Sequential and Direct Multicomponent Reaction (MCR)-based Dearomatization Strategies

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Abstract: Dearomatization strategies in a multicomponent fashion have often resulted in complex heterocyclic frameworks that have always craved the imagination of chemists due to their natural product like structure. The combination of these two processes is able to easily reach extended molecular complexity and diversity from simple starting materials with a high atom-economy. Henceforth, the field has attracted extensive interest owing to its potential significance in both asymmetric catalysis and convenient build-up of libraries of molecules with novel three-dimensional scaffolds that might find application in medicinal chemistry. A systematic review on such topic will provide the synthetic organic community a conceptual overview and comprehensive understanding of the different multicomponent reaction (MCR) cascades involving dearomatization as a characteristic step. In addition, this review will help the researchers to look at this promising area from a different perspective with respect to drug discovery, new MCR based disconnections and often hidden opportunities.

1. Introduction

The rapid assembly of complex and diverse (hetero)cyclic frameworks is an important pursuit in organic chemistry. To build such structurally complex scaffolds starting from simple and abundant building blocks, dearomatization (disruption of the aromaticity of arenes) has emerged as a powerful approach.[1-4] Aromatic compounds are the fundamental building blocks of chemicals used in everyday life ranging from polymers, paints, cosmetics, and pharmaceuticals.[5] Upon dearomatization of (hetero)aromatic derivatives, extremely reactive intermediates are usually formed leading to the facile formation of multiple carbon–carbon and carbon–heteroatom bonds, spontaneous cycloadditions as well as domino or cascade reactions. The formation of multiple bonds can be in a domino- or sequential-manner leading mostly to a three-dimensional (3D) molecule with enhanced sp^3-character.[6] Thus, the dearomatization chemistry offers unique possibilities of assembling sophisticated polycyclic architectures from simple arenes as well as promising applications for asymmetric transformations leading to enantio- and/or diastereo-enriched synthetic building blocks.[7-11] However, despite the elegant achievements in two-component systems, including those of our research groups, reaction with three or more distinct starting materials leading to a complex 3D structure are relatively sparse and without a dedicated review on the topic.

The expansion of chemical space *via* multicomponent transformations provides unprecedented possibilities to access diverse molecular architectures with ultimate applications in medicinal chemistry research and functional materials.[12-15] Multicomponent reactions (MCRs) lead to the assembly of three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency. These reactions date back to the mid-19th century, when Strecker first prepared *α*-aminonitriles through the condensation of aldehydes with ammonia and hydrogen cyanide.[16] The combination of MCRs with dearomatization strategy in one synthetic operation, mostly leads to highly functionalized and architecturally complex molecules from simple starting materials (Figure 1).

In addition, linear MCR adducts provide an opportunity for a myriad of post-condensation cyclizations depending on the functional groups introduced during the MCR.[17-20] Therefore, post-MCR cascade cyclizations involving dearomatization as a characteristic step also increases the molecular diversity and complexity in a fast and often experimentally simple fashion. This strategy has been broadly applied for the past two decades to streamline the drug-discovery process in diverse fields, ranging from synthetic biology, material sciences, to complex natural product synthesis. Numerous reviews on the dearomatization chemistry have appeared during the last decade, covering various aspects of dearomatization chemistry such as dearomative elaborations of (hetero)arenes,[21-28] their enantioselective,[4,7-11,29,30] transition-metal-mediated,[31,32] and photochemical reactions,[33] besides detailed synthetic applications.[3,34] However, the core idea of

this review is to provide a conceptual overview of the different MCR dearomatization cascades (up to December 2019) employed towards the synthesis of (poly)heterocycles.

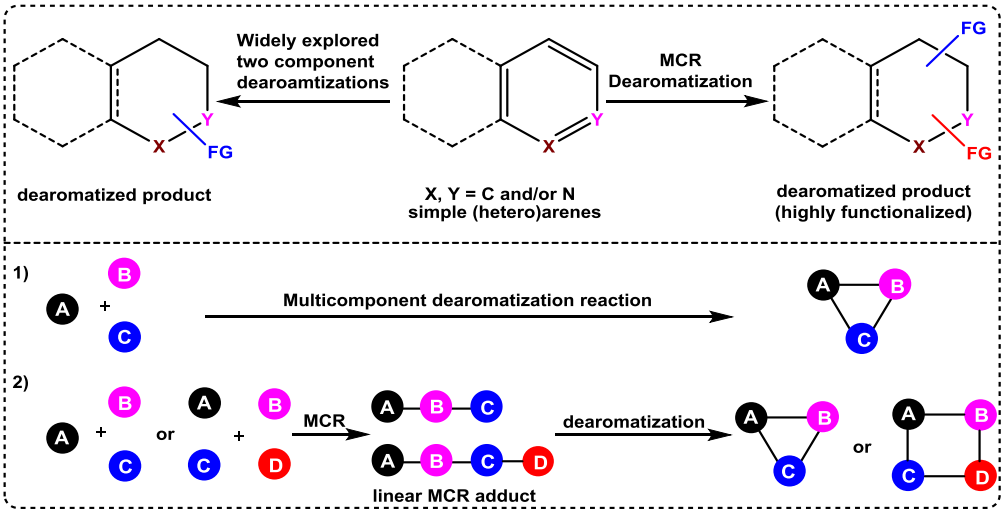


Figure 1: Diversity-oriented synthesis of saturated (poly)heterocycles.

2. Direct multicomponent reaction/cascade dearomatization processes

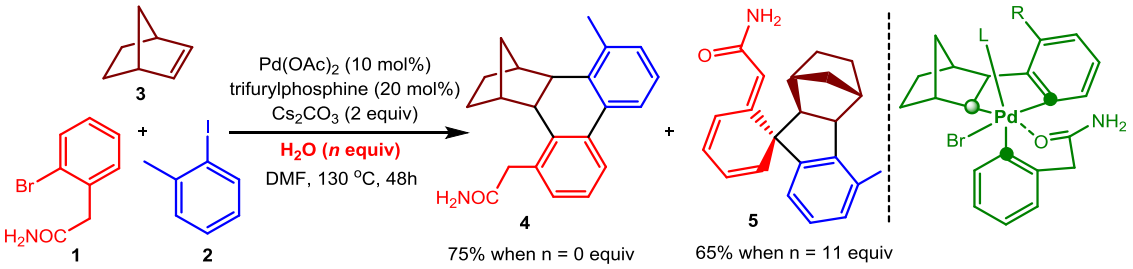
This section will cover a concise overview of the uninterrupted multicomponent dearomative reactions of various (hetero)arenes that include oxidative, cycloadditions and cascade reactions. In addition, some important mechanisms will be highlighted and discussed. For the sake of clarity, we have divided this part into the following sub-sections.

2.1 Dearomative MCRs of arenes

Arenes belong to one of the most abundantly available fundamental class of compounds. By disturbing their aromaticity, a variety of complex value-added and synthetically useful intermediates can be synthesized. This section is mainly focused on simple arenes such as phenols, naphthols, amines and their participation in MCR processes along with a compulsory dearomatization step.

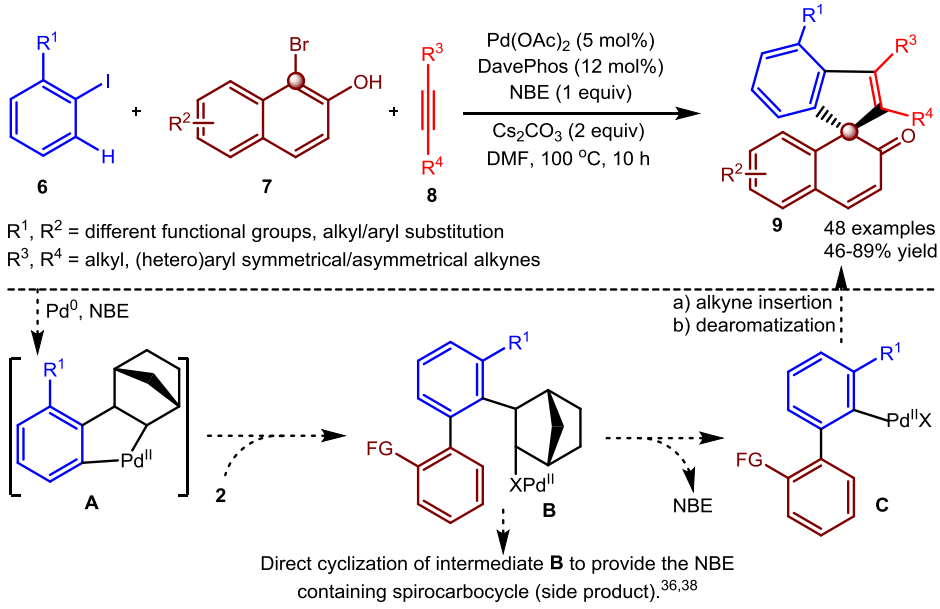
As is evident from the literature, palladium/norbornene cooperative catalysis[35] has emerged as a noticiable approach to synthesize polyfunctionalized arenes from readily available starting materials. Despite several elegant achievements on two-component processes, the discovery of related annulations with three distinct starting materials to assemble complex (spiro)cyclic frameworks is still a developing field. The association of palladium and norbornene opens access to a myriad of polycyclic and heterocyclic frameworks through sequential coupling reactions of aryl halides or triflates. In one such chelation-controlled sequences, Lacôte, Malacria and co-workers[36] observed an appreciable amount of the spiro derivative **5** as a by-product, together with the desired **4** (Scheme 1), especially when the substrates were not carefully dried. Moreover, when excess water (11 equiv relative to palladium) was added, **5** was obtained as a sole product. Further addition of water led to degradation of the product. DFT calculations have suggested the

role of a suitably placed amide group in the reductive elimination pathway involving a chelated Pd^{IV} intermediate. Water is assumed to play an important role *via* apical ligand exchange, hydrogen bonding or stabilization of a pentavalent Pd^{IV}-species besides hampering the usual norbornene extrusion through β-hydride elimination, thus favoring the dearomatization process.



Scheme 1. Multicomponent synthesis of dihydrophenanthrene and spirocyclic adduct.

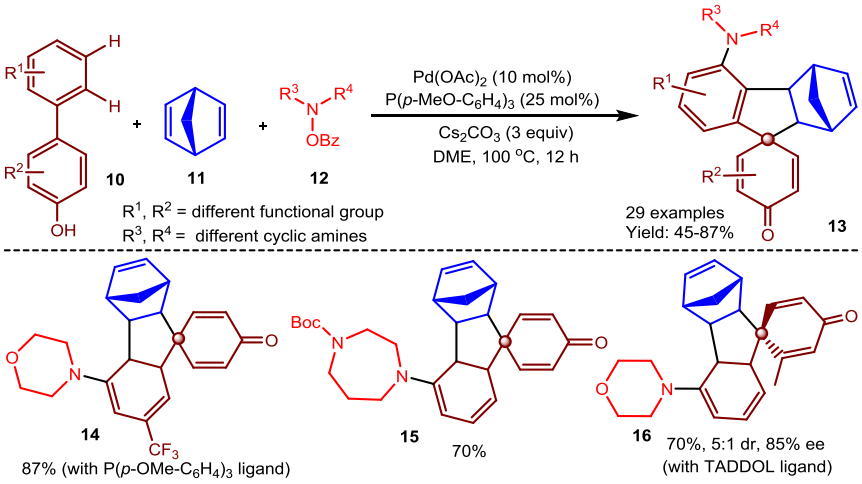
In a related work, Luan and co-workers[37] developed an elegant Pd(0)-catalyzed norbornene (NBE)-mediated dearomatizing [2+2+1] spiroannulation of bromonaphthols with aryl iodides and alkynes, which provides a variety of spirocyclic molecules in moderate to good yields. With NBE as a transient mediator, this three-component domino process is likely realized through a sequence of Catellani-type C-H activation, biaryl coupling, alkyne migratory insertion, and naphthol dearomatization (Scheme 2). In this process, there were multiple possibilities of side product formation, *viz*. direct cyclization of intermediate **B** to provide NBE-containing spiro product.[36,38] However, the authors were able to find the suitable conditions to steer the reaction in the desired direction by effectively preventing unwanted side reactions.



Scheme 2. A three-component dearomatizing [2+2+1] spiroannulation of bromonaphthols.

Besides the broad substrate scope and gram scale synthesis, the potential utility of this method was highlighted through the construction of the structural cores of immunosuppressive polyketides dalesconols A and B.

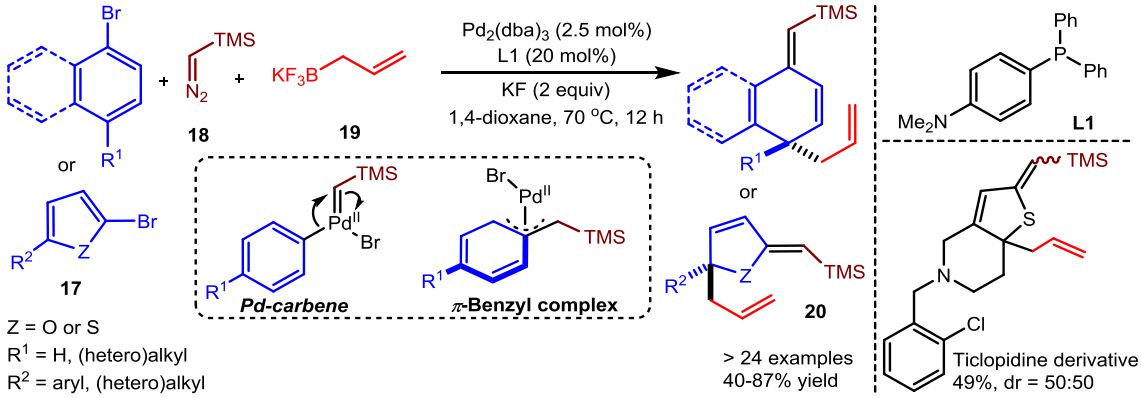
Soon after, the same group[39] described another three-component reaction, wherein Pd(0)-catalyzed norbornadiene (NBD)-assisted C-H amination/phenol dearomatization allows the rapid assembly of a new class of highly functionalized spiroindenes **13** from phenol-derived biaryls **10**, NBD (**11**) and N-benzoyloxyamines **12** (Scheme 3). The key issue for such method is that if palladium-induced phenol dearomatization can compete with more common NBD extrusion *via* β-carbon elimination. Notably, $Pd(OAc)_2$ in the presence of an electron-rich monophosphine ligand (P(*p*-OMe-C_6H_4)$_3$) was found to be crucial for this reaction. However, in case of electron-deficient biaryls P(*p*-F-C_6H_4)$_3$ was found to be a more effective ligand for the desired transformation. This transformation was realized through the formation of one C-N and two C-C bonds in a single chemical operation. In addition, preliminary studies indicated that asymmetric control of this transformation was feasible with TADDOL chiral ligand (up to 85% ee for the major diastereoisomer of **16**). This discovery opens a new window for developing asymmetric dearomatization reactions.



Scheme 3. A three-component palladium-catalyzed C-H amination/phenol dearomatization.

