrrolidines and piperidines from readily available starting materials. Stabilization of Cu(II) by an 2-acylpyridyl directing group plays an important factor for the overall process, suggesting an intermediate **150** in the course of the reaction.[54]

Visible-light irradiation of the Fukuzumi catalyst **153** allows the oxidation of alkenes to radical cation intermediates **154**, which was exploited by Nicewicz and co-workers to achieve the hydroamination of **151** leading to pyrrolidines **152**.[55] In a related approach, Zhu and co-workers were able to combine visible-light-mediated one-electron amine oxidation, giving rise to α-amino radicals after proton loss, with one-electron carbonyl reduction. This way, starting from **155** the diradical **157** is generated which undergoes carbon−carbon coupling to pyrrolidines or piperidines **156**.[56] Combining visible light and photoredox catalysis, Glorius and co-workers could demonstrate the gold-catalyzed hydroamination of **158** via intermediate **161**, which is terminated by photochemically generated aryl radicals from diazonium salts **159**, ultimately leading to saturated oxygen and nitrogen heterocycles **160**.[57] The high reactivity of rhodium(II)carbenoids **164** for C,H-insertions was elegantly utilized by Sarpong and co-workers[58] for the synthesis of tetrahydrofurans and pyrrolidines **163** from triazoles **162**, which serve as a synthetic equivalent for azavinylcarbenes being generated by ring opening and metal-catalyzed decomposition of the resulting diazo compounds.

■ FURANS: TOMORROW’S HETEROCYCLIC STARTING MATERIALS FOR ORGANIC SYNTHESIS

Having so far highlighted some recent developments for the de novo syntheses of heterocyclic scaffolds, some of them should also be considered as starting materials for organic synthesis given the large quantities Nature provides. In a future world without oil, fine chemicals, drugs, and commodities will have to come from renewable resources. Carbohydrates in the form of lignocellulosic biomass represent the most abundant raw material on earth. Despite great efforts to establish carbohydrates as feedstock materials for organic chemistry, the current stage of development lacks far behind the production lines

Scheme 18. Platform Chemicals 6-Hydroxymethylfurfural (167, HMF) and Furfural (173)



based on oil and gas that were developed during the last 150 years. One of the problems involved with lignocellulosic biomass is that it occurs as a mixture of highly complex compounds with virtual identical hydroxyl functionalities, making selective transformations difficult. A "cracking" process of such biomass consists of its acid-catalyzed breakage and conversion to furans, namely 6-hydroxymethylfurfural (**167**, HMF) from hexoses and furfural (**173**) from pentoses, which have already been proven to be a formidable starting point for the production of biofuels, solvents, and polymers (Scheme 18).[59]

The development of catalytic and economically benign methodology to functionalize furans and to transform them into new entities appears therefore to be of special importance. The great diversity in reactivity furans display, e.g., for cycloadditions, rearrangements, and ring-opening reactions, makes them attractive starting materials for target and diversity-oriented synthesis.[60]

The ability to involve furans as 4π- or 2π-systems into cycloadditions allows the facile generation of complex polycyclic structures with multiple stereogenic centers that has been exploited in many variations for natural product synthesis. A challenge, however, is to achieve high diastereo- and enantiocontrol in the initial cycloaddition step (Scheme 19). Martin and co-workers have identified vinyl sulfoxide **181** as a dienophile for furans **180** that exhibits remarkable stereocontrol in Diels–Alder reactions: after oxidation of the sulfoxide with oxone, bicyclic **182** was obtained in high yield and enantioselectivity up to 99% ee. Ring-opening/cross-metathesis gave rise to highly substituted tetrahydrofurans **183** that should prove to be valuable preucursor to natural products such as coristatin A, davanone, or caruifolin.[61]

