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Synthesis of Alkaloids and Compounds Containing the 3,4-Benzomorphan Scaffold

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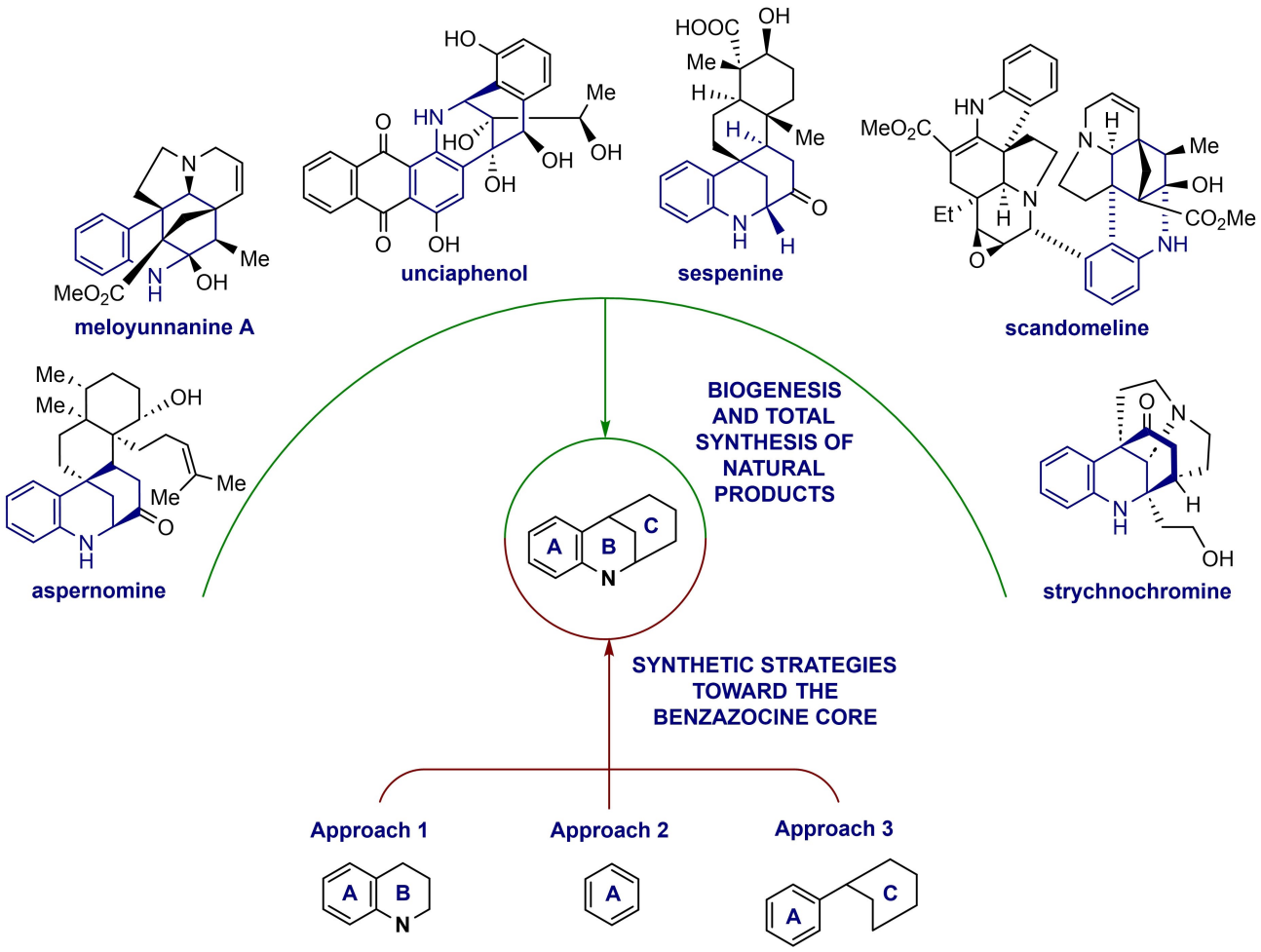

Several natural products, bearing an embedded hexahydro-2,6-methano-1-benzazocine framework (3,4-benzomorphan) – a heterocyclic regioisomer of the 6,7-benzomorphan substructure found in morphine alkaloids, have therapeutic potential for a variety of diseases. Biogenesis, biosynthetic approaches, and total syntheses of alkaloids or synthetic azapolycyclic compounds featuring the aforementioned azatricyclic ring system (*i.e.*, a 3,4-benzomorphan scaffold) are reviewed.

1. Introduction

Since their discovery, 6,7-benzomorphans have been extensively targeted by both synthetic and pharmaceutical chemists (Figure 1a). The morphinan alkaloids are a subclass of a diverse and numerous group of benzylisoquinolines produced most abundantly by the opium poppy (*Papaver somniferum*).[1] The most notorious members of this group are morphine and codeine, important analgesics used to treat the severe pain associated with cancer, rheumatism, and dental conditions.[2] The literature contains extensive information about morphinan alkaloids[3–5] as well as the 6,7-benzomorphans (**I**),[6] synthetically related compounds with a simpler structure. However, structurally related scaffolds with promising biological properties, such as 3,4-benzomorphans (**II**), have received considerably less attention. Moreover, the work developed in the field of 6,7-benzomorphans cannot be extrapolated to the synthesis of 3,4-benzomorphans. To address this gap, this review is focused on compounds embodying the hexahydro-2,6-methano-1-benzazocine scaffold **II**. In this framework, the morphan unit has an edge-on fusion with the benzene moiety through the C3–C4 bond (3,4-benzomorphan ring system). In contrast, in the scaffold of morphinan alkaloids, the morphan nucleus is attached through the C6-C7 bond, thereby including a 6,7-benzomorphan fragment. This review summarizes the biogenetic, biosynthetic, and synthetic approaches toward compounds embodying the hexahydro-2,6-methano-1-benzazocine (3,4-benzomorphan) framework in the literature.

The 3,4-benzomorphan ring is present in a variety of natural products such as aspernomine, strychnochromine,[7] sespenine,[8] unciaphenol,[9] meloyunnanines A–C, scandomeline and episcandomeline,[10] most of which have interesting biological properties (Figure 1b). The cytotoxic insecticide aspernomine, produced by *Aspergillus nomius*, has shown activity against A549 lung carcinoma, MCF7 breast adenocarcinoma, and HT29 colon adenocarcinoma cell lines.[11] Sespenine, an indole sesquiterpenoid produced by *Streptomyces*, an endophyte of the mangrove tree *Kandelia candel*, has antiviral activity, being reported to suppress herpes simplex virus (HSV-1) propagation in a dose-dependent manner.[12] A recent computational study by Muhammad *et al.* assessed fifty novel bioactive compounds of mangrove actinomycetes for their inhibitory potential against nsp10, the major activator of SARS-CoV-2 replication. Interestingly, based on its high binding energy (−8.8 Kcal/mol) and low inhibition constant (0.335 μM), sespenine was found to be the most promising inhibitor of SARS-CoV-2 replication, providing an opportunity to test this natural product as a therapeutic agent through clinical trials.[13] Strychnochromine, an indoline alkaloid from *Strychnos gossweileri*, was