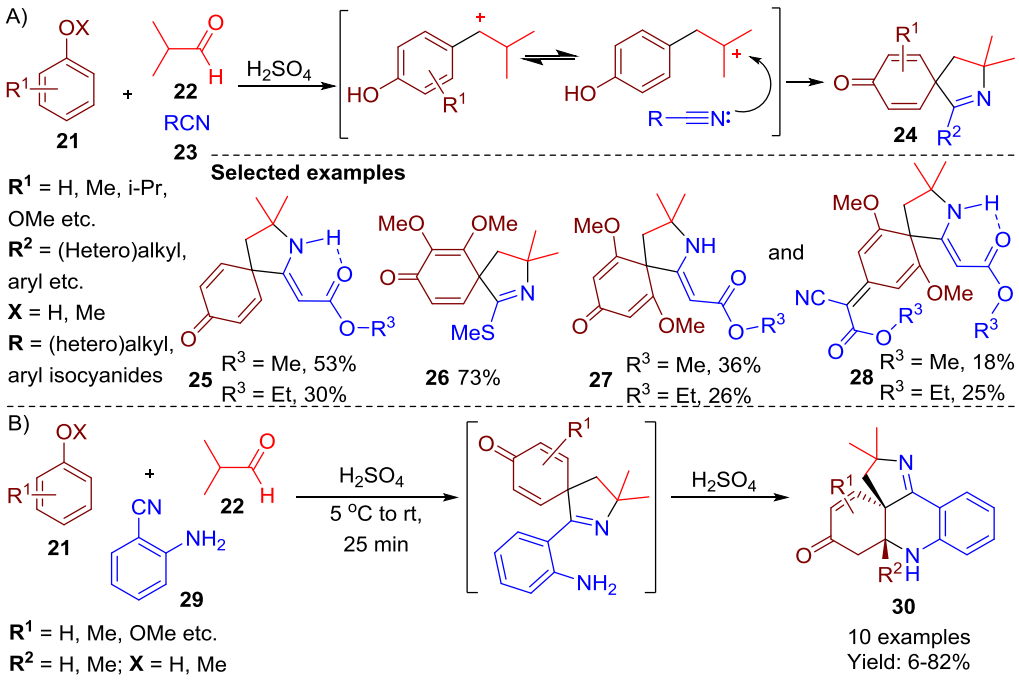
The generation of palladium π-benzyl complexes as catalytic intermediates and their participation in dearomative functionalization is well known in two-component systems.[40] Recently, Muto, Yamaguchi and co-workers[41] described a pioneering dearomative three-component reaction of bromoarenes with TMS-diazomethane and allyl borates. The key feature of this assembling reaction is the use of a diazo compound to generate a Pd-π-benzyl intermediate through a Pd-carbene species. Heteroaryl bromides were also able to give dearomatized structures under these reaction conditions (Scheme 4). The authors successfully demonstrated the viability of this method by further functionalization of the generated cyclic core, as well as of

the drug molecule ticlopidine, to generate the corresponding dearomatized compound in 49% yield (Scheme 4).



Scheme 4. A dearomative three-component reaction of bromoarenes with TMS-diazomethane and allyl borate.

A simple and efficient one-pot protocol for the construction of 2-azaspiro[4.5]deca-1,6,9-trien-8-ones (**24**) *via* a three component condensation of a set of alkoxy arenes or substituted phenols with isobutyric aldehyde and various nitriles, in the presence of concentrated sulfuric acid, has been reported (Scheme 5A). 1,3,5-Trimethoxybenzene was found to react with alkyl cyanoacetates in an unusual way: besides the expected spiranes **27** (26-36% yield), the products **28** of a four-component condensation were also isolated **28** (18-25% yield), which can be regarded as a result of a formal Knöevenagel condensation (Scheme 5A).[42]



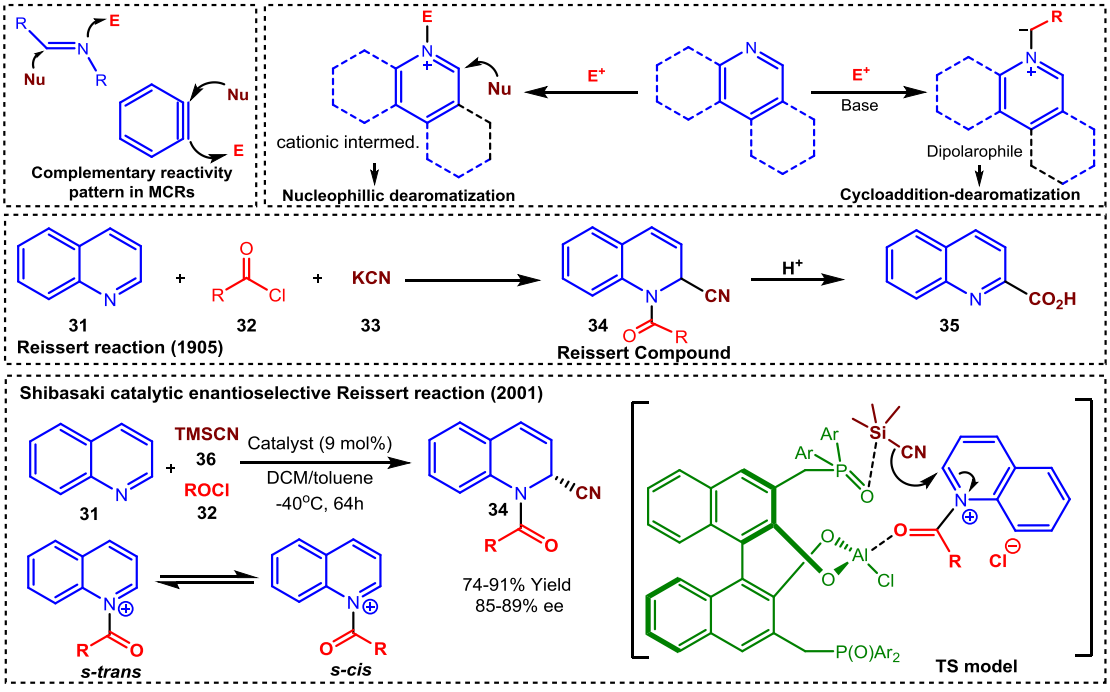
Scheme 5. Multicomponent synthesis of 2-azaspiro[4.5]deca-1,6,9-trien-8-ones and complex spirocycles.

In case of the chloroacetonitrile **23**, formation of the spiranes **24** was detected only by GC/MS as the spiranes were easily hydrolyzed during the isolation procedure to form the respective amides.[43] Moreover, the 2-azaspiro[4.5]deca-1,6,9-trien-8-ones could be suitable substrates for the 1,4-conjugate addition. In this direction, Rozhkova and co-workers reported a one-pot, three-component synthesis of novel pyrroloacridinones from a set of activated arenes, isobutyric aldehyde, and 2-aminobenzonitrile. The reaction proceeded *via* an intramolecular electrophilic ipso-dearomatization of the suitable aromatic compounds leading to spiro-substituted cyclohexa-2,5-dienones and intramolecular aza-Michael addition for the preparation of complex azaheterocyclic systems (Scheme 5B).[44]

2.2 Dearomative MCRs of heteroarenes (pyridines, quinolines and isoquinolines):

2.2.1 Dearomatization *via* Reissert-type reactions

Saturated nitrogen-containing compounds are found in a variety of natural products, pharmaceuticals, agrochemicals and are extremely desirable building blocks in chemical industry.[45,46] A strategic approach involving reduction of the corresponding hetero-aromatic compounds continues to be widespread, due to the readily available starting materials and synthetic ease at a bigger scale. Substrates or intermediates having more than one reactive site as e.g. isocyanides, arynes, and imines that work in a complementary fashion, are the most commonly employed species in MCRs. Azines, being heterocyclic surrogates of imines are also useful for such chemistry. In 1905, Arnold Reissert described the addition of cyanide to the *a*-position of a quinoline activated by an acylating agent (Scheme 6).[47]

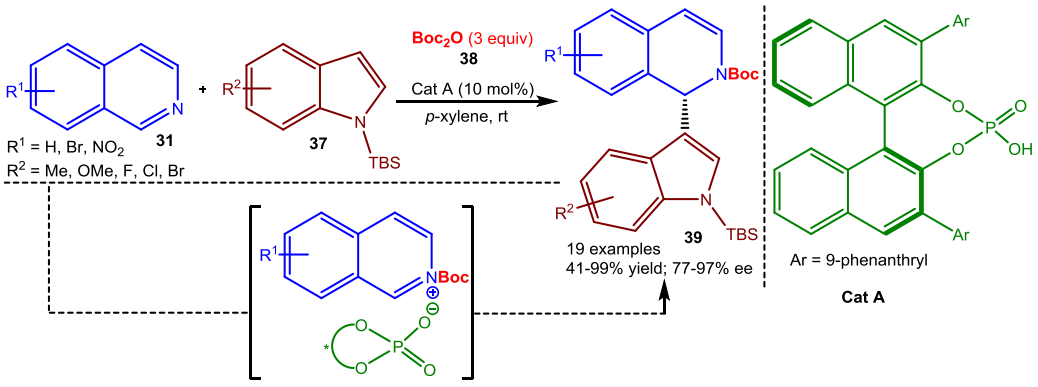


Scheme 6. Background to the Reissert reaction and its enantioselective version.

The resulting substituted dihydroquinoline, generally called Reissert compound, can be hydrolyzed with aqueous HCl to afford quinoline-2-carboxylic acid. This reaction can be described as an early example of *dearomatizing MCRs*. Later, multiple variants of this reaction appeared with respect to activating agent, type of nucleophile and asymmetric induction using chiral catalysts, and has been reviewed in detail with different perspectives.[48, 24, 26, 27] However, latest additions to this important class of MCRs with respect to enantioselective versions and metal-catalyzed steps will be discussed herein briefly. This section will focus on the multicomponent reactions of various heteroarenes such as pyridines, quinolones and isoquinolines.

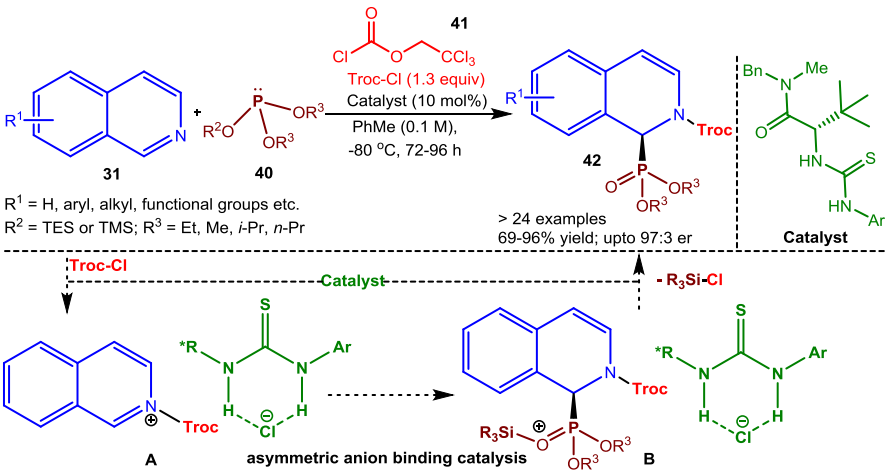
The catalytic asymmetric dearomatization (CADA) reaction[7] has emerged as a powerful organic transformation for the construction of complex molecules from relatively simple aromatic compounds. In the context of CADA reactions of isoquinoline derivatives, the main focus has been on Reissert-type reactions. In 2000, Shibasaki and co-workers[49] overcame the key issue of enantio-control of the process which was largely hindered by highly dynamic amide *s-trans*/*s-cis* interconversion. They employed a chiral BINOL-aluminum Lewis acid catalyst for the dual activation of TMSCN and the quinolinium salt and set the precedent for further improvements.[50-52] Thereafter, numerous studies have been carried out in a two-component manner with pre-activated heteroarenes or in a three-component one-pot fashion but not being in a true MCR fashion.[53-56]

Chiral phosphoric acid has also been employed towards enantioselective heteroarylation of isoquinolines.[57] In total, 19 chiral dihydroisoquinolines with indole substituent at the C1-position were synthesized in excellent yields and overall good enantioselectivity (Scheme 7). However, the catalytic system was found unsuitable to other heteroaromatics such as *N*-TBS-pyrrole, furan, thiophene, 1,3,5-trimethoxybenzene with exception to *N*-benzyl pyrrole (with 40% yield in racemic form). The absolute configuration of the newly formed stereocenter was found to be (*S*) as determined by X-ray analysis. The mechanism was believed to go through an intermediate iminium ion which was then trapped by the indole nucleophile.



Scheme 7: Enantioselective dearomative heteroarylation of isoquinolines.

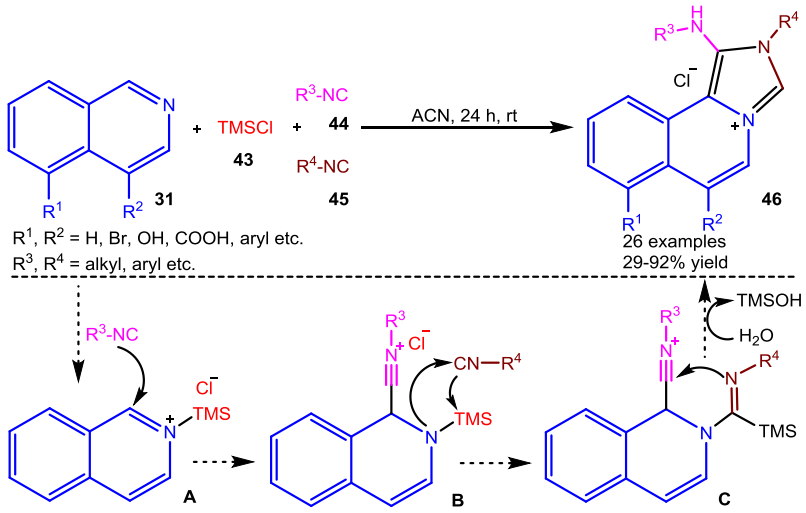
Phosphorous substituted saturated heterocycles are an important class of organophosphorus compounds with wide applications in biologically active molecules, pharmaceuticals and agrochemicals. The construction of such heterocyclic compounds involving MCR and dearomatization strategy (Reissert type reactions) has been recently reviewed.[58] In one particular example, Choudhury and Mukherjee described an enantioselective dearomatization of diversely substituted isoquinolines through the acyl activation and nucleophilic addition of silyl phosphites through anion-binding catalysis. A simple and easy-preparable *tert*-leucine derived thiourea was employed as an anion-binding catalyst to deliver optically active cyclic phosphorylated *α*-aminophosphonates **42**. Mechanistically, the thiourea catalyst facilitates the formation of intermediate **A**, in which the chloride ion is bound to thiourea by dual H-bonding. The formation of **A** not only solubilizes the reactive ionic form, but also favored the enantioface-selective attack by silyl phosphite owing to its proximity to the chiral thiourea-bound chloride anion. The resulting silylated intermediate **B** then collapses to release the product **42**, R_3Si-Cl and regenerated catalyst (Scheme 8).[59]



Scheme 8: Enantioselective dearomatization of isoquinolines by anion-binding catalysis.

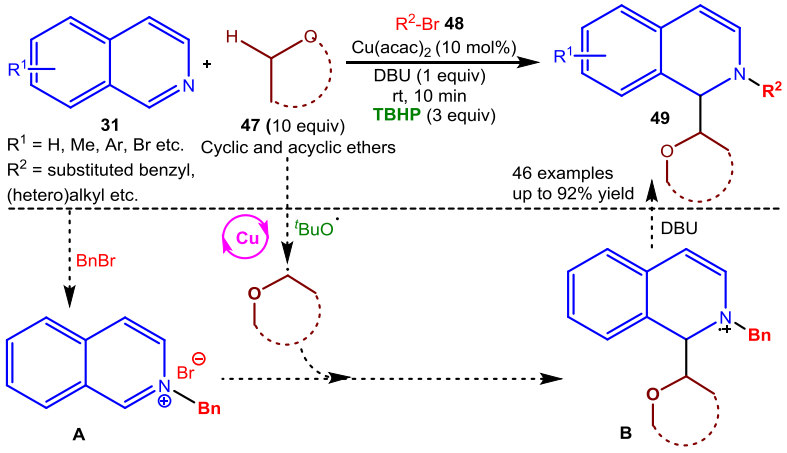
Isocyanides have remained as irreplaceable components in many multicomponent reactions *viz*. Ugi-4CR and Passerini-3CR. Their divalent character makes them an ideal partner for MCR chemistry.[13] In this context, Lavilla and co-workers have described a trimethylsilyl chloride based *N*-activation of isoquinolines, followed by nucleophilic attack of an isocyanide in a Reissert-type process.[60] Lastly, a second equivalent of the same or a different isocyanide inserts into the N-Si bond leading to the final product **46**. In contrast, the reaction of isoquinolines with chloroformate (or a similar reagent) and isocyanides gave dihydroisoquinolines with amide functionality at the *α*-position.[61] A mechanism was provided based on the computational and experimental studies, which began with the activation of the isoquinoline by TMSCl to *in situ* generate *N*-silyl isoquinolinium ion **A**. Intermediate **A** is subsequently attacked by an isocyanide to yield nitrilium cation **B**, likely stabilized by a chloride counter ion. Thereafter, a second (less nucleophilic) isocyanide inserted into the N-Si bond of this intermediate to yield intermediate **C** (a silylated amidine). The final product was obtained by an intramolecular N-addition to the nitrilium moiety

and spontaneous hydrolysis of the resulting adduct (Scheme 9). In addition, the resulting products exhibited significant *in vitro* activity against *Trypanosoma brucei and T. cruzi*, in the low micromolar range.



