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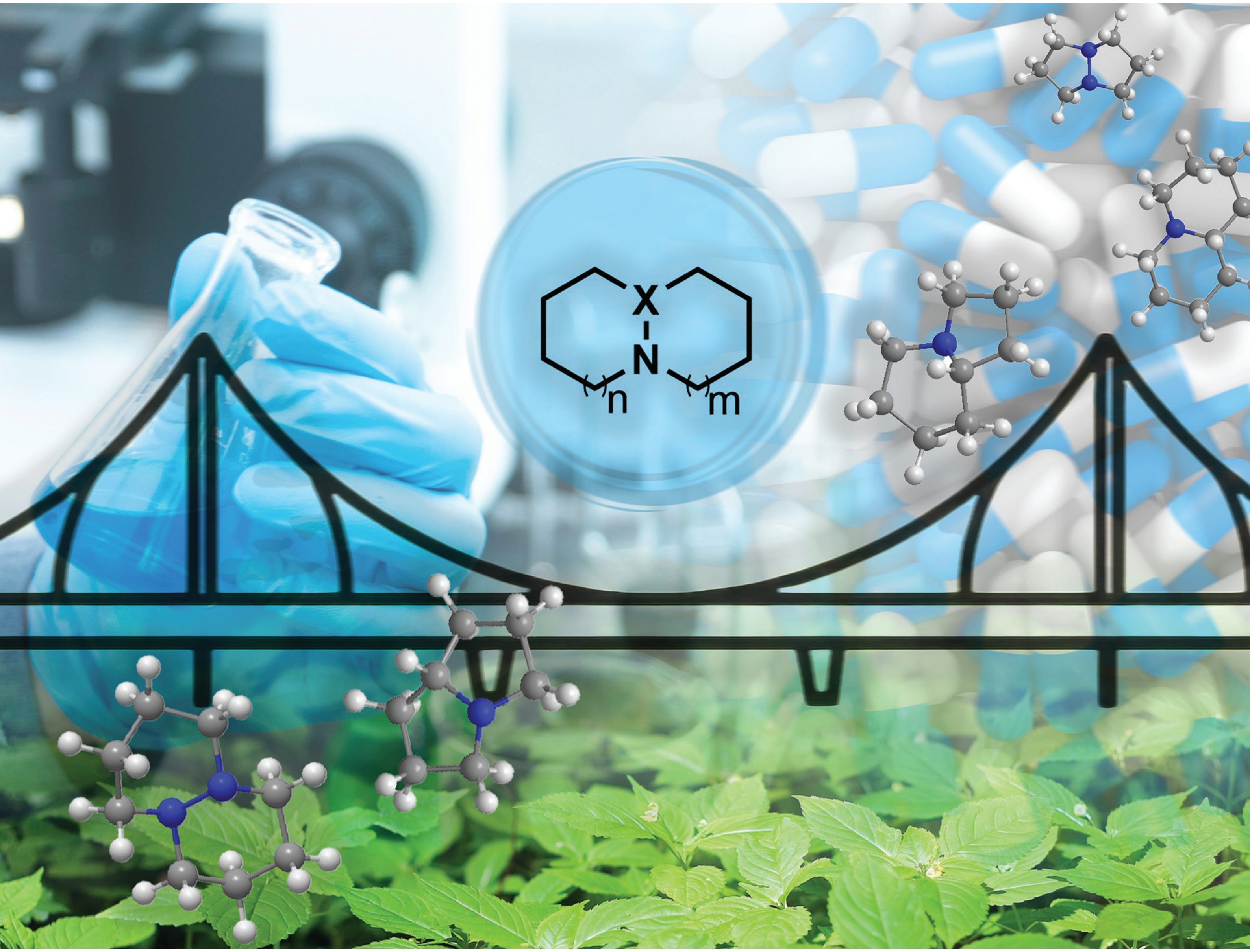

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REVIEW

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Nitrogen-bridgehead compounds: overview, synthesis, and outlook on applications

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The nitrogen-bridgehead is a common structural motif present in a multitude of natural products. As many of these abundant compounds exhibit biological activities, *e.g.* against cancer or bacteria, these derivatives are of high interest. While natural products are often associated with problematic characteristics, such as elaborate separation processes, high molecular complexity and limited room for derivatization, purely synthetic approaches can overcome these challenges. Many synthetic procedures have been reported for preparation of artificial nitrogen bridgehead compounds, however, to our surprise only a fraction of these has been tested for their bioactivity. This review is therefore meant to give an overview of existing synthetic methods that provide scaffolds containing bridgehead nitrogen atoms, covering the period from 2000 to 2023. Reviews which cover subunits of this topic are referenced as well.

1 Introduction

Natural products, the first medicines known to man, have been used to treat many different diseases.[1] Despite advances in organic synthesis methodology, drug discovery research continues to focus on natural products for, as examples, anti-resorptive activity,[2] hypertension,[3] and, currently, treatment of coronavirus infection.[4] Therefore, it is not surprising that almost half of drugs used today are based on natural products,[5] a selection of which are shown in Fig. 1. While this compound pool offers a broad variety of structures, natural products remain challenging to extract and purify,[6–8] structurally complex (which can make identification of active substructures difficult)[9] and difficult to modify.[10,11] Total synthesis or synthesis of core structures can address these limitations,[12] especially as a step-by-step build of the desired motif can give access to additional simplified derivatives. Nitrogen atoms are common in natural products and their derivatives (Fig. 1, marked in red). In fact, 59% of FDA approved drugs contain at least one nitrogen atom.[13] Many of the compounds depicted in Fig. 1 bear another interesting feature in their scaffold: a bridgehead nitrogen, two rings connected by a nitrogen atom (Fig. 1, marked in blue). As all of these compounds exhibit bioactivity, the N-bridgehead, which all have in common, can be considered a key feature for their activity.[14,15]

A synthetic chemist would rightly assume that the compounds shown in Fig. 1 are natural alkaloids or semi-synthetic derivatives thereof, because installation of a bridgehead nitrogen is synthetically challenging. For this reason, to access this important source of structural complexity, chemists have had to rely on naturally occurring structures.

Synthetic access to the full array of complexity associated with the bridgehead nitrogen would offer an expanded structural ‘pool’ from which new molecules could be drawn and would allow researchers to overcome previously listed drawbacks of the natural pool. The ability to build N-bridgehead scaffolds from scratch would allow synthesis of compound families around new structural motifs, which would be crucial for structure relationship investigations, including, for example, optimization of bioactivity, toxicity and ADME properties. Optimization of these properties will require robust synthetic methods, which will give access to both broad structural diversity and the selectivity required to isolate material with high isomeric purity and high ee and dr values. Ready access to additional structural diversity will be beneficial in areas of drug discovery research, such as cancer treatment, where there is an urgent need for new molecules with enhanced bioactivity, especially against special cancer types and resistant forms and with decreased side effects.

Keeping these challenges in mind, we summarized the synthetic work toward compounds bearing a nitrogen bridgehead during the period of 2000–2022. As the scope of this review is extensive, in our schemes, we summarized the key step for N-bridgehead formation for each reaction. Many elegant approaches toward N-bridgehead compounds have been developed and reported, but to our surprise relatively few of these have included evaluation of bioactivity. We hope that this

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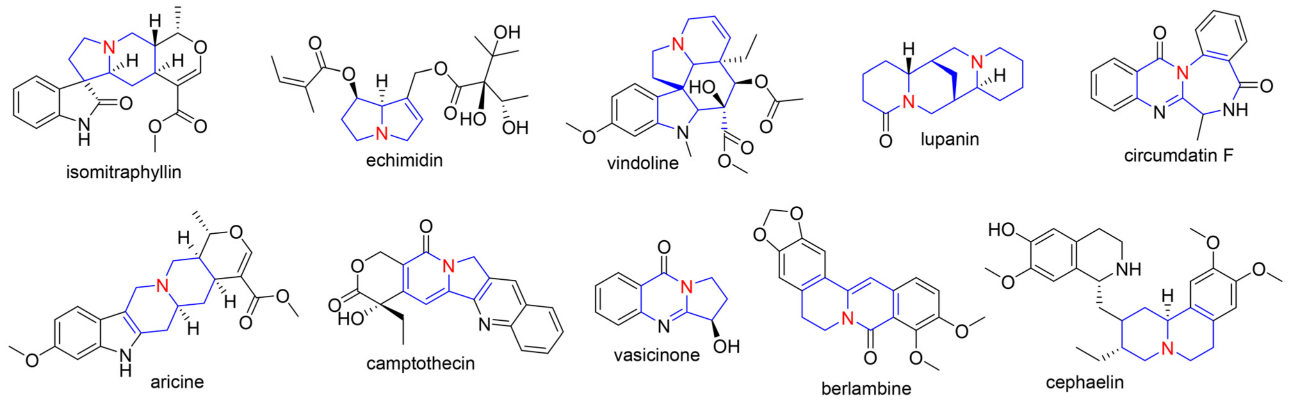
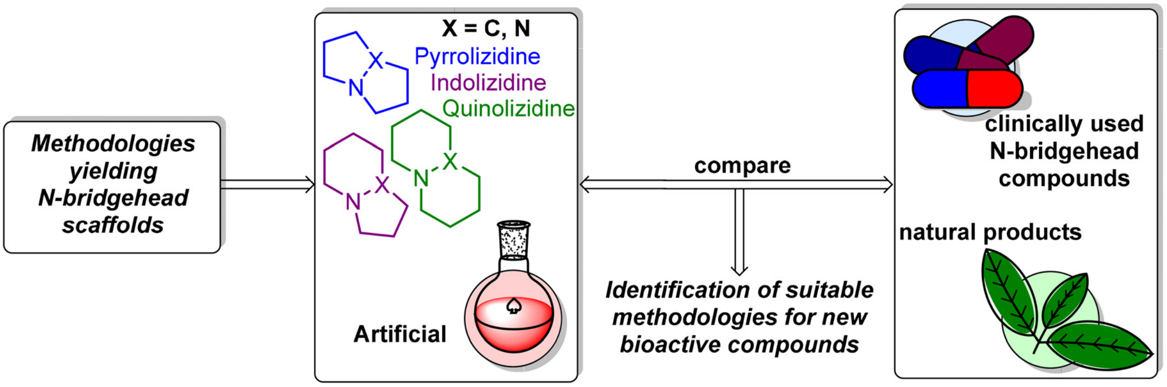


Fig. 1 Natural products that have a bridgehead nitrogen and are used as drugs.



Scheme 1 Scope and goals of the review.

review will serve as both an overview of the many exciting methods available for the synthesis of a vast array of N-bridgehead compounds and as an opportunity for researchers to identify promising scaffolds that have yet to be investigated for their potential bioactivity (Scheme 1).

2. Pyrrolizidines (5,5 ring; 1-azabicyclo[3.3.0]-octane)

In the first part of the review, pyrrolizidines are discussed. The pyrrolizidine motif is a commonly found element in natural products, such as pyrrolizidine alkaloids, which are secondary metabolites of plants.[16] The biological activities of many different alkaloids of this type have been investigated, and their importance is underlined by the numerous different approaches to their synthesis.[17–20] It should be noted that many pyrrolizidines, especially 1,2-unsaturated pyrrolizidines, are toxic to humans, therefore much research has focused on their exclusion from food.[21,22]

Pyrrolizidines have a multitude of different applications as bioactive compounds.[23,24] Examples are shown in Fig. 2. The *N*-oxide of indicine was tested for its activity against Leukemia in two different publications.[25] In the first study, indicine *N*-oxide was used for the treatment of twenty-two patients with acute lymphoblastic leukemia, while the second study describes a phase II treatment of thirty-one patients. Retronecin and three other natural products were tested against *Escherichia coli* and *Penicillium chrysogenum*.[26] Retronecin exhibited pronounced activity against both microorganisms. 7,7a-diepialexine is a natural product isolated from *Alexa leiopetala*.[27] It was tested for its inhibition of human immunodeficiency virus (HIV) growth, where it restricted viral replication with an IC_{50} value of 0.38 mM. This correlates with inhibitory activity against purified pig kidney-glucosidase 1 of the glycoprotein processing enzymes and the reduced cleavage of the precursor HIV-1 glycoprotein gp160. Pyrrolizidines like heliotrine, which can be isolated from the seeds of *Heliotropium indicum*, exhibited ganglion blocking activity.[28] As one of four different natural products, europine inhibited the production of nitric oxide in lipopolysaccharide induced murine macrophages RAW 264.7 cells with an IC_{50} value of 7.9 μM.[29] Australine is a polyhydroxylated pyrrolizidine with anti-HIV activity.[30] The activity of glycosidases, particularly the nitrogen-linked glycosylation process of HIV, was greatly inhibited at concentrations between 0.1 and 10 mM. Heliosupine is

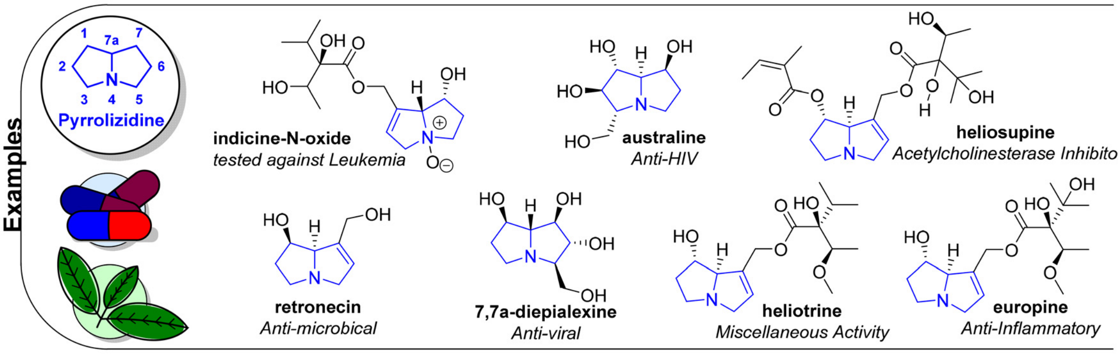


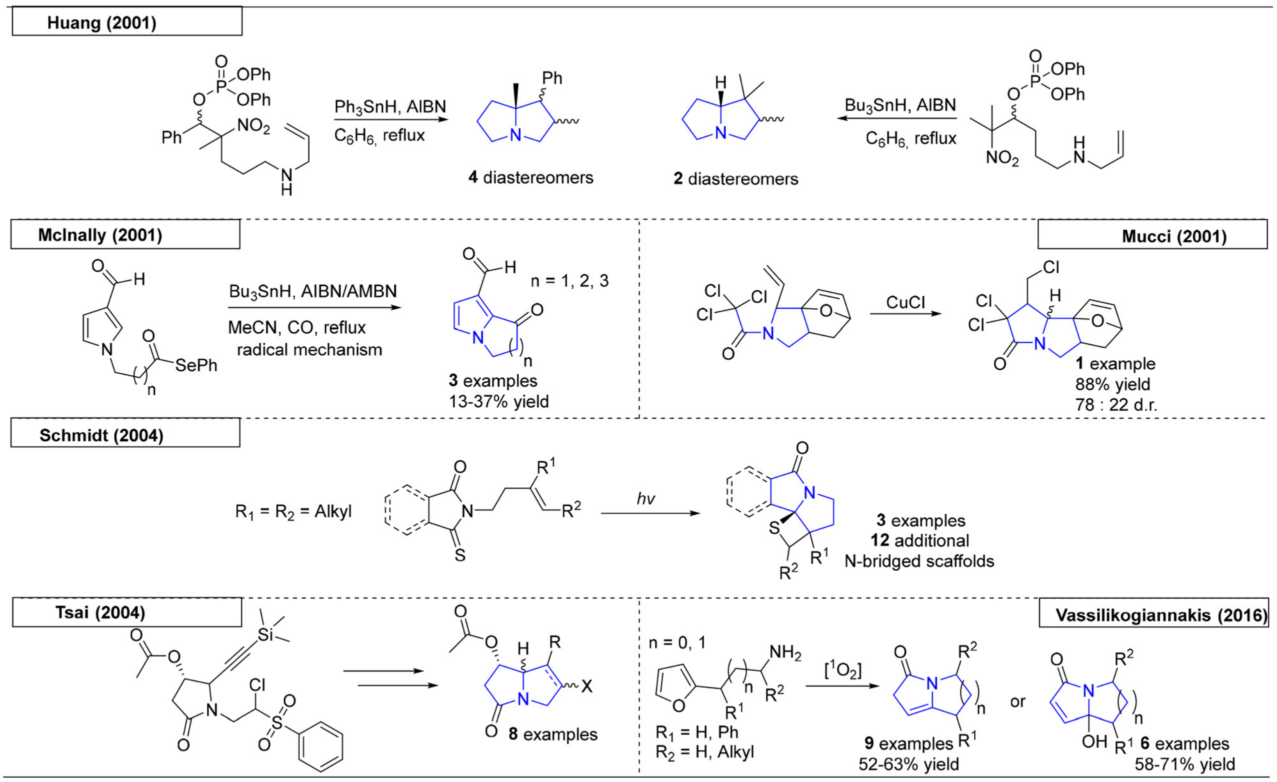
Fig. 2 Examples of pyrrolizidine-derived compounds.

an acetylcholinesterase (AchE) inhibitor with an IC_{50} value below 0.60 mM. AchE is an enzyme that catalyses the hydrolysis of esters that act as neurotransmitters.[31,32] While overstimulation of acetylcholine receptors is related to disorders like depression, under stimulation can cause other diseases, such as Alzheimer's and *Myasthenia gravis*.

Over the last 20 years, many synthetic pyrrolizidines have been prepared. To our surprise and to the best of our knowledge, relatively few of the reported compounds have been tested for biological activity. Because many of these derivatives are not 1,2-unsaturated, there may be a potential non-toxic bioactive application.

2.1. Free radical and photochemical reactions

In the early 2000s, several different free radical approaches were reported to yield the desired pyrrolizidine scaffolds (Scheme 2). The first example, which was reported by the Huang research group utilized a phosphorous-derived homolytic cleavage.[33] They disclosed the synthesis of substituted N-bridgehead heterocycles from β-phosphatoxy nitroalkanes on treatment with triphenyltin hydride (Ph_3SnH) or tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN). The tributyltin hydride reaction took advantage of the Thorpe–Ingold effect[34] to provide the bicyclic product. The first bridgehead



Scheme 2 Free radical and photochemical approaches to pyrrolizidines.

compound was isolated as a mixture of four diastereomers (ratio 2.7 : 1.6 : 1 : 1), with the major diastereomer being in *trans*-configuration about the newly formed bond. The second pyrrolizidine has only two diastereomers (isolated in 1 : 1 ratio) but has limited utility for drug discovery, because of the constraints of further derivatisation.

Another example, published by McInally and coworkers,[35] utilized an acyl selenium moiety to provide the initial free radical *via* homolytic cleavage (Scheme 2). Reaction with AIBN or azobismethylisobutyronitrile (AMBN) and Bu_3SnH afforded a pyrrole ring fused to a 5-, 6- or 7-membered ring. Mechanistic studies indicated that the AIBN and AMBN act as radical initiators as well as oxidants of intermediate π-radicals to provide the final aromatic product. In the course of exploring a novel [4 + 2] cycloaddition reaction, the Mucci research group exploited a copper chloride-initiated free radical reaction to form a pyrrolizidine scaffold. Because the scope of this study was limited, only one pyrrolizidine derivative was reported.[36]

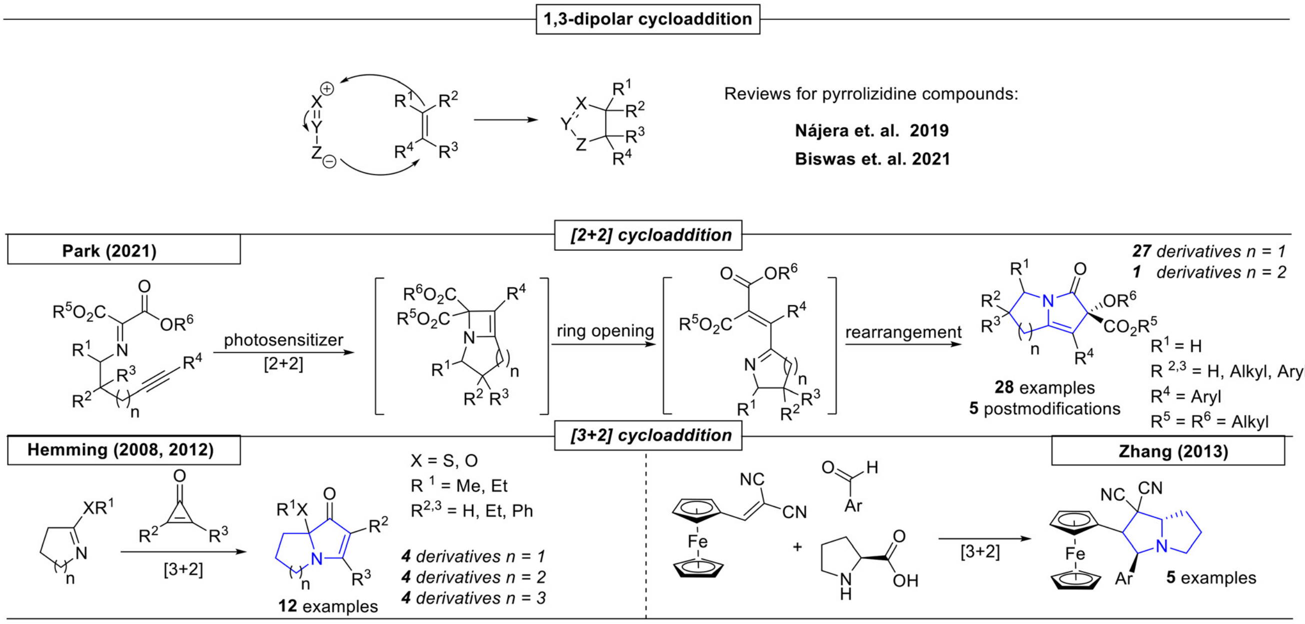
An elegant free radical approach reported by the Schmidt research group used UV light to form the di-radical that was involved in the subsequent cyclization (Scheme 2).[37] Variations of the starting materials and post-cyclization modifications gave access to twelve additional N-bridgehead scaffolds that spanned from indolizidines to 5,7-fused ring systems. In 2004, another free radical approach was reported by the research group of Tsai.[38] Starting from a silyl-protected alkyne precursor, AIBN and Bu_3SnH were used to obtain the desired pyrrolizidine scaffold with excellent stereoselectivity. The paper contains eight pyrrolizidine scaffolds, including the naturally occurring derivatives (+)-heliotridine and (−)-retronecine. The last example of a free radical pyrrolizidine synthesis was reported in 2016 by Vassilikogiannakis and coworkers.[39] This methodology employed readily accessible alkyl furan precursors with photooxygenation conditions, which transformed the starting materials into pyrrolizidine and indolizidine scaffolds. The first step involved the addition of singlet oxygen, which facilitated the furan ring opening and conversion toward pyrrolizidines.

2.2. Cycloaddition reactions

2.2.1 1,3-Dipolar cycloadditions. One of the most common ways to synthesize artificial pyrrolizidines is the 1,3-dipolar cycloaddition reaction (Scheme 3). Since these approaches have already been summarized in excellent recent reviews by Nájera *et al.*[40] and Biswas *et al.*,[41] they are not reviewed here.

2.2.2 [2 + 2] cycloadditions. In 2021, Park and coworkers reported a reaction sequence involving an imine alkyne [2 + 2] cycloaddition as a key-step (Scheme 3),[42] which forms a four membered ring that undergoes ring opening. Visible light photochemical conditions were used to facilitate the following rearrangement, which yielded twenty-seven different pyrrolizidine derivatives. Additionally, a [4 + 2] cycloaddition was reported, which gave access to twenty different dihydro-1,4-oxazine derivatives.

2.2.3 [3 + 2] cycloadditions. The Hemming research group reported a novel formal [3 + 2] cycloaddition reaction toward highly functionalized pyrrolizidines, indolizidines and 5,7-fused ring systems, depending on the ring size associated with the imine precursor (Scheme 3).[43] In a subsequent publication, nine additional derivatives were reported by the same research group.[44] In 2013, Zhang and coworkers reported a novel [3 + 2] cycloaddition of a ferrocene-derived dicyanoolefin with benzaldehyde-proline condensates, utilizing L-proline as catalyst.[45] All five examples were pyrrolizidine-ferrocene hybrid compounds.



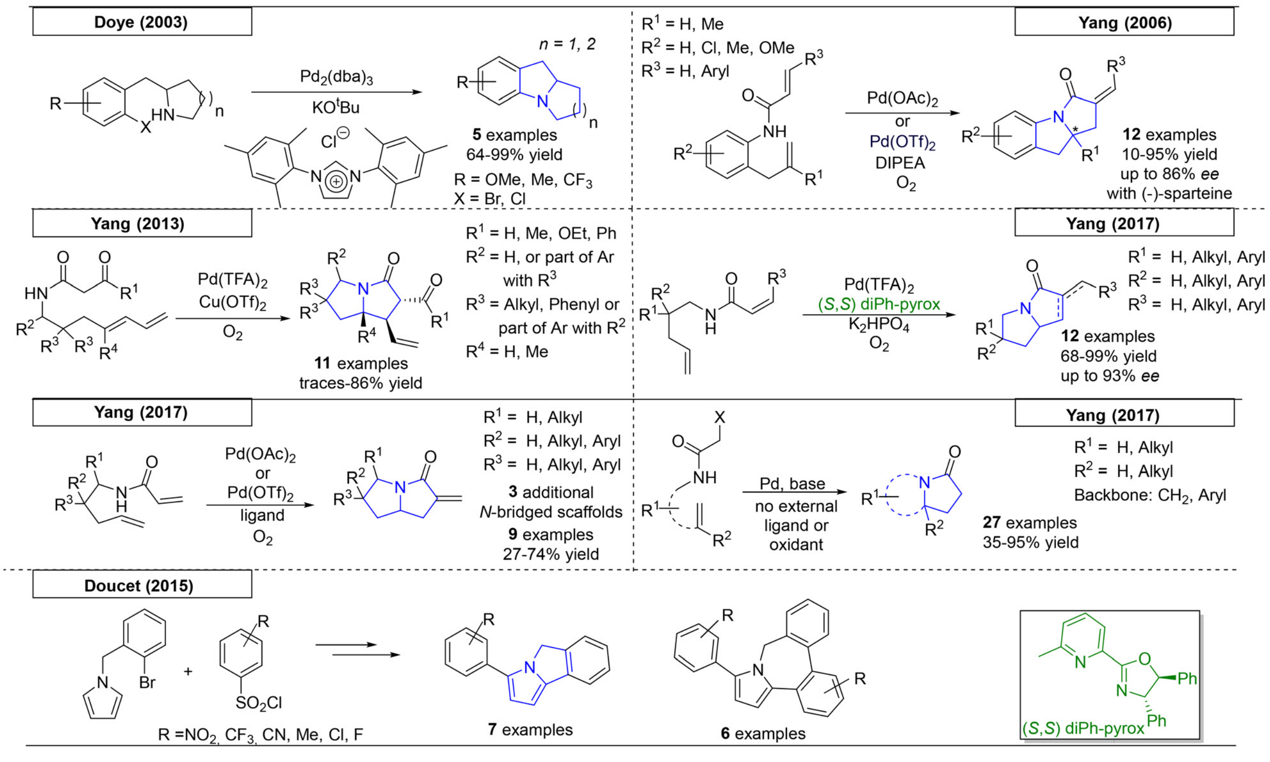
Scheme 3 Cycloaddition reactions that produce pyrrolizidines.

2.3 Palladium-catalysed reactions

Palladium catalysed carbon–nitrogen cross coupling reactions, among them the Buchwald–Hartwig reaction, are useful tools for the synthesis of highly substituted amines.[46] A number of approaches have exploited this technique to obtain pyrrolizidine structures. In addition, various intramolecular 1,2-aminoalkylation reactions have been developed, which will be discussed in the following section. In 2003, Doye and coworkers reported the synthesis of six different pyrrolizidine derivatives starting from readily available di-halogenated benzenes (Scheme 4).[47] The amine-derived precursors used for the palladium-catalysed cyclization were prepared from the corresponding alkyne derivatives *via* a procedure that involved hydroamination followed by *in situ* reduction.

The Yang research group has been responsible for much research in this area. In 2006, they reported a novel oxidative tandem reaction that employed palladium acetate or palladium triflate as a catalyst and provided twelve examples of pyrrolizidines (Scheme 4).[48] The formation of both rings was enabled by the palladium catalyst. By adding a chiral ligand to the system, (−)-sparteine was synthesized using this approach with an enantiomeric excess of up to 86%. In 2013, a 1,3-diketo-pyrrolizidine scaffold example was published by the same research group, which utilized a 1,3-diketone and addition of copper triflate to the palladium catalyst system.[49] In the course of this work, eleven examples of highly substituted pyrrolizidine derivatives were synthesized. In 2017, the same research group added an additional variation of the palladium-catalysed cyclization reaction.[50] By omitting the benzene backbone present in their 2006 publication, Yang and coworkers were able to synthesize twelve novel derivatives with varying substitution patterns and no fused benzene ring. In the same year, the Yang research team published an additional variation of the reaction using (S,S)-diPh-pyrox as a ligand, which resulted in the preparation of the desired pyrrolizidine compounds in high enantiomeric excess (up to 93% ee).[51] Additionally, by modifying the starting material, three additional N-bridgehead heterocycles were obtained. In a fifth publication, the Yang research group demonstrated that α-halo-acetamides can also be utilized as starting materials for their palladium-catalysed cyclization reaction.[52] This change allowed for the synthesis of an additional twenty-seven scaffolds without the need for a vinyl moiety in the starting material.

The last example of a palladium-catalysed procedure was reported in 2015 by Doucet and coworkers, who described a novel two-step procedure for the preparation of pyrrolizidines (Scheme 4).[53] In this process, a desulfitative addition of a substituted benzene ring to the pyrrole system was followed by C–H bond arylation to yield the closed ring system. By using an excess of the sulfonyl chloride derivative (2.5 equivalents), two rings were added to the pyrrole. As the α-position was now occupied, the C–H bond arylation took place on one of the aryl rings, forming a 5,7-fused ring system with a bridgehead nitrogen.



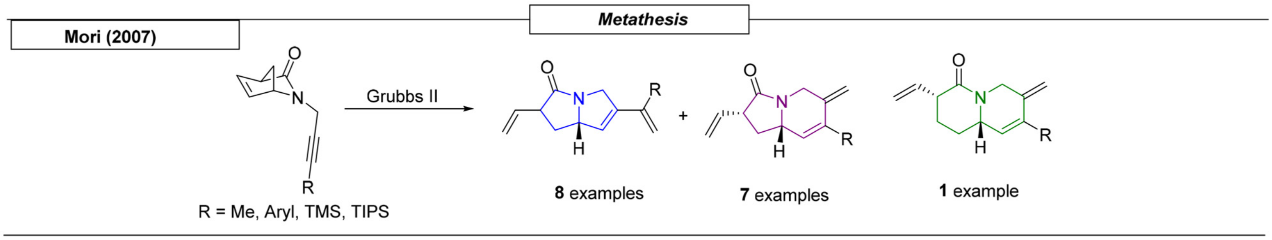
Scheme 4 Palladium-catalysed reactions that produce pyrrolizidines.

2.4 Metathesis reactions

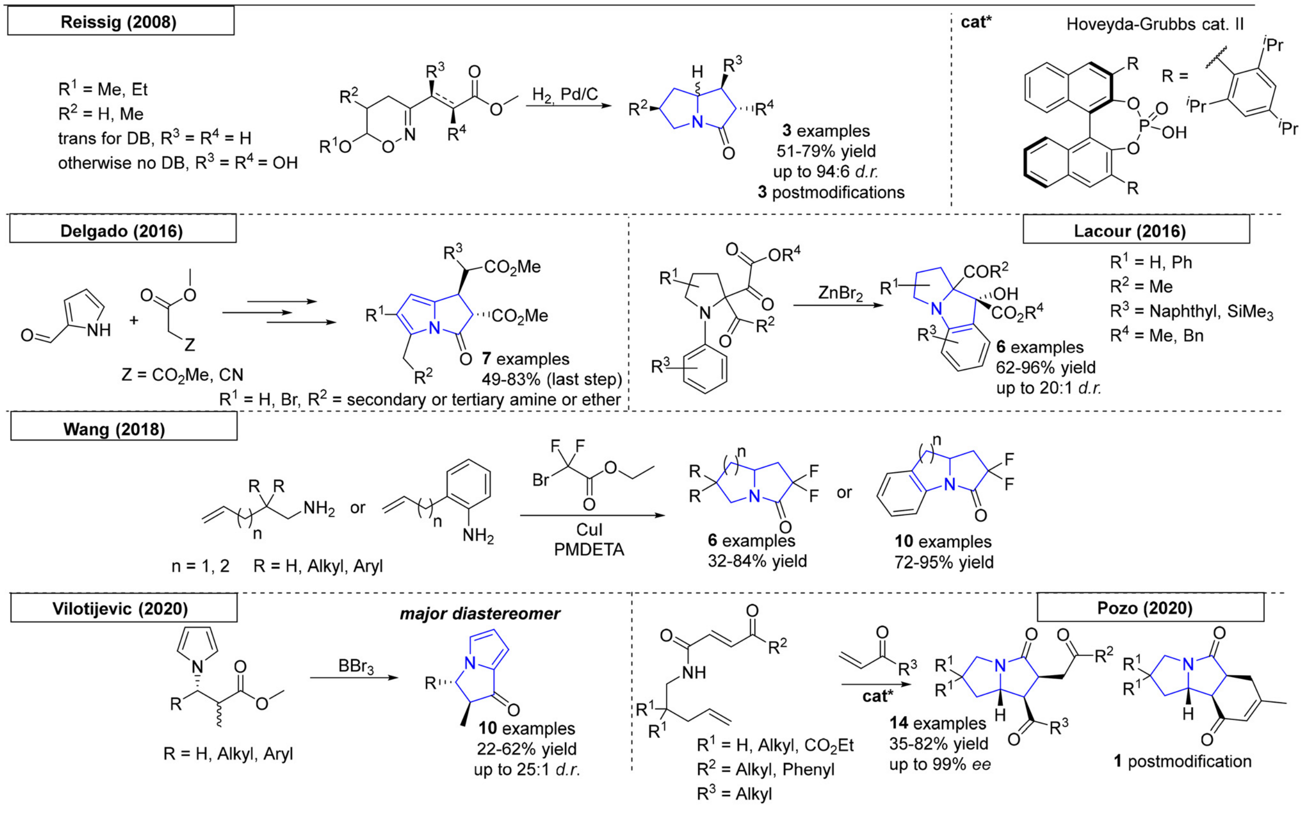
A well-established tool for the synthesis of ring systems is the metathesis reaction.[54] In 2007, Mori and coworkers utilized this powerful methodology to prepare pyrrolizidines, indolizidines and one quinolizidine using a successive ring-opening metathesis (ROM)/ring-closing metathesis (RCM) approach (Scheme 5). Depending on the starting material, different ring sizes were provided.[55]

2.5 Cascade and multicomponent reactions

Cascade reactions, procedures with successively triggered reactions in a single approach, were found to be versatile tools capable of providing a multitude of complex molecules. Cascade reactions are of additional interest, because they are often considered 'green' chemistry.[56] In this section, we highlight cascade reactions and one-pot processes, as both combine multiple reaction steps in a single reaction flask, toward pyrrolizidines. Reissig and coworkers synthesized various 1,2-oxazines, which were used in reductive cascade reactions (Scheme 6).[57] Ring cleavage at the N–O bond followed by subsequent cyclization yielded three different pyrrolizidinone compounds. Modification of these compounds provided three additional pyrrolizidine scaffolds. In the same year, the Delgado research group published two novel routes of synthesis toward pyrrolizidines starting from pyrrole-aldehydes.[58] Knoevenagel condensation of a pyrrole aldehyde with an activated methylene compound yielded the corresponding precursors, which were used in a Michael addition of dimethylmalonate and a sub-



Scheme 5 Pyrrolizidine scaffolds obtained *via* metathesis reactions.



Scheme 6 Cascade and multicomponent reactions that produce pyrrolizidines.

sequent lactamization. In total, seven different pyrrolizidine scaffolds were obtained.

In 2016, Lacour and coworkers developed a novel method for the synthesis of pyrrolidines bearing both a carbonyl and an ester moiety (Scheme 6).[59] A Lewis acid-induced intramolecular nucleophilic reaction with a ketone provides an alcohol-functionalized pyrrolizidine scaffold. In total, six examples were reported with diastereomeric ratios as high as 20 : 1. Wang and coworkers reported a new cascade approach utilizing amine-functionalized olefins and ethyl bromodifluoroacetate.[60] Catalysed by copper(I), difluorinated nitrogen-containing polycycles were obtained in up to 95% yield *via* a radical cascade annulation. In 2020, the Vilotijevic research group reported an enantioselective *N*-allylation of *N*-silyl pyrrole latent nucleophiles with allylic fluorides followed by hydrogenation. The resulting diastereomeric mixtures were used as starting material in a diastereoselective Friedel–Crafts-type cyclization sequence.[61] This procedure yielded ten examples of enantioenriched, substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones (enrichment due to steric hindrance).

The last protocol, published by Pozo and coworkers in 2020, described a triple-tandem reaction for the synthesis of pyrrolizidinones (Scheme 6).[62] The mechanism can be described as a cross metathesis–intramolecular aza-Michael reaction–intramolecular Michael addition tandem sequence utilizing *N*-pentenyl-4-oxo-2-alkenamides and conjugated ketones. As the products bore two ketone groups, post-modification *via* Robinson annulation was possible and was demonstrated in one example.

2.6 One-pot procedures

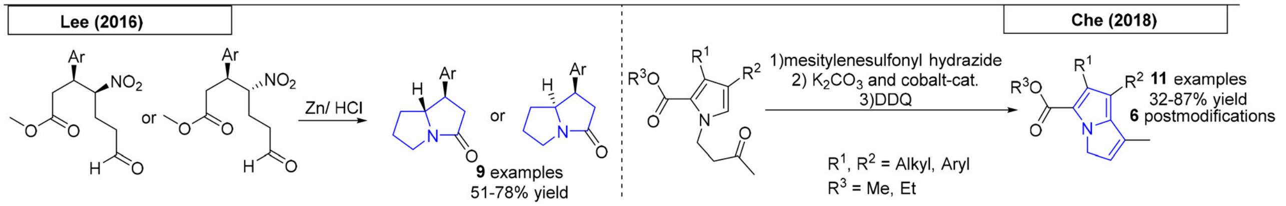
One-pot procedures are synthetic preparations involving multiple reactions that occur in a single reaction vessel. In 2016, Lee and coworkers synthesized valuable pyrrolizidine precursors from α,β-unsaturated aldehydes (Scheme 7).[63] Subsequently, a one-pot nitro reduction/reductive amination/lactamization sequence was conducted using zinc powder to give access to nine different pyrrolizidine derivatives. Che and coworkers reported a one-pot synthesis of pyrrolizidines in 2018.[64] This preparation of poly-substituted 3*H*-pyrrolizines and pyrrolizidines employed a cobalt(II) porphyrin catalyst. The reaction sequence, which consisted of an intramolecular cyclopropanation/ring-opening cascade reaction of hydrazones derived from pyrrolyl ketones, provided eleven examples. Six additional pyrrolizidines were obtained *via* post modification.

2.7 Multistep procedures

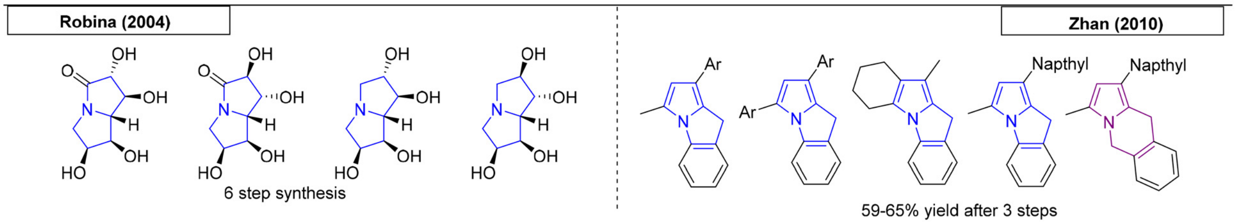
Two research groups have published multistep procedures that gave access to pyrrolizidines. Robina and coworkers developed a stereoselective route toward two enantiopure tetrahydroxy pyrrolizidin-5-ones and tetrahydroxy pyrrolizidines (Scheme 8).[65] The starting material, D-allitol, was transformed into the desired compounds over six reaction steps. In 2010, the Zhan research group reported a zinc-catalysed, regioselective sequence of propargylation, amination and cyclo-isomerization reactions of propargylic acetates, enoxysilanes and primary amines.[66] In this work, five new nitrogen bridgehead compounds were synthesized, including four pyrrolizidines and one indolizidine.

