Advances in dearomatization strategies of indoles

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Dedicated to Professor Phillip D. Magnus for his overall career accomplishments and his innovative contributions in developing indole dearomatization strategies for the synthesis of complex natural products

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1. Introduction

Over the years, alkaloids derived from indole deamortization, such as indolene and indolines have been evolved as promising therapeutic agents due to their important biological activity against cancer, inflammation and hypertension.1 Since the middle of the 20th century, tremendous efforts and creativity have been devoted toward the functionalization of indoles, tryptamines, tryptophans, and other β-carboline building blocks. Many transformations have been developed for the functionalization at the C3 position (e.g., indole 1) or at C2 when the aforementioned position is already substituted (e.g., indole 2). In fact, the indole nucleus owes to its structural features both selective nucleophilic reactivities on the nitrogen and at C3 due to the enamine moiety (depending on soft or hard electrophiles). Only if the C3 position is blocked, the indole nucleus may then react towards electrophiles at the C2 position (likely via delocalization from the inside of the benzene ring) before undergoing deamortization to deliver 2,3-disubstituted indoles. On the other hand, when deamortization occurs at the C3 position, the resulting indolium 3 can further endure either a direct nucleophilic attack at C2 (path a) leading to indolenine 6, or an intramolecular rearrangement typically generated by a [1,2]-shift from a substituent at C3 to C2 (path b) followed by the nucleophile addition at C3 trapping the benzylic carbocation 4. This important array of reactivity from the indole nucleus upon activation by different electrophiles became an exciting portfolio of reactivity from the indole nucleus upon activation.

Scheme 1.

There is perhaps no better illustration of the history and power of indole deamortization than the rich history of efforts toward the indole alkaloid strychnine (7). As appropriately asked by Overman, “Is There No End to the Total Syntheses of Strychnine?”2 there are no less than 17 reported total and formal syntheses strychnine (7) with 5 relying on indole deamortization at some stage. Efforts toward strychnine began more than 70 years ago. After the epic endeavors regarding the synthesis quinine during the final years of WWII, and in constant competition with Sir D. Robinson, Woodward undertook the daunting synthesis of strychnine (7) in the late 1940s. In 1954, Woodward utilized a deamortative strategy to construct the C ring of strychnine (7) via a Pictet–Spengler type reaction of an activated tryptamine-derived iminium 9 affording indolene 10 in 64% yield (Scheme 2, Eq. 1).3 Thirty years later, both syntheses by Magnus and Kuehne also demonstrated the efficacy of deamortative strategies highlighted by a transannular Mannich reaction or a Lewis acid–catalyzed cascade reaction, respectively (Scheme 2, Eqs. 2 and 3). Magnus reported the dehydrogenation of the tetracyclic indole 11 using mercury acetate producing regioselectively iminium 12, which spontaneously endured the intramolecular indolic attack from the C3 position to generate pentacyclic indoline 13 in 68% yield, after a final iminium–enamine tautomerization mechanism (Scheme 2, Eq. 2).4 Kuehne reported the year after a cascade reaction also involving a Mannich reaction in the first step to enable the deamortization of tryptamine 14 (Scheme 2, Eq. 3). The boron trifluoride catalysis promoted a proposed [3,3]-sigmatropic rearrangement of indoline 15 to indole 16, which after several enamine–iminium tautomerization interplays secured the access to the four A, B, C, and E rings of strychnine in a single step (over 51% yield).5

These classical examples of indole deamortization (selected from Ref. 2) clearly highlight that achiral racemic syntheses of polycyclic indole alkaloids were paramount until most recently. In the past 10 years, the efforts of several groups re-explored the chemistry of indole and tryptamines under asymmetric catalysis has blossomed and offered new possibilities for asymmetric construction of complex alkaloids. MacMillan, who is a recognized as one of the pioneers in the arena of organocatalysis, reported the brilliant use of imidazolidinone as chiral catalyst to synthesize in high enantiopurity the common tetracyclic alkaloidal scaffold 23 of several Strychnos, Aspidosperma, and Kopsia alkaloids through a cascade reaction (Scheme 2, Eq. 4).6 MacMillan used an enantiodiscriminating activation of propargyl aldehyde to trigger the complex cascade reaction and the deamortization of the relatively simple selenyl-derived tryptamine 19 starting via a Diels–Alder
cycloaddition. The resulting enamine 21 may then undergo β-elimination to expulse the selenyl leaving group generating therefore a novel reactive iminium specie, which presumably cyclized in a 1,4-addition producing the desired tetracyclic core 22, which after enamine–iminium tautomerization and hydrolysis to regenerate the catalyst delivered compound 23 in 82% yield and 97% enantiomeric excess (ee).

While the dearomatization of miscellaneous arenes 7 and functionalization of indoles 8 have been extensively covered elsewhere, only a few recent reviews covered specific indolic dearomatization strategies 9 and recent advances in asymmetric dearomatization. 10 Many syntheses of complex target molecules incorporating indolic fragments have set the stage for new chemistry to be explored and for novel applications of dearomatization to be developed. In this review, we will have a broader overview of indoles dearomatization through cycloaddition (Section 2), arylation (Section 3), protonation (Section 4), alkylation (Section 5), and oxidation with several heteroatoms (Section 6), with a special emphasis and comparison in each section on unprotected versus protected indole nitrogens and asymmetric and/or catalytic dearomative methods and cascade reactions for the synthesis of complex alkaloids. In addition, to outline several selected dearomatization strategies in the context of complex natural product synthesis, we will also describe future perspectives in the field including prospects for development of enantioselective dearomatization processes (Section 7). The authors apologize for any published work that would not have been selected and shown in the present review due to the large amount of literature covering the topic of indole deearomatization and the personal selection. Where relevant, we have included mechanistic details and have emphasized differences between unprotected and N-protected indole reactivities with the aim that this report will stimulate the development of novel asymmetric and catalytic enantioselective methods for the deearomatization of indoles.

2. Deearomatization via cycloadditions

Cycloadditions are powerful maneuvers for the formation of complex polycyclic structures while controlling the simultaneous emergence of several stereocenters. This section will outline examples of cyclopropanation strategies, [2+2] photocycloadditions, 1,3-dipolar cycloadditions, and many variants of the well-established Diels–Alder reaction in the process of indole deearomatization.

2.1. Cyclopropanations

Numerous examples of indole cyclopropanations have been reported mostly in an achiral fashion 11 and it is only recently that diastereoselective cyclopropanations 12 and enantioselective deearomatative cyclopropanations 13 have been utilized in the context of complex alkaloid synthesis. Based on the chemical ability of indoles to endure cyclopropanation and the fact that cyclopropane fragmentation is a well-established transformation, tactics taking advantages of both reactivities have emerged to synthesize complex polycyclic indoline scaffolds (Scheme 3). Copper and rhodium carbenoid species have been reported to catalyze these types of cyclopropanation–rearrangement sequences. Jung reported that 3-substituted indole β-diazoo-α-keto esters 24 endured the formation of a rhodium(II) carbenoid followed by cyclopropanation to compound 25, subsequent cyclopropane ring opening affording the iminium intermediate 26, which underwent cyclization via the ester enolate attack to deliver, after hydrolysis, the final tetracyclic compound 28 as minor product of the reaction in 18% yield (Scheme 3, Eq. 1). 14

A similar strategy was exploited to its full potential by Qin in several total syntheses endeavors as exemplified by the concise synthetic sequences of (+)-minfiensine (33) and (−)-ardeemins (38) (Scheme 3, Eqs. 2 and 3). At first, Qin reported the achiral copper-catalyzed
dearomatization/rearrangement sequence of tryptamine derivatives, as exemplified by cyclopropanation–ring opening of the tryptamine derivative 29, leading to the interception of indolennium 31 by the pendant amine to form tetracyclic indoline 32 in 62% yield (Scheme 3, Eq. 2). Soon after, Qin also reported an intermolecular modification of the reaction, which was conducted on tryptophan 34 to achieve a diastereoselective dearomatization leading to the tetracyclic hexahydropyrroloindoline 37 in 73% yield (2:1 dr) on a 50 g scale (Scheme 3, Eq. 3). In 2013, Davies reported for the first time an enantioselective rhodium-catalyzed annulation of 3-alkylindoles (Scheme 3, Eq. 4). In this reaction, 4-aryl-1-sulfonyl-1,2,3-triazoles 39 were used as diazo precursors, which upon activation with a chiral rhodium(II) adamantanyl-tetracarboxylate catalyst 41 enabled the dearomatization and further rearrangement sequence of N-protected indoles 40 to afford tricyclic pyrroloindolines 44 in excellent yields and high enantioselectivity (up to 95% ee). This extremely versatile reaction was also achieved on unprotected indoles resulting in lower enantiodiscrimination.

2.2. [2+2] Cycloaddition followed by a retro-Mannich fragmentation

Photocycloaddition involving the C2–C3 π-bond of indoles has been elegantly utilized by Winkler during his investigations toward the formal synthesis of vindorosine (Scheme 4). The bulky orthoester moiety installed on the tryptophan derivative 45 was found crucial to improve facial diastereoselectivity during the key [2+2] photocycloaddition. Photocycloaddition using Pyrex filter through the favored transition state 46 was achieved simultaneously with a retro-Mannich reaction leading to the cyclobutane ring opening to synthesize the rearranged photoadduct 48 in 91% yield.
yield as a single diastereomer. Treatment of cycloadduct 48 with LDA and a silyl triflate enables the ring closure to furnish the required tetracyclic carbon skeleton and achieve a formal synthesis of the vindorosine natural product 50.

Several years later, White reported a similar strategy using a [2+2] photocycloaddition and retro-Mannich fragmentation sequence, to access several β-carbolines and oxindole natural products (Scheme 5).20 This useful sequence of [2+2] photocycloaddition followed by a retro-Mannich fragmentation enabled the formation of a pyrrolidine fragment while functionalizing simultaneously the C2 position of the indole precursor 49 to afford indoline 51 in 62% yield. Using this tactic, White reported the total synthesis of oxindole elacomine (52) in eight steps.

2.3. 1,3-Dipolar cycloadditions

Two main strategies to construct complex heterocyclic indolines have taken advantage of 1,3-dipolar cycloaddition reactions. The first approach mediated by Lewis acids enables three-membered ring cycles to be opened (e.g., cyclopropanes, epoxides), thus generating 1,3-dipoles that further trigger the desired dipolar cycloadditions (Scheme 6), while the second approach is usually catalyzed by rhodium complexes to promote metal insertion into 1,3-diazocarbonyls moieties to further generate carbonyl ylides as dipolarophile for cycloadditions with the indolic C2–C3 double bond (Scheme 7).

In the first approach to dipolar cycloadditions, several research groups have studied the regio and stereoselectivity of the 1,3-dipole additions to indole dipolarophiles. For instance, 1,1-cyclopropane diesters have been first reported by Kerr to enable efficient dearomatizations of 3-alkylated indoles through activation with ytterbium triflate, which overall promoted cyclopentannulation reactions.21 Recently, a similar transformation was reported in a catalytic and highly enantioselective manner by Xie and Tang by activation of 1,1-cyclopropane diesters with BOX/Cu(II) catalysts.22 Venkatesh reported a similar and very convenient [3+2] cyclo)penta [b]annulation with a broader scope of indole substrates 53 through the activation of cyclopropanes 54 catalyzed by boron trifluoride (Scheme 6, Eq. 1).23 Interestingly this annulative reaction is taking advantages of electron rich arylated cyclopropanes to favor carbo-annulation formation, which further triggered the unprotected indole dipolarophile to react. In some cases, titanium tetrachloride was found to be a better catalyst to perform the annulation and obtain the desired tricyclic indolines 56. A similar transformation was accomplished by Wu and Zhang on epoxide substrates 58 leading to the synthesis of oxygenated indoline derivatives 59 (Scheme 6, Eq. 2).24 In this case nickel perchlorate was used as catalyst to enable the [3+2]-cycloaddition to take place. Wu also described a catalytic enantioselective version of the transformation, using a BOX-60/Ni(II) catalysts, which enable the synthesis of indoline 59 in 72% yield with high diastereoselectivity while low enantiomeric excess were observed (>20:1 dr, 19% ee). Finally, an original oxyamination reaction of N-acylindoles 61 was recently reported by Yoon, on the ground of oxido-reductive possibilities of copper, which enable the regiospecific reactivity of oxaziridines 62 through a plausible radical mechanism (Scheme 6, Eq. 3). In fact, upon radical initiation on the oxaziridine 62, N-acetylated indole proved to react at C2 position before enduring the C3 ring closure to afford the heterocyclic indolenine 63 in good yields. When N-Boc-proline was utilized as a chiral auxiliary attached to the indolic nitrogen of compound 61, the two-step sequence oxyamination followed by ring opening and closure delivers the pyrroloindoline core 64 in 78% yield and 91% ee (note: the chiral auxiliary was simultaneously extruded). Recently two other examples of enantioselective oxyamination of indoles have been reported by Feng and Ooi separately. While Feng and Liu reported the use of a chiral oxaziridine to induce a highly enantioselective dearomatization,25 Ooi developed a very powerful...
catalytic enantioselective reaction highlighted by the situ formation of a chiral oxaziridine based on the catalytic action of a chiral triaminooiminophosphorane base.\(^\text{26}\)

As mentioned above, rhodium(II)-catalyzed cyclization and 1,3-dipolar cycloaddition cascade also represents a powerful maneuver amenable to indole dearomatization as well as assembling complex heterocyclic ring systems in a single operation. Pioneering work by Padwa described such elegant cyclization–cycloaddition cascade in 1995 to access the desacetoxy-4-oxo-6,7-dihydrovindorosine en route to \textit{Aspidosperma} alkaloids (Scheme 7, Eq. 1).\(^\text{27}\) In this approach, the 1,4-diazo imide \(^65\) endures a Rh(II)-catalyzed cyclization, which generates 1,3-carbonyl ylide dipole \(^66\), which further enable the \(C_2-C_3\) indole double to react as a 2\(\pi\) component in the desired 1,3-dipolar cycloaddition (Scheme 7, Eq. 1). In this case, the hexacyclic indoline \(^67\) was formed in 95\% yield as a single diastereomer revealing the perfect stereochemical outcome (at \(C_2, C_3, C_5,\) and \(C_12\)) required to achieve the total synthesis of vindorosine (\(^68\)). Since this early work, the carbonyl ylides reactivity in \([3+2]\)-cycloadditions with indole has been blossoming\(^\text{28}\) as highlighted by the selected modification in Scheme 7 (Eq. 2).\(^\text{28c}\) Oguri expanded the rhodium-catalyzed cyclization–cycloaddition cascade, by the development of a divergent synthetic pathway, which enables access to both polycyclic skeleton \(^71\) and \(^72\) selectively. Depending on the length of the pendant alkenyl side chain of the tertiary amide in the diazo keteoster \(^69\) \((n=1\) or \(2)\), either the indolic \(C_2-C_3\) double bond or the terminal alkene moieties participated in the cycloaddition reactions. After formation of a common carbonyl ylide intermediate \(^70\), if the pendant alkene comprises two carbons \((n=1)\) both alkene and indole reacted unselectively to afford a mixture of both hexacyclic products \(^71\) and \(^72\) in 22\% and 65\% yields, respectively, but a divergent and selective process occurred when the pendant alkene contained three carbons \((n=2)\), then only the indoline skeleton \(^71\) was obtained in an exquisite 94\% yield. Such design is very interesting in view of developing library of biologically active small-molecules via a diversity oriented synthesis (DOS).