Scheme 9: Reissert-type isocyanide based multicomponent reaction.

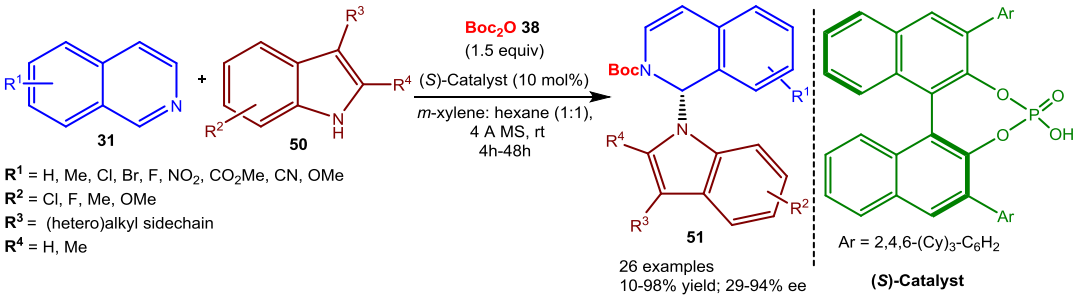
Despite various reports of catalytic Reissert-type reaction as a one-pot reaction or as a true MCR, the radical addition over the iminium ion is scarcely reported. In one such example, Yan and co-workers described a Cu-catalyzed 1,2-difunctionalization of different N-heteroarenes involving the combination of oxidative coupling and reduction process by DBU under very mild conditions (Scheme 10).[62] This method provides an efficient way to prepare substituted dihydro azaarene derivatives *via* a free-radical process.



Scheme 10: Cu-catalyzed radical based multicomponent dearomatization of isoquinolines.

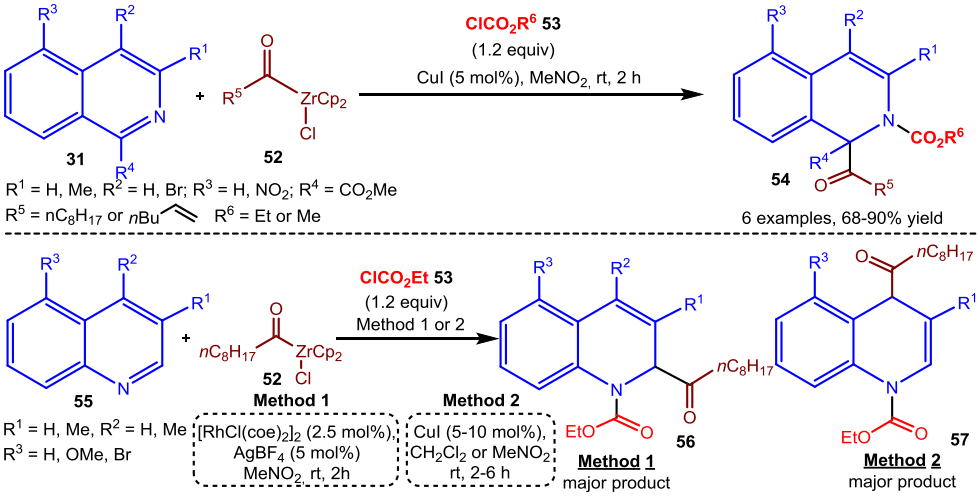
Enantioselective alkylation of indoles has been largely reported at the C3- or C2-position. You and co-workers have reported an asymmetric N-alkylation of indole derivatives **50** *via* the Reissert-type reaction in the presence of a chiral phosphoric acid.[63] This strategy offered the

synthesis of various enantioenriched indoles **51** with 1,2-dihydroisoquinoline N-substitution at room temperature (Scheme 11). The method was compatible with gram-scale synthesis and offered the possibility of further chemical transformations. Interestingly, the optimization studies revealed that 2,2,2-trichloroethyl chloroformate (TrocCl) as an activator provides the racemic product.



Scheme 11: Reissert-type enantioselective *N*-alkylation of indoles.

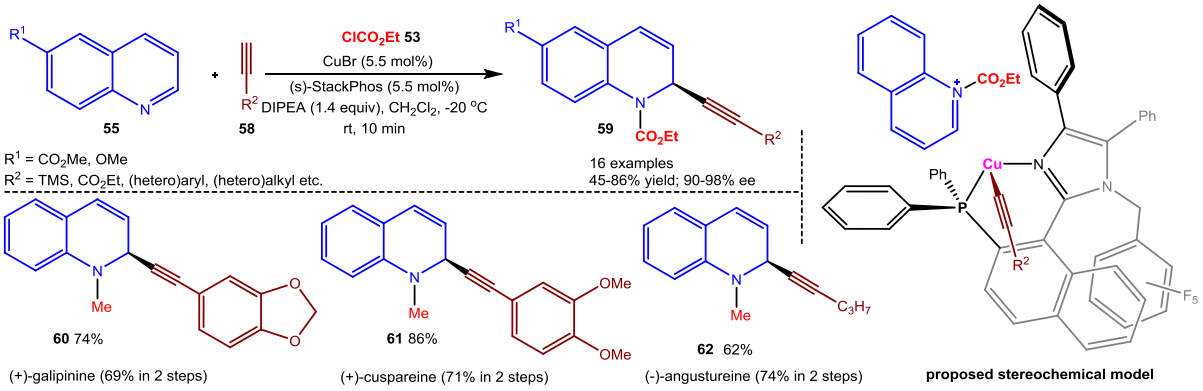
Saito and co-workers have reported a Reissert-type acylation of isoquinoline derivatives **31** with acylzirconocene chlorides **52** and chloroformates **53**.[64] During this study it was observed that the choice of catalyst and solvent was crucial for the regioselective formation of dearomatized adducts **54**. While the cationic Rh^{I}-catalyzed ($[RhCl(coe)_2]_2$ + $AgBF_4$) reaction in nitromethane preferentially afforded 1,2-adducts **56**, the CuI-catalyzed reaction in dichloroethane gave 1,4 adducts **57** (Scheme 12).



Scheme 12: Reissert-type acylation of isoquinoline derivatives with acylzirconocene chlorides.

Tetrahydroquinoline is one of the most significant nitrogen heterocycles, being widespread in nature and is present in a variety of pharmacologically active compounds.[65] Aponick and co-workers have developed a catalytic enantioselective dearomative alkynylation of quinolines enabled by the use of ligand StackPhos. The reaction is high yielding and delivers the products in

high enantiomeric excess (90–98%) in a three-component manner among a quinoline, a terminal alkyne and ethyl chloroformate.[66] The absolute configuration of the products was assigned by conversion into *galipea* alkaloids **60**-**62** with known optical rotation. An extremely broad range of substrate scope with regard to both alkyne **58** and quinoline **55** was demonstrated. The likely mechanistic scenario for this reaction involves the generation of a quinolinium salt followed by acetylide addition with the chiral (S)-StackPhos complex (Scheme 13). A possible rationale for the absolute stereochemistry observed using the C1 -symmetric complex is the generation of a chiral biaryl axis creating in turn a chiral environment around the metal center.

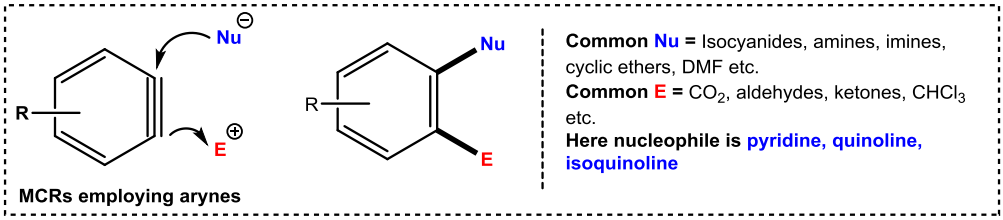


Scheme 13: Cu-catalyzed enantioselective dearomative alkynylation of quinolines.

Dihydropyridines (DHPs) can be seen in various natural products and drug molecules with interesting biological properties. DHPs can be easily synthesized in varying substitutions employing Reissert-type reactions with a variety of activating agents and nucleophiles. Most commonly used activation methods employs *N*-acyl, *N*-sulfonyl and *N*-alkylpyridinium salts. However, a regioselectivity issue is pretty obvious with the pyridine nucleus (between C-2 or C-6 and C-4) which is largely governed by steric bulk besides the hard and soft nature of nucleophiles. Hard nucleophiles are found to be selective towards the C-2 position, whereas softer nucleophiles are reactive towards the C-4 position. However, this topic is quite broad and seems out of context of this review article. In addition, a review on nucleophilic dearomatization of pyridines[27] has been published in 2018 along with some other interesting reviews/book-chapters.[24,26,29,48] Still, a few examples (before or after 2018) which are deemed necessary for the better comprehension of the topic are included in this review.

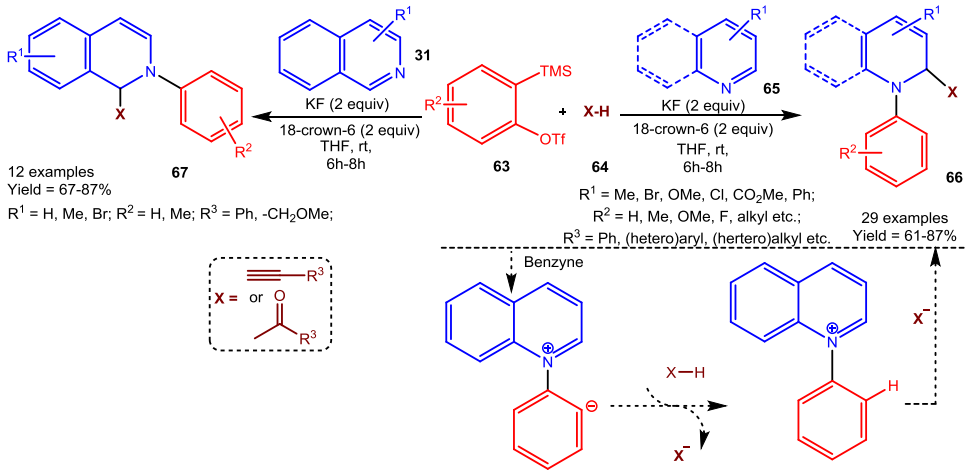
2.2.2 Dearomatizing MCRs *via* dipolar intermediates

Another important reaction series that has been developed for the heteroarene dearomatization is based on arynes as electrophilic activating reagents. Owing to the pronounced electrophilicity and a highly strained triple bond in the ring system, arynes are widely employed in various bond forming reactions, including MCRs.[67] This part of the review is focused on the dearomatizing capabilities of arynes in a multicomponent fashion (Scheme 14).



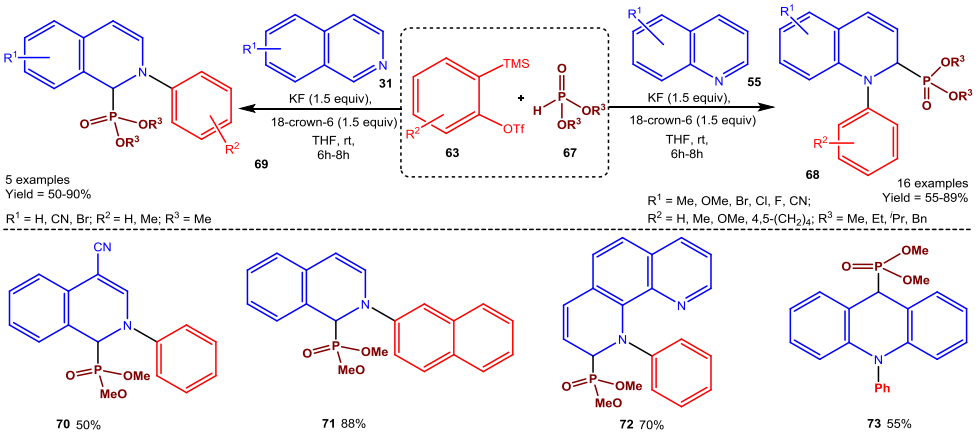
Scheme 14: Arynes in MCRs.

Cheng and co-workers described a three-component coupling of arynes with *N*-heteroarenes (quinolines, isoquinolines, and pyridines) and terminal alkynes or ketones with an *α*-hydrogen in the presence of KF and 18-crown-6 in THF at room temperature, giving various *N*-arylated 1,2-dihydro products **66** and **67**.[68] Benzyne was generated *in situ* from the reaction of precursor **63** and KF in the presence of 18-crown-6. The three-component coupling proceeds through the nucleophilic addition of quinoline to benzyne generating a zwitterionic species. The latter then attracts a proton from the terminal alkyne or ketones with an *α*-hydrogen to generate an *N*-arylated quinolinium cation and an acetylide anion. Further reaction of these two ionic species provides the desired product (scheme 15).



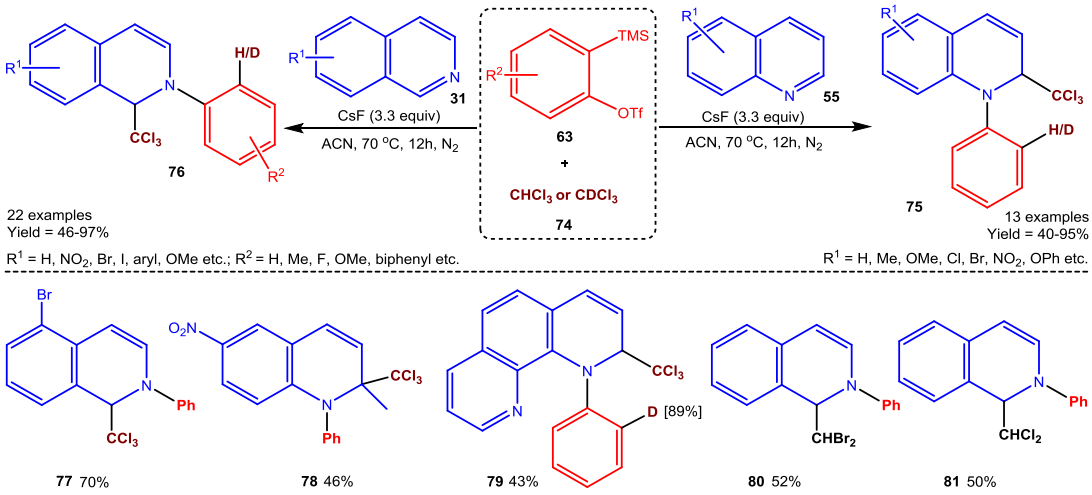
Scheme 15: A three-component coupling of arynes, *N*-heteroarenes and terminal alkynes or ketones.

In another example, Dai, He and co-workers described an efficient approach employing aryne-induced dearomatized phosphonylation of electron-deficient azaarenes such as quinolines, isoquinolines, phenanthroline and acridine.[69] These azaarenes undergo multicomponent reaction with arynes and dialkylphosphites to afford the corresponding dearomatized phosphonylated heterocycles in 50–90% yields. The protocol was also extended to acridine which underwent dearomatized phosphonylation *via* 1,4-addition to give the desired product **73** (Scheme 16).



