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Recent advances in dearomatization of heteroaromatic compounds

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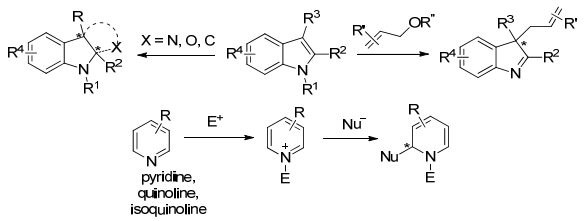
Dearomatization reactions provide the most efficient method for the synthesis of spiro- or fused-ring systems from readily available compounds. This review summarizes the recent developments in dearomatization reactions of indoles, pyridines, quinolines, isoquinolines, and some other heteroaromatic compounds. The applications of these methods in total synthesis of natural products are also briefly introduced.

Introduction

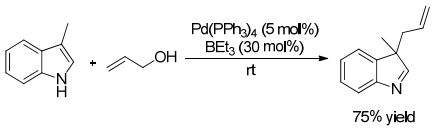
Dearomatization of aromatic compounds is a powerful synthetic strategy providing a direct and economical way to construct architecturally complex molecules, particularly heterocyclic and 3D spirocyclic skeletons, which frequently exist in biologically active natural products and pharmaceuticals. The fascination of such an approach has drawn significant attention in the past decades. Several recent reviews on dearomatization reactions have shown the tremendous potentiality in this aspect.[1-14] For example, the review on the nucleophilic dearomatizing reactions of aromatic C,H-systems by the group of Ortiz,[8] the review on hypervalent iodine-mediated phenol dearomatization in natural product synthesis by the group of Quideau,[10] the review on the application of dearomatization strategies in the synthesis of complex natural products by the group of Porco Jr,[12] and the review on the catalytic asymmetric dearomatization reactions by the group of You,[13] All of these reviews focus on the dearomatization of benzene derivatives. Another family of significance in aromatic compounds, heteroaromatic compounds, is also attractive starting materials for dearomatization. The inherent functionalities stored within the heteroaromatic systems make it possible to be dearomatized by a variety of reactions, such as inter or intramolecular allylation, benzylation, arylation, alkynylation, alkylation, halogenation, hydroboration, olefination, cycloaddition, and cyclization (Scheme 1). Herein, we summarize recent developments in dearomatization reactions of heteroaromatic compounds.



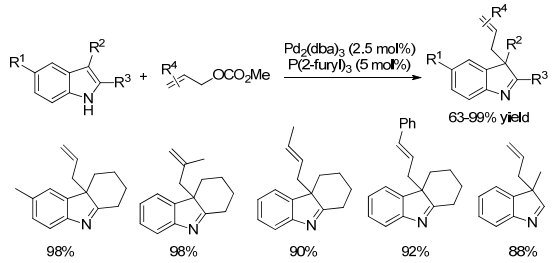
Scheme 1 Dearomatization of heteroaromatic compounds

Dearomatization of indoles

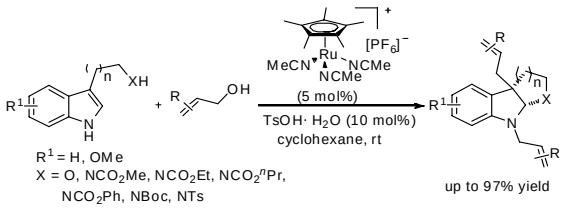
Indoles are the most frequently utilized substrates for dearomatization to access various complex nitrogen-containing molecules. In 2005, Tamaru and co-workers reported a Pd-catalyzed selective C-3 allylation of indoles by allylic alcohols.[15] In the presence of triethylborane, the palladium catalyzed allylation of 3-substituted indoles leads to the allylic dearomatized indolenine derivatives bearing a quaternary stereocenter (Scheme 2). Palladium-catalyzed C-3 allylation of 2,3-disubstituted indoles was reported by Rawal (Scheme 3).[16] A variety of substituted or fused indoles including highly functionalized complex natural products are suitable substrates, and a series of substituted allylic carbonates are efficient ally sources. The group of You also developed a dearomatization of indoles with allylic alcohols catalyzed by a Ru-complex in the presence of catalytic amount of TsOH (Scheme 4).[17] The reaction was proposed mainly through a cascade allylic dearomatization/cyclization/allylic amination sequence. Substituted tryptophols, tryptamines, indolyl carboxylic acids, and carboxyl amides were suitable substrates leading to furoindolines, pyrroloindolines, lactones, and lactams with an allylic substituent at both the C-3 and the N-1 positions of indoles. This methodology was applied into the synthesis of debromoflustramine B with 78% overall yield (Scheme 5).