Adding complexity to the original reports from Padwa, Boger reported the brilliant tandem multi-step process with an initial intramolecular Diels–Alder of 1,3,4-oxadiazole with an internal alkene, which after extrusion of nitrogen delivered the required carbonyl ylide \(^75\), ready to undergo the desired 1,3-dipolar cycloaddition to afford hexacyclic indoline \(^76\) as a single diastereomer in 71\% yield (Scheme 8).\(^\text{29}\)

This elegant maneuver by which the nitrogen extrusion unveils the highly reactive carbonyl ylide fragment (1,3-dipole) required for 1,3-dipolar cycloadditions represents an extremely useful and powerful strategy that Boger exploited numerous times to construct polycyclic alkaloids with important biological activity.\(^\text{30}\)

On the other hand, efforts have also been reported for the development of catalytic enantioselective 1,3-dipolar cycloaddition with indoles (Scheme 9, Eq. 1). For example, \(1,4\)- and \(1,5\)-diazoketone \(^79\) have been reported by Hashimoto to participate efficiently in intermolecular Rh(II)-catalyzed 1,3-dipolar
cycloadditions to afford tetracyclic indoline 80 with high enantioselectivity and high exo/endo diastereoselectivity.\textsuperscript{12} Also fused indolines 82 can be synthesized by a rhodium-catalyzed [3+2] annulation of indoles 81 (Scheme 9, Eq. 2). In this particular reaction, the authors reported that tricyclic indolines 82 were obtained in excellent yields and with high enantioselectivity and that substitution pattern at either C2 or C3 of the indole 81 was extremely influential for the diastereoselectivity outcome of the reaction.\textsuperscript{14}

### 2.4. Diels–Alder cycloadditions

Indolic substrates have been extensively studied in Diels–Alder reactions, either as dienophiles (C2–C3 double bond) (Sections 2.4.1 and 2.4.2), or as dienes when substituted with vinylic pendant side-chains at either the C2 or the C3 position (Section 2.4.3).

#### 2.4.1. Indole acting as dienophile in Diels–Alder cycloadditions

Normal electron demand Diels–Alder cycloadditions of indoles are challenging reactions, usually requiring specific substitution patterns of the indolic ring (electronic factors) as well as high temperature or pressure for the reaction to occur. Because of its low tendency to act as a dienophile, only indole substituted at the N-1 and C3 positions with electron-withdrawing groups is amenable to normal electron demand Diels–Alder cycloadditions.\textsuperscript{13} Work by Piettre and Wenkert showed that high pressure accelerates the normal demand Diels–Alder to achieve the irreversible dearomatization of the indole nucleus (Scheme 10).\textsuperscript{15} For example, dearomatization of indole 83 through a Diels–Alder cycloaddition with the Danishefsky’s diene 84 was achieved at 45 °C under a 12 kbar pressure! to deliver tricyclic indoline 86 in 60% yield and 3:1 endo/exo ratio. Also, normal demand Diels–Alder with 1,3-butadienes can be performed under high-energy photochemical irradiations.\textsuperscript{16}

The intramolecular variant of a normal electron demand Diels–Alder cycloaddition of indoles was reported by Padwa with the reaction of indole 87 with 1,2,3,4-tetrazine in a single step tetracyclic indolines \(87\) (90–91% yield) (Scheme 11).\textsuperscript{17,18} In this reaction, a tertiary amide is necessary (R2=alkyl or allyl) to promote the equilibration between s-cis and s-trans conformers therefore placing the furanyl moiety in close proximity of the indolic ring. One can observe that even though this strategy is extremely efficient, high temperature and pressure are again required.

Some other examples supporting that indole C2–C3 double bond acts as dienophile were reported from inverse demand Diels–Alder cycloadditions with electron poor dienes partners. Seminal work from Snyder demonstrated that indoles may react in formal 1,3-dipolar cycloadditions with [1,2,4,5-tetrazines, 1,2,4-triazine, and pyridazines at afford polycyclic indolines in a unique manner.\textsuperscript{37} As shown in Scheme 12 (Eq. 1), the triazinotryptophan derivative 91 undergoes an intramolecular an inverse demand cycloaddition followed by nitrogen extrusion to deliver the aza-analog 93 of Aspidosperma alkaloids. Related to the same concept, Bodwell reported soon after an extremely concise racemic synthesis of strychnine highlighted by a transannular inverse electron demand cycloaddition of compound 94, which after nitrogen extrusion delivered the natural product pentacyclic core 96 in a quantitative manner.\textsuperscript{38} Finally, another example of inverse electron demand cycloaddition was reported by Liao with the reaction of various indoles 97 and some highly reactive masked ortho-phenylenediamines 98 leading to densely functionalized tetracyclic indolines 99 in good yields (23–71%) (Scheme 12).\textsuperscript{39}

Another approach to circumvent the harsh conditions required for Diels–Alder cycloadditions using the C2–C3 indolic double bond as dienophile is to take advantage of the enhanced reactivity of deprotonated indoles.\textsuperscript{40} As reported in an early work by Markó for a synthetic approach to manzamine alkaloids,\textsuperscript{41} the bis-deprotonation of N-2 carbonyl and C2 of the indole 102 with t-BuOK in THF at 80 °C in a sealed tube afforded the tetracyclic indole structure \(105\) (single diastereomer) in 84% yield, presumably via a formal Diels–Alder cycloaddition (or double anionic addition) spontaneously followed by the olefin isomerization of aldehyde 104. Even though a stepwise or concerted mechanism for this dearomatization cascade has not yet been elucidated, this spectacular transformation via anionic bis-cyclization of 103 established, in a single dearomatization step, the tetracyclic core of the Strychnos-type alkaloids.

#### 2.4.2. Hetero-Diels–Alder cycloadditions

Most of the hetero-Diels–Alder reactions are inverse electron demand type cycloadditions
involving quinone methide-like dipolarophiles to react with the \( \text{C}_2\text{--C}_3 \) \( 2\pi \) electrons of the indole nucleus. Early work by Funk demonstrated that such synthetic strategy was very efficient to assemble complex alkaloids as exemplified by the communesin B' skeleton \( 109 \) synthesis (Scheme 14, Eq. 1) as well as a total synthesis of \( (+/\text{-})\)-perophoramidine \( 115 \).\(^{43}\)

Effectively, Funk described a highly stereoselective intramolecular cycloaddition of an indole moiety tethered to an aniline bearing a leaving group at the nitrogen \( \beta \)-position. Upon heating or acidic treatment, a plausible aza-quinone methide intermediate \( 108 \) could be formed, thereof triggering the intramolecular aza-Diels–Alder reaction to occur and deliver the \textit{endo}-cycloadduct \( 109 \) in high yield. A diastereoselective and intermolecular variation of this transformation was also developed by Qin for the total synthesis of \( (+/\text{-})\)-perophoramidine \( 115 \) (Scheme 14, Eq. 2).\(^{12a,b,44}\) In this event, the reaction between indole \( 111 \) and a putative aza-quinone methide generated from aniline \( 112 \) delivered the hexacyclic indoline \( 114 \) in a single step, 88% yield and with high stereoselectivity (\textit{exo}-selectivity). A silver(I) Lewis acid facilitated the formation of a reactive aza-quinone methide intermediate from the \( N \)-protected aniline \( 112 \) via extrusion of the chloride leaving group (double \( s\text{-}trans \) conformation as shown in the \textit{exo}-transition state \( \text{TS-113} \)), which underwent an inverse electron demand Diels–Alder cycloaddition with indole \( 111 \) yielding the particularly complex products.
Spirocyclic indoline 114 in 88% yield with a high diastereocontrol (11:1 dr).

Inspired from the reports from Funk, the groups of Stoltz and Cossy have both reported the utilization base-mediated aza-quinone methide formation to initiate inverse electron demand Diels-Alder cycloadditions with indoles (Scheme 15).

Upon exposure to cesium carbonate, the chloromethyl-aniline 117 smoothly formed the required aza-quinone methide 118, which reacted with a (+)-aurantioclavine (116) derivative to form cycloadduct 119 in 89% yield and a moderate diastereomeric ratio (2:1 dr) demonstrating a poor stereoinduction from the remote stereocenter at C11 (Scheme 15, Eq. 1). Cossy reported that under similar basic conditions, a probable indol-2-one derivative 120 reacted with the tryptamine derivative 121 under acidic conditions to afford the bis-alkylated oxindole 124 in 75% yield and high diastereoselectivity. Upon the treatment of oxindole 124 with Red-Al, all stereochemical information was lost and the desmethyl-chimonanthine (125) was synthesized as a meso-product.

Recently, Porco reported the use of another o-quinone methide-like reagent 128 to trigger indole dearomatization (Scheme 16). During this hemi-synthesis endeavor towards pleiomaltinine (129) from the complex pleiocarpamine alkaloid 126, the authors examined a possible biomimetic approach for the introduction of a pyrone unit in the pleiomaltinine’s skeleton. Under acidic conditions, silyloxypyrone 127 likely generated a dearomatized form of pyrones as presented by the ortho-quinone methide 128, which likely triggered an inverse electron demand Diels-Alder cycloaddition with the indolic moiety of the natural product pleiocarpamine (126). The plausible cycloaddition resulted in the obtention of the highly functionalized alkaloid natural product 129 in a single step and 51% yield as a single diastereomer.

2.4.3. Indole acting as diene in Diels–Alder cycloadditions. The two structural isomers of vinylc indoles (substituted at C3 130 or at C2 132) have been documented to react as electron rich dienes in normal demand Diels–Alder cycloadditions (Scheme 17).

Pioneering work by Magnus reported in 1993 described a strategy for C2-vinlylic indole dearomatization via a Diels–Alder...
cycloaddition, which through an intramolecular cycloaddition generates, in a single step, three rings (C–E rings) present in numerous Strychnos alkaloids.\(^4^8\) Soon after, Kuehne described a similar intramolecular Diels–Alder cycloaddition strategy, with asymmetric control, using a chiral ferrocenyl-auxiliary amenable to high facial-diastereodifferentiation during the reaction to access the tetracyclic indoline core \(^1^3^6\) (Scheme 18, Eq. 1).\(^4^9\) Fukuyama also utilized the Diels–Alder cycloaddition strategy to assemble in a single step the A–E rings of vindoline, a powerful tool that the author also employed for the biomimetic construction of vinblasetine and several other complex alkaloids.\(^5^0,^5^1\) Basic conditions using pyrrolidine on indole \(^1^3^7\) promoted a succession of several steps with a deprotection, followed by the aminolactol moiety rearrangement to the cyclic enamine \(^1^3^8\), which upon heating underwent the desired inverse electron demand Diels–Alder to afford compound \(^1^3^9\) in 73% overall yield.

More recently, MacMillan reported a remarkable total synthesis of \((+)-\text{minfiensine (33)}\) with the following key features: (i) organocatalytic [4+2]-cycloaddition coupled with hemi-aminization/cyclization to allow rapid access to a complex tetracyclic framework and (ii) a second radical cyclization to install the last ring of the alkaloid (Scheme 19, Eq. 1).\(^5^2\) Basic conditions using pyrrolidine on indole \(^1^3^7\) promoted a succession of several steps with a deprotection, followed by the aminolactol moiety rearrangement to the cyclic enamine \(^1^3^8\), which upon heating underwent the desired inverse electron demand Diels–Alder to afford compound \(^1^3^9\) in 73% overall yield.

In the first event, protected tryptamine \(^1^4^0\) participated in a dearomatizing cascade via a catalyzed Diels–Alder reaction (fromimidazolidinone catalyst \(^1^4^2\)) with the propyne 4-imidazolidonium \(^1^4^1\) to generate enamine intermediate \(^1^4^3\), which underwent spontaneous isomerization to indolinium \(^1^4^5\). Further cyclization of the pendant protected amine in a 5-exo-trig manner furnished pyrroloindoline \(^1^4^6\). The authors proposed a specific arrangement for the Diels–Alder cycloaddition wherein the acetylenic group of the iminium intermediate \(^1^4^3\) may be positioned away from the tert-butyl substituent of catalyst \(^1^4^1\), thereby facilitating endo selectivity during the cycloaddition (cf. \(^1^4^3\)) and establishing the C\(^3\) stereocenter of indoline intermediate \(^1^4^4\). Reductive workup in the same pot delivered product \(^1^4^7\) in 87% yield and 96% ee. This impressive organocatalytic cascade sequence allowed MacMillan and co-workers to produce the tetracyclic core of minfiensine \(^1^4^7\) in a single step with high enantioselectivity and diastereocontrol.