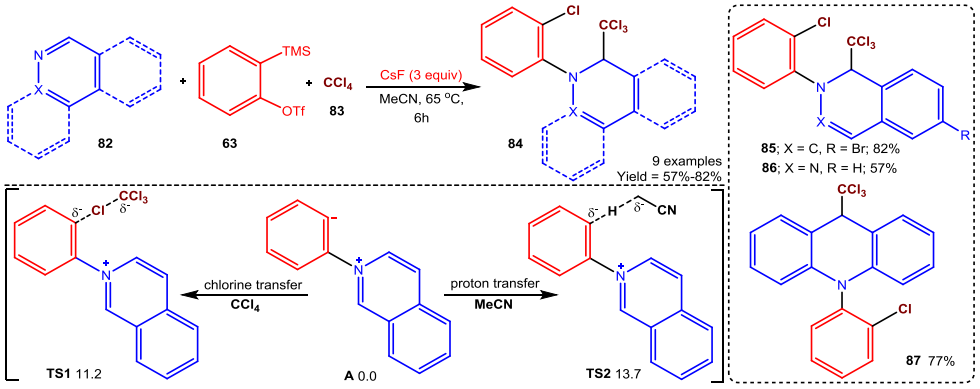
Scheme 16: Aryne-induced dearomatized phosphonylation of electron-deficient azaarenes.

Recently, chloroform has also been described as a nucleophile in the direct dearomatization reaction of isoquinolines and quinolines through *in situ* electrophilic aryne activation (Scheme 17).[70] The reaction was inspired by the isolated artifacts of palmatine and berberine natural products generated *via* nucleophilic attack of simple molecules such as water, alcohol or chloroform on the polarized isoquinolinium motif. There was an noticeable temperature effect on the reaction as 70 °C was found to be optimal while the yield decreased considerably when the temperature was lowered to 40 °C or less. The control experiment indicated the negative effects of air on this transformation as nitrogenous atmosphere was deemed necessary. Interestingly, using $CDCl_3$ as a deuterium source, a wide variety of deuterium labeled compounds **79** were prepared. Also, the deuterium-labelling experiments supported the proposed reaction pathways between the zwitterionic intermediate and chloromethane. In addition, the protocol was also suitable for both dichloromethane and dibromomethane as nucleophile with 52% (**80**) and 50% (**81**) yields, respectively.



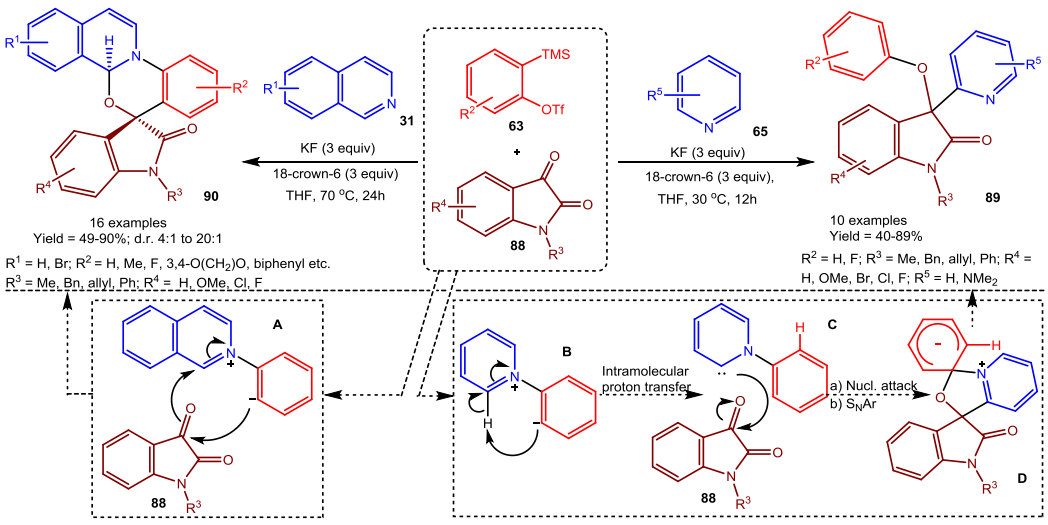
Scheme 17: Aryne triggered dearomatization of heteroarenes with chloroform.

Carbon tetrachloride (CCl_4), frequently serves as a solvent in chemical synthesis and spectroscopic analysis, and is also capable of participating in some chemical reactions *viz*.the Appel reaction.[71] In 2018, Tian, Yu and co-workers described a new strategy for the utilization of CCl_4 in the chemical synthesis *via* the formal insertion of C=N and C≡C bonds into the C–Cl bond under mild conditions.[72] A range of electron-deficient nitrogen-containing heteroarenes smoothly reacted with arynes and carbon tetrachloride in a three-component reaction through dearomatization, to afford a range of functionalized nitrogen-containing heterocycles in moderate to good yields (Scheme 18). In addition, acridine participated in the three-component reaction through 1,4-addition rather than 1,2-addition, affording **87**. The chlorine transfer from CCl_4 *via* transition state **TS1** is kinetically favored over the proton transfer from CH_3CN *via* transition state **TS2** (by 2.5 kcal/mol) as supported by DFT calculations.



Scheme 18: Aryne triggered dearomatization of heteroarenes with carbon tetrachloride.

In all the above examples with Reissert-type reactions of arynes, the heteroarenes were acting as nucleophiles. In a particular report, Biju and co-workers employed *N*-substituted isatins as the electrophilic component. With the aryne generated *in situ* from 2-(trimethylsilyl)aryl triflate **63** using KF and [18]crown-6, a facile reaction occurred with isoquinolines **31** and *N*-substituted isatins **88**, leading to the formation of the spirooxazino isoquinoline derivatives **90** (Scheme 19).[73] The reaction tolerated various substitutions on all three components. Isoquinolines and quinolines both worked well, leading to the formation of the desired products. When pyridine **65** was used as the nucleophilic trigger, the reaction afforded indolin-2-one derivatives **89** and likely proceeded through a pyridylidene intermediate **B**. Mechanistically, the reaction can be considered to proceed through the initial generation of the 1,4-dipolar intermediate from the heteroarene and aryne (Scheme 19). The zwitterion (**A** or **B**) can add to the electrophilic carbonyl group of isatins **88** in a concerted manner or in a step-wise path, leading to the formation of the final product. In case of pyridines, the generated 1,4-dipolar intermediate undergoes an intramolecular proton transfer in the absence of an external proton source, to generate pyridylidene intermediate **C**. The nucleophilic intermediate **C** then adds to isatin **88** followed by an intramolecular nucleophilic aromatic substitution (SNAr) reaction to furnish the final product.

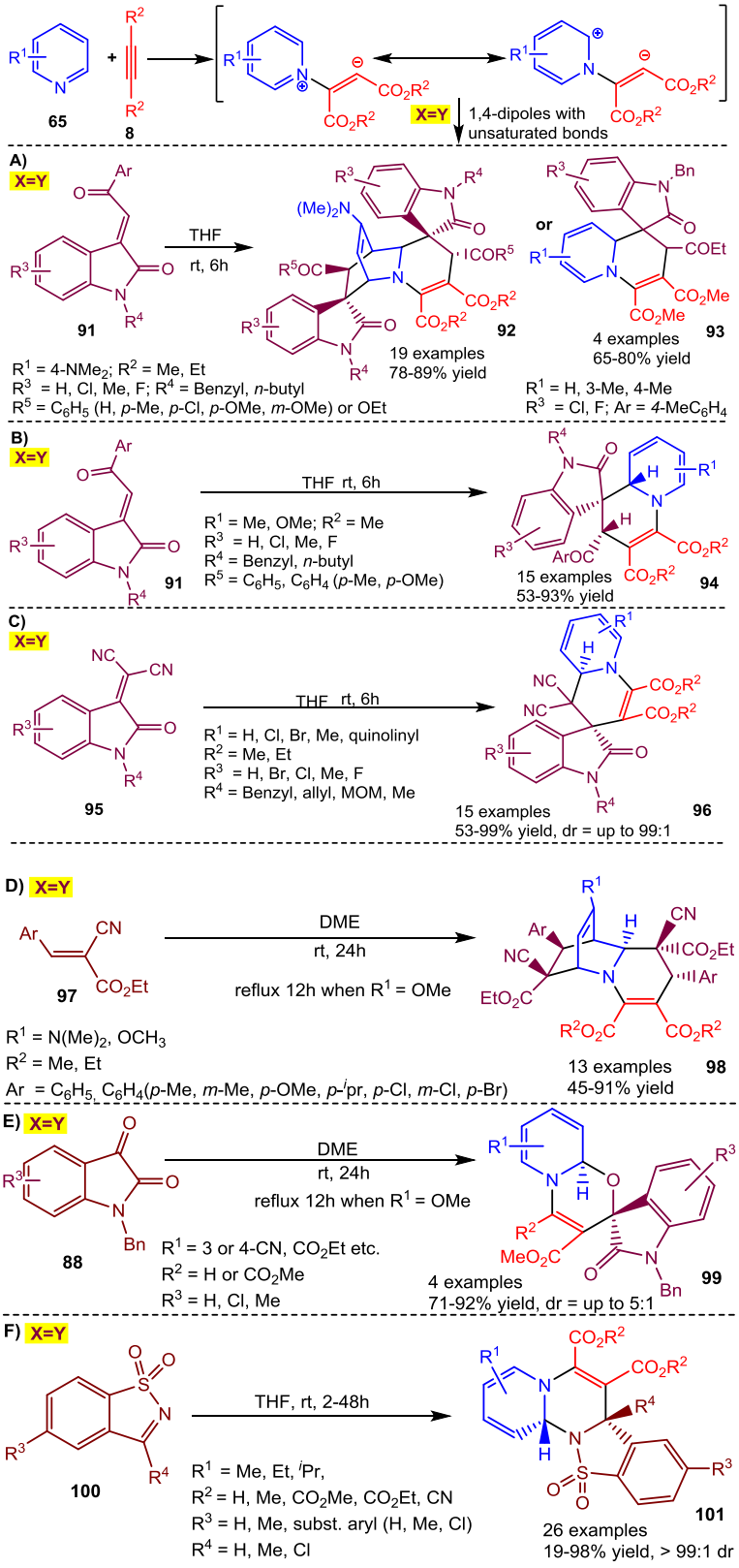


Scheme 19: A dearomative MCR involving *N*-heteroarenes, arynes and isatins.

2.2.3 Dearomatizing [m + n] cycloaddition reactions

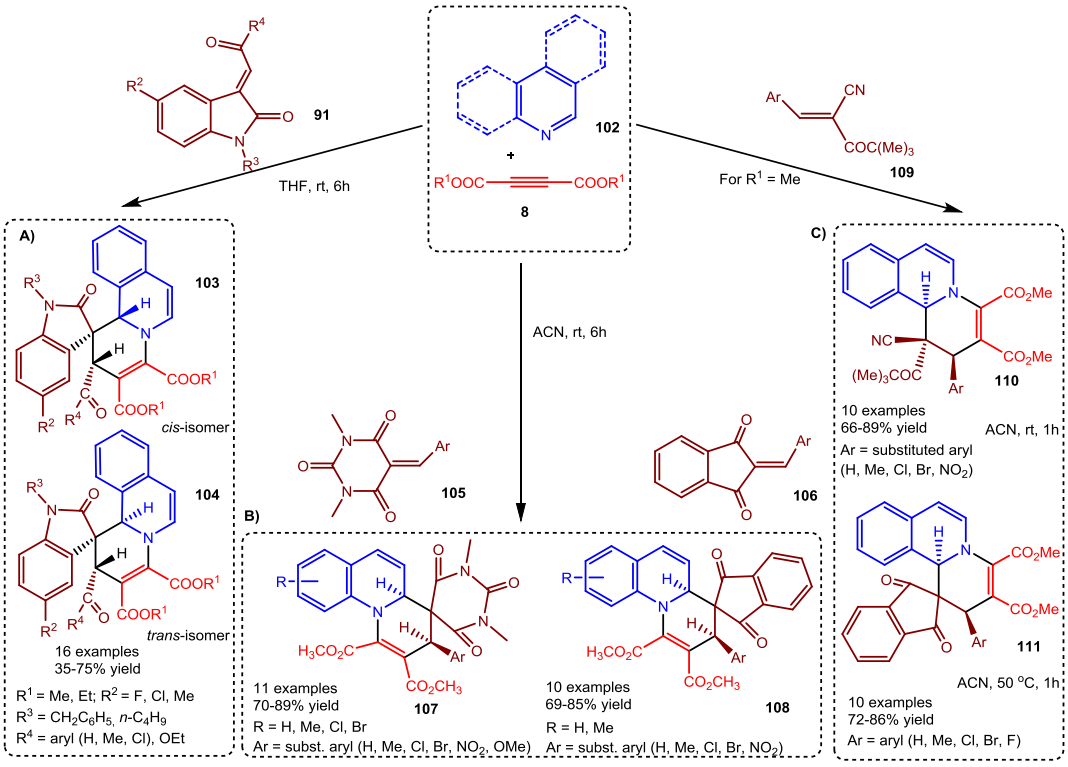
Catalytic (asymmetric) cycloaddition reactions have been figured out as a fundamental transformation in the chemical synthesis for the construction of heterocycles. The Huisgen reaction, involving the cycloaddition of a 1,3-dipolar species to a π-system, leading to a five membered heterocycle, paved the way for devising the homologous version of this reaction *viz*. 1,4-cycloaddition reaction.[74] Reactive intermediates such as azomethine ylides, *e.g*. pyridinium ylides, can act as 1,3-dipoles to efficiently construct an *N*-containing heterocycles.[75] Henceforth, multiple [m+n] cycloaddition reactions have been established as a powerful tool to construct heterocycles from simple starting materials.

Huisgen's 1,4-dipole from heteroarenes and electron-deficient alkynes is a broadly explored topic for the dearomatization chemistry generating (poly)cyclic heterocycles with excellent diastereoselectivity. Synthesis of complex dispirooxindole-fused heterocycles **92** *via* a domino three-component reaction of 4-dimethylaminopyridine (DMAP), an acetylenedicarboxylate, and a 3-phenacylideneoxindole has been reported (Scheme 20A).[76] The key strategy involves a domino 1,4-dipolar addition and Diels-Alder reaction of the *in situ* generated Huisgen 1,4-dipole with two molecules of phenacylideneoxindoles **91** to construct the dispiro compound **92**. In the absence of a strong electron-donating group on the pyridine ring, the further Diels-Alder reaction of the spirooxindole with the second molecule of 3-phenacylideneoxindole did not take place (**93**). Later, the same group extended the work with a wider substrate scope and optimized conditions for a three-component reaction between a pyridine, dimethyl acetylenedicarboxylate, and a 3-phenacylideneoxindole to afford spiro[indoline-3,1-quinolizine] **94** in moderate to good yields (53-93%) and with high diastereoselectivity. However no dr ratio was mentioned (scheme 20B).[77] Shi and co-workers have reported a three-component condensation of a pyridine, an acetylenedicarboxylates, and an *N*-substituted isatylidene to afford the spiro[indoline-3,3-



Scheme 20: A dearomative MCRs involving *in situ* generated Huisgen 1,4- dipoles from electron-deficient alkynes and pyridines.

piperidin]-2-one skeleton **96** under mild reaction conditions (Scheme 20C).[78] A variety of 1,9a-dihydrospiro[indoline-3,2-quinolizin]-2-one derivatives **96** were obtained in moderate to excellent yields (53-99%) and with good to excellent dr values (up to 99:1). Similarly, a three-component reaction of a 4-dimethylamino- or a 4-methoxypyridine with an acetylenedicarboxylate and an arylidene cyanoacetate showed very interesting molecular diversity resulting in the formation of a polysubstituted 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizine **98** (Scheme 20D).[79] The products were formed in good to high yields and good diastereoselectivity depending on the substrates and reaction conditions. The three-component reaction of 4-dimethylaminopyridine proceeded at room temperature for 24 h whereas with 4-methoxypyridine refluxing DME was needed for 12 h. A three-component reaction of 4-cyanopyridine (ethyl isonicotinate), methyl propiolate (dimethylacetylenedicarboxylate), and an *N*-alkylisatin was also described towards the synthesis of a spiro compound **99** (Scheme 20E).[80a] Zhao and coworkers elaborated a cycloaddition of a cyclic *N*-sulfonylimine with an *in situ* produced Huisgen 1,4-dipole from a dialkyl acetylenedicarboxylate and a pyridine.[80b] The tandem cyclization occurred smoothly under mild reaction conditions furnishing the highly functionalized polycyclic 1,2,3,4-tetrahydropyrimidine-fused benzosultam **101** in 19-98% yield with excellent diastereoselectivities (Scheme 20F).