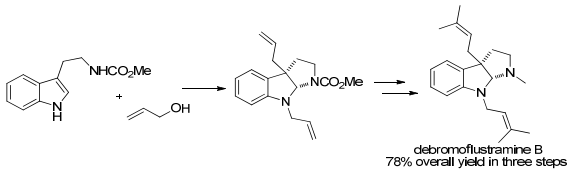
Scheme 2 Palladium-catalyzed C-3 allylation of 3-substituted indoles



Scheme 3 Palladium-catalyzed C-3 allylation of 2,3-disubstituted indoles

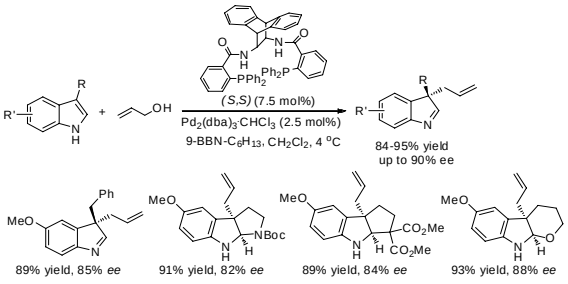


Scheme 4 Ruthenium-catalyzed C-3 allylation of 3-substituted indoles

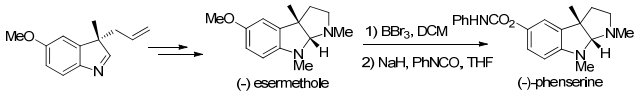


Scheme 5 Synthesis of debromoflustramine B

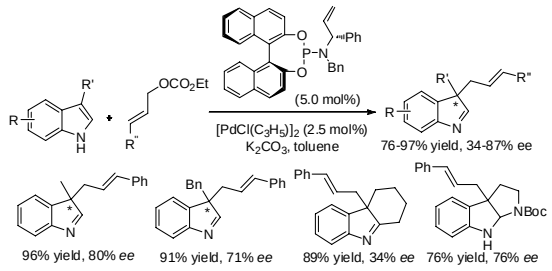
In 2006, Trost and Quancard reported a palladium-catalyzed enantioselective C-3 allylation of 3-substituted indoles (Scheme 6).[18] High enantioselectivities of 3,3-disubstituted indolenines and indolines could be obtained using 9-BBN-C_6H_{13} as the promoter. The resultant indolenines could be easy transformed into (-)-phenserine, a drug candidate for treatment of Alzheimer's disease (Scheme 7). Recently, the group of Du used a chiral phosphite/olefin ligand to promote this reaction (Scheme 8).[19] The synthetic potential of this reaction was demonstrated by the synthesis of natural product Angelicastigmin in 4 steps in good yield (Scheme 9).



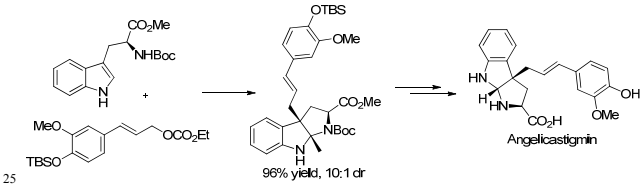
Scheme 6 Palladium-catalyzed enantioselective C-3 allylation



Scheme 7 Synthesis of (-)-phenserine.

