Dearomatizing Amination Reactions

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Abstract: Dearomatization reactions allow the direct synthesis of structurally complex sp³-rich molecules from readily available "flat" precursors. Established dearomatization processes commonly involve the formation of new C-C bonds, whereas methods that enable the introduction of C-N bonds have received less attention. Because of the privileged position of nitrogen in drug discovery, significant recent methodological efforts have been directed towards addressing this deficiency. Consequently, a variety of new processes are now available that allow the direct preparation of sp³-rich amino-containing building blocks and scaffolds. This review gives an overview of C-N bond forming dearomatization reactions, particularly with respect to scaffold assembly processes. The discussion gives historical context, but the main focus is on selected methods that have been reported recently.

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1. Introduction

Dearomatization reactions continue to fascinate synthetic chemists.¹ Outside of simple reduction processes, established methods that have found widespread use in target directed synthesis include the alkylative Birch reduction,² the arene-olefin *meta*-cycloaddition³ and enzymatic arene dihydroxylations (Scheme 1A).⁴ Exciting recent developments include wide ranging methodological advances in catalytic asymmetric dearomatizations (CADA),⁵ as well as new strategies for the dearomatization of non-activated arenes.⁶

(A) Established dearomatization processes:

Alkylative Birch reduction (example by Schultz and Puig, 1985):



Arene-olefin meta-cycloaddition (example by Wender and Howbert, 1981):



Arene dihydroxylation (example by Myers and co-workers, 2005):







Scheme 1 Dearomatization reactions.

The most striking feature of dearomatization reactions is that they allow the direct synthesis of structurally complex sp³-rich molecules from readily available "flat" precursors (Scheme 1B). Because the generation of sp³-rich compound libraries has been a focus of pharmaceutical research over the last decade,⁷ it is

likely that dearomatization processes will find increasing application in industry. With this in mind, an important consideration is that well established dearomatization processes commonly involve the formation of new C-C bonds. Methods that instead introduce new C-heteroatom bonds, particularly where the heteroatom is nitrogen, are less well represented. Nevertheless, processes that enable the introduction of C-N bonds are especially valuable, because they allow the direct preparation of sp³-rich N-heterocycles and amino-containing building blocks. The privileged position of nitrogen in drug discovery means that these classes of compound are highly sought after.

The aim of this review is to give an overview of C-N bond forming dearomatization reactions (termed "dearomatizing aminations"), particularly with respect to scaffold assembly processes. The discussion is limited to processes where the new C-N bond is formed directly to the dearomatized carbon atom. The discussion gives historical context, but the main focus is on a selection of methods reported in the last decade. As will be seen, advances in catalysis and synthesis design have provided increasingly sophisticated dearomatizing amination protocols, including asymmetric variants.

2.1 Dearomatizing aminations via nitrenium ions

In 1984, Kikugawa⁸ and Glover⁹ independently reported the conversion of N-chloro-N-methoxyamides 1 into lactams 2 by These electrophilic aromatic substitution (Scheme 2). transformations invoked the intermediacy of N-methoxynitrenium ions 3, which were generated by treatment of 1 with silver salts in TFA or benzene. These highly electrophilic species induced cyclization with the pendent arene to generate lactam products. Efficient cyclization via a nitrenium ion was attributed primarily to the stabilizing effect of the oxygen lone pair of the N-alkoxy group through electron donation, which enables the nitrenium ion to be long-lived enough to undergo cyclization. As expected, based on an electrophilic aromatic substitution mechanism, cyclization proceeded efficiently with electron-donating or mildly electronwithdrawing substituents on the arene; however, strongly electron-withdrawing groups resulted in low yields.



Scheme 2 Nitrenium ion-induced aryl amination of N-chloro-Nalkoxyamides.

Both Kikugawa¹⁰ and Glover¹¹ expanded the application of nitrenium ion-induced cyclizations to the synthesis of spirolactams through a dearomative transformation (Scheme 3). Using N-methoxyamides 4 with pendent ortho- or paramethoxyphenyl groups, the generation of spirolactams 5 was achieved through intramolecular ipso-attack onto the nitrenium ion intermediate. As before, this was generated via the conversion of 4 to the corresponding N-chloro compound. The electrondonating methoxy group increases electron density at the ipsoposition leading to cyclization to intermediate 6, which then undergoes hydrolysis to the spirodienone compound. By using this approach, Kikugawa demonstrated the synthesis of a variety of spirocycles, including β -, γ - and δ -lactams **5a-c**.¹⁰ The synthesis of spirocyclic systems 7a-b was also possible by this method, whilst spirocyclization occurred with a para-chloro substituent in place of a methoxy group to give 8 in good yield.