3 Indolizidine (5,6)

Indolizidines and various unsaturated analogs, including indolizines,[67] are privileged structures that are present in many natural products (Fig. 3).[68,69] Reported biological activities include antitumor, antimalarial, antibacterial, antifungal, antiparasitic, antiviral and anti-inflammatory.[70] Coniceine, a well-known example of a bioactive indolizidine, was used to execute criminals in ancient Greece.[71] Castanospermine



Scheme 7 One-pot procedures that provided pyrrolizidines.



Scheme 8 Multistep procedures that gave access to pyrrolizidines.

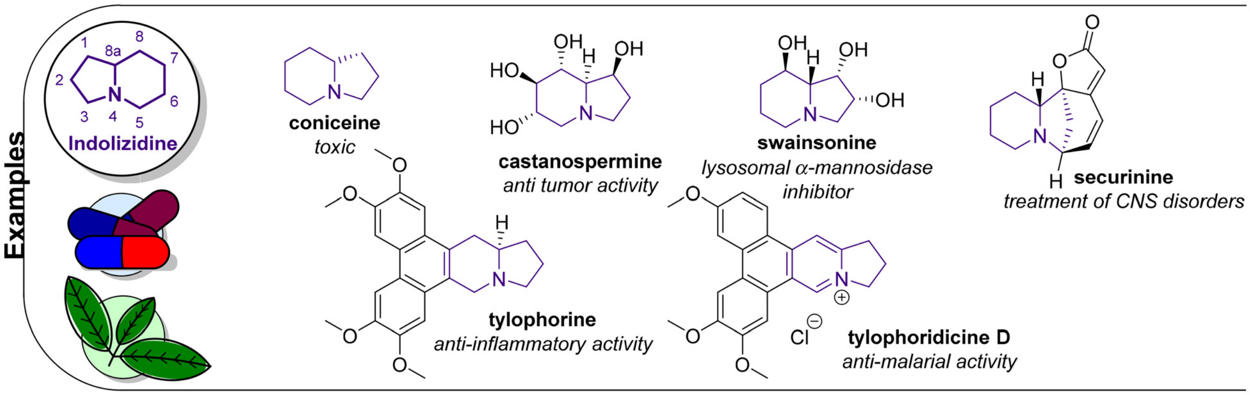


Fig. 3 Examples of indolizidine compounds.

(1,6,7,8-tetrahydroxyoctahydroindolizine) exerts diverse biological activities and has been investigated for its antitumor activities, specifically for use against multidrug-resistant breast cancer cell lines.[72,73] The data suggested that this compound may be beneficial for the treatment of cancer, and, as a result, its synthesis has been reported many times. Tylophorine exerted anti-inflammatory activity by enhancing the phosphorylation of Akt and downregulating AP1, thereby suppressing nitric oxide (NO) production in lipopolysaccharide (LPS)/interferon-γ (IFN-γ)-stimulated RAW264.7 cells.[74] When administered to animals, swainsonine, a specific directional inhibitor of the active site of lysosomal α-mannosidase, caused a phenocopy of mannosidosis, which is a genetic lysosomal storage disease.[70] Securinine has been established clinically to treat CNS disorders, *e.g.* poliomyelitis and amyotrophic lateral sclerosis.[75] Investigation of its mechanism of action in microglia and astrocytic cultures revealed the inhibition of NO formation and activation of the inflammatory mediator NF-κB and mitogen-activated protein kinases in BV2 cells stimulated by LPS. Securinine was also found to be capable of inhibition of both iNOS mRNA expression and the level of NO-induced by IFN-γ. Furthermore, securinine significantly reduced the neurotoxicity of midbrain dopamine compared to conditioned medium (CM) from LPS-stimulated microglia. Tylophoridicine D was tested for its *in vitro* antiplasmodial activity against a chloroquine-sensitive strain of *Plasmodium falciparum*. With an IC_{50} of 0.028 μM, its potency was comparable to artemisinin and chloroquine.[76] Due to rising interest in the investigation of this compound class, efforts were made to develop stereocontrolled strategies toward naturally occurring derivatives.[77–80] Even though numerous patents have been filed connected to this compound class, an indolizidine-based drug has not yet been approved.[81]

3.1 Reviews

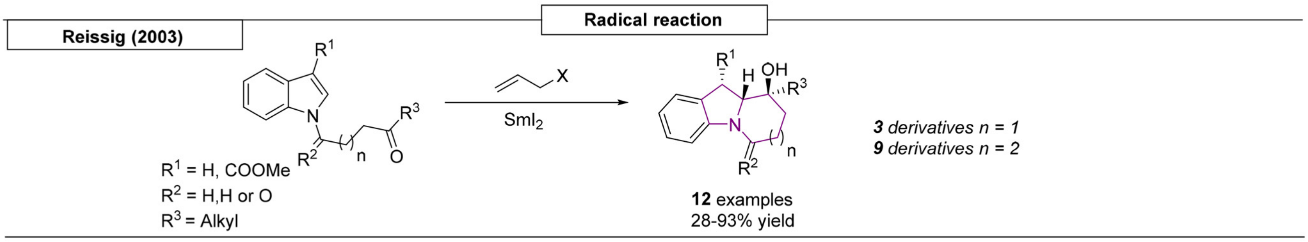
In 2015, Burtoloso *et al.* reviewed the synthesis of indolizidines and quinolizidines starting from diazo derivatives.[82]

3.2 Free radical reactions

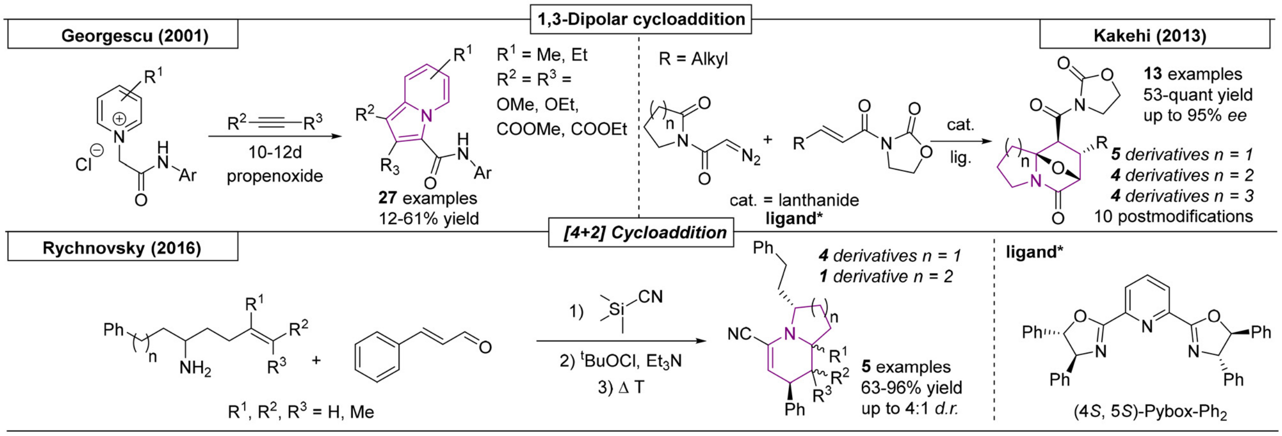
One method has been reported for the synthesis of pyrrolizidines and indolizidines using free radical chemistry. In 2003, the Reissig research group developed a samarium iodide-initiated reaction and used it to produce twelve different variants (Scheme 9).[83] The diastereoselectivity can be explained by samarium alcoholate favouring an equatorial position for steric and electronic reasons.

3.3 Cycloadditions

3.3.1 1,3-Dipolar cycloadditions. Two research groups have reported methods for the synthesis of indolizidines using 1,3-dipolar cycloaddition reactions. In 2001, the Georgescu research group described the 1,3-dipolar cycloaddition of activated, quaternary pyridinium or naphthalene salts with alkynes, yielding carbamoyl-substituted indolizines and benzoindolizines (Scheme 10).[84] The salts were activated using propenoxide. In total, twenty-seven novel compounds were syn-



Scheme 9 Synthesis of pyrrolizidines and indolizidines using free radical chemistry.



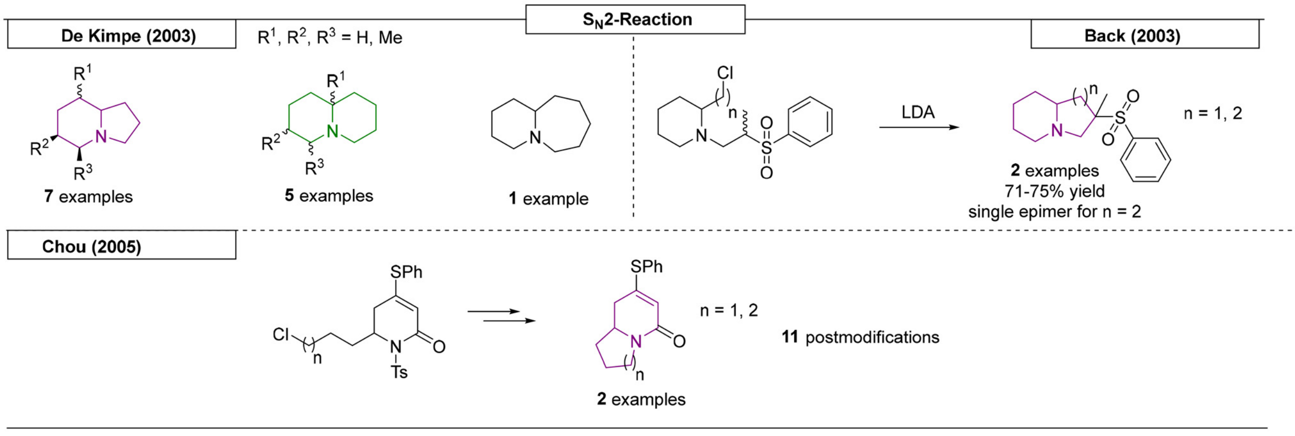
Scheme 10 Synthesis of indolizidines *via* cycloaddition reactions.

thesized. A second 1,3-dipolar cycloaddition reaction example was reported by the Kakehi research group.[85] The lanthanide-based, Lewis acid-catalysed reactions were highly enantioselective and utilized 3-(2-alkenoyl)-2-oxazolidinones and carbonyl ylides generated from *N*-diazoacetyl lactams. Quinolizidines and 7-membered ring systems were also synthesized.

3.3.2 [4 + 2] cycloadditions. In 2016, Rychnovsky and coworkers described the intramolecular [4 + 2] cycloaddition of the *in situ* prepared (*via* Strecker reaction) 2-cyano-1-azadiene (Scheme 10).[86] The reaction, which yielded five different indolizidine derivatives and one quinolizidine derivative, showed moderate stereoselectivity (up to 1 : 4 dr) of the *endo* and *exo* reaction pathways. The reaction is enabled by direct reaction of the intermediate *N*-methylcarbamoyl pyridinium salts with activated alkynes in an epoxide, as acid acceptor and reaction solvent.

3.4 S_N2 reactions

Several research groups have published methods for the synthesis of indolizidines using S_N2 reactions. A very effective synthetic route for the construction of simple N-bridgehead scaffolds was reported by De Kimpe and coworkers in 2003 (Scheme 11).[87] Starting with a kinetic deprotonation of 2-methyl-1-pyrroline (indolizidine) or 6-methyl-2,3,4,5-tetrahydropyridine (quinolizidine), addition of a dihalogenated alkyl chain resulted in the desired core structures after two subsequent S_N2-reactions. Another example of an S_N2 reaction yielding an indolizidine scaffold was reported by the Back research group.[88] LDA was utilized as a strong base to deprotonate the most acidic proton next to the sulfone group. The free electron pair then attacked the halogenated carbon *via* S_N2-reaction to form the N-bridgehead motif. In one example, an indolizine scaffold occurred as an epimeric mixture, while in another example a quinolizidine scaffold was prepared as a single epimer. A similar reaction was reported by the Chou research group in 2005.[89] After removal of a nitrogen protecting group, NaH was used as a strong base to deprotonate a secondary amide. The electron pair then reacted with the halogenated carbon to form the second ring of the N-bridgehead scaffold. Oxidative and reductive post modifications were used to produce nine additional derivatives.



Scheme 11 Synthesis of indolizidines *via* S_N2 reactions.

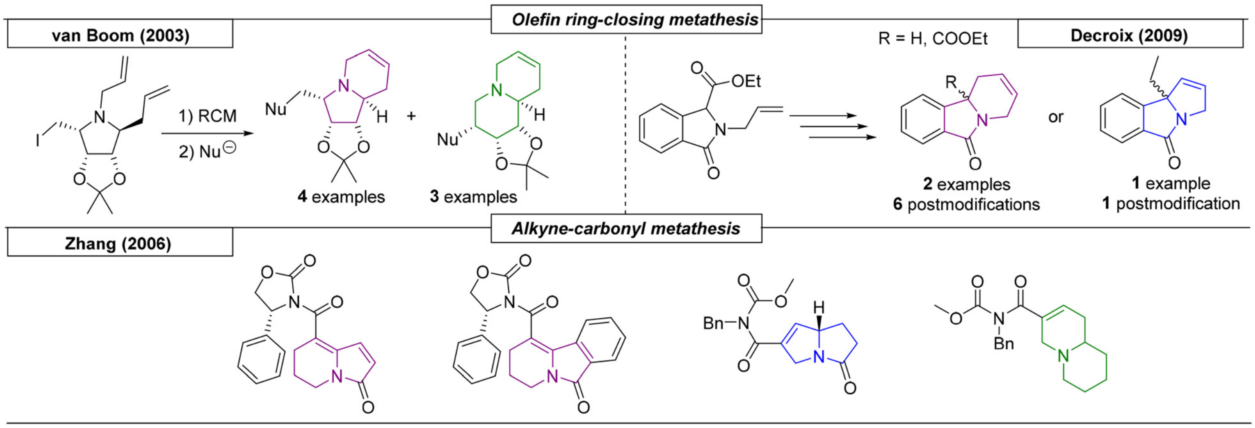
3.5 Metathesis reactions

Several research groups have published methods for the preparation of indolizidines and quinolizidines using metathesis reactions. Van Boom and coworkers reported a synthesis of novel indolizidine and quinolizidine derivatives *via* a three step sequence starting from (3aS,4S,6R,6aR)-4,5-diallyl-6-(iodomethyl)-2,2-dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyrrole (Scheme 12).[90] The ring closure was achieved by a ring-closing metathesis reaction. The resulting indolizidine was in equilibrium with the corresponding quinolizidine, and, by exploiting this equilibrium, additional derivatives were synthesized *via* nucleophilic substitution. In 2006, the Zhang research group described a boron trifluoride etherate-catalysed alkyne-olefin metathesis reaction that yielded two indolizidine scaffolds.[91] By variation of the starting materials and reaction conditions, pyrrolizidine and quinolizidine derivatives were also prepared. The last metathesis reaction example was reported by Decroix and coworkers.[92] A bicyclic lactam precursor was modified by S_N2 reaction with an allyl-halogen reagent to introduce a second double bond, which participated in a RCM reaction to yield indolizidines and one pyrrolizidine. The obtained N-bridgehead compounds were then postmodified by oxidation of the resulting double bonds with OsO_4 to introduce 1,2-dihydroxy functionalities, which allowed for further modification.

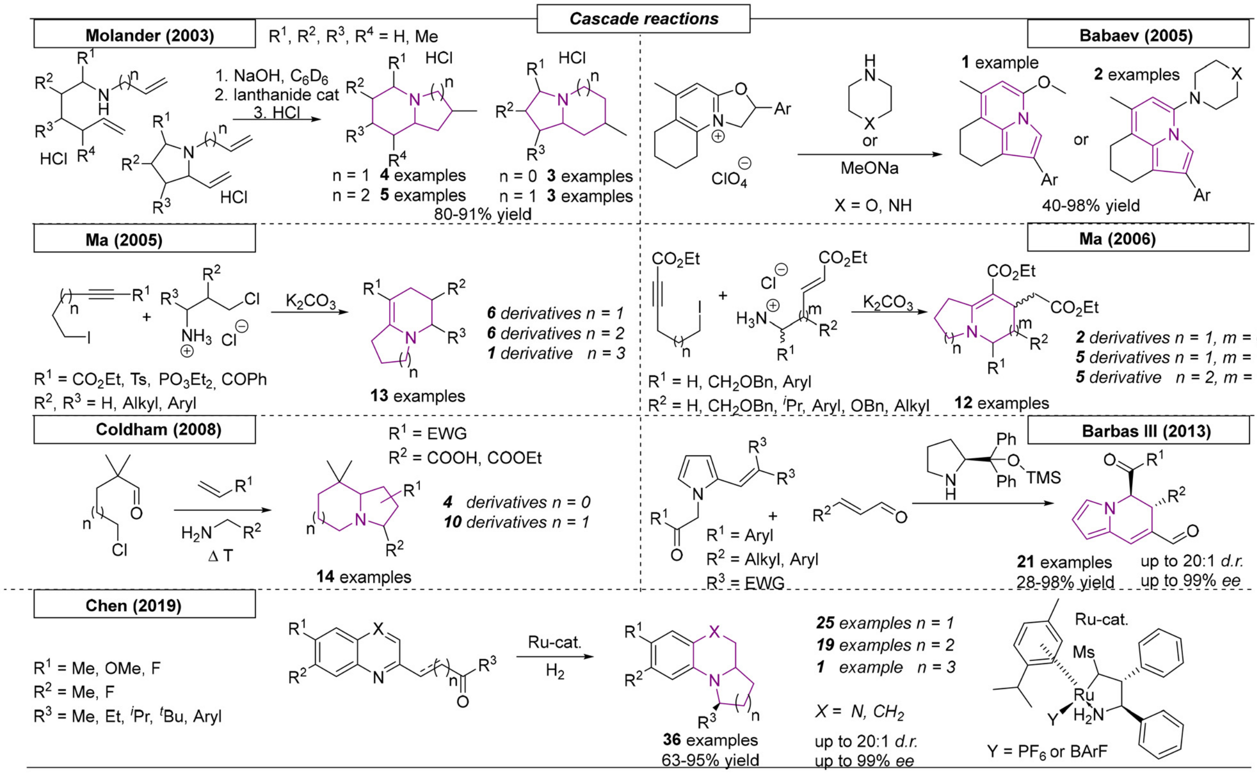
3.6 Cascade and multicomponent reactions

Many methods for the preparation of indolizidine-type compounds using cascade and multicomponent reactions have been published. The Molander research group employed various amino-di-olefin compounds in an organo-lanthanide catalysed intramolecular amination/cyclization sequence, which gave access to different N-bridgehead scaffolds, including indolizidines, pyrrolizidines and quinolizidines (Scheme 13).[93] The procedure allowed the straightforward synthesis of simple core structures and, for some indolizidines and quinolizidines, gave high diastereoselectivities. Babaev and coworkers discovered an unusual oxazole-to-pyrrole recyclization reaction.[94] The oxazole was synthesized from a tetrahydroquinolone *via* a three-step transformation. By employing piperidine, morpholine or methanol as nucleophiles, three different indolizine compounds were synthesized. In 2005, the Ma research group developed a sequential S_N2/Michael addition/S_N2/S_N2 reaction process, which involved the combination of iodo alkyne compounds and δ-chloropropylamines or β-amino esters (not shown).[95] In addition to quinolizidines and a 6 : 7 ring-fused N-bridgehead system, natural occurring alkaloid *indolizidine 223A* was synthesized in a 12-step linear sequence with an overall yield of 14.5%. One year later, the same group exploited this reaction to synthesize twelve additional N-bridgehead scaffolds from different starting materials.[96] During the course of this investigation, two pyrrolizidine, five indolizidine and five quinolizidine derivatives were obtained.

In 2008, the Coldham research group developed a three-component coupling reaction, which utilized a primary amine (amino acid, aminoester or hydroxylamine), an alkene or alkyne dipolarophile, and an aldehyde bearing a halogen leaving group (Scheme 13).[97] The reaction sequence, which involved a condensation and subsequent cyclization followed by a dipolar cycloaddition, was used to produce four pyrrolizidine and nine indolizidine derivatives. In 2013, Barbas III and coworkers reported a novel organocascade reaction toward indolizidine derivatives.[98] Pyrrole-derived substrates were reacted with α,β-unsaturated aldehydes *via* iminium enolate activation, which enabled a Michael–Michael bond formation. After elimination of the condensed $C(R^3)_2$ units, the desired indolizidine derivatives were obtained in excellent yields and with excellent stereoselectivities. The last method reviewed here, a ruthenium-catalysed asymmetric cascade reaction, was published by Chen and coworkers in 2019.[99] Quinolinyl- and quinoxalinyl-containing ketones underwent a hydrogenation/reductive amination sequence, which was catalysed by an enantiopure ruthenium complex. The indolizidine and quinolizidine derivatives were obtained with high stereoselectivities,



Scheme 12 Methods for the preparation of indolizidines and quinolizidines utilizing metathesis reactions.



Scheme 13 Methods for the preparation of indolizidine-type compounds using cascade and multicomponent reactions.

diastereomeric ratios exceeding 20 : 1 and enantiomeric excesses of up to 99%. A set of sixteen compounds with an additional nitrogen in the core structure were also synthesized. Additionally, this methodology was used in the formal synthesis of (+)-gephyrotoxin.

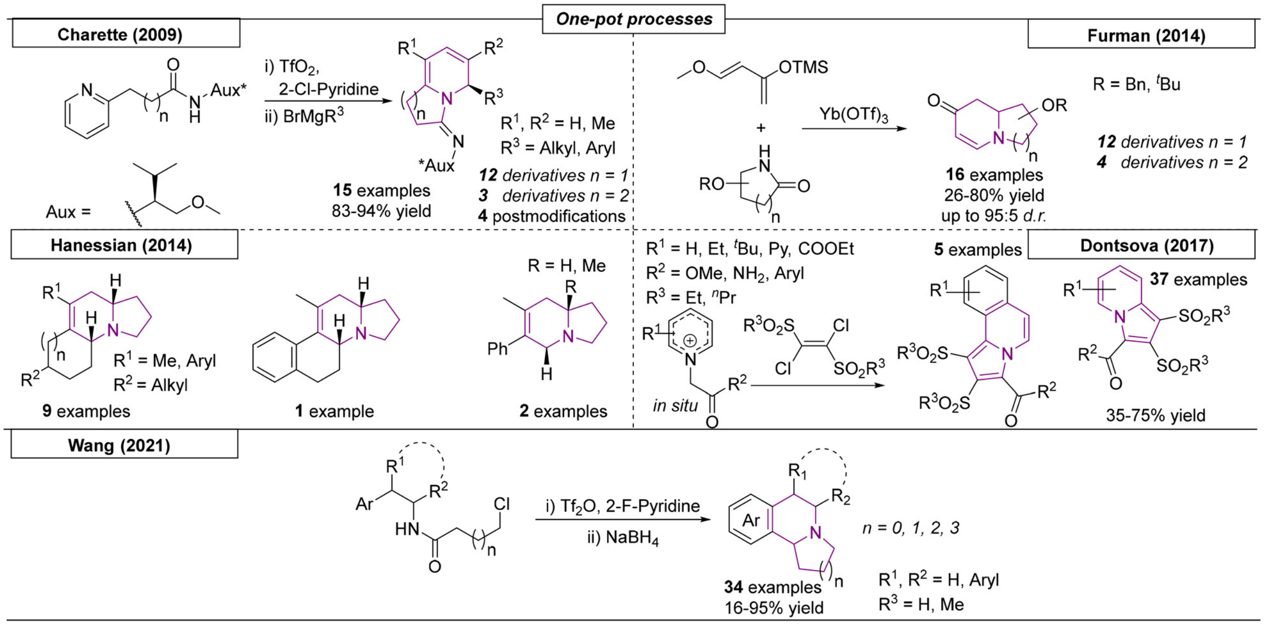
3.7 One-pot syntheses

Many one-pot procedures have been used to produce indolizidines and quinolizidines. In 2009, the Charette research group reported a two-step, one-pot process that consisted of a pyridine activation step and a subsequent Grignard reaction (Scheme 14).[100] In the first step, the cyclization resulted in a pyridinium salt, which was then attacked by the nucleophilic Grignard reagent. This resulted in the reduction of the ring system and introduction of an R^3 substituent. The regioselectivity and stereoselectivity was explained by coordination of the Aux functionality to the Mg at the position α to the amide nitrogen. Furman and coworkers published a one-pot strategy toward indolizidines and quinolizidines in 2014.[101] In the first step, a sugar-derived lactam was reduced with Schwartz's reagent. Subsequently, a Lewis acid-catalysed diastereoselective Mannich/Michael tandem reaction of the resulting sugar imine with Danishefsky's diene was carried out. The desired N-bridgehead scaffolds were obtained in yields as high as 81% and with diastereomeric ratios as high as 98 : 2.

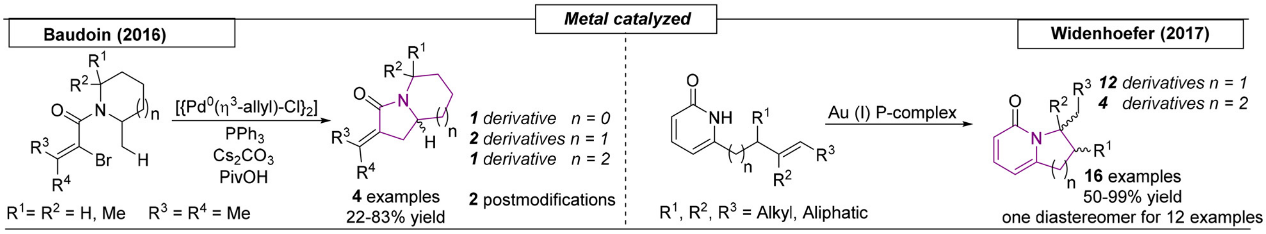
The Hanessian research group developed a novel one-pot method starting from L-proline and L-pipecolic acid, which consisted of a two component iminium ion/enamine sequence and employed mild reaction conditions (Scheme 14).[102] In addition to indolizidines, azasteroids and other complex alkaloids were obtained by variation of the starting materials. Dontsova and coworkers developed a novel one pot reaction toward a multitude of indolizidine scaffolds.[103] In this work, *in situ*-generated pyridinium ylides were reacted with *E*-1,2-di(alkyl-sulfonyl)-1,2-dichloroethene, yielding a total of forty-two novel indolizidine compounds. The last and most recent one-pot process reviewed here was developed by Wang and coworkers in 2021.[104] In this work, fused indolizidine and quinolizidine frameworks were constructed by a one-pot tandem route starting from amides. In the first step, triflic anhydride (Tf_2O) enabled the ring formation toward a secondary amide, which, after reduction with $NaBH_4$, attacked the halogenated carbon *via* an S_N2 reaction. The novel procedure was also employed as a key step in the total synthesis of (I)-xylopinine.

3.8 Metal-catalysed methods

Two research groups have published metal-catalysed methods that produce indolizidines and quinolizidines. Baudoin and coworkers reported a C(sp^3)–H alkenylation, which was used to synthesize N-bridgehead compounds from tertiary cyclic amides (Scheme 15).[105] In this work, one of the indolizidine compounds was further converted to the naturally-occurring alkaloid (±)-coniceine *via* two additional steps. In 2017, the Widenhoefer research group developed an Au(I)-catalysed intramolecular hydroamination reaction of alkenes attached to



Scheme 14 One-pot procedures used to produce indolizidines and quinolizidines.

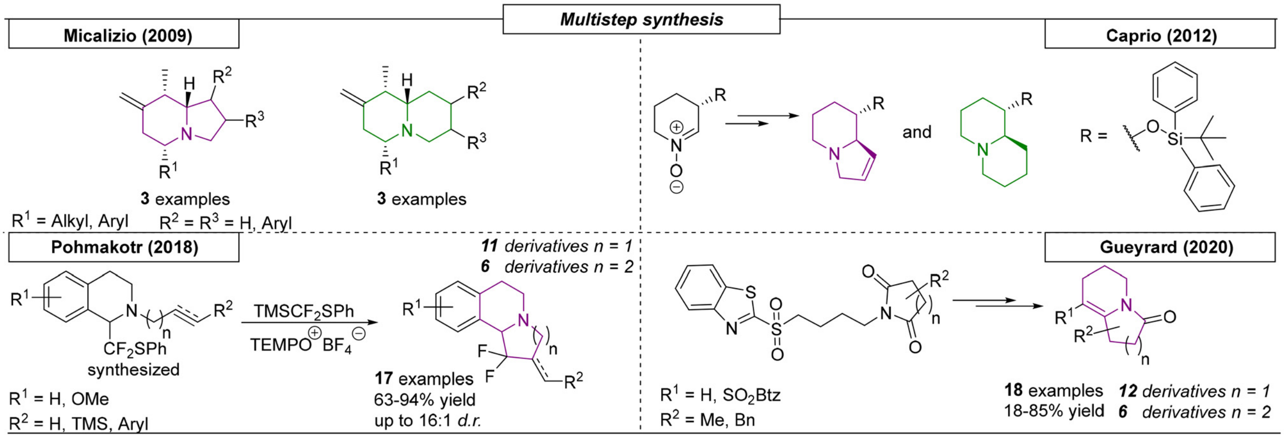


Scheme 15 Metal-catalysed methods that have been used to produce indolizidines and quinolizidines.

2-pyridones.[106] For substances with two enantiomeric centers, the reaction gave diastereoselectivities of up to 25 : 1 dr. In addition to the ten indolizidine and four quinolizidine derivatives produced, compounds with an additional nitrogen in the core structure were obtained.

3.9 Multistep syntheses

Since 2009, four research groups have published multistep procedures that provide indolizidines and quinolizidines. In 2009, the Micalizio research group developed an efficient multistep synthetic strategy toward indolizidines and quinolizidines (Scheme 16).[107] The first step yielded highly-substituted and stereo-defined allylsilanes through chemoselective coupling of functionalized allylsilanes. These were further transformed *via* acid-promoted, cationic annulation toward the desired scaffolds with diastereomeric ratios greater than 20 : 1. Caprio and coworkers exploited the stereoselective synthesis of nitrones as a starting point toward the construction of indolizines and quinolizidines.[108] The nitrones were reacted with oxygen-functionalized lithium acetylides. Reduction of the resulting hydroxylamines and alkynes resulted in the corresponding secondary amines and *cis*-alkenes or alkyl chains, respectively. Conversion of the oxygen functionality to a leaving group followed by S_N2 cyclization with the secondary amine provided the nitrogen bridgehead. This strategy was used to enable the synthesis of (+)-swainsonine. Another example of the synthesis of indolizidines was described by the Pohmakotr research group in 2018.[109] The approach focused on the oxidative difluoromethylation of tetrahydroisoquinolines. Subsequent reductive desulfenylation resulted in free radical cyclization toward the indolizidine and quinolizidine scaffolds. In total, the procedure yielded seventeen N-bridgehead derivatives. The final multistep synthetic strategy toward indolizines and quinolizidines reviewed here was developed by the Gueyrard research group in 2020.[110] Methyl- and benzyl-substituted succinimide and glutarimide derivatives were converted to the corresponding benzothiazolyl sulfones in four steps. The resulting cyclization precursors were then used in a regioselective olefination reaction to yield eighteen examples of the desired indolizine and quinolizidine compounds. This route was also used to synthesize Pundalizine A.



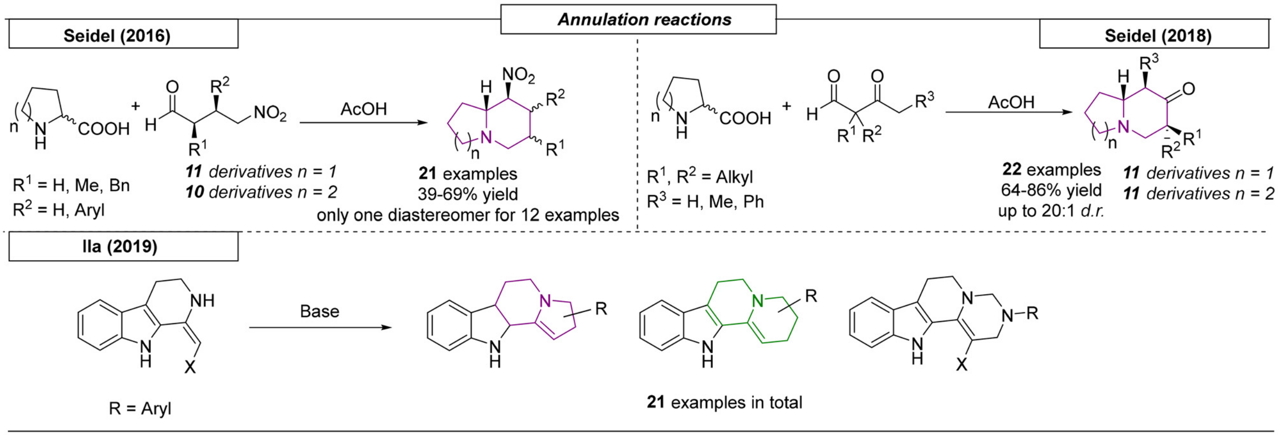
Scheme 16 Multistep procedures that provide indolizidines and quinolizidines.

3.10 Annulation reactions

Several research groups have published the synthesis of indolizidines and quinolizidines using annulation reactions. The first example of an annulation reaction yielding nitrogen bridgehead scaffolds was described by Seidel and coworkers in 2016 (Scheme 17).[111] In this approach proline or pipecolic acid were condensed with a γ-nitrobutyraldehyde. Acetic acid-promoted decarboxylation formed an azomethine ylide, which underwent nucleophilic annulation to form the final product. In addition to twenty-one examples of indolizidines and quinolizidines, an epiquinamide analog was synthesized. Two years later, the same research group published a decarboxylative annulation reaction of α-amino acids with β-ketoaldehydes.[112] In this work, twenty-two additional indolizidine and quinolizidine derivatives were reported with excellent diastereoselectivities (up to 20 : 1 dr). The last annulation process reviewed here was described by Ila and coworkers.[113] This approach investigated the aza-annulation of novel 1,2,3,4-tetrahydro-β-carboline-derived enaminones and nitroenamines, which were reacted with various 1,2- and 1,3-bis electrophiles. This simple reaction enabled the construction of highly functionalized tetrahydro-β-carboline and 1,2-fused five- and six-membered heterocyclic frameworks including indolizidine and quinolizidine scaffolds.

4 Quinolizidines

The quinolizidine motif is present in various naturally occurring alkaloids, including berberin and spartein, as shown in Fig. 4.[114] Many of these interesting scaffolds are present in plants, such as *Lupinus albus*, and possess a broad range of biological applications.[115–117] An example of a quinolizidine subgroup is the 1-hydroxy-substituted derivatives, which are in some cases poisonous to herbivores.[118] Zou and coworkers isolated a multitude of quinolizidine compounds from *Sophora tonkinensis* that showed anti-tobacco mosaic virus (TMV) properties.[116] In other cases, compounds of this type exhibited activity against leukemia.[119] Another example is the benzo[*a*] quinolizidines, which have been subjected to a multitude of



Scheme 17 Indolizidines and quinolizidines *via* annulation reactions.

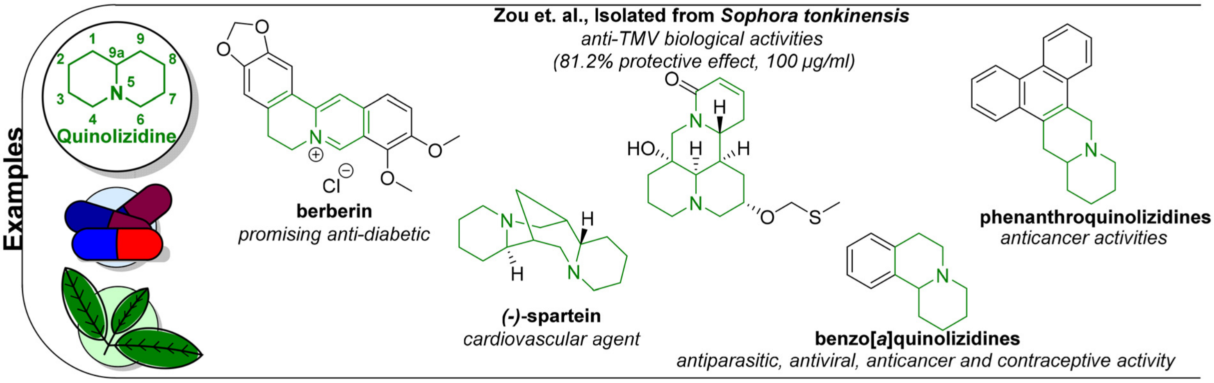


Fig. 4 Examples of various quinolizidine-derived compounds.

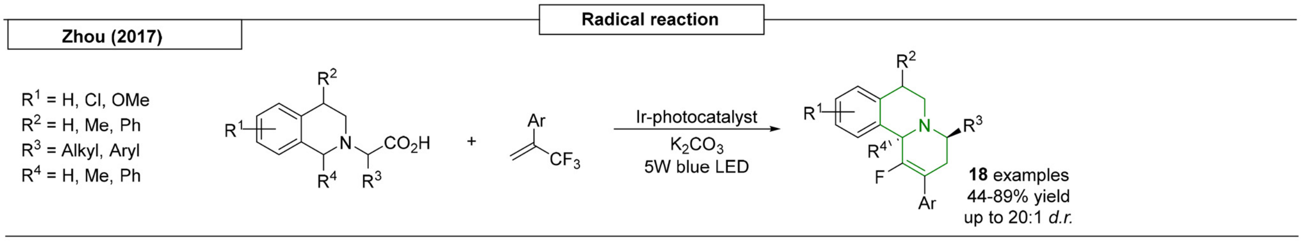
physiological activity investigations.[120] The last example of a bioactive quinolizidine subgroup is the naturally occurring phenanthroquinolizidine scaffold, which has anticancer (due to cytotoxicity), anti-inflammatory and antiviral applications.[121] Many synthetic approaches toward quinolizidines have been reported. However, few of these compounds have been evaluated for biological activity.

4.1 Free radical reactions

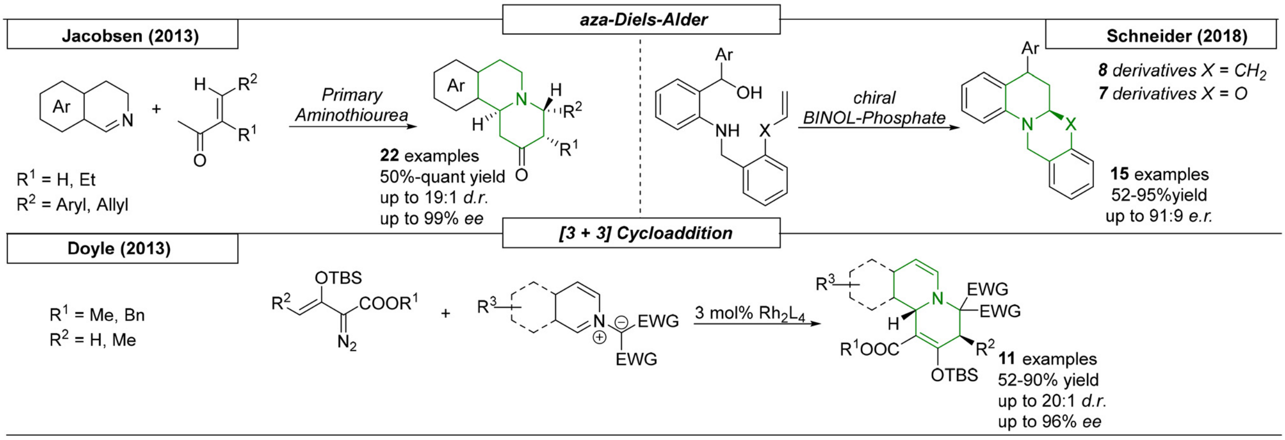
In 2017, the Zhou research group developed a light-induced tandem substitution reaction of two fluorine atoms toward novel fluorinated benzo[*a*]quinolizidines (Scheme 18).[122] This radical-initiated sequence was facilitated by an iridium photocatalyst and provided access to sixteen different compounds with yields as high as 89% and diastereomeric ratios of up to 20 : 1.

4.2 Cycloadditions

Several research groups have published cycloaddition reactions that give access to quinolizidines. In 2013, a highly enantio- and diastereoselective procedure toward indolo- and benzoquinolizidine scaffolds was developed by Jacobsen and coworkers



Scheme 18 Radical reactions that have been used to produce quinolizidines.