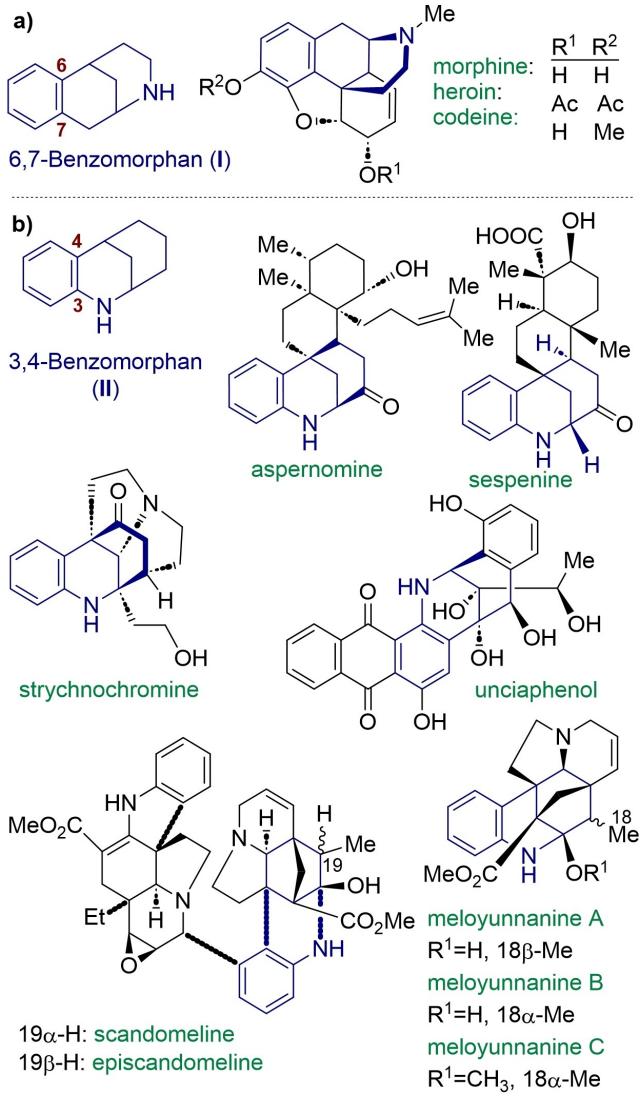

Figure 1. (a) 6,7-Benzomorphans: Morphinan alkaloids (b) 3,4-Benzomorphan scaffold in alkaloids.

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active against malaria-producing FCA and W2 *Plasmodium falciparum* strains.[14] Unciaphenol, an oxygenated analogue of uncialamycin from the actinomycete *Streptomyces*, exhibited anti-HIV activity, remaining relatively unaffected by evolved resistances when tested against strains resistant to the marketed anti-retroviral drugs.[15]

Studies on *Melodinus yunnanensis* by Cai *et al.*[16] resulted in the discovery of the monoterpenoid indole alkaloids meloyunnanines A–C, which feature a caged-6/6/5/6/5/5 ring system containing the benzazocine scaffold. Nevertheless, biological testing of the substrates revealed a lack of relevant cytotoxicity. A phytochemical investigation of *Melodinus fusiformis* led to the isolation of the bioactive bisindole alkaloids scandomeline and episcandomeline, which are structurally closely related to meloyunnanines A–C. A recent study assessed the cytotoxic, immunosuppressive, and anti-inflammatory activity of episcandomeline, among other bisindole alkaloids, and surprisingly, it showed potent cytotoxicity against the MOLT-4 leukemia cell line. The reported IC_{50} value (1.5 μM) indicated therapeutic capacities similar to those of *cis*-platin.[17–18]

Despite the highly promising therapeutic properties of the benzazocine framework, its synthesis has been scarcely reported, a reflection of the synthetic challenges it poses. In the present review, we have summarized the synthetic and biosynthetic approaches to this azatricyclic system reported to date. The different synthetic strategies have been classified according to the order of the ring formation (Figure 2). Strategy 1 comprises the routes where a preformed tetrahydroquinoline scaffold is fused with ring C. In strategy 2, the phenyl ring is transformed to incorporate a 2-azabicyclo[3.3.1] nonane moiety. Finally, in strategy 3, the one applied most frequently, an initial cyclohexylbenzene structure reacts to form the nitrogenated ring in the targeted azatricyclic system.

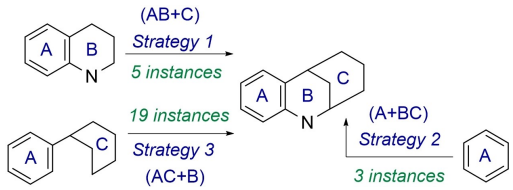
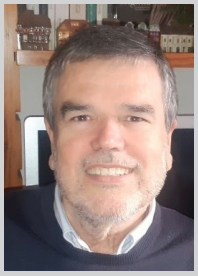


Figure 2. Strategies employed to furnish the benzazocine scaffold.

2. Biogenesis and biosynthetic approaches

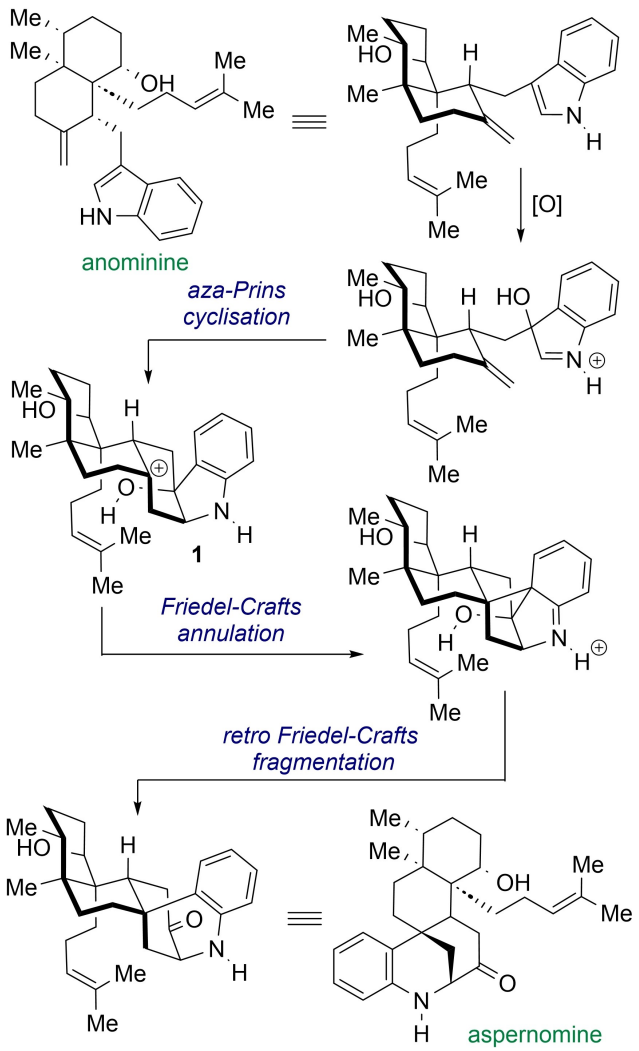
Investigating and understanding nature's chemical diversity can lead to the discovery of new bioactive entities and the design of effective synthetic routes to access a wide range of complex natural products. In this context, we concisely describe the biogenesis and the biosynthetic pathways of all the reported natural products bearing the targeted 2,6-methano-1-benzazocine framework. Aspernomine is a tetrahydroquinoline alkaloid found in the reproductive organ of the fungus *Aspergillus nomius*.[11] A study of the sclerotia of *Aspergillus* by Gloer *et al.* resulted in the isolation of a number of unique and bioactive metabolites, including the complex indole diterpenoid anominine, most likely the parent structure from which the other compounds are biogenetically derived.[19–20] As depicted in Scheme 1, oxidation of the indole 3-position in anominine combined with protonation of the nitrogen atom sets the functionality required for an attack by the exocyclic alkene via an aza-Prins like cyclization. The resulting carbocation intermediate **1** positions the phenyl ring which then undergoes a Friedel-Crafts annulation reaction. Formation of the carbonyl group triggers a retro Friedel-Crafts fragmentation to alleviate the ring tension and provide the final structure of aspernomine (Scheme 1).

Laura G. Rodríguez received her degree in Chemistry at the University of Barcelona in 2018 and her master's degree in Pharmaceutical Chemistry at the Ramon Llull University in 2020. Currently, she is a Ph.D. student in the Pharmacology, Toxicology, and Therapeutic Chemistry department at the Faculty of Pharmacy and Food Sciences (University of Barcelona) under the supervision of Professor Josep Bonjoch and Dr. Ben Bradshaw.