Scheme 3 Synthesis of spirodienones by nitrenium ion-induced cyclization.

These 'first generation' nitrenium ion-induced dearomative cyclizations relied on the generation of nitrenium ions from Nchloro-N-alkoxyamides. These were in turn prepared by reaction of the corresponding N-alkoxyamides with t-BuOCI. However, the use of t-BuOCI is not ideal due to environmental factors and so an improved route to N-alkoxynitrenium ions was developed by Kikugawa, which involved the direct oxidation of N-alkoxyamides with hypervalent iodine reagents, such as [bis(trifluoroacetoxy)iodo]benzene (PIFA).12 Using this improved protocol, Wardrop and co-workers harnessed the reactivity of nitrenium ion intermediates in a number of natural product syntheses. In a series of reports, nitrenium ion-induced C-N bond forming dearomatizations of phenol derivatives were used as key steps in the total syntheses of (-)-TAN1251A,¹³ (\pm)-adalinine,¹⁴ (+)-Kishi lactam,¹⁵ (-)-dysibetaine¹⁶ and (\pm)-desmethylamino FR901483 (Scheme 4).¹⁷ In each case the reactive nitrenium ion **9** was generated from the corresponding *N*-methoxyamide using PIFA, before undergoing dearomative cyclization. This work highlights the scope of dearomatizing amination reactions for accessing a wide range of natural products.



Scheme 4 Applications of nitrenium ion-induced spirocyclization in natural product synthesis.

As part of the same group's studies into dearomative cyclizations, stereoselective spirocyclizations of α - and β substituted 3-(methoxyphenyl) propiohydroxamates were reported.^{18,19} Until this point substrates used in spirocyclic cyclizations to afford hexa-2,5-dienones typically contained an arene with a plane of symmetry and, as such, led to the formation of a non-stereogenic nitrogen-bearing center. However, if the arene is instead substituted in a way that breaks the symmetry, then the π -faces become enantio-/diastereotopic and a new stereogenic center is formed upon spirocyclization. Wardrop and co-workers harnessed this to carry out spirocyclizations with high levels of diastereoselectivity. For example, reaction of α -substituted N-methoxyamide **10** with PIFA afforded the spirocycle with complete stereoselectivity for the anti-product 11a (Scheme 5).¹⁸ The selectivity was rationalized by the preference of the reaction to proceed via conformation 12a. Cyclization via conformation 12b, which leads to syn-product 11b, is disfavored due to unfavourable steric interactions between the benzyl substituent on the side chain and the methoxy substituent on the aromatic ring. This transformation was also extended to 6-ring cyclizations: *N*-methoxyamide **13** was converted to δ -lactam **14** in high yield and excellent diastereoselectivity.¹⁹



Scheme 5 *Nitrenium ion-induced diastereoselective spirocyclizations.*

The nitrenium ion intermediates described so far rely on electron-donating N-alkoxy groups for stabilisation; however, other stabilized nitrenium ion-induced cyclizations have also been explored. In 2003, Kikugawa and co-workers reported the use of N-phthalimido-N-acylnitrenium ions as a new class of electrophilic intermediates. These were used to carry out electrophilic aromatic substitutions as well as dearomative spirocyclizations.²⁰ Treatment of N-acylaminophthalimide 15, containing a paramethoxy group (15a), with PIFA in TFE afforded spirocycle 16 in 77% yield (Scheme 6A). In addition to a para-methoxy substituent, substrates containing halogen substituents, such as chloro- or fluoro-groups in the para position (15b and 15c), also underwent efficient spirocyclization. Whilst the reaction of unsubstituted phenyl substrate 15d with PIFA in HFIP led to the expected benzannulated product 17, when TFE was used as the solvent the unexpected formation of spirocyclic product 18 was instead observed (Scheme 6B). The formation of 18 can be attributed to the attack of the ipso-carbon onto the nitrenium ion formed from 15d followed by trapping of the resulting carbocation with a molecule of solvent.





Scheme 6 (A) Spirocyclizations of para-substituted Nacylaminophthalimides. (B) Effect of solvent on the cyclization of an unsubstituted phenyl system.