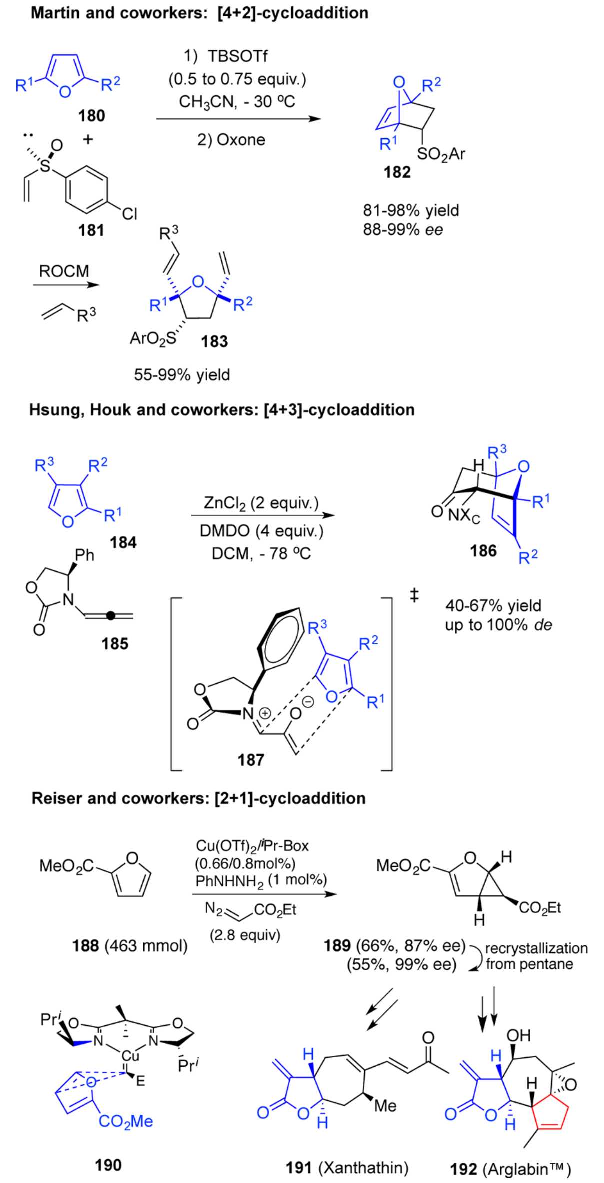
Hsung and Houk developed diastereo- and enantioselective [4 + 3]-cycloadditions with oxaallyls, being accessible from allenamide **185** upon epoxidation. The stereochemistry of the resulting biyclic structures of type **186** is highly dependent on the substitution pattern of the furan **184**, nevertheless, generally very high stereocontrol is achieved, opening a facile access to 7-membered carbocycles.[62]

The enantioselective cyclopropanation of **188** can be carried out on large scale in the presence of chiral Cu(I)–bis(oxazoline) complexes, giving access to **189**. Using the valine-derived *i*Pr-Box ligand for this transformation provided a cost-effective solution compared to the more selective *t*Bu-Box ligand derived from *tert*-leucin, given that **189** can be rapidly upgraded to enantiopurity by recrystallization. The latter proved to be a versatile building block for the facile synthesis of paraconic acids or sesquiterpene lactones such as the antibiotic xanthathin (**191**) or the antitumor drug arglabin (**192**).[63] In the latter, it should be noted that also the cyclopentane ring was derived from a furfural derivative, i.e., from furfurylalcohol (**176**).