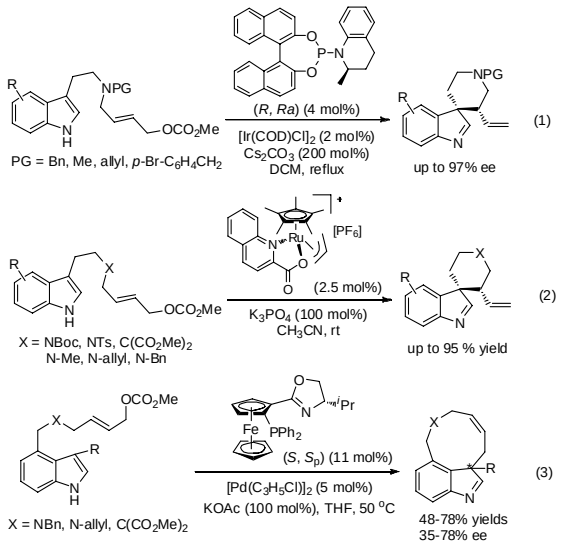


Scheme 8 Pd-catalyzed C-3 allylation using phosphite/olefin ligands



Scheme 9 Synthesis of Angelicastigmin

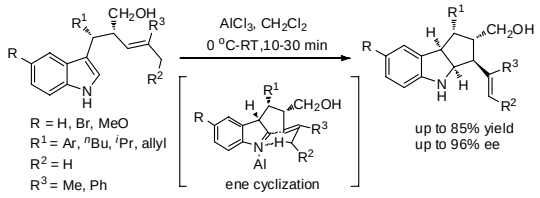
In 2010, You and co-workers described an Ir-catalyzed asymmetric intramolecular allylation of indoles (Scheme 10, eq 1).[20] The reaction gave rise to spiroindolenine products in good yields with excellent *dr*, and *ee* (up to >99/1 *dr* and 97% *ee*). In the cases of those substrates bearing an electron-withdrawing protecting group on the linking N atom or the C-linker, the reaction did not occur. Recently, this group reported a ruthenium-catalyzed allylation (Scheme 10, eq 2).[21] Compared with the Ir-catalytic system, the Ru-catalytic system possesses several notable advantages: high reactivity, a cheaper and easily prepared catalyst, broader substrate scope, insensitivity to water, and mild conditions. Additionally, the You group developed a Pd-catalyzed intramolecular allylation of indole fused through C4–C3 (Scheme 10, eq 3).[22] When substrates bearing a nucleophilic side chain at the 3-position of indole were employed, a cascade reaction afforded polycyclic products.



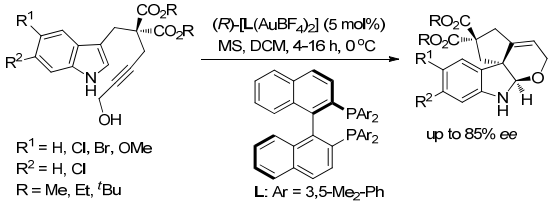
Scheme 10 Enantioselective intramolecular C-3 allylation

The $AlCl_3$-promoted diastereoselective intramolecular imino-

ene reaction of indoles bearing a tethered olefinic functionality was used for the synthesis of a range of highly enantioenriched and versatile cyclopentyl[*b*]indolines (Scheme 11).[23] Bandini and co-workers reported the synthesis of architecturally complex polycyclic fused indolines *via* a gold-catalyzed cascade hydroindolination/iminium trapping synthetic sequence (Scheme 12).[24] Highly functionalized tetracyclic fused furoindolines and dihydropyranylindolines were synthesized from indoles with a propargylic alcohol at C-3 position in a chemo-, regio-, and stereodefined manner.

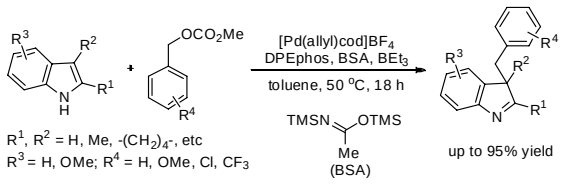


Scheme 11 $AlCl_3$-catalyzed intramolecular imino-ene reactions of indoles

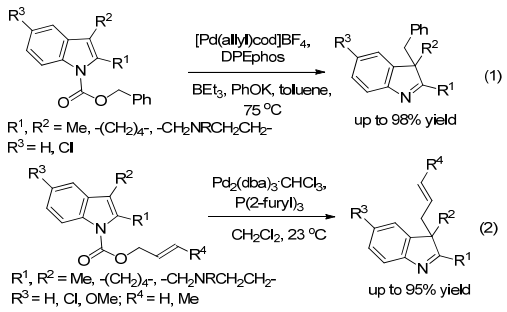


Scheme 12 Gold-catalyzed synthesis of polycyclic indolines

The C3-benzylation of 3-substituted or 2,3-disubstituted indoles with benzyl carbonates was reported by Rawal and Zhu (Scheme 13).[25] N,O-bis(trimethylsilyl)acetamide (BSA) was proposed to facilitate the formation of amide anion which subsequently deprotonates of indole to generate the indolyl anion. The group of Rawal also reported a palladium-catalyzed decarboxylative C3-allylation or C3-benzylation of indoles (Scheme 14).[26] The decarboxylative benzylation reaction required more forcing conditions than the allylation. A wide range of functionalized indolenines were prepared starting from the *N*-alloc or *N*-Cbz indoles. Almost at the same time, Cook reported a palladium catalyzed decarboxylative allylic rearrangement of alloc indoles. This reaction could be combined with a Suzuki-Miyaura cross-coupling reaction in a single pot transformation.[27]