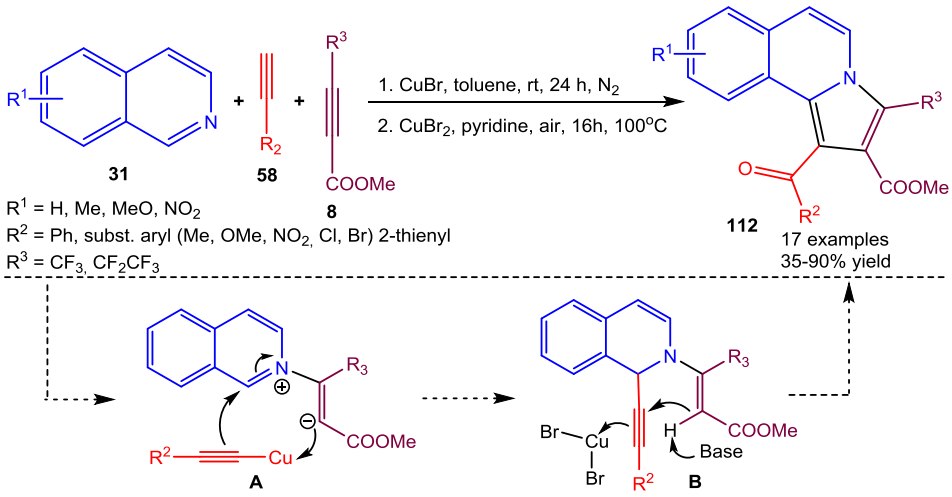


Scheme 21: Dearomatized (spiro)heterocycles from Huisgen's 1,4-dipoles and various dipolarophiles.

Similarly, Huisgen's 1,4-dipole generated from an (iso)quinoline and an electron-deficient alkyne is broadly explored for the dearomatization chemistry generating (poly)cyclic

heterocycles. In this direction, Yan and co-workers have described a three-component reaction of an isoquinoline, an acetylenedicarboxylate and 3-phenacylideneoxindole towards the generation of a diastereoisomeric mixture of 2′,11b′-dihydrospiro [indoline-3,1′-pyrido[2,1-a]isoquinoline] derivative in ethanol at room temperature.[81] The three-component reaction of isoquinoline gave the two diastereoisomers in nearly equal yields. Mechanistically, the generated 1,4-dipole could react with 3-phenacylideneoxindole (**91**) directly to give the products **103** and **104** preferable in a concerted 1,4-cycloaddition pathway (Scheme 21A). Similarly, a three-component reaction of an isoquinoline, dimethyl acetylenedicarboxylate (DMAD) and an alkene dipolarophile (arylidene-substituted 1,3-indanedione, Meldrum acid, and *N*,*N*′-dimethylbarbituric acid etc.) successfully provided a convenient method for the synthesis of functionalized spirocyclic derivatives (**107,108,110,111**) under mild reaction conditions (Scheme 21B and C).[82,83]

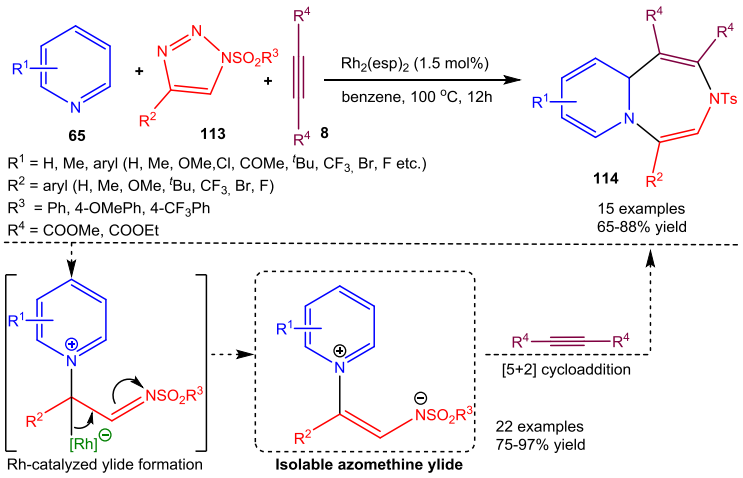
Zhang, Cao and co-workers have reported a copper-catalyzed sequential one-pot two-step three-component reaction of a substituted isoquinoline, a terminal alkyne, and methyl 4,4,4-trifluorobut-2-ynoate for the synthesis of 3-(trifluoromethyl)pyrrolo[2,1-a]isoquinolines **112** with air as an oxygen source (Scheme 22).[84] This oxidative cyclization proceeds through an initial copper(I)-catalyzed C-H alkynylation to give alkynyl-1,2-dihydroisoquinoline **B**, which subsequently undergo a copper(II)-assisted intramolecular cyclization to give the desired product. The reaction proceeds *via* a cascade process, involving intermolecular nucleophilic substitution, Michael addition, and intramolecular cyclization, wherein the first step of the reaction is the generation of a dipolar intermediate **A**.



Scheme 22: Copper-catalyzed sequential one-pot two-step three-component reaction of a substituted isoquinoline.

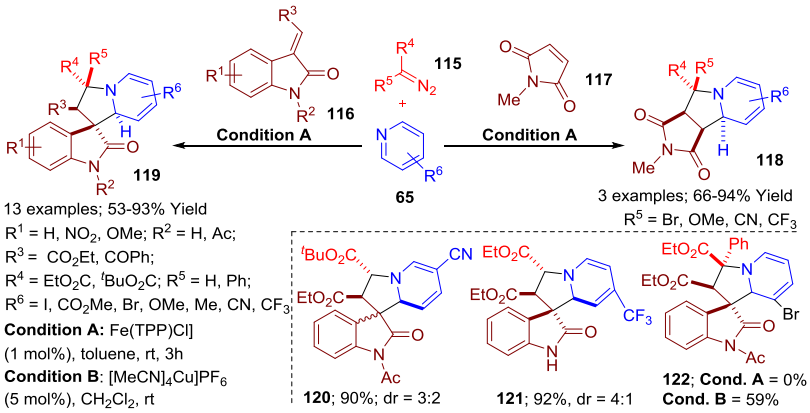
7-Membered heterocyclic compounds exist extensively in various natural products as well as pharmaceuticals as e.g. the 1,4-diazepine core. The strategic use of [5+2] cycloaddition for the construction of seven-membered heterocycles has been relatively less explored. Yoo and

coworkers have reported a catalytic multicomponent [5+2] cycloaddition reaction using a simple pyridine, a 1-sulfonyl-1,2,3-triazoles, and an activated 2π dipolarophile *viz*. alkyne *via* an isolable azomethine ylide, which results in an 1,4-diazepine **114** (Scheme 23).[85] In addition, a multicatalytic system with four reactants was also attempted, in which the first step was carried out by a Cu-catalyst to afford a 1-sulfonyl-1,2,3-triazole followed by the formation of the ylide. In the final step, the *in situ* generated ylide undergoes a thermal annulation with the alkyne to form the desired product.



Scheme 23: A dearomative [5+2] cycloaddition for the construction of seven-membered heterocycles.

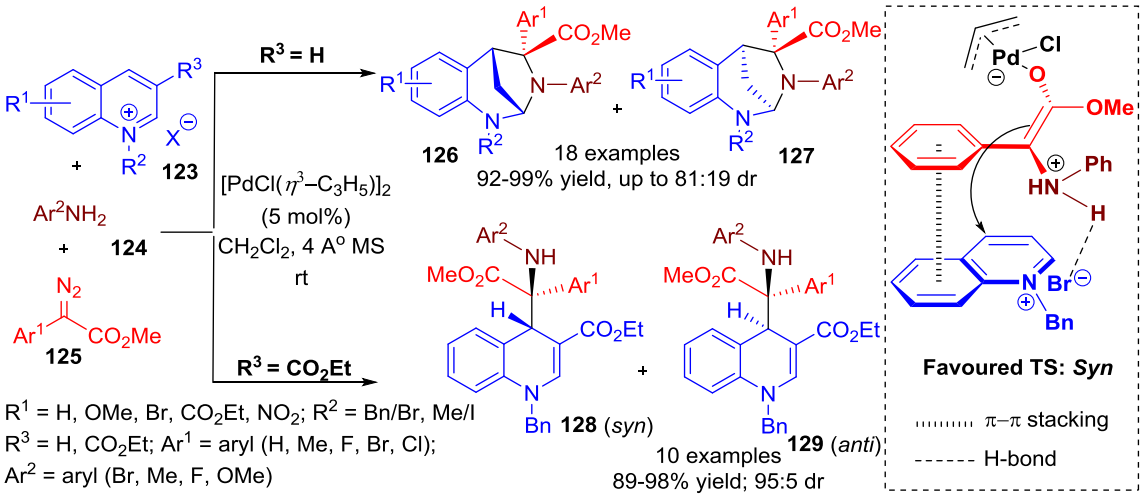
Spirooxindoles have been touted as privileged scaffolds for drug discovery research, thus, efficient and versatile routes for their synthesis are highly desirable. The catalytic formation of pyridinium ylides from metal carbenes and their participation in MCRs has remained a poorly developed field. In this particular direction, Dowden and co-workers have developed an iron- and copper catalyzed stereoselective reaction of a pyridine, a diazo compound, and an electrophilic alkene *via* a multicomponent cycloaddition reaction for the synthesis of alkaloid-like tetrahydroindolizidines **118, 119** (Scheme 24).[86]



Scheme 24: Fe- and Cu-catalyzed stereoselective MCR of pyridines, diazo compounds, and electrophilic alkenes.

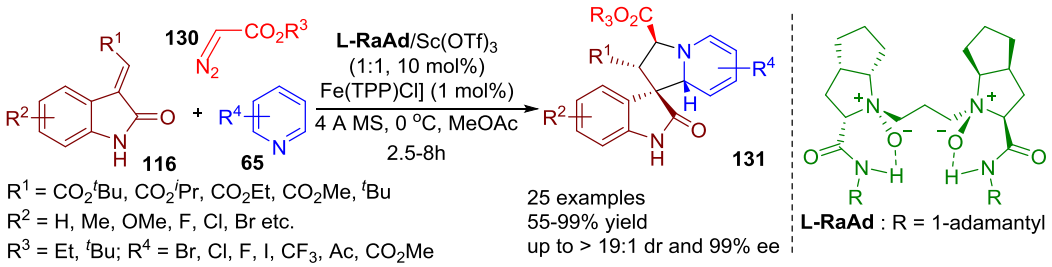
The reaction involves the catalytic generation of a pyridinium ylide *via* a metallocarbene and the *in situ* cycloaddition with an electrophilic alkene giving N_2 as the only byproduct. Substitution on the pyridine, especially with a 3-cyano or 4-trifluoromethyl functional group, resulted in decreased diastereoselectivity (**120**, **121**). The ylide generated from ethyl diazophenylacetate worked only in the presence of copper-catalyst to deliver **122** *via* condition B. In addition, the authors have successfully investigated the *in situ* generation of diazo compounds from tosyl-hydrozone salts with a promising yield of cycloadduct (57%).

Bolstering the importance of dearomatized (iso)quinoline derivatives, Hu and co-workers described a Pd(II)-catalyzed three-component reaction of a diazo compound, an aniline and a quinolinium salt with regiospecific C-4 addition (Scheme 25).[87] A bench-stable quinolinium salt was used in this process to avoid possible side reactions. These reactions provided complex tetrahydroquinolines or 4-substituted 1,4-dihydroquinolines in good yields with high regioselectivities and moderate to good diastereoselectivities (up to 95:5 dr) at room temperature. In the absence of substitution at the C-3 position of *N*-alkylquinolinium salts, the reaction underwent an uncommon regioselective 1,4-conjugate addition/intramolecular cyclization sequence to give bridged medium-ring 1,3-benzodiazepine derivatives **126**, **127**.



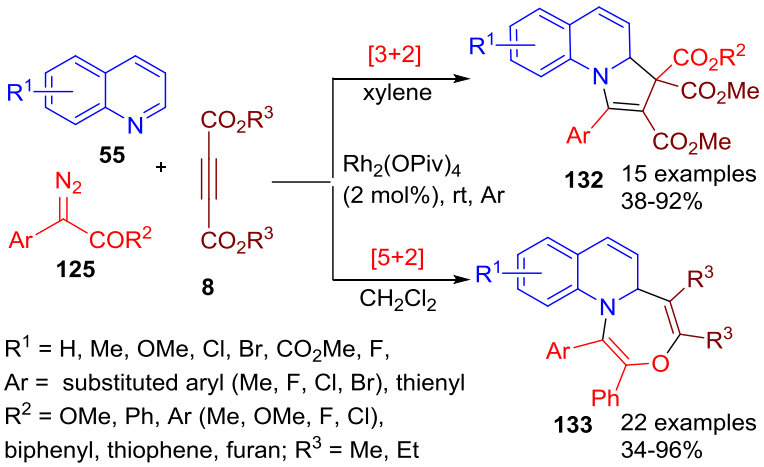
Scheme 25: Regio- and diastereoselective three-component reactions via trapping of ammonium ylides with *N*-alkylquinolinium salts.

Feng and co-workers have described an elegant cascade enantioselective synthesis of tetrahydroindolizines by a multicomponent cycloaddition reactions of a diazoacetate, a pyridine, and an alkenyloxindole employing an achiral iron(III) catalyst and chiral *N,N'*-dioxide-scandium(III) complex (Scheme 26).[88] A series of tetrahydroindolizines bearing different substituents were obtained in moderate to high yields with excellent diastereo- and enantioselectivities (> 19:1 dr, upto 99% ee). The steric bulk of the R^1 substituent was found necessary for the stereocontrol in this enantioselective 1,3-dipolar cycloaddition reaction of the pyridinium ylide.



Scheme 26: Iron(III)-catalyzed three-component asymmetric synthesis of tetrahydroindolizines.

Peng and co-workers described a rhodium-catalyzed multicomponent cycloaddition of a quinoline **55**, a diazo compound **125**, and an electron-deficient alkyne **8**, which resulted in a [3+2] indolizine derivative and a [5+2] 1,4-oxazepine compound, respectively (Scheme 27).[89] Additionally, quinolinium ylides derived from different types of donor–acceptor diazo compounds exhibit distinct selectivity and reactivity for the reactions. The [3+2] cycloadditions involve an unusual meta-assisted 1,3-ester migration process,. whereas, the pyridium ylides of *α*-diazoketones could act as active 1,5-dipole intermediates to intrigue [5+2] cycloadditions with electron-deficient alkynes, resulting in highly substituted 1,4-oxazepine structures (Scheme 27).



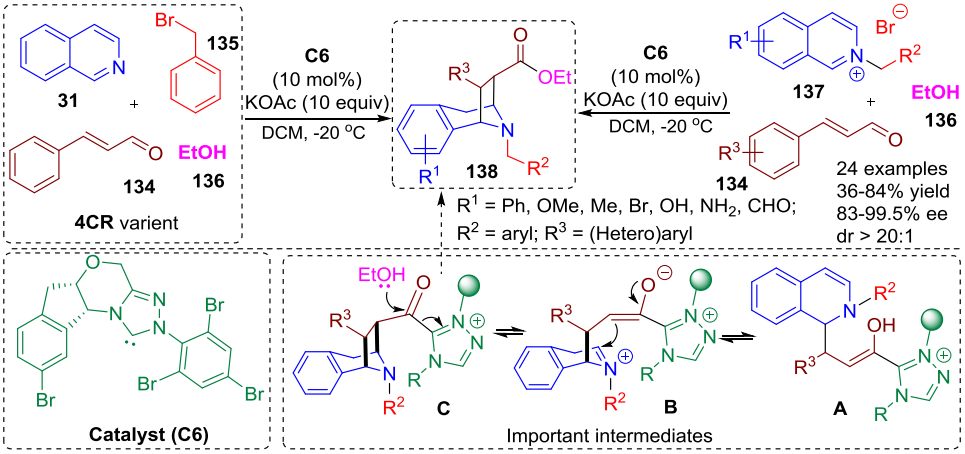
Scheme 27: Rhodium catalyzed multicomponent cycloaddition of a quinoline, a diazo compound, and an electron deficient alkyne.