A related electrophilic amination of aromatic compounds was reported in 1994 by Prabhakar and co-workers; this approach harnessed the electrophilicity of azodicarbonyl intermediates $20^{21,22}$ These highly electrophilic species were generated by oxidation of the corresponding bishydrazide 19 and underwent Lewis acid-promoted cyclization with pendent arenes to generate *N*-substituted amino dihydrocarbostyrils 21 or spiro- γ -lactams 22 depending on the nature of substitution on the aryl ring (Scheme 7). Other *N*-heterocycles were also accessed by this method, including oxindoles 23, benoxazinones 24, benzimidazolones 25, benzazepinones 26 and benzazocinones 27. A limitation of this reaction is that it is restricted to the cyclization of highly electron rich arenes.

Scheme 7 Intramolecular electrophilic amination of azodicarbonyls.

The realization of enantioselective nitrenium ion mediated spirocyclizations is highly appealing yet also very challenging. A significant development was reported by Cai and co-workers who showed that a chiral iodine(III) reagent, generated from **29** and *m*-CPBA, could be used catalytically for the enantioselective desymmetrization of systems **28** (Scheme 8).²³ The optimized protocol uses a *O*-cyclopentyl group on **28**, and provides the targets in 18-81% ee. To account for enantioinduction, the authors proposed that the iodine(III) unit may remain closely associated with the *N*-center during cyclization, such that a "free" nitrenium ion may not be involved.



Scheme 8 Enantioselective spirocyclizations via nitrenium ions.

2.2 Other oxidative dearomatizing amination reactions

The dearomative amination reactions described so far rely on generating an electrophilic nitrogen source which reacts with a nucleophilic arene. Dearomative transformations which harness the more common nucleophilicity of nitrogen are also wellestablished. Ciufolini and co-workers have pioneered an 'oxidative amidation' approach for the conversion of phenols into spirodienones. Mechanistically, these reactions can be rationalized via initial oxidation of the phenol ring to generate an electrophilic intermediate (phenoxenium ion), which is then intercepted by a suitable nucleophilic nitrogen source.²⁴ Typically, hypervalent iodine reagents such as DIB or PIFA serve as the external oxidant; these reagents are known to be effective oxidants for the oxidation of phenols and other arenes.²⁵⁻²⁸

In 1998, Ciufolini and co-workers demonstrated that cyclize oxazolines 30 upon treatment with (diacetoxyiodo)benzene (DIB) in TFE or HFIP to the corresponding spirolactams 31 (Scheme 9).29 The spirolactam products showed a strong propensity to cyclize to oxazines 32 upon chromatographic purification. This reactivity was suppressed by in situ O-acetylation of the crude spirolactam products and a range of spirolactams 33a-d were obtained in modest yields via this two-step process (Scheme 10A). The reaction is believed to proceed via DIB-mediated oxidation of the phenol to generate electrophile 34, which is intercepted by the oxazoline nitrogen to afford intermediate 35. The iminium ion of 35 is then captured by another nucleophile present in the reaction mixture, such as an acetate ion or solvent molecule, and the resulting intermediate affords the desired spirolactam product upon aqueous work-up. Earlier work by Kita had demonstrated that amides are ineffective as substrates for this transformation due to a preference for reaction through oxygen to form spirolactones.25



Scheme 9 Oxidative amidation of phenolic oxazolines.

For the cyclization of oxazoline **30d**, containing a carbamate functional group, a low yield of 22% was obtained (Scheme 10A). This poor result was rationalized as being due to competition

between the oxazoline nitrogen and the carbonyl oxygen of the carbamate group for interception of the electrophile. Reaction via the carbonyl leads to formation of an unstable intermediate **36** which unravels to a variety of side products (Scheme 10B). As such, a limitation of this approach is the unsuitability of substrates containing nucleophilic functionality which may compete with the oxazoline for capture of the electrophile.



Scheme 10 (A) Oxidative amidation of phenolic oxazolines. (B) Competitive reactive pathways of oxazoline **30d**.