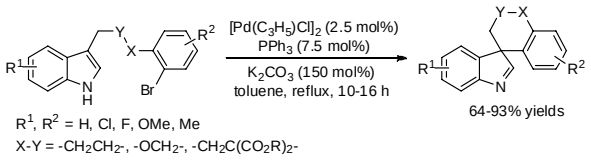


Scheme 13 C3-benzylation of indoles

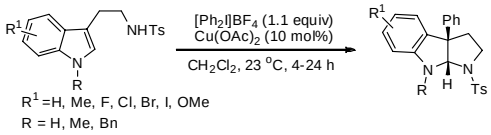


Scheme 14 Decarboxylative C3-allylation or benzylation

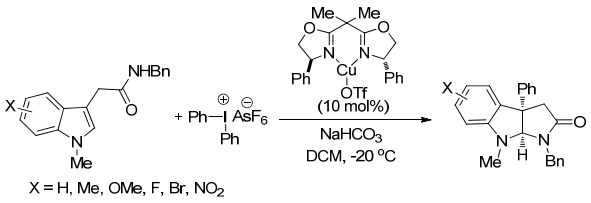
The Pd-catalyzed C-3 arylation reaction of indol-3-yl aryl bromide afforded spiroindolenine derivatives with a quaternary center at the C-3 position (Scheme 15)[28]. Chiral spiroindolenine with moderate enantioselectivity could be obtained by using chiral spiro phosphoramidate as ligand. The group of Reisman developed a copper-catalyzed arylation of *N*-tosyltryptamines for the direct synthesis of C-3-aryl pyrroloindolines (Scheme 16).[29] The enantioselective arylation-cyclization reaction using diaryliodonium salts was described by MacMillan (Scheme 17).[30] Various C-3-aryl pyrroloindolines could be constructed in excellent yields and enantioselectivity. The process was proposed through copper-catalyzed arylative dearomatization and amine-iminium cyclization.



Scheme 15 Palladium-catalyzed dearomative arylation of indoles



Scheme 16 Copper-catalyzed arylation of *N*-tosyltryptamines

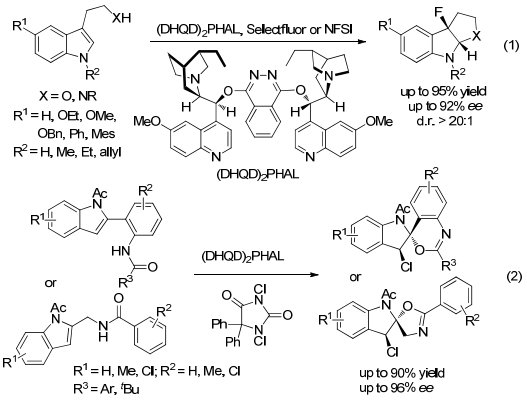


Scheme 17 Copper-catalyzed enantioselective arylation-cyclization

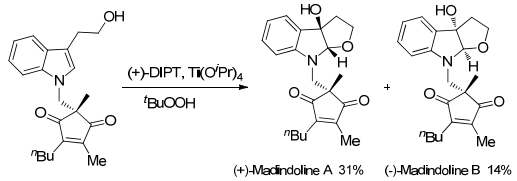
In 2011, Gouverneur and co-workers reported an organocatalyzed enantioselective dearomatization-fluorocyclization reaction (Scheme 18, eq 1).[31] The reaction was carried out in the presence of selectfluor or NFSI and cinchona alkaloid [$(DHQD)_2PHAL$]. The protocol provides an efficient way to access fluorosubstituted tetrahydrofuroindoles and tetrahydropyrroloindoles. You reported an enantioselective electrophilic chlorocyclization of indoles bearing a nucleophile at

the C-2 position to construct a spiro-indoline containing a continuous *spiro* quaternary carbon center and tertiary carbon center (Scheme 18, eq 2).[32] Indol-2-yl benzamides were also suitable substrates. The resultant products containing a chiral C−Cl bond provide an opportunity for diverse transformations. The group of Õmura described the Sharpless asymmetric epoxidation-ring-closure of tryptophol.[33] The process involved the intramolecular enantioselective dearomative etherification transformation. This method was used as the key step for the total synthesis of (+)-madindoline A and (-)-madindoline B (Scheme 19).