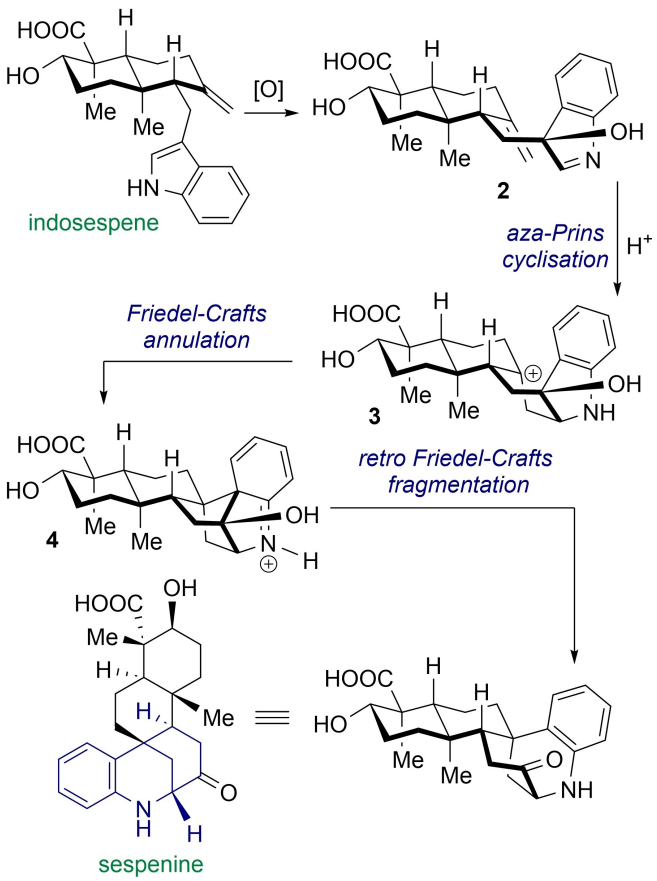


Josep Bonjoch (Barcelona, 1952) received his Ph.D. under the under the supervision of Prof. Joan Bosch at the Chemistry Faculty of the University of Barcelona (1979). He became Full Professor of Organic Chemistry in 1992 at the Faculty of Pharmacy (UB). His main research is focused on the synthesis of complex nitrogen-containing natural products with the aim of developing new synthetic methodology. He has reported the first total synthesis of twenty natural products.

Ben Bradshaw was born in 1974 in Southport, England. He studied chemistry at the University of Manchester, where he obtained his PhD in 2001 under the supervision of Professor John Joule. After postdoctoral work with Professor Jim Thomas, he joined the group of Professor Josep Bonjoch at the University of Barcelona. In 2014, he was promoted to Associate Professor, where his research interests include the application of Metal-Catalyzed Hydrogen Transfer reactions to the total synthesis of complex natural products.



Scheme 1. Biogenesis of aspernomine.



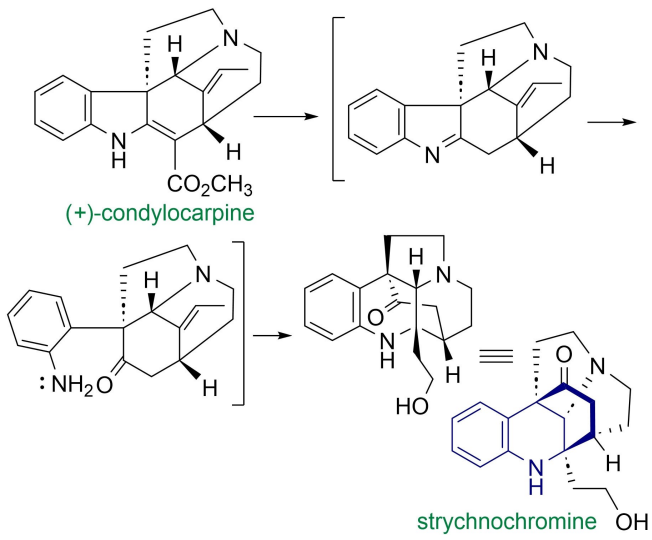
Scheme 2. Biogenesis of sespenine.

Another natural product structurally very similar to aspernomine is sespenine, an indosesquiterpenoid derivative isolated from an endophytic *Streptomyces* species in 2011.[8] It features a spiro-tetrahydroquinoline scaffold attached to a cyclic ketone bridge. Biogenetically, sespenine derives from indosespene in a manner analogous to the formation of aspernomine from anominine. Li proposed that the rearrangement proceeds via a cationic cascade reaction,[21] as depicted in Scheme 2.[22] Oxidation at the indole C3-position leads to the formation of hydroxyindolenine **2**, with the appropriate functionality for the attack of the exocyclic alkene. Activation of the imine moiety under acidic conditions followed by an *aza*-Prins cyclization furnishes the cationic species **3**.[23] A Friedel-Crafts annulation and subsequent retro Friedel-Crafts fragmentation give access to sespenine by means of the dearomatized intermediate **4**. Two driving forces in this biogenetic pathway have been proposed: it may be initially promoted by the proximity of the positive charges and electron-rich functionalities, whereas the rearomatization of intermediate **4** might favor the formation of the natural product.

Strychnochromine, a distinctive alkaloid bearing a pentacyclic skeleton, was isolated from the root bark of *Strychnos gossweileri*.[24] From a biogenetic point of view, strychnochromine might derive from condylocarpine, previously found in other *Strychnos* species.[25] Hypothetically, acid hydrolysis and decarboxylation of the condylocarpine would lead to the formation of an imine,[26] which could evolve by reaction of the aniline fragment with the alkene moiety. Further oxidation would generate strychnochromine (Scheme 3).

Unciaphenol is an oxygenated analogue of the Bergman cyclization product of the eneydine-containing uncialamycin, both of which were simultaneously isolated from the same extract of the actinomycete *Streptomyces uncialis*[27] (Scheme 4). This highly unusual result raised the question of whether unciaphenol was an isolation artifact of uncialamycin, resulting from spontaneous Bergman cyclization during the sample processing, or a product of further biogenetic transformation. However, the presence of the phenol moiety at C(22) confirmed the latter.[28]

The origin of the hydroxyl group at C(22) in unciaphenol is of considerable interest. Since the C(22) position of the enediyne corresponds to one of the radical sites in the putative *p*-benzyne intermediates in the Bergman cyclization, the hydroxylation was attributed to the trapping of the



Scheme 3. Tentative biogenesis of strychnochromine.

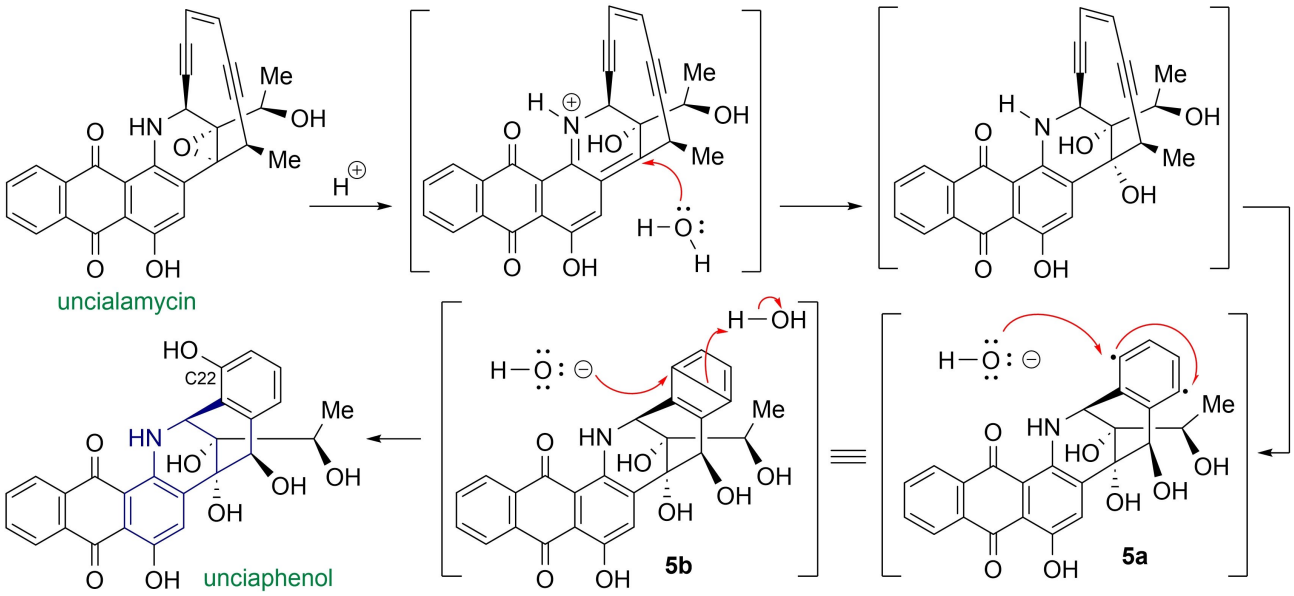
radical by an R–O$^-$ species. This theory is seconded by Perrin *et al.*, who demonstrated that acetate ions could add to a *p*-benzyne diradical.[29–30]