Since this seminal work, several other complex alkaloidic natural products have been synthesized by the MacMillan group, which clearly demonstrates that organocatalysis is amenable to novel, rapid, and most importantly highly enantioselective ways of constructing complex indolic alkaloids.\(^5^3\) A related strategy of bis-annulation was reported by Zhao for an expedient assembly of highly functionalized tetrahydrocarbazoles (Scheme 19, Eq. 2).\(^5^4\) In this event, a prolinol-derived catalysts dictated the enantioselectivity outcome of the Diels–Alder cycloaddition between the indole derivative \(^1^4^8\) and an \(\alpha,\beta\)-unsaturated aldehyde via a possible assembly \(^1^4^9\). The Diels–Alder cycloadduct \(^1^5^0\), obtained in a 16:1 endo/exo diastereomeric ratio and 95% ee, spontaneously isomerized to endure the second annulation leading to isolation of the tetracyclic indolenine \(^1^5^1\) in 67% yield.

Armstrong and Pindur demonstrated independently that C\(^3\)-vinyl indoles are also potential substrates for Diels–Alder reactions.\(^5^5\) In 2008, Bernardi and Ricci reported a first example of catalytic enantioselective dearomatization of 3-vinylindoles with
several maleimide and quinones as dipolarophiles and bifunctional-thioureaquinuclidines organocatalysts. Following this work, thiourea catalysts were also attractively exploit by Barbas III for the Diels–Alder cycloaddition between 3-vinylindoles and α,β-unsaturated oxindoles to assemble hexacyclic spiro-oxindoles in a single step and with high enantioselectivity (Scheme 20, Eq. 1).57

Finally, the indolic heterodiene was described by Piettre and Chataigner to undergo inverse demand cycloaddition under high pressure with ethyl vinyl ether (Scheme 20, Eq. 2) leading to a high endo/exo diastereoselectivity during the cycloaddition. Upon cyclization a novel 1,3-dipole was generated, which reacted spontaneously with the other acrylate partner already present in the reaction media to deliver in a single operation the tetracyclic indolines in high yields. This well-designed sequence of [4+2]- and [3+2]-cycloadditions was achieved with high chemoselectivity.

To conclude this section on dearomative cycloaddition, we should not forget about the seminal work from Vollhardt, who clearly demonstrated the viability of a [2+2+2]-cycloaddition strategy during his epic synthesis of strychnine. While this method has been rarely employed, cobalt-mediated [2+2+2]-cy-

3. Arylative dearomatization

Dearomatization of indole at the C3 position by any electrophilic arene surrogates is proposed to be involved in many natural product biosyntheses. Synthetic methods have thereof been
developed, notably for indole dimerization with the C2 or C3 arylations to generate various types of indoline and indolenine products. Palladium and other transition metals as well as Brønsted acids and iodane reagents have been largely utilized to promote such controlled arylative dearomatizations, which will be discussed in this section.

3.1. Palladium-catalyzed dearomatization of indoles

Palladium-catalyzed cross-coupling reactions and arylations methods have been widely developed in synthesis. In contrast, utilization of palladium to dearomatize arenes and heteroarenes such as indoles is still very limited.

Three recent examples are paving the way for novel strategies to be developed with palladium(0) or palladium(II) to create useful and complex indolic polycyclic ring systems. As described in Scheme 21 (Eq. 1), Pd(II) under oxidative conditions in the presence of silver acetate enabled the oxidative Heck reaction (C2 intramolecular arylation) of substrate such as 159 leading after β-hydride elimination to the tetracyclic styrenylindoline 160 in good yields.60 Other substitution patterns on the starting indole as shown in structure 161 are also amenable to react through oxidative Heck reactions thus generating a pyrroloindolenine type skeleton 162 (Scheme 21, Eq. 2).61 Compounds 162 can be diversely modified either to oxindole such as 163 or reduced to tetracyclic indolines 164 in useful yields. Finally, a third substitution pattern at C3 was studied by You showing that substrates like 165 can easily undergo spirocyclization again via an oxidative Heck type reaction (Scheme 21, Eq. 3).63 The authors demonstrated a large scope of reactivity as well further reduction of the indolenine scaffold using sodium borohydride to deliver indoline 167. In the same study, You reported the catalytic enantioselective variation of the reaction thus employing the chiral ligand 168 to access the desired compound 166 in 71% yield and 61% ee. This example stands today as the only report of a dearomative and enantioselective oxidative Heck reaction.

3.2. Transition metal and Brønsted acid mediated dearomatization of indoles

Several other methods have also been reported for the arylative dearomatization at both C2 and C3 positions of indoles (Scheme 22). Liu reported an innovative approach for the dearomatization of keto-indole derivative like 168 (Scheme 22, Eq. 1) via a highly regioselective addition of a Grignard reagent at the C2 carbon-center of the indole.64 Product 169 was obtained after a diastereoselective reprotonation under kinetic control as the cis-indoline stereoisomer 169. Treatment of the cis-derivative 169 with base at higher temperature allows for the C3 epimerization and full inversion to deliver the trans-indoline 169 in 82% yield as the sole product of the reaction. In a second campaign towards the natural product haplophytine, Chen reported the arylative dearomatization of β-carboline substrates such as 170 at the C3 position by means of a para-quinone electrophile 171 (Scheme 22, Eq. 2).65 Triflic acid was found to be the best promoter for this transformation while the substitution pattern of the quinone appears capricious in dictating the regioselectivity during the ring closure event. Similar products from the fusion between indoles and quinones were also synthesized by Vincent using a Friedel–Crafts hydroarylation method mediated by FeCl3 (Scheme 22, Eq. 3).66 In the present three-step process, iron(III) facilitated the highly regioselective arylation of acylindoles 173 with phenols 174. Further removal of the protecting group by an acidic treatment followed by an oxidative cyclization afforded the polycyclic indoline 176 in good overall yield.

3.3. Iodane-mediated dearomatization of indoles

Dearomative dimerization of indoles, tryptamine, and tryptophans building blocks has been a long-standing problem for synthetic chemists in term of reactivity, but also scalability and stereocontrol. Barton first reported that organobismuth (bismuth(V)) reagents were amenable to oxidative arylation at the C3 position of indoles.67 A later work from Takayama, demonstrated...
that hypervalent iodine(III) reagents enable the desired arylative
dearomatization of tryptamine substrates with a concomitant an-
nulation to furnish the pyrroloindoline dimeric products of the
oxidative cascade. Until to date, several mechanism have been
proposed for the formation of such arylative indole dearomatiza-
tion, either via single electron transfer (SET), or nitrene aziridina-
tion or most presumably through the in situ formation of
$\text{I}_3^-$-iodane at the indole C3 position as proposed in a seminal work by Moriarty.
In Takayama's report, the authors isolated after reduction three main
products having the meso and the racemic mixture of the natural
product chimonanthine (meso/racemic, 2.5:1.0 dr) in 43% overall
yield. These results were later advantageously utilized by Willis
through an ingenious meso-desymmetrization of the dearomatized
dimer 178 (Scheme 23, Eq. 1). Taking advantages of the well-
established Trost asymmetric allylic alkylation strategy (AAA),
Willis was able to desymmetrize diamine 178 in 76% yield and 99%
enantiomeric excess on gram scale quantities. These efforts cul-
mulated with the total synthesis of hodgkinsine B (180) in 11 steps.
More recently, Liang reported the dimerization of N-tosyl trypt-
amine 181 unexpectedly mediated by iodine in presence of oxygen
(Scheme 23, Eq. 2). The overall yield in dimer 182 was reported as
90% while the isomeric ratio was not commented by the authors.
The crystallographic structure reported in the study presents both
concave pyrroloindoline moieties dimerized as a C2-racemic product 182 different from the previously reported meso-products.
This efficient dimerization strategy may pave the way to many
asymmetric variations of arylative dimerization annulation cas-
cades to be discovered.

Since the seminal work from Haran during the total synthesis
campaign of diazonamide A, and the formal [3+2]-cycloaddition,
revealing a C3 arylation strategy coupled with a C2 aminal cyclization, hypervalent iodine chemistry has been recognized as an extremely productive and somehow controllable tool for indole dearomatization.71

Haran demonstrated of the indole dearomatization through the impressive oxidative macrocyclization strategy designed for the synthesis of diazonamide A (Scheme 24). The key step of the synthesis the hypervalent iodine reagent PIDA promoting the activation of the phenol moiety in substrate 183 for which the presence of lithium acetate salt facilitates the electrophilic activation and the indole attack and further ring closure to the furanoindoline 185 in reproducible range of 30% yield with useful diastereoselection (3:1 dr).

Later on, similar annulated products, from formal [3+2]-cycloadditions were obtained by Danishefsky in a model study toward the natural product phalarine.72 Soon after, Nicolaou and Chen also reported an arylative dearomatization of new substrates such as β-carboline 186 using the trifluoroacetate variant of PIDA (PIFA) to hindered C–C bond link of a quaternary carbon and aryl sp² carbon centers for the junction of the heterodimer haplophytine (189) (Scheme 25).73 Study for the diastereocontrol during the key dearomatizing step concluded that the acetate protecting group on the β-carboline 186 was crucial to achieve high diastereodiscrimination (10:1 dr) during the formation of the hexacyclic intermediate 188, which was obtained in 23% yield.

Taken together, the studies of Haran and Nicolaou (Schemes 24 and 25, respectively) demonstrate how remote stereo-electronic factors and innate structural conformation can affect the course of the oxidative arylation in terms of facial diastereo-induction. Inspired from Haran’ seminal work, Yao reported in 2013 the total synthesis of ent-(—)–azonazine via a biomimetic oxidative annulation, which enabled a concise synthesis and the natural product structural reassignment to a cis-benzofuranoidoline ring junction.74

Recently, several groups have been involved in optimizing arylation transformations and reported elegant synthetic methods for the dearomatization of simpler substrates than the aforementioned to showcase arylation reactions from hypervalent arylated-iodines (Scheme 26). First in this series of reports, Baran studied the dearomatization of tryptamine, tryptophan, and β-carboline derivatives such as 190 applying oxidative reaction conditions using a bisaryl λ3-iodane reagent (Scheme 26, Eq. 1).75 The use of a strong hindered organic base was presented as crucial by the authors to achieve the dearomative step as shown below for the dearomatization of β-carboline 190 with a bisaryl tetrafluoroborate hypervalent iodine reagent, leading after reduction to isolate indolines 192 in excellent overall yields. You reported a more efficient dearomatization of tryptophols such as compound 193, tolerating electron withdrawing or donating (R1) on the indole ring, but also alkyl groups at the C2 position (R2). Arylation was shown to be catalyzed by copper(I) and (II) and optimized for copper(I) triflate with some bisaryl iodonium reagent affording the desired aryl group for transmetalation (Scheme 26, Eq. 2).76

Even though no discussion was offered in this paper, the use of mesytil residue (R3) as a dummy ligand on the λ3-iodane reagent provided a very efficient and more economically viable method for arylation and vinylation (for the prospect of complex substrates). Extremely similar chemistry was described by Reisman for the dearomatization study of N-tosyl-tryptamines 195 to access in a single step the C3 arylated pyrroloindoline building blocks 196 in high yields (Scheme 26, Eq. 3).77 First attempts of a catalytic enantioselective variation of this reaction have failed and represent certainly a desirable goal for new developments of this chemistry. In the same time, MacMillan reported an impressive step forward in the same direction of asymmetric catalysis with the dearomatization tryptamides 197 to afford pyrroloamidoindoline 199 in high enantiopurity (Scheme 26, Eq. 4).78 Once again, the copper(I)
strategy to achieve oxidative insertion of a mesityl-aryl $^3$-iodane reagent proved to be an efficient maneuver for transmetalation while several Box ligands were screened to achieve the best enantiodiscrimination possible (see the proposed transition state 198). In 2013, Reisman offered a novel diastereoselective arylative dearomatization of tryptophan derivatives 200 combined with a substrate annulation (Scheme 27). As shown in the postulated copper(III) assembly 201, using the appropriate copper catalyst enables a decisive intramolecular chelation with the pendant diketopiperazine moiety, which forces the arylation to occur at the C3 position from the bottom face of the substrate leading to the pentacyclic hexahydro-[2,3-b]pyrroloindole 202 in a single step with a high level of diastereocontrol. For this particular substrate 200, the ligand used and the catalyst loading were optimized in order to achieve this successful transformation in 62% yield. Following two more steps with aniline deprotection and a modified Larock indolization delivered the natural product nasesezaine B (203) in a very concise manner (only five linear steps from tryptophan).

As a conclusion of these related studies, it appears that copper(I)-catalyzed transmetalation of $^3$-iodane reagents emerged as a powerful strategy for the simultaneous C3 arylation and C2 functionalization of indolic substrates. While subtlety on the iodonium reagents is noticeable (counter anion, and dummy ligand effects), the ligand influence on the steric course of the copper-catalyzed transformation is presumably governed by the positioning of the aryl group as shown in the proposed transition state TS-198 (Scheme 26). These recent results reveal that opportunities exist for the development of some more general asymmetric methods for the catalytic arylative dearomatization of indoles.

### 4. Protonative dearomatization

Protonation of free indole preferentially occurs at the C3 position leading to the corresponding indoleninium, which can spontaneously be trapped by the formation of a new bond at C2. In this respect, cyclic tautomers of tryptophan and tryptamine derivatives have been prepared in various acids such as phosphoric acid or...
trifluoroacetic acid at room temperature.\(^8\) Thus, tryptophan derivative \(^{204}\) can be cyclized to afford a mixture of hexahydropyrroloindole (HPI) tautomers \(^{205}\) endo- and \(^{205}\) exo- \((9:1\ dr)\) respectively in 85% yield (Scheme 28). N-Sulfonylation of the latter mixture provided the more stable HPI \(^{206}\) as a single diastereoisomer, which presumably involves a dynamic kinetic resolution.\(^8\) Movassaghi and Schmidt utilized this method and disclosed an elegant enantioselective total synthesis of \((-\)chimonanthine \((178)\), \((+\)folicanthine \((208)\), and \((-\)calycanthine \((209)\). Radical benzyl bromination of \(^{206}\) afforded the key intermediate \(^{207}\) (Scheme 28).\(^8\) Intermediate \(^{207}\) was subsequently transformed in a very concise manner (five or six steps) to the aforementioned natural products.