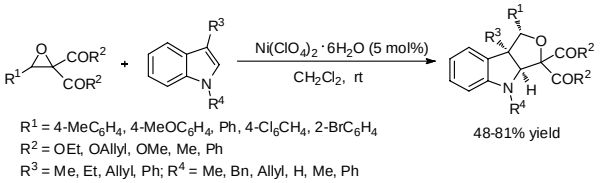
In 2012, Zhang and co-workers demonstrated a $Ni(ClO_4)_2$-catalyzed regio- and diastereoselective [3 + 2] cycloaddition of aryl oxiranyl-dicarboxylates/diketones and indoles (Scheme 20).[34] Recently, the group of Tang reported a highly diastereo- and enantioselective $Cu(OTf)_2$-catalyzed formal [3 + 2] cycloaddition of indoles with cyclopropanes (Scheme 21).[35] The application of this method for the four-step synthesis of the core structure of borreverine was carried out successfully in 23% overall yield.



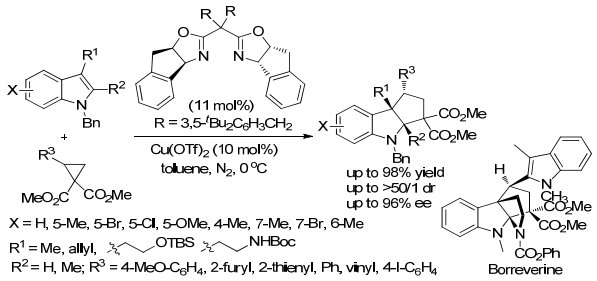
Scheme 18 Organocatalyzed enantioselective fluorocyclizations



Scheme 19 Synthesis of (+)-madindoline A and (-)-madindoline B

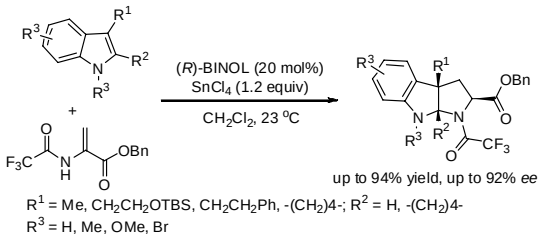


Scheme 20 $Ni(ClO_4)_2$-catalyzed [3 + 2] cycloaddition of indoles with epoxides

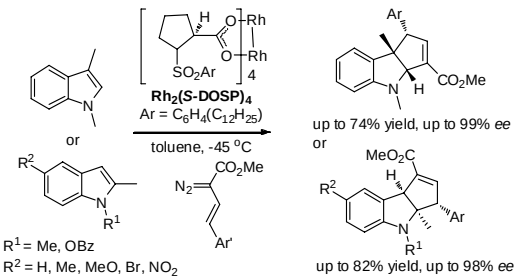


Scheme 21 $Cu(OTf)_2$-catalyzed [3 + 2] cycloaddition of indoles with cyclopropanes

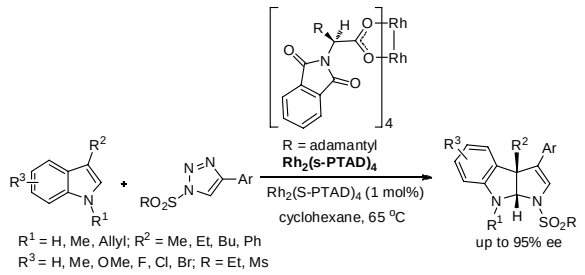
Reisman reported a BINOL/$SnCl_4$-catalyzed enantioselective [3 + 2] cycloaddition between indoles and 2-amidoacrylates for the synthesis of pyrroloindolines (Scheme 22).[36] Davies reported a Rh(II)-catalyzed formal [3 + 2] cycloaddition of indoles with carbenoids derived from vinyl diazoacetates (Scheme 23).[37] When 1,2-disubstituted indoles were used as substrates, only exo diastereomer of each fused indoline was formed with very high asymmetric induction. When the reaction was extended to 1,3-disubstituted indolyl derivatives, only endo diastereomer was observed with excellent enantioselectivity. In 2013, the group of Davies reported another rhodium(II)-catalyzed dearomatization annulation reactions of indoles (Scheme 24).[38] A variety of aryl-substituted pyrroloindolines were prepared *via* a formal [3 + 2] cycloaddition of indoles with the Rh(II)-bound carbenoids derived from 4-aryl-1-sulfonyl-1,2,3-triazoles.