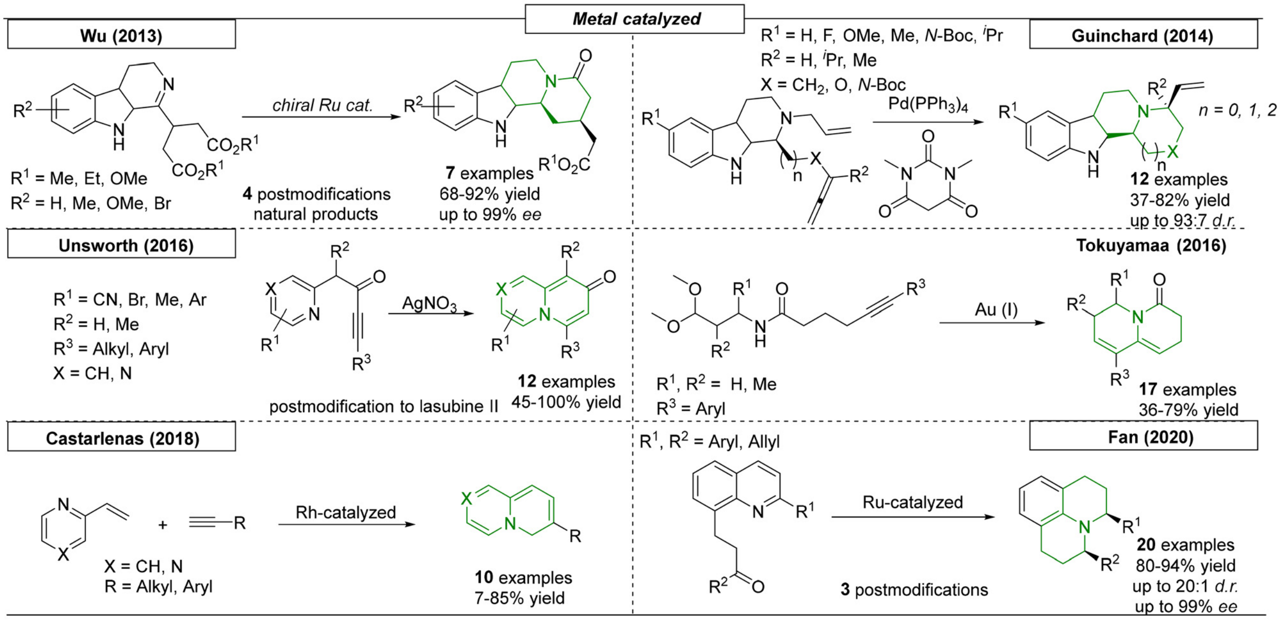
Scheme 19 Cycloaddition reactions that provide quinolizidines.

(Scheme 19).[123] The formal aza-Diels–Alder reaction was catalysed by a bifunctional primary aminothiourea, which was capable of activating both starting materials, cyclic imines and enones. In total, twenty-two examples were presented in the publication with up to quantitative yields and 99% ee. A second aza-Diels–Alder process was reported by Schneider and coworkers in 2018.[124] A chiral Brønsted acid catalysed the intramolecular cycloaddition reaction of an *ortho*-quinone methide imine with a dienophile. The resulting quinolizidines and oxazinoquinolines were obtained in yields as high as 93% and diastereomeric ratios of up to 91 : 9. In 2013, the Doyle research group published a [3 + 3] cycloaddition reaction catalysed by a chiral dirhodium reagent.[125] In this transformation, isoquinolinium or pyridinium methylides reacted with enol diazoacetates. By using enough catalyst, the concurrent [3 + 2] side reaction was suppressed. In addition to yields as high as 90%, enantiomeric excesses of up to 96% were also achieved.

4.3 Metal-catalysed reactions

Many examples of the synthesis of quinolizidines *via* metal-catalysed reactions have been published. In 2013, Wu and coworkers developed a novel cascade sequence toward indoloquinolizidines that started with imino diesters and featured an asymmetric catalytic hydrogenation/lactamization step (Scheme 20).[126] By employing a chiral ruthenium catalyst for the stereoselective hydrogenation, high optical purities of up to 99% were obtained with yields as high as 92%. *2-Epideviyl anthirine*, *Isogeissoschizol* and other natural products were synthesized using this approach. Guinchard and coworkers developed a palladium(0)-catalysed, two-step cascade reaction toward the quinolizidine core structure.[127] Precursors were synthesized from *N*-allyl tryptamine and 1,5-allenals using an asymmetric Pictet–Spengler reaction. Quinolizidines were used in subsequent deprotection and cyclization sequences to form the corresponding products in yields as high as 82% and with diastereomeric ratios of up to 93 : 7.

In 2016, the Unsworth research group investigated a silver-catalysed cyclization reaction that gave access to pyridine-, isoquinoline-, and pyrazine-ynone scaffolds (Scheme 20).[128] The high yielding reaction (up to quantitative yield) employed pyridine-ynone starting materials, which were readily available from 2-picoline. In addition to the twelve quinolizidine examples, this new approach was used to prepare *lasubine II*, a naturally occurring alkaloid, in five steps. In the same year, Tokuyama and coworkers published a novel gold-catalysed reaction sequence toward highly substituted quinolizidines.[129] The acationic gold complex facilitated a double cyclization cascade sequence of yn-amides, which were converted to enamides in the first cyclization and to the final quinolizidines in the second cyclization. The novel methodology was also used in the total synthesis of the naturally occurring alkaloid *lupinine*. In another example, the Castarlenas research group reported a rhodium-catalysed hydroalkenylation reaction of 2-vinylpyridine that yielded a quinolizidine.[130] By changing 2-vinylpyridine to 2-vinylpyridazine, an additional nitrogen atom was introduced into the quinolizidine scaffold. In the last approach reviewed here, published by Fan and coworkers in 2020, 2-(quinolin-8-yl)ethyl ketones were transformed into their corresponding julolidines, which bear the quinolizidine structure with an additional aromatic ring.[131] The employed ruthenium complex catalysed both the hydrogenation and subsequent reductive amination reactions with yields as high as 94%, diastereomeric ratios exceeding 20 : 1 and ee values of up to 99%. Three post modifications were reported, including the preparation of two chiral compounds and a molecular motor.



Scheme 20 Quinolizidines *via* metal-catalysed reactions.

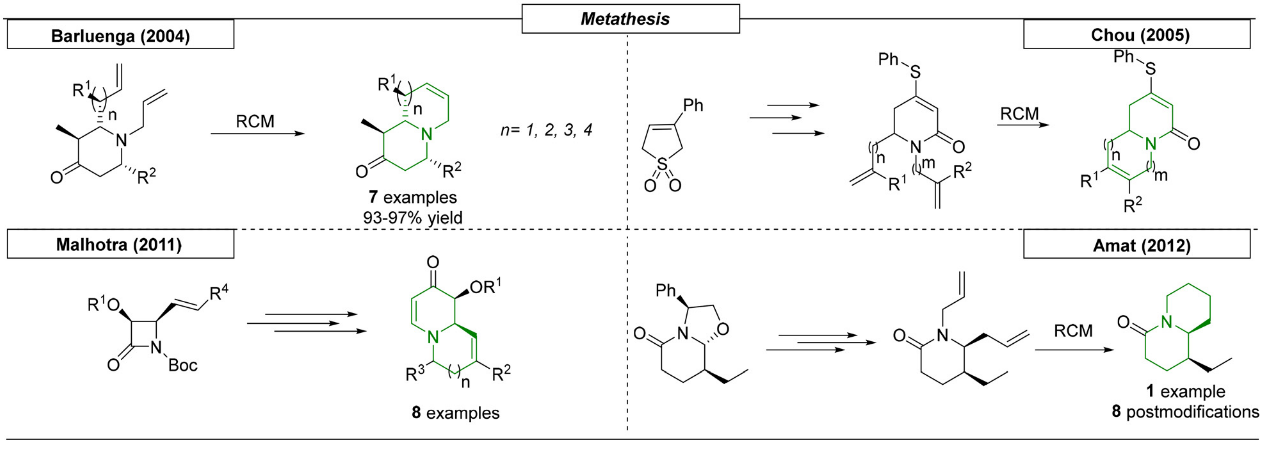
4.4 Metathesis reactions

Four research groups have reported the synthesis of N-bridgehead compounds using metathesis reactions. A straightforward synthetic procedure toward N-bridgehead scaffolds with different ring sizes was published by the Barluenga research group in 2004 (Scheme 21).[132] RCM precursors were prepared by aza Diels–Alder reaction of amino trienes with imines. The subsequently RCM reaction formed the N-bridgehead system. In total, seven examples with ring sizes of up to nine atoms were synthesized. The Chou research group published four different papers about the use of thiophene-derived precursors to synthesize a multitude of different N-bridgehead heterocycles.[133–136] Using this approach, the precursors were transformed into diallyl compounds, which were then used in RCM reactions to access various bicyclic scaffolds. In a different approach, Malhotra and coworkers reported the use of *N*-Boc β-lactams to construct N-bridgehead bicyclic compounds with varying ring sizes in a stereoselective fashion.[137] The β-lactams were opened with an ethynyl Grignard reagent, and the resulting ynones were cyclized to form dihydropyridones. *N*-Alkylation of the pyridone nitrogen provided di-olefin intermediates, which were used in subsequent RCM reactions. In total, eight N-bridgehead compounds were synthesized. The last reviewed procedure for the RCM synthesis of quinolizidines was developed by Amat and coworkers in 2012.[138] A chiral bicyclic lactam was stereoselectively opened with allyltrimethylsilane to provide an *N*-substituted pyridone. Removal of the *N*-substituent, followed by *N*-allylation provided the di-olefin that was used in the subsequent RCM reaction to prepare the target quinolizidine. Eight additional compounds were provided *via* postmodification.

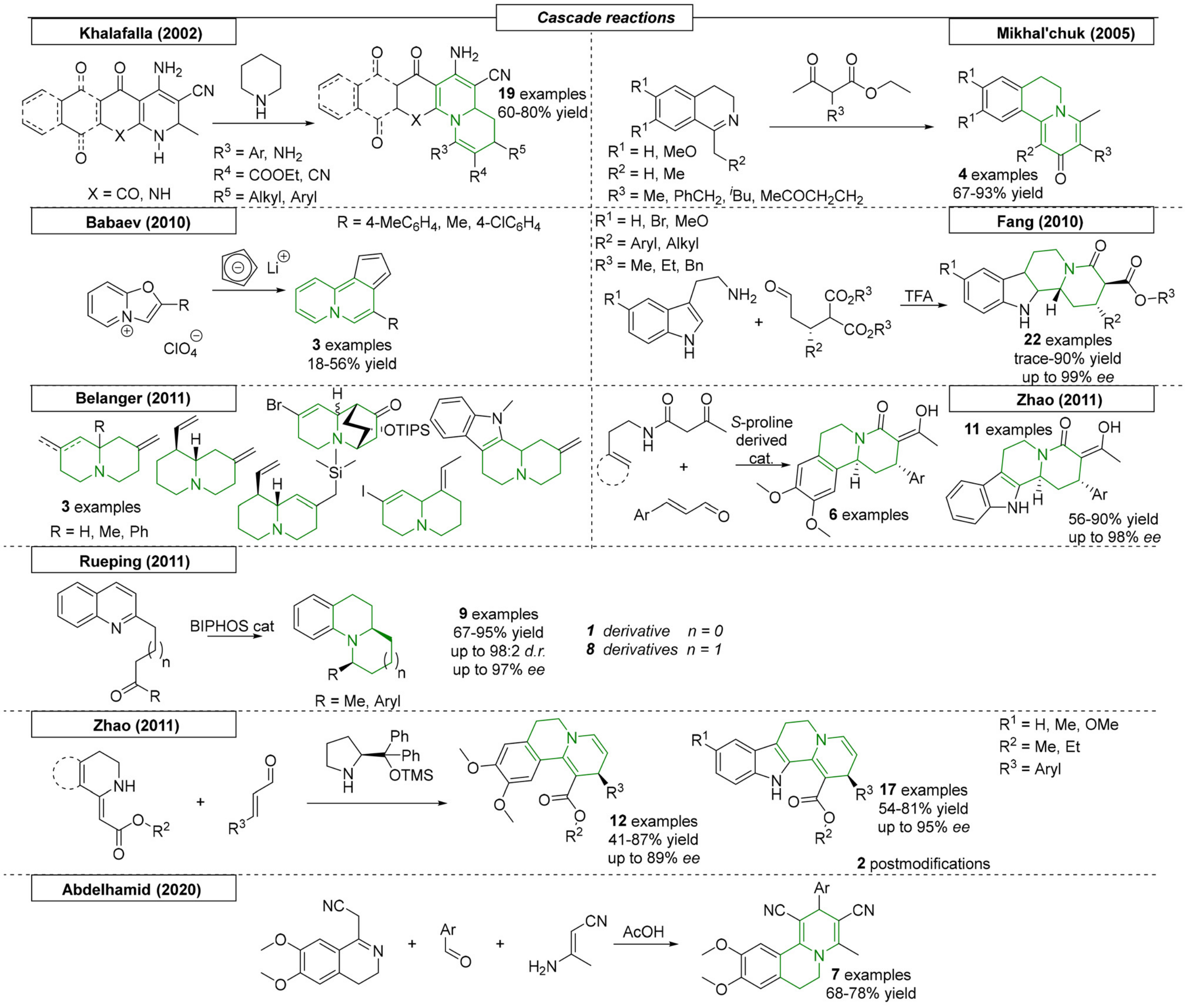
4.5 Cascade reactions

Many research groups have published methods for the preparation of quinolizidines *via* cascade and multicomponent reactions. Khalafalla and coworkers developed a cascade reaction strategy for the preparation of nineteen N-bridgehead compounds (Scheme 22).[139] The precursors used in the work were readily available from 1,4-naphthoquinone and a suitable alkylidyne malononitrile reagent. The intermediates obtained from the initial cycloaddition were reacted with Knoevenagl condensates of benzaldehyde to yield the corresponding quinolizidine scaffolds. In 2005, the Mikhal'chuk research group discovered a reaction sequence of an iso-quinoline Schiff base with α,β-keto esters that the authors described as a 'cyclo-condensation'.[140] This straightforward method gave access to four derivatives with yields as high as 93%. Another interesting approach was published by Babaev and coworkers in 2010,[141] further expanding their work from 2005.[94] Here, lithium cyclopentadienylide was reacted with oxazolo[1,2-*a*]pyridinium to obtain a novel ring-expanded pyrrolizidine scaffold. The yields of the four reported examples spanned from 11 to 44%. In the same year, the Zhao research group developed a Pictet–Spengler/lactamization cascade sequence toward a set of twenty-two indoloquinolizidines.[142] The aldehydes used for this sequence were reacted with an *S*-proline-derived catalyst, which gave access to the enantiopure starting material. After the TFA-catalysed cascade sequence, the corresponding products retained high enantiopurities (up to 99% ee) with yields as high as 90%.

In 2011, Belanger and coworkers synthesized a set of novel quinolizidine derivatives using a cyclization reaction cascade (Scheme 22).[143] A tertiary amide, which bore two nucleophilic groups on the two alkyl chains, was chosen as the starting material. First, a Vilsmeier–Haack reaction occurred, resulting in a highly reactive imine intermediate, which was then attacked by the second nucleophile to yield the desired quinolizidine motifs with yields as high as 70%. In total, eight derivatives were synthesized. In the same year, the Zhao research group reported an enantioselective organocatalysed cascade reaction toward highly functionalized quinolizidines.[144] In this process, catalysed by an *S*-proline-derived chiral catalyst, cinnamic aldehyde was reacted with β-ketoamide. As in their 2010 publication,[142] the sequence was



Scheme 21 Metathesis reactions toward N-bridgehead compounds.



Scheme 22 Quinolizidines *via* cascade and multicomponent reactions.

described as a Michael addition/Pictet Spengler cascade. During the investigation, seventeen examples were reported with yields as high as 90% and ee values of up to 98%. The Zhao research group continued their organocatalytic cascade investigations by changing their starting material to cyclic enamine esters, which were used in a novel sequence toward highly substituted indole[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines.[145] α,β-Unsaturated aldehydes were reacted with cyclic enamine esters using an enantiopure *S*-proline-derived catalyst. The activated LUMO of the aldehyde was attacked by the nucleophilic enamine derivative. After cyclization and dehydration, the corresponding N-bridgehead derivatives were obtained in yields as high as 87% and with up to 95% ee.

In 2011, an innovative approach toward quinolizidines and indolizidines was reported by Rueping *et al.*, who enabled an enantioselective synthesis *via* a catalytic asymmetric hydrogenation cascade (Scheme 22).[146] Starting from 5-(2-quinolinyl)-2-pentanone, a catalytic system of Hantzsch ester and BINOL-phosphate was optimized to provide nine examples of N-bridgehead derivatives. Depending on substitution and ring size, yields ranged from 67–95% and diastereomeric ratios of up to 98 : 2 and optical purities of up to 97% ee were obtained. The last quinolizidine cascade reaction reviewed here was reported by Abdelhamid and coworkers in 2020.[147] In this Hantzsch ester synthesis inspired work, 3-aminocrotononitrile, benzaldehyde and 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile were reacted in acetic acid to yield the desired benzo-quinolizidine scaffolds. By varying the benzaldehyde, this novel sequence gave access to seven examples in yields as high as 78%.

4.6 One-pot syntheses

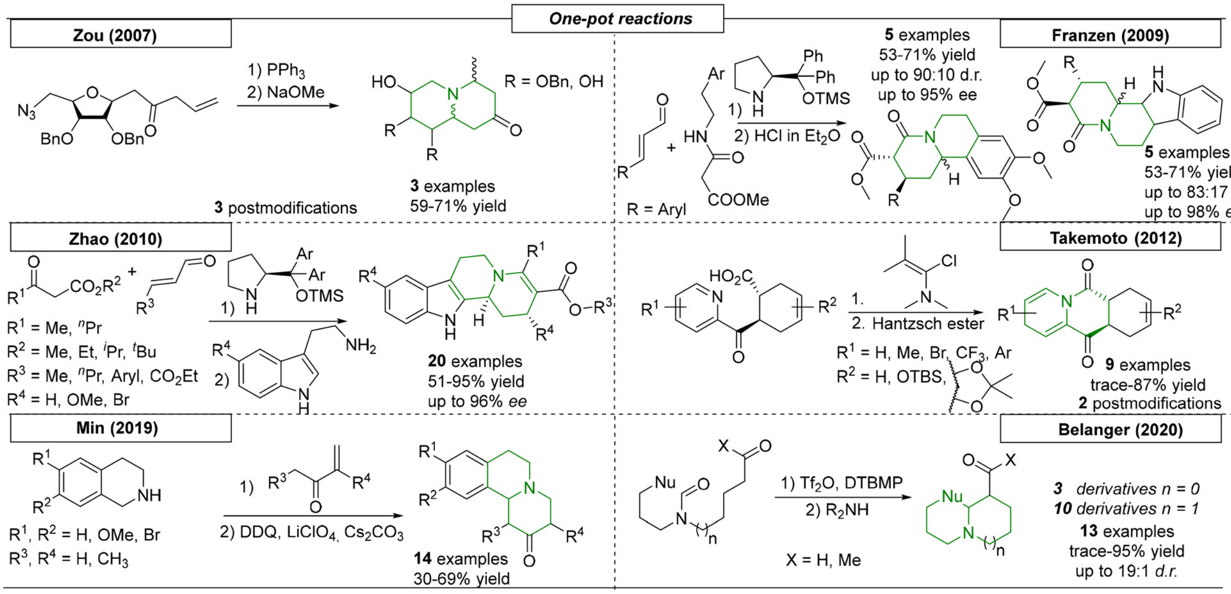
Many one-pot procedures have been used to produce quinolizidines. In 2007, Zou reported a one-pot, stereoselective synthesis toward polyhydroxylated quinolizidines (Scheme 23).[148] The procedure used C-glycoside sugars from the natural pool in a one-pot, double-conjugate-addition procedure. Two quinolizidine derivatives were synthesized *via* a double-Michael addition. The hydroxy and ketone functional groups on the synthesized molecules were used in further modifications. Another one-pot procedure that gave access to novel quinolizidine derivatives was described by Franzén and coworkers 2009.[149] The authors developed a novel procedure for the addition of amides to α,β-unsaturated aldehydes catalysed by optically pure proline derivatives. In total, ten new compounds were synthesized with stereoselectivities of up to 9 : 1 dr and 98% ee. Additional work pertaining to these scaffolds was published one year later.[150] The Zhao research group reported an enantioselective, three-component, one-pot procedure that yielded indoloquinolizidines.[151] The first part of the process was a conjugate addition enabled by an *S*-proline-derived optically pure catalyst. In the second part, tryptamine was added to allow a Pictet–Spengler cyclization to occur, which provided the desired compounds in yields of 56 to 95% and with enantiomeric excesses of up to 96%.

In an innovative approach, Takemoto and coworkers synthesized oxidized quinolizidine derivatives *via* reduction of acylpyridinium cations (Scheme 23).[152] The first reaction of the two-step, one-pot sequence was the acylation, which was enabled by Ghosez's reagent, while the second reaction was a Hantzsch ester reduction. In addition to nine new quinolizidines, 207I and 1-*epi*-207I were synthesized in five steps. In 2019, the Min research group reported a novel, one-pot synthesis of benzo[*a*]quinolizidines.[153] The procedure consisted of a copper(I) bromide-catalysed, aza Michael addition reaction followed by a DDQ-oxidized Mannich process. In total, fourteen substrates were synthesized using the one-pot procedure or by performing each step separately. In addition, the authors showed that it was possible to combine the reactions into one-pot procedures in four more examples. The last quinolizidine one-pot sequence reviewed here was reported by Bélanger and coworkers, who described a sequential one-pot Vilsmeier–Haack and organocatalysed Mannich cyclization,[154] which was inspired by their previous work.[143] To overcome the reactivity issues of the second cyclization in the previous approach, an *in situ*-prepared enamine was used. In total, fourteen derivatives were synthesized with yields as high as 95% and stereoselectivities of up to 19 : 1 dr.

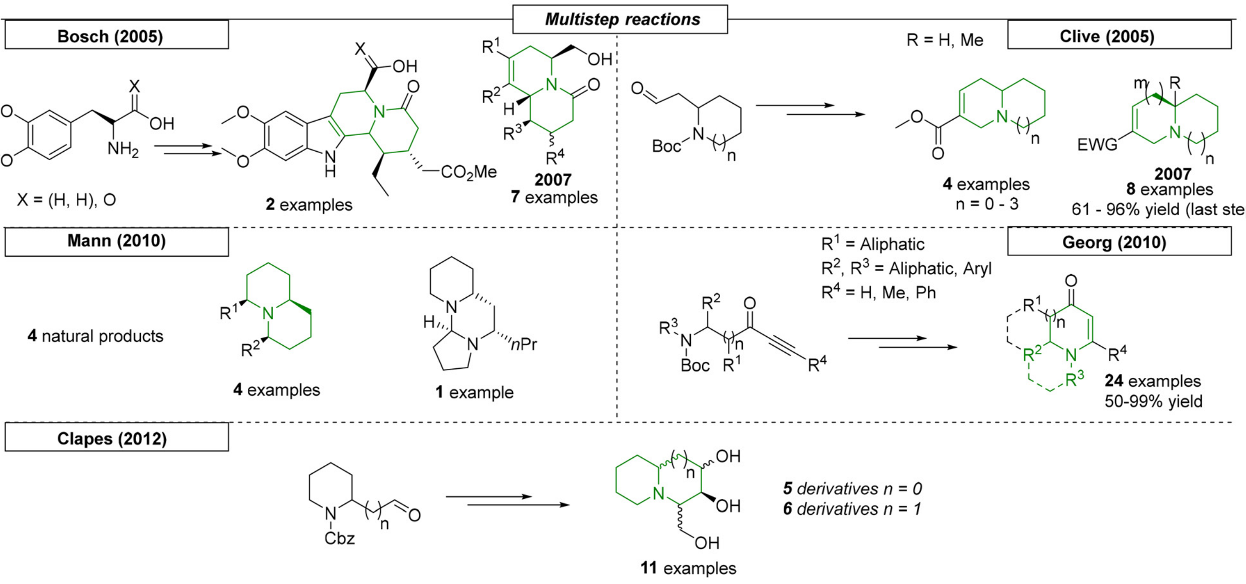
4.7 Multistep syntheses

Many research groups have published syntheses of quinolizidines using multistep procedures. In 2005, Bosch and coworkers developed a biogenetically inspired enantioselective synthesis of indolo[2,3-*a*]- and benzo[*a*]quinolizidines (Scheme 24).[155] In the first step, they synthesized an aglycone of naturally occurring secologanin. This compound was subjected to a tandem kinetic resolution/desymmetrization sequence and then employed in a stereoselective cyclo-condensation with two different (*S*)-tryptanols. In total, four quinolizidine derivatives were synthesized. In 2007, this procedure was further developed to produce an additional seven examples.[156] In 2005, Clive and coworkers described a synthetic procedure toward N-bridgehead compounds with various ring sizes.[157] Methyl acrylate was reacted with cyclic Boc-protected β-amino aldehydes with ring sizes ranging from 5 to 8. Removal of the protecting group allowed cyclization to occur *via* an intramolecular Michael addition reaction. In a subsequent publication, the Clive research group expanded the scope to include additional sizes of both rings.[158] Overall, eight additional examples were reported.

In 2010, Mann and coworkers developed a hydroformylation of alkenylamines, which was used as a key step in the con-



Scheme 23 One-pot procedures used to produce quinolizidines.



Scheme 24 Quinolizidines *via* multistep procedures.

struction of quinolizidine compounds (Scheme 24).[159] The protected cyclic amines, obtained by the aza-Sakurai–Hosomi hydroformylation, were stereoselectively converted to either an aldehyde or an α,β-unsaturated ketone, which were used to form the second quinolizidine ring. They also synthesized four natural products using this reaction sequence. In the same year, the Georg research group developed a novel multistep synthetic strategy toward enaminones.[160] In the first step, various ynones, prepared from β-amino acids, were transformed to their corresponding heterocycles. If cyclic amines were used, quinolizidine and indolizidine derivatives were obtained, twenty-four examples in all. The last multistep quinolizidine synthesis reviewed here was reported by Clapés and coworkers.[161] Using a two-step sequence, eleven novel quinolizidine and indolizidine derivatives were synthesized. All compounds were tested for their ability to inhibit α-L-rhamnosidase from *P. decumbens*; four indolizidines and two quinolizidines showed inhibitory activity.

4.8 Annulation reactions

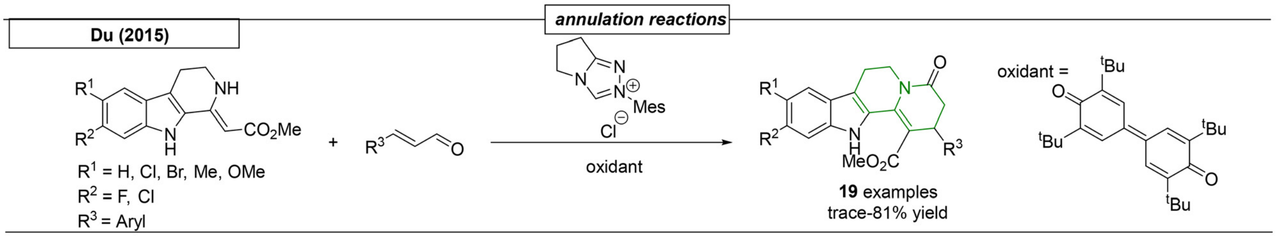
Du and coworkers developed an N-heterocyclic carbene-catalysed annulation reaction of cyclic β-enamino esters with enals (Scheme 25). This approach gave entry to functionalized indolo[2,3-*a*]quinolizidines, which are present in Latifoliamide A, Corynantheol and Geissoschizine.[162] The methodology was used to synthesize nineteen different derivatives.

4.9 Other

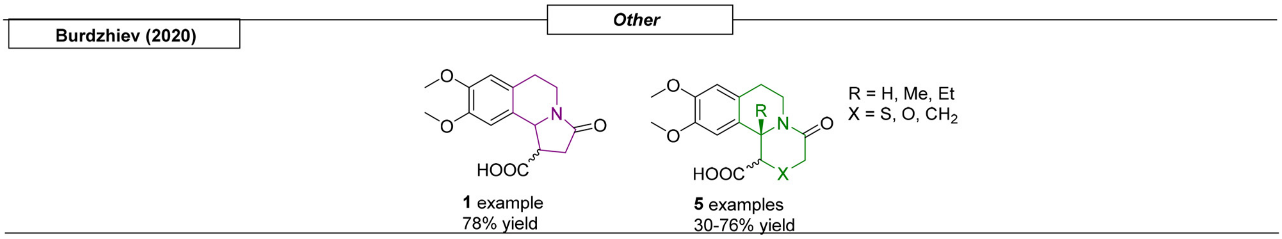
In 2020, the Burdzhiev research group synthesized a set of quinolizidines while developing a one-step route toward isoquinoline derivatives (Scheme 26).[163] This straightforward method used dihydro-isoquinoline precursors, which were reacted with cyclic anhydrides to yield the corresponding N-bridgehead compounds.

5 Other N-bridgehead compounds

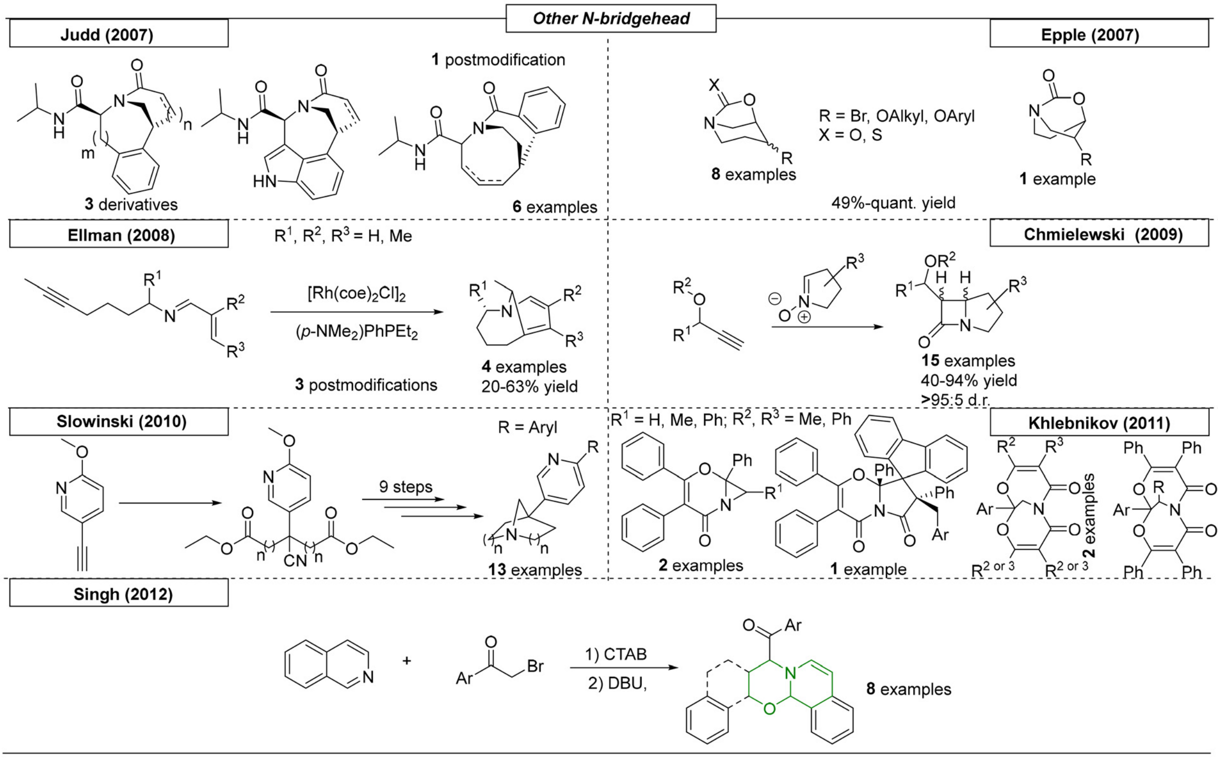
Other than the main scaffolds, pyrrolizidine, indolizidine and quinolizidine, a multitude of additional compounds classes exist bearing a bridgehead nitrogen atom. This section summarizes publications of N-bridged heterocycles that cannot be assigned to one of the main compound classes. In 2007, the Judd research group reported a concise construction of various bicyclic bridged lactam compounds (Scheme 27).[164] In this



Scheme 25 Annulation reactions that have been used to prepare quinolizidines.



Scheme 26 Other reactions that have been used to obtain quinolizidines.



Scheme 27 Synthesis of other related N-bridgehead compounds.

publication, a three-step sequence utilizing simple starting materials was developed. The first reaction was an Ugi four component coupling reaction. The resulting diallyl compound was then used in an RCM and a Heck reaction to provide six novel bridged lactam compounds. In the same year, Epple and coworkers synthesized a set of bicyclic carbamates as non-peptide based inhibitors of papain-like cathepsin proteases.[165] The core structure was identified during a high throughput screening based on monitoring cleavage rate of a coumarin-labelled synthetic tetrapeptide highly reactive to *Cathepsin S*. A set of compounds was synthesized starting from tetrahydropyridine, which was converted to its corresponding nitrogen-protected epoxide. After hydrolysis, the carbamate was formed.

A rhodium-catalysed, tandem reaction toward bicyclic enamines with bridgehead nitrogen was developed by Ellman and coworkers in 2008 (Scheme 27).[166] The stereoselective transformation comprised activation, alkylation and electrocyclization steps. During this investigation, four examples and two post-modification examples were synthesized. By reacting cyclic nitrones with nonracemic acetylenes, the Chmielewski research group was able to synthesize fourteen novel N-bridgehead lactams with fused four- and five-membered rings.[167] The asymmetric Kinugasa reaction was catalysed by copper(I) and gave access to the lactams in yields as high as 94% and diastereomeric ratios of up to 95 : 5.

Slowinski *et al.* synthesized novel azabicyclo-[2.2.1]heptane and -[3.3.1]nonane derivatives, which contained a pyridinyl substituent at the bridgehead position, *via* a ten step reaction sequence starting from commercially available (6-methoxypyridin-3-yl)acetonitrile (Scheme 27).[168] The synthesized derivatives were subsequently evaluated *in vitro* for their affinity for α7-nicotinic receptors. The compounds were both highly active, with nanomolar EC50s, and selective, without significant affinity for the α4β2-nicotinic receptor subtype.

Khlebnikov and coworkers published a non-concerted cycloaddition of 3-aryl, 2*H*-azirines and acylketenes that gave access to a set of N-bridgehead heterocycles.[169] A cycloaddition reaction provided 3-membered ring systems, which were reacted with an additional acylketene to form complex bicyclic scaffolds. Structures were verified by X-ray analysis. A novel synthetic route toward fused heterocyclic oxa-aza-phenanthrene and -anthracene scaffolds was developed by the Singh research group in 2012.[170] In this one-pot sequence, isoquinoline was reacted with various phenacyl bromides, and the resulting intermediates were subsequently reacted with styrene oxides. This process gave excellent yields, ranging from 90–98%, and is considered 'green' chemistry, because water is used as a solvent and DBU as an organic base. Additional structures and synthetic methodologies have been reviewed recently in separate works. As they have a small overlap with our review, we added these in the table below (Table 1).

6 Tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*] pyrazoles

Relative to their single bridgehead nitrogen analogs, fewer studies have been published that feature pyrazolo-pyrazoles. However, they are also known to exhibit important bioactivity.[177] For example, Jungheim *et al.* have reported synthetic efforts to access lactam analogs, which are known antibacterial agents (Fig. 5).[178] In another example, the Yanni research group reported the antibacterial and antifungal activity of the pyrazolo-pyrazole scaffold. Here we have reviewed all synthetically available analogs.

6.1 Multistep procedures

Three research groups have published multistep procedures that produce pyrazolo-pyrazoles. The first multistep approach reviewed here was described by Boros and coworkers in 2001 (Scheme 28).[179] Starting from Boc-protected hydrazine, the authors were able to obtain the target pyrazole compound in four steps with a 46% overall yield. The Harmata research group employed a set of Trögers bases as starting materials to access nine examples of pyrazolo-pyrazole compounds.[180] The two-step sequence started with the oxidation of one bridgehead nitrogen atom with dimethyldioxirane and concluded with a rearrangement in acetic anhydride to provide the desired scaffolds. In the last example reviewed here, Gozin and coworkers synthesized an 'energetic butterfly' in a four-step sequence.[181] The authors started from the condensation of 2-cyano-*N*′-(2-cyanoacetyl)acetohydrazide and acetylacetone. The condensation product was converted into 3,7-diamino-1*H*-5*H*-pyrazolo[1,2-*a*]-pyrazole-1,5-dione bimane. Treatment of the pyrazolo-pyrazole derivative with concentrated nitric acid in acetic anhydride yielded the target compound. Because the molecule was both explosive and resembled a butterfly, it was referred to as an 'energetic butterfly' in the publication. However, it has been included here, because it adopts its explosive character only after the final nitration reaction.

6.2 1,3-Dipolar cycloaddition reactions

By far the most developed synthetic methodology toward the pyrazolo-pyrazole motif is the 1,3-dipolar cycloaddition. Most of the reported approaches employ (*E*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide in combination with a diene as shown in Scheme 29.

Table 1 related reviews published from 2000–2023

Year	Title	Ref.
2017	Benzopyrroloxazines containing a bridgehead nitrogen atom as promising scaffolds for the achievement of biologically active agents	171
2018	Synthetic approaches to non-tropane, bridged, azapolycyclic ring systems containing seven-membered carbocycles	172
2018	A review on recent advances in nitrogen-containing molecules and their biological applications	173
2018	Recent advances in the synthesis of bridgehead (or ring-junction) nitrogen heterocycles *via* transition metal-catalysed C–H bond activation and functionalization	174
2019	Chemistry of bridged lactams: recent developments	175
2021	Construction of heterocyclic bridgehead *via* de-aromatisation strategies	176

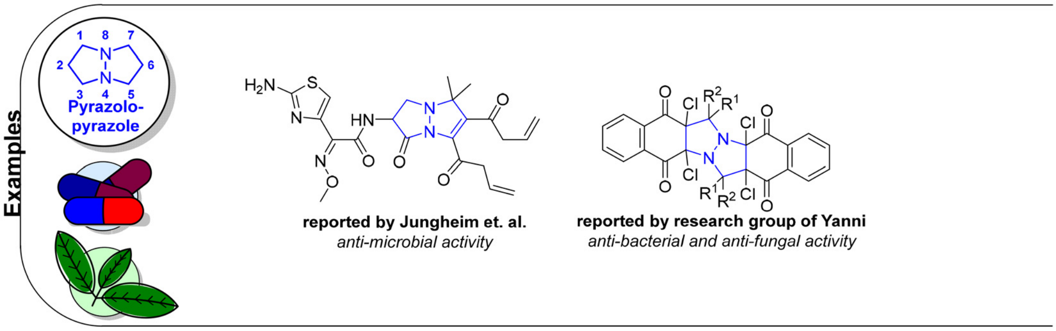
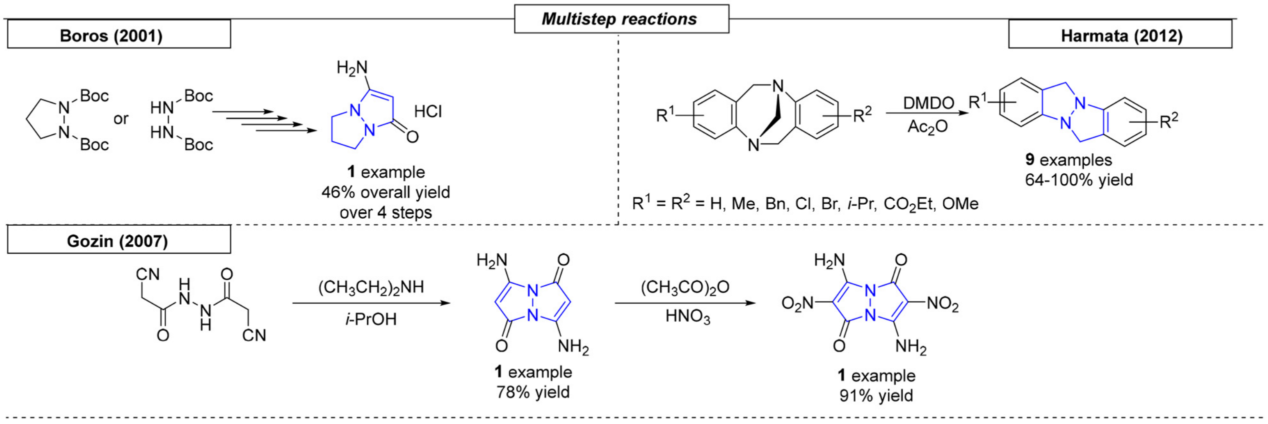
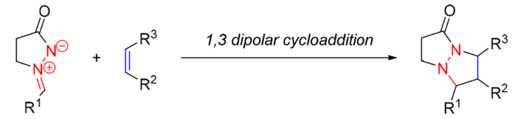


Fig. 5 Examples of pyrazolo-pyrazole-derived compounds.