Due to the marginally acidic reaction conditions, secondary amines are generally problematic substrates for oxidative aminations of this type. Nevertheless, there are several instances in the literature of electronically deactivated secondary amines undergoing successful oxidative cyclization to form spiropyrrolidines; these transformations represent key steps in natural product synthesis. In 2000, Sorensen and co-workers reported a synthesis of FR901483, a fungal-derived natural product with potent immunosuppressant properties.³⁰ For the construction of the core azaspiro[4.5]decane motif, the authors performed an oxidative amination of the tyrosine-derived compound 37 (Scheme 11). Using PhI(OAc)₂ in HFIP, the desired spirocyclic product 38 was obtained in good yield and subsequently transformed into the natural product. A related transformation was reported by Honda as a key step in the formal synthesis of the alkaloid natural product (-)-TAN1251A (Scheme 11).³¹ Reaction of compound **39** under the same reaction conditions as used by Sorensen gave the desired spirocyclic amine 40 in 69% yield. Initially, the authors had attempted to convert 39 into the spirocompound 40 via formation of a nitrenium ion; however, attempted chlorination of **39** with NCS, followed by treatment with silver oxide failed to deliver the desired product, possibly because of the lack of stabilizing functionality. In the examples in Scheme 11, the success of oxidative cyclization is due to inductive effects of the neighboring functionality, which decreases the basicity of the amines so that they remain unprotonated and can function as nucleophiles.



Scheme 11 Oxidative amination of secondary amines for the synthesis of natural products.

Whilst oxidative amidations are effective for constructing spirocyclic pyrrolidines, attempts to perform more challenging 6-ring cyclizations to form spirocyclic piperidines have met with less success. Ciufolini and co-workers reported the oxidative cyclization of oxazoline **41** to afford spiropiperidine **42**, but the reaction was low yielding (Scheme 12). Higher yields were obtained with more conformationally restricted substrates such as **43**; however, this transformation remains a challenge.³²



Scheme 12 Formation of piperidines by oxidative amidation of oxazolines.

A significant improvement in the area of oxidative amidation chemistry emerged when Ciufolini and co-workers reported the oxidative dearomative cyclization of sulfonamides. A series of sulfonamides **44** were cyclized with PhI(OAc)₂ in HFIP to afford spirocyclic sulfonamide products **45** with much greater efficiency than that obtained with previous systems (Scheme 13A).³³ The choice of solvent was crucial to obtaining high yields, as, when TFE was used, competition between the sulfonamide nitrogen and the solvent for capture of the electrophile was observed. In addition to the reaction being effective for a variety of sulfonamides, phosphonamide **46** cyclized to spirocycle **47** in excellent yield (Scheme 13B).³²



Scheme 13 (A) Oxidative amidation of phenolic sulfonamides. (B) Oxidative amidation of a phosphonamide.

Oxidative cyclizations of *ortho*-linked sulfonamides were also successfully demonstrated by Ciufolini and co-workers, although these reactions were generally less efficient than for *para*-phenol substrates. By coupling oxidative cyclization of allylic sulfonamide **48** with a Diels-Alder reaction, tetracycle **49** was obtained in good yield (Scheme 14A).³⁴ In addition to the dearomatization of phenols, the scope of the reaction was also extended to the oxidative amidation of naphthols. Upon exposure to PhI(OAc)₂ a variety of 1-naphthols **50a-d** cyclized efficiently to the corresponding spirocyclic compounds **51a-d** (Scheme 14B).³⁵



Scheme 14 (*A*) Tandem oxidative amidation/Diels-Alder reaction of an ortho-linked sulfonamide. (B) Oxidative amidation of naphthols.

All the previous examples of oxidative cyclization involve intramolecular reactions; however, precedence for an intermolecular oxidative amidation of phenols was set by Kita in 1996, who observed the competing formation of amidation product **54** (in addition to the desired product **53**) during the oxidative cyclization of **52** (Scheme 15).³⁶ **54** likely arises by a Ritter-type reaction involving trapping of the electrophile by a molecule of acetonitrile.



Scheme 15 Observation of intermolecular oxidative amidation as a side process.

Inspired by this result, Ciufolini developed efficient intermolecular oxidative amidations of phenols to provide dearomatized products **55a-e**; optimized conditions use $PhI(OAc)_2$ in a 1:1 mixture of MeCN and HFIP (Scheme 16).³⁷ The reaction proved to be compatible with a variety of functional

groups including esters, nitriles, halides, sulfonamides and protected alcohols. Through treatment of compound **55e** with NaH, cyclization to spirocyclic piperidine **56** was achieved (Scheme 16B).



Scheme 16 (*A*) Intermolecular oxidative amidation of phenols. (*B*) Application to the synthesis of spirocyclic piperidines.