Scheme 22 BINOL/$SnCl_4$-catalyzed enantioselective [3 + 2] cycloaddition of indoles with 2-amidoacrylates



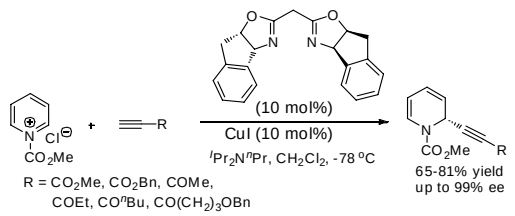
Scheme 23 Rhodium-catalyzed [3 + 2] cycloaddition of indoles with carbenoids



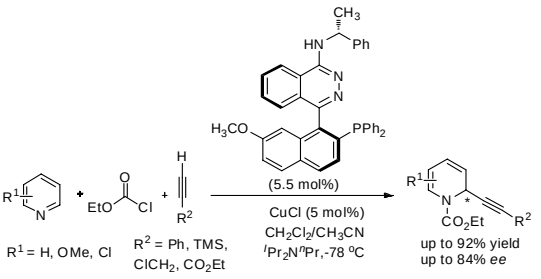
Scheme 24 Rhodium-catalyzed [3 + 2] cycloaddition of indoles with carbenoids

Dearomatization of pyridines

In 2007, the group of Ma reported a CuI/bisoxazoline-catalyzed enantioselective dearomatization/alkynylation of acylpyridinium salts with activated terminal alkynes (Scheme 25).[39] This protocol was used to synthesize a wide range of polysubstituted piperidines and indolizidines. It is noteworthy that the reactions showed good yields and high *ee*s only to those 1-alkynes with a carbonyl group in the 3-position. Shortly thereafter, Arndtsen and co-workers reported a CuCl-catalyzed enantioselective dearomatization/alkynylation of pyridines, quinolines, and isoquinolines with terminal alkynes (Scheme 26).[40] A range of alkynes including various functionalized, electron-rich and electron-poor alkynes could be used in this reaction.

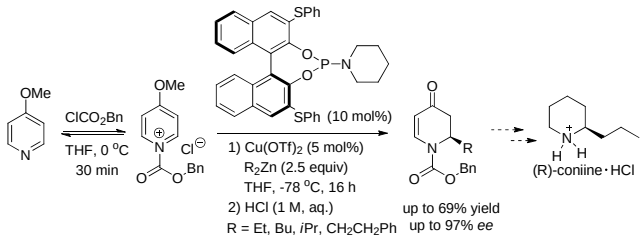


Scheme 25 Copper-catalyzed addition of 1-alkynes to 1-acylpyridinium salts

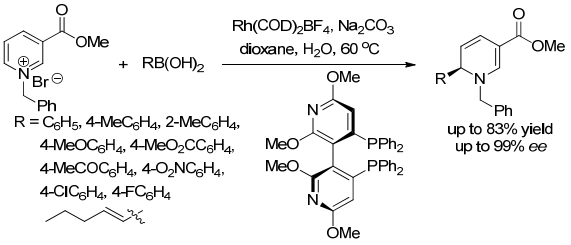


Scheme 26 Copper-catalyzed addition of 1-alkynes to pyridines

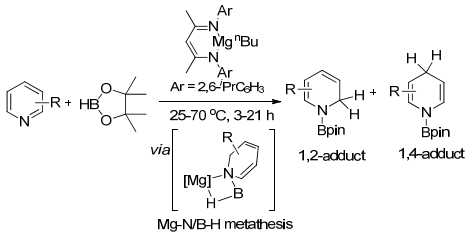
In 2009, Feringa developed an asymmetric dearomatization of pyridines by a direct alkylative Reissert-type process catalyzed by copper/phosphoramidite catalysts (Scheme 27).[41] To demonstrate the synthetic versatility of the method, the formal synthesis of the alkaloid (-)-coniine was presented efficiently from 4-methoxypyridine. In 2011, Nadeau and co-workers reported the Rhodium-catalyzed enantioselective dearomatization/arylation of *N*-benzylnicotinate salt with boronic acids (Scheme 28).[42] Pent-1-en-1-ylboronic acid was also a suitable reagent. The dearomatization−hydroboration of pyridine derivatives with pinacol−borane catalyzed by a *β*-diketiminato *n*-butylmagnesium complex was reported by Hill (Scheme 29).[43] The reaction was proposed to proceed through a sequence of Mg−H/pyridine dearomatization and Mg−N/B−H sigma bond metathesis steps.