Another application of dearomatization driven by tautomeric protonation was described by Loh during the chemical synthesis of some HPI-derived organocatalysts.\(^8\) This sequence involved a cyclization strategy of tryptophan derivatives in TFA giving a mixture of cyclic tautomers. Subsequent amine protection and hydrogenolysis efficiently furnished the desired HPI-derived organocatalysts.

In 2010, Chen reported an unexpected indole dearomatization in the presence of a stoichiometric amount of Lewis acid (Scheme 29).\(^8\) In this reaction, the indolic substrate \(^{210}\) was transformed into the substituted cyclopentyl[\(b\)]indoline \(^{212}\) through a Lewis acid mediated tautomeric dearomatization. The authors believed that \(\text{AlCl}_3\) enhances an enamine-imine isomerization through proton transfer followed by intramolecular imino-ene reaction via the formal assembly \(^{211}\) to form the cyclic indoline tautomer \(^{212}\) in high yield and excellent stereocontrol.

In this section of protonative dearomatization, we will also present several examples of asymmetric hydrogenation of indoles. For instance, Kuwano was first to report a catalytic asymmetric hydrogenation of indole derivatives \(^{213}\) and \(^{214}\) (Scheme 30).\(^8\) Protected indoles substrates have been efficiently reduced, in good to excellent yield and ee, by rhodium and ruthenium complexes with a trans-chelate chiral bispiphosphate PhTRAP ligand \(^{217}\). The chiral induction and the catalytic activity are significantly affected by the N-protecting group nature on the indole nucleus.

Rhodium catalysts with monodentate phosphoramidite ligand PipPhos have also been used for the asymmetric hydrogenation of methyl \(N\)-acetyl-indole-2-carboxylate to yield the corresponding indoline in quantitative yield with 74% ee.\(^8\) Pfaltz and Baeza disclosed an efficient base free, hydrogenation of \(N\)-protected indoles, which are substituted at \(C2\) or \(C3\) positions, using air and moisture stable cationic iridium catalysts and some chiral \(N,P\)-ligands. Again, the chiral induction and the catalytic activity in this report can be significantly affected by the \(N\)-protecting group appended on the starting indoles.\(^8\)

A related and interesting approach is the asymmetric reduction of highly stable and complexation free 2-substituted and 2,3-disubstituted indoles. The direct asymmetric reduction provides an atom-economic variant, avoiding the use of chelating groups (for the transition metal used as catalyst) and the production of waste. Accordingly, Zhou reported the first highly enantioselective reduction of \(N\)-unprotected indoles by using a palladium catalyst in the presence of Brønsted acid (Scheme 31).\(^8\)

It is likely that protonation of 2-substituted indoles \(^{218}\) by \(\text{L}-\text{camphorsulfonic acid (L-CSA)}\) led to the corresponding highly electrophilic iminium salt \(^{219}\), which is then reduced in situ by \(\text{Pd(OCCF}_3)_2(\text{L})\text{-HR-BINAP}\) catalysts to provide the corresponding indolines \(^{220}\) (Scheme 31). This methodology has been successfully extended to other 2,3-disubstituted indoles, leading to cis-
indolines in good yields and with high ee. Mechanistic studies suggested that the protonation and hydrogenation sequence involves a dynamic kinetic resolution (k_1 \gg k_2), which favored the rearomatization of indolenium ent-219 leading to a highly diastereoselective reduction of 219 to indoline 220.

Soon after, Zhou disclosed a simple, efficient, and rapid access to 2,3-disubstituted indolines 226, in a sequential manner, from either the 3-(α-hydroxyalkyl)indole 223a or the 3-(toluenesulfonyl-α-methoxy)-indoles 223b intermediates, or a one-pot manner, from reactions between 2-substituted indoles and aldehydes or N-tosyl imine (Scheme 32). The first step in this process is a Friedel–Crafts reaction between a 2-substituted indole 222 and an aldehyde (or N-tosyl imine) catalyzed by para-toluenesulfonic acid monohydrate (TsOH·H_2O), giving the corresponding 3-substituted indoles 223a,b. Water (or tosylamine) is then eliminated to give the corresponding vinylogous iminium 224. Finally, a double in situ asymmetric reduction of this iminium 224 gives rise to the 2,3-disubstituted indolines 226 with excellent yields and high enantioselectivity.

5. Alkylative dearomatization

5.1. Reaction of indole with oxo- and thiocarbeniums

Reactions involving dearomative and nucleophilic attacks of indoles to carbenium-like electrophiles are described in the following section. Interestingly, the literature involving dearomatization of indole through Friedel–Crafts-like reaction between the C3 position of the indole and aldehydes is quite limited presumably because of the high instability of the resulting 3-(α-hydroxyalkyl)indole products (hydroxyl leaving group abilities to facilitate elimination reactions).90

Cook reported an effective biomimetic strategy toward complex vincamajine-related indole alkaloids 230–232 as shown in Scheme 33. The complex indole derivatives 227 were prepared in several steps starting from d-tryptophan methyl ester or Nα-methyl-6-methoxy-d-tryptophan ethyl ester. When aldehyde 227 was treated in a mixture of Ac_2O/TFA, a stereospecific intramolecular Friedel–Crafts reaction, followed by an acetylation resulted in the aminocarbinol 229 in 84% yield. It is interesting to note that TFA enhanced the exclusive formation of the kinetic product 229 whereas in a mixture of Ac_2O/HCl(gas), the other thermodynamic diastereoisomer was obtained as the major product. The central aminocarbinol 229 was subsequently transformed in several steps to (−)-vincamajinine (230), (−)-vincamajine, (+)-quebrachidine, (−)-11-methoxy-17-epi-vincamajine (231), and (−)-vincarine.

Cyclopropanes are interesting reagents in organic chemistry, particularly 2-alkoxycyclopropanoate esters (donor–acceptor), as they readily fragment through a retro-Aldol reaction to produce zwitwitterionic intermediates, thus allowing possible annulation strategies with appropriate dipolarophile substrates (e.g., indole). In this regards, Pagenkopf developed a useful synthetic methodology for the synthesis of polycyclic compounds, based on the annulation of free indole and cyclopropane 2-alkoxycyclopropanoate esters in the presence of a Lewis acid (Scheme 34).92 2-Alkoxycyclopropanoate ester 232 undergoes annulation with free indole in the presence of Me_2SiOTf, to afford the indoline carbinol-derivative 236 as sole diastereomer in 78% yield. It is noteworthy that this reaction has been extended to a number of indole derivatives and other cyclopropanes. However, it should be noticed that reactions of 3-substituted indoles do not provide similar annulated products.

In 1990, Bosch described an approach for the construction pyrrolidine of Strychnos alkaloids (Scheme 35). In this reaction the indole bearing a dithioacetal unit was activated by dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to afford a thionium ion, which undergoes an Friedel–Crafts-type reaction.93 This methodology has culminated in the total synthesis of (±)-tubifolidine, (±)-tubifoline, and (±)-19,20-dihydrokuammicinic.

More recently, this synthetic method has been readily applied by Overman for the synthesis of Strychnos alkaloids (+)-condylocarpine (239), (+)-isocondylocarpine (240), and (+)-tubotaiwine (241) from the dithioacetal 237 (Scheme 35).94

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Scheme 32.

Scheme 33.
Finally, an example of Friedel–Crafts-like reactivity was also reported by Seidel with a one-step total synthesis of the natural product neocryptolepine (245) \(\text{Scheme 36}\).95 The Friedel–Crafts between the aminobenzaldehyde 242 and indole 233 was followed by the iminium \(243\) intramolecular capture and a final aerobic oxidation to conclude an efficient cascade.

5.2. Interrupted Pictet–Spengler and related aza-Friedel–Crafts reactions

The Pictet–Spengler reaction is originally a condensation of \(\beta\)-phenylethylamine and formaldehyde dimethylacetal in the presence of acid, followed by a cyclization that produces some 1,2,3,4-tetrahydroisoquinoline (THIQ) molecules.96 In 1928, Tatsui extended this reaction to tryptamine, which affords 1,2,3,4-tetrahydro-\(\beta\)-carboline (THBC) derivatives.97 Since then, the Pictet–Spengler has become an efficient widely used tool (e.g., with tryptamine or tryptophan derivatives) for the total synthesis of complex natural products. While the original Pictet–Spengler reaction ends through a rearomatization process, several type of polycyclic structures can be obtained through the interruption of the reaction, depending on the events occurring after the spirocyclization at the \(C_3\) position (migration or internal/external trapping of the imine), which mainly depend on the structure of the starting aldehyde involved in the reaction.

For example, modified trimines such as, \(N_\beta\)-hydroxytryptamines,\(^{58}\) \(N_\beta\)-alkoxytryptamine,\(^{99}\) have been successfully used in interrupted Pictet–Spengler reaction to access a spiroindolenine scaffold intermediate (see Scheme 2).\(^{1,100}\) The interrupted Pictet–Spengler reaction with \(\alpha\)-amino aldehydes and \(L\)-tryptophan methyl ester is also well known to afford dearomatized afforded \(N_\beta\)-hydroxyoctahydro-\(\beta\)-pyrroloindoles derivatives.\(^{101}\) Following this synthetic approach, \(\beta\)-(\(\pm\))-\(N_\beta\)-benzyltryptophan methyl ester and methyl \((E)\)-5-methoxy-3-oxopent-4-enoate, a synthetic equivalent of the corresponding unstable aldehyde in presence of methanesulfonic acid, was used by Cook to synthesize the tetracyclic core structure of several \(Strychnos\) alkaloids with high diastereocountrol and yields.102 Similarly, an example of interrupted Pictet–Spengler via iminium ion trapping by an alcohol was reported by Töke.103 Delgado and Blakey developed a methodology to generate \(b\),\(g\)-unsaturated iminium ion (from sensitive \(b\),\(g\)-unsaturated aldehyde) in situ, which underwent polycyclization to deliver some tetracyclic alkaloidic skeleton and the structural core of the malagashanine alkaloids.104

One of the most impressive example of interrupted Pictet–Spengler was reported by Corey for the total synthesis of aspidosphytine, a natural product isolated from \(Haplophyton cimicidum\) (Scheme 37). To synthesize this structurally daunting molecule, the strategy from Corey entailed a double condensation/Pictet–Spengler/allylation/isomerization/reduction sequence of tryptamine derivative 246 and chiral di-aldehyde 247, which provided the complex core 251 in 66\% overall yield (Scheme 37).\(^{105}\) It is noteworthy that, the stereochemistry outcome of the 251 is controlled at the Pictet–Spengler reaction stage from the remote quaternary center stereo-information.

Pandey and Kumara also disclosed a related and very impressive domino reaction for the synthesis of pentacyclic \(Aspidosperma\) alkaloid (\(\pm\))-vincadifformine in which the resulting iminium species from the interrupted Pictet–Spengler was tautomerized to an enamine to enable the final nucleophilic ring formation.106
A recent example of interrupted and diastereoselective Pictet–Spengler is presented in the impressive enantioselective total synthesis of (−)-phalarine (257) designed and executed by Danishefsky and co-workers (Scheme 38).

In the key cyclization, the 2-substituted-L-tryptophan derivative 252 reacts smoothly with formaldehyde in the presence of camphorsulfonic acid (CSA) giving rise to the core structure 256 in 91% yield. Danishefsky conducted a diastereoselective Pictet-Spengler reaction using the enantiopure tryptophan derivative 252 and a dearomatization of the common iminium 253 either at C2 or C3 (via intermediates 254 or 255, respectively) to afford pentacycle 256 as a single diastereomer in 91% yield. Both pathways via the iminium 254 or stabilized carbocation 255 are plausible and provide a good handle for chirality transfer at both the C2 and C3 positions during the dearomatization step. The total synthesis of (−)-phalarine (257) was further completed with reductive decarboxylation and installation of the tryptamine portion via the Gassman oxindole synthesis.

Recently, Matsuo developed a new strategy for the preparation of hydrocarbazoles (Scheme 40). Conceptually, cyclobutanones in the presence of a Lewis acid led to the corresponding zwitterionic dipole intermediates, which could subsequently react with indoles to provide the hydrocarbazoles through a formal [4+2]-cycloaddition. The authors applied this new method to the total synthesis of (±)-aspidospermidine (266). In the key intramolecular step, Me3SiOTf triggered first the cyclobutane ring opening in a retro-Mannich like fashion, thus creating the reactive acyl-iminium intermediate 264, which endured the attack of the indole through a aza-Friedel–Crafts reaction and the final silylenolether cyclization to give rise to the pentacyclic compound 265 in 46% yield.
In 2010, Floreancig devised a strategy for the construction of quaternary carbon center of spirooxindole amides \(269\) (Scheme 41). Indolyl cyanohydrin ether substrate \(267\) was first synthesized from readily accessible indoles by chlorination with NCS. Treatment of \(267\) with the Schwartz’s reagent \([\text{Cp}_2\text{Zr(H)Cl}]\) followed by addition of acid chlorides provided the acylimine \(268\) in situ, which after addition at the C3 position of the indole and hydrolysis of the fragile chloroiminium ion intermediate provided a mixture of spiro-oxindoles stereoisomers \(269\text{a}\) and \(269\text{b}\) in 73% and 10% yields, respectively.

Another efficient and elegant access to tetrahydro-5\(\text{H}\)-indolo[3,2-c]quinoline heterocycles from benzyl azides and protected indoles in the presence of triflic acid was reported in 2011 (Scheme 42). It is noteworthy that the N-tosyl group is optimal to facilitate the formal \([4+2]\)-cycloaddition. The mechanism proposed by the authors started with the decomposition of the benzyl azide \(272\) through a protonation and a rearrangement delivering the iminium ion \(273\) releasing molecular nitrogen. The first aza-Friedel-Crafts reaction (intermolecular) occurred between the indole and the iminium \(273\) followed by a second aza-Friedel-Crafts reaction (intramolecular) to generate the corresponding annulated tetrahydro-5\(\text{H}\)-indolo[3,2-c]quinoline scaffold \(274\) and \(275\). It is noteworthy that depending on the substitution pattern from the starting indole, different skeletal isomers can be obtained.