2.2.4. Other multicomponent dearomatizing reactions of heteroarenes

This part will focus on the reactions which do not fall in the above-described categories in the previous sections, but have set an important benchmark towards multicomponent dearomatization strategies.

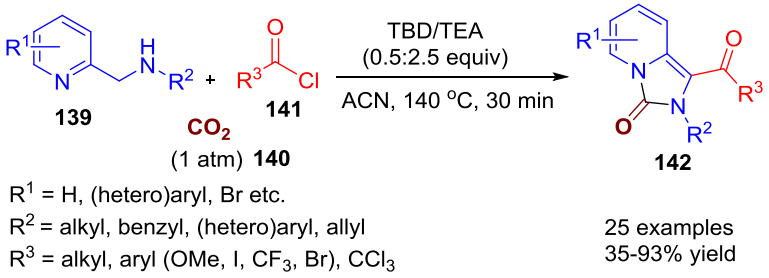
Tan and co-workers have reported a chiral-NHC-catalyzed diastereo- and enantioselective dearomatizing double Mannich reaction of isoquinolines **31** towards substituted tropane derivatives **138** with four adjoining stereocenters.[90] In contrast to regular Reissert-type reactions, this work utilizes two reactive sites of isoquinolines for dearomatization, leading to the synthesis of tropane derivatives with excellent stereoselectivity. To demonstrate the utility of this

transformation, the authors carried out a synthesis of the product at millimole scale resulting in a 50% yield with high stereoselectivity (99.5% ee, d.r. > 20:1). Mechanistically, the addition of the NHC catalyst to the enal **134** resulted in an intermediate with a nucleophilic *β*-carbon center. Nucleophilic Mannich attack at the C1 position of isoquinonium **137** results in the formation of enol intermediate **A**, followed by proton transfer to generate the enolate **B** with an active iminium ion moiety, which participates in an intramolecular Mannich reaction to deliver the key tropane skeleton **C**. A final esterification reaction leads to ester formation through attack by ethanol **136** and regenerates the catalyst (Scheme 28).



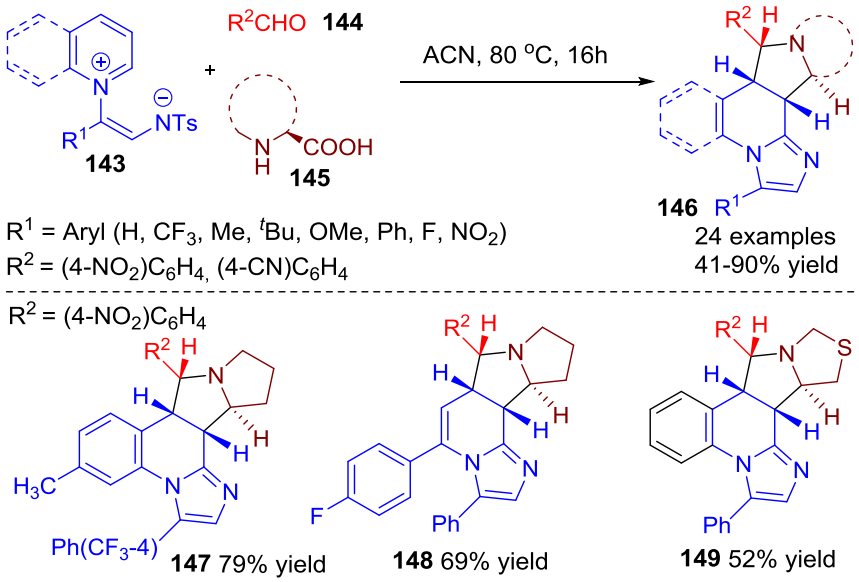
Scheme 28: Chiral-NHC-catalyzed diastereo- and enantioselective dearomatizing double Mannich reaction of isoquinolines.

The use of "electrophilic" CO_2 as a reaction partner in dearomatization processes is rare and can be explained by the fact that both dearomatization as well as CO_2 activation demand high energy. A redox-neutral 1,3,5-triazabicyclodec-5-ene (TBD)-assisted three-component synthesis of imidazopyridinones **142** has been described *via* pyridine **139** dearomatization with CO_2 as a benign CO surrogate (Scheme 29).[91] The methodology enables the synthesis of densely functionalized imidazo-pyridinones in high yields (35-93%) and excellent chemoselectivity. The role of TBD as a promoter and RCOCl **141** as an electrophilic CO_2 co-activator cum acylating agent was supported by combined experimental, spectroscopic and computational investigations.



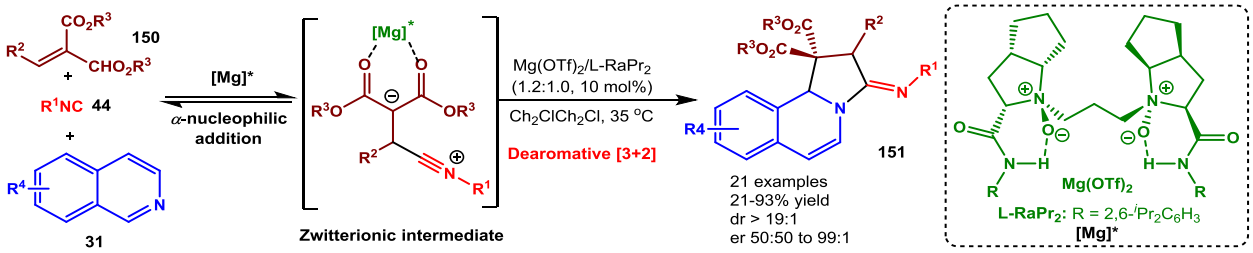
Scheme 29: Three-component carbonylative dearomatization of pyridine derivatives with CO_2.

A catalyst-free multicomponent reaction of an amino acid **145**, an aldehyde **144**, and an *N*-aromatic zwitterion **143** to construct polycyclic fused pyrrolizidines *via* [3+2] cycloadditions was described by Yoo and co-workers.[92] These polycyclic fused pyrrolizidines **146** were constructed in moderate to good yields via *in situ* formation of an azomethine ylide from decarboxylative reaction of an aldehyde and an amino acid followed by the [3+2] cycloaddition with an *N*-aromatic zwitterions (Scheme 30).



Scheme 30: A multicomponent cycloaddition reaction of an amino acid, an aldehyde, and an *N*-aromatic zwitterion *via* an azomethine ylide intermediate.

Although isocyanide-based multicomponent reactions are proven to be simple, elegant and facile strategies for the synthesis of highly valuable nitrogen-containing heterocycles, their asymmetric versions leading to optically active nitrogen heterocyclic compounds are rather limited. Relying on the enantioselective addition of simple isocyanides **44** to C=C bonds, a three component reaction was designed for the synthesis of chiral 1,2-dihydroisoquinolines employing a chiral Mg^{II}-*N,N'*-dioxide catalyst (Scheme 31).[93] Thus, taking advantage of this zwitterionic intermediate as a 1,3-dipole, an enantioselective dearomative [3+2] annulation reaction of nonactivated isoquinolines is achieved, furnishing chiral 1,2-dihydroisoquinolines **151** in moderate to good yields with acceptable enantioselectivity.



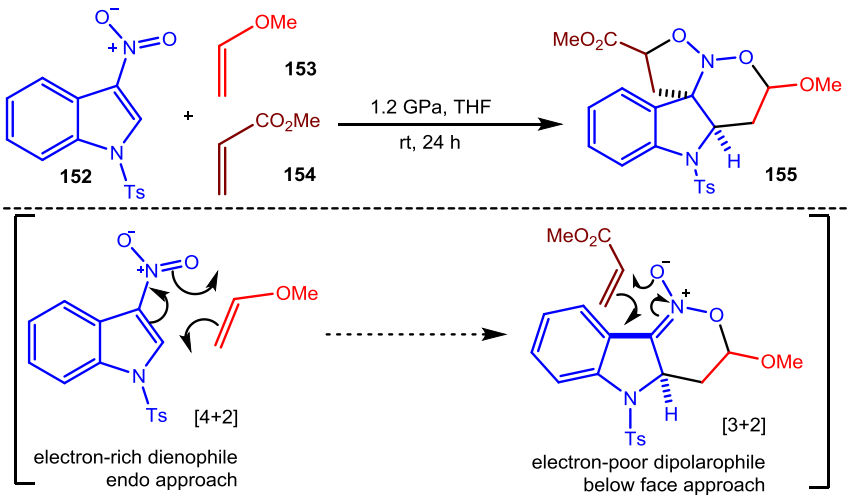
Scheme 31: Asymmetric synthesis of 1,2-dihydroisoquinolines *via* an MCR approach.

2.3. Dearomative MCRs of indoles

Indole alkaloids represent a large array of complex natural products with diverse and potent biological activity. Asymmetric dearomatization reactions of indole derivatives have recently attracted a lot of attention and of late has played an significant role in the total synthesis of natural products.[10,25] This section will highlight dearomative reactions of indoles along with cycloadditions, aza-Diels-Alder, and radical addition.

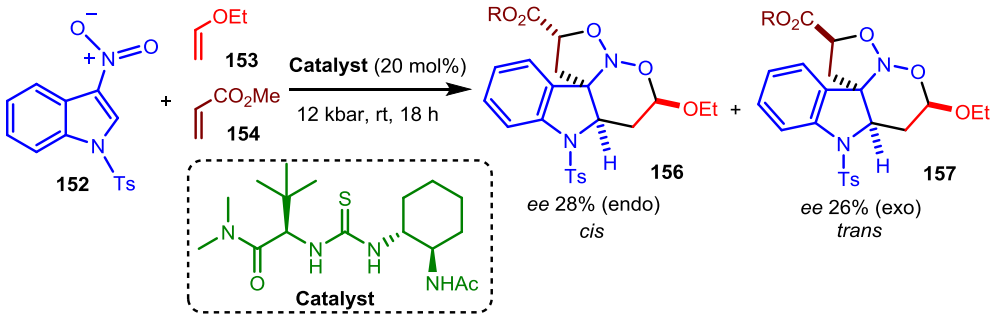
2.3.1. Dearomative cycloaddition reactions of indoles

Nitro-group containting heterodienes are one of the most exploited synthons to generate useful synthetic intermediate *via* the cycloaddition reaction. Installation of a nitro-group on the C(3) position of an indole is one of the most important approaches for the reversal of the natural reactivity of an indole in cycloaddition reactions. In 2007, Chataigner and Piettre utilized this inverse electron demand of 3-nitroindole **152** to construct tetracyclic dearomatized diamines **155** *via* a multicomponent [4+2]/[3+2] cycloaddition.[94] Later in 2013, Gérard and Chataigner performed DFT calculation to unveil the chemo-, regio-, and stereoselectivity of the multicomponent cycloaddition reaction involving nitroindole derivatives **152** with vinyl ethers **153** and acrylates **154**.[95] In this study, the authors proposed the mechanistic details of an electron-deficient 3-nitroindole undergoing a [4+2] cycloaddition with an electron-rich alkene. The *insitu* generated intermediate then exclusively form the [3+2] cycloaddition product with an electron deficient alkene in a selective manner (Scheme 32).



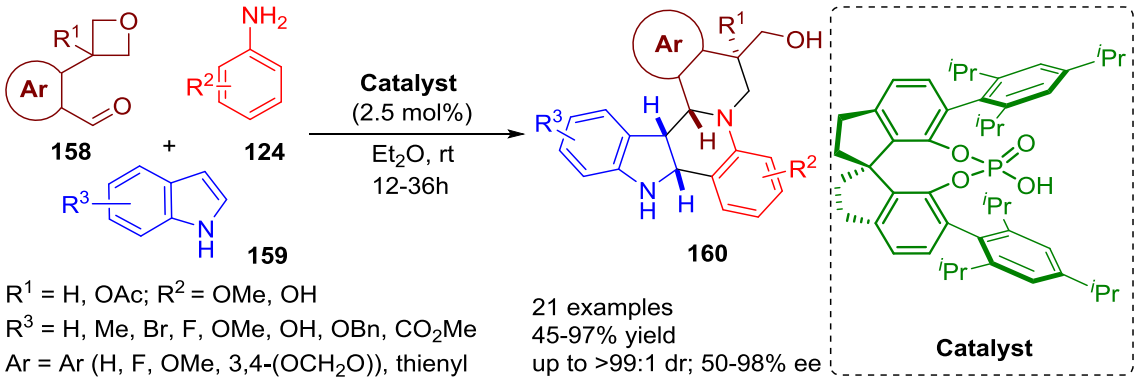
Scheme 32: Multicomponent domino [4+2]/[3+2] cycloaddition of nitroindoles.

In 2015, Chataigner and co-workers employed chiral thiourea as an organocatalyst to facilitate the enantioselective synthesis of 3-component [4+2]/[3+2] cycloaddition reactions (Scheme 33).[96] The authors successfully use a Lewis acid activation approach in the presence of acid sensitive reaction conditions generating products **156**, **157** with modest enantioselectivity.



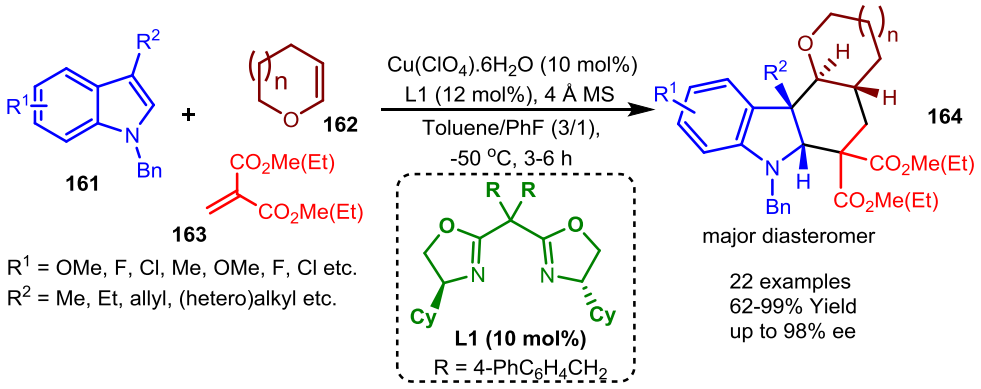
Scheme 33: Thiourea-catalyzed dearomatizing [4+2] cycloadditions of 3-nitroindole.

In 2013, Zhu, Sun and co-workers accomplished a chiral phosphoric acid (CPA) catalyzed multi-component reaction, using *in situ* generated imines as electrophiles, to realize the asymmetric dearomatization of indoles (Scheme 34).[97] This asymmetric three-component aza-Diels-Alder reaction employs indole **159** as the dienophile. The oxetane **158** stands out as a superb directing group, which plays a crucial role in achieving high yields as well as high enantioselectivities. A range of complex polycyclic alkaloid-type molecules **160** that contain indoline, tetrahydroquinoline, and tetrahydroisoquinoline moieties were rapidly assembled from a simple achiral starting materials with multiple diversity points.



Scheme 34: CPA-catalyzed asymmetric aza-Diels–Alder reaction of indoles.