Scheme 27 Alkylative Reissert reaction of pyridines

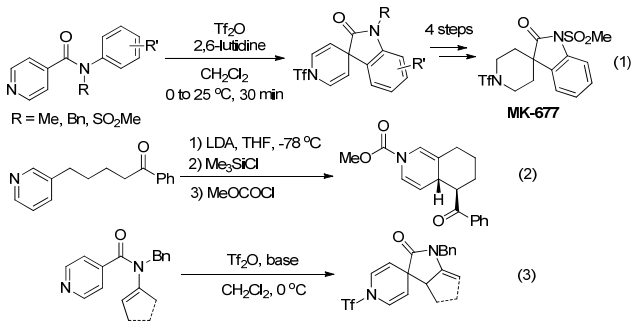


Scheme 28 Rhodium-catalyzed dearomatization/arylation of *N*-benzylnicotinate salt with boronic acids



Scheme 29 Magnesium-catalyzed hydroboration of pyridines

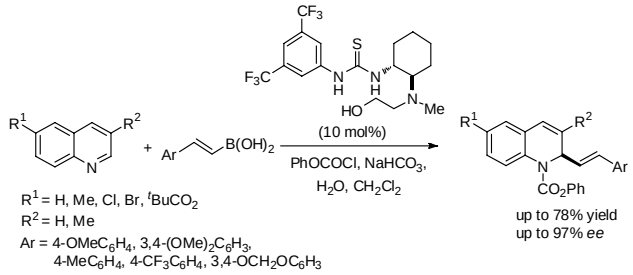
The group of Clayden described the Tf_2O-induced dearomatizing spirocyclization of *N*-arylisonicotinamides in the presence of a hindered base (Scheme 30, eq 1).[44] The reaction generates valuable benzo-fused spirocyclic dihydropyridines which can be converted to valuable biologically active spirocyclic piperidines such as MK-677 (a growth hormone receptor). In 2010, this group realized the synthesis of fused bicyclic dihydropyridine by dearomatizing cyclization of the enolate of nicotinyl-substituted ketone (Scheme 30, eq 2).[45] Recently, Clayden et al. reported another electrophile-induced dearomatizing cyclization of *N*-alkenyl pyridinecarboxamides (Scheme 30, eq 3).[46] A range of spirocyclic dihydropyridines were obtained from a series of *N*-alkenylisonicotinamides incorporating variously substituted alkenes in the presence of triflic anhydride or chloroformates. The resultant products could be further elaborated to spirocyclic heterocycles with drug-like features.



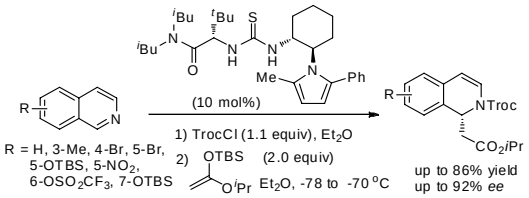
Scheme 30 Electrophile-induced dearomatizing cyclization of pyridines

Dearomatization of quinolines and isoquinolines

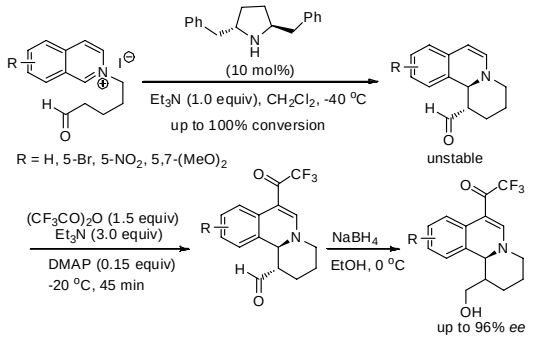
In 2007, Takemoto and co-workers designed a thiourea catalyzed enantioselective dearomative olefination of quinolines with organoboronic acids (Scheme 31).[47] In 2005, Jacobsen reported a thiourea-catalyzed asymmetric dearomatization of isoquinolines via an acyl-Mannich process (Scheme 32).[48] Isoquinolines were activated by acylating reagents (TrocCl) and subjected to nucleophilic attack by the silyl ketene acetal derived from isopropyl acetate. Almost at the same time, the group of Jørgensen described an organocatalytic enantioselective dearomatization reaction of alkylated isoquinolines (Scheme 33).[49] The unstable annulation products could be conveniently transformed into stable 1,2-dihydroisoquinolines under treatment with TFFA and $NaBH_4$.