Scheme 28 Various multistep procedures have been used to prepare pyrazolo-pyrazole.

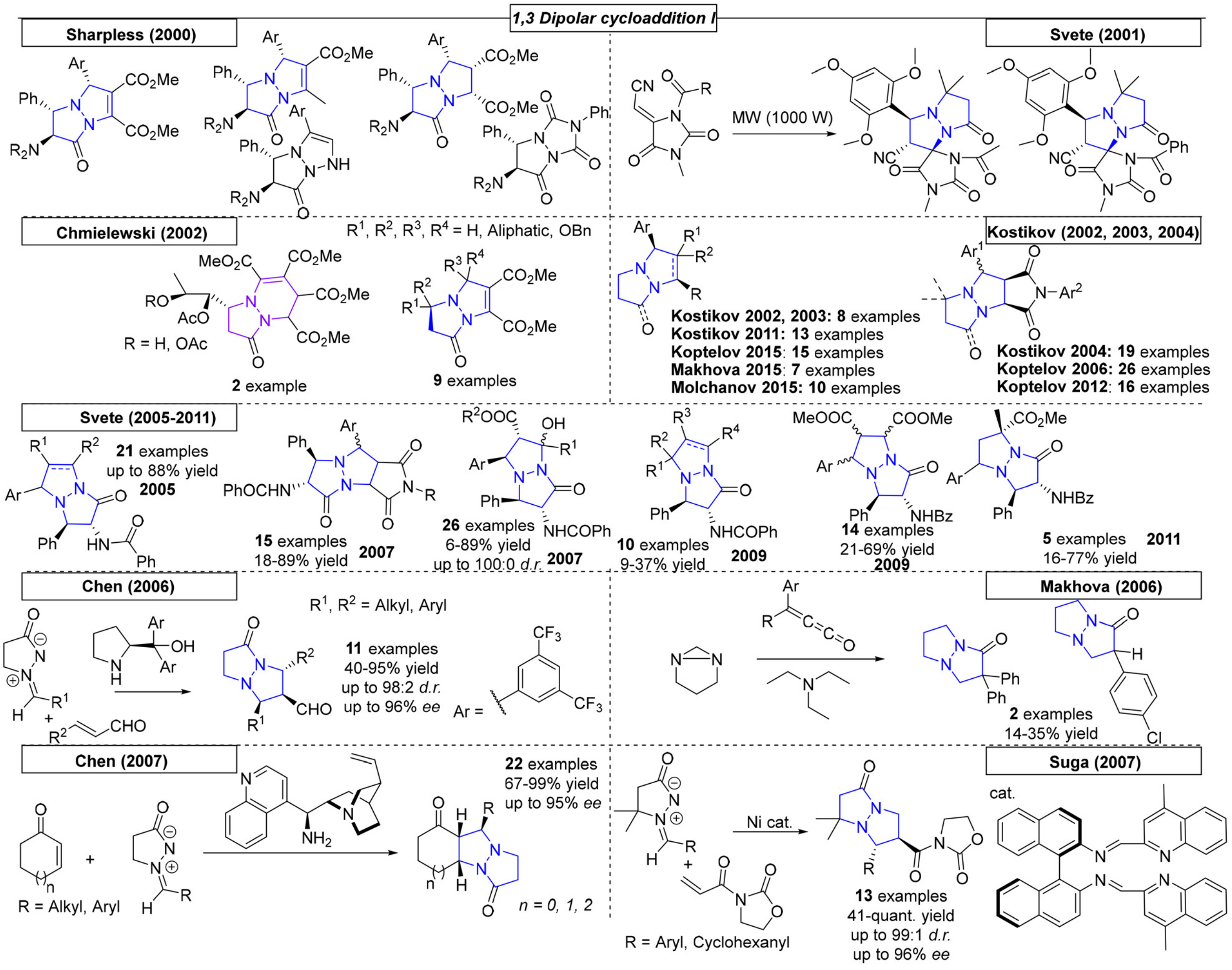


Scheme 29 Generalized 1,3-dipolar cycloaddition reaction toward pyrazolo-pyrazoles.

Over the past twenty years over seventy publications have employed a 1,3-dipolar cycloaddition reaction to prepare a multitude of pyrazolo-pyrazole compounds. The first 1,3-dipolar cycloaddition toward multiple pyrazole scaffolds was described by the Sharpless research group in 2000 (Scheme 30).[182] Azomethine precursors were synthesized in a four-step sequence and provided the corresponding twenty cycloadducts after reaction with various dipolarophiles. Products that were formed by attack on the less hindered site of the azomethine were favored by this reaction. In 2001, Svete and coworkers synthesized a novel (2*Z*)-2-(1,3-dimethyl-2,5-dioxoimidazolidin-4-ylidene)acetonitrile compound, which was converted to its 1-acetyl and 1-benzoyl analogs.[183] By using azomethine, two pyrazolo-pyrazole-derived spiro compounds were obtained. Another 1,3-dipolar cycloaddition was published by Svete and coworkers in 2005.[184] Various dipolarophiles were employed to provide twenty-three examples of pyrazolo-pyrazole derivatives in yields as high as 88%. In the same year, Svete and coworkers reacted β-ketoester enol dipolarophiles with various azomethines.[185] Twenty-six diastereomerically pure compounds were synthesized in yields as high as 86%. In the same year, by swapping *N*-arylmaleimides for the β-keto esters, the Svete research group was able to synthesize additional examples of N-bridgehead compounds in yields as high as 89%.[186] In some follow-up work in 2009, Svete and coworkers reported the reaction of alkynes and alkenes with the previously synthesized azomethine precursors.[187] At no higher than 32%, the yields were relatively low. In the same year, Svete and coworkers reacted *cis*- or *trans*-dimethyl maleate with various benzyl-protected azomethine derivatives.[188] The reaction selectively gave one diastereomer for six of the fourteen examples. In 2011, Svete and coworkers published a 1,3-dipolar cycloaddition reaction that provided five examples.[189] In the course of their investigation, the structures of two representative compounds were unambiguously determined by NMR spectroscopy and X-ray diffraction. In a similar reaction published by the Chmielewski research group, alkynes substituted with electron withdrawing groups were used as dipolarophiles.[190] By using various azomethines, ten derivatives were synthesized.

In three publications from 2002–2004, Kostikov and coworkers demonstrated that thermolysis of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes resulted in azomethines, which could be utilized in 1,3-dipolar cycloadditions (Scheme 30).[191–193] In the first report, *N*-arylmaleimides, alkenes and diphenylcyclopropenones were employed to provide thirty-two N-bridgehead compounds. To obtain insight into the diastereoselectivity of the 1,3-dipolar cycloaddition of azomethines and *N*-arylmaleimides, additional derivatives were synthesized by Kopetlov and coworkers. NMR studies were conducted on the twenty-six pyrazolo-pyrazoles in this and a subsequent study, but chemical yields were not reported.[194,195] Koptelov and coworkers reported additional compounds provided by the reaction of stable azomethine imines and *N*-arylmaleimides with yields as high as 78% and stereoselectivities of up to 76 : 24.[196] Following their procedure from 2011, an additional sixteen examples with dimethyl substitution on the azomethine imine backbone were prepared with yields as high as 82%.[197] In the final Koptelov paper reviewed here, various *N*-arylmaleimides were employed to investigate the effects of steric hindrance in dipolar cycloadditions with azomethine imines.[198] The authors found that the *trans* adduct is formed as the major product due to the favorability of the *endo* approach.

Makhova and coworkers described the dipolar cycloaddition of azomethine imines with various (arylmethylidene) malononitriles in dichloroethane (Scheme 30).[199] The reaction showed complete regio- and stereoselectivity following the classical Michael mechanism, resulting in *cis*-positioned aryl

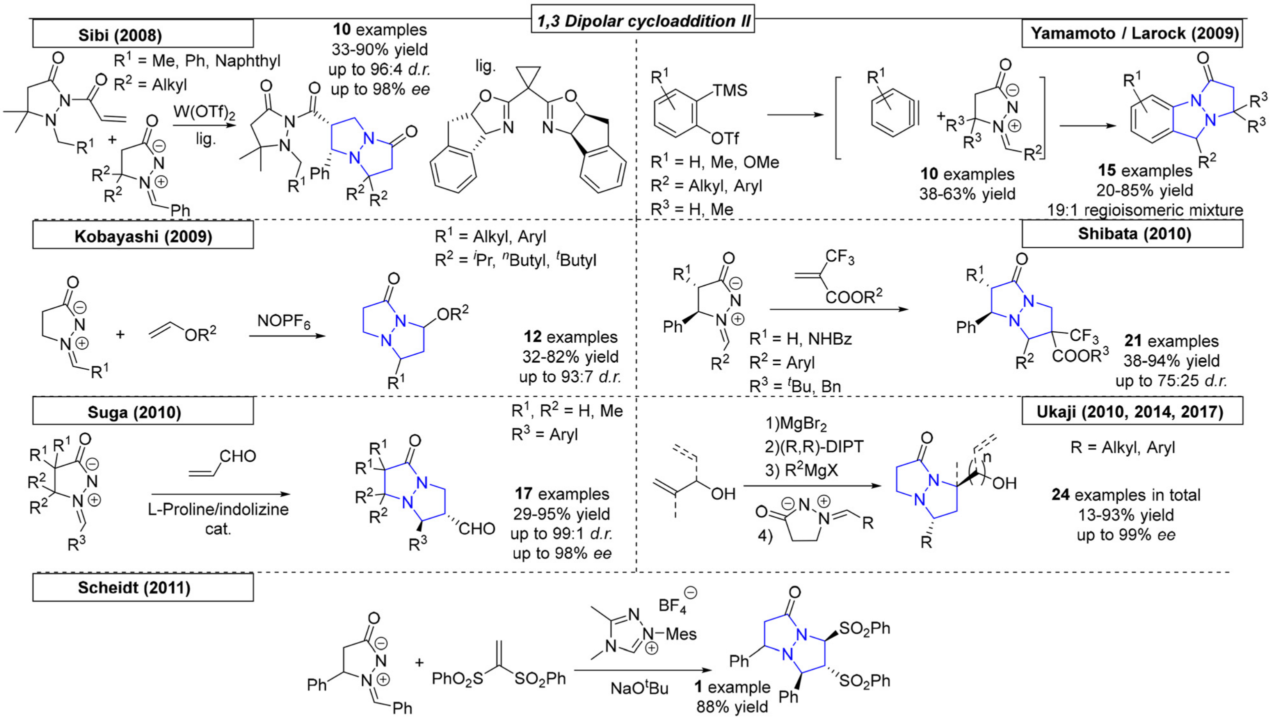


Scheme 30 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part I.

groups. Molchanov and coworkers reported *N*-vinylpyrroles as highly efficient reactants in [3 + 2] cycloadditions.[200] Heating various nitrile oxides and azomethine imines in a microwave reactor provided ten different N,N-bridgehead compounds in yields as high as 85% and with moderate *cis–trans* stereoselectivity. In 2006, the Chen research group reported a 1,3-dipolar cycloaddition of azomethine with various α,β-unsaturated aldehydes.[201] By employing a chiral, secondary amine-derived organocatalyst to activate the aldehydes, diastereoselectivities of up to 98 : 2 and ee values of up to 96% were achieved. In the same year, the research group of Makhova investigated the reactivity of arylketenes with *in situ*-formed azomethines.[202] In the course of this investigation, two novel pyrazolo-pyrazole derivatives were obtained, though with relatively low yields. Another organocatalytic approach toward pyrazolo-pyrazoles was published by Chen and coworkers in 2007.[203] An organocatalyst bearing primary amine, tertiary amine and phenol functional groups enabled a reaction with various cyclic α,β-unsaturated ketones that provided twenty-two novel N,N-bridgehead compounds in yields as high as 99% and with up to 95% ee.

Suga and coworkers reported a highly enantioselective 1,3-dipolar cycloaddition reaction between azomethine imines and 3-acryloyl-2-oxazolidinone catalysed by a nickel(II) complex (Scheme 30).[204] The oxygen atoms of 3-acryloyl-2-oxazolidinone interact nicely with the Ni catalyst. The reaction, which was carried out at room temperature, yielded the desired pyrazolo-pyrazoles in up to quantitative yield. Diastereomeric ratios of up to 99 : 1 and enantiomeric excesses of up to 97% were reported.

In 2008, the Sibi research group published a dipolar cycloaddition using dipolarophiles similar to those described by Suga (Scheme 31).[205] In this work, a chiral copper(II) catalyst enabled the reaction at room temperature with yields as high as 90% and stereoselectivities of up to 96 : 4 dr and 98% ee. In 2009, Yamamoto and coworkers generated a set of benzynes *in situ* that were employed in a dipolar cycloaddition reaction with azomethine dipolarophiles.[206] The benzynes were generated by potassium fluoride/18-crown-6 ether in THF and gave access to ten examples in yields as high as 68%. Similar to the work of Yamamoto, Larock and coworkers synthesized a set of novel pyrazolo-pyrazoles *via* the 1,3-cycloaddition of an azo-



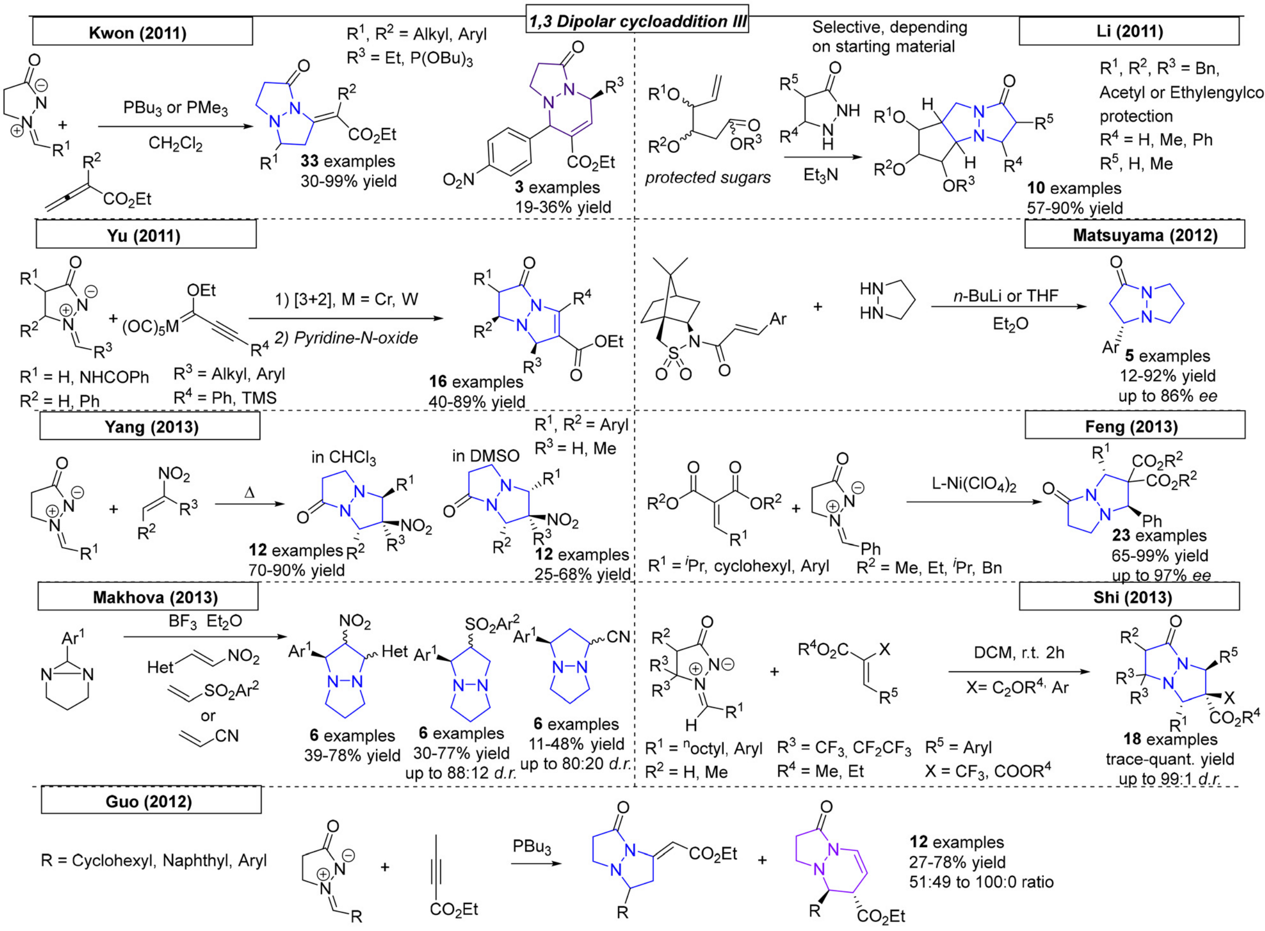
Scheme 31 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part II.

methine with various *in situ*-generated benzynes.[207] The novel derivatives were substituted on the backbone of the azomethine and were obtained in 19 : 1 regioisomeric mixtures with yields as high as 85%. A different approach for the 1,3-dipolar cycloaddition was enabled by Kobayashi and coworkers by employing a $NOPF_6$ catalyst.[208] By using various azomethines and vinyl ethers, fifteen N,N-bridgehead compounds were synthesized in yields as high as 82% and diastereoselectivities of up to 93 : 7.

To access trifluormethylated heterocycles, Shibata and coworkers developed a noncatalytic methodology employing azomethine imines and (trifluoromethyl)prop-2-enoates as extremely electron deficient reagents (Scheme 31).[209] Twenty-one examples were obtained in yields as high as 94% and with up to 75 : 25 dr. The regiochemistry was found to be opposite to that observed by Svete, which indicated that the electronic effect could be utilized to influence the resulting regiochemistry.[188] In 2010, Suga and coworkers used *S*-proline or proline-derived compounds as catalysts to activate acrolein for a 1,3-dipolar cycloaddition reaction with various azomethine imine compounds.[210] The investigations provided seventeen derivatives with yields as high as 95% and excellent selectivities, up to 99 : 1 dr and up to 98% ee. Another elegant approach toward pyrazoline-pyrazoles was published by the Ukaji research group in the same year.[211] For the dipolar cycloaddition, a vinyl alcohol was activated by a Grignard reagent in the presence of a chelating chiral ligand; a precise mechanism was not proposed. Six compounds were prepared in yields as high as 74% and with excellent selectivities, up to 93% ee. In yet another example from 2010, a similar reaction was published by the same group that utilized homoallylic alcohols as dipolarophiles, which gave access to seven N,N-bridgehead compounds in yields as high as 93% and with up to 95% ee.[212]

Ukaji and coworkers utilized the asymmetric 1,3-dipolar cycloaddition reaction to de-symmetrize 1,4-pentadien-3-ol (Scheme 31).[213] The magnesium-mediated, multi-nucleating chiral reaction system transferred chiral information from di-isopropyl (*R*,*R*)-tartrate, resulting in ee values of up to 98%. By further developing their highly enantioselective approach, the Ukaji research group synthesized five additional examples of N,N-bridgehead compounds, one of which was used as the starting point for the formal synthesis of Manzacidin C.[214] An organocatalytic approach toward pyrazolo-pyrazoles was published by Scheidt and coworkers in 2011.[215] In this publication, the use of vinyl sulfones in 1,3-dipolar cycloaddition reactions was investigated. One N-bridgehead compound was synthesized in 88% yield.

In 2011, Kwon and coworkers synthesized a multitude of N,N-bridgehead compounds *via* phosphine-catalysed [3 + *N*] reactions (Scheme 32).[216] In addition to thirty-three pyrazolo-pyrazole compounds, 5,6-, 5,7- and 5,8-fused ring systems were synthesized. To access linear diaza-triquinanes, the Li research group developed a methodology employing an azomethine imine and sugar-derived hex-5-enals.[217] The stereocontrolled cycloaddition was catalysed by triethylamine and yielded the corresponding diaza-triquinanes in up to 90% yield. In the same year, a metal-catalysed, 1,3-dipolar cycloaddition



Scheme 32 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part III.

approach was published by Yu and coworkers.[218] The authors employed chromium or tungsten Fisher carbene complexes, which were reacted with azomethine imines. After treatment of the intermediates with pyridine *N*-oxide, sixteen N,N-bridgehead compounds were obtained with yields as high as 89%. In 2012, Matsuyama and coworkers published an asymmetric conjugate addition–cyclization reaction.[219] Deprotonation of pyrazolidine with *n*-BuLi enabled the 1,3-dipolar cycloaddition reaction. The authors synthesized an additional example of a 5,6-fused ring system by using hexahydropyridazine as the starting material.

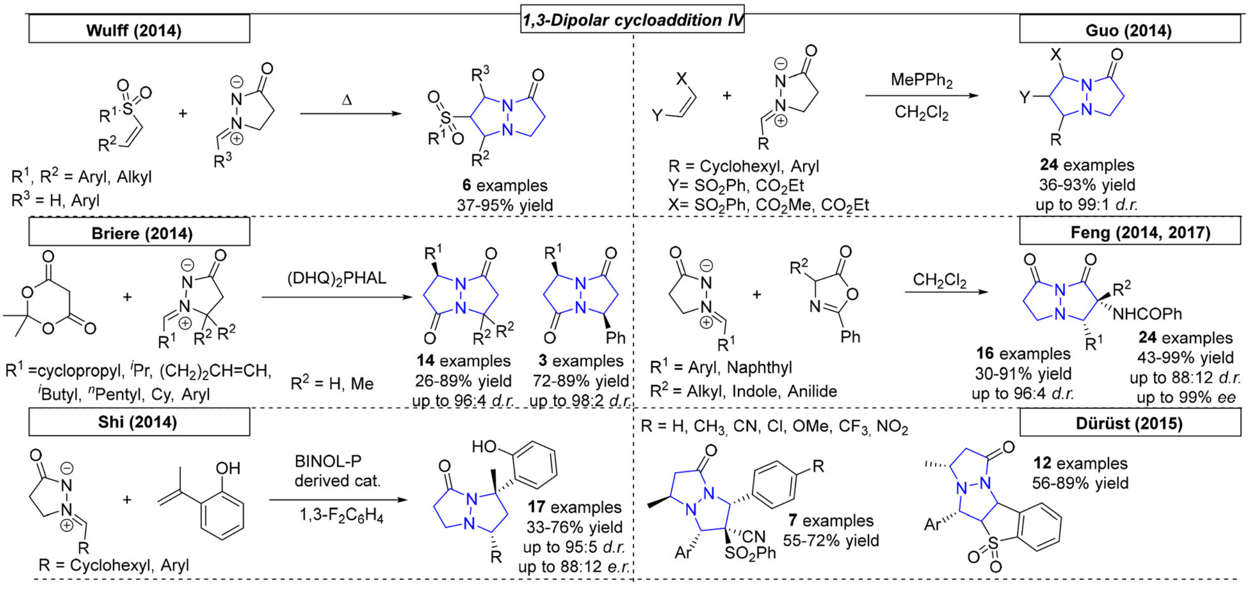
Many examples were published in 2013. Yang and coworkers employed various nitrostyrene compounds as dipolarophiles in a 1,3-dipolar cycloaddition reaction with azomethine imines (Scheme 32).[220] The formation of the corresponding diastereomer was found to depend on the solvent choice; both diastereomers were selectively synthesized in up to 78% yield and 100 : 0 dr. In the same year, the Feng research group utilized a nickel complex as a catalyst for a 1,3-dipolar cycloaddition reaction between various alkylidene malonate derivatives and azomethine imines.[221] Twenty-three pyrazolopyrazole compounds were prepared with excellent yields (up to 99%) and ee values as high as 97%. Investigation of the relationship between the enantiomeric excesses of the ligand and the resulting product revealed a slightly positive, nonlinear effect. Makhova and coworkers reported a novel, 1,3-dipolar cycloaddition reaction between *in situ* generated azomethine imines and six different nitrostyrene derivatives.[222] The diastereoselective reaction, which tolerated different heterocycles as nitrostyrene substituents, was carried out in acetonitrile or [bmim][PF_6] solvents with yields as high as 78% for five examples. The same group used similar reaction conditions in a dipolar cycloaddition reaction between various azomethine derivatives and acrylonitrile or 4-nitrophenyl vinyl sulfones.[223] These reactions were carried out in ionic liquid solvent and gave opposite diastereoselectivities for the two substrates, which was rationalized by quantum chemistry calculations. Shi and coworkers developed a novel methodology toward trifluoromethylated heterocycles.[224] The reaction, which employed azomethine imine and trifluoromethyl-functionalized olefins, yielded eighteen examples in up to quantitative yield. The electron-deficient olefins had either CF_3 or CF_2CF_3 substituents on R^5. The Guo research group reported phosphine-catalysed [3 + 2] and [3 + 3] annulations similar to those published by Kwon in 2011 that lead to various N,N-bridgehead compounds. Depending on the starting material, 5,5- and/or 5,6-fused ring systems were prepared in yields as high as 78% and of up to 100 : 0 dr.[225]

While studying the synthesis of dual conformation tricycles, Wulff and coworkers developed a dipolar cycloaddition reaction of azomethine imines and various vinyl sulfones (Scheme 33).[226] Bicyclic vinyl sulfones can be used to synthesize, for example, an inhibitor of viral neuraminidase. NMR was used to confirm the fluxional behavior of synthesized compounds in solution at room temperature. The Guo research group used a phosphor-derived catalyst for the synthesis of various dinitrogen fused heterocycles.[227] In the course of this work, twenty-four examples were synthesized in yields as high as 93%. Three cyclic systems with one bridgehead nitrogen were also prepared.

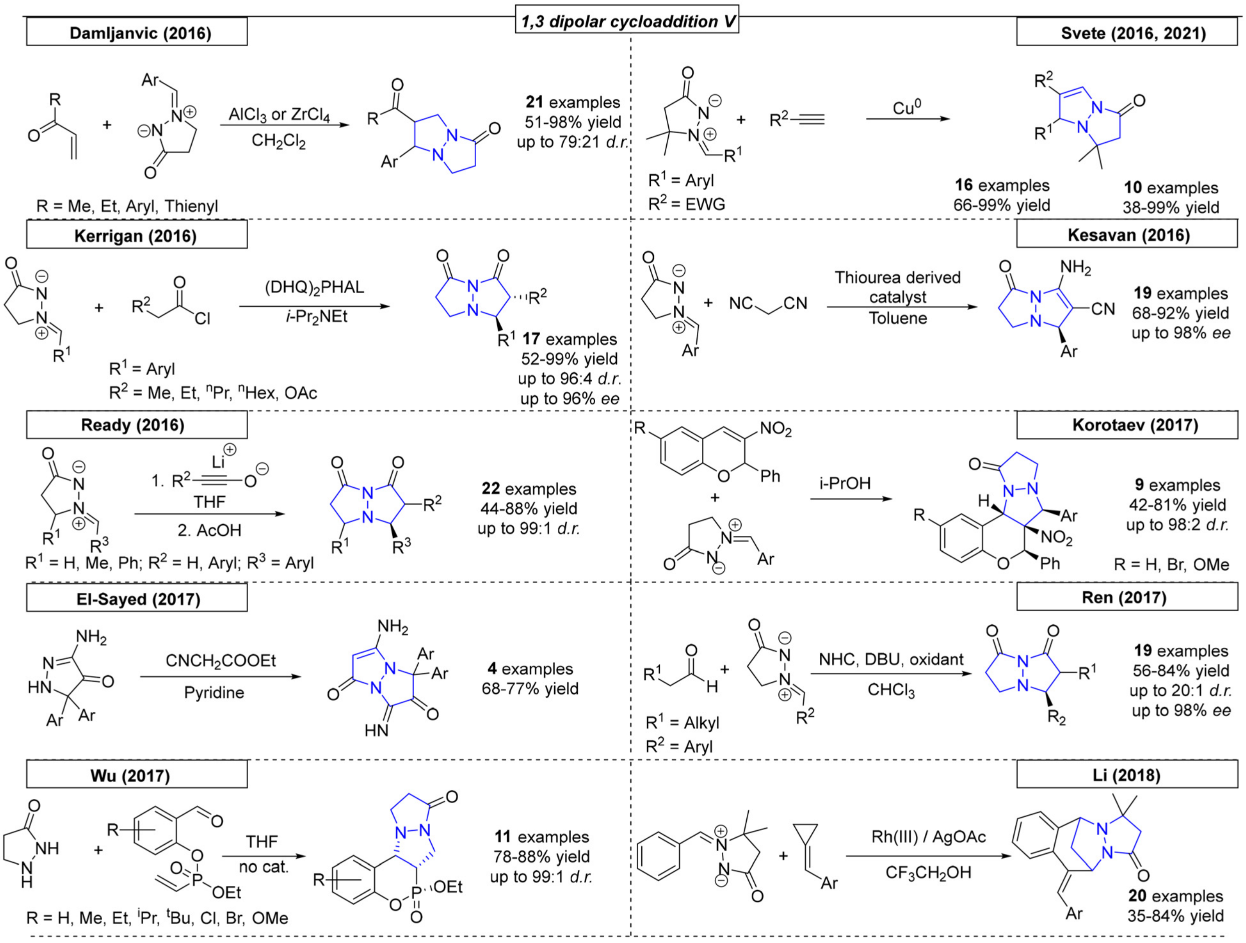
An organocatalytic approach was developed by Briere and coworkers (Scheme 33).[228] Interestingly, R^1 was confirmed to be opposite of the expected site of the derived N,N-bridgehead compound, as confirmed by X-ray analysis. This multicomponent domino Knoevenagl-aza-Michael cyclo-condensation process used $(DHQ)_2PHAL$ as a multifunctional catalyst (except in three cases, where DIPEA was used) to provide the desired compounds in yields as high as 89% and with up to 98 : 2 dr. A catalyst-free variation of the 1,3-dipolar cycloaddition of azomethine imines was published by the Feng research group.[229] The authors prepared *N*-(1,7-dioxotetrahydropyrazolo[1,2-*a*]pyrazol-2-yl)benzamide derivatives in dichloromethane at room temperature. The proposed mechanism included a rearrangement step after the cycloaddition. In total, sixteen examples were reported. Later, Feng and coworkers reported a reaction of azlactones with azomethine imines *via* an asymmetric formal [3 + 2]-cycloaddition.[230] The reaction was catalysed by a chiral bifunctional bisguanidinium hemisalt and provided twenty-four compounds with high diastereomeric ratios (up to 20 : 1 dr) and high enantioselectivities (up to 99% ee). Another organocatalytic approach was reported by the Shi research group in 2014.[231] In this work, a chiral BINOL-phosphate catalyst was used in the reaction of azomethine imines and *o*-hydroxystyrenes that provided eighteen examples of N,N-bridgehead compounds in yields as high as 76% and with selectivities of up to 95 : 5 dr and 88 : 12 er.

In 2015, Dürüst and coworkers reacted various azomethane imines with benzothiophene 1,2-dioxide under microwave conditions to obtain twelve N,N-bridgehead compounds (Scheme 33).[232] Regio- and stereochemistry were confirmed by X-ray analysis. In a second publication, the same research group published a dipolar cycloaddition reaction between various azomethane imines and 2-phenylsulfonyl acrylonitrile derivatives.[233] They showed that the resulting seven compounds can also be obtained in lower yields by using (*E*)-3-(2-hydroxyphenyl)-2-(phenyl-sulfonyl)acrylonitrile, however, two equivalents of the corresponding azomethane imines were required.

In 2016, Damljanović and coworkers used aluminum(III) chloride and zirconium(IV) chloride as Lewis acids to enable the [3 + 2]-cycloaddition reaction of enones and azomethine imines (Scheme 34).[234] The two diastereomers formed in the reaction were easily separable, and the configurations of the diastereomers were confirmed by X-ray analysis. The Svete research group published a method for the synthesis of N,N-bridgehead compounds that was inspired by the Huisgen or 'click' reaction.[235] Similar to the [3 + 2]-dipolar azide–alkyne cycloaddition, copper was used to enable the cycloaddition of azomethine imines and alkynes in high yields. The scope of this novel approach was also demonstrated in various model reactions, the most recent having been reported in 2022.[177] The syntheses of six of the ten compounds prepared have



Scheme 33 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part IV.



Scheme 34 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part V.

already been described in literature. Fluorescent compounds were prepared that also possessed promising properties, including a remarkably large Stokes shift (150–268 nm). The authors showed that the emission wavelengths and intensities of these compounds were influenced by solvent polarity and pH.

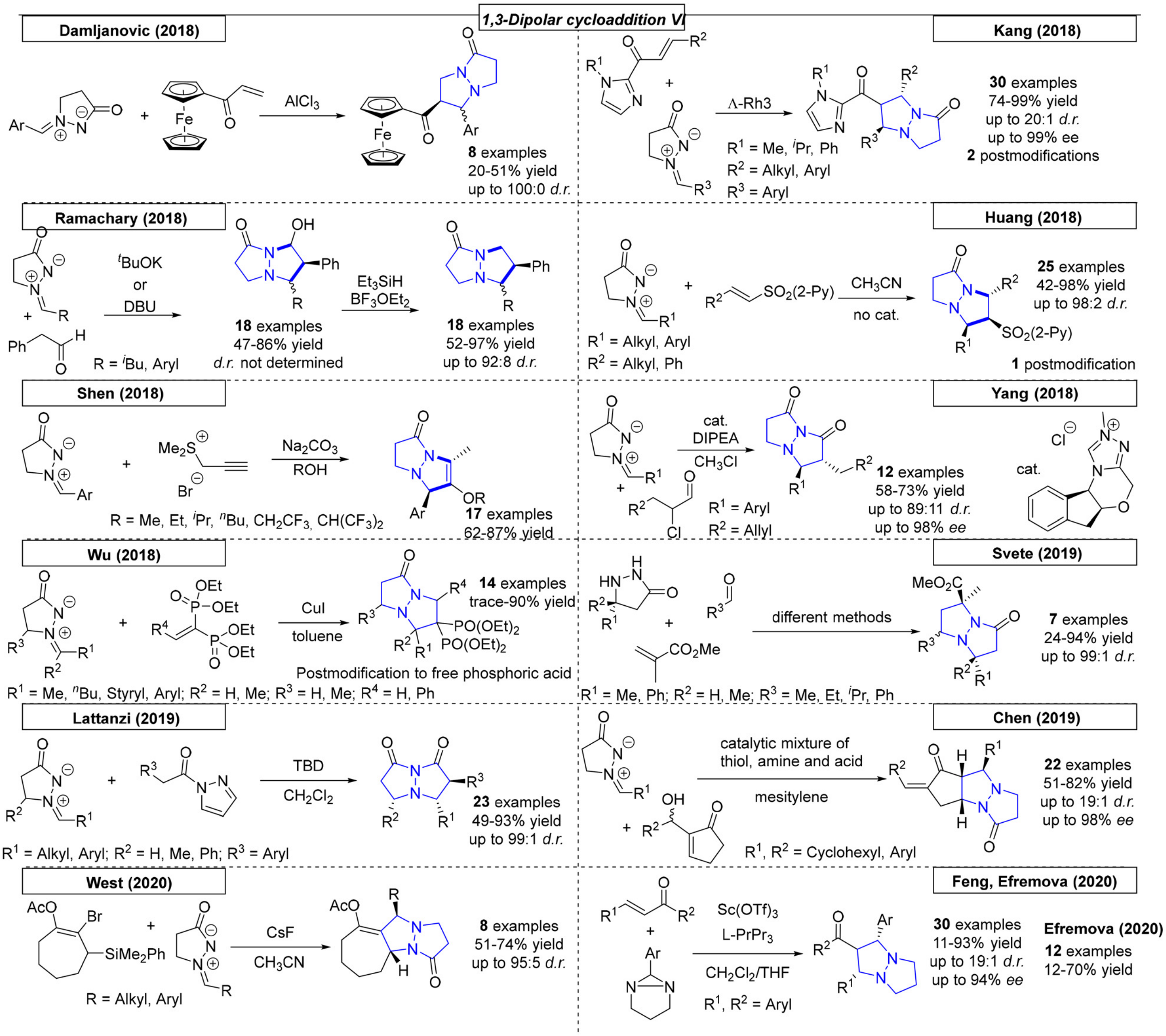
Kerrigan and coworkers reported an alkaloid-catalysed, enantioselective approach to the reaction of azomethine imines with *in situ*-formed ketenes (Scheme 34).[236] When an organocatalyst ((DHQ)$_2$PHAL) and Hünig's base (i-Pr$_2$NEt) were used to form the ketene, yields as high as 99% and stereoselectivities of up to 96 : 4 dr and 96% ee were obtained. In another organocatalytic approach, a bifunctional thiourea-derived catalyst enabled the synthesis of N,N-bridgehead compounds.[237] The procedure, reported by Kesavan and coworkers, used malonitrile, which can undergo dipolar cycloaddition after deprotonation. The thiourea catalyst both deprotonates the malonitrile and transfers stereo information, resulting in ee values as high as 98%.

In 2016, Ready and coworkers reported the reaction of azomethines with various ynolate dipolarophiles (Scheme 34).[238] The ynolates were generated *in situ* from the corresponding alkynes using *t*-BuOOH and LiHMDS. In total, twenty-two examples with yields as high as 88% and selectivities of up to 99 : 1 dr were obtained. In 2017, the Korotaev research group reacted 3-nitro-2-phenyl-2*H*-chromenes with various azomethine imines in a highly stereoselective fashion.[239] The reaction proceeded over two days and gave access to nine N,N-bridgehead compounds. The configurations of the stereoisomers were confirmed *via* X-ray analysis. In the same year, El-Sayed and coworkers reported the synthesis of novel pyrazole derivatives for use as antineoplastic agents.[240] In addition to various nitrogen-containing scaffolds, four pyrazolo-pyrazole examples were synthesized. Unfortunately, the authors evaluated the bioactivity of only eleven compounds, and no N,N-bridgehead compounds were included.

The Ren research group reported the oxidative, asymmetric [2 + 3] annulation of aldehydes with azomethine imines (Scheme 34).[241] For this reaction, an N-heterocyclic carbene bearing stereochemical information was used as a catalyst, while DBU was used as both a base and an oxidizing agent. Nineteen examples were produced with high enantioselectivities, up to 98% ee. A one-pot domino condensation, intramolecular 1,3-dipolar cycloaddition of 2-(vinylphosphoryloxy) benzaldehydes with azomethines was reported by Wu and coworkers.[242] The reaction sequence does not require a catalyst and yielded the phosphadihydrocoumarin-fused *N*,*N*-bicyclic pyrazolidin-3-ones in yields as high as 88% and with diastereomeric ratios of up to 99 : 1. The Li research group reported a protocol for the C–H activation of alkylidenecyclopropanes with a rhodium catalyst, which enabled their reaction with azomethine imines.[243] Twenty compounds were afforded by the broad substrate scope of this protocol, which can also be used for the reaction of nitrones.

In two separate publications in 2018, Damljanović and coworkers reported the synthesis of some new scaffolds that are likely to draw interest from biological investigators (Scheme 35).[244] The reaction utilized aluminium chloride as a Lewis acid. In the course of this work, it was shown that these compounds exhibit strong antioxidant properties and good antimicrobial activities. The Kang research group reported a variation of the 1,3-dipolar cycloaddition with a chiral rhodium catalyst that employed α,β-unsaturated 2-acyl imidazoles and azomethine imines as reagents.[245] The methodology was notable for its broad substrate scope, high yields (up to 99%) and excellent diastereomeric ratios (up to 20 : 1) and enantiomeric excesses (up to 99%). Ramachary and coworkers reported the synthesis of various *N*,*N*-bicyclic pyrazolidine derivatives starting from enolizable aldehydes and azomethine imines.[246] The enolates were generated using KO*t*Bu or DBU as a base. Reduction of the obtained compounds removed the hydroxyl group and resulted in eighteen additional derivatives.