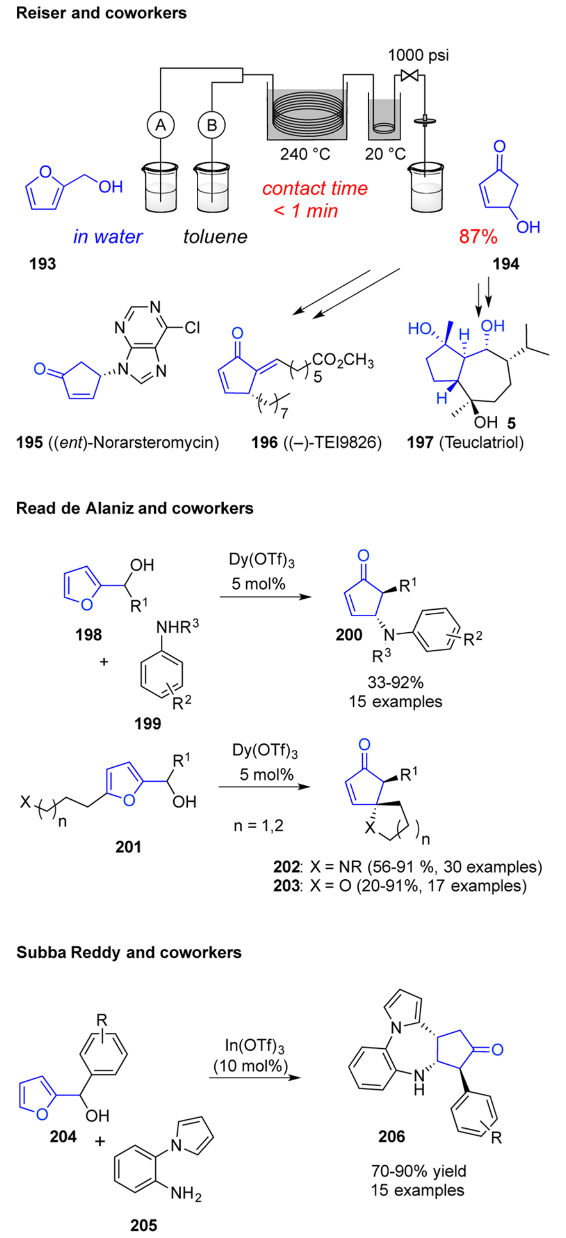
The Piancatelli rearrangement[64] of furfuryl alcohol (**193**) into 4-hydroxycyclopentenone (**194**) is of special value since it is one of the few reactions that converts a heterocycle into a carbocycle (Scheme 20). Discovered in the 1970s, this reaction was hampered by long reaction times, moderate yields, and impure product that required extensive purification procedures. Transferring this reaction into a flow reactor and thereby drastically increasing temperature and pressure but greatly reducing the exposure time of the materials to these conditions brought a significant advancement, allowing the production of **194** in a continuous process on hundreds of gram per day.[65a] Utilizing the Tsuji–Trost allylation allows the facile kinetic resolution of **194** to enantiopurity via its *O*-Boc derivative, which has been applied for the synthesis of *ent*-norarsteromycin (**195**), the *anti*-cancer drug (−)-TEI9826 (**196**), or teuclatriol (**197**) with high efficiency.[65b,c]

Read de Alaniz and co-workers developed the aza-Piancatelli rearrangement of **198** to **200** with remarkably high *trans*-selectivity when anilines **199** are employed as reaction partners.[66a] Next to scandium(III) triflate, dysprosium(III) triflate was found to be the most efficient catalyst, the latter being less expensive than the former. The same group also disclosed intramolecular variants of the process, allowing the efficient synthesis of spiroannelated cyclopentenones **202** or **203**.[66b,c] Very recently, Subba Reddy and co-workers disclosed a notable variant of the aza-Piancatelli rearrangement employing aniline **205**, which allowed the termination of the process

Scheme 19. Stereoselective Cycloadditions of Furans



Scheme 20. Recent Applications in the Piancatelli Rearrangement of Furfuryl Alcohols



by a Friedel−Crafts alkylation to access diazepine frameworks of type **206**.[67] In this study, besides Dy(OTf)$_3$, In(OTf)$_3$ was found to be an equally suitable catalyst.