2.3 Transition metal free dearomatizing aminations via N-O cleavage

The methods described so far use strong external oxidants and this can present issues because electron rich aromatic systems, as well as many other functional groups, are prone to side reactions under oxidative conditions. Additionally, strong oxidants are often hazardous and this can be problematic for scale-up. These considerations have prompted the development of redox neutral methods that use internal oxidants located on the reacting *N*-center. This provides a more controlled approach that allows potentially more sensitive aromatics units, such as indoles, to participate efficiently. Within this broad design, recent transition metal free methods that exploit the inherent electrophilicity of N-O units are of particular significance.

Early work on the direct displacement of N-O bonds by electron rich arenes used oxime derivatives to provide dihydropyrroles; however, in these processes competing Beckmann rearrangement is often problematic.^{38,39} More recently, Bower and co-workers have reported a base mediated method that exploits direct displacement of the N-O bond of activated hydroxylamine based systems **57**.⁴⁰ For processes involving indoles, smooth dearomatization occurred under very simple conditions to provide spirocyclic pyrrolidines such as **58a-e** (Scheme 17A). Here, the O-based leaving group is either tosylate or pentafluorobenzoate, and a variety of carbamate and sulfonamide N-protecting groups are tolerated. The key C-N bond of the substrate is easily installed by Mitsunobu alkylation of preactivated reagents **59**. This then allows readily accessible enantioenriched secondary alcohols to be used as precursors.

The process also offers wide scope with respect to the arene, such that complementary dearomatizations of phenols and naphthols can be achieved (Scheme 17B).



Scheme 17 Base mediated dearomatizations of (A) indoles, and (B) phenols and naphthols via N-O cleavage.

Under acidic conditions, dearomatizations involving OTs activated N-Boc hydroxylamines (60 and 61) occur to provide spirocyclic pyrrolidines, where the N-center is unprotected (Scheme 18A).⁴¹ As with the previous processes, the substrates are easily setup by Mitsunobu alkylation; however, rather than using a base to activate the arene, TFA is used instead to activate the N-O unit. This likely occurs by N-Boc deprotection to provide highly reactive intermediate 62. This engages the pendant arene via its ipso position in an SEAr-like process. Because the dearomatization process is run under acidic conditions, the product amine is protonated, such that competing intermolecular reaction with the sensitive enone unit is prevented. For certain systems, competing aryl C-H amination was observed. Additionally, depending on the equivalents of acid used, the initial spirocycles can undergo subsequent aza-dienone-phenol rearrangement. The amine and enone functionalities of the spirocyclic products allow further annulations to be achieved directly, such as in the conversion of **63** to **64** (Scheme 18B).



Scheme 18 Acid mediated dearomatizations of phenols and naphthols via N-O cleavage.

2.4 Dearomatizing aminations via metalnitrenoids

The previous section described metal-free C-N bond forming dearomatizations that exploit an N-O bond as an internal oxidant. Complementary methods are available that achieve related transformations via the intermediacy of electrophilic metalnitrenoids. These processes offer distinct scope with respect to those described so far.

In 2018, Chang and co-workers reported an approach to spirolactams via the decarboxylative generation of iridiumnitrenoid intermediates **67**, which were generated from dioxazolones **65** (Scheme 19).⁴² Using this method, a variety of unprotected five-membered spirolactams **66** were accessed in excellent yield, and the scope was also extended to the more challenging synthesis of a four-membered spirolactam **68**. The protocol is very mild and can be considered complementary to nitrenium ion based processes, which are usually limited to the generation of lactams bearing *N*-alkoxy groups (vide supra). Dearomatizations of indoles result in dimeric dispiroindolines, and the process also extends to aryl C-H amination. The dioxazolone precursors are easily accessed by treatment of the corresponding hydroxamic acid with CDI.



Scheme 19 *Iridium-catalyzed intramolecular dearomatizing amination.*

In 2019, Shibasaki and co-workers reported related processes that involve the rhodium catalyzed conversion of *O*-acylhydroxylamines **69** to spirocycles **70** (Scheme 20).⁴³ The reaction is proposed to proceed via the formation of a rhodiumnitrenoid species **71** with concomitant cleavage of the N-O bond of **69**. In these transformations, the *O*-based leaving group is retained to provide the carboxylate moiety of the targets. The process therefore provides an interesting method for the formation of cyclic β -amino acids. As with the Chang method, processes involving non-phenolic arenes resulted in aryl C-H amination.



Scheme 20 Rhodium-catalyzed dearomative amination of O-acylhydroxylamines.