Regarding the mechanistic rationalization of the transformation, two options were considered. The first approach (**5 a**) features the unusual combination of a two-headed arrow pushing two electrons and a one-headed arrow pushing one electron during the nucleophilic attack, forming a new covalent bond between the aromatic ring and the nucleophilic species. Also generated is an aromatic carbanion that abstracts a proton from an acidic species in the reaction mixture to form the substitution product. Perrin's second rationalization illustrated in **5 b** suggests there is an antibond across the ring in the *p*-benzyne diradical, and the attack is an S_N2-like process.

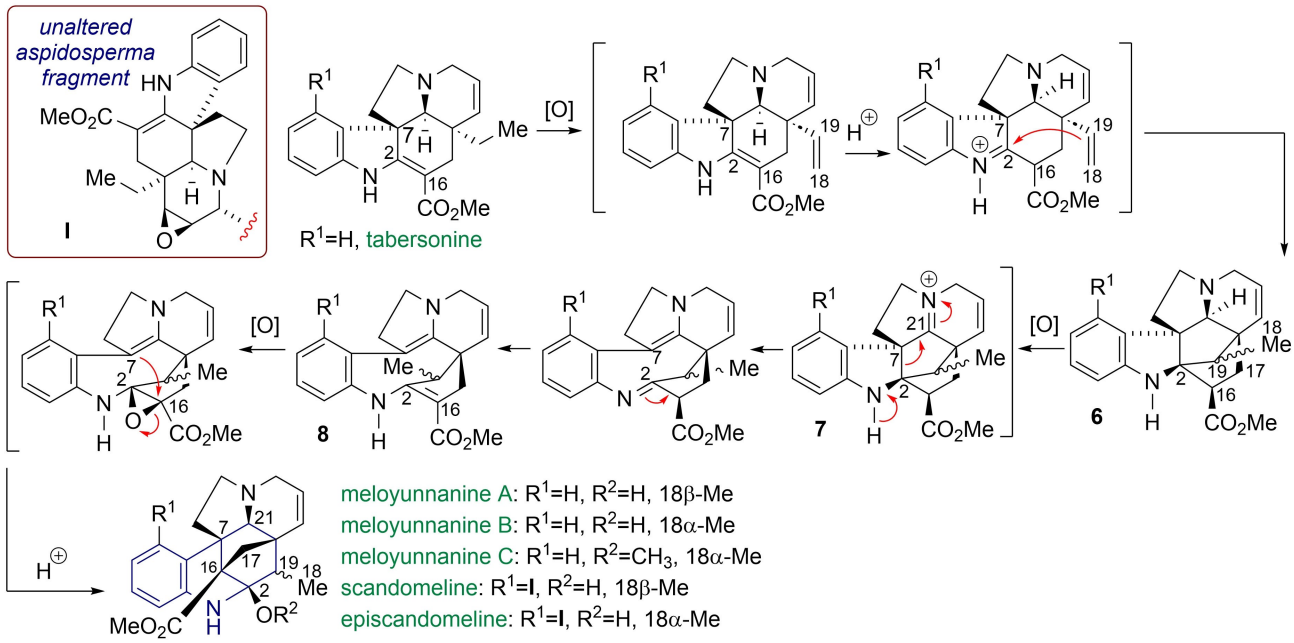
Monoterpenoid indole alkaloids are a large group of plant-produced complex natural products originating from the glucoalkaloid strictosidine. However, the rearrangement of this metabolite leads to several subgroups, among which we find monoterpenoid quinoline alkaloids.[31–32] In 2020, Cai *et al.* isolated meloyunnanines A–C from *Melodinus yunnanensis*. These monoterpenoid quinoline alkaloids, which contain the hexahydro-2,6-methano-1-benzazocine fragment, arise biogenetically from tabersonine.[33] Firstly, the oxidation of tabersonine leads to the formation of a double bond at C18/C19. The subsequent generation of an iminium under acidic conditions, followed by the nucleophilic addition between C19 and C2, gives vindolinine **6**, which is converted to intermediate **7** via oxidation. The rearrangement of iminium **7** followed by isomerization gives enamine **8**. Oxidation of the enamine functionality then leads to the formation of a C2/C16 epoxide, which undergoes a rearrangement to provide meloyunnanines A–C.[16]

Interestingly, monoterpenoid indole alkaloids are found in nature as monomeric species, such as those previously discussed or as dimers, commonly known as bisindole alkaloids. Therefore, the *Melodinus* alkaloids scandomeline and episcandomeline feature an aspidosperma-scandine skeleton linked by a C–C bond.[18] The biogenesis of the scandine fragment in these natural products is analogous to that of meloyunnanines A–C (Scheme 5).

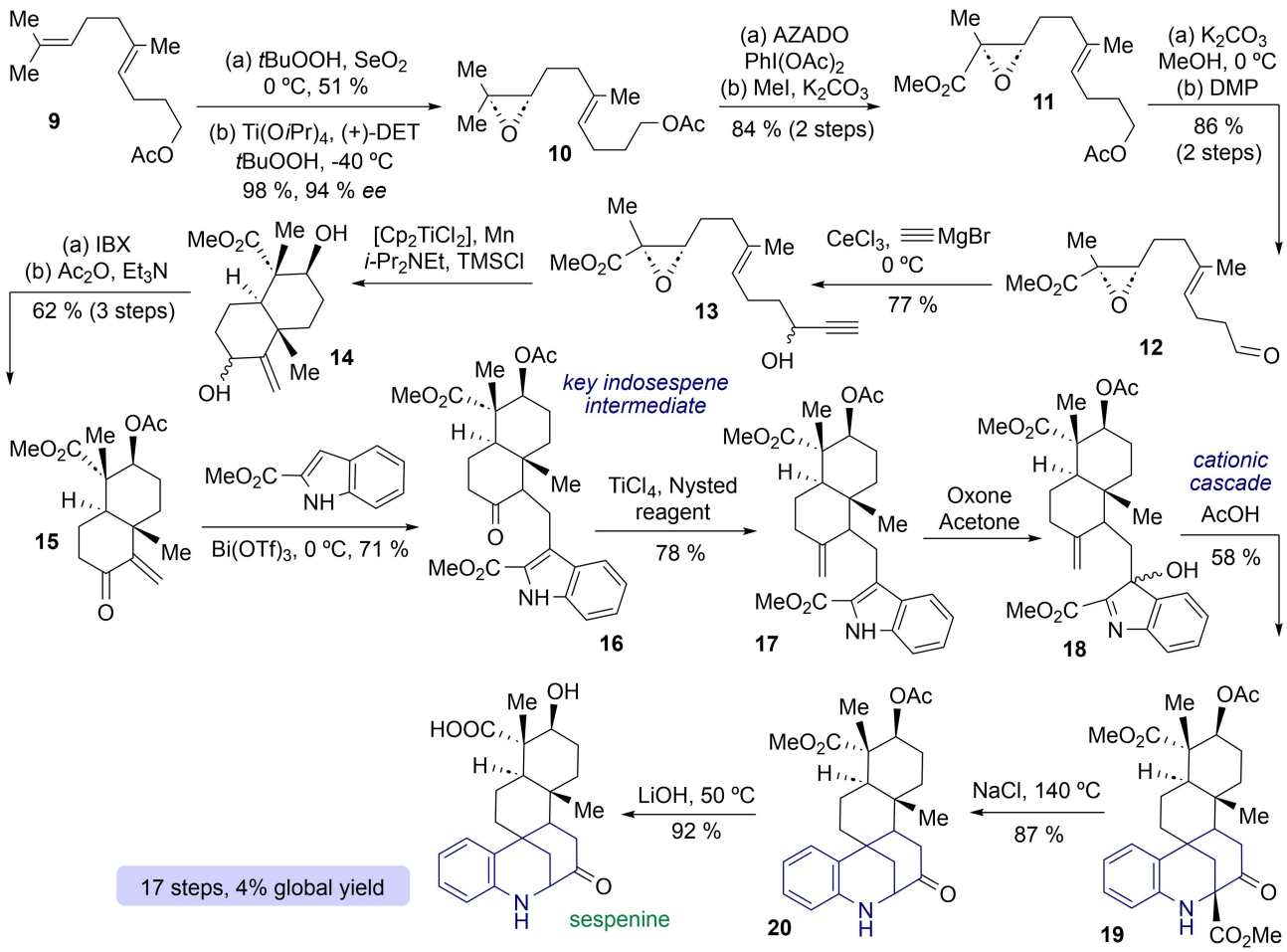
Even though a vast number of total syntheses of natural products have been achieved over the years, the strategies employed are generally less efficient than the corresponding enzymatic transformations. Enzymes exert strict control over the reaction pathway and chemo-, regio- and stereoselectivity, frequently employing multistep cascade reactions that rapidly build molecular complexity. In this regard, biomimetic