In 2012, Movassaghi and Medley designed and executed a biomimetic inspired synthesis of the monomeric alkaloid \((-\text{C}_6\text{-})\text{-methylaspidospermidine} (289)\) and its dimeric form as \((\pm\text{-})\text{-didee-poxytabernaebovine} (290)\) from the common precursor \(286\), obtained through an interrupted Bischler–Napieralski reaction (Scheme 44). In this cascade of events, iminium \(285\) was presumably trapped by an ene-type addition of the pendant alkene, which after elimination of the chloroaminal intermediate released the common and presumably highly reactive di-iminium specie \(286\).

### 5.3. Interrupted Bischler–Napieralski reaction

In 1893, Bischler and Napieralski reported a new method for the synthesis of isoquinolines. This type of Friedel–Crafts acylation reaction on electrophilic reactive imidates has been exploited on many indolic substrates and is amenable to indole dearomatization and cascade reactions due to the higher oxidation state of the reactive intermediate involved.

During the racemic synthesis by Magnus of the pentacyclic skeleton of \(Kopsia\) alkaloids, a cascade reaction involving a Bischler–Napieralski-like transformation was developed (Scheme 43). Treatment of the elaborated carbamate \(276\) with triflic anhydride enabled a Bischler–Napieralski to be achieved leading to the final iminium \(282\) providing after quenching (with aqueous NaHCO\(_3\) or trimethylsilyl cyanide), the tetracyclic indoline dienes \(283\). Further transformations of the common core structure \(283\) led to the synthesis of numerous alkaloids: \((\pm\text{-})\text{-pauciflorine B}, (\pm\text{-})\text{-lahadinine B}, (\pm\text{-})\text{-kopsidasine}, (\pm\text{-})\text{-kopsidasine-}N\text{-oxide}, (\pm\text{-})\text{-kopsjasminilam}, (\pm\text{-})\text{-11-methoxykopsilogine}, and (\pm\text{-})\text{-11,12-demethoxylahadinine B.}\)

### 5.4. Oxidative cross-coupling

Within a few decades, dearomatizing oxidative coupling of indoles has emerged as a powerful methodology for the synthesis of polycyclic skeletons and complex natural products. Generally, the C3 position of an indole anion and a tethered enolate reacts in
the presence of an oxidant leading to radical cyclization to afford and indolenine intermediate, which can endure a second cyclization in the presence of an internal nucleophile.

In 2010, Ma reported an asymmetric total synthesis of \((-\)-communesin F (295) (Scheme 45).\(^{117}\) The indole precursor 291 (prepared in three steps in 63% yield) was first deprotonated with lithium hexamethyldisilazide (LiHMDS) at low temperature to generate the required dianion 292. Upon addition of iodine, the key oxidative cross-coupling reaction was achieved and spirolindolenine 294 was delivered. The nitro group was subsequently reduced and selectively methylated leading to the correct diastereomer, which was further transformed to \((-\)-communesin F (295)) in a total of 13 steps.

A year later, the same group published enantioselective total syntheses of communesin A (296) and B (110) using the same strategy (Scheme 46).\(^{118}\) In this case the chirality from the azepine precursor induced a higher stereoselectivity (due to steric hindrance) during the oxidative coupling of the diradical intermediate 297, thus providing the annulated product as a single diastereomer.

In 2012, Ma and Xie developed a general procedure using LiHMDS and iodine as oxidizing agents to prepare polycyclic spirolindolines 299 and polycyclic pyrroloindolines 301 (Scheme 47).\(^{119}\) These polycyclic skeletons were, respectively, synthesized from the corresponding \(\beta\)-ketoamides 298 and malonic diamides 300 via a domino intramolecular oxidative coupling/condensation with yields ranging from 20 to 87%. In both cases, the substitution pattern on the indole ring (R\(^1\) group) did not affect the reactivity during the polycyclization.

During the enantioselective total synthesis endeavor towards \((-\)-vincorine (305)), the indole derivative 302 was cyclized by employing intramolecular oxidative coupling conditions (Scheme 48).\(^{120}\) Following the deprotonation step with LiHMDS, oxidative environment afforded the annulated product 304 as a single isomer with 67% yield. The later intermediate 304 led to an
efficient synthesis of the \((-\)-vincorine \((305)\) with an overall 5% yield.

5.5. Radical cyclization

At the beginning of the 19th century, Gomberg generated and characterized the first example of free radical. Since then, carbon-centered radicals have been used in many reactions and specifically for indole dearmatizations. In 2007, Stevens and co-workers reported a straightforward synthesis of racemic benzospiro-indolizidinepyrrolidinones.\(^{121}\) The key reaction sequence of this work was accomplished by a copper(I) chloride/tetramethyl ethylene diamine catalyzed atom transfer radical cyclization (ATRC) via a domino reaction involving a 5-\textit{exo}-trig, followed by a 6-\textit{endo}-trig cyclization and represents a clear example of radical-mediated cascade reaction.

Another radical-mediated transformation was achieved by Reissig though an extremely efficient and highly diastereoselective intramolecular indole dearmatization by addition of a ketyl radical specie to the indole nucleus (Scheme 49).\(^{122}\) Under the action of samarium diiodide, indole substrates such as \(306\) (N-alkylated or N-acetylated indoles) generate a samarium ketyl intermediate \(307\), which adds to the activated aromatic system through a six-membered ring-like transition state. It is noteworthy that conversions of 3-methoxycarbonyl-substituted indole derivatives to the corresponding polycyclic products can also be accomplished without use of hexamethylphosphoramide (HMPA). The authors also demonstrated that the samarium enolates intermediate can be trapped with alkyl halides in an inter- or intra-molecular fashion. The Reissig group showcased their methodology in a racemic formal total synthesis of strychnine (Scheme 47).\(^{123}\)

The synthesis begins with N-acylation of 3-indolylacetonitrile with 4-oxopimelic acid monoester to yield the indole unit \(306\) in 64% yield. A subsequent domino cyclization of \(306\) in the presence of samarium diiodide and HMPA yields the tetracyclic core \(309\) in 70–75% yield as the major product and as a single diastereomer. The tetracyclic acylated-indoline intermediate \(306\) was then further transformed to the known Rawal intermediate \(309\) to complete the formal total synthesis.

In 2001, Jones reported a route to \(Aspidosperma\) and \(Strychnos\) alkaloids core based on translocation-cyclization—cyclization of aryl radical.\(^{124}\) In this case, an aryl radical undergoes a 1,5-hydrogen atom transfer to generate a nucleophilic amido radical triggering two successive radical cyclizations leading to complex tetracyclic indoline structures.\(^{125}\)

In 2004, Baldwin also reported the preparation of spiroindolines by an intramolecular radical \textit{ipso}-type cyclization.\(^{126}\)
dearomizing spirocyclizations with aryl radicals (high energy) afford the corresponding spirocycles in good yield.

Nicolau’s total synthesis of aspidophytine also illustrated the efficacy of radical to deaerate the indole nucleus (Scheme 50). In this reaction, the xanthate substrate 310 was heated in benzene in the presence of n-Bu3SnH and AIBN to generate the reactive primary radical 311, which underwent spirocyclization to afford the pentacyclic indoline 312 as a single diastereomer in 58% yield (allyl regioisomers in 16% yield). The pivotal intermediate 312 was subsequently transformed in a single pot to the aspidophytine (313) natural product in 63% yield.

![Scheme 50](image)

Takayama and co-workers reported a chemoselective synthesis of a pentacyclic skeleton containing a 1-aza-tricyclo[5.3.0.0\(^2\)]decane core wherein they utilized a domino radical cyclization (Scheme 51). Treatment of the \(\beta\)-carboline derivative 314 in the presence of Et3B and n-Bu3SnH generated the vinylic carbon-centered radical 315, which attacked the indole via a 5-exo-trig cyclization (onto C2 position), before collapsing onto the Michael acceptor pendant in a second 5-exo-trig manner to obtain the complex indolinedione architecture 316 in 72% yield (cis and trans mixture). Interestingly, when other \(\beta\)-carboline derivatives (without ester moiety) were used as starting material, a mixture of products were isolated (the octahydroquinolizine derivatives and the pentacyclic-bridged compounds), depending on the generation radicals method used. The authors believe that in the case of the \(\beta\)-carboline derivatives 314, a strong steric repulsion in the transition state between the tert-butoxycarbonyl and the \(\text{N}\)-allyl groups is unfavorable thus avoiding the formation of the octahydroquinolizine by-product.

![Scheme 51](image)

Lastly, El Kaim, Grimaud, and Miranda reported a spectacular one pot synthesis of spiroindolines combining a multicomponent Ugi reaction followed by an in situ copper(II) triggered oxidative coupling as depicted in Scheme 52. The authors described that the key indole deaeromatization of the Ugi adduct 317 undergoes an oxidation initiated by copper, leading to the corresponding peptidyl radical 319, which cyclized at the C3 position of the indole. The generated \(\alpha\)-amido radical 320 oxidized spontaneously to the corresponding iminium 321, which subsequently suffered cyclization to the spiroindoline 322 in 43–78% yield (one pot process).

5.6. Carbon-centered electrophiles for deaeromatization

5.6.1. \(sp^3\) Hybridized carbon-centered electrophiles. Numerous examples of intramolecular alkylation reactions involving \(sp^3\)-hybridized carbons as electrophile are related to synthetic studies or total synthesis of natural products and are found in studies of Styrchnos and Aspidosperma alkaloids. Thus we chose the natural product spirodermepidarine (266) as a case study to simplify the presentation of this rich literature. The four main alkylation deaeromatizing strategies are described in this section: Harley-Masson/Kaplan, Heathcok/Toczko, Magnus/Gallagher, and Rubiralta (Scheme 53). However there are a number of strategies in addition, which we will also consider.

In the Harley-Masson and Kaplan strategy, the cyclization of the advanced alcohol precursor was accomplished in acidic conditions, probably through a carbocation, followed by a ring rearrangement, and subsequent reduction of the amide afforded aspidospermidine (266).

Magnus and Gallagher’s strategy is based on the construction of the pyrrolidine ring by an intramolecular alkylation at the C3 position of the indole via a thionium ion (Pummerer reaction) followed by heating. Subsequent reduction of the thioether and the amide completed the synthesis of aspidospermidine.

Langlois also successfully applied this alkylation, and rearrangement induced by the Pummerer reaction for the total synthesis of other Aspidosperma alkaloids vindorosine and vindoline.

Heathco and Toczko constructed the pyrrolidine ring from a chloroacetate through a Finkelstein reaction, in the presence of sodium iodide, followed by a silver triflate assisted deaeromatization and final reduction of the amide to afford the aspidospermidine (266).

Finally, Rubiralta and co-workers reported the construction of the pyrrolidine by an alkylative annulation. In this single step procedure, the primary alcohol was converted in situ by generating a tosylate leaving group triggering the concomitant alkylative deaeromatization of the indole moiety. Recently, Fukuyama reported a stereoselective synthetic route to the core skeleton of chartelline C (321) following the Heathco and Toczko’ strategy described above (Scheme 54). In this synthesis, an intramolecular alkylative deaeromatization of indole 323 was used for the construction of the \(\beta\)-lactam fragment leading to the isolation of indolene 324 in good yield.

Activation of the primary allylic alcohol 326 (related to the Rubiralta’ strategy) to trigger indolic deaeromatization under action of base was first reported by Magnus under well-established Mitsunobu conditions en route to (+)-koumine (328) (Scheme 55).
In 2002, the Rawal disclosed the synthesis of (+)-aspidospermidine (266) through an intramolecular two-step procedure involving the activation of the primary alcohol with methanesulfonyl chloride following by the alkylative dearomatization in the presence of potassium tert-butoxide (related to the Rubiralta’s strategy, Scheme 53).138 This alkylative strategy was reutilized several years later by Bach for a synthesis of (+)-aspidospermidine.139 In 2012, Smith applied the same exact process to the synthesis of (+)-scholarisine A (332) (Scheme 56).140 In this synthesis, the pendant alcohol from indole 329 was activated as a mesylate leaving group to trigger cyclization upon action of BTPP leading to the cage product 331.

In 2010, Andrade executed a sequential, one-pot, alkylation/intramolecular aza-Baylis-Hillman (or an alternate intramolecular vinylogous Mannich/olefin isomerization cascade).141 Soon after, the same authors published the asymmetric total syntheses of Strychnos alkaloids (-)-leuconicines A and B, highlighted by the same strategy to build the tetracyclic indolenine framework 335 (Scheme 57).142 The key precursor 333 (prepared in six steps) was treated with AgOTf and a hindered base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) followed by another base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the double annulated compound 335 as a single stereoisomer in 60% yield. Further synthetic steps were accomplished to access both (-)-leuconicines A and B in 9 and 10% overall yields, respectively. Recently, this methodology was also applied to the total synthesis of (-)-melotene A, which showed potent cytotoxic activity against several cancer cell lines.143

The exceptional nucleophilicity of 2-thioindole was exploited during the total synthesis of (+)-dehaloperophoramide (339) designed by Rainier (Scheme 58).144 Once again, an advanced alcohol precursor 336 was reacted through a sequential one-pot process involving first the activation of the secondary alcohol as a mesylate, followed by an in situ intramolecular alkylation and cyclization in the presence of DBU to afford the polycyclic indole-nine 338 in 70% yield.

Finally, Sakai described the semi-synthesis of Gelsemium-type alkaloids (342) through a transannular S$_{N}$2’ cyclization between the C3 position of the indole moiety and allylic acetate from precursor 340 (Scheme 59).145 In the presence of palladium(0) and sodium hydride the deprotonated indole as shown in the proposed assembly 341 may intramolecularly attack the palladated π-allyl...
moiety to give indolenine 342 in 54% yield. The later was then converted in two steps to provide 11-methoxykoumine.