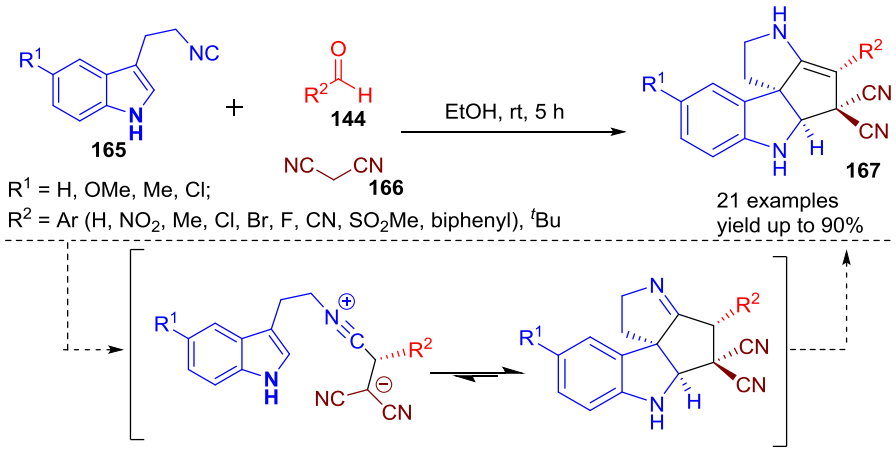
Tang and co-workers reported a highly regio-, diastereo-, and enantioselective Cu(II)/BOX-catalyzed multicomponent reaction between an indoles **161**, 2,3-dihydropyran **162** and a methylene malonate **163** to give highly enantio-enriched tetracyclic indolines **164** with four contiguous stereocenters (Scheme 35).[98] The Cu(II)/BOX catalytic system displayed an effective synergetic tandem enantiomeric enrichment in contrast to the moderate enantioselectivities achieved by either formal cyclobutanation or by similar [4+2] cycloaddition reactions.



Scheme 35: Enantioselective construction of tetracyclic indolines with four contiguous stereocenters.

2.3.2. Isonitrile-based MCRs for indole dearomatizations

In 2013, Ji and co-workers reported a catalyst-free multicomponent approach for the synthesis of polycyclic spiroindolines **167** employing a 2-isocyanoethylindole **165**, malononitrile **166** and various aromatic aldehydes **144** (Scheme 36).[99] The reaction started with a Knoevenagel condensation of malononitrile and aldehyde, followed by nucleophilic attack of isocyanide. Subsequent protonation and nucleophilic attack by C-3 of the indole afforded the desired products in good to high yields and diastereoselectivity.

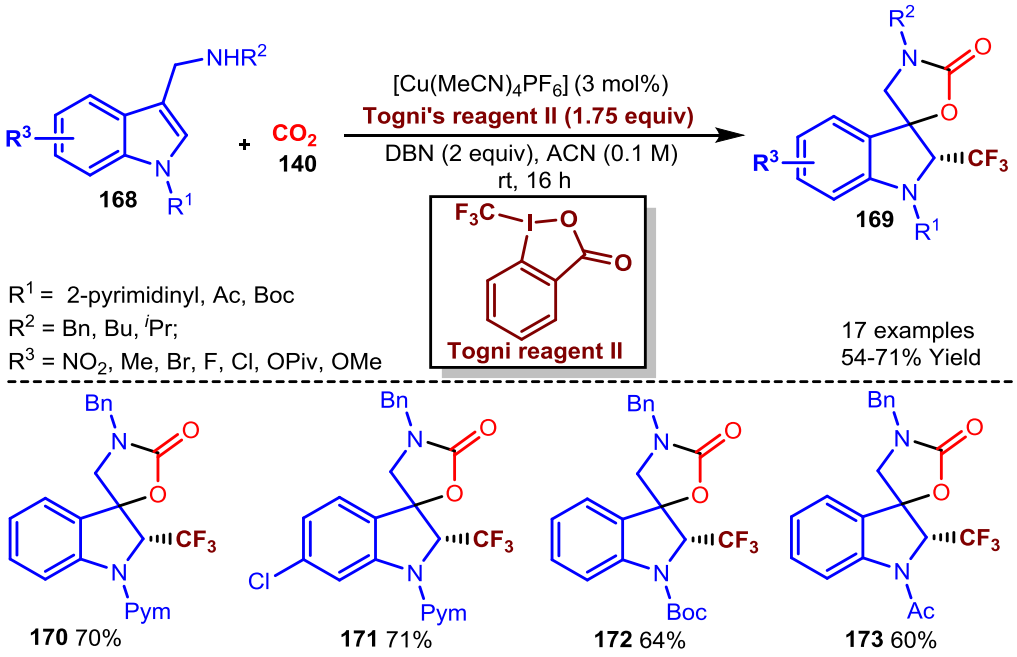


Scheme 36: Catalyst-free stereo-selective construction of polycyclic spiroindolines.

2.3.3. Indole dearomatization *via* radical addition

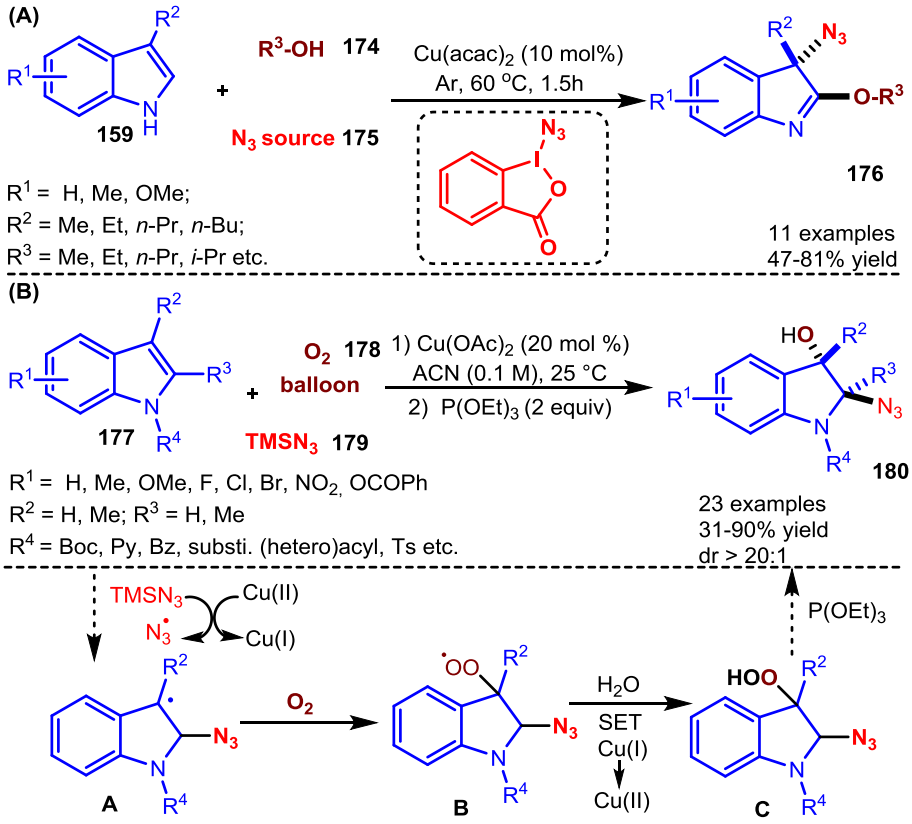
Lan, Yu and co-workers disclosed an efficient approach to synthesize spiro 2-oxazolidones **169** through trifluromethylative dearomatization of indoles **168** with CO_2 **140** employing copper-catalysis and 1,5-diazobicyclo[4.3.0]non-5-ene (DBN) as a base (Scheme 37).[100] A variety of important CF_3-containing spirocyclic indolines and spiroacetals was synthesized with atmospheric CO_2 under mild reaction conditions. The reaction proceeded with deprotonation of the amine, followed by insertion of CO_2 (free energy barrier 14.1 kcal/mol) into the Cu-N bond to generate copper carboxylate species. The electrophilic addition of the CF_3 radical onto the C-2 position of the indole copper carboxylate species and subsequent radical-radical cross-coupling delivered the desired product. The mechanism was supported by DFT calculations and

experimental data. A wide range of functional groups were compatible under this mild conditions to furnish products in good to excellent yields.



Scheme 37: Radical trifluoromethylative dearomatization of indoles and furans with CO_2.

Azides are widely used precursors for click chemistry as well as for constructing amines and N-containing heterocycles. In 2014, Jiao and co-workers employed azidoiodinane **175** as N_3 radical source to synthesize 3-azido indolenine **176** and oxindole derivatives in good to moderate yields. After the screening of various transition metal-catalyst, copper-catalyst, in particularly $Cu(acac)_2$, was found to be best (Scheme 38A) for this three-component reaction.[101] Following this report, Xu, Ji and co-workers further explored this approach for the C-2 functionalization of indole by combining a cheap copper catalyst with $TMSN_3$ **179** and O_2 to furnish 2-azidoindolin-3-ol derivatives **180** under mild reaction conditions.[102] The reaction proceeds via oxidation of $TMSN_3$ by Cu^{II}, followed by addition of the azido radical on the C-2 position of the indole to produce radical intermediate **A**, which was further trapped by molecular oxygen to afford peroxy radical **B**. Subsequent SET and reduction by $P(OEt)_3$ delivered 2-azidoindolin-3-ols in good to excellent yields with high diastereoselectivity (Scheme 38B).



Scheme 38: Copper-catalyzed dearomatizing azidation of indoles.

2.3.4. Indole dearomatization *via* other reactions

Panda and Ready revealed a three-component reaction with an *insitu* generated lithiated indole, an allylic acetate **182**, **184** and boronic ester **183** to furnish indoline derivatives **185** and **186** (Scheme 39A).[103] The enantioselective 1,2-boronate rearrangement in the presence of a chiral Pd-catalyst delivered the dearomatized 3-component products in good to excellent yields with high enantiomeric excess. In addition, to obtain optically active indolines, the boronic esters were deborylated using $Bu_4NF{\cdot}3H_2O$. The deborylation occurred stereospecifically with retention of stereochemistry to yield the indolines **187**-**190** with three contiguous stereocenters. Diastereoselectivities were generally >10:1 with cyclic allylic acetates and around 4:1 with acyclic allylic acetates. Many of the valuable transformations of organoboranes involve 1,2-metalate rearrangements. These processes involve a 1,2-migration of an organic fragment from boron to carbon. Following their previous work, the same group in 2018 reported another three-component reaction with lithiated indoles, boronate esters **192** and allylic acetates **191** (Scheme 39B).[104] The authors were the first to report the use of phosphoramidite as a chiral ligand in a Pd-catalyzed asymmetric synthesis. The end product utility was demonstrated by employing photocatalytic diastereoselective functionalization of indoline boronic esters **193**.

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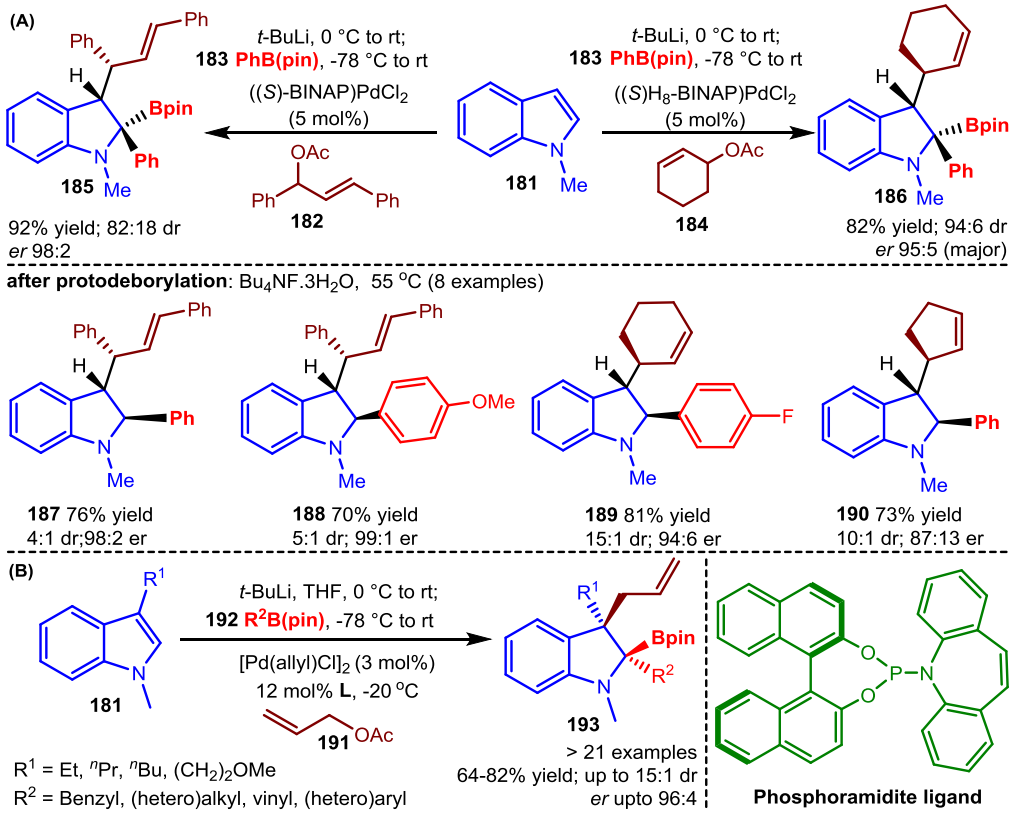
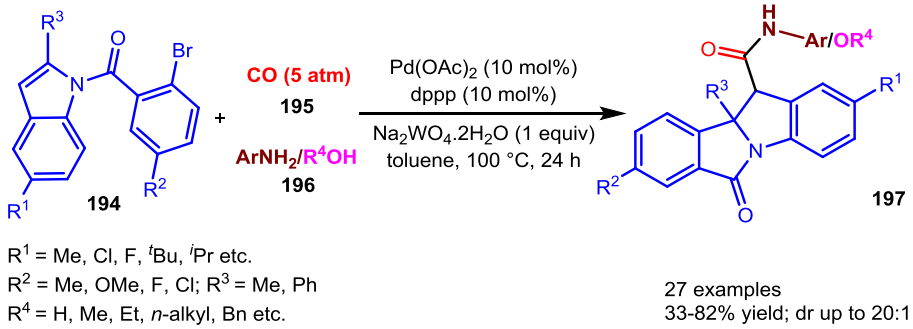


Scheme 39: Asymmetric synthesis of indolines *via* a tandem allylation/1,2-boronate rearrangement.

Wang and Wu described a dearomative carbonylation strategy towards *N*-(2-bromobenzoyl)indoles **194** to furnish the desired amide or ester **197** by employing a commercially available $Pd(OAc)_2$ catalyst and DPPP ligand (Scheme 40).[105] The authors demonstrated the wide substrate scope with good functional group tolerance. Out of the several bases tested, $Na_2WO_4.2H_2O$ gave the best results along with 5 bar of CO pressure. With alcohols, slightly different conditions were used to enhance the yield and diastereoselectivity.



Scheme 40: Palladium-catalyzed carbonylative dearomatization of indole derivatives.

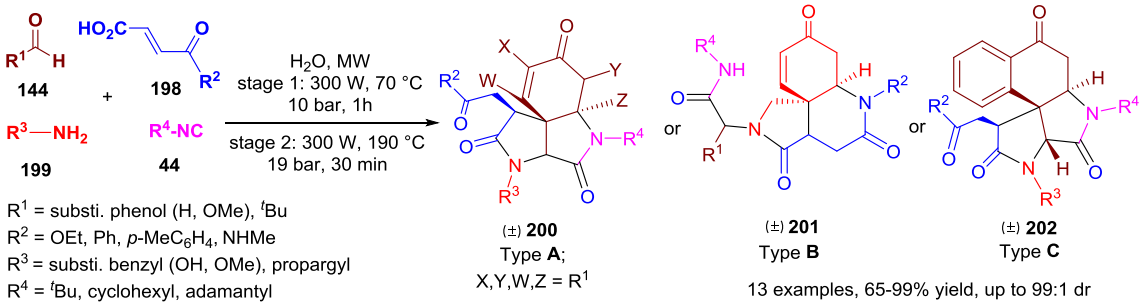
3. Sequential multicomponent reaction/cascade dearomatization processes

This section will cover a concise overview of sequential multicomponent dearomative reactions of various (hetero)arenes. As there are already several review articles[18,19,106,107] that cover this

topic, a few selected examples with a focus on recent reports will be discussed here. In addition, some important mechanisms will be discussed. For the sake of clarity, we have divided this part into sub-sections. Since the Ugi 4-CR has played an important role in the post-MCR dearomative cascade cyclizations, it would be covered as a separate topic.