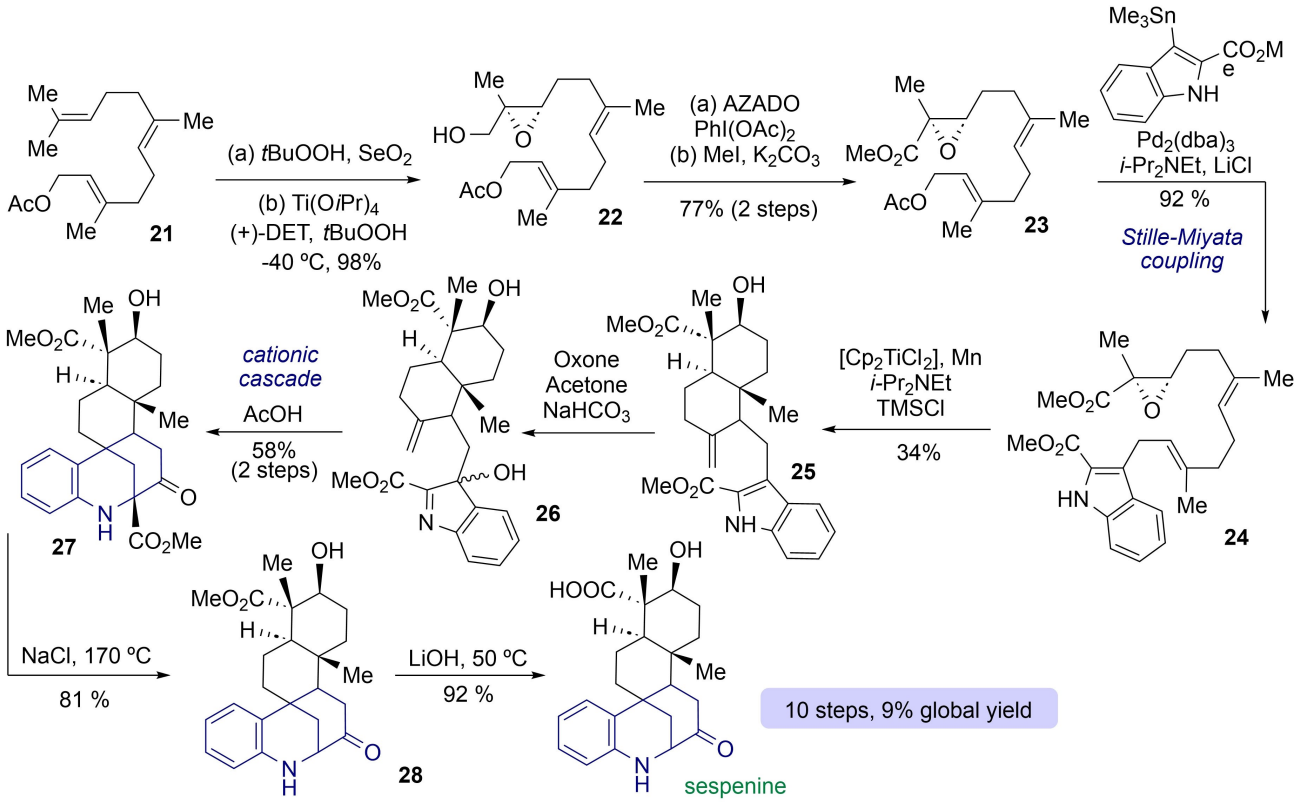
Scheme 4. Biogenesis of unciaphenol.



Scheme 5. Biogenesis of *Melodinus* alkaloids.



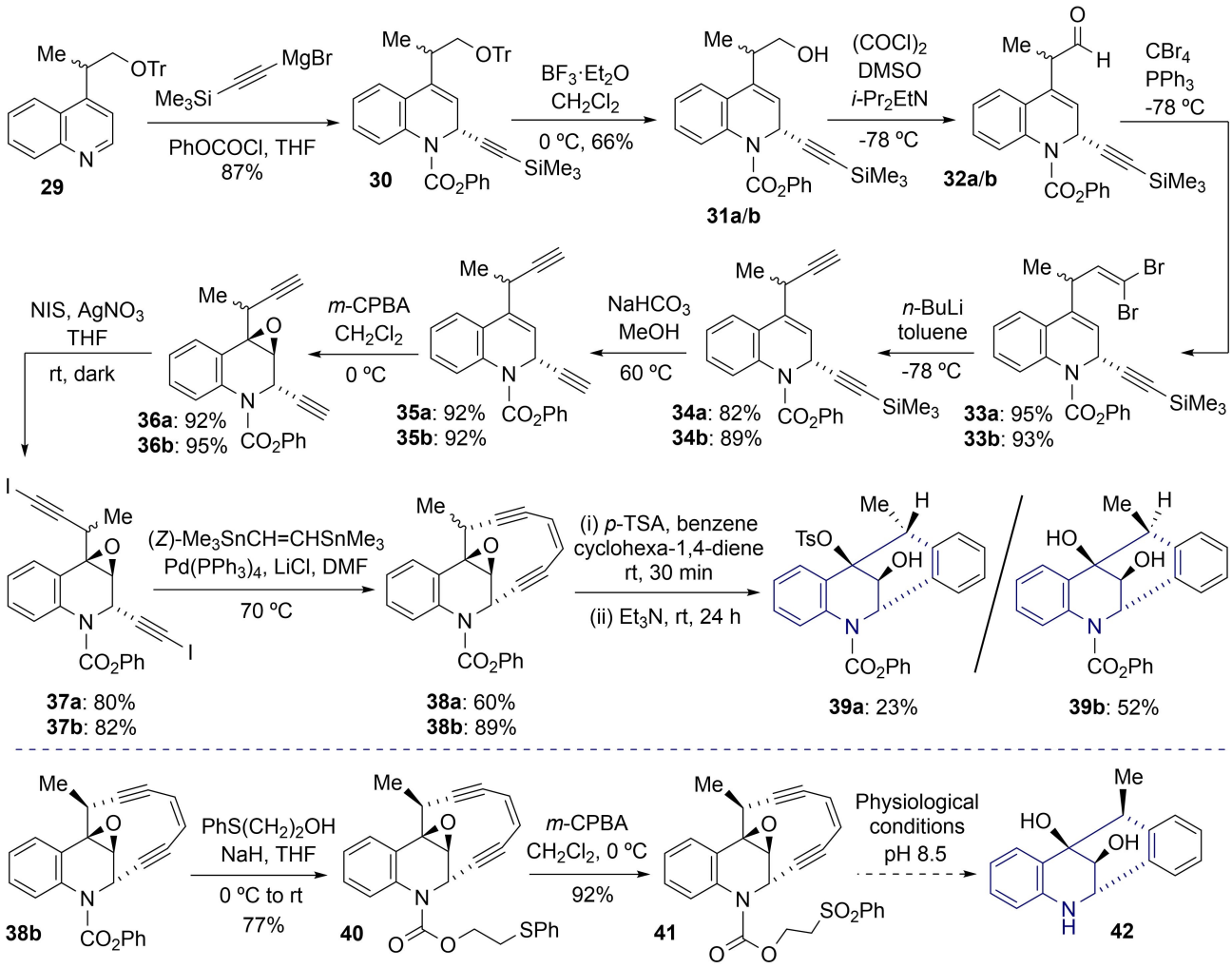
Scheme 6. First bioinspired total synthesis of sespenine by Li *et al.* (2014).