In 2018, the Huang research group described the synthesis of pyrazolidinones and isoxazolidines using fluorinated α,β-unsaturated 2-pyridylsulfones as electron deficient dipolarophiles (Scheme 35).[247] The catalyst- and additive-free procedure provided twenty-five examples in yields as high as 98% and diastereoselectivities of up to 98 : 2. The observed stereo-



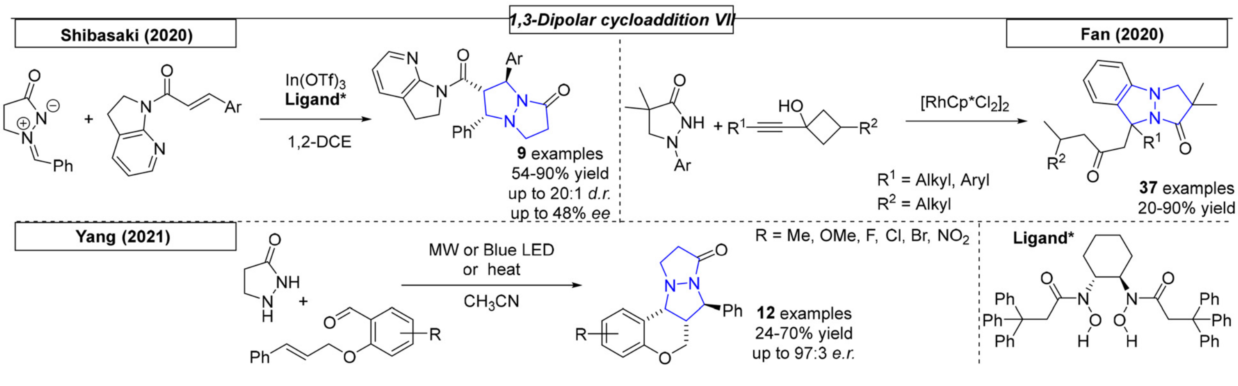
Scheme 35 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part VI.

selectivity was further investigated *via* DFT calculations. As a postmodification, it was possible to remove the SO_2(2-Py) group from the ring system. By generating novel allelic sulfonium salts by deprotonation of propargyl sulfur ylides, Shen and coworkers were able to synthesize a set of novel *N*,*N*-bicyclic pyrazolidinone derivatives.[248] The alcohol solvent takes part in this reaction as a nucleophile, substituting –OR for $-SMe_2$. In 2018, Yang and coworkers published a chiral N-heterocyclic carbene-catalysed dipolar cycloaddition of α-chloroaldehydes with various azomethine imines.[249] The enolates, which act as dipolarophiles, were generated *in situ* by carbine-catalysed formal elimination of HCl from the α-chloroaldehydes. The dipolar cycloaddition products were obtained in yields as high as 73% and selectivities of up to 89 : 11 dr and 98% ee. The Wu research group used copper(I) iodide to catalyze the [3 + 2] cycloaddition of hindered vinylidenebisphosphonates with azomethine imines toward novel phosphate-substituted pyrazolo-pyrazoles.[250] The fourteen examples were converted to their corresponding free phosphoric acids by reaction with Me_3SiBr.

Svete and coworkers used a one-pot method to synthesize a series of tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-1-carboxylates and showed that these compounds selectively inhibit the dihydroorotate dehydrogenase (DHODH) mitochondrial enzyme of *Plasmodium falciparum*, a parasite that causes malaria (Scheme 35).[251] The most active derivatives had an *anti*-configuration and a methyl ester functional group and showed selective inhibition of the parasite enzyme relative to the human enzyme. Free carboxylic acids, carboxamides and derivatives with a *syn*-configuration showed no activity. In 2019, Lattanzi and coworkers investigated the cycloaddition of pyrazoleamides to azomethine imines catalysed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene.[252] The pyrazoleamides were enolizable with the pyrazole moiety functioning as a leaving group. Depending on the reactants, yields as high as 93% and diastereomeric ratios of up to 99 : 1 were obtained. In the same year, a formal [5 + 3] cycloaddition of azomethine imines with unmodified Morita–Baylis–Hillman alcohols was published by the Chen research group.[253] The usage of a double catalytic system was reported to be crucial for the observed chemo- and enantioselectivities. Products were obtained in yields as high as 82% and with selectivity of up to 19 : 1 dr and 98% ee. The authors proposed a reaction mechanism and identified key intermediates *via* mass spectrometry. West and coworkers developed a methodology for the generation of 1,2-cycloheptadienes, which were reacted with various 1,3-dipoles, including azomethine imines.[254] The resulting pyrazolo-pyrazoles were obtained in yields as high as 74% and diastereomeric ratios of up to 95 : 5.

In 2020, the Feng research group reported a highly enantioselective method for the synthesis of pyrazolo-pyrazoles that employed a chiral scandium(III) *N*,*N*′-dioxide catalyst (Scheme 35).[255] The 1,3-dipole azomethine imine was generated *in situ* from *meso*-diaziridines and reacted with a chalcone, which was activated by ligand exchange from the scandium complex. The reaction provided selectivity of up to 19 : 1 dr and up to 94% ee. The Efremova research group used microwave irradiation to react similar chalcone substrates with azomethine imines.[256] In this work, no second diastereomers were reported, and the configurations of the products were supported by X-ray analysis. In the same year, a similar approach was reported by Shibasaki and coworkers.[257] In this case, an indium(III) complex with a chiral ligand was used to transfer stereo information and activate the chalcone-derived substrates (Scheme 36).

Fan and coworkers developed a Rh(III)-catalysed reaction toward pyrazolo[1,2-*a*]pyrazolones and 2-acylindoles, dependent on the chosen reaction conditions (Scheme 36).[258] The optimized conditions, sodium acetate and dichloromethane, gave selective access to N,N-bridgehead compounds in high yields (up to 90%) and with a broad substrate scope (thirty-nine derivatives). Absolute configurations of the products were not explicitly determined in this work. The synthesis of similar derivatives was reported by the Yu research group in a publication from the same year.[259] The Yang research group accessed tetrahydrochromeno[4,3-*c*]pyrazolo[1,2-*a*]pyrazol-9-ones *via* a novel dipolar cycloaddition of *in situ*-formed azomethines to 2-(cinnamyloxy)benzaldehyde.[260] The reaction was performed using three different sources of energy (heating, microwave or 3 W blue LED irradiation) and yielded only one



Scheme 36 Pyrazolo-pyrazoles *via* 1,3-dipolar cycloaddition reactions, part VII.

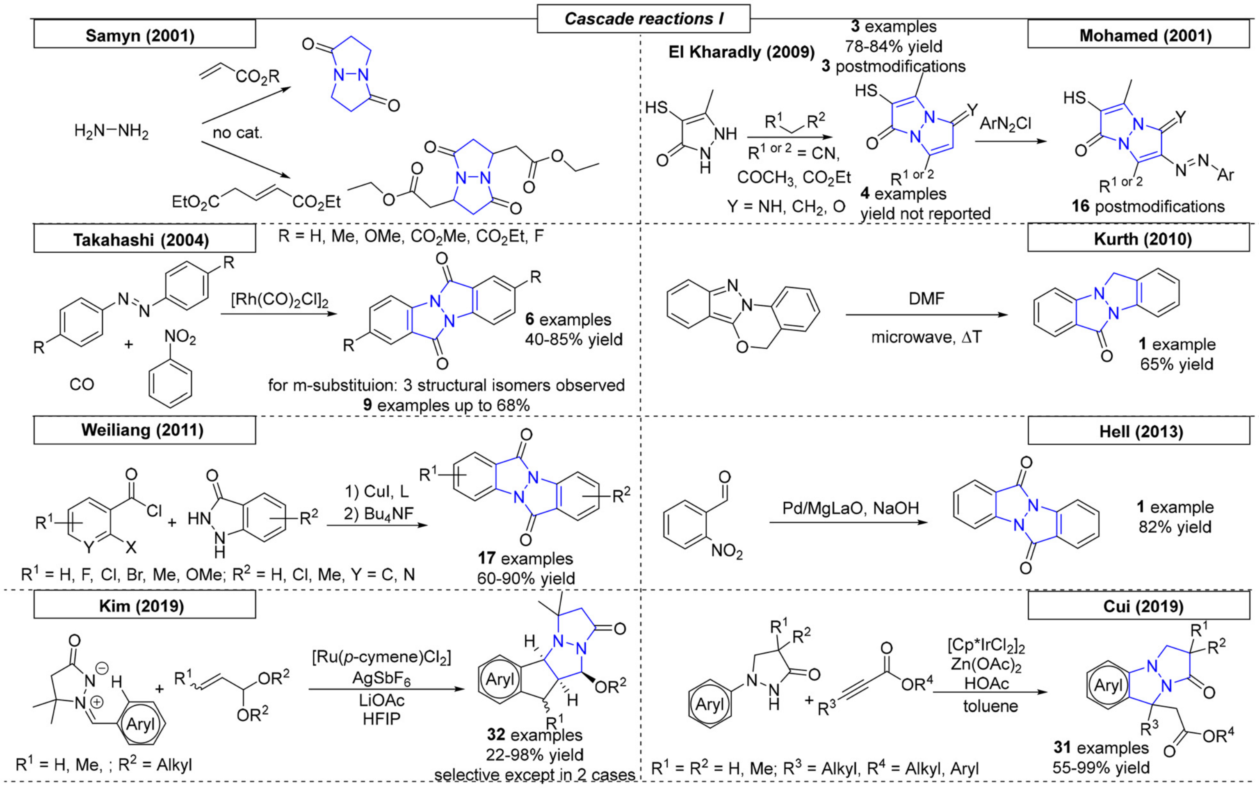
diastereomer in all cases. The absolute configurations of the products were determined by X-ray analysis.

6.3 Cascade reactions

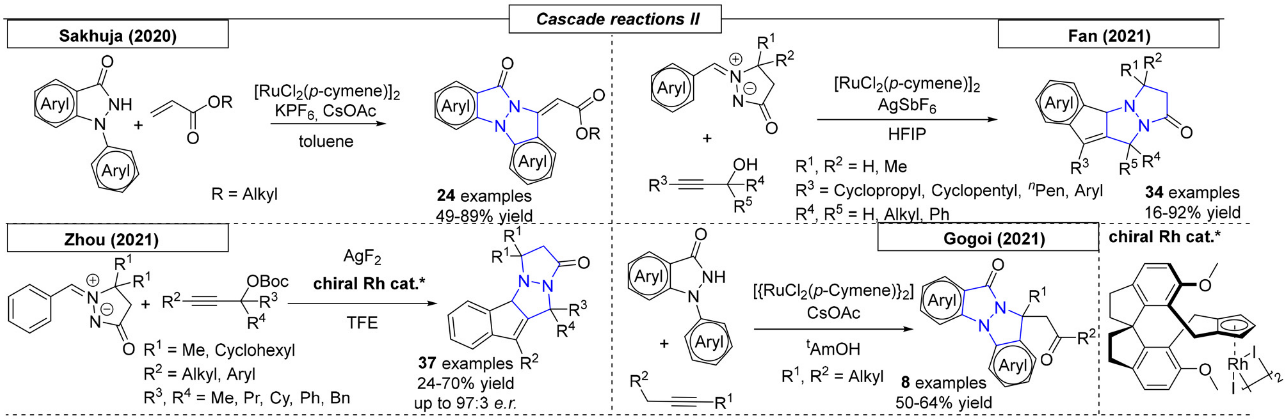
There are many examples of cascade and multicomponent reactions that have been used to produce pyrazolo-pyrazoles. In 2001, Samyn and coworkers reported the unexpected reaction of various α,β-unsaturated esters with hydrazine hydrate (Scheme 37).[261] Reaction temperatures of greater than 200 °C were required to favour the cycloaddition reaction over the competing Michael addition reaction. In the same year, the Mohamed research group reported the synthesis of a series of novel polyfunctional group-substituted pyrazole azo dyes; four core structures and sixteen dyes were obtained.[262] The dyes were also investigated for their ability to provide new shades of color on nylon and acetate fabrics. In a very similar work, the El-Kharadly research group reported the synthesis of three additional, novel pyrazolo-pyrazole dyes.[263] The azomethine precursors were synthesized by reacting 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one with various diazo reagents. Treatment of the resulting derivatives with ethylcyanoacetate gave the corresponding N,N-bridgehead compounds as yellow or orange dyes.

In 2004, Takahashi and coworkers reported the formation of various pyrazolo-pyrazole compounds *via* the reaction of azobenzene derivatives, carbon monoxide and nitrobenzene catalysed by a rhodium complex (Scheme 37).[264] *meta*-Substituted regio-isomers resulted from reaction at the two positions *ortho* to the diazo functional group. Kurth and coworkers reported the isolation of an N,N-bridgehead compound by microwave irradiation of indazole in DMF.[265] In a later publication, the same rearrangement was observed, but it was catalysed by a nucleophile.[266] In 2011, a copper-catalysed cascade process was reported by the Weiliang research group.[267] The reaction utilized various 2-halobenzoyl chlorides and 1,2-dihydroindazol-3-ones in an *N*-acylation/intramolecular C–N coupling cyclization process sequence and provided seventeen derivatives in yields as high as 90%. The Hell research group observed the formation of a pyrazolo-pyrazole derivative while investigating the palladium-catalysed chain elongation of aromatic nitro compounds.[268] The reported example was isolated in 82% yield.

Kim and coworkers developed a reaction sequence that consisted of an acrolein oxonium formation/tandem C–H allylation/[3 + 2] dipolar cycloaddition for the synthesis of a set of thirty-two novel pyrazolo-pyrazole compounds (Scheme 37).[269] Post modifications, including late stage C–H functionalization and diazocine formation of complex bioactive molecules, demonstrated the potential applicability of this method to medicinal chemistry. Cui and coworkers reported an iridium-catalysed annulation of pyrazolidinones with propiolates.[270] In the subsequent C–H bond activation/[4 + 1] cyclization that proceeds under mild reaction conditions the propiolates act as C_1-synthons. In total, thirty-one examples were reported with yields as high as 99%.



Scheme 37 Cascade and multicomponent reactions that have been used to produce pyrazolo-pyrazoles.

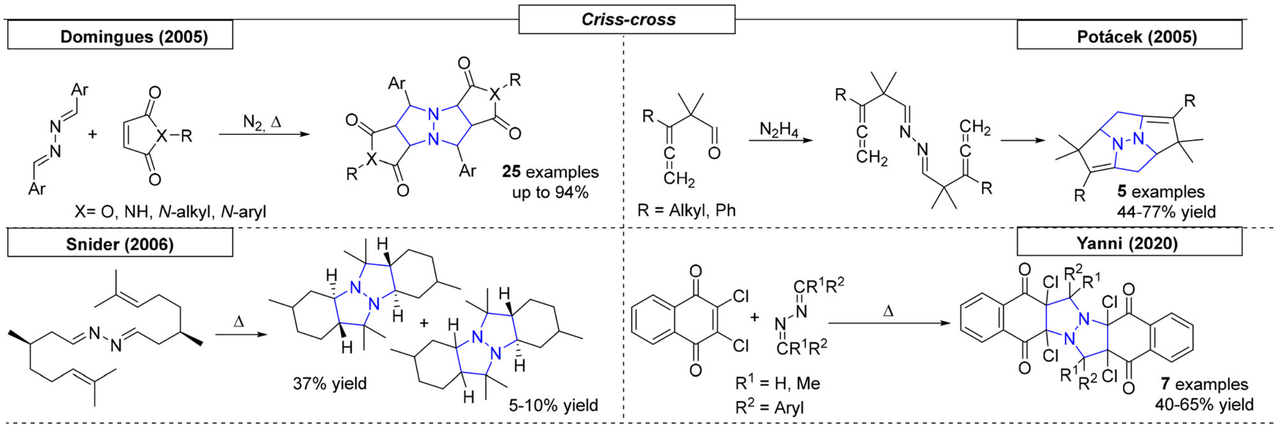


Scheme 38 cascade and multicomponent reactions.

In 2020, an indazolone-assisted sequential *ortho*-alkenylation-oxidative aza-Michael addition was developed by the Sakhuja research group (Scheme 38).[271] In this work, the Rh (II)-catalysed reaction of acrylates and 1-arylindazolones provided a set of twenty-four indazolo[1,2-*a*]indazolylidenes in up to 89% yield. The imido group acted as a directing group for the C–H activation. The next example of a cascade sequence that lead to the formation of the pyrazolo-pyrazole scaffold was reported by Fan and coworkers in 2021.[272] In this publication, a catalytic system consisting of a ruthenium complex and an antimony salt provided the reactive species that was necessary for the 1,3-dipolar cycloaddition. Anticancer testing of the resulting compounds revealed significant activity; some compounds were superior to the positive control, 5-fluoro uracil. In the same year, a very similar rhodium-catalysed approach was published by Zhou and coworkers.[273] The procedure, which included a C–H coupling/intramolecular cyclization step, provided twenty-five examples in yields as high as 70% and with up to 97 : 3 er. The reaction pathways were also investigated using Gibbs free energy calculations. Gogoi and coworkers developed an unprecedented procedure toward all-carbon quaternary carbon-centered indolo[1,2-*a*]quinazolinones and indazolo[1,2-*a*]indazolones.[274] The latter can be obtained by reacting dialkyl alkynes with phenylindazolone after Csp^2–H activation, alkyne insertion and a 1,2-phenylshift. In total, eight examples were reported.

6.4 Criss-cross cycloaddition reactions

The first example of a 'criss-cross' cycloaddition reaction approach toward pyrazolo-pyrazoles was published by Domingues and coworkers in 2005 (Scheme 39).[275] Various diaryl azines were reacted with maleic acid derivatives, such as maleic anhydride, maleimide, and *N*-alkyl and *N*-arylmaleimides. In total, twenty-five examples with yields as high as 94% were reported. In the same year, the Potácek research group was able to synthesize 3-substituted homo allenylaldazines, which were used in an intramolecular 'criss-cross' reaction.[276] Nitrogen-containing branched and heterocyclic aliphatics and phenyl were introduced as R-groups. Snider and coworkers reported a 'criss-cross' reaction of (*R*)-*citronellal*-derived azine that provided a *C*2-symmetric pyrazolo-pyrazole and its diastereomer.[277] These compounds were subsequently converted into eight-membered heteroatom-containing ring systems. The last example of a 'criss-cross' reac-



Scheme 39 Synthesis of pyrazolo pyrazoles using 'criss-cross' cycloaddition reactions.

tion toward the pyrazolo-pyrazole scaffold was reported by Yanni and coworkers in 2020. Substituted 2,3-diaz-1,3-butadienes were reacted with 2,3-dichloro-1,4-naphthoquinone in benzene to obtain bisnaphth[2,3-*c*]pyrazolidinetetrones in yields as high as 65%.[278] These compounds were shown to exhibit antifungal and antibacterial activity.

7 5,6-Ring systems

The pyrazolo-pyridazine structure is similar to that of indolizidine, except that it contains two bridgehead nitrogen atoms (Fig. 6). This compound class is known to exhibit biological activity. For example, antiexudative activity with low toxicity has been reported.[279] In a very well-explored one-pot pathway toward the pyrazolo-pyridazine scaffold, the reaction of a cyclic anhydride derivatives and hydrazine resulted in an intermediate that reacts with a condensate of a CH_2-acidic compound and an aldehyde. In over 150 publications, the reaction has been tested with various catalytic systems, resulting in a multitude of different derivatives. A general reaction equation and mechanism is shown in Scheme 40.

7.1 1,3-Dipolar cycloaddition reactions

As stated before, many different methodologies exist for the synthesis of pyrazolo-pyridazines using a 1,3-dipolar cycloaddition reaction, as shown in Scheme 41.

The first examples of 1,3-dipolar cycloaddition reactions used to produce pyrazolo-pyridazines reviewed here involve polymeric catalysts. In total, seven different approaches were reported (Table 2). While Shaterian,[280] Hasaninejed,[281] Deshmukh[282] and Mouradzadegun[283] used polymers functionalized with sulphur-based groups, Abedini[284] and Schirini[285] employed PVP and PVP-based polymers. The last example, reported by Mohamadpour,[286] used a cellulose polymer functionalized with carboxymethyl groups.

The 1,3-dipolar cycloaddition reaction can also be conducted without the benefit of a catalyst (Table 3). While the Patel[287] and Davoodnia[288] research groups used ethanol as a solvent, Khalafi-Nezhad[289] and Sadek (with micro wave irradiation)[290] used glycerol.

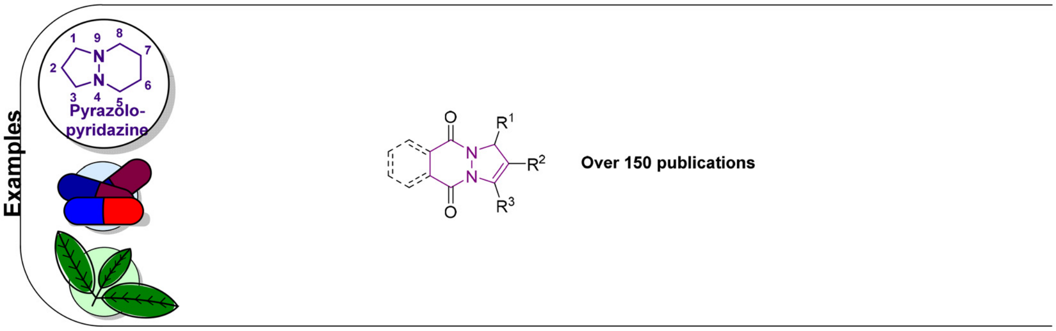
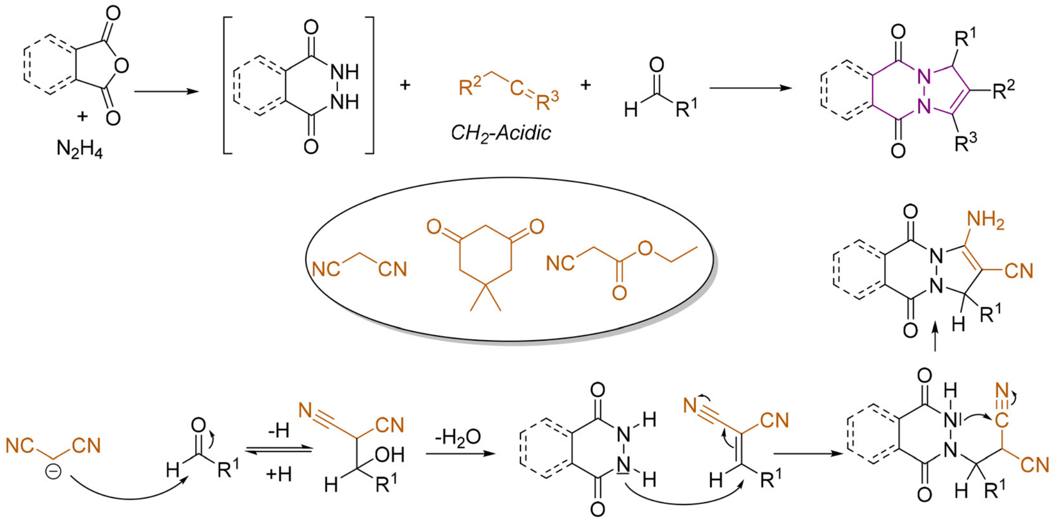
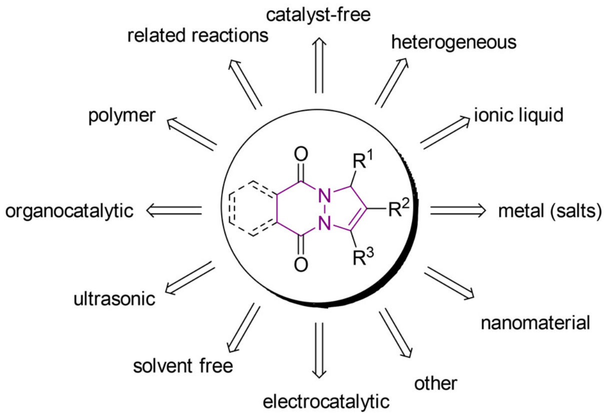


Fig. 6 Examples of various pyrazolo-pyridazine-derived compounds.



Scheme 40 General reaction equation and mechanism for synthesis of pyrazolo-pyridazines *via* 1,3-dipolar cycloaddition reactions.



Scheme 41 Overview of 1,3-dipolar cycloaddition reaction approaches leading to the pyrazolo-pyridazine scaffold.

There are examples of 1,3-dipolar cycloaddition reactions toward pyrazolo-pyridazines that use combinations of catalytic systems and irradiation, either microwave or ultrasonic (Table 4). Bazgir and coworkers used triethylamine in EtOH under ultrasonic irradiation conditions.[291] A microwave irradiation example using montmorillonite as a catalyst was published by the Jeong research group.[292] Rostamnia,[293] Homayoon[294] and Helal[295] developed three additional ultrasonic irradiation reactions. A final microwave example, published by Kamanna and coworkers, was catalysed by burned mango peel.[296]

Over the last two decades, interesting examples of 1,3-dipolar cycloaddition reactions using heterogeneous catalysis were reported (Table 5). The majority of heterogeneous systems feature catalysts supported on silica, as published by the research groups of Shaterian,[297] Sabitha,[298] Rostamnia,[299] Reddy,[300] Javanshir,[301] Doustkhah,[302] and Jeong.[303] Other solid materials include solid acid catalysts as published by the research groups of Shaterian,[304] Shaterian,[305] Das,[306] Shirini,[307] and Massah.[308] It is important to note that many of the resulting compounds have been converted to their corresponding sulfonamides and tested for antibacterial activity against *S. aureus* and *E. coli*. Tayebee[309] and Nikoorazm[310]

Table 2 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions catalysed by polymeric catalysts

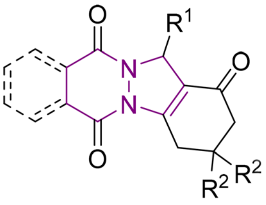
	Year	Condition	Examples	Yield	Ref.
	2011	Starch sulfate	20	72–92%	280
	2011	Sulfuric acid-modified PEG-6000	23	80–93%	281
	2015	Polymer-supported sulfonic acid	12	80–92%	282
	2018	Sulfamic acid functionalized nano-catalyst	11	0–98%	283
	2019	[PVPH]ClO$_4$	20	90–97%	284
	2020	[PVP-SO$_3$H]Cl	22	47–96%	285
	2020	Carboxymethyl cellulose	20	77–94%	286

Table 3 Pyrazolo-pyridazine-yielding catalyst-free 1,3-dipolar cycloaddition reactions

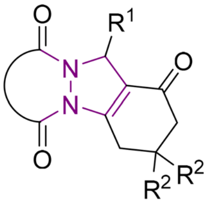
	Year	Condition	Examples	Yield	Ref.
	2012	EtOH	16	69–83%	287
	2015	Glycerol	23	89–94%	288
	2019	Glycerol, MW irradiation	14	80–92%	289
	2019	EtOH, reflux	6	70–91%	290

Table 4 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions supported by ultrasonic or microwave irradiation

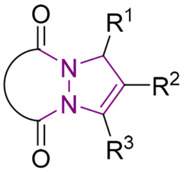
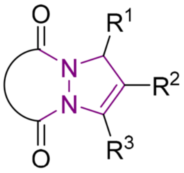
	Year	Condition	Examples	Yield	Ref.
	2010	US, Et$_3$N, EtOH	21	85–98%	291
	2012	MW, montmorillonite K-10, solv. free	20	80–96%	292
	2013	US, SBA-15 sulfonic acid nanoreactor, EtOH	9	92–96%	293
	2016	US, TBAF, H$_2$O	12	86–95%	294
	2017	US, Et$_3$N, EtOH	4	71–88%	295
	2020	MW, burned mango peel, EtOH	12	83–89%	296

Table 5 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions performed in a heterogeneous catalytic system

	Year	Condition	Examples	Yield	Ref.
	2008	Silica-SO_3H, solvent free	8	80–91%	297
	2010	Phosphomolybdic acid-SiO_2	19	80–92%	298
	2013	Phosphoric acid supported on alumina	15	76–93%	305
	2013	Cellulose-SO_3H	14	0–91%	304
	2014	Carbon-based solid acid catalyst	18	80–94%	306
	2014	Mesoporous/trifluoroethanol	8	89–94%	299
	2014	Silica gel-supported tungstic acid	20	85–93%	300
	2014	SO_3H-functionalized mesoporous silica	16	90–95%	301
	2015	Al-SBA-15-TPI/$H_6P_2W_{18}O_{62}$	21	45–84%	309
	2016	[PVP-SO_3H]HSO_4, solv. free	18	88–95%	307
	2017	Diatomite-SO_3H	15	73–83%	308
	2018	Cu(II)-adenine-MCM-41	9	85–95%	310
	2019	Mesoporous SBA-15/PIDA	8	85–95%	302
	2019	Silica-supported tungstic acid, solv. free	16	87–94%	303
	2020	Eggshell powder	16	93–98%	311

reported the use of alumina- and copper metal-based catalytic systems. A final example, reported by the Jonnalagadda research group, was catalysed by powdered eggshells.[311]

Many examples of 1,3-dipolar cycloaddition reactions toward pyrazolo-pyridazines using organocatalytic systems have been reported (Table 6). While the research groups of Roy (L-proline),[312] Bouraiou (DMAP),[313] Lalitha,[314] (2-aminopyridne) and Mohamadpour (Theophylline)[315] catalysed the reaction using organic bases, the groups of Singh,[316] Farahmand,[317] Jeong,[318] Saghanezhad,[319] and Karhale[320] established acid-catalysed reaction procedures. Similar approaches have been reported with organic salts as catalysts by the research groups of Li,[321] Wu,[322] Guo,[323] Shirini,[324] and Mamaghani.[325] The research groups of Mohamadpour,[326] Gill[327] and Dalal[328] reported the use of various sugars catalysts.

The only example of an electrocatalytic approach toward pyrazolo-pyridazines was reported by Kefayati and coworkers in 2014 (Table 7).[329]

Table 6 Pyrazolo-pyridazine-yielding organocatalytic 1,3-dipolar cycloaddition reactions

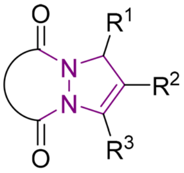
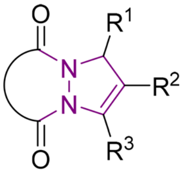
	Year	Condition	Examples	Yield	Ref.
	2011	(*S*)-Camphorsulforic acid	20	90–94%	316
	2012	Citric acid	12	81–92%	317
	2012	Proline triflate, solv. free	10	87–94%	321
	2014	Methylimidazolium-3-yl-1-ethyl sulfate	26	80–93%	322
	2015	β-Cyclodextrine-SO_3H	26	85–95%	318
	2016	Saccarin	18	82–93%	326
	2016	L-Proline	12	87–90%	312
	2016	Caffeine-H_2SO_4	10	45–96%	319
	2017	β-Cyclodextrin	19	77–94%	328
	2017	DMAP	12	85–97%	313
	2017	β-Cyclodextrin	15	82–93%	327
	2018	Hydroxyethylammonium acetate	13	61–96%	323
	2018	NS-[C_4(DABCO-$SO_3H)_2$]·4Cl, solv. free	23	85–96%	324
	2019	[cmdmim]I, EtOH	15	71–89%	325
	2020	5-Sulphosalicylic acid	14	0–92%	320
	2020	2-Aminopyridine	14	90–98%	314
	2020	Theophylline	23	75–93%	315

Table 7 Pyrazolo-pyridazine-yielding electrocatalytic 1,3-dipolar cycloaddition reactions

	Year	Condition	examples	Yield	Ref.
	2014	Electrolysis, NaBr, PrOH	11	85–98%	329

Procedures toward pyrazolo-pyridazine scaffolds that use inorganic catalysts to enable a 1,3-dipolar cycloaddition reaction are summarized in the following paragraph (Table 8). In the cases of procedures reported by Guan,[330] Reddy,[331] Karimi-Jaberi,[332] Khan,[333] Foroumadi,[334] Turgut,[335] Varala,[336] Ethiraj,[337] Türkan[338] and Taslimi,[339] inorganic salts were used in combination with ethanol as a solvent. The Türkan research group tested the synthesized derivatives in assays that implicate Alzheimer's disease and diabetes mellitus. Kidwai and coworkers established a procedure that employed ceric ammonium nitrate and PEG-400 to access over fifty derivatives in two publications.[340,341] Nickel-based complexes in acetic acid were used by Ebrahimipour and coworkers in two publications.[342,343] A final example, reported by the Shajari research group, used zirconium nitrate as a catalyst and water as a 'green' solvent.[336]

Over the last twenty years, various solvent-free approaches toward pyrazolo-pyridazines have been reported (Table 9). The majority of these procedures feature metal salts or metal-derived compounds as catalysts, as reported by the research groups of Zhang ($H_4SiW_{12}O_{40}$),[345] Mosaddegh ($Ce(SO_4)_2$),[346] Azarifar ($Cu(CH_3CN)_4PF_6$),[347] Bazgir ($ZrOCl_2 \cdot 8H_2O$),[348] Jeong ($InCl_3$),[349,350] and Mohamadpour ($Cu(OAc)_2 \cdot H_2O$).[351] Organocatalysts were featured in the procedures developed by the research groups of Bazgir,[352] Wu,[353] Ghorbani-Vaghei,[354,355] Kidwai,[356] Wang[357] and Kiasat.[358] Other solvent free methodologies include: iodine as reported by Varghese and coworkers,[359] HFIP as described by Maleki and coworkers,[360] $B(OSO_3H)_3$ as reported by the Soheilizad research group[361] and simple inorganic compounds as described by the research groups of Davoodnia,[362] Gomha[363] and Habibi.[364]

Ionic liquids can be employed in the synthesis of pyrazolo-pyridazines (Table 10). These versatile reagents can be used as a solvent, a catalyst or for both purposes. Bazgir,[365] Khurana,[366] and Fazaeli,[367] reported the use of [bmim]-based ionic liquids as solvents in combination with various acid catalysts. Interestingly, many systems have been reported that use an ionic liquid as both a solvent and a catalyst. Singh,[368]

Table 8 Pyrazolo-pyridazine-yielding metal-/metal salt-catalysed 1,3-dipolar cycloaddition reactions

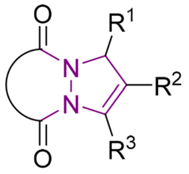
	Year	Condition	Examples	Yield	Ref.
	2012	$(NH_4)_2[Ce(NO_3)_6]$, PEG 400	19	62–94%	340
	2012	$NiCl_2$, EtOH	17	71–94%	330
	2014	$(NH_4)_2[Ce(NO_3)_6]$, PEG 400	40	84–92%	341
	2014	$InCl_3$, EtOH	24	70–85%	331
	2015	K_2CO_3, EtOH	10	85–96%	332
	2015	$[M + II(pzca)_2(H_2O)_2]$; M = (Ni, Co, Cu), AcOH	7	80–94%	342
	2015	$[Fe_2(SO_4)_3H_2O]$, EtOH	21	79–93%	333
	2017	$NiCl_2 \cdot 6H_2O$, EtOH	21	70–95%	334
	2018	Mixed-ligand Ni(II) schiff base complex, AcOH	6	84–94%	343
	2019	$Y(OTf)_3$, EtOH	5	76–86%	335
	2020	Cs_2CO_3, TBAB, EtOH	16	80–95%	336
	2020	$[ZrO(NO_3)_2 \cdot 2H_2O]$, H_2O	3	75–83%	344
	2020	$(NH_4)_2[Ce(NO_3)_6]$		2–95%	337
	2020	$Cu(OTf)_2$, EtOH	6	—/—	338
	2020	$Y(OTf)_3$, EtOH	4	76–83%	339

Table 9 Solvent free 1,3-dipolar cycloaddition reactions that provide pyrazolo-pyridazines

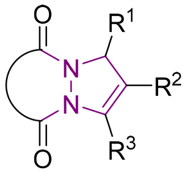
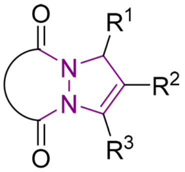
	Year	Condition	Examples	Yield	Ref.
	2008	*p*-PTSA	13	73–97%	352
	2010	$H_4SiW_{12}O_{40}$	17	60–95%	345
	2010	TCT	11	89–97%	353
	2011	TBBDA, PBBS	20	51–91%	354
	2011	$Ce(SO_4)_2$	10	71–95%	346
	2012	$Cu(CH_3CN)_4PF_6$	14	76–92%	347
	2012	DPA	16	79–96%	356
	2013	*p*-TSA	12	83–92%	357
	2013	PSA	11	75–98%	358
	2013	I_2	13	87–95%	359
	2013	$ZrOCl_2$	7	80–89%	348
	2013	$InCl_3$	25	83–94%	349
	2014	TBBDA or PBBS	14	63–90%	355
	2014	HFIP	16	75–92%	360
	2014	$B(OSO_3H)_3$	12	65–94%	361
	2015	$NaHCO_3$	13	85–92%	362
	2016	$[Cu(OAc)_2H_2O]$	15	73–89%	351
	2018	NaOH, grinding	10	73–92%	363
	2019	$InCl_3$	35	85–94%	350
	2021	$KHSO_4$ or CF_3SO_3H	11	27–86%	364

Table 10 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions that employ ionic liquids

	Year	Condition	Examples	Yield	Ref.
	2008	[bmim]Br, PTSA	13	73–97%	365
	2009	[bmim]BF$_4$, H$_2$SO$_4$	22	83–94%	366
	2010	[bmim]BF$_4$, H$_3$PW$_{12}$O$_{40}$	6	82–92%	367
	2011	[bmim]OH	26	89–98%	368
	2011	[(CH$_2$)$_4$SO$_3$HMIM]HSO$_4$	10	55–86%	369
	2012	([Hnhp][HSO$_4$]) and other ionic liquids	15	70–95%	370
	2012	DBU[CH$_3$COO], [Pyrr][HCOO]	28	0–94%	371
	2012	[BSO$_3$HmIm]HSO$_4$	19	70–96%	372
	2013	[C$_4$(MIm)$_2$](FeCl$_4$)$_2$	12	85–90%	388
	2014	[DMSBP][HSO$_4$]	14	0–94%	373
	2015	[SuSA-H] HSO$_4$	19	88–97%	374
	2015	DABCO(HSO$_3$)$_2$(HSO$_4$)$_2$	23	83–95%	375
	2015	[Simp]HSO$_4$	17	33–88%	376
	2015	PEG-MIDL	12	85–90%	377
	2016	[Et$_3$N–SO$_3$H]Cl	17	80–95%	378
	2016	[bmim]OH	10	80–93%	379
	2016	[Et$_3$N–SO$_3$H]HSO$_4$	14	85–98%	380
	2017	[H-Suc]HSO$_4$	2	89–97%	381
	2018	[DBUH][OAc]	8	30–83%	382
	2018	[Bu$_3$NH][HSO$_4$]	13	85–94%	383
	2020	[TBP]$_2$SO$_4$	28	65–95%	384
	2020	[Bn-DBU][TFA]	26	76–93%	385
	2020	[[C$_4$(H-DABCO)$_2$]HSO$_4$]$_4$	17	87–96%	386
	2021	Alkylated phenanthroline and piperazine ClO$_4$ IL	13	86–96%	387
	2021	[DMDSP]Cl, [DMDSP]SnCl$_3$	13	88–98%	389
	2013	[C$_8$DABCO]Br, H$_2$O	12	85–92%	390
	2016	[bmim]OH, EtOH	12	84–97%	391
	2019	ChCl/*p*-TsOH, MeOH	11	83–93%	392

Xu,[369] Shaterian,[370] Shaterian,[371] He,[372] Habibi,[373] Abedini,[374] Shirini,[375] Tayebee,[376] Godajddr,[377] Kermani,[378] Kermani,[379] Masihpour,[380] Shirini,[381] Raghavendra,[382] Shaikh,[383] Amirmahani,[384] Rad-Moghadam,[385] Shirini,[386] and Keshavarz[387] reported the use of inorganic ionic liquids, while Mombani Godajdar[388] used an imidazole dimer-based ionic liquid in combination with FeCl$_4^-$ as a counter ion. In a final example, the Nakhaei research group[389] reported a reaction using an ionic liquid containing SnCl$_3$ as a counter ion. Three research groups showed that an ionic liquid could be used as catalyst in combination with various polar solvents. Deshmukh and coworkers reported an example where water was used as a 'green' solvent.[390] The Hongyun research group published twelve examples where ethanol was used as a solvent,[391] and He and coworkers performed an ionic liquid-catalysed reaction using methanol as a solvent.[392]

Nanoparticles can be used as catalysts for 1,3-dipolar cycloaddition reactions toward pyrazolo-pyridazines (Table 11). Metal-based nanoparticles, such as iron or iron oxide-based nanostructures, are the most commonly used nanomaterials.[393] Metal nanomaterials were successfully employed in the synthesis of pyrazolo-pyridazines by Azarifar (ZnO),[394] Kiasat (Al),[395] Pal (Ni),[396] Safaei-Ghomi (CuI),[397] Mosaddegh (Ca/Cu based),[398] Albadi (Co/Al$_2$O$_3$-based),[399] and Maleki (Cu/ZnO-based).[400] These procedures do not require an additional solvent.