The Kobayashi group reported a completely different activation of sp3-hybridized carbon electrophiles, which is an efficient and highly diastereoselective method for the synthesis of 3-spiro-2-oxindole compounds such as 345 from 2-substituted haloindoles 343 (Scheme 60). This domino reaction proceeds through an intramolecular copper-mediated Ullmann coupling, followed by a Claisen rearrangement of the cyclic intermediate 344.

Historically, strong and nucleophilic bases such as Grignard reagents or sodium amide (NaNH₂) were used to generate the ambident indoyl anion before the addition of the alkylating reagent. Nevertheless, this synthetic process is limited in terms of functionality, tolerance, and regioselectivity, thus decreasing the synthetic utility of this transformation. A number of other electrophiles such as 1,2-dibromoethane, 1,1-cyclopropane diesters, ethyl 2-nitrosoacrylate, Corey–Kim reagent or activated aziridine have been successfully used for this biomimetic dearomatization of 3-substituted and 2,3-substituted indoles. Furthermore, magnesium nitrate hexahydrate and zinc triflate have also demonstrated their potency to promote this alkylative dearomatizing process.

More recently, different metal-catalyzed indole dearomatization tactics have emerged. Work by Tamaru has shown the feasibility of C3 selective palladium-catalyzed allylation of unprotected 3-substituted indoles with allylic alcohols in the presence of
triethylborane.\(^{155}\) Rawal also developed two general methods for racemic allylation and benzyla- tion of 3-substituted and 2,3-disubstituted indoles.\(^{156,157}\) This palladium-catalyzed reaction al- lows the transformation of such substrates (3-substituted and 2,3-disubstituted indoles) using allyl or benzyl carbamates into the corresponding 3-alkyldenines in good to high yields. While tri- furylphosphine is the best ligand for the allylation, benzyla- tion reaction proceeds more efficiently in the presence of DPEphos ligand. The Rawal allylation methodology has recently been applied in the total synthesis of \((\pm)-\)minifensine.\(^{158}\) Recently, the same group demonstrated that N-alloc and N-Cbz 3-substituted indoles are excellent substrates for palladium-catalyzed decarboxylative allylation to produce corresponding C3-allyl and C3-benzylidenedolines.\(^{159}\)

In 2006, Trost and Quancard were the first to apply an intermolecular enantioselective allylic alkylation using various allyl alcohols 347 as the electrophile with unprotected 3-substituted indoles 346 in the presence of 9-BBN-C6H13, as the promoter and a chiral ligand 349 (Scheme 61).\(^{160}\) In the cases of 3-substituted indole bearing a pendant nucleophile such as alcohol, phenol, carbamate, and malonate, indole with cis-5,5- or 5,6-fused rings were obtained, nicely underscoring the high level of chemo- selectivity of this reaction.

![Scheme 61.](image)

Similarly, You accomplished an iridium-catalyzed asymmetric intramolecular allylic alkylation reaction of unprotected 3- substituted indoles 350 (derived from tryptamine), in presence of ligand 353 to provide spiroindolenines 352 in good yields with high diastero- and enantioselectivity (Scheme 62).\(^{161}\) The same authors further extended this reaction to carbon-tethered substrate, which led to spiro cyclopentane-1,3'-indoles after the reduction with NaBH3CN.\(^{162}\) Recently, the You group also reported palladium\(^{163}\) and ruthenium\(^{164}\) mediated enantioselective intramolecular syn- theses of fused spiroindoles from substituted-indolyl allylic carbonates.

![Scheme 62.](image)

5.6.2. \(sp^2\) Hybridized carbon-centered electrophiles. The innate re- activity of indoles allows them to undergo addition to activated \(\pi\)-systems, in both inter- and intramolecular fashions. In this context 3-substituted indoles are substrates of choice to react with Michael acceptors due to the stability of the resulting imino-spiroindoles, furthermore, this functionality can be trapped in the presence of internal or external nucleophiles.

In 1971, Büchi reported the total synthesis of racemic vindor- osine (68), a pentacyclic \(Aspidosperma\) alkaloid (Scheme 63).\(^{165}\) As mentioned above, the pivotal step of this synthesis is an intra- molecular domino Michael–Mannich mediated by the action of boron trifluoride, which delivers the desired indoline 356 in a single step and 38% yield.

Since this Büchi group’s disclosure of the tandem dearomatizing domino Michael–Mannich transformation, this strategy has been modified for the total of many other \(Aspidosperma\) and \(Strychnos\) alkaloids. The most recent modifications in this strategy involved the replacement of boron trifluoride etherate with titanium tetrachloride.\(^{166}\) Others main modifications are anionic poly- cyclization\(^{41b,48}\) and sequential Michael additions assisted by silica gel followed by the potassium tert-butoxide mediated Mannich cyclization.\(^{41c,67}\) An intermolecular cascade dearomatization be- tween N-substituted tryptophols and 3-acryloyloxazolidin-2-one, in the presence of Lewis acid, has also been recently reported by You.\(^{163}\) Among the Lewis acid tested in this particular case, scandium triflate (Sc(OiPr)3) proved to be best suited for the cascade reaction.

Similar cascades can be achieved using dehydro-\(\alpha\)-amino esters as Michael acceptors. In 2010, Pierzanti described a simple syn-thetic method to access hexahydropyrrol[2,3-b]indole structures (HPI). This domino Michael–Mannich transformation involves 3- substituted indoles and N-acetamidoacrylate (dehydro-\(\alpha\)-amino esters derivative) in the presence of stoichiometric amount of zirconium chloride.\(^{166}\) It should be noted that N-H and N-alkylindoles are fine substrates for this reaction and that the authors were able to achieve the racemic total synthesis of the esermethole natural product using this methodology. Later, the Reisman group reported the first enantioselective variant of this reaction with the synthesis of chiral HPI molecules 361 from 1,3-disubstituted indoles 357 and benzyl 2-trifluoroacetamidoacrylate 358 in the presence of tin Lewis acid catalyst with (R)-BINOL-ligands (Scheme 64).\(^{170}\) This stepwise formal [3+2]-cycloaddition process started by a Michael conjugate addition between the indole derivative 357 and the Lewis acid activated 2-amidoacrylate 358 leading to the electro- philic iminium salt 359. Subsequent asymmetric protonation under
furnish the indolenium 364 in an enantioselective fashion. A 5-exo-heterocyclization of the latter ion 364 and subsequent hydrolysis provide pyrroloindoline and furanoindoline derivatives with excellent yield, enantio- and diastereoselectivity (in the case of $\beta$-substituents). This elegant organocatalytic cascade addition/cyclization cascade was successfully applied to the synthesis of (−)-flustramine B (366) and debromoflustramine B.

5.6.3. sp Hybridized carbon-centered electrophiles. Alkynes and isonitriles have been successfully used in indole dearomatization processes, but some of the postulated mechanisms still remain ambiguous and could be depicted in the following section as stepwise or concerted.

For example, Barluenga reported a proposed stepwise annulation of polysubstituted indole 367 with the alkynyl Fischer carbene of tungsten 368 (Scheme 66, Eq. 1).172 Upon indole attack to the alkynyl fragment and further cyclization of the allenyl-tungsten derivative 369, the menthol-derived chiral auxiliary was simultaneously extruded to deliver the tricyclic indolinone 371 in good yields and high enantioselectivity (up to 99% ee). Another interesting reaction for which the mechanism remains unclear is presented in Scheme 66 (Eq. 2). Wang and Ji reported an efficient construction of polycyclic indolines 376 based on an isocyanide multicomponent type reaction.173 Mixing the three components isonitrile 372, malonodinitrile 373 and aldehyde 374 may result in a Knoevenagel condensation forming alkylidenemalonodinitrile, which upon addition of the isonitrile 372 should produce the 1,3-dipole intermediate 375. Through either a stepwise or concerted mechanism, the indolic moiety will attack the nitrilium electrophile, therefore triggering the final annulation step via the malonodinitrile anion collapse to form the polycyclic indoline 376 in high yields.
Mainly electrophilic transition-metal complexes with the ability to behave as soft Lewis acid may activate unsaturated functionalities such as alkynes and others, thus enabling the creation of new carbon—carbon and carbon—heteroatom bonds under mild conditions. Zhang disclosed a divergent indole dearomatization catalyzed by different metals. The reaction of the substrate 377 in the presence of cationic Au(I) or PtCl₂ provides, respectively, 2,3-indolene-fused cyclobutanes 382 or 2,3-indolone-fused cyclopentenes 383 in good yields depending on the metal engaged in the reaction. A plausible and divergent reaction pathway is outlined in Scheme 67.

![Scheme 67](image)

Initial complexation of the metal (Au(I) or PtCl₂) to alkyne 378 leads to a 3,3-rearrangement into the allenyl intermediate 379. Subsequent activation of the allenyl functionality with the same metal generates to oxocarbenium specie 380, which upon nucleophilic addition of the indole (at the C3 position) affords the reactive spiro-intermediate 381. At this stage, the allenylgold(I) traps the iminium to deliver 382, whereas the allenylplatinum(II) derivative cyclizes in a vinylogous manner to the cyclopentene 383 after β-hydride elimination of the platinum catalyst. The authors proposed that the divergent regioselectivities of the two catalysts intrinsically originates from their different metal—ligand interactions. In PtCl₂, the strong π-electron-donating chlorine ligands induce the intramolecular nucleophilic addition to give the [3+1] cycloisomerization products. While in AuCl(PPh₃)/AgSbF₅, the strong σ-electron-donating phosphine ligand results in an intramolecular nucleophilic addition reaction to form the [2+2] cycloisomerization products. Another example of indole dearomatization via alkynie electrophilic activation (sp hybridization) really demonstrates that enantioselective transformations can be implemented on indolic substrates (Scheme 68). Specifically, the alkenylation was followed by an intramolecular cyclization leading to tetracyclic indolines 385 or 386 in a cascade of events from a variety of N—H protected or unprotected alkynylindoles 384. These transformations are mediated by gold(I) in a chiral manner. In this double annulative process reported by Bandini, the activation of the alkynie moiety by Au(I) facilitated a Friedel–Crafts alkenylation (endo or exo) followed by the iminium trapping by the pendant alcohol nucleophile, providing tetracyclic indolines 385 or 386, in good yields and up to 87% ee.

Finally, an approach to enantioselective dearomatization through alkynie activation was reported by MacMillan during the total synthesis campaign towards diazonamide A (185) (Scheme 69).

In this endeavor, the C-10 quaternary center of the central furanoindoline core was formed by employing an iminium-catalyzed alkylation—cyclization cascade of the highly elaborated and functionalized compound 387 with propynal. This astonishing reaction was performed with a small organic molecule as catalyst affording the desired tetracyclic indoline 388 in 86% yield with an extremely high diastereoregion (20:1 dr). After several steps, intermediate 388 was transformed into the diazonamide A (185) to conclude the most efficient synthesis of this natural product reported to date.

6. Heteroatomic oxidative dearomatization

6.1. Electrophilic heteroatoms

6.1.1. Selenium electrophile. As an element, selenium is rarely present in any natural product (except for selenoproteins), but as a reagent, N-phenylenephthalimide (N-PSP) proved to be an extremely useful source of electrophilic selenium for indole dearomatizations. The early developments of N-PSP in indole dearomatization are attributed to Danishefsky, who intensely studied the facial selectivity occurring during the dearomatization of tryptophan derivatives 389 (Scheme 70). From these studies, Danishefsky was pleased to observe that the formation of one major stereoisomer was favored; which was attributed to a preferential pre-endol-394a versus pre-exo-394b ensemble (the exo notation refers to syn-relationship between the methyl ester and phenylseleno moiety). In the endo pre-transition state assembly 394a, the authors proposed that a steric clash between the methyl ester and the indole core may occur (see also Section 2.2), therefore explaining the more favorable attack of the nitrogen from the backside of the exo-isomer leading to the HPI 390 as the major diastereomer. Note worthy, the indole requires being N-protected to perform the dearomatization, since it was proved that a free indole would not react with the N-PSP reagent.

Danishefsky also developed the prenylation reaction of seleno-HPI 390 to access the C3-prenylated product 391 and achieve the
synthesis of the natural products 5-N-acetylardeemin and amaur-omine. In a separate report, Ley substituted the phenylseleno moiety of HPI 390 by an oxygen atom by using m-CPBA to obtain 392 while De Lera performed a photochemical dimerization of HPI 390 to obtain the core of the chimonanthine natural product pre-cursor 393 as a single diastereomer.