The metal-nitrenoids discussed so far are highly electrophilic and this facet allows related intermolecular processes. You and co-workers developed an efficient rhodium-catalyzed intermolecular aminative dearomatization of 2-naphthols to generate a variety of unprotected α -amino- β -naphthalenones **72** (Scheme 21A).⁴⁴ In this transformation *O*-2,4-dinitrophenylhydroxylamine (DPH) was utilised as the aminating agent; however, the application of DPH is limited by its high price and safety concerns, and so the authors subsequently reported a procedure where DPH was replaced with the safer electrophilic nitrogen source hydroxylamine-*O*-sulfonic acid (Scheme 21B).⁴⁵ Overall, the process provides very useful amine containing units that seem well suited to applications in target directed settings.



Scheme 21 Rhodium-catalyzed dearomative aminations of naphthols using (A) DPH and (B) hydroxylamine-O-sulfonic acid.

Intermolecular aminations using metal-nitrenoids derived from N-O bond cleavage can also be used to effect 1,1-

aminofunctionalizations of the C2-C3 π-bond of indoles. Xie and co-workers have shown that aminated products 74 can be generated from indoles 73 upon exposure to DPH in the presence of Rh₂(esp)₂ (Scheme 22A).⁴⁶ By varying the nature of the nucleophilic unit on 73, 1,2-diamination and 1.2aminooxygenation processes could be realized. Although a detailed mechanism was not advanced, the process likely commences with amination at the C3 position of the indole (perhaps via aziridination of the C2-C3 π-system). This mechanistic paradigm was advanced significantly by Tang, You and co-workers, who showed that chiral Cu(I)-catalysts can render these types of process asymmetric (Scheme 22B).47 This provides a range of challenging indole derivatives with very high levels of enantioselectivity. Note that Cu(II)-catalyzed cleavage of oxaziridine N-O bonds has been used previously to effect dearomatizing 1,2-oxyaminations of indoles; however, in these cases a radical-based mechanism was proposed that installs the C-O bond first.48



Scheme 22 (*A*) *Rhodium- and (B) copper-catalyzed dearomative aminations of indoles.*

The intermolecular aminative dearomatizations described so far in this section install primary amines directly. This contrasts more established metal-nitrenoid approaches that usually install protected amino-units.⁴⁹⁻⁵² For example, Dauban and co-workers have previously described Rh-catalyzed 1,2-aminooxygenations of indoles that provide protected products, such as **75a-c** and **76a** (Scheme 23).⁴⁹ Here, an iminoiodane is generated *in situ* by reaction of TcesNH₂ (Tces = Cl₃CCH₂OSO₂-) with an iodine(III) reagent [PhI(OCOR)₂] – this acts as a nitrene transfer agent to generate the key Rh-nitrenoid. For processes with external nucleophiles, C2 selective C-N bond formation occurs for C3 substituted indoles, whereas C3 selectivity is observed for C3-unsubstituted systems. These results are consistent with initial aziridination of the C2-C3 π -system.



Scheme 23 Rhodium-catalyzed dearomative aminations of indoles using an external oxidant.

The processes described so far in this section achieve dearomatizing amination via the introduction of (protected) amines or amides. Zhong, Deng and co-workers have developed an iron-catalyzed protocol that allows the direct introduction of anilines (Scheme 24).⁵³ The process uses an aryl azide as the electrophilic nitrogen source and a mechanism involving C-N reductive elimination from Fe(III)-complex **78** was proposed. Amongst several possibilities, it was suggested that **78** arises via an Fe-nitrene complex, and this was supported by DFT studies. The process is limited to β -naphthols, but offers relatively wide scope with respect to substitution on both reaction partners.



Scheme 24 Iron-catalyzed dearomative aminations using aryl azides.

2.5 Other transition metal catalyzed dearomatizing aminations

In the previous section, C-N bond forming dearomatizations that proceed via metal-nitrenoids were outlined. Other types of metal-catalyzed nitrogen transfer processes can also be exploited for C-N bond forming dearomatizations. Wang and co-workers have reported a copper-catalyzed dearomative amination of phenols using O-benzoylhydroxylamines (Scheme 25).54 In this transformation, C-N bond formation occurs exclusively at the ortho-position to afford aminocyclohexa-2,4-dienones 79 under very mild conditions. To rationalize the observed ortho-selectivity, the authors proposed the mechanism shown in Scheme 25. Oxidative addition of the amine electrophile to a Cu(I)-phenol species generates amino-Cu(III) complex 80. This species might equilibrate to the corresponding N-centred radical/Cu(II) complex 81, and then either 80 or 81 undergo C-N bond formation via a five-membered cyclic transition state. The reaction tolerates a wide variety of cyclic O-benzoylhydroxylamines, such as morpholines, piperidines and piperazines. Acyclic systems were found to be less efficient.