Many examples of this reaction using iron-derived nanomaterials have been published, most commonly with Fe$_3$O$_4$ nanoparticles: Shaterian,[401] Rostami,[402] Kiasat,[403] Rostami,[404] Ghasemzadeh,[405] Rostamnia,[406] Esmaeilpour,[407] Lee,[408] Shirini,[409] Druzhinin,[410] Khaleghi Abbasabadi,[411] Bamoniri,[412] Taherpour,[413] Ebrahimiasl[414] and Pourmousavi (tested for antibacterial activity)[415] (Table 11). Other systems feature iron-containing metal composite materials such as those established by Maleki,[416] Azarifar,[417] Zaheer,[418] Arora[419] and Hamidinasab.[420] Zhang prepared CoFe$_2$O$_4$ sulfonic acid-derived nanoparticles, which were employed under solvent free conditions.[421] Pal and coworkers synthesized nineteen derivatives with nano-FGT.[422]

Functionalized silica-based nanoporous materials were established by three different research groups (Table 11). The first two procedures, developed by Ziarani and coworkers, employed SBA-Pr-NS-functionalized nanomaterials with additional amine and sulphate functionalization.[423–425] Kiasat and coworkers developed a method using a silica-based nanocomposite and a nano-Brønsted solid acid to access the desired derivatives.[426,427] The final example reviewed here, published by the Veisi research group, employed a sulfonic acid-functionalized SBA under solvent free conditions.[428]

In addition to silica-based nanoporous materials, functionalized silica nanoparticles can be used in the synthesis of pyrazolo-pyridazines (Table 11). The Esmaeilpour research group used a nanosilica-supported dendrimer as a catalyst.[429] Other examples used nanomaterials that were either base-functionalized as published by Rezaee and coworkers (DABCO)[430] or acid-functionalized as reported by the Sadeghi research group.[431]

As discussed in previous sections, nanoparticles and ionic liquids are effective catalytic systems for this reaction. It is therefore not surprising that additional procedures have been developed that combine these approaches (Table 12).

Table 11 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions that employ nanomaterials as catalysts

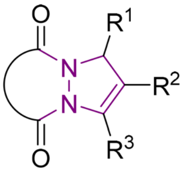
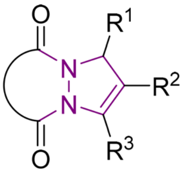
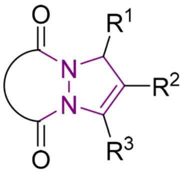
	Year	Condition	Examples	Yield	Ref.
	2012	Nano-ZnO, solv. free	14	86–92%	394
	2013	Nano-alumina, solv. free	12	70–98%	395
	2013	Ni-NP, solv. free	14	88–94%	396
	2014	CuI-NP, solv. free	12	82–93%	397
	2015	$Ca_2CuO_3/CaCu_2O_3/CaO$, solv. free	10	80–94%	398
	2017	Co/Al_2O_3, solv. free	15	88–94%	399
	2020	Cu-doped ZnO hollow spheres	17	81–93%	400
	2012	Fe_3O_4-NP, (3-aminopropyl)-Si(OEt)$_3$ coat., solv. free	28	0–93%	401
	2013	Fe_3O_4-NP supported guanidine, solv. free	21	80–93%	402
	2013	Fe_3O_4-NP, silica coated@sulforic acid, solv. free	15	84–94%	403
	2013	Fe_3O_4-NP, *N*-propylsulfamic acid	20	82–93%	404
	2014	Fe_3O_4@ SiO_2-NP, solv. free	17	85–96%	405
	2014	$CoFe_2O_4$-CS-SO_3H-NP, solv. free	22	83–95%	421
	2015	$Ni_{0.5}Zn_{0.5}Fe_2O_4$@HAP-Cs_2CO_3, solv. free	16	76–98%	416
	2016	Urea-functional. silica-coat. $Fe_{3-x}Ti_xO_4$ NP, solv. free	10	87–98%	417
	2016	Nano-FGT, solv. free	19	87–97%	422
	2016	Fe_3O_4@GO-Pr-SO_3H, EtOH	8	90–95%	406
	2016	Fe_3O_4@SiO_2-imid-PMAn, solv. free	35	73–96%	407
	2016	$PrxCoFe_{2-x}O_4$ (x = 0.1), EtOH	12	84–94%	418
	2017	STA-amine-Si-magnetite, CH_3OH	27	76–99%	419
	2017	$H_3PW_{12}O_{40}$@Fe_3O_4/EN-MIL-101, solv. free	4	31–94%	408
	2017	Fe_3O_4@SiO_2–$ZrCl_2$-MNPs	18	85–95%	409
	2019	Nano-$NiFe_2O_4$@TiO_2-ILPip, PEG 400	13	85–97%	420
	2019	Cu@Fe_3O_4 MNP, solv. free	16	81–96%	410
	2020	Fe_3O_4@GOQDs-*N*-(β-alanine)	9	90–98%	411
	2020	g-$Al_2O_3/BF_n/Fe_3O_4$, solv. free	8	90–98%	412
	2020	g-$Al_2O_3/BF_3/Fe_3O_4$, solv. free	10	50–98%	413
	2021	Fe_3O_4@SiO_2-imine/phenoxy-Cu(II), solv. free	8	88–96%	414
	2022	PAmPDA@Fe_3O_4 nanocomposite, solv. free	—/—	—/—	415
	2014	SBA-Pr-NH_2, solv. free	10	70–92%	423
	2014	SBA-Pr-SO_3H, solv. free	11	70–90%	424 and 425
	2015	SBA@$BiPy_2$ + Cl^-	10	86–96%	426
	2015	RH@[SiPrDABCO@BuSO_3H]HSO_4, EtOH	12	86–94%	427
	2015	SBA-15-Ph-SO_3H, solv. free	9	75–96%	428
	2015	Nanosilica supported dedritic polymer, solv. free	27	74–95%	429
	2020	RH@DABCO, EtOH	15	80–95%	430
	2020	SiO_2–H_2SO_4 NP, EtOH	10	85–95%	431

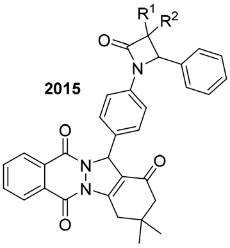
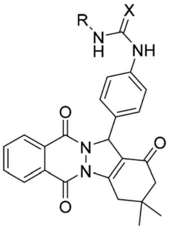
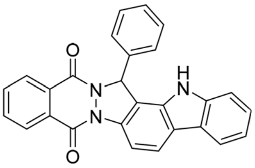
Table 12 Pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions that employ nanopartical and ionic liquids

	Year	Condition	Examples	Yield	Ref.
	2013	IL@nano-SiO_2, solvent free	12	77–96%	432
	2015	[SBA-Im]HSO_4, EtOH	13	83–90%	433
	2017	Piperidinium benzene-1,3-disulfonate nanomagnetic ionic liquid, solvent free	26	60–94%	437
	2011	Basic ionic liquid ([SiPMIM]OH@MNPs), solvent free	9	82–96%	434
	2017	Phosphotungstic acid-containing ionic liquid immobilized on $CuFe_2O_4$@SiO_2, solvent free	10	88–95%	436
	2017	Ionic liquid coated sulfonated carbon@titania composites, water	12	80–96%	438
	2017	Heteropolyacid-based ionic liquid $[Simp]_3PW_{12}O_{40}$ nanoparticle, solvent free	19	0–92%	439
	2018	[MSPP]HSO_4@nSiO_2, solv. free	18	63–96%	435
	2020	4-Methylpyridinium chloride ionic liquid grafted on Mn@zeolite-Y, EtOH/H_2O	16	88–98%	440

Mohammadpoor-Baltork,[432] Rezaee,[433] Mohammadpoor-Baltork[434,435] and Davoodnia[436] used silica-derived materials for ionic liquid functionalization. Other examples used metal-derived nanoparticles as reported by the research groups of Ghorbani-Vaghei (Fe_3O_4),[437] Paul (Ti),[438] Tayebee ($[Simp]_3PW_{12}O_{40}$)[439] and Kalhor (Mn@zeolite-Y).[440]

In the last section, special cases are summarized (Table 13). The research groups of Perumal,[441] Zhang,[442] Nabid,[443] Wang,[444] and Shi[445] reported pyrazolo-pyridazine derived spiro-compounds. A review summarized additional reactions.[446] The Salehi[447] and MaGee[448,449] research groups expanded the one-pot synthesis of pyrazolo-pyridazines with a 'click' reaction. By exchanging an alkyne-derived compound for malononitrile, a subsequent dipolar cycloaddition reaction was conducted. In a very similar one-pot procedure, published by both the Shaabani[450] and Yoosefian[451] research groups, alkyne and iso-cyano compounds were reacted with maleic acid and hydrazine. The Fu research group used various vinylk-

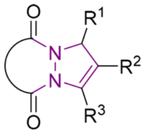
Table 13 Special case examples of pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions

	Year	Condition	Examples	Yield	Ref.
	2010	L-Proline, EtOH	10	86–92%	441
	2011	$NiCl_2$, PEG 600	26	80–95%	442
	2012	NEt_3, EtOH	3	93–96%	443
	2012	Piperidine, EtOH	14	42–93%	444
	2013	Piperidine, CH_3CN	11	74–89%	445
	2013	Dipyridine/Fe_3O_4, review	REVIEW		446
	2011	$Cu(OAc)_2$, Na L-ascorbate, [Hmim](CF_3COO)	14	75–92%	447
	2012	$Cu(OAc)_2$, Na L-ascorbate, *p*-TSA, EtOH	19	79–95%	448
	2014	$Cu(OAc)_2$, Na L-ascorbate, [Hmim](CF_3COO)	16	65–82%	449
	2012	EtOH/acetone	15	54–73%	450
	2012	Acetone	5	42–59%	451
	2017	Phosphotungstic acid, PhCN	19	0–95%	452
	2017	1. TFAA/HOAc, 2. $PhNH-NH_2$	9	56–87%	453
	2013	—/—	16	48–84%	454
	2015	—/—	10	26–53%	455
	2017	Fe_3O_4-MNP, PEG-400	10	75–86%	456

etones and phthalhydrazide in the synthesis of highly functionalized pyrazolo-pyridazines.[452] It was possible to run this domino reaction at gram scale. Bouraiou and coworkers developed a method for the synthesis of carbazole-fused heterocycles.[453] Instead of isolating the pyrazolo-pyridazine, phenylhydrazine was added to the crude mixture, resulting in pyrazolo-pyridazine carbazole-fused structures. In two publications, the Gencer research group used nitro-pyridazolo-pyridazines as starting points for various post modification reactions.[454,455] After reduction of the nitro group, various lactate and urea derivatives were synthesized. Mohebat and coworkers reacted benzo[*a*]phenazin-5-oles with phthalhydrazide and benzaldehydes toward quinoxaline-fused compounds.[456] The one-pot procedure was catalysed by Fe_3O_4 nanoparticles and provided fused heterocyclic compounds in yields as high as 86%.

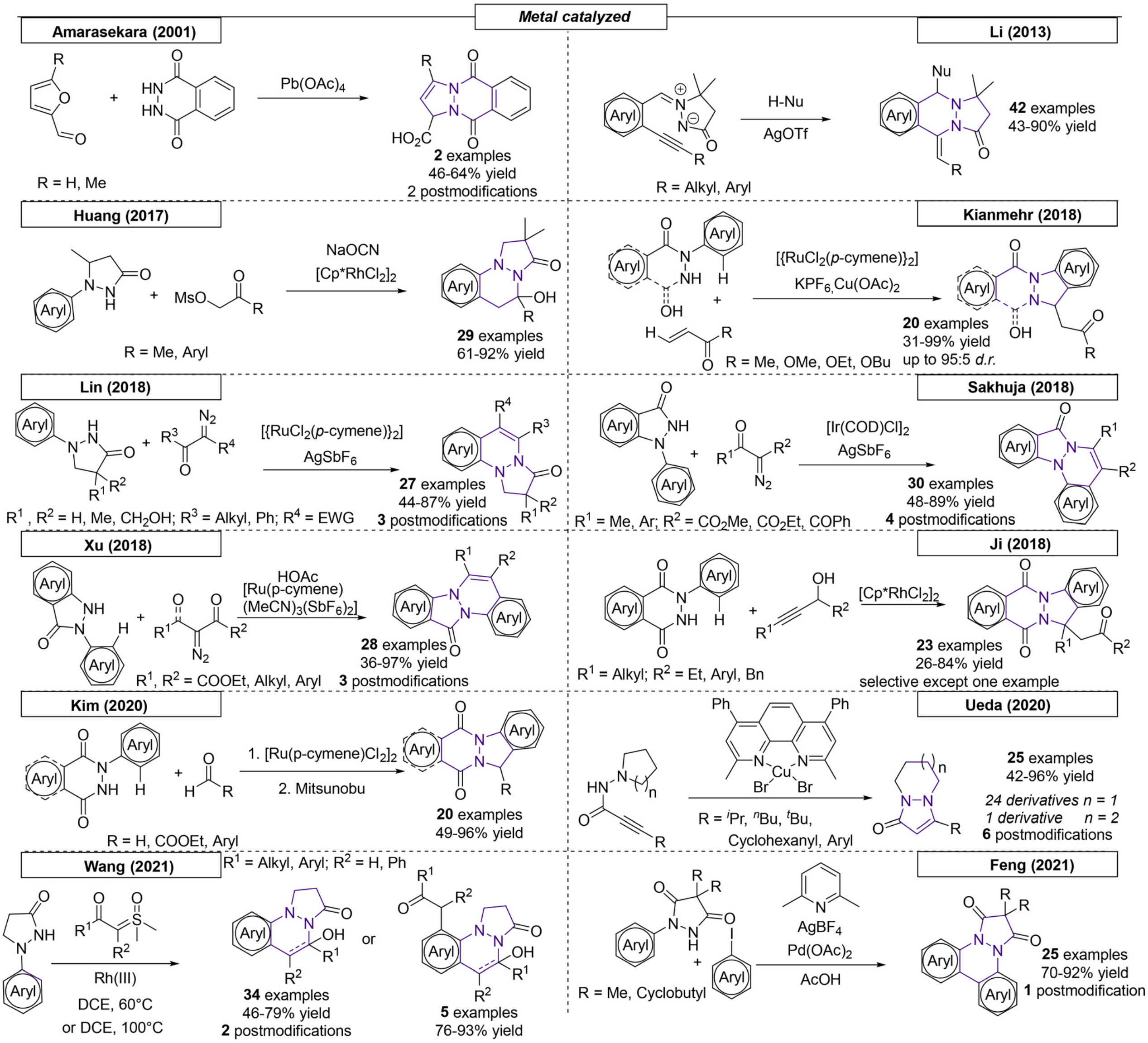
The last three examples use catalytic systems that do not fit into the previous sections (Table 14). Nagarapu and coworkers employed trimethylsilyl chloride as a catalyst and acetonitrile as a solvent.[457] The Ma research group developed a methodology that employed elemental iodine as a catalyst in ethanol.[458] Finally, sodium hydroxide was established as a readily available and inexpensive catalyst by the Sangani research group.[459]

Table 14 Other pyrazolo-pyridazine-yielding 1,3-dipolar cycloaddition reactions

	Year	Condition	Examples	Yield	Ref.
	2009	TMSCl, CH_3CN	16	86–95%	457
	2011	I_2, EtOH	11	86–96%	458
	2015	NaOH, EtOH	16	70–89%	459

7.2 Metal-catalysed reactions

There are many examples of metal-catalysed reactions that have been used to produce pyrazolo-pyridazines. In 2002, Amarasekara and coworkers reported the reaction of two furfural derivatives with 1,4-phthalazinedione to form two pyrazolo-pyridazine compounds in yields as high as 64% (Scheme 42).[460] This [4 + 2] dipolar cycloaddition reaction was catalysed by lead acetate. In 2013, the Li research group developed a novel silver-catalysed tandem addition/cyclization reaction of alkyne azomethines with various soft nucleophiles.[461] In this work, ketones, nitroalkanes, water, and terminal alkynes were used to form forty-two derivatives in yields as high as 90%. Though the chemoselectivities were high, diastereoselectivities were moderate to low. Huang and coworkers reported a rhodium-catalysed C–H activation reaction that provided novel *N*,*N*-bicyclic pyrazolo-pyridazine derivatives.[462] The *ortho* C–H activation was found to be directed by the pyrazolidine moiety, which initiated the formation of the desired benzopyridazine analogs in yields as high as 92%. A ruthenium-catalysed synthetic approach was reported by the Kianmehr research group in 2018.[463] The reaction sequence included an alkenylation/annulation step, was initiated by a



Scheme 42 Metal-catalysed reactions that produce pyrazolo-pyridazines.

C–H activation and was carried out in water. In total, twenty derivatives were synthesized in yields as high as 99% and with up to 95 : 5 dr.

Lin and coworkers reported a redox neutral annulation of pyrazolidinones with diazo compounds that provided twenty-seven derivatives that had the pyrazolo-pyridazine core structure (Scheme 42).[464] The reaction sequence, which was catalysed by a ruthenium complex, was described as a C–H activation/cyclization/dehydration process and gave only N_2 and H_2O as byproducts. In addition to a broad substrate scope, three postmodifications were reported. In the same year, a similar approach was published by Sakhuja and coworkers, who used an iridium complex instead of a ruthenium complex.[465] In total, thirty examples and four postmodifications were reported. The Xu research group reported a related reaction in which diazo reagents were reacted with 2-phenylindazol-3-ones.[466] In this sequence, C–H ruthenation, Ru(II)-carbene formation, migratory insertion, and condensation take place in a sequential fashion. The scope included twenty-eight examples with yields as high as 97% and three postmodifications. Additional derivatives were reported in a follow-up publication in which the bioactivities of the novel molecules were also investigated.[467] Ji and coworkers reported a rhodium-catalysed [4 + 1] cyclization *via* C–H activation that was used to synthesize various quaternary carbon-containing heterocycles.[468] The reaction, which featured various heterocyclic and propargyl alcohol starting materials, provided twenty-three pyrazolo-pyridazine examples in yields as high as 84% and with excellent stereoselectivities in almost all cases.

In 2020, the Kim research group developed a C–H hydroxyalkylation/Mitsunobu/cyclization sequence starting from *N*-aryl phthalazinones (Scheme 42).[469] The ruthenium-catalysed procedure, which involved aldehydes or activated ketones, provided twenty indazolophthalazinone examples in yields as high as 96%. In the same year, Ueda and coworkers reported a copper-catalysed sequential cyclization/migration reaction toward pyrazolo-pyridazines.[470] Control experiments revealed the importance of the copper catalyst in the reaction of phenylalkynyl hydrazide. In total, twenty-five examples with two different ring sizes were synthesized in yields as high as 96%. Wang and coworkers developed a sequence that included a rhodium(III)-catalysed C–H activation of pyrazolidinones followed by a [4 + 2] sulfoxonium ylide annulation toward pyrazolo[1,2-*a*]cinnolines.[471] Depending on the reaction temperature, two different substitution patterns were obtained. It was also reported that the synthesis could be performed at gram scale. In 2021, the Feng research group published a palladium-catalysed dual C–H activation that enabled the construction of C–C and C–N bonds between pyrazolones and aryl iodides leading to phenylpyrazolidine-3,5-diones.[472] The derivatives were obtained in yields as high as 94% and were readily converted into benzo[*c*]cinnoline analogs by reaction with NaOH in ethanol.

7.3 Condensation reactions

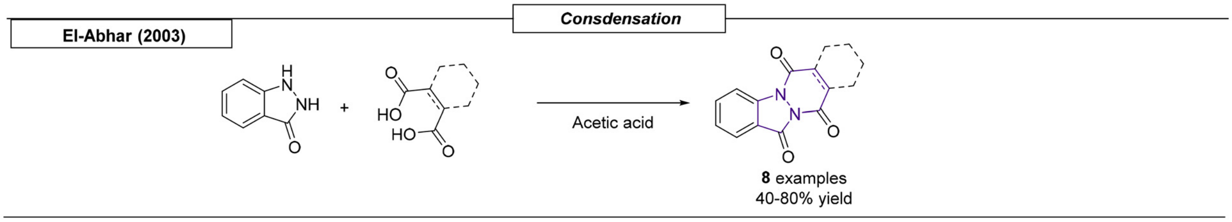
El-Abhar and coworkers synthesized a set of pyrazolo and pyridazino compounds by condensation of 1,2-dihydro-3*H*-indazol-3-one with various dicarboxylic acids (Scheme 43).[473] The anti-inflammatory activity of these compounds was determined, and one pyrazolo-pyridazine exhibited significant anti-inflammatory potential.

7.4 Multistep syntheses

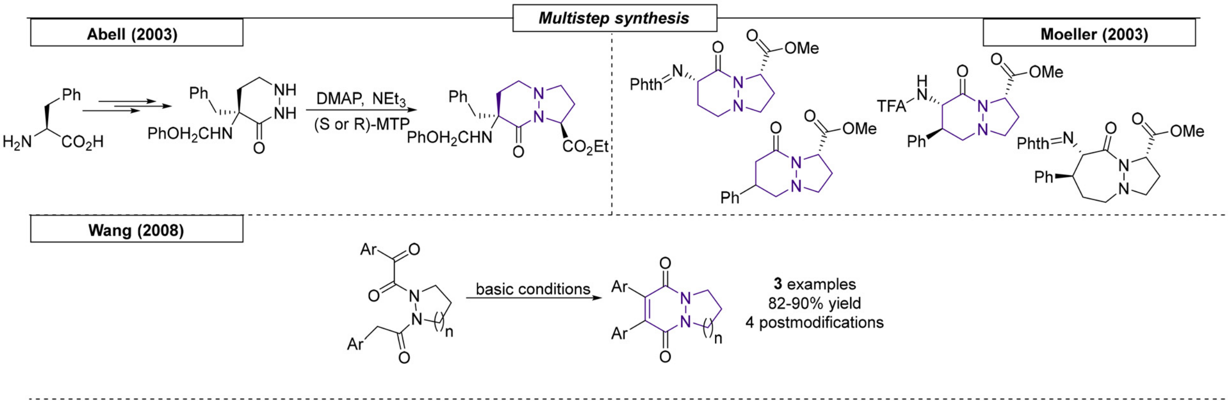
Several examples of multistep synthetic procedures that produce pyrazolo-pyridazines have been published. Abell and coworkers described the eight-step, enantioselective synthesis of a peptidic tetrahydropyridazinone starting from (S)-phenylalanine (Scheme 44).[474] The derivative was further converted into a bicyclic peptidomimetic, which is an important class of β-strand mimetics. In 2003, the Moeller research group developed a synthetic method for the incorporation of pyrazoline derivatives into substituted bicyclic lactam peptidomimetics.[475] The bicyclic products have either a six- or seven-membered lactam ring in their core structure. In 2008, Wang and coworkers constructed three different aza-phenanthroindo(quino)lizidine alkaloid analogs.[476] The reaction sequence started with the four-step synthesis of a biacylhydrazine. The N,N-bridgehead scaffold was then obtained using an aldol condensation reaction. The authors also demonstrated that the two aryl rings could be oxidatively coupled. Some of the compounds demonstrated anticancer potential in an *in vitro* assay.

7.5 Domino reactions

Two research groups have published cascade or multicomponent reactions that produce pyrazolo-pyridazines. Kostikov and coworkers reported the reaction of thermolized 6-aryl-1,5-dia-



Scheme 43 Pyrazolo-pyridazine *via* condensation reactions.

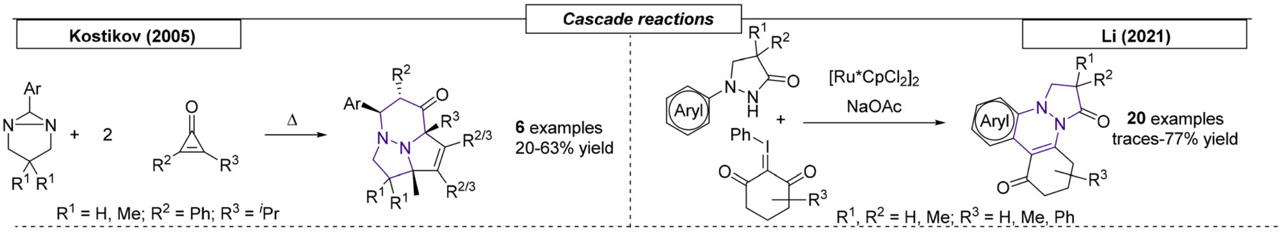


Scheme 44 Multistep synthetic procedures that produce pyrazolo-pyridazines.

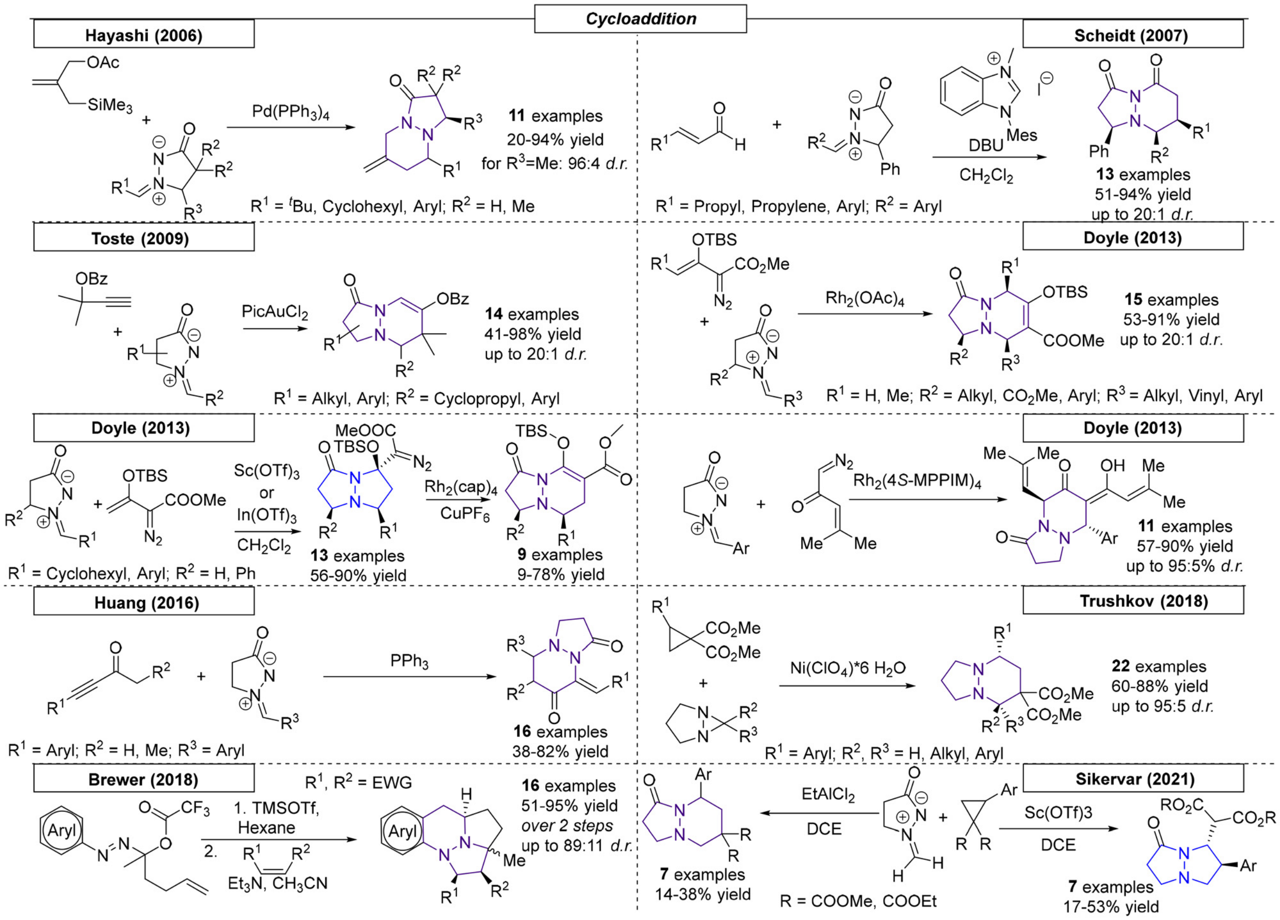
zabicyclo[3.1.0]hexanes with 2-alkyl-3-phenylcyclopropenones (Scheme 45).[477] The fused polycyclic systems, 4a,7b-diazacyclopenta[*cd*]inden-7-ones, were found to be the result of two cyclopropenone molecules added with extrusion of a CO molecule. In total, six substrates were synthesized in yields as high as 63%. In 2021, Li and coworkers developed a rhodium-catalysed cascade reaction consisting of C–H bond activation/intramolecular cyclization toward pyrazolo[1,2-*a*]cinnoline derivatives.[478] Starting from pyrazolidiones and an iodonium ylide, which served as carbene precursor, twenty examples bearing various functional groups were obtained in yields as high as 77%.

7.6 Cycloaddition reactions

There are many examples of cycloaddition reactions that have been used to produce pyrazolo-pyridazines. The first example was published by Hayashi and coworkers in 2006 (Scheme 46).[479] In this palladium-catalysed [3 + 3] cycloaddition, reaction of azomethine imines with trimethylenemethane provided eleven pyrazolo-pyridazine compounds in yields as high as 94%. An absolute configuration was postulated and confirmed by X-ray analysis. Another approach that exploited azomethine imines as starting materials was developed by the Scheidt research group.[480] Using NHC catalysis,



Scheme 45 Cascade and multicomponent reactions that produce pyrazolo-pyridazines.



Scheme 46 Cycloaddition reactions that provide pyrazolo-pyridazines.

the authors created homo-enolates, which underwent subsequent [3 + 3] reactions to produce the desired N,N-bridgehead compounds. The thirteen examples were obtained in yields as high as 94% and with diastereoselectivities of up to 20 : 1 dr. Toste and coworkers reported a [3 + 3] cycloaddition reaction between an azomethine imine and propargyl esters.[481] The mechanism represented the first example of a formal cycloaddition of alkenyl-gold-carbenoids and 1,3-dipoles. Fourteen examples were reported with yields as high as 98% yield and diastereoselectivities of up to 20 : 1 dr.

The Doyle research group synthesized pyrazolo-pyridazines by reacting vinylcarbene intermediates, obtained from enoldiazoacetates, with azomethine imines using a rhodium catalyst (Scheme 46).[482] The absolute configuration of the major diastereomer was identified by X-ray analysis. All examples were obtained by this [3 + 3] cycloaddition process in yields as high as 91% and with diastereoselectivities of up to 20 : 1 dr. In the same year, Doyle and coworkers published the [3 + 2] cycloaddition reaction of enoldiazoacetates and azomethine imines using gold or copper triflate catalysts.[483] The obtained pyrazolo-pyrazole derivatives were then used for selective 1,2-C → C and –N → C migrations that provided the target pyrazolo-pyridazine compounds in yields as high as 78%. The Doyle research group also published a [3 + 2 + 1] annulation of azomethine imines with two diazo ketone molecules.[484] The reaction provided the desired *N*,*N*-bridgehead compounds in yields of up to 90% and diastereoselectivities of up to 95 : 5 dr.

In 2016, Huang and coworkers developed a phosphine-catalysed [3 + 3] domino cycloaddition of ynones and azomethine imines toward pyrazolo-pyridazine derivatives (Scheme 46).[485] Triphenylphosphine was used to generate a zwitterionic species, which enabled the formation of the desired products. The authors obtained nineteen different derivatives with high stereoselectivities and yields as high as 82%. The Trushkov research group reported the [3 + 3] annulation of donor–acceptor cyclopropanes with diaziridines.[486] The reaction, which was catalysed by a Lewis acid nickel catalyst, provided the desired pyrazolo-pyridazines in yields of up to 88% and with high diastereoselectivities, up to 95 : 5 dr. Brewer and coworkers described a novel two-step sequence of cycloadditions toward tetracyclic 1,2,3,4-tetrahydrocinnolines.[487] The structurally complex derivatives were constructed by consecutive [4 + 2] and [3 + 2] cycloadditions in yields as high as 95% over 2 steps and with up to 89 : 11 dr. Another Lewis acid-mediated cycloaddition reaction was reported by the Sikervar research group.[488] In this work, pyrazolo-pyrazoles or pyrazolo-pyridazines were obtained by [3 + 2] or [3 + 3] cycloadditions, respectively, depending on the catalyst employed, $Sc(OTf)_3$ or $EtAlCl_2$, respectively. Seven examples were produced for each scaffold, and their absolute configurations were confirmed using X-ray analysis. Additionally, three tetrahydrofuran-fused systems were reported.

7.7 Organocatalysed reactions

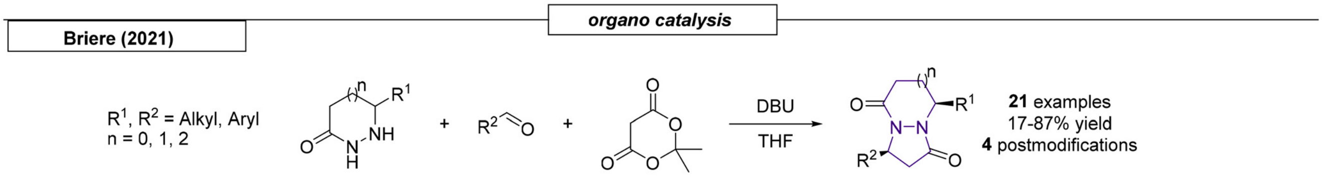
In 2021, Briere and coworkers reported an organocatalytic approach toward the pyrazolo-pyridazine core structure (Scheme 47).[489] In this multicomponent Knoevenagel/aza-Michael/cyclocondensation approach, pyridazinones were added to alkylidene Meldrum's acid intermediates using the organic base DBU as a catalyst. The procedure provided twenty-one examples in yields as high as 87% and with high regio- and diastereoselectivities.

8 Octahydro pyridazino[1,2-*a*] pyridazine

The final compound class to be discussed in this review is the pyridazino[1,2-*a*]pyridazines. Since the 1970s, partially or fully saturated derivatives of the pyridazino[1,2-*a*]pyridazine ring system have been considered as potential drug molecules (Fig. 7).[490]

8.1 Metal-catalysed reactions

As the synthesis of these pyridazino-pyridazines is very difficult, relatively few approaches that yield expanded scaffolds have been published. In 2018, the Shang research group developed a ruthenium- or iridium-catalysed procedure for the synthesis of 8*H*-isoquinolino[1,2-*b*]quinazolin-8-ones and phthalazino[2,3-*a*]cinnoline-8,13-diones (Scheme 48).[491] The latter were obtained using various 2-phenyl-2,3-dihydrophthalazine-1,4-diones, cyclic diazo-1,3-diketones and an iridium catalyst. Twenty-four examples were obtained in yields as high as 95%. Kim and coworkers reported a rhodium-catalysed C–H annulation of *N*-aryl heterocycles toward cinnolines.[492] *N*-Aryl phthalazinones were reacted with vinylene carbonate to obtain the pyridazolo-pyridazine or pyridazino-pyridazine core structures, depending on starting materials and reaction conditions. In total, twenty-eight derivatives were synthesized in yields as high as 98%.



Scheme 47 Pyrazolo-pyridazines *via* organocatalytic reactions.

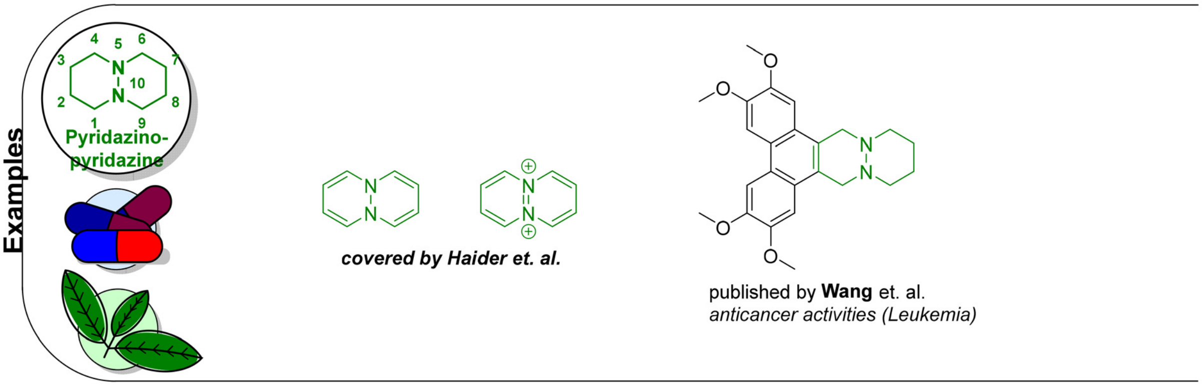
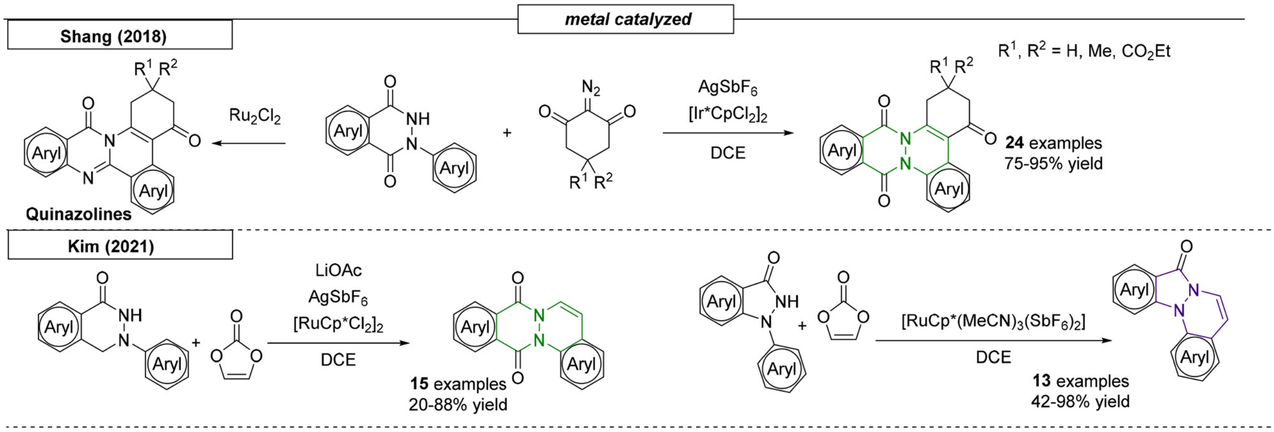
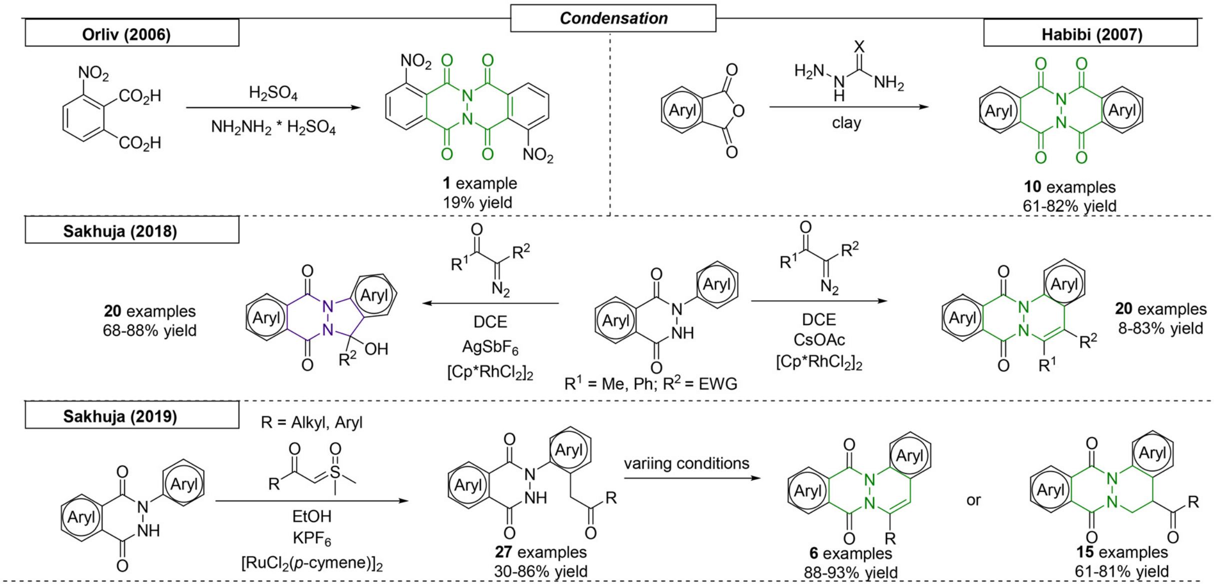


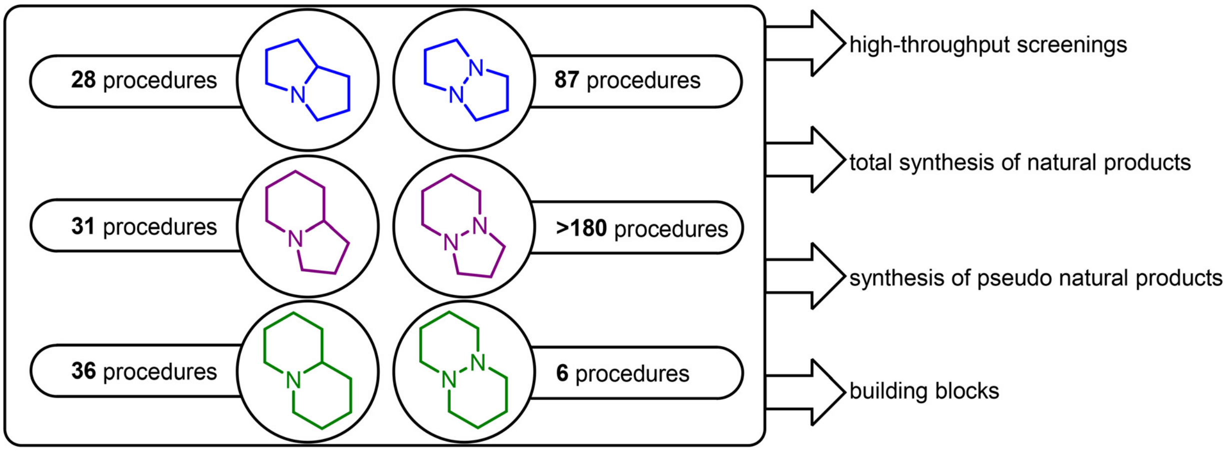
Fig. 7 Examples of pyridazino-pyridazine-derived compounds.