6.1.2. Sulfur electrophile. Dearomatization examples involving a sulfur atom as an electrophile remain scarce in the current dearomatization literature and only a few sources of electrophilic sulfur reagents have been studied. A trifluoromethane sulfomation of tryptamines has been developed by Qing (Scheme 71, Eq. 1) to synthesize the corresponding trifluoromethanesulfomylated HPI building block 396 in 96% yield. Interestingly, (+)-CSA was successfully used as additive in the reaction, but did not induce any noticeable stereoselectivity (dr <5%). Also, the intramolecular sulfur promoted dearomatization exemplifies a second pathway for inserting a sulfur atom at the indolic C3
position (Scheme 71, Eq. 2). This can be achieved by means of a methyl carbamodithioate, as Kutschy proposed during the preparation of spirobrassinin analogs.\(^\text{185}\) The methyl carbamodithioate substrate \(^\text{398}\) is therefore activated by elementary bromine, forming the reactive intermediate \(^\text{399}\), which triggers the ensuing dearomatization to form indolenium \(^\text{400}\), which is finally quenched by water to afford the 4,5-dihydrothiazole skeleton \(^\text{401}\), characteristic of the spirobrassinin core, in 63% yield and an 82:18 diastereomeric ratio. A similar transformation was also proposed by Pedras, for the synthesis of the natural product erucalexin.\(^\text{186}\)

### 6.1.3. Nitrogen electrophile.

In the field of indole dearomatizations nitrogen atoms often react as nucleophiles, mostly to trap indole-nium reaction intermediates on the indolic \(C_2\) position after the dearomatization step. On the other end, the challenging insertion of a nitrogen atom on the indolic \(C_3\) position requires an electrophilic nitrogen atom. To achieve this nitrogen insertion, Padwa recently reported the use of some hypervalent iodine reagents (Scheme 72, Eq. 1).\(^\text{187}\) The first step is the formation of an iminoiodinane intermediate \(^\text{403}\) (nitrene) followed by a loss of iodon benzene, catalyzed by the Rh(II) metal insertion, to give the metallonitrene \(^\text{404}\). The intramolecular dearomatization occurs onto the electrophilic nitrogen to form intermediate \(^\text{405}\), followed by the attack of an acetate nucleophile at the \(C_2\) position. This attack is only taking place from the same face of the amide anion, due to the internal deprotonation of the nucleophile, affording the syn-disubstituted indoline \(^\text{407}\) as a single diastereomer in 85% yield. Recently, a similar enabling method using rhodium was described by Xu.\(^\text{188}\) A similar method has been successfully used by Iwabuchi (Scheme 72, Eq. 2).\(^\text{189}\) Iwabuchi described the dearomatization of an indolic carbamate \(^\text{408}\) in which the presence of deuterium substituents is crucial to confer robustness onto the methylene position that supports the acyl nitrenoid moiety complexed to rhodium. Since the deprotonation and nucleophilic attack are oriented by the carbenoid intermediate, chiral ligands on the rhodium are required to obtain enantiomeric discrimination in the first step of the process. Overall, the resulting indolenine \(^\text{409}\) was obtained in 70% yield and 96% ee. A diastereoselective example of this reaction with hypervalent iodine was reported by Ciufolini (Scheme 72, Eq. 3).\(^\text{190}\) The authors performed a dearomative double annulation of the tryptophane derivative \(^\text{410}\) leading to two diastereomers (1:1 diastereomeric ratio) of the morpholinonindole \(^\text{412}\) in 42% yield.

An alternative to hypervalent iodine and rhodium was developed by Baran for the synthesis of the kapakahine F natural product \(^\text{417}\) (Scheme 73).\(^\text{205}\) Facing the difficulty of forming the \(\alpha\)-carbolinone moiety required in the kapakahine core structure, Baran reported a novel type of nitrogen electrophiles generated from anilines. For that purpose, \(\alpha\)-iodoaniline and \(N\)-iodosuccinimide were mixed to generate the electrophilic nitrogen species. The mechanistic considerations stemming from the authors’ and the extensive studies suggest that two intermediates \(^\text{414a}\) and \(^\text{414b}\) may reasonably be involved for the dearomatization to occur. Indeed, \(^\text{414a}\) and \(^\text{414b}\) arising from either \(C_3\)-activation of the indole or aziridinium formation, respectively, afford plausible explanations for the observed dearomatization. After ring closure of the indolenium \(^\text{415}\), the \(C_3\)-aniline-derived HPI \(^\text{416}\) was obtained in 78% yield as a single diastereomer. This innovative method allows for the nitrogen electrophilic fragment to be inserted in one single operation and offers new opportunities for complex indole alkaloids syntheses.

### 6.1.4. Oxygen electrophile.

Due to a substantial amount of natural products bearing an oxygen atom at the \(C_3\) position of indolenine or indoline substructures, numerous methods have been developed to achieve the oxygen promoted dearomatization of indoles. When an enantiopure dearmatized compound is desired, either a chiral source of oxygen can be engaged onto an achiral indolic substrate or a diastereoselective dearomatization of tryptophan derivatives can be easily accomplished. Examples of both synthetic tactics will be presented in the next two sections.

#### 6.1.4.1. Dearomatization of achiral indolic substrates.

For the synthesis of the \((-\text{)}\)-trigonoliimines A–C, Movassagi
accomplished the dearomatization of bistryptamine 418, by means of 2 equiv of a camphor-derived Davis’ oxaziridine (Scheme 74, Eq. 1).191 As a result, the two hydroxyindolenines regioisomers 419a and 419b were obtained in excellent yields and with high enantioselectivity (96% ee). Preparing the pair of hydroxyindolenines regioisomers 419a and 419b, was part of Movassaghi’s strategy, which implied to carry the two isomers abreast to the penultimate step to achieve in parallel both syntheses of the trigonolimines A and B. Later on, Movassaghi and Miller developed together a powerful catalytic enantioselective oxidation of tryptamines as shown from compound 420 (Scheme 74, Eq. 2).192 Pentapeptide 421 bearing an aspartic acid residue was utilized as chiral catalyst in conjunction with hydrogen peroxide to catalytically form an aspartic peracid residue in situ (chiral alternative to m-CPBA), which will operate the required asymmetric oxidation and deliver the C3-hydroxyindolenine 422 in 57% yield and 88% ee. Numerous examples were reported for the scope of this method in which the enantiodiscrimination reached up to 90% ee.

In 2007, Martin has developed a concise approach to the spirocyclic ring system of citrinadin A, by an enantioselective oxidative rearrangement of the tetrahydrocarbazole 423, employing the Shi catalysts proved to be efficient on this particular substrate. Thus the chiral dioxirane generated from ketone 424 enabled the desired oxidative dearomatization followed by the scaffold rearrangement.
of intermediate 425 to access to the spirocyclic oxindole 426 in 77% yield and 74% ee.194

6.1.4.2. Dearomatization of chiral indolic substrates. During his studies on the formation of hydroxyl-HPI,195 Perrin planned to dearomatize some tryptophan-alanine dipeptides using dimethyldioxirane (DMDO), expecting that the chirality of the substrate would induce a facial selectivity (Scheme 75, Eq. 1). Moreover, a bulky trityl group was attached at the dipeptide N-terminus to induce better diastereocontrol (Danishefsky also exploited successively this strategy for the synthesis of the himastatin).196 Unfortunately, these two features did not induce the desired selectivity during the dearomatization, leading to an equimolar mixture of the two endo and exo diastereomers isolated in 53% yield.

Very interestingly, when the N-methylated tryptophan-alanine dipeptide 427 was engaged in the same reaction conditions, the desired HPI product 428 was obtained with in good yield and with an outstanding 99:1 diastereomeric ratio (exo/diastereomer being the major product). DMDO has also been employed by Martin to perform the dearomatization of the chiral indole derivative 429 bearing the (−)-8-phenylmenthol auxiliary (Scheme 75, Eq. 2).193 This substrate was part of a larger study related to the synthesis of citrinadin A (see Scheme 74, Eq. 3) in which Martin evaluated both chiral and achiral oxidation strategies. The spirocyclic oxindole 431 was obtained in 78% yield and 94:6 diastereomeric ratio (improved stereoselectivity compared to the original enantioselective reaction with the Shi’ catalyst providing 74% ee, see Scheme 74, Eq. 3). During the total synthesis of isatisine A, the preparation of the oxindole tetracyclic core 433 (2:1 diastereomeric mixture) was achieved by Kerr using m-CPBA (Scheme 75, Eq. 3).197 The configuration of 433 could not be unambiguously determined, leading the authors to further perform a cascade reaction on the diastereomeric mixture of 433 via indole addition and spontaneous lactamization. Interestingly, product 434 was obtained with an excellent diastereoselectivity. This result is likely due to the equilibrium at the hemi-aminal center and even at the aminal center after the insertion of indole, which under thermodynamic control favors the formation of a single tetracyclic diastereomer 434 after the final lactamization (99:1 diastereomeric ratio). During his first synthesis of the (−)-chaetominine (437), Evano performed the deearomatization of the α-carbolinone 435 using DMDO (Scheme 75, Eq. 4).208 At low temperature, the stereoselectivity during the epoxidation was likely dictated by the approach of the dioxirane on the opposite face away from the bulky N-phthalimide group. The epoxide was readily open to form the α-carbolinone 436 with both excellent yield and diastereomeric excess (94% and 95%, respectively). This oxidative strategy inspired Evano to develop a second generation synthesis of (−)-chaetominine (437), employing a combination of chlorine and singlet oxygen for the deearomatization to diastereoselectively form the desired core structure from a tryptophan containing dipeptide in a single operation (see Scheme 80).207
The synthesis of the Okaramine N (440) was achieved through the photooxidation of the diindole 438, mediated by the N-methyltriazolinedione (Scheme 76). In this example, the authors took advantage of the N-methyltriazolinedione (MTAD) as a protecting group of the free indole, in order to selectively perform the photooxidation on the targeted N-prenylated indole subunit. Thus, the dearomatization of the N-unsubstituted indole by MTAD occurs most rapidly and the ene product on the C3 position is exclusively formed. The subsequent photooxidation on the N-tert-prenylated indole subunit catalyzed by methylene blue was followed by a reduction with Me₂S to afford the hydroxylated HPI 439, with a 1:5 diastereomeric ratio. The synthesis of the Okaramine N (440) was then completed by the thermolysis of 439 through a retro-ene reaction in 70% yield (brsm).

6.1.4.3. Oxygen mediated indole opening. If the precedent examples were dedicated to the development of polycyclic structures, several examples of stronger oxidative conditions are reported to deconstruct indoles by means of the C2-C3 bond breakage leading to interesting macrocycles. Different sources of oxygen can be used to achieve this efficient ring opening. For the synthesis of the daptomycin, Li prepared one of the required building blocks for the total synthesis, by opening the N-Fmoc-tryptophan substrate 441 via ozonolysis (Scheme 77, Eq. 1). While the acid moiety does not need to be protected for this transformation, better results were obtained when the indolic nitrogen was protected by a carbamate group, leading to a quantitative yield of the dicarbonyl compound 442. Using m-CPBA, Kozman performed the dearomative opening of the β-carboline 443 through C2-C3 bond full oxidation producing the nine-membered ring macrocycle 444 in 71% yield (Scheme 77, Eq. 2). During his attempts to insert an oxygen atom in the C3 position of the indole, Evano also observed the formation of the dicarbonyl by-product using m-CPBA at low temperature in methylene chloride. This efficient reaction also occurred during the synthesis of the (-)-21-isopentenylpaxilline reported by Smith, in which a dicarbonyl adduct (undesired by-product) was obtained quantitatively.

Finally, to synthesize the natural product melohenine B (447), Westwood planned to open the pentacyclic β-carboline 445 in a proposed biomimetic fashion to form the targeted nine-membered ring macrocycle 447 in a single step (Eq. 3). In fact, melohenine B (447) was obtained in a quantitative manner via a photochemical reaction induced by singlet oxygen with was produced by visible light irradiation of methylene blue in presence of oxygen. It is noteworthy, that other oxidations with m-CPBA or by ruthenium-mediated cleavage proved to be unsuccessful in this reaction.

6.2. Halogenation and halocyclization

6.2.1. Iodine electrophile. A unique example of a 3-iodoindolenine was reported by Fukuyama and Tokuyama, for the synthesis of the (+)-haplophytine (189) (Scheme 78), in which the enantiopure tetrahydro-β-carboline 448 was converted into the C3-iodoindolenine product 449 by treatment with NIS. Further activation of the iodoindolenine 449 by silver triflate in the presence of 2,3-dimethoxy-N,N-diallylaniline led smoothly to the formation of the desired carbon–carbon bond affording arylated-indolenine 450.
6.2.2. Chlorine electrophile. Sources of electrophilic halogens are most widely represented by chlorine in the field of halogen-triggered dearmatizations. As a first example of halocyclization triggered dearmatization of indoles, we will examine the total synthesis of the natural product flustramine C (454), which is characterized by an indolene core substituted by a reversed prenyl group at the C3 position. Bohrer took advantage of a dearmatization process to propose a biomimetic synthesis of flustramine C (454) from the deformylflustrabromine (451) (Scheme 79, Eq. 1).204 tert-Butyl hypochlorite under basic conditions was used to form the desired indolenine 452 leading to a collapse of the secondary amine to generate theazaquinone methide 453, which further initiated a 1,2-shift of the prenylated side chain onto the C3 position to access directly flustramine C (454) in 60% yield. An improved procedure using N-bromosuccinimide was also evaluated by the same authors, leading to synthesize flustramine C (454) in 90% yield. A similar reaction, which was interrupted at the indolenine stage, likely due to the protecting group present on the tryptamine a-nitrogen was reported by Baran. To insert a chlorine atom on the C3 position, Baran employed the common reagent N-chlorosuccinimide under neutral conditions and obtained the corresponding chlorinated product 456 in 94% yield (Scheme 79, Eq. 2).205 In another example, You...
performed an enantioselective chlorination of 2-arylated indole derivative 457 using 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) and the Cinchona alkaloid dimer (DHQD)$_2$PHAL 460 as a chiral phase transfer reagent to achieve the desired enantioselective halocyclization (Scheme 79, Eq. 3). N-Protected indoles 457 are ideal substrates in this transformation as the increased electrophilicity of the acyl-indolenium 458 intermediate, therefore facilitating the spirocyclization step from the amide side chain.

Another use of chlorine in dearomative strategies was explored by Evano for the synthesis of the (−)-chaetominine (437) (Scheme 80).207 Facing the challenge of forming a α-carbolinone fragment from a tryptophan containing dipeptide 461, Evano reported a double dearomative process to access stereoselectively to the core of the (−)-chaetominine (437). Using similar conditions to Bohrer,204 indole 461 was first dearomatized by N-chlorosuccinimide, leading to the chloroindoline 462, which after elimination delivered the rearomatized indole product 463. The resulting indole then underwent a second dearomatisation under a photochemical irradiation in presence of oxygen to afford the α-carbolinone 464 in 64% yield with excellent diastereocntrol (98:2 dr).