Scheme 31 Thiourea catalyzed dearomative olefination of quinolines

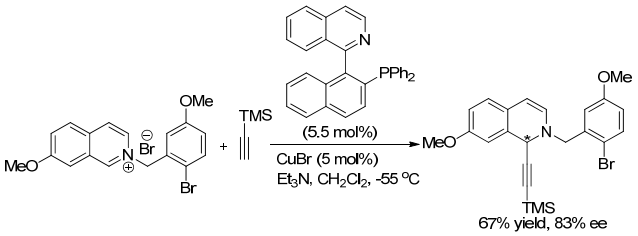


Scheme 32 Thiourea-catalyzed acyl-Mannich reactions of isoquinolines



Scheme 33 Organocatalyzed annulation of alkylated isoquinolines

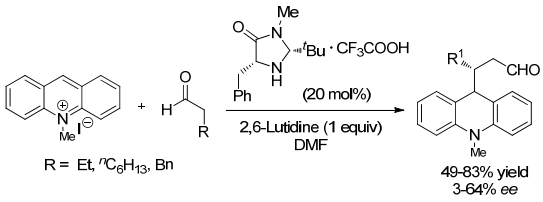
The enantioselective addition of terminal alkyne to the isoquinolinium ion catalyzed by CuBr/quinap was reported by Taylor and Schreiber in 2006 (Scheme 34).[50] This reaction inspired the further developments of direct enantioselective dearomatization/alkynylation.



Scheme 34 Copper-catalyzed addition of terminal alkyne to isoquinolinium salt

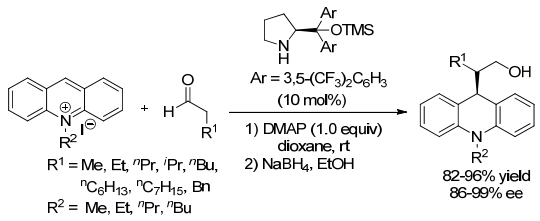
Dearomatization of other heterocycles

In 2010， Cozzi and co-workers described the α-alkylation of aldehydes with the methylacridinium carbocation promoted by the MacMillan catalyst imidazolidinonium and in the presence of a stiochiometric amount of 2,6-lutidine as a base (Scheme 35).[51] Regrettably, the reactions showed low enantiomeric excesses under the optimized conditions.



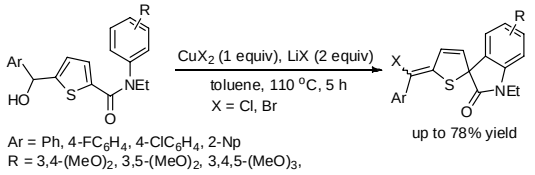
Scheme 35 Dearomatization of methylacridinium carbocation

Recently, Li and co-workers also reported the similar reaction catalyzed by diarylprolinol silyl ether (Scheme 36).[52] This method provided a way to the highly enantioenriched chiral acridane derivatives.



Scheme 36 Organo-catalyzed 1,4-addition of aldehydes to acridiniums

In 2012, Yin and co-workers developed the construction of halogenated spirothienooxindoles *via* Cu(II)-promoted dearomatizing Friedel−Crafts reaction of α-thienylcarbinols (Scheme 37).[53] The reaction involved an unprecedented CuX_2-mediated C−H functionalization/halogenation of dienyl sulfether containing electron-rich aryl rings.



Scheme 37 Synthesis of halogenated spirothienooxindoles

Conclusions

We have summarized herein the major developments of dearomatization reactions of heterocycles in the past decade. Significant progress has been made in this field, and dearomatization reactions of heterocycles have been shown great potential in construction of various carbon-carbon and carbon-heteroatom bonds. As outlined in this review, dearomatization methods are the most efficient tools for chemical synthesis, especially for the construction of poly or spiro-heterocyclic scaffolds. Future advances in this area are likely to develop new highly efficient chiral ligands or organocatalysts, to develope more heterocycles, especially electron-deficient heterocycles, and to expand the applications in natural products and pharmaceuticals.

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Notes and references

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