Scheme 48 Pyridazino-pyridazines *via* metal-catalysed reactions.



Scheme 49 Condensation reactions that produce pyridazino-pyridazines.



Scheme 50 Numbers of publications and outlook.

8.2 Condensation reactions

Four methods for the synthesis of pyridazino-pyridazines using condensation reactions have been published. In 2006, Orlov and coworkers reported the synthesis of a pyridazino[1,2-*a*]pyridazine derivative by reaction of 3-nitrophthalic acid with hydrazine in fuming sulfuric acid. The product was isolated in 19% yield (Scheme 49).[493] Another approach, yielding the same core structure, was reported by Habibi and coworkers one year later.[494] Instead of the free acids, anhydrides were brought to reaction with semi carbazides or thiosemicarbazides under solvent free conditions with K-10 clay under microwave irradiation. In total, ten examples were obtained in yields as high as 82%. The Sakhuja research group developed an additive-driven, rhodium-catalysed annulation reaction of *N*-arylphthalazine-1,4-diones and α-diazo carbonyl compounds.[495] A [4 + 1] or a [4 + 2] annulation took place, depending on the additive, CsOAc or $AgSbF_6$, respectively. Twenty examples of both motifs were prepared in yields as high as 88%. One year later, the same research group published a C–H acylmethylation of *N*-arylphthalazine-1,4-diones with α-carbonyl sulfoxonium ylides.[496] The direct ruthenium-catalysed, *ortho*-Csp^2–H acylmethylation with an α-carbonyl sulfoxonium ylide featured high functional group tolerance. The product was used as a key intermediate for the synthesis of various pyridazino-pyridazine scaffolds in yields ranging from 61 to 93%.

9 Conclusion

We have reviewed the available structures and synthetic methods for N-bridgehead compounds published since 2000. These compounds, which have been reported in over 450 publications, offer the potential to serve as first-generation bioactive compounds or building blocks for novel pharmaceutics. We believe that these compounds have great potential, as the bioactivity of a broad majority of them has yet to be determined. Given the broad spectrum of synthetic methods reviewed here, historical drawbacks associated with these structures, such as availability or limited possibility of modification, can now be almost completely avoided.

As the *de novo* synthesis of these compounds is well-documented, we hope that this review is useful for drug design and discovery in multiple ways (Scheme 50): first, exemplary N-bridgehead compounds can be added to high-throughput compound libraries to cover the chemical space of these scaffolds. Compounds that are identified as potential drug candidates can be easily optimized by variation of the corresponding starting materials and, therefore, tailored to the desired purposes. Second, methodologies used for the construction of the N-bridgehead core can be utilized in the design of total synthesis procedures of natural products. In addition, research around pseudo natural products can profit from the multiple possibilities of constructing the complex core structure. Finally, this review can serve as a collection of N-bridgehead building blocks for drug design in general.

Author contributions

B. W. G. and S. V. M. developed the general concept of the review. B. W. G. developed outlay, conducted literature research, writing of the manuscript and design of schemes, figures, and tables. P. K. and A. N. refined the concept and improved schemes, figures, and tables of the review. All authors contributed to editing, proofreading and finalizing the article.

Data availability

This is a review article on nitrogen bridgehead compounds, summarizing 20 hears of literature, that has not been done in two decades.

There is no data to be transferred.

Conflicts of interest

There are no conflicts to declare.

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References

1 B. A. P. Wilson, C. C. Thornburg, C. J. Henrich, T. Grkovic and B. R. O'Keefe, *Nat. Prod. Rep.*, 2020, **37**, 893–918.

2 A. L. Q. Franca, H. V. Chaves, J. M. O. Freire, L. H. T. de Sousa, A. T. A. Pimenta, M. A. S. Lima, B. R. de Oliveira, M. C. de Mattos, V. P. T. Pinto, A. Portela, K. M. A. Pereira, J. Costa, P. Goes, R. J. B. Jorge, J. A. M. Silveira, H. L. B. Braz, M. E. A. de Moraes and M. M. Bezerra, *Clin. Oral Investig.*, 2022, **26**, 1701–1711.

3 M. G. da Silva, S. L. F. Barbosa, D. S. Silva, I. B. M. Bezerra, E. A. Bezerra, A. G. Coelho, I. C. P. da Silva Morais, L. M. Rezende-Junior, I. S. do Carmo, J. S. Lima-Neto, S. G. Comerma-Steffensen, A. Cito and D. D. R. Arcanjo, *J. Evidence-Based Complementary Altern. Med.*, 2022, **2022**, 8499625.

4 Y. D. Singh, B. Jena, R. Ningthoujam, S. Panda, P. Priyadarsini, S. Pattanayak, M. K. Panda, M. C. Singh and K. B. Satapathy, *Adv. Tradit. Med.*, 2020, **22**, 259–270.

5 D. L. Chen, B. W. Wang, Z. C. Sun, J. S. Yang, X. D. Xu and G. X. Ma, *Molecules*, 2020, **25**, 2485.

6 X.-Y. Zong, D.-C. Xu, J.-Y. Yin, S.-P. Nie and M.-Y. Xie, *Bioact. Carbohydr. Diet. Fibre*, 2022, **27**, 100284.

7 E. Karrar, I. A. M. Ahmed, M. F. Manzoor, W. Wei, F. Sarpong and X. Wang, *Food Chem.*, 2022, **373**, 131436.

8 M. Kumar, A. Dahuja, S. Tiwari, S. Punia, Y. Tak, R. Amarowicz, A. G. Bhoite, S. Singh, S. Joshi, P. S. Panesar, R. Prakash Saini, A. Pihlanto, M. Tomar, J. Sharifi-Rad and C. Kaur, *Food Chem.*, 2021, **353**, 129431.

9 C. Wawrosch and S. B. Zotchev, *Appl. Microbiol. Biotechnol.*, 2021, **105**, 6649–6668.

10 M. Oliverio, M. Nardi, M. L. Di Gioia, P. Costanzo, S. Bonacci, S. Mancuso and A. Procopio, *Nat. Prod. Rep.*, 2021, **38**, 444–469.

11 V. Sharma, T. Sharma, S. Kaul, K. K. Kapoor and M. K. Dhar, *Phytochem. Rev.*, 2016, **16**, 513–526.

12 C. Kibayashi, *Chem. Pharm. Bull.*, 2005, **53**, 1375–1386.

13 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

14 T. A. Crabb, R. F. Newton and D. Jackson, *Chem. Rev.*, 1970, **71**, 109–126.

15 J. T. Kim and V. Gevorgyan, *J. Org. Chem.*, 2005, **70**, 2054–2059.

16 P. Brugnerotto, S. K. T. Seraglio, M. Schulz, L. V. Gonzaga, R. Fett and A. C. O. Costa, *Food Chem.*, 2021, **342**, 128384.

17 S. V. Kauloorkar, V. Jha, G. Jogdand and P. Kumar, *Org. Biomol. Chem.*, 2014, **12**, 4454–4460.

18 C. Bhat and S. G. Tilve, *RSC Adv.*, 2014, **4**, 5405.

19 Y. Quevedo-Acosta, I. D. Jurberg and D. Gamba-Sanchez, *Org. Lett.*, 2020, **22**, 239–243.

20 J. Robertson and K. Stevens, *Nat. Prod. Rep.*, 2014, **31**, 1721–1788.

21 J. R. Liddell, *Nat. Prod. Rep.*, 2002, **19**, 773–781.

22 T. Kopp, M. Abdel-Tawab and B. Mizaikoff, *Toxins*, 2020, **12**, 320.

23 X. Wei, W. Ruan and K. Vrieling, *Molecules*, 2021, **26**, 1970.

24 R. Moreira, D. M. Pereira, P. Valentao and P. B. Andrade, *Int. J. Mol. Sci.*, 2018, **19**, 1668.

25 J. S. Miser, W. A. Smithson, W. Krivit, C. H. Hughes, D. Davis, M. D. Krailo and G. D. Hammond, *Am. J. Clin. Oncol.*, 1992, **15**, 135.

26 B. Singh, P. M. Sahu and S. Singh, *Fitoterapia*, 2002, **73**, 153–155.

27 D. L. Taylor, R. Nash, L. E. Fellows, M. S. Kang and A. S. Tyms, *Antiviral Chem. Chemother.*, 2016, **3**, 273–277.

28 V. B. Pandey, J. P. Singh, Y. V. Rao and S. B. Acharya, *Planta Med.*, 1982, **45**, 229–233.

29 M. Aboelmagd, K. Elokely, M. A. Zaki, A. Said, E. G. Haggag and S. A. Ross, *Med. Chem. Res.*, 2018, **27**, 1066–1073.

30 P. Cos, D. Berghe, T. Bruyne and A. Vlietinck, *Curr. Org. Chem.*, 2003, **7**, 1163–1180.

31 H. Khan, Marya, S. Amin, M. A. Kamal and S. Patel, *Biomed. Pharmacother.*, 2018, **101**, 860–870.

32 H. Benamar, L. Tomassini, A. Venditti, A. Marouf, M. Bennaceur and M. Nicoletti, *Nat. Prod. Res.*, 2016, **30**, 2567–2574.

33 D. Crich, K. Ranganathan and X. Huang, *Org. Lett.*, 2001, **3**, 1917–1919.

34 R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc., Trans.*, 1915, **107**, 1080–1106.

35 S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2001, **42**, 7887–7890.

36 F. Ghelfi, A. F. Parsons, D. Tommasini and A. Mucci, *Eur. J. Org. Chem.*, 2001, **2001**, 1845–1852.

37 A. Padwa, M. N. Jacquez and A. Schmidt, *J. Org. Chem.*, 2004, **69**, 33–45.

38 J.-M. Huang, S.-C. Hong, K.-L. Wu and Y.-M. Tsai, *Tetrahedron Lett.*, 2004, **45**, 3047–3050.

39 D. Kalaitzakis, M. Triantafyllakis, M. Sofiadis, D. Noutsias and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2016, **55**, 4605–4609.

40 C. Nájera and J. M. Sansano, *Pure Appl. Chem.*, 2019, **91**, 575–596.

41 R. G. Biswas and V. K. Singh, *Tetrahedron Lett.*, 2021, **69**, 152954.

42 H. Oh, B. Ryou, J. Park, M. Kim, J.-H. Choi and C.-M. Park, *ACS Catal.*, 2021, **11**, 13670–13679.

43 P. A. O'Gorman, T. Chen, H. E. Cross, S. Naeem, A. Pitard, M. I. Qamar and K. Hemming, *Tetrahedron Lett.*, 2008, **49**, 6316–6319.

44 V. V. R. Kondakal, M. Ilyas Qamar and K. Hemming, *Tetrahedron Lett.*, 2012, **53**, 4100–4103.

45 Y.-M. Zhang, P. Liu and H.-L. Zhang, *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.*, 2013, **43**, 340–342.

46 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564–12649.

47 I. Bytschkov, H. Siebeneicher and S. Doye, *Eur. J. Org. Chem.*, 2003, 2888–2902.

48 K. T. Yip, M. Yang, K. L. Law, N. Y. Zhu and D. Yang, *J. Am. Chem. Soc.*, 2006, **128**, 3130–3131.

49 D. Xing and D. Yang, *Org. Lett.*, 2013, **15**, 4370–4373.

50 W. Du, Q. Gu, Y. Li, Z. Lin and D. Yang, *Org. Lett.*, 2017, **19**, 316–319.

51 D. Yang, K.-Y. Lo and L. Ye, *Synlett*, 2017, 1570–1575.

52 L. Ye, K. Y. Lo, Q. Gu and D. Yang, *Org. Lett.*, 2017, **19**, 308–311.

53 W. Hagui, K. Yuan, N. Besbes, E. Srasra, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2015, **7**, 3544–3554.

54 M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036–2056.

55 H. Wakamatsu, Y. Sato, R. Fujita and M. Mori, *Adv. Synth. Catal.*, 2007, **349**, 1231–1246.

56 R. A. Batey, *J. Am. Chem. Soc.*, 2007, **129**, 7476–7476.

57 R. Zimmer, M. Collas, R. Czerwonka, U. Hain and H.-U. Reissig, *Synthesis*, 2008, 237–244.

58 J. Tamariz, E. Martínez-Mora, M. Caracas, C. Escalante, C. Espinoza-Hicks, H. Quiroz-Florentino and F. Delgado, *Synthesis*, 2016, 1055–1068.

59 S. Goudedranche, C. Besnard, L. Egger and J. Lacour, *Angew. Chem., Int. Ed.*, 2016, **55**, 13775–13779.

60 X. Wang, M. Li, Y. Yang, M. Guo, X. Tang and G. Wang, *Adv. Synth. Catal.*, 2018, **360**, 2151–2156.

61 M. Lange, Y. Zi and I. Vilotijevic, *J. Org. Chem.*, 2020, **85**, 1259–1269.

62 M. Escolano, J. T. Fernández, F. Rabasa-Alcaniz, M. Sanchez-Rosello and C. D. Pozo, *Org. Lett.*, 2020, **22**, 9433–9438.

63 C.-H. Lin, B.-C. Hong and G.-H. Lee, *RSC Adv.*, 2016, **6**, 8243–8247.

64 F. Hao, A. R. Reddy, C.-Y. Zhou and C.-M. Che, *Adv. Synth. Catal.*, 2018, **360**, 1433–1438.

65 A. T. Carmona, J. Fuentes, P. Vogel and I. Robina, *Tetrahedron: Asymmetry*, 2004, **15**, 323–333.

66 X. T. Liu, L. Hao, M. Lin, L. Chen and Z. P. Zhan, *Org. Biomol. Chem.*, 2010, **8**, 3064–3072.

67 V. Sharma and V. Kumar, *Med. Chem. Res.*, 2014, **23**, 3593–3606.

68 J. P. Michael, *Alkaloids: Chem. Biol.*, 2016, **75**, 1–498.

69 J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod.*, 2005, **68**, 1556–1575.

70 J. Zhang, S. L. Morris-Natschke, D. Ma, X. F. Shang, C. J. Yang, Y. Q. Liu and K. H. Lee, *Med. Res. Rev.*, 2021, **41**, 928–960.

71 B. Reddy, D. Chaya, J. Yadav and R. Grée, *Synthesis*, 2011, 297–303.

72 K. Whitby, T. C. Pierson, B. Geiss, K. Lane, M. Engle, Y. Zhou, R. W. Doms and M. S. Diamond, *J. Virol.*, 2005, **79**, 8698–8706.

73 K. Wojtowicz, R. Januchowski, P. Sosinska, M. Nowicki and M. Zabel, *Oncol. Rep.*, 2016, **35**, 2896–2906.

74 C. W. Yang, W. L. Chen, P. L. Wu, H. Y. Tseng and S. J. Lee, *Mol. Pharmacol.*, 2006, **69**, 749–758.

75 D. Leonoudakis, A. Rane, S. Angeli, G. J. Lithgow, J. K. Andersen and S. J. Chinta, *Mediators Inflammation*, 2017, **2017**, 8302636.

76 M. Kubo, W. Yatsuzuka, S. Matsushima, K. Harada, Y. Inoue, H. Miyamoto, M. Matsumoto and Y. Fukuyama, *Chem. Pharm. Bull.*, 2016, **64**, 957–960.

77 S. Veeraswamy, A. Anjaiah, S. Yennam and A. Jayashree, *Asian J. Chem.*, 2015, **27**, 1667–1670.

78 Y. H. Jung and I. S. Kim, *Heterocycles*, 2011, **83**, 2489.

79 A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero and A. Goti, *Chemistry*, 2009, **15**, 7808–7821.

80 F. Abels, C. Lindemann and C. Schneider, *Chemistry*, 2014, **20**, 1964–1979.

81 K. M. Dawood and A. A. Abbas, *Expert Opin. Ther. Pat.*, 2020, **30**, 695–714.

82 A. C. Burtoloso, R. M. Dias and B. Bernardim, *Acc. Chem. Res.*, 2015, **48**, 921–934.

83 S. Gross and H. U. Reissig, *Org. Lett.*, 2003, **5**, 4305–4307.

84 E. Georgescu, F. Georgescu, M. G. Danila, P. I. Filip, C. Drăghici and M. T. Căproiu, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3382–3392, DOI: 10.1039/b106832f.

85 H. Suga, Y. Hashimoto, S. Yasumura, R. Takezawa, K. Itoh and A. Kakehi, *J. Org. Chem.*, 2013, **78**, 10840–10852.

86 G. C. Tay, N. Sizemore and S. D. Rychnovsky, *Org. Lett.*, 2016, **18**, 3050–3053.

87 K. A. Tehrani, M. D'Hooghe and N. De Kimpe, *Tetrahedron*, 2003, **59**, 3099–3108.

88 T. G. Back, M. Parvez and H. Zhai, *J. Org. Chem.*, 2003, **68**, 9389–9393.

89 S.-S. P. Chou and C.-W. Ho, *Tetrahedron Lett.*, 2005, **46**, 8551–8554.

90 S. H. Verhelst, B. Paez Martinez, M. S. Timmer, G. Lodder, G. A. van der Marel, H. S. Overkleeft and J. H. van Boom, *J. Org. Chem.*, 2003, **68**, 9598–9603.

91 K. C. Kurtz, R. P. Hsung and Y. Zhang, *Org. Lett.*, 2006, **8**, 231–234.

92 R. Ben-Othman, M. Othman, K. Ciamala, M. Knorr, C. Strohmann and B. Decroix, *Tetrahedron*, 2009, **65**, 4846–4854.

93 G. A. Molander and S. K. Pack, *J. Org. Chem.*, 2003, **68**, 9214–9220.

94 E. V. Babaev, A. A. Tsisevich, D. V. Al'bov, V. B. Rybakov and L. A. Aslanov, *Russ. Chem. Bull.*, 2005, **54**, 259–261.

95 W. Zhu, D. Dong, X. Pu and D. Ma, *Org. Lett.*, 2005, **7**, 705–708.

96 D. Ma and W. Zhu, *Synlett*, 2006, 1181–1184.

97 I. Coldham, S. Jana, L. Watson and C. D. Pilgram, *Tetrahedron Lett.*, 2008, **49**, 5408–5410.

98 X. Jiang, B. Tan and C. F. Barbas 3rd, *Angew. Chem., Int. Ed.*, 2013, **52**, 9261–9265.

99 Y. Chen, Y. M. He, S. Zhang, T. Miao and Q. H. Fan, *Angew. Chem., Int. Ed.*, 2019, **58**, 3809–3813.

100 G. Barbe, G. Pelletier and A. B. Charette, *Org. Lett.*, 2009, **11**, 3398–3401.

101 P. Szczesniak, S. Stecko, E. Maziarz, O. Staszewska-Krajewska and B. Furman, *J. Org. Chem.*, 2014, **79**, 10487–10503.

102 S. Hanessian and A. K. Chattopadhyay, *Org. Lett.*, 2014, **16**, 232–235.

103 N. E. Dontsova and A. M. Shestopalov, *Russ. Chem. Bull.*, 2017, **66**, 1030–1043.

104 Q. Song, Y. Liu, L. Cai, X. Cao, S. Qian and Z. Wang, *Chin. Chem. Lett.*, 2021, **32**, 1713–1716.

105 P. M. Holstein, D. Dailler, J. Vantourout, J. Shaya, A. Millet and O. Baudoin, *Angew. Chem., Int. Ed.*, 2016, **55**, 2805–2809.

106 J. C. Timmerman, S. Laulhe and R. A. Widenhoefer, *Org. Lett.*, 2017, **19**, 1466–1469.

107 D. Yang and G. C. Micalizio, *J. Am. Chem. Soc.*, 2009, **131**, 17548–17549.

108 G. Archibald, C. P. Lin, P. Boyd, D. Barker and V. Caprio, *J. Org. Chem.*, 2012, **77**, 7968–7980.

109 T. Punirun, D. Soorukram, C. Kuhakarn, V. Reutrakul and M. Pohmakotr, *J. Org. Chem.*, 2018, **83**, 765–782.

110 B. Raison, N. Dussart, L. Levy, P. G. Goekjian and D. Gueyrard, *J. Org. Chem.*, 2020, **85**, 864–875.

111 Y. Kang and D. Seidel, *Org. Lett.*, 2016, **18**, 4277–4279.

112 A. Paul, N. R. Thimmegowda, T. G. Cruz and D. Seidel, *Org. Lett.*, 2018, **20**, 602–604.

113 A. Avadhani, P. Iniyavan, A. Acharya, V. Gautam, S. Chakrabarti and H. Ila, *ACS Omega*, 2019, **4**, 17910–17922.

114 N. Veerasamy and R. G. Carter, *Tetrahedron*, 2016, **72**, 4989–5001.

115 J. C. Li, W. F. Dai, D. Liu, Z. J. Zhang, M. Y. Jiang, K. R. Rao, R. T. Li and H. M. Li, *Bioorg. Chem.*, 2021, **110**, 104781.

116 J. Zou, L. Zhao, P. Yi, Q. An, L. He, Y. Li, H. Lou, C. Yuan, W. Gu, L. Huang, Z. Hu and X. Hao, *J. Agric. Food Chem.*, 2020, **68**, 15015–15026.

117 D. Mancinotti, K. M. Frick and F. Geu-Flores, *Nat. Prod. Rep.*, 2022, **39**, 1423–1437.

118 M. Wink, *J. Chem. Ecol.*, 2019, **45**, 109–115.

119 S. Davies, A. Fletcher, P. Roberts and J. Thomson, *Synlett*, 2017, 2697–2706.

120 A. S. Pashev, N. T. Burdzhiev and E. R. Stanoeva, *Org. Prep. Proced. Int.*, 2016, **48**, 425–467.

121 X. H. Jia, H. X. Zhao, C. L. Du, W. Z. Tang and X. J. Wang, *Phytochem. Rev.*, 2020, **20**, 845.

122 H. Chen, T. Xiao, L. Li, D. Anand, Y. He and L. Zhou, *Adv. Synth. Catal.*, 2017, **359**, 3642–3647.

123 M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 1891–1894.

124 M. Kretzschmar, F. Hofmann, D. Moock and C. Schneider, *Angew. Chem., Int. Ed.*, 2018, **57**, 4774–4778.

125 X. Xu, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 12439–12447.

126 Y. Liu, Q. Wang, Y. Zhang, J. Huang, L. Nie, J. Chen, W. Cao and X. Wu, *J. Org. Chem.*, 2013, **78**, 12009–12017.

127 V. Gobe and X. Guinchard, *Org. Lett.*, 2014, **16**, 1924–1927.

128 M. J. James, N. D. Grant, P. O'Brien, R. J. Taylor and W. P. Unsworth, *Org. Lett.*, 2016, **18**, 6256–6259.

129 S. Nonaka, K. Sugimoto, H. Ueda and H. Tokuyama, *Adv. Synth. Catal.*, 2016, **358**, 380–385.

130 R. Azpíroz, A. Di Giuseppe, V. Passarelli, J. J. Pérez-Torrente, L. A. Oro and R. Castarlenas, *Organometallics*, 2018, **37**, 1695–1707.

131 L. R. Wang, D. Chang, Y. Feng, Y. M. He, G. J. Deng and Q. H. Fan, *Org. Lett.*, 2020, **22**, 2251–2255.

132 J. Barluenga, C. Mateos, F. Aznar and C. Valdes, *J. Org. Chem.*, 2004, **69**, 7114–7122.

133 S.-S. P. Chou, C.-F. Liang, T.-M. Lee and C.-F. Liu, *Tetrahedron*, 2007, **63**, 8267–8273.

134 S.-S. P. Chou and C.-F. Liu, *J. Chin. Chem. Soc.*, 2010, **57**, 811–819.

135 S.-S. P. Chou, C.-W. Huang and C.-C. Chang, *Tetrahedron*, 2011, **67**, 4505–4513.

136 S.-S. P. Chou, C.-L. Lu and Y.-H. Hsu, *J. Chin. Chem. Soc.*, 2012, **59**, 365–372.

137 A. Pepe, M. Pamment, G. I. Georg and S. V. Malhotra, *J. Org. Chem.*, 2011, **76**, 3527–3530.

138 M. Amat, V. Semak, C. Escolano, E. Molins and J. Bosch, *Org. Biomol. Chem.*, 2012, **10**, 6866–6875.

139 A. K. Khalafallah, R. M. Abd Elal and N. A. A. El Kanzi, *Heterocycl. Commun.*, 2002, **8**, 397.

140 O. V. Gulyakevich, P. V. Kurman and A. L. Mikhal'chuk, *Russ. J. Org. Chem.*, 2005, **41**, 1806–1809.

141 P. V. Gormay, V. B. Rybakov and E. V. Babaev, *Eur. J. Org. Chem.*, 2010, 5364–5368.

142 H. Fang, X. Wu, L. Nie, X. Dai, J. Chen, W. Cao and G. Zhao, *Org. Lett.*, 2010, **12**, 5366–5369.

143 G. Belanger, G. O'Brien and R. Larouche-Gauthier, *Org. Lett.*, 2011, **13**, 4268–4271.

144 X. Dai, X. Wu, H. Fang, L. Nie, J. Chen, H. Deng, W. Cao and G. Zhao, *Tetrahedron*, 2011, **67**, 3034–3040.

145 X. Wu, L. Nie, H. Fang, J. Chen, W. Cao and G. Zhao, *Eur. J. Org. Chem.*, 2011, 6755–6763.

146 M. Rueping and L. Hubener, *Synlett*, 2011, 1243–1246.

147 I. A. Abdelhamid, F. M. Saleh and H. M. Hassaneen, *Synlett*, 2020, 1126–1128.

148 W. Zou, M. Sandbhor and M. Bhasin, *J. Org. Chem.*, 2007, **72**, 1226–1234.

149 J. Franzén and A. Fisher, *Angew. Chem., Int. Ed.*, 2009, **48**, 787–791.

150 W. Zhang and J. Franzén, *Adv. Synth. Catal.*, 2010, **352**, 499–518.

151 X. Wu, X. Dai, L. Nie, H. Fang, J. Chen, Z. Ren, W. Cao and G. Zhao, *Chem. Commun.*, 2010, **46**, 2733–2735.

152 C. Tsukano, A. Oimura, I. Enkhtaivan and Y. Takemoto, *Org. Lett.*, 2012, **14**, 1902–1905.

153 A. Jung and S. J. Min, *Asian J. Org. Chem.*, 2019, **8**, 1617–1620.

154 J. Outin, P. Quellier and G. Bélanger, *J. Org. Chem.*, 2020, **85**, 4712–4729.

155 O. Bassas, N. Llor, M. M. Santos, R. Griera, E. Molins, M. Amat and J. Bosch, *Org. Lett.*, 2005, **7**, 2817–2820.

156 M. Amat, M. M. Santos, O. Bassas, N. Llor, C. Escolano, A. Gomez-Esque, E. Molins, S. M. Allin, V. McKee and J. Bosch, *J. Org. Chem.*, 2007, **72**, 5193–5201.

157 D. L. Clive, M. Yu and Z. Li, *Chem. Commun.*, 2005, 906–908, DOI: 10.1039/b413481h.

158 D. L. Clive, Z. Li and M. Yu, *J. Org. Chem.*, 2007, **72**, 5608–5617.

159 E. Airiau, N. Girard, M. Pizzeti, J. Salvadori, M. Taddei and A. Mann, *J. Org. Chem.*, 2010, **75**, 8670–8673.

160 M. J. Niphakis, B. J. Turunen and G. I. Georg, *J. Org. Chem.*, 2010, **75**, 6793–6805.

161 L. Gomez, X. Garrabou, J. Joglar, J. Bujons, T. Parella, C. Vilaplana, P. J. Cardona and P. Clapés, *Org. Biomol. Chem.*, 2012, **10**, 6309–6321.

162 S. Hu, B. Wang, Y. Zhang, W. Tang, M. Fang, T. Lu and D. Du, *Org. Biomol. Chem.*, 2015, **13**, 4661–4667.

163 A. Pashev, N. Burdzhiev and E. Stanoeva, *Beilstein J. Org. Chem.*, 2020, **16**, 1456–1464.

164 T. P. Ribelin, A. S. Judd, I. Akritopoulou-Zanze, R. F. Henry, J. L. Cross, D. N. Whittern and S. W. Djuric, *Org. Lett.*, 2007, **9**, 5119–5122.

165 R. Epple, H. D. Urbina, R. Russo, H. Liu, D. Mason, B. Bursulaya, C. Tumanut, J. Li and J. L. Harris, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1254–1259.

166 S. Yotphan, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 2452–2453.

167 S. Stecko, A. Mames, B. Furman and M. Chmielewski, *J. Org. Chem.*, 2009, **74**, 3094–3100.

168 F. Slowinski, O. B. Ayad, J. Vache, M. Saady, O. Leclerc and A. Lochead, *Org. Lett.*, 2010, **12**, 5004–5007.

169 A. F. Khlebnikov, M. S. Novikov, V. V. Pakalnis and D. S. Yufit, *J. Org. Chem.*, 2011, **76**, 9344–9352.

170 M. Srivastava, J. Singh, S. B. Singh, K. Tiwari, V. K. Pathak and J. Singh, *Green Chem.*, 2012, **14**, 901.

171 F. Grande, M. A. Occhiuzzi, G. Ioele, G. Ragno and A. Garofalo, *Eur. J. Med. Chem.*, 2018, **151**, 121–144.

172 D. R. Griffith and A. H. Shoemaker, *Synthesis*, 2020, 65–78.

173 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 3067.

174 B. Nie, W. Wu, Y. Zhang, H. Jiang and J. Zhang, *Org. Chem. Front.*, 2020, **7**, 3067–3099.

175 R. Szostak and M. Szostak, *Molecules*, 2019, **24**, 274.

176 Z. Zhang, H. Han, L. Wang, Z. Bu, Y. Xie and Q. Wang, *Org. Biomol. Chem.*, 2021, **19**, 3960–3982.

177 N. Petek, B. Erjavec, D. Slapšak, A. Gaber, U. Grošelj, F. Požgan, S. Ričko, B. Štefane, M. Klemenčič and J. Svete, *Dyes Pigm.*, 2022, **201**, 110224.

178 L. N. Jungheim, S. K. Sigmund and J. W. Fisher, *Tetrahedron Lett.*, 1987, **28**, 285–288.

179 E. E. Boros, F. Bouvier, S. Randhawa and M. H. Rabinowitz, *J. Heterocycl. Chem.*, 2001, **38**, 613–616.

180 X. Gao, C. S. Hampton and M. Harmata, *Eur. J. Org. Chem.*, 2012, 7053–7056.

181 P. Zhang, D. Kumar, L. Zhang, D. Shem-Tov, N. Petrutik, A. K. Chinnam, C. Yao, S. Pang and M. Gozin, *Molecules*, 2019, **24**, 4324.

182 T.-H. Chuang and K. B. Sharpless, *Helv. Chim. Acta*, 2000, **83**, 1734–1743.

183 U. Grošelj, A. Drobnič, S. Rečnik, J. Svete, B. Stanovnik, A. Golobič, N. Lah, I. Leban, A. Meden and S. Golič-Grdadolnik, *Helv. Chim. Acta*, 2001, **84**, 3403–3417.

184 L. Pezdirc, V. Jovanovski, D. Bevk, R. Jakše, S. Pirc, A. Meden, B. Stanovnik and J. Svete, *Tetrahedron*, 2005, **61**, 3977–3990.

185 L. Pezdirc, D. Bevk, U. Groselj, A. Meden, B. Stanovnik and J. Svete, *J. Comb. Chem.*, 2007, **9**, 717–723.

186 L. Pezdirc, J. Cerkovnik, S. Pirc, B. Stanovnik and J. Svete, *Tetrahedron*, 2007, **63**, 991–999.

187 L. Pezdirc, U. Grošelj, A. Meden, B. Stanovnik and J. Svete, *J. Heterocycl. Chem.*, 2009, **45**, 181–188.

188 L. Pezdirc, B. Stanovnik and J. Svete, *Collect. Czech. Chem. Commun.*, 2009, **74**, 835–856.

189 A. Novak, J. Bezenšek, L. Pezdirc, U. Grošelj, M. Kasunič, Č. Podlipnik, B. Stanovnik, P. Šimůnek and J. Svete, *Tetrahedron*, 2011, **67**, 9729–9735.

190 I. Panfil, Z. Urbańczyk-Lipkowska, K. Suwińska, J. Solecka and M. Chmielewski, *Tetrahedron*, 2002, **58**, 1199–1212.

191 A. P. Molchanov, D. I. Sipkin, Y. B. Koptelov, J. Kopf and R. R. Kostikov, *Russ. J. Org. Chem.*, 2004, **40**, 67–78.

192 A. P. Molchanov, D. I. Sipkin, Y. B. Koptelov and R. R. Kostikov, *Eur. J. Org. Chem.*, 2002, 453–456.

193 A. P. Molchanov, D. I. Sipkin, Y. B. Koptelov, J. Kopf and R. R. Kostikov, *Russ. J. Org. Chem.*, 2003, **39**, 1338–1345.

194 Y. B. Koptelov, *Russ. J. Org. Chem.*, 2006, **42**, 1510–1515.

195 Y. B. Koptelov, S. P. Saik, A. P. Molchanov and S. I. Selivanov, *Russ. J. Org. Chem.*, 2011, **47**, 421–432.

196 Y. B. Koptelov and M. V. Sednev, *Russ. J. Org. Chem.*, 2011, **47**, 547–555.

197 Y. B. Koptelov, M. V. Sednev and R. R. Kostikov, *Russ. J. Org. Chem.*, 2012, **48**, 804–814.

198 Y. B. Koptelov, D. O. Antuganov, A. P. Molchanov and R. R. Kostikov, *Russ. J. Org. Chem.*, 2015, **51**, 972–981.

199 M. I. Pleshchev, N. V. D. Gupta, M. I. Struchkova, A. S. Goloveshkin, I. S. Bushmarinov, D. V. Khakimov and N. N. Makhova, *Mendeleev Commun.*, 2015, **25**, 188–190.

200 M. M. Efremova, A. P. Molchanov, A. V. Stepakov, R. R. Kostikov, V. S. Shcherbakova and A. V. Ivanov, *Tetrahedron*, 2015, **71**, 2071–2078.

201 W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding and Y.-C. Chen, *Adv. Synth. Catal.*, 2006, **348**, 1818–1822.

202 A. V. Shevtsov, V. V. Kuznetsov, A. A. Kislukhin, V. Y. Petukhova, Y. A. Strelenko, N. N. Makhova and K. A. Lyssenko, *J. Heterocycl. Chem.*, 2006, **43**, 881–888.

203 W. Chen, W. Du, Y. Z. Duan, Y. Wu, S. Y. Yang and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2007, **46**, 7667–7670.

204 H. Suga, A. Funyu and A. Kakehi, *Org. Lett.*, 2007, **9**, 97–100.

205 M. P. Sibi, D. Rane, L. M. Stanley and T. Soeta, *Org. Lett.*, 2008, **10**, 2971–2974.

206 T. Jin, F. Yang and Y. Yamamoto, *Collect. Czech. Chem. Commun.*, 2009, **74**, 957–972.

207 F. Shi, R. Mancuso and R. C. Larock, *Tetrahedron Lett.*, 2009, **50**, 4067–4070.

208 Y. Yamashita and S. Kobayashi, *Chem. Lett.*, 2009, **38**, 678–679.

209 N. Shibata, S. Ogawa, T. Nishimine and E. Tokunaga, *Synthesis*, 2010, 3274–3281.

210 H. Suga, T. Arikawa, K. Itoh, Y. Okumura, A. Kakehi and M. Shiro, *Heterocycles*, 2010, **81**, 1669.

211 Y. Ukaji, K. Inomata, K. Tanaka and T. Kato, *Heterocycles*, 2010, **80**, 887.

212 K. Tanaka, T. Kato, S. Fujinami, Y. Ukaji and K. Inomata, *Chem. Lett.*, 2010, **39**, 1036–1038.

213 M. Yoshida, N. Sassa, T. Kato, S. Fujinami, T. Soeta, K. Inomata and Y. Ukaji, *Chemistry*, 2014, **20**, 2058–2064.

214 T. M. Tong, T. Soeta, T. Suga, K. Kawamoto, Y. Hayashi and Y. Ukaji, *J. Org. Chem.*, 2017, **82**, 1969–1976.

215 R. L. Atienza, H. S. Roth and K. A. Scheidt, *Chem. Sci.*, 2011, **2**, 1772–1776.

216 R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo and O. Kwon, *J. Am. Chem. Soc.*, 2011, **133**, 13337–13348.

217 Y. Li, Y. Meng, X. Meng and Z. Li, *Tetrahedron*, 2011, **67**, 4002–4008.

218 N. Luo, Z. Zheng and Z. Yu, *Org. Lett.*, 2011, **13**, 3384–3387.

219 H. Matsuyama, C. Seki, M. Hirama, T. Sato, S. Takeda, Y. Kohari, K. Ishigaki, M. Ohuchi, K. Yokoi, H. Nakano, K. Uwai, N. Takano and K. Umemura, *Heterocycles*, 2012, **85**, 1045.

220 M. Fan, D. Yang, H. Zhu, Y. Guo and J. Guo, *Synthesis*, 2013, 1325–1332.

221 J. Li, X. Lian, X. Liu, L. Lin and X. Feng, *Chemistry*, 2013, **19**, 5134–5140.

222 M. I. Pleshchev, M. A. Epishina, V. V. Kachala, V. V. Kuznetsov, A. S. Goloveshkin, I. S. Bushmarinov and N. N. Makhova, *Mendeleev Commun.*, 2013, **23**, 206–208.

223 M. I. Pleshchev, V. V. Kachala, A. S. Goloveshkin, I. S. Bushmarinov, V. V. Kuznetsov, D. V. Khakimov and N. N. Makhova, *Mendeleev Commun.*, 2013, **23**, 271–273.

224 D. Wang, H.-P. Deng, Y. Wei, Q. Xu and M. Shi, *Eur. J. Org. Chem.*, 2013, 401–406.

225 J. Liu, H. Liu, R. Na, G. Wang, Z. Li, H. Yu, M. Wang, J. Zhong and H. Guo, *Chem. Lett.*, 2012, **41**, 218–220.

226 S. S. Wong, M. G. Brant, C. Barr, A. G. Oliver and J. E. Wulff, *Beilstein J. Org. Chem.*, 2013, **9**, 1419–1425.

227 Z. Li, H. Yu, H. Liu, L. Zhang, H. Jiang, B. Wang and H. Guo, *Chemistry*, 2014, **20**, 1731–1736.

228 E. Pair, C. Berini, R. Noel, M. Sanselme, V. Levacher and J. F. Briere, *Chem. Commun.*, 2014, **50**, 10218–10221.

229 Y. Xu, W. Liu, X. Sun, D. Lu and L. Guo, *Synlett*, 2014, 1093–1096.

230 Q. Zhang, S. Guo, J. Yang, K. Yu, X. Feng, L. Lin and X. Liu, *Org. Lett.*, 2017, **19**, 5826–5829.

231 R. Y. Zhu, C. S. Wang, J. Zheng, F. Shi and S. J. Tu, *J. Org. Chem.*, 2014, **79**, 9305–9312.

232 Y. Dürüst, E. Sagirli and A. Sagirli, *Turk. J. Chem.*, 2015, **39**, 789–800.

233 Y. Dürüst, E. Sağırlı and A. Sağırlı, *Tetrahedron*, 2015, **71**, 9307–9312.

234 I. Damljanović, J. Jovanović and G. Bogdanović, *Synlett*, 2016, 664–668.

235 E. P. Kirar, U. Groselj, G. Mirri, F. Pozgan, G. Strle, B. Stefane, V. Jovanovski and J. Svete, *J. Org. Chem.*, 2016, **81**, 5988–5997.