Scheme 7. Second generation total synthesis of sespenine by Li *et al.* (2016).

chemistry seeks to push the boundaries of organic chemistry by emulating natural processes toward complex natural products and promoting the implementation of more efficient synthetic protocols.[34]

Of all the natural products discussed above, only sespenine has been accessed by total synthesis to date. In 2014, Li *et al.* reported a bioinspired total synthesis of sespenine that proceeded through indosespene-type intermediates[21] (Scheme 6). The strategy began with an allylic oxidation[35] followed by enantioselective Sharpless epoxidation of compound **9**. Then, regioselective oxidation[36] mediated by the nitroxyl radical catalyst AZADO and $PhI(OAc)_2$ and methylation furnished ester **11**. The ester was deacetylated, and DMP oxidation of the resulting alcohol gave aldehyde **12** in excellent yield. The aldehyde reacted with an *in situ* generated ethynylcerium reagent to give alcohol **13** as a diastereomeric mixture.[37] This alcohol was subjected to epoxide opening followed by radical cyclization with an *in situ* generated titanium(III) species to furnish the *trans*-decalin **14**. Selective oxidation of the allylic hydroxy group with IBX and subsequent acetylation of the remaining alcohol provided enone **15**, which underwent a conjugate addition mediated by $Bi(OTf)_3$[38] to give ketone **16**. Upon olefination with the Nysted reagent and $TiCl_4$, the key indosespene-type intermediate **17** was obtained.[39] Exposure of this intermediate to oxone/acetone cleanly provided the hydroxylated indosespene **18** with no over-oxidation products. Then, the cationic cascade cyclization mediated by acetic acid furnished aniline **19**, which was subjected to Krapcho demethoxycarbonylation, affording benzomorphan **20**.[40] Finally, hydrolysis of **20** provided sespenine in a global 4% yield over 17 steps. Based on their first-generation synthesis, in 2016, Li *et al.* designed a second synthetic route to obtain sespenine in ten steps from commercially available materials (Scheme 7).[41] This improved approach employed a more advanced epoxy ester intermediate with the indole fragment pre-installed prior to biomimetic cyclization, thereby reducing the number of unproductive interconversions, such as protection/deprotection steps. The previously published strategy involving allyl oxidation, Sharpless asymmetric epoxidation, chemoselective oxidation, and methylation, followed by Stille-Miyata coupling, gave the functionalized epoxy ester **24**.[42] Subsequent titanium(III)-mediated reductive radical cyclization furnished *trans*-decalin intermediate **25** bearing a 2-methoxycarbonylindole side chain, which was oxidized to render an isomeric mixture of 3-hydroxyindolenines **26**. The major isomer entered a cationic cascade consisting of a Prins cyclization/Friedel-Crafts/retro Friedel-Crafts sequence under acidic conditions to give 3,4-benzomorphan **27**. Finally, Krapcho demethoxycarbonylation and basic hydrolysis furnished sespenine in a global 9% yield over ten steps. On the same note, Riva et al. have reported another bioinspired strategy to access simplified structures bearing the benzazocine scaffold (Scheme 8).[43] Natural enediyne antibiotics such as the aforementioned uncialamycin (see Scheme 4) contain a 10-membered 3-ene-1,5-diyne



Scheme 8. Diastereoselective approach to simplified dynemicin analogs by Riva *et al.*

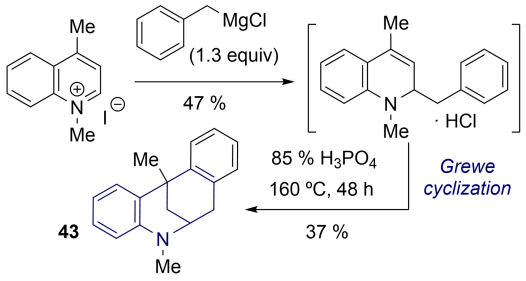
cyclic scaffold and exhibit a particular mode of action by functioning as natural prodrugs. Essentially, enediyne antibiotics contain an epoxide fragment that, upon opening, triggers a Bergman cycloaromatization to generate a benzazocine framework, which could be responsible for their bioactivity. Due to the structural complexity of these natural products, Riva and co-workers focused on preparing simpler substrates equipped with the required moieties to emulate the mechanism of action. The synthetic sequence began with the nucleophilic addition of an acetylide to the racemic quinolinic scaffold **29**. Next, the trityl group was removed, and the isomers readily separated chromatographically and were subjected independently to the remaining transformations. The deprotected alcohols **31a/b** were subsequently oxidized under slightly modified Swern conditions.[44] Afterwards, the treatment with CBr_4/PPh_3 following the Corey-Fuchs protocol[45] gave dibromoolefins **33a/b**, which underwent a facile conversion into alkynes **34a/b** with *n*-BuLi. The next step consisted of C-desilylation under mild conditions leading to diacetylenic compounds **35a/b**, which were epoxidized under standard conditions. Upon forming (bis)iodides **37a/b**, a Stille coupling was employed to obtain the key 3-ene-1,5-diyne cyclic scaffolds **38a/b**. Once the enediyne analogs were synthesized, **38a/b** were treated with *p*-TSA to demonstrate the propensity of the enediyne framework to undergo Bergman cyclization upon epoxide opening. Interestingly, the formation of the azatricyclic scaffold proceeded smoothly, giving monotosylate **39a** and diol **39b**.

Notably, even though the benzazocines were successfully prepared, the epoxide opening of **38a** and **38b** could not be triggered under physiological conditions. Therefore, the phenyl carbamate in **38b** was substituted by a 2-sulfonylethyl carbamate, which is known to undergo a facile β-elimination at pH values of around 8.5. Then, after oxidation with *m*-CPBA, substrates **38a**, **38b**, and **40** were tested against supercoiled plasmid pBR322 to evaluate their DNA-cleaving properties. As expected, enediynes **38a** and **38b** showed no cytotoxic activity. However, engineered eneydine **40** was active at concentrations ranging between 1 and 5 μM by means of a β-elimination/nitrogen-promoted epoxide opening/ cycloaromatization sequence.