Scheme 25 Copper-catalyzed dearomative amination of phenols.

In the presence of an external oxidant, Cu-catalysis can be used to promote dearomatizing azidations of *ortho*-naphthols. For example, Prabhu and co-workers have shown that the use of catalytic CuBr and TBHP can promote azide transfer from TMSN₃ to give targets **82** in high yield (Scheme 26A).⁵⁵ The mechanism of this process is unclear but radical-based pathways are likely. Sarkar and co-workers have described similar process, but using phenyl trimethyl ammonium tribromide (PTAB) as the oxidant and NaN₃ as the azide source (Scheme 26B).⁵⁶ Notably, this protocol also tolerates cyclic and acyclic amine nucleophiles, as outlined in Scheme 26C.



Scheme 26 Copper-catalyzed dearomative azidations (A) and aminations (B and C) of naphthols and phenols.

By using a Cu-catalyst modified with chiral N,N-ligand **84**, Deng and co-workers have shown that highly enantioselective dearomatizing azidation reactions are possible (Scheme 27).⁵⁷ In this method, hypervalent iodine-based azide transfer reagent **83** is used and the method requires a carbonyl substituent at C2 of the naphthol. This facilitates two-point binding of the substrate to the Cu-center in advance of enolate-like attack onto the azide electrophile. Within the confines of the substrate design requirements, the method offers very broad scope.



Scheme 27 Enantioselective copper-catalyzed dearomative azidations of naphthols.

2.6 Brønsted and Lewis acid catalyzed dearomatizing aminations

The intramolecular process described in Scheme 7 of Section 2.1 suggest that *intermolecular* dearomatizing aminations might be achievable via Lewis or Brønsted acid catalyzed activation of diazodicarboxylates. Indeed, the area of enantioselective acid catalyzed dearomatization reactions has seen extensive growth, and this encompasses amination reactions.⁵⁸

Concurrent reports from the groups of You, Luan and Feng have outlined distinct catalyst systems for the dearomatizing amination of β -naphthols with diazodicarboxylates (Scheme 28).⁵⁹⁻⁶¹ You's study revealed that BINOL or SPINOL derived chiral phosphoric acids **85** and **86** are effective. Luan developed a scandium-based system modified with chiral ligand **87**, whereas Feng used a scandium catalyst ligated to chiral N,N'-dioxide ligand **88**. In the Luan study, an example involving the highly enantioselective *para*-amination of a specific class of phenol was also disclosed. You demonstrated that the Magnus protocol is suitable for effecting N-N cleavage of the products.⁶²



Scheme 28 Enantioselective dearomatizations of β -naphthols via chiral Brønsted or Lewis acid catalysis.

In an elegant extension of the approach, You and coworkers developed a tandem process involving enantioselective and *para*-selective amination of α -naphthols or phenols (Scheme 29A).⁶³ Here, the initially generated enone is trapped by a pendant *N*-, *O*- or *C*-based nucleophile to provide polycyclic systems **89ad** with very high levels of efficiency. Conceptually, this sequence is related to Antilla and Zhang's methodology involving indole systems **90** (Scheme 29B).⁶⁴ Here, C3 selective amination of the indole unit generates an imine, which is intercepted by a pendant *N*-nucleophile to form an additional ring. A similar process was developed by Toste and co-workers, but, in this work, the electrophilic nitrogen source was instead an aryl diazonium salt (Scheme 29C).⁶⁵



Scheme 29 Enantioselective dearomatizing cascades of (A) αnaphthols and phenols, and (B and C) indoles via chiral Brønsted acid catalysis.