236 M. Mondal, K. A. Wheeler and N. J. Kerrigan, *Org. Lett.*, 2016, **18**, 4108–4111.

237 M. Vishwanath, K. Sivamuthuraman and V. Kesavan, *Chem. Commun.*, 2016, **52**, 12314–12317.

238 S. E. Winterton and J. M. Ready, *Org. Lett.*, 2016, **18**, 2608–2611.

239 A. Y. Barkov, N. S. Zimnitskiy, I. B. Kutyashev, V. Y. Korotaev and V. Y. Sosnovskikh, *Tetrahedron Lett.*, 2017, **58**, 3989–3992.

240 S. A. Rizk, A. A. El-Sayed and M. M. Mounier, *J. Heterocycl. Chem.*, 2017, **54**, 3358–3371.

241 S. Yuan, Y. Luo, J. Peng, M. Miao, J. Xu and H. Ren, *Org. Lett.*, 2017, **19**, 6100–6103.

242 M. Wu, J. Jiang, Z. Zhu, Q. Wang and D. Kong, *Synthesis*, 2017, 139–145.

243 D. Bai, T. Xu, C. Ma, X. Zheng, B. Liu, F. Xie and X. Li, *ACS Catal.*, 2018, **8**, 4194–4200.

244 J. P. Jovanović, S. B. Novaković, G. A. Bogdanović, A. Minić, A. Pejović, J. Katanić, V. Mihailović, B. Nastasijević, D. Stevanović and I. Damljanović, *J. Organomet. Chem.*, 2018, **860**, 85–97.

245 J. Gong, Q. Wan and Q. Kang, *Org. Lett.*, 2018, **20**, 3354–3357.

246 J. Gujral, T. P. Reddy, B. Gorachand and D. B. Ramachary, *ChemistrySelect*, 2018, **3**, 7900–7905.

247 Y.-D. Kou, Z.-N. Zhao, X. Yang, S. J. Kalita, X.-J. Chen, Z.-Z. Xie, Y. Zhao and Y.-Y. Huang, *Asian J. Org. Chem.*, 2018, **7**, 1830–1834.

248 S. Shen, Y. Yang, J. Duan, Z. Jia and J. Liang, *Org. Biomol. Chem.*, 2018, **16**, 1068–1072.

249 L. Yang, Y. Lv, F. Wang and G. Zhong, *Org. Biomol. Chem.*, 2018, **16**, 4433–4438.

250 Z. Zhu, Q. Wang, D. Kong, T. Huang and M. Wu, *Synthesis*, 2018, 2601–2607.

251 N. Strasek, L. Lavrencic, A. Ostrek, D. Slapsak, U. Groselj, M. Klemencic, H. B. Žugelj, J. Wagger, M. Novinec and J. Svete, *Bioorg. Chem.*, 2019, **89**, 102982.

252 C. Volpe, S. Meninno, A. Capobianco, G. Vigliotta and A. Lattanzi, *Adv. Synth. Catal.*, 2019, **361**, 1018–1022.

253 Q.-Q. Yang, X. Yin, X.-L. He, W. Du and Y.-C. Chen, *ACS Catal.*, 2019, **9**, 1258–1263.

254 Y. A. Almehmadi and F. G. West, *Org. Lett.*, 2020, **22**, 6091–6095.

255 H. Hu, J. Xu, F. Wang, S. Dong, X. Liu and X. Feng, *Org. Lett.*, 2020, **22**, 93–97.

256 A. P. Molchanov, M. M. Efremova, M. A. Kryukova and M. A. Kuznetsov, *Beilstein J. Org. Chem.*, 2020, **16**, 2679–2686.

257 Z. Li, N. Kumagai and M. Shibasaki, *Chem. Pharm. Bull.*, 2020, **68**, 552–554.

258 Y. Xu, M. Shen, X. Zhang and X. Fan, *Org. Lett.*, 2020, **22**, 4697–4702.

259 J. Zhou, L. Zhang, J. Chen, J. Chen, C. Yin and C. Yu, *Tetrahedron Lett.*, 2020, **61**, 152350.

260 M.-C. Wu, P.-J. Xia, Y.-Z. Hu, Z.-P. Ye, K. Chen, H.-Y. Xiang and H. Yang, *Tetrahedron*, 2021, **83**, 131992.

261 T. Kozlecki, C. Samyn, R. W. Alder and P. G. Green, *J. Chem. Soc., Perkin Trans. 2*, 2001, 243–246, DOI: 10.1039/b000828l.

262 H. Z. Shams, M. H. Helal and F. A. Mohamed, *Pigm. Resin Technol.*, 2001, **30**, 99–108.

263 H. Z. Shams, Y. A. Youssef, F. A. Mohamed, M. M. El-Zawahry, M. H. Helal and E. A. El-Kharadly, *Pigm. Resin Technol.*, 2009, **38**, 372–379.

264 D.-Y. Zhou, T. Koike, S. Suetsugu, K. Onitsuka and S. Takahashi, *Inorg. Chim. Acta*, 2004, **357**, 3057–3063.

265 M. B. Donald, W. E. Conrad, J. S. Oakdale, J. D. Butler, M. J. Haddadin and M. J. Kurth, *Org. Lett.*, 2010, **12**, 2524–2527.

266 W. E. Conrad, R. Fukazawa, M. J. Haddadin and M. J. Kurth, *Org. Lett.*, 2011, **13**, 3138–3141.

267 Z. Wang, B. Yu, Y. Cui, X. Sun and W. Bao, *Chin. J. Chem.*, 2011, **29**, 2769–2774.

268 J. Németh, Á. Kiss and Z. Hell, *Tetrahedron Lett.*, 2013, **54**, 6094–6096.

269 H. Lee, D. Kang, S. H. Han, R. Chun, A. K. Pandey, N. K. Mishra, S. Hong and I. S. Kim, *Angew. Chem., Int. Ed.*, 2019, **58**, 9470–9474.

270 Z. Yang, Z. Song, L. Jie, L. Wang and X. Cui, *Chem. Commun.*, 2019, **55**, 6094–6097.

271 C. K. Mahesha, S. K. Mandal and R. Sakhuja, *Asian J. Org. Chem.*, 2020, **9**, 1199–1204.

272 L. Zhang, J. Zhao, Y. Jiang, X. Zhang and X. Fan, *Org. Chem. Front.*, 2021, **8**, 3734–3739.

273 M. Wu, H. Gao, H. Xu, W. Yi and Z. Zhou, *Chin. Chem. Lett.*, 2022, **33**, 842–846.

274 K. Gogoi, B. R. Bora, G. Borah, B. Sarma and S. Gogoi, *Chem. Commun.*, 2021, **57**, 1388–1391.

275 A. C. Tomé, J. A. S. Cavaleiro, F. M. J. Domingues and R. J. Cremlyn, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 2617–2634.

276 H. Zachová, S. Man, M. Nečas and M. Potáček, *Eur. J. Org. Chem.*, 2005, 2548–2557.

277 B. B. Snider, J. F. Grabowski, R. W. Alder, B. M. Foxman and L. Yang, *Can. J. Chem.*, 2006, **84**, 1242–1249.

278 E. F. Kirolos and A. S. Yanni, *Int. J. Org. Chem.*, 2020, **10**, 104–110.

279 F. Al'-Assar, K. N. Zelenin, E. E. Lesiovskaya, I. P. Bezhan and B. A. Chakchir, *Pharm. Chem. J.*, 2002, **36**, 598–603.

280 H. R. Shaterian and F. Rigi, *Starch/Staerke*, 2011, **63**, 340–346.

281 A. Hasaninejed, M. R. Kazerooni and A. Zare, *Catal. Today*, 2012, **196**, 148–155.

282 A. Mulik, D. Chandam, P. Patil, D. Patil, S. Jagdale, S. Sankpal and M. Deshmukh, *J. Heterocycl. Chem.*, 2015, **52**, 931–937.

283 A. Mouradzadegun, M. A. Mostafavi and M. R. Ganjali, *React. Kinet., Mech. Catal.*, 2018, **124**, 741–755.

284 M. Mousapour, F. Shirini and M. Abedini, *Polycyclic Aromat. Compd.*, 2019, **41**, 419–426.

285 S. Z. D. Heirati, F. Shirini and A. F. Shojaei, *J. Iran. Chem. Soc.*, 2020, **17**, 3217–3225.

286 F. Mohamadpour, *Polycyclic Aromat. Compd.*, 2020, 1–12, DOI: 10.1080/10406638.2020.1768412.

287 N. M. Shah, M. P. Patel and R. G. Patel, *J. Heterocycl. Chem.*, 2012, **49**, 1310–1316.

288 M. Elmi-Mehr, A. Davoodnia and M. Pordel, *Russ. J. Gen. Chem.*, 2019, **88**, 2595–2600.

289 M. Shekouhy, A. M. Sarvestani, S. Khajeh and A. Khalafi-Nezhad, *RSC Adv.*, 2015, **5**, 63705–63710.

290 O. S. Zaky, M. A. Selim, M. M. Ebied and K. U. Sadek, *J. Heterocycl. Chem.*, 2019, **56**, 2796–2803.

291 M. R. Nabid, S. J. Rezaei, R. Ghahremanzadeh and A. Bazgir, *Ultrason. Sonochem.*, 2010, **17**, 159–161.

292 M. V. Reddy, G. C. S. Reddy and Y. T. Jeong, *Tetrahedron*, 2012, **68**, 6820–6828.

293 S. Rostamnia, H. Xin, X. Liu and K. Lamei, *J. Mol. Catal. A: Chem.*, 2013, **374–375**, 85–93.

294 H. Kefayati, A. Delafrooz and S. Homayoon, *Russ. J. Gen. Chem.*, 2016, **86**, 1735–1740.

295 N. Ghareb, H. A. Elshihawy, M. M. Abdel-Daim and M. A. Helal, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 2377–2383.

296 P. B. Hiremath and K. Kamanna, *Polycyclic Aromat. Compd.*, 2020, 1–17, DOI: 10.1080/10406638.2020.1830129.

297 H. R. Shaterian, M. Ghashang and M. Feyzi, *Appl. Catal., A*, 2008, **345**, 128–133.

298 G. Sabitha, C. Srinivas, A. Raghavendar and J. S. Yadav, *Helv. Chim. Acta*, 2010, **93**, 1375–1380.

299 S. Rostamnia and E. Doustkhah, *Tetrahedron Lett.*, 2014, **55**, 2508–2512.

300 M. V. Reddy, P. C. R. Kumar, G. C. S. Reddy and C. S. Reddy, *C. R. Chim.*, 2014, **17**, 1250–1256.

301 A. A. Amiri, S. Javanshir, Z. Dolatkhah and M. G. Dekamin, *New J. Chem.*, 2015, **39**, 9665–9671.

302 E. Doustkhah, A. Baghban, M. H. N. Assadi, R. Luque and S. Rostamnia, *Catal. Lett.*, 2019, **149**, 591–600.

303 A. M. Jadhav, S. G. Balwe and Y. T. Jeong, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2019, **195**, 201–210.

304 H. R. Shaterian and F. Rigi, *Res. Chem. Intermed.*, 2013, **40**, 1989–1995.

305 H. R. Shaterian, N. Fahimi and K. Azizi, *Res. Chem. Intermed.*, 2013, **40**, 1879–1898.
306 K. Pradhan, S. Paul and A. R. Das, *Monatsh. Chem.*, 2014, **145**, 1343–1352.
307 O. Goli-Jolodar, F. Shirini and M. Seddighi, *RSC Adv.*, 2016, **6**, 44794–44806.
308 M. Abbasi, S. M. R. Nazifi, Z. S. Nazifi and A. R. Massah, *J. Chem. Sci.*, 2017, **129**, 1257–1266.
309 R. Tayebee, M. M. Amini, S. Pouyamanesh and A. Aliakbari, *Dalton Trans.*, 2015, **44**, 5888–5897.
310 M. Nikoorazm, A. Ghorbani-Choghamaranai, M. Khanmoradi and P. Moradi, *J. Porous Mater.*, 2018, **25**, 1831–1842.
311 N. Kerru, L. Gummidi, S. V. H. S. Bhaskaruni, S. N. Maddila and S. B. Jonnalagadda, *Res. Chem. Intermed.*, 2020, **46**, 3067–3083.
312 H. N. Roy, M. Rana, A. Z. A. Munsur, K.-I. Lee and A. K. Sarker, *Synth. Commun.*, 2016, **46**, 1370–1376.
313 E. Lamera, S. Bouacida, H. Merazig, A. Chibani, M. Le Borgne, Z. Bouaziz and A. Bouraiou, *Z. Naturforsch., B: J. Chem. Sci.*, 2017, **72**, 361–368.
314 C. S. Maheswari, V. Tamilselvi, R. Ramesh and A. Lalitha, *Org. Prep. Proced. Int.*, 2020, **52**, 22–36.
315 F. Mohamadpour, *Org. Prep. Proced. Int.*, 2020, **52**, 64–68.
316 G. Shukla, R. K. Verma, G. K. Verma and M. S. Singh, *Tetrahedron Lett.*, 2011, **52**, 7195–7198.
317 M. A. Zolfigol, M. Mokhlesi and S. Farahmand, *J. Iran. Chem. Soc.*, 2012, **10**, 577–581.
318 A. B. Atar, S. D. Lee, B. G. Cho, D. W. Cho and Y. T. Jeong, *Res. Chem. Intermed.*, 2015, **42**, 1707–1728.
319 S. J. Saghanezhad and S. Sayyahi, *Res. Chem. Intermed.*, 2016, **43**, 2491–2500.
320 S. Karhale and V. Helavi, *SN Appl. Sci.*, 2020, **2**, 1227.
321 X. Shi, J. Li, W. Zhong and J. Li, *J. Chem. Res.*, 2012, **36**, 17–20.
322 Y. Wan, C. Wang, X.-X. Zhang, J. Shi, S.-Y. Huang, G.-X. Liu, L.-F. Chen, L.-L. Zhao, H.-Y. Wang and H. Wu, *J. Heterocycl. Chem.*, 2014, **51**, E77–E83.
323 X. Shi, M. Ding, C. Li, W. Wang and H. Guo, *J. Heterocycl. Chem.*, 2018, **55**, 440–446.
324 O. Goli-Jolodar, F. Shirini and M. Seddighi, *J. Nanosci. Nanotechnol.*, 2018, **18**, 591–603.
325 P. Jahanshahi and M. Mamaghani, *New J. Chem.*, 2019, **43**, 8266–8278.
326 F. Mohamadpour, M. T. Maghsoodlou, R. Heydari and M. Lashkari, *J. Iran. Chem. Soc.*, 2016, **13**, 1549–1560.
327 A. V. Chate, P. K. Bhadke, M. A. Khande, J. N. Sangshetti and C. H. Gill, *Chin. Chem. Lett.*, 2017, **28**, 1577–1582.
328 Y. A. Tayade and D. S. Dalal, *Catal. Lett.*, 2017, **147**, 1411–1421.
329 H. Kefayati, S. H. Amlashi, R. Kazemi-Rad and A. Delafrooz, *C. R. Chim.*, 2014, **17**, 894–898.
330 S.-H. Song, J. Zhong, Y.-H. He and Z. Guan, *Tetrahedron Lett.*, 2012, **53**, 7075–7077.
331 Y. D. Reddy, B. S. Narayana, C. V. Ramana Reddy and P. K. Dubey, *Synth. Commun.*, 2014, **44**, 3037–3046.
332 M. Abdesheikhi and Z. Karimi-Jaberi, *J. Chem. Res.*, 2015, **39**, 482–483.
333 A. Choudhury, S. Ali and A. T. Khan, *J. Korean Chem. Soc.*, 2015, **59**, 280–283.
334 L. Jalili-Baleh, H. Nadri, A. Moradi, S. N. A. Bukhari, M. Shakibaie, M. Jafari, M. Golshani, F. H. Moghadam, L. Firoozpour, A. Asadipour, S. Emami, M. Khoobi and A. Foroumadi, *Eur. J. Med. Chem.*, 2017, **139**, 280–289.
335 K. Turhan and Z. Turgut, *Russ. J. Org. Chem.*, 2019, **55**, 250–253.
336 P. M. Pisal, V. T. Kamble, R. Varala and P. B. Gujarathi, *Org. Commun.*, 2020, **13**, 194–201.
337 D. Pavithra and K. R. Ethiraj, *Polycyclic Aromat. Compd.*, 2020, 1–14, DOI: 10.1080/10406638.2020.1732430.
338 P. Taslimi, K. Turhan, F. Türkan, H. S. Karaman, Z. Turgut and I. Gulcin, *Bioorg. Chem.*, 2020, **97**, 103647.
339 P. Taslimi, F. Türkan, K. Turhan, H. S. Karaman, Z. Turgut and İ. Gulcin, *J. Heterocycl. Chem.*, 2020, **57**, 3116–3125.
340 K. Mazaahir, C. Ritika and J. Anwar, *Chin. Sci. Bull.*, 2012, **57**, 2273–2279.
341 M. Kidwai and R. Chauhan, *J. Heterocycl. Chem.*, 2014, **51**, 1689–1696.
342 B. Afzalian, J. T. Mague, M. Mohamadi, S. Y. Ebrahimipour, B. P. Amiri and E. T. Kermani, *Chin. J. Catal.*, 2015, **36**, 1101–1108.
343 F. K. Nejad, M. Khosravan, S. Y. Ebrahimipour and F. Bisceglie, *Appl. Organomet. Chem.*, 2018, **32**, e3907.
344 S. S. Biroon, N. Shajari and H. Yahyaei, *J. Heterocycl. Chem.*, 2020, **57**, 2433–2445.
345 H.-J. Wang, X.-N. Zhang and Z.-H. Zhang, *Monatsh. Chem.*, 2010, **141**, 425–430.
346 E. Mosaddegh and A. Hassankhani, *Tetrahedron Lett.*, 2011, **52**, 488–490.
347 D. Azarifar, R. Nejat-Yami, Z. Akrami, F. Sameri and S. Samadi, *Lett. Org. Chem.*, 2012, **9**, 128–132.
348 H. R. Tavakoli, S. M. Moosavi and A. Bazgir, *J. Korean Chem. Soc.*, 2013, **57**, 472–475.
349 M. V. Reddy and Y. T. Jeong, *Tetrahedron Lett.*, 2013, **54**, 3546–3549.
350 A. M. Jadhav, S. G. Balwe, J. S. Kim, K. T. Lim and Y. T. Jeong, *Tetrahedron Lett.*, 2019, **60**, 560–565.
351 F. Mohamadpour, M. T. Maghsoodlou, R. Heydari and M. Lashkari, *Res. Chem. Intermed.*, 2016, **42**, 7841–7853.
352 M. Sayyafi, M. Seyyedhamzeh, H. R. Khavasi and A. Bazgir, *Tetrahedron*, 2008, **64**, 2375–2378.
353 X. Wang, W.-W. Ma, L.-Q. Wu and F.-L. Yan, *J. Chin. Chem. Soc.*, 2010, **57**, 1341–1345.
354 R. Ghorbani-Vaghei, R. Karimi-Nami, Z. Toghraei-Semiromi, M. Amiri and M. Ghavidel, *Tetrahedron*, 2011, **67**, 1930–1937.
355 R. Ghorbani-Vaghei, S. Noori, Z. Toghraei-Semiromi and Z. Salimi, *RSC Adv.*, 2014, **4**, 47925–47928.
356 M. Kidwai, A. Jahan, R. Chauhan and N. K. Mishra, *Tetrahedron Lett.*, 2012, **53**, 1728–1731.

357 X.-C. Jia, J. Li, Y. Ding, B. Zhang, N. Wang and Y.-H. Wang, *J. Chem.*, 2013, **2013**, 1–5.

358 R. Kiasat, A. Mouradezadegun and J. Saghanezhad, *J. Serb. Chem. Soc.*, 2013, **78**, 469–476.

359 A. Varghese, A. Nizam, R. Kulkarni and L. George, *Eur. J. Chem.*, 2013, **4**, 132–137.

360 B. Maleki, S. S. Ashrafi and R. Tayebee, *RSC Adv.*, 2014, **4**, 41521–41528.

361 M. Soheilizad, M. Adib and S. Sajjadifar, *Monatsh. Chem.*, 2014, **145**, 1353–1356.

362 A. Vafaee, A. Davoodnia, M. Pordel and M. Bozorgmehr, *Orient. J. Chem.*, 2015, **31**, 2153–2158.

363 H. R. M. Rashdan, S. M. Gomha, M. S. El-Gendey, M. A. El-Hashash and A. M. M. Soliman, *Green Chem. Lett. Rev.*, 2018, **11**, 264–274.

364 D. Habibi, S. Shojaei and S. Heydari, *Russ. J. Org. Chem.*, 2021, **57**, 85–90.

365 A. Bazgir, R. Ghahremanzadeh and G. Shakibaei, *Synlett*, 2008, 1129–1132.

366 J. M. Khurana and D. Magoo, *Tetrahedron Lett.*, 2009, **50**, 7300–7303.

367 R. Fazaeli, H. Aliyan and N. Fazaeli, *Open Catal. J.*, 2010, **3**, 14–18.

368 D. S. Raghuvanshi and K. N. Singh, *Tetrahedron Lett.*, 2011, **52**, 5702–5705.

369 F. Yang, H. J. Zang, Q. K. Wang, B. W. Cheng, Y. L. Ren and X. L. Xu, *Adv. Mater. Res.*, 2011, **332–334**, 1884–1887.

370 H. R. Shaterian and M. Aghakhanizadeh, *C. R. Chim.*, 2012, **15**, 1060–1064.

371 H. R. Shaterian and M. Mohammadnia, *J. Mol. Liq.*, 2012, **173**, 55–61.

372 S. Song, X. Deng, Z. Guan and Y. He, *Z. Naturforsch., B: J. Chem. Sci.*, 2012, **67**, 717–724.

373 D. Habibi and A. Shamsian, *Res. Chem. Intermed.*, 2014, **41**, 6245–6255.

374 M. Abedini, F. Shirini and J. M.-A. Omran, *J. Mol. Liq.*, 2015, **212**, 405–412.

375 F. Shirini, M. S. N. Langarudi and O. Goli-Jolodar, *Dyes Pigm.*, 2015, **123**, 186–195.

376 R. Tayebee, M. Jomei, B. Maleki, M. K. Razi, H. Veisi and M. Bakherad, *J. Mol. Liq.*, 2015, **206**, 119–128.

377 B. Godajddr, M. Etamad and S. Soliemani, *Orient. J. Chem.*, 2015, **31**, 1231–1236.

378 B. Pouramiri and E. T. Kermani, *Tetrahedron Lett.*, 2016, **57**, 1006–1010.

379 B. Pouramiri and E. T. Kermani, *J. Iran. Chem. Soc.*, 2016, **13**, 1011–1017.

380 A. Zare and F. Masihpour, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2016, **191**, 1160–1165.

381 O. Goli-Jolodar and F. Shirini, *Theor. Exp. Chem.*, 2017, **52**, 349–357.

382 G. Jeevan Raghavendra and V. Siddaiah, *Russ. J. Gen. Chem.*, 2018, **88**, 1892–1898.

383 M. A. Shaikh, M. Farooqui and S. Abed, *Res. Chem. Intermed.*, 2018, **44**, 5483–5500.

384 N. Amirmahani, N. O. Mahmoodi, M. Malakootian and A. Pardakhty, *Mol. Divers.*, 2022, **26**, 15–25.

385 S. Fallah-Ghasemi Gildeh, M. Mehrdad, H. Roohi, K. Ghauri, S. Fallah-Ghasemi Gildeh and K. Rad-Moghadam, *New J. Chem.*, 2020, **44**, 16594–16601.

386 N. Safari, F. Shirini and H. Tajik, *J. Mol. Struct.*, 2020, **1201**, 127143.

387 F. Arian, M. Keshavarz, H. Sanaeishoar and N. Hasanzadeh, *J. Mol. Struct.*, 2021, **1229**, 129599.

388 B. Mombani Godajdar, A. R. Kiasat and M. M. Hashemi, *Heterocycles*, 2013, **87**, 559.

389 A. Vafaee, A. Davoodnia, A. Nakhaei, S. Yadegarian and M. Nejatianfar, *Russ. J. Gen. Chem.*, 2021, **91**, 273–278.

390 A. G. Mulik, D. R. Chandam, D. R. Patil, P. P. Patil, G. N. Mulik, S. T. Salunkhe and M. B. Deshmukh, *Res. Chem. Intermed.*, 2015, **41**, 10085–10096.

391 W. Wang, L. Cong-Hao, Y. Yi, L. Xiao-Jun and G. Hong-Yun, *J. Chem. Res.*, 2016, **40**, 354–357.

392 L. Wang, M. Zhou, Q. Chen and M.-Y. He, *J. Chem. Res.*, 2019, **37**, 598–600.

393 H. Wu, J. J. Yin, W. G. Wamer, M. Zeng and Y. M. Lo, *J. Food Drug Anal.*, 2014, **22**, 86–94.

394 A. Azarifar, R. Nejat-Yami and D. Azarifar, *J. Iran. Chem. Soc.*, 2012, **10**, 297–306.

395 A. R. Kiasat, S. Noorizadeh, M. Ghahremani and S. J. Saghanejad, *J. Mol. Struct.*, 2013, **1036**, 216–225.

396 M. Saha, S. Phukan, R. Jamatia, S. Mitra and A. K. Pal, *RSC Adv.*, 2013, **3**, 1714–1721.

397 J. Safaei-Ghomi, H. Shahbazi-Alavi, A. Ziarati, R. Teymuri and M. R. Saberi, *Chin. Chem. Lett.*, 2014, **25**, 401–405.

398 E. Mosaddegh and A. Hassankhani, *Catal. Commun.*, 2015, **71**, 65–69.

399 J. Albadi, M. Jalali and A. Momeni, *Res. Chem. Intermed.*, 2017, **44**, 2395–2404.

400 B. Maleki, R. Nejat, H. Alinezhad, S. M. Mousavi, B. Mahdavi and M. Delavari, *Org. Prep. Proced. Int.*, 2020, **52**, 328–339.

401 H. R. Shaterian and M. Mohammadnia, *Res. Chem. Intermed.*, 2012, **40**, 371–383.

402 B. Atashkar, A. Rostami, H. Gholami and B. Tahmasbi, *Res. Chem. Intermed.*, 2013, **41**, 3675–3681.

403 A. R. Kiasat and J. Davarpanah, *J. Mol. Catal. A: Chem.*, 2013, **373**, 46–54.

404 A. Rostami, B. Tahmasbi and A. Yari, *Bull. Korean Chem. Soc.*, 2013, **34**, 1521–1524.

405 B. Mirhosseini-Eshkevari, M. A. Ghasemzadeh and J. Safaei-Ghomi, *Res. Chem. Intermed.*, 2014, **41**, 7703–7714.

406 E. Doustkhah and S. Rostamnia, *J. Colloid Interface Sci.*, 2016, **478**, 280–287.

407 M. Esmaeilpour, J. Javidi, F. N. Dodeji and S. Zahmatkesh, *Res. Chem. Intermed.*, 2016, **47**, 2629–2652.

408 A. Hashemzadeh, M. M. Amini, R. Tayebee, A. Sadeghian, L. J. Durndell, M. A. Isaacs, A. Osatiashtiani, C. M. A. Parlett and A. F. Lee, *Mol. Catal.*, 2017, **440**, 96–106.

409 F. Kamali and F. Shirini, *New J. Chem.*, 2017, **41**, 11778–11791.

410 L. Jiang and Z. Druzhinin, *RSC Adv.*, 2019, **9**, 15061–15072.

411 M. Khaleghi Abbasabadi and D. Azarifar, *Appl. Organomet. Chem.*, 2020, **34**, e5872.

412 M. M. F. Chegeni, A. Bamoniri and B. B. F. Mirjalili, *Polycyclic Aromat. Compd.*, 2020, 1–9, DOI: **10.1080/10406638.2020.1735457**.

413 M. M. F. Chegeni, A. Bamoniri and A. A. Taherpour, *J. Heterocycl. Chem.*, 2020, **57**, 2801–2814.

414 M. Nesarvand, D. Azarifar and H. Ebrahimiasl, *Res. Chem. Intermed.*, 2021, **47**, 3629–3644.

415 S. M. Nezhad, S. A. Pourmousavi and E. N. Zare, *Curr. Org. Synth.*, 2022, **19**, 246–266.

416 B. Maleki, S. B. N. Chalaki, S. S. Ashrafi, E. R. Seresht, F. Moeinpour, A. Khojastehnezhad and R. Tayebee, *Appl. Organomet. Chem.*, 2015, **29**, 290–295.

417 D. Azarifar, O. Badalkhani, Y. Abbasi and M. Hasanabadi, *J. Iran. Chem. Soc.*, 2016, **14**, 403–418.

418 Z. Zaheer, F. A. Khan, J. N. Sangshetti, R. H. Patil and K. S. Lohar, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1696–1703.

419 P. Arora and J. K. Rajput, *Appl. Organomet. Chem.*, 2017, **32**, e4001.

420 M. Hamidinasab and A. Mobinikhaledi, *J. Iran. Chem. Soc.*, 2019, **16**, 1255–1263.

421 X.-N. Zhao, G.-F. Hu, M. Tang, T.-T. Shi, X.-L. Guo, T.-T. Li and Z.-H. Zhang, *RSC Adv.*, 2014, **4**, 51089–51097.

422 B. Dam, M. Saha, R. Jamatia and A. K. Pal, *RSC Adv.*, 2016, **6**, 54768–54776.

423 G. M. Ziarani, N. H. Mohtasham, N. Lashgari and A. Badiei, *Res. Chem. Intermed.*, 2014, **41**, 7581–7591.

424 G. M. Ziarani, N. H. Mohtasham, A. Badiei and N. Lashgari, *J. Chil. Chem. Soc.*, 2014, **61**, 990–994.

425 G. M. Ziarani, A. Badiei, N. H. Mohtasham and N. Lashgari, *J. Chil. Chem. Soc.*, 2014, **59**, 2271–2274.

426 A. Bashti, A. R. Kiasat and B. Mokhtari, *RSC Adv.*, 2015, **5**, 25816–25823.

427 J. Davarpanah and A. R. Kiasat, *RSC Adv.*, 2015, **5**, 7986–7993.

428 H. Veisi, A. Sedrpoushan, A. R. Faraji, M. Heydari, S. Hemmati and B. Fatahi, *RSC Adv.*, 2015, **5**, 68523–68530.

429 M. Esmaeilpour, J. Javidi and F. Dehghani, *J. Iran. Chem. Soc.*, 2015, **13**, 695–714.

430 M. Ghahremani, J. Davarpanah, P. Rezaee and G. Davoodi, *Res. Chem. Intermed.*, 2020, **46**, 2683–2704.

431 S. R. Shafe-Mehrabadi, B. Sadeghi and A. Hassanabadi, *Polycyclic Aromat. Compd.*, 2020, 1–8, DOI: **10.1080/10406638.2020.1747094**.

432 S. Safaei, I. Mohammadpoor-Baltork, A. R. Khosropour, M. Moghadam, S. Tangestaninejad and V. Mirkhani, *Catal. Sci. Technol.*, 2013, **3**, 2717.

433 J. Davarpanah, P. Rezaee and S. Elahi, *Res. Chem. Intermed.*, 2015, **41**, 9903–9915.

434 F. H. Sabour, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, S. Tangestaninejad, M. Moghadam and V. Mirkhani, *J. Iran. Chem. Soc.*, 2017, **15**, 671–683.

435 A. Khalili, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, S. Tangestaninejad, V. Mirkhani and M. Moghadam, *J. Mol. Liq.*, 2018, **253**, 1–10.

436 N. Hosseininasab, A. Davoodnia, F. Rostami-Charati and A. Khojastehnezhad, *Russ. J. Gen. Chem.*, 2017, **87**, 2436–2443.

437 R. Ghorbani-Vaghei, J. Mahmoodi and Y. Maghbooli, *Appl. Organomet. Chem.*, 2017, **31**, e3717.

438 M. Kour, M. Bhardwaj, H. Sharma, S. Paul and J. H. Clark, *New J. Chem.*, 2017, **41**, 5521–5532.

439 R. Tayebee, M. F. Abdizadeh, B. Maleki and E. Shahri, *J. Mol. Liq.*, 2017, **241**, 447–455.

440 M. Kalhor, Z. Orouji and M. Khalaj, *Microporous Mesoporous Mater.*, 2022, **329**, 111498.

441 G. Shanthi and P. T. Perumal, *J. Chem. Sci.*, 2010, **122**, 415–421.

442 X.-N. Zhang, Y.-X. Li and Z.-H. Zhang, *Tetrahedron*, 2011, **67**, 7426–7430.

443 S. J. T. Rezaei, Y. Bide and M. R. Nabid, *Tetrahedron Lett.*, 2012, **53**, 5123–5126.

444 J. Wang, X. Bai, C. Xu, Y. Wang, W. Lin, Y. Zou and D. Shi, *Molecules*, 2012, **17**, 8674–8686.

445 H. Chen and D.-Q. Shi, *J. Heterocycl. Chem.*, 2013, **50**, 56–60.

446 S. M. Sadeghzadeh and M. A. Nasseri, *Catal. Today*, 2013, **217**, 80–85.

447 L. Torkian, M. Dabiri, P. Salehi and M. Bararjanian, *Helv. Chim. Acta*, 2011, **94**, 1416–1425.

448 P. Salehi, D. I. MaGee, M. Dabiri, L. Torkian and J. Donahue, *Mol. Divers.*, 2012, **16**, 231–240.

449 M. Dabiri, D. MaGee, P. Salehi, L. Torkian, M. Fakharian and J. Donahue, *Synth. Commun.*, 2014, **44**, 2037–2044.

450 S. Keshipour, S. Shojaei and A. Shaabani, *Tetrahedron*, 2012, **68**, 6141–6145.

451 M. Yoosefian, H. Raissi, E. Davamdar, A. A. Esmaeili and M. Azaroon, *Chin. J. Chem.*, 2012, **30**, 779–784.

452 Y.-L. Xu, J.-Y. Fu, C.-H. Liu and T. Ding, *RSC Adv.*, 2017, **7**, 38733–38736.

453 E. Lamera, S. Bouacida, M. Le Borgne, Z. Bouaziz and A. Bouraiou, *Tetrahedron Lett.*, 2017, **58**, 1305–1307.

454 N. Berber, M. Arslan, E. Yavuz, C. Bilen and N. Gencer, *J. Chem.*, 2013, **2013**, 1–8.

455 N. Berber, M. Arslan, Ç. Bilen, Z. Sackes, N. Gençer and O. Arslan, *Russ. J. Bioorg. Chem.*, 2015, **41**, 414–420.

456 A. Yazdani-Elah-Abadi, R. Mohebat and M. Lashkari, *Polycyclic Aromat. Compd.*, 2017, **40**, 268–279.

457 L. Nagarapu, R. Bantu and H. B. Mereyala, *J. Heterocycl. Chem.*, 2009, **46**, 728–731.

458 X. Wang, G. Lu, W. Ma and L. Wu, *E-J. Chem.*, 2011, **8**, 1000–1005.

459 C. B. Sangani, J. A. Makwana, Y.-T. Duan, N. J. Thumar, M.-Y. Zhao, Y. S. Patel and H.-L. Zhu, *Res. Chem. Intermed.*, 2015, **42**, 2101–2117.

460 A. S. Amarasekara and S. Chandrasekara, *Org. Lett.*, 2002, **4**, 773–775.

461 Y. Liu, W. Zhen, W. Dai, F. Wang and X. Li, *Org. Lett.*, 2013, **15**, 874–877.

462 C. Yang, F. Song, J. Chen and Y. Huang, *Adv. Synth. Catal.*, 2017, **359**, 3496–3502.

463 M. Gholamhosseyni and E. Kianmehr, *Org. Biomol. Chem.*, 2018, **16**, 5973–5978.

464 P. Li, X. Xu, J. Chen, H. Yao and A. Lin, *Org. Chem. Front.*, 2018, **5**, 1777–1781.

465 C. K. Mahesha, D. S. Agarwal, P. Karishma, D. Markad, S. K. Mandal and R. Sakhuja, *Org. Biomol. Chem.*, 2018, **16**, 8585–8595.

466 L. Su, Z. Yu, P. Ren, Z. Luo, W. Hou and H. Xu, *Org. Biomol. Chem.*, 2018, **16**, 7236–7244.

467 X. Zhang, R. Bai, H. Xiong, H. Xu and W. Hou, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 126916.

468 X. Wu and H. Ji, *J. Org. Chem.*, 2018, **83**, 4650–4656.

469 K. Kim, S. H. Han, D. Jeoung, P. Ghosh, S. Kim, S. J. Kim, J. M. Ku, N. K. Mishra and I. S. Kim, *J. Org. Chem.*, 2020, **85**, 2520–2531.

470 K. Konishi, M. Yasui, H. Okuhira, N. Takeda and M. Ueda, *Org. Lett.*, 2020, **22**, 6852–6857.

471 S. Hu, X. Han, X. Xie, F. Fang, Y. Wang, A. Saidahmatov, H. Liu and J. Wang, *Adv. Synth. Catal.*, 2021, **363**, 3311–3317.

472 H. Li, J. Zhao, S. Yi, K. Hu and P. Feng, *Organometallics*, 2021, **40**, 880–889.

473 K. A. Abouzid and H. S. El-Abhar, *Arch. Pharmacal Res.*, 2003, **26**, 1–8.

474 J. Gardiner and A. D. Abell, *Tetrahedron Lett.*, 2003, **44**, 4227–4230.

475 B. Liu, J. D. Brandt and K. D. Moeller, *Tetrahedron*, 2003, **59**, 8515–8523.

476 K. Wang, W. Wang, Q. Wang and R. Huang, *Lett. Org. Chem.*, 2008, **5**, 383–390.

477 A. P. Molchanov, D. I. Sipkin, Y. B. Koptelov and R. R. Kostikov, *Russ. J. Org. Chem.*, 2005, **41**, 567–574.

478 Z. Yang, Y. Zhou, H. Li, J. Lei, P. Bing, B. He and Y. Li, *Asian J. Org. Chem.*, 2021, **11**, e202100656.

479 R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2006, **128**, 6330–6331.

480 A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 5334–5335.

481 N. D. Shapiro, Y. Shi and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 11654–11655.

482 Y. Qian, P. J. Zavalij, W. Hu and M. P. Doyle, *Org. Lett.*, 2013, **15**, 1564–1567.

483 X. Xu, Y. Qian, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 1244–1247.

484 X. Xu, X. Xu, P. Y. Zavalij and M. P. Doyle, *Chem. Commun.*, 2013, **49**, 2762–2764.

485 L. Liang and Y. Huang, *Org. Lett.*, 2016, **18**, 2604–2607.

486 A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova and I. V. Trushkov, *Angew. Chem., Int. Ed.*, 2018, **57**, 10338–10342.

487 R. Dhakal, M. Ivancic and M. Brewer, *J. Org. Chem.*, 2018, **83**, 6202–6209.

488 R. Sonawane, V. Sikervar, R. Mandadapu, A. S. Dehade, S. A. Shete and M. Montgomery, *Synthesis*, 2021, 2865–2873.

489 A. Lebrene, T. Martzel, L. Gouriou, M. Sanselme, V. Levacher, S. Oudeyer, C. Afonso, C. Loutelier-Bourhis and J. F. Briere, *J. Org. Chem.*, 2021, **86**, 8600–8609.

490 N. Haider and W. Holzer, *Product Class 11: Pyridazino[1,2-a]pyridazines*, 2004, DOI: 10.1055/sos-SD-016-00455.

491 P. Cai, E. Zhang, Y. Wu, T. Fang, Q. Li, C. Yang, J. Wang and Y. Shang, *ACS Omega*, 2018, **3**, 14575–14584.

492 S. Kim, S. B. Choi, J. Y. Kang, W. An, S. H. Lee, H. Oh, P. Ghosh, N. K. Mishra and I. S. Kim, *Asian J. Org. Chem.*, 2021, **10**, 3005–3014.

493 V. V. Ganzha, A. D. Kotov, T. V. Kesareva and V. Y. Orlov, *Chem. Heterocycl. Compd.*, 2006, **42**, 963–964.

494 D. Habibi, N. Mahmoudi and O. Marvi, *Synth. Commun.*, 2007, **37**, 3165–3171.

495 P. Karishma, C. K. Mahesha, D. S. Agarwal, S. K. Mandal and R. Sakhuja, *J. Org. Chem.*, 2018, **83**, 11661–11673.

496 P. Karishma, D. S. Agarwal, B. Laha, S. K. Mandal and R. Sakhuja, *Chem. – Asian J.*, 2019, **14**, 4274–4288.