3. Synthetic strategies

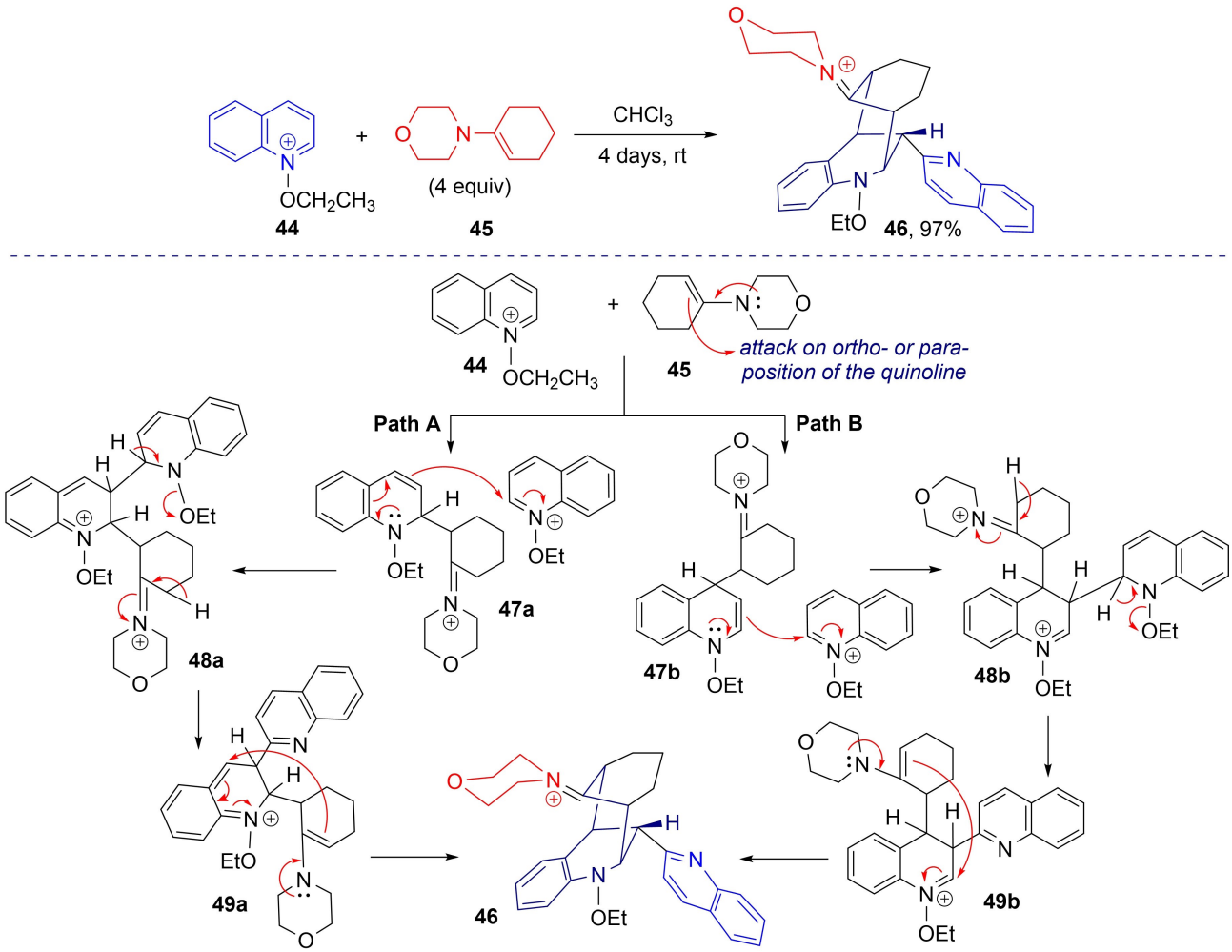
3.1. Strategy 1: Starting with a quinoline framework

Between 1970 and 1990, three groups designed strategies to access the hexahydro-2,6-methano-1-benzazocine scaffold using quinolinium salts. In one of the first ever reported syntheses of the benzazocine core, Joshi *et al.* explored how 4-alkyl and 3,4-dialkyl pyridine aryl iodides produced morphan derivatives when subjected to Grewe's morphinan synthesis.[46] To achieve the targeted framework, 1,4-dimethyl quinolinium iodide was treated with an excess of benzyl magnesium chloride to give an unstable dihydro intermediate,[47] which was subjected to a H_3PO_4-catalyzed intramolecular Friedel-Crafts cyclization, also known as Grewe cyclization (Scheme 9), to furnish the tetracyclic scaffold **43** bearing the benzazocine core.[48]



Scheme 9. Morphinan synthesis by Joshi *et al.*

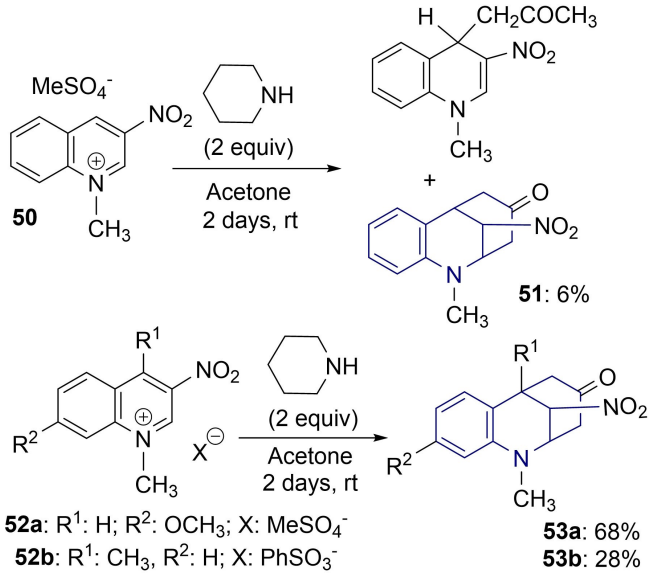
In the presence of acylating reagents, aromatic *N*-oxides are known to react with enamines to form α- or γ-substituted heterocyclic derivatives via an addition-elimination pathway.[49] However, it was accidentally discovered by Ueda *et al.* that *N*-ethoxyquinolinium salts reacted with enamines, adding at the quinoline 2- and 4- positions. This constituted the first reported example of a tricyclic product bearing the targeted benzazocine structure (Scheme 10).[50] The reaction starts with a nucleophilic addition of enamine **45** to quaternary salt **44** to give 1,2- or 1,4-dihydroquinoline intermediates **47a** and **47b**, respectively. Afterwards, the 3-position of the newly generated intermediates **47a/b** again attacks the 2-position of isoquinoline **44** using its enamine-like polarization to afford the second intermediate **48a/b**, which contains both dihydroquinolinium and 1,2-dihydroqui-



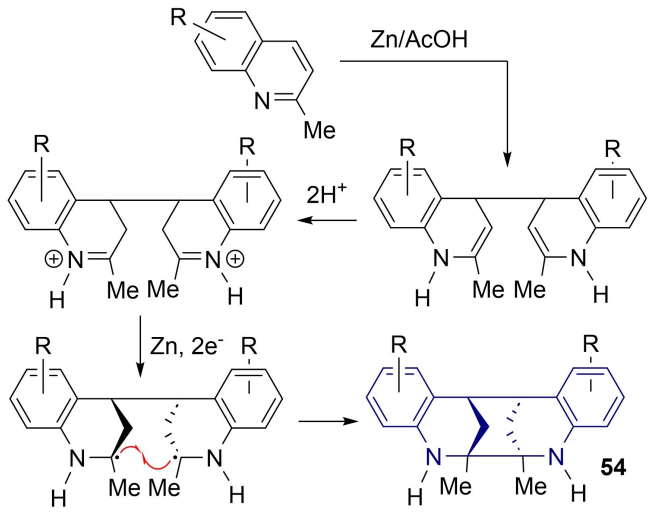
Scheme 10. The first tricyclic example of the benzazocine core by Ueda *et al.* and the reaction mechanism of *N*-ethoxyquinolinium salts with enamines.

noline structures. Subsequently, ethanol is eliminated to furnish the 2-quinolyl substituent, and with no substituent at the end of the double bond, the cyclohexylidenemorpholinium moiety is transferred into an enamine. The final step is the intramolecular attack of the enamine moiety at the election-deficient 4- or 2-position of the dihydroquinolinium ring in **49a** and **49b**, respectively, to furnish the azatricyclic product **46**.