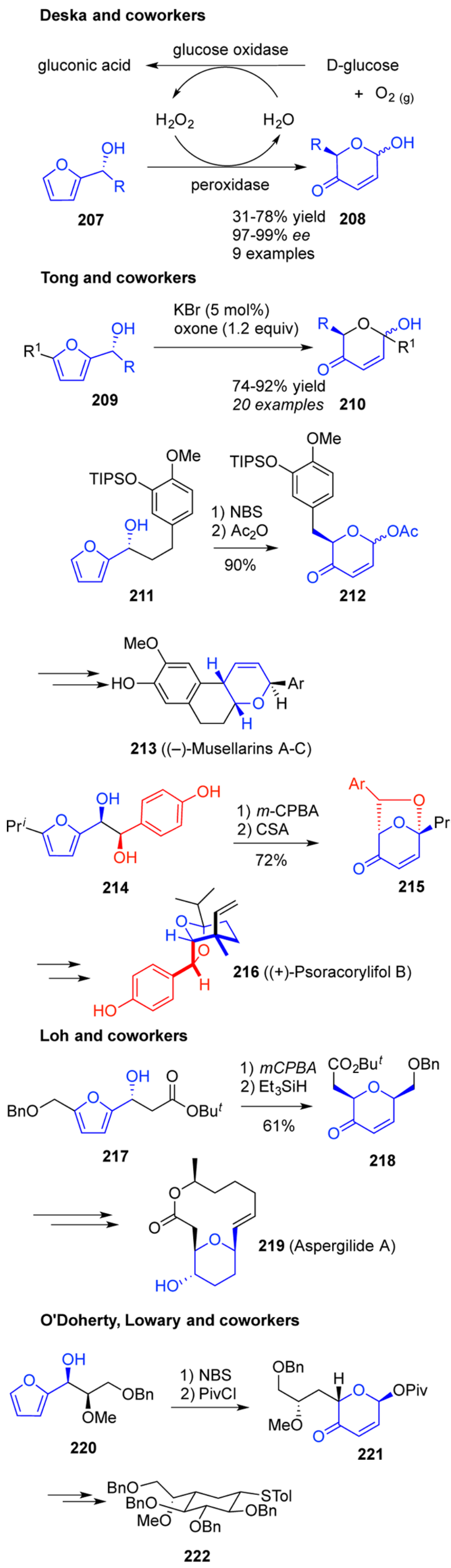
Another powerful transformation of furfuryl alcohols is their oxidative rearrangement to dihydropyrans, known as the Achmatowicz rearrangement (Scheme 21).[68] Generally triggered by *m*-chloroperbenzoic acid (*m*-CPBA) or *N*-bromosuccinimide (NBS), there have been notable alternatives with respect to catalysts[69,70] or solvent-free reaction conditions[71] aiming at a sustainable overall process. Deska and co-workers developed an enzymatic protocol via an oxygen activation cascade with commercially available biocatalysts for the conversion of **207** to **208**.[72] Excellent good functional group tolerance with no erosion of enantiopurity was achieved. Tong and co-workers reported that catalytic amounts of KBr and stoichiometric Oxone as the terminal oxidant efficiently promoted the Achmatowicz rearrangement of **209** to **210**, reducing purification problems owing to the fact that no organic byproducts are formed.[73]

The same authors demonstrated impressive applications with the synthesis of the naturally occurring (−)-musellarins A-C **213** or (+)-psoracorylifol B (**216**),[74] in the latter case generating directly the bicyclic ketal **215** by acetalization of the initially formed Achmatowicz product via the hydroxyl group in the side chain. Loh and Koh efficiently assembled aspergilide A (**219**), coupling the Achmatowicz rearrangement of **217** with Et$_3$SiH-mediated reduction of the anomeric center to give rise to **218**.[75] Finally, O'Doherty, Lowary, and co-workers demonstrated the application of the Achmatowicz rearrangement for the synthesis of a thioglycoside derivative of heptopyranose **222**, found in the *Campylobacter jejuni* NCTC11168 (HS:2) capsular polysaccharide.[76]

■ CONCLUSION

Many more reactions and processes for the construction and manipulation of heterocyclic compounds could have been

Scheme 21. Recent Applications in the Achmatowicz Rearrangement of Furfuryl Alcohols



included in this Perspective. Web of Science lists for the first eight months of 2016 more than 2000 publications to which the keywords heterocyclic or heterocycle had been assigned, as opposed to less than 80 publications found for the keywords carbocyclic or carbocycle. Heterocyclic chemistry clearly is a vibrant research area, and we are excited to contribute to this field. When I (O.R.) was invited in 2004 to speak for the first time at the International Heterocyclic Conference, I was sure this must have been a mistake since I did not consider myself a heterocyclic chemist. The real question, however, seems to be "who is not?"

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The authors declare no competing financial interest.

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