This brilliant strategy allowed Evano to form the natural product α-carbolinone ring structure and insert an oxygen atom at the C3 position during the same operation, which remains a remarkable performance among the few reported syntheses of the (−)-chaetominine (437), all sharing similar indole dearomatization strategies.208

6.2.3. Bromine electrophile. N-Bromosuccinimide (NBS) has been also widely used to introduce a bromine atom on indoles while initiating dearomatization processes. Among the different bromine promoted dearomatization reported,209 the study of De Lera on electrophilic activation of tryptophan derivatives is remarkable.210 During the course of this work, De Lera developed an efficient method to form a bromo-HPI unit, which was also employed by Rainer later on for the synthesis of the kapakahines B and F (Scheme 81, Eq. 1). Upon exposure to NBS, tryptophan 465 was readily converted to the corresponding bromo-HPI 466 in good yield and with an excellent exo-selectivity. The facial selectivity observed in this reaction is likely due to the configuration and the substitution (protecting groups) of the starting tryptophan, which favors the formation of the pre-exo assembly (see Scheme 70). This substrate 466 was further functionalized by Rainier to form indolo-HPI 469 (key intermediate of the total synthesis) with a complete retention of configuration at the C3 position. Mechanistically,
led to the formation of product 469 in 82% yield and an exo/endo ratio of 1:5. This important discovery from the Rainer group led to an elegant synthesis of the kapakahine F (417) natural product.

It is only recently that the first catalytic and enantioselective bromocyclization of tryptamine substrates was reported by Ma, using a DABCO-derived bromonium reagent as the electrophilic bromine source and a chiral phosphoric acid catalyst (Scheme 81, Eq. 2). From this successful method, numerous bromo-HPI were then further transformed (arylation, azide or dimerization) without any important erosion of synthetically free indoles or tetrahydro-2H-furo-[2,3-b]indoles 481 to be formed in relatively good yields. Interestingly, the (DHQ)2PHAL was introduced as a catalyst with NFSI while selectfluor required a stoichiometric amount of the same alkaloid to perform the required deaeromatization and induce similar stereoselectivity.

A very impressive example of dearomative strategy promoted by NBS was also reported by Baran for the total synthesis of the natural product chartelline C (321) (Scheme 82). After removal of the carbamate under thermal conditions, the indole moiety was deaeromatized by NBS to form the plausible bromoindolenine intermediate 475, which was subsequently trapped by the nearby nitrogen in a spectacular transannular fashion, causing the extrusion of the bromine atom from the C3 position. The proposed resulting intermediate 476 finally underwent a [1,2]-shift to form the required and unique spiro β-lactam ring structure of the chartelline core (477) in 88% yield.

6.2.4. Fluorine electrophile. The field of deaeromatization involving electrophilic fluorine has been less extensively studied among all halogens. Pioneering work from Barton on N-acetylindoles in 1977 described the first utilization of trifluoromethyl hypofluorite to synthesize several 3-fluoroindoxoles, 2,2-difluoroindolines or 2,3-difluorodihydropyridines. The first example of fluorocyclization was reported by Shibata in 2001 (Scheme 83, Eq. 1) in the course of developing fluorinated analogs of the natural products brevianamides E and gypsetin. To achieve the desired deaeromatization, the fluoropryridinium FP-T300 was employed. The diketopiperazine amide moiety being a poor nucleophile, the reaction on 478 occurred at 65 °C to enable the cyclization, leading to a 1:1 ratio of the exo and endo diastereomers of the tetracyclic indole 479 in good yields (67–88%).

A similar fluorocyclization was later reported by Gouverneur while studying several sources of fluorine electrophile such as selectfluor or the N-fluorosulfonimide (NFSI) to perform enantioselective fluorocyclizations of tryptophols and tryptamines catalyzed by the Cinchona alkaloid (DHQ)2PHAL (Scheme 83, Eq. 2). Similarly to the work of You (Scheme 79, Eq. 3), the role of the Cinchona alkaloid in this reaction is to carry the electrophilic fluoride in a chiral environment to approach the indole derivatives allowing for high enantiodiscrimination to occur during deaeromatization and multiples hexahydropyrro-[2,3-β]indoles or tetrahydro-2H-furo-[2,3-b]indoles 481 to be performed in relatively good yields. Interestingly, the (DHQ)2PHAL was introduced as a catalyst with NFSI while selectfluor required a stoichiometric amount of the same alkaloid to perform the required deaeromatization and induce similar stereoselectivity.

In this impressive cascade of events, the fluorine atom is first deaeromatizing indole 482, the resulting indolenium 483 was then intercepted by water to access indole 484, which prompted the elimination of fluorine prior to the final rearrangement through to a [1,2]-shift creating simultaneously both oxindole and cyclobutane moieties of (+)-welwitindolinone A (486) in an astonishing 44% overall yield.

6.3. Dearomative cascade reactions

Oxidative deaeromatizations of unprotected indoles, regardless the oxidant employed, can be part of a strategy to access complex polycyclic structures, by forming three carbon–heteroatom bonds in a single process. In this event, the deaeromatization would trigger the cascade by forming the first indolenium intermediate 487, which will be later trapped by a nucleophile to form a tricyclic...
indolenine core \(488\) \((n = 0\) HPI or \(n = 1\ \alpha\)-carboline). The cascade could be further concluded by the formation of the last cycle if a proper C-terminus (Y group) enables the final cyclization to occur from the proximate indoline nitrogen to deliver a complex tetra cyclic structure as highlighted in compound \(489\) (Scheme 85).

A first approach to such double annihilative cascade was reported by Herranz on the nitrile-functionalized tryptophan \(490\) via a protonative tautomerization as dearomative strategy using TFA (see Section 4) leading to the synthesis of tetracyclic amidine \(491\) as a single exo-diastereomer in a quantitative manner.\(^{219a}\) Since then, Herranz reported a complete study of this elegant cascade reaction with many different electrophiles for the C3-functionalization of the nitrile-functionalized tryptophan \(490\) (Scheme 86).\(^{219}\) In this study, the authors noticed the steric effect of the cyclohexyl moiety on the stereoselectivity outcome of the reaction. By obtaining the exo and/or the endo tetracyclic compounds depending on reaction conditions, the authors concluded that unhindered nitriles exclusively provide tetracyclic exo-products \(491\) while more hindered nitrile derivatives provide predominantly exo-products under kinetic control while endo-products can be obtained under thermodynamic control.

Later on, the nature of the dearomatizing agent was evaluated and Herranz identified that N-PSP was not amenable for the dearomatization of compound \(490\).\(^{219d}\) On the other hand, NBS promoted dearomatization in acidic media successfully yielded the corresponding brominated tetracyclic compound \(492\) in a 91\% yield as a single exo-diastereomer. Also the Corey-Kim reagent\(^{220}\) was employed and promoted the formation of the interrupted cascade product alkylated-HPI \(493\) in 52\% yield as a single exo-diastereomer. In this case, the cascade of events does not proceed to form the last ring, requiring an extra step (TFA/CH\(_2\)Cl\(_2\)) to access the corresponding tetracyclic amidine product. Finally, under acidic conditions, DMDO also proved to be effective in promoting the desired cascade.\(^{219c}\) In this particular situation, the presence of a 10\% TFA/CH\(_2\)Cl\(_2\) mixture is again essential to perform the full cascade (the hydroxyl-HPI intermediate is obtained otherwise) and obtained the tetracyclic amidine \(494\) in 85\% yield (1:7 ratio of endo/exo-diastereomers). In conclusion, Herranz reported the first cascade forming three carbon-heteroatom bonds in a single step involving an unprotected indole as substrate, which affords numerous complex tetracyclic indoline-derived structures with high diastereoselectivity.

A similar approach was studied by Roche to accomplish a unified biomimetic approach to both families of natural products kapakine F (417) and \((-\)chaetominine (437). Dearomatization of several tryptophan containing dipeptides was performed in presence of selectfluor,\(^{216,217}\) under basic conditions and was utilized to successfully trigger a dearomative cascade to synthesize the complex tetracyclic compound \(497\) (Scheme 87).\(^{221}\) Activated dipeptide NPhth-Trp-Phe-OPFP \(495\) suffering from an epimerization on the
of the phenylalanine residue (1:1 epimeric mixture) was engaged in the dearomatization promoted by selectfluor\(^8\) in acetone leading to the formation of the fluoroindolenine 496 intermediate, which endured a double annulation cascade via the first amide cyclization followed by indolenine lactamization through ejection of the pentafluorophenol activating group. The tetracyclic fluorinated analogue 497 of the kapakahine core was obtained in a reasonable 42% yield with modest diastereocontrol (3:5 overall anti/syn-ratio).

In this study, the authors also explored the effect of additional chiral promoters, such as (DHQ\(_2\))PHAL, on the reaction diastereoselectivity and were able on a model dipeptide NPhth-Trp-Gly-OPFP to achieve a cascade with higher diastereoselectivity (4.1:1 anti/syn-ratio).

A similar strategy was reported earlier by Huang for a proposed biomimetic synthesis of (\(-\))-chaetominine (437) providing the shortest synthesis of this natural product reported to date (Scheme 88).\(^222\) The key reaction features a DMDO-promoted dearomatization of the tryptophan containing dipeptide 498 (prepared in three steps from L-Trp), followed by the intramolecular trapping of the indolenium intermediate 499 by the proximate amide moiety to form, after final lactamization in DMSO and extrusion of methoxide as leaving group, (\(-\))-chaetominine (437) in a single step and 42% yield. This impressive cascade enabled Huang to assemble the complex ring structure of the natural product in a single step and remarkably as the last step of the total synthesis.

The DMDO dearomatization was very efficient as shown by the isolated syn-\(\alpha\)-carbolinone by-product 500 in 51% yield, resulting by the fact that the syn-diastereomer 500 did not endure the full cascade under the reaction conditions and stopped at the \(\alpha\)-carbolinone stage. The authors suggested that the syn-relationship between the hydroxyl and the quinazolinone in 500 prevented the lactamization to happen. Through this cascade strategy, Huang was able to achieve an impressive four-step synthesis of (\(-\))-chaetominine (437).

The challenges associated with the synthesis of complex indole-containing alkaloids, in conjunction with their interesting biological activity, have prompted chemists to develop numerous elegant methods for their preparation that are ever more efficient. In this report, we wished to summarize seminal work on indole dearomatization as well as the most recent advances in asymmetric syntheses of complex polycyclic indole-containing alkaloids, while also attempting to discuss the various reactivities of indoles induced by their \(C_2\)–\(C_3\) substitution patterns and by the presence or absence of indolic nitrogen protecting groups.

It should appear from this report that whilst a number of innovative synthetic methods exist, there is a relative rareness of catalytic enantioselective means in total synthesis of complex alkaloids. In Section 2, while Diels–Alder and 1,3-dipolar cycloadditions proved to be extremely powerful tactics to embed high complexity during the dearomatization step, only a few reactions on \(N\)-protected indoles are really amenable to enantioselective catalysis. Arylative dearomatizations of indoles (section 3) also follows the same trend, with only rare examples of enantioselective and catalyst-controlled diastereoselective arylation methods mediated by copper with arylidenonium reagents. Alkylative dearomatizations of indole (Section 5) provide enabling methods for carbon–carbon and carbon–heteroatom bonds formation in organic synthesis. The use of indolic substrates in this context has inspired many research groups, allowing for the development of powerful methods for the synthesis of extremely complex structures. Finally, Heteroatomic oxidative dearomatization stands as a privileged tool to functionalize indoles at both \(C_2\) and \(C_3\) positions (Section 6). Depending on the nature of the oxidant, the indole moiety may require protecting manipulations to avoid over-oxidation events. Most oxidative dearomatizations were reported on tryptophan-derived scaffolds to exploit the chirality of the latter and innate facial stereocontrol during dearomatization. Recently,
several efficient and catalytic enantioselective advances for oxidation and halocyclization have been reported, paving the way to chiral deamination of indoles to be utilized in alkylidene synthesis. Furthermore, heteroatoms installed at the C3 position enable late stage functionalization to be easily accomplished (alkylation, arylation, and dimerization), which provides valuable routes to complex alkylidene natural products.

While the lessons of the past clearly present methods by which to prepare nearly any indolic-based natural products and drug-like molecules, the search for even more selective and asymmetric means for their preparation remains an exciting area of research.

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References and notes


Biographical sketch

Stéphane P. Roche was born in Thiers (France) in 1979. He received his Ph.D. degree (2006) in chemistry from the Blaise Pascal University under the supervision of Professor D.J. Aitken. Afterward, he joined the Institute of Chemical and Engineering Sciences (ICES, Star) in Singapore, as research fellow with Professor K.C. Nicolaou (2006–2008). As a second Post-doctoral position, Stéphane worked with Professor John Porco Jr. at Boston University (2008–2011). He started his independent career as Assistant Professor at Florida Atlantic University and his research interests include the development of novel ‘bio-inspired’ synthetic methodologies and dearomatization strategies to achieve concise total syntheses of biologically active small-molecules and natural products.

Jean-Jacques Youte Tendoung earned his Ph.D. degree at Université René Descartes, Paris in 2000, working under the direction of Dr. François Frappier and Dr. Christian Marazano, working on the Zincke reaction at room temperature and application toward herveline C. He carried out his post-doctoral studies with Professor Robert A. Holton at Florida State University, working on the synthesis of second and third generation of taxol analogs and with Professor Roland Barret at Université de Lyon I. Jean-Jacques then held several positions in medicinal organic chemistry groups, respectively, at the Institute of Chemical and Engineering Sciences in Singapore, the Auckland Cancer Research Center in New Zealand and The Walter and Eliza Hall Institute of Medical Research in Australia. In 2011, he joined Schering-Plough-Merck in France as Team Leader. In 2012, Jean-Jacques became a Visiting Assistant Professor at Florida Atlantic University working on a new synthetic approach to peptides. Currently, Jean-Jacques is starting a business focused in the areas of sustainable chemistry.

Bret Tréguière was born in 1982 in southern France (Tarbes) and studied fine chemistry at the University of Nantes, where he graduated. In 2011, he obtained his Ph.D. in medicinal chemistry, at the faculty of pharmacy of Châténay-Malabry (France), under the supervision of Professor M. Alami and Dr. A. Hamzé. He next joined the Roche group at Florida Atlantic University, as a post-doctoral associate to work on the synthesis of complex natural products based on dearomatization of tryptophan containing peptides.