2.7 Photochemical and photocatalytic dearomatizing aminations

Photocatalytic substrate activation provides a mild and clean method for accessing open shell reaction manifolds. This area has seen an increasing focus on its use for the generation of electrophilic nitrogen centered radicals.66,67 Interestingly, this provides an alternative approach for achieving intramolecular dearomatizing amidation reactions related to those shown in Scheme 19. As demonstrated by Wang and co-workers, irradiation of N-aryl amides 91 by blue LEDs in the presence of Ru(bpy)₃Cl₂ and acetoxybenziodoxole (BI-OAc) results in dearomatization to provide spirocyclic lactams 92 (Scheme 30A).68 Under the same conditions, but in the presence of a carboxylic acid, indole systems 93 undergo 1.2aminooxygenation to provide products 94 (Scheme 30B). This method is complementary to other recently reported indole 1,2aminooxygenation processes.69-71 For indole systems, it was proposed that excitation of the Ru(II) photocatalyst leads to reductive cleavage of BI-OAc to provide BI-radical 95. This abstracts the hydrogen atom from the N-H unit to provide an electrophilic nitrogen centered radical that undergoes 5-exo cyclization onto the indole unit. Subsequent oxidation of carbon centered radical 96 (by Ru(III)) provides carbocation 97 which is trapped by the carboxylic acid.



Scheme 30 Oxidative dearomatizations of (A) phenols and (B) indoles under photocatalytic conditions.

Photocatalytic dearomatizing cascades, where C-C bond formation occurs before C-N bond formation, have been develop by Dixon and co-workers.⁷² This method was inspired by the Minisci reaction,⁷³ and uses an Ir-photocatalyst in combination with a Hantzsch ester for the reductive conversion of *N*-aryl imines

99 to α -amino radical radicals **101**. Nucleophilic addition of the radical to the C4 position of quinolines **98** is followed by electron transfer and protonation to provide **102**. Cyclization under the reaction conditions generates complex bridged 1,3-diazepanes **100**. Detailed mechanistic studies were undertaken and these included a rationalization for the C4 selectivity of the process.



Scheme 31 Dearomative photocatalytic construction of bridged 1,3-diazepanes.

Visible light can also be used to effect C-N bond forming dearomatizations in the absence of a photocatalyst. Sarlah and co-workers have developed a range of process that exploit the light mediated cycloaddition of *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) with non-activated arenes. This area has been

reviewed recently, and so is not covered in depth here.^{74,75} Instead, as an exemplar of this chemistry, it is pertinent to highlight its application to a short synthesis of (+)-pancratistatin (Scheme 32).⁷⁶ Here, cycloaddition between benzene and MTAD occurs at low temperature to provide **106**. This is followed by addition of Ni(cod)₂, chiral ligand **104** and aryl Grignard reagent **103**. The Ni-catalyst promotes enantioselective desymmetrization of **106** to provide Ni η^5 -complex **107**, which undergoes transmetallation with **103** and reductive elimination to provide *trans*-1,2-carboamination product **105** in 65% yield and 96% ee [>10g scale]. Conversion of this to (+)-pancratistatin was achieved in a further six steps. The generalization of the methodology used for the conversion of benzene to *trans*-1,2carboamination products was reported subsequently.⁷⁷



Scheme 32 Synthesis of (+)-pancratistatin by MTAD mediated dearomatization of benzene.

3. Conclusion and Outlook

This review provides an outline of recently reported dearomatizing aminations. As can be seen, there has been a substantial expansion of available methodologies, especially with respect to more general intramolecular reactions and asymmetric processes. The latter has been facilitated by wider advances in catalysis, and progress in this broader field will continue to stimulate the development of more powerful processes. There are many options here because reaction design can exploit a range of mechanistic frameworks; for example, the reacting *N*-center

can function as a nucleophile or electrophile, via either polar or radical pathways.

The dearomatizing aminations that are now available already offer unrivalled power for the rapid assembly of stereochemically complex heterocyclic scaffolds and aminocontaining building blocks. Nevertheless, there are significant areas where opportunities remain. For example, there are relatively few redox neutral processes that exploit nucleophilic sources of nitrogen. Efforts to realize such reactions will require careful substrate design, likely encompassing less typically exploited electron poor (hetero)arenes. Intramolecular processes that are able to generate larger (>five-membered) ring systems are also underrepresented, especially in enantioselective processes. New methodologies in this area might act as forerunners to more powerful and general intermolecular variants. Finally, dearomatizing aminations of minimally activated arenes are still in their infancy. This is perhaps the most important area, as it offers the prospect of methods with genuinely broad utility.

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Keywords: amination • dearomatization • spirocycle • heterocycle • electrophilic nitrogen

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C-N bond forming dearomatization reactions allow the direct generation of complex three-dimensional amino-containing scaffolds and building blocks. A variety of powerful methods have emerged recently and these are highlighted in this review.