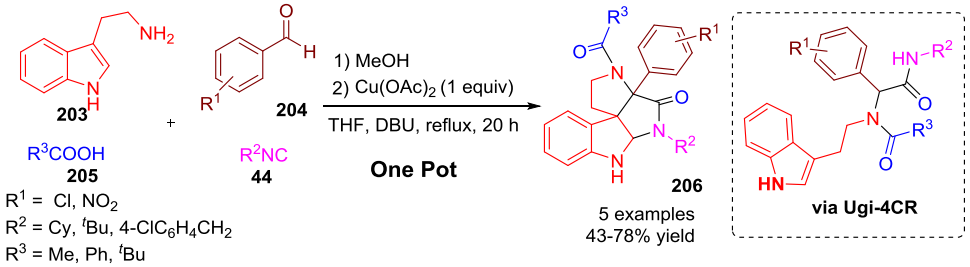
3.1. Post-MCR one-pot dearomatization reactions

Santra and Andreana reported one-pot Ugi/Michael/aza-Michael cascade reaction for the synthesis of complex natural-product like fused azaspiro tricycles **200, 201** and tetracyclic structures **202** employing microwave irradiation and water as a solvent (Scheme 41).[108] The authors have successfully presented a wide scope with good regioselectivity and considerable diastereoselectivity. Three different kinds of products were obtained based on the substrate chosen during the Ugi reaction. Further, the authors revealed the effect of a bulky group in the regioselective outcome based on Bürgi-Dunitz trajectory and proximity effect. An electron-donating group on the aldehyde was found to favor the formation of the desired product, whereas an electron-withdrawing group resulted in decomposition.



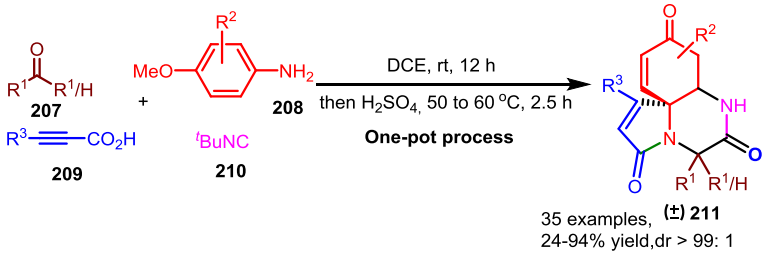
Scheme 41: A bioinspired Ugi/Michael/aza-Michael cascade reaction.

Miranda and co-workers reported a one-pot procedure to build complex spiroindolines *via* a radical mechanism involving a copper-catalyzed oxidative process (Scheme 42).[109] The cheap and atom economical approach allows the synthesis of the complex alkaloids **206** in good to moderate yields under mild conditions. The reaction mechanism probably involves the oxidative generation of a peptidyl radical triggered by copper(II) salts.



Scheme 42: Spiroindolines via a one-pot procedure combining an Ugi coupling and a copper-catalyzed oxidative process.

The Ugi reaction with cascade dearomative cyclization has successfully led to the synthesis of numerous polyheterocycles. Srivastava and co-workers have developed a method for the synthesis of alkaloid-mimicking azaspiro fused tricyclic skeletons **211** employing a one-pot Ugi reaction and acid mediated ipsocyclization/aza-Michael addition in a highly diastereo- and regioselective manner (Scheme 43).[110] The use of inexpensive sulfuric acid and the easy purification procedure makes this process highly adoptable for library generation of small molecules for drug discovery.



Scheme 43: Alkaloid-mimicking tricyclic skeletons by Ugi/ipso-cyclization/aza-Michael cascade.

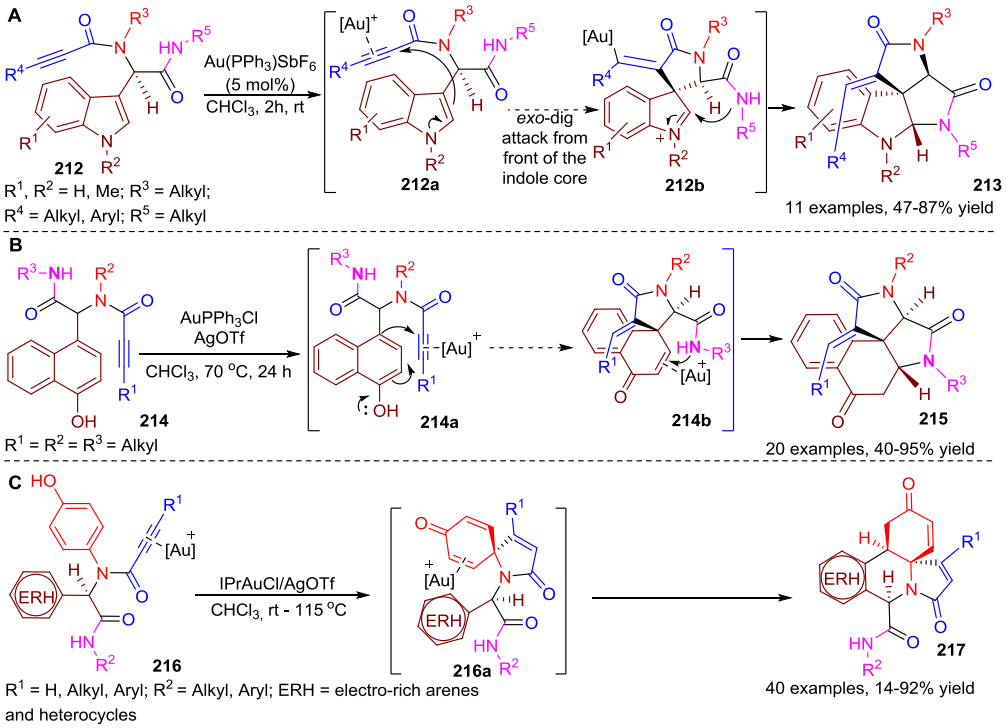
3.2 Dearomative transformation of multicomponent adducts

Using Ugi-MCR, highly functionalized linear scaffolds can be easily constructed. In this section, a concise and recent overview of sequential cascade cyclizations of MCR adducts with different metals or under metal-free conditions is discussed. Functionalities introduced in the linear Ugi-adduct provides a myriad of post-condensation transformations.

Spirocyclizations have been perceived as interesting methods for the generating the complex heterocyclic systems with inbuilt of stereo- or regio-selectivity in most cases. Access of highly diverse alkaloids in a one-pot cascade fashion is highly desirable from the sustainable chemistry viewpoint. In this context, Van der Eycken and co-workers have effectively exploited the catalytic activity of π-acidic gold salts for triple bond transformations for the synthesis of fused polycyclic spiroindolinones **213** (Scheme 44A).[111] The developed post-Ugi, gold(I)-catalyzed diastereoselective cascade cyclization process involved a "branched-handed" pre-cyclization architecture resulting from the chiral center present in the Ugi adduct **212**. The expected outcome of the reaction was an indoloazepinone through an *endo*-dig cyclization and rearrangement sequence. Instead an *exo-dig* cyclization followed by intramolecular trapping of the spiro-intermediate occurred, resulting in the diastereoselective formation of a tetracyclic spiroindolinone this led to several works in this direction.

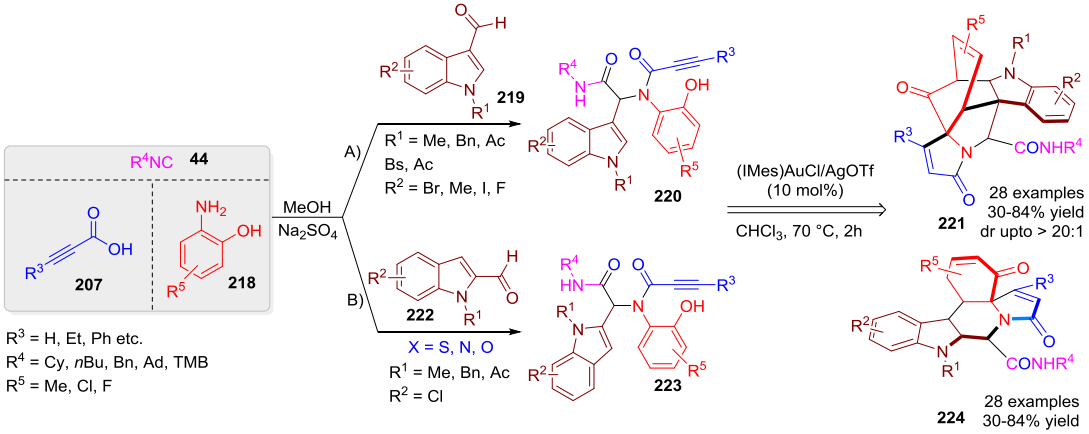
Fused azaspiro tetracyclic *N*-heterocycles are prominent molecular motifs that are widely present in different alkaloids such as (+)-plicamine, (+)-tazettine and (+)-erysotramidine. The dearomatization/ipso-cyclization of phenols has already attracted a lot of attention due to its unique capacity to generate highly functionalized spirocarbocycles as discussed previously. In this direction, Van der Eycken and co-workers reported a gold(I)-catalyzed post-Ugi domino dearomatization/ipso-cyclization/aza-Michael sequence to construct diverse and complex fused azaspiro tetracyclic scaffolds **215** in only two operational steps (Scheme 44B).[112] A postulated

reaction mechanism involves π-activation of the triple bond by *in situ* formed cationic gold(I) species (**214a**) followed by nucleophilic attack at the C-4 position of the 1-naphthol in a *5-exo-dig* fashion, resulting in the formation of the spirocarbocyclic intermediate **214b**. Subsequently, aza-Michael addition facilitated by π-activation of the cationic gold species, generates the tetracyclic scaffold **215**. Very recently, in continuation of this idea, the authors developed an efficient gold(I)-catalyzed post-Ugi domino dearomatization/ipso-cyclization/Michael sequence towards a library of diverse (hetero)-arene-annulated polyheterocycles (Scheme 44C).[113] The reaction proceeded well not only with aliphatic isonitriles, but also with aromatic ones which has been unprecedented in most of the previous reports.



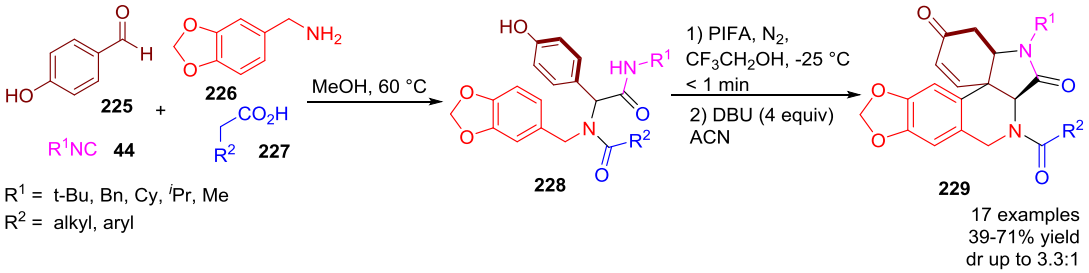
Scheme 44: Gold(I)-catalyzed post-MCR regioselective cascade dearomative cyclizations towards (spiro)polyheterocycles.

Recently, Van der Eycken and co-workers employed a gold catalyst to contrive architecturally complex bridged indole alkaloid-like heterocyclic scaffolds **221** via intramolecular dearomative cascade cyclization followed by [4+2] cyclization (Scheme 45A).[114] Interestingly, the concerted [4+2] cyclization in this developed process introduced complexity in the final product **221** which is generally challenging to achieve in a step-wise manner. Following this report, the same group reported a post-Ugi cascade ortho-dearomatization/spirocarbocyclization/1,6-conjugated addition sequence in case of 2-substituted indole Ugi-4CR adduct (Scheme 45B).[115]



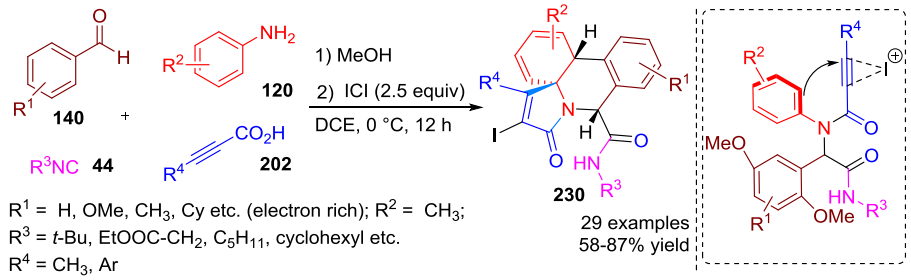
Scheme 45: Complex bridged indole alkaloids *via* intramolecular dearomative cascade cyclizations.

In 2016, Mijangos and Miranda employed Ugi-4CR and post condensation modification towards the synthesis of seventeen plicamine derivatives **229** (*Amaryllidaceae*-type alkaloid) along with the formal synthesis of (±)-plicamine (Scheme 46).[116] The dearomative-intramolecular coupling was achieved in the presence of electrophilic PIFA followed by aza-Michael addition facilitated by DBU to furnish the desired products in good to moderate yields. The authors presented the one-pot oxidative phenol coupling Michael addition sequence to minimize the cost and waste production towards the efficient synthesis of plicamine-type indoloisoquinolines.



Scheme 46: Ugi-4CR and post condensation modification towards the synthesis of plicamine derivatives.

Recently, Sharma and co-workers reported a metal-free diastereo-/regioselective synthesis of a polycyclic phenanthridine-fused constrained heterocyclic scaffold by employing strong electrophile (I^+) under mild reaction conditions (Scheme 47).[117] The authors utilized an unactivated amine to form the Ugi-4CR-adduct which further undergoes ispo-cyclization to deliver desired the complex scaffold **230** in good to excellent yield with high diastereoselectivity. In addition, the authors tested the selected compounds for anticancer activity against human cancer cell lines. A few compounds displayed promising antiproliferative activity against MCF-7 (breast cancer) cell lines, with IC_{50} values in low µM range.



Scheme 47: Phenanthridine-fused tetracyclic ring system *via* a modular post-Ugi dearomative cascade cyclization.

4. Summary and Outlook

In this review, we have presented various multicomponent dearomatization methods to obtain diversely substituted saturated (poly)heterocyclic scaffolds, many of which are key motifs of bioactive natural products or pharmaceuticals, or serve as a versatile synthon for the construction of complex molecules. The multicomponent dearomatization approach is an efficient way to access new carbon–carbon and carbon–heteroatom bonds in a single operation along with the installation of multiple functional groups. The field is somehow scattered; though the first example dates back to 1905 (Reissert reaction), with much development in the field of cycloaddition chemistry and post-MCR modifications. Henceforth, this review might stimulate the progress toward the facile synthesis of natural products (like structures) and rational design of pharmaceutically relevant molecules with dearomatizing MCRs- being an easiest way to construct complex 3D structures. In addition, while generating complexity through these reactions, new reactivity patterns and unexpected complex molecules with potential new applications might also be discovered. Therefore, this review will help the researchers to look at this promising area from different perspectives, with respect to drug discovery and new MCRs based disconnections.

It is pertinent to mention that some of the gaps have clearly been identified and the pursuit for solutions is going on. Most importantly, examples of asymmetric cycloadditions, aryne activation chemistry, dearomative activation of unactivated arenes *via* transition metal-catalysis have already opened doors in the field for the synthesis of diverse heterocyclic scaffolds. The development of novel post-MCR transformations for generating synthetically challenging structures *via* tuning of the gold catalytic system is also catching up fast; albeit more efforts are needed regarding asymmetric synthesis. The underlying idea is that broader diversity in the chemical library will lead to the generation of additional information from biological screenings. Therefore, the synthesis of complex polycyclic molecular scaffolds bearing resemblance to pharmaceutically relevant natural products *via* combination of multicomponent reactions (MCRs) and (asymmetric) dearomatization chemistry is an interesting preposition for organic chemists in a minimum number of steps.

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