In 1988, Bundel *et al.* demonstrated that in the reaction of 3-nitroquinolinium salts with aliphatic ketones and amines, the addition of ketone to the 2- and 4-positions results in the formation of tricyclic systems containing the desired benzazocine core (Scheme 11).[51] When working with the unsubstituted 3-nitroquinolinium salt **50**, an intermediate product



Scheme 11. Reaction of 3-nitroquinolinium salts with ketones by Bundel *et al.*



Scheme 12. Reduction of heteroaromatic systems with the zinc-acetic acid couple by Grignon-Dubois *et al.*

of the monoaddition of the ketone to the 4-position of the heteroring was isolated together with benzazocine **51**.

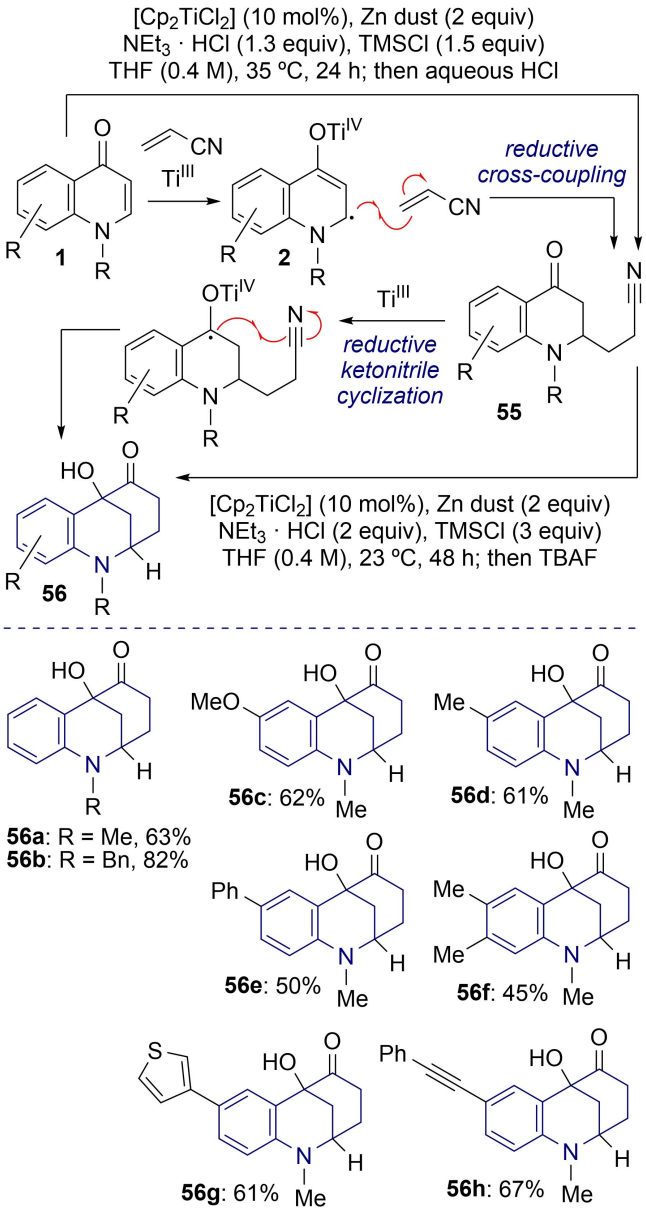
However, when a donor methoxy group was introduced at C7 (**52a**) or a methyl group at C4 (**52b**), only the azatricyclic products **53a**/**b** were isolated.

Although the zinc-acetic acid couple is a well-known reducing agent,[52] it has rarely been used in heteroaromatic systems. In 1995, Grignon-Dubois *et al.* developed a strategy involving acetic acid consumption to access Heller's dimer by treating quinaldine with Zn/AcOH (Scheme 12).[53] Mechanistically, the product arises from an intramolecular reductive cyclization, followed by the addition of a hydrogen atom at the 3- and 3'-positions and the formation of a new C–C bond between the 2- and 2'-positions. This process is enabled by protonation of the enamine followed by the transfer of two electrons and cyclization of the resulting diradical.[54]

More recently, Streuff *et al.* proposed a Ti(III)-catalyzed[55] double-reductive umpolung approach that allows the rapid assembly of bridged benzazocines and benzoxocines from readily available quinolone and chromone precursors (Scheme 13).[56] The first step of the transformation consists of a titanium(III)-catalyzed C2-functionalization in the form of a reductive cross-coupling with a Michael acceptor, such as acrylonitrile. The resulting series of tetrahydroquinoline-4-ones (e.g., **55**) and 4-chromanones[57] represent the core structures of several compounds with interesting biological properties.[58] The catalyst was generated *in situ* to obtain an allylic radical, which then attacked the Michael acceptor and led to the formation of a new carbon-carbon bond.

Several variations in the aromatic backbone were introduced to test the reaction's versatility. A good response was observed to the introduction of electron-donating phenyl and methyl groups, as well as thiophenyl and phenylacetylene groups, especially when present at the 3-position. In addition, the model Michael acceptor, acrylonitrile, could be substituted by ethyl acrylate, phenyl acrylate, or mesityl acrylate without affecting the reaction performance. The second step comprised a Ti(III)-catalyzed reductive ketonitrile cyclization.[59] The catalyst was believed to initiate a ketyl radical attack on the nitrile group, which smoothly furnished the benzomorphan ring system **56**. The reaction successfully afforded eight different benzazocines (**56a**–**h**) with yields ranging from 45 to 82%.

Yokoshima *et al.* demonstrated that ketones with a 2-nitrophenyl group at the α-position reacted with NaOH in methanol at 60 °C to give several nitrones.[60] As shown in Scheme 14, the process began with the intramolecular addition of the enolate to the nitro group to furnish oxazepane **57**. The newly generated oxazepane ring was cleaved by electron donation of the remaining oxygen atom to access nitroso compound **58**. Afterwards, a Cannizzaro-like hydride shift from the secondary alcohol to the nitroso functionality formed diketone **59**, which, upon condensation between the indicated carbonyl group and the hydroxylamine fragment, gave nitrone **60**. Once successfully synthesized, the intramolecular 1,3-dipolar cycloaddition of the nitrones with a range of olefins to access tricyclic isoxazoli-

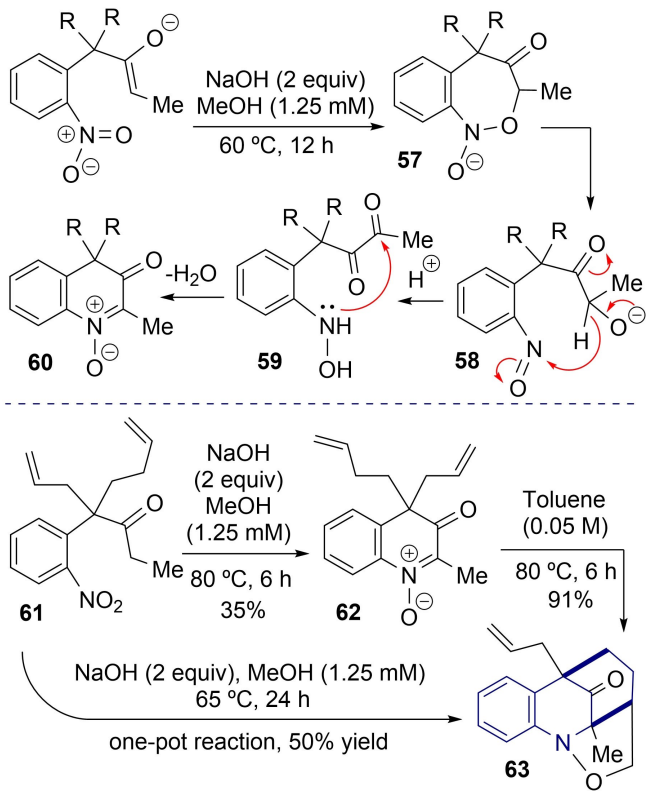


Scheme 13. Metal-catalyzed double-reductive approach toward the benzazocine core by Streuff *et al.* and scope of the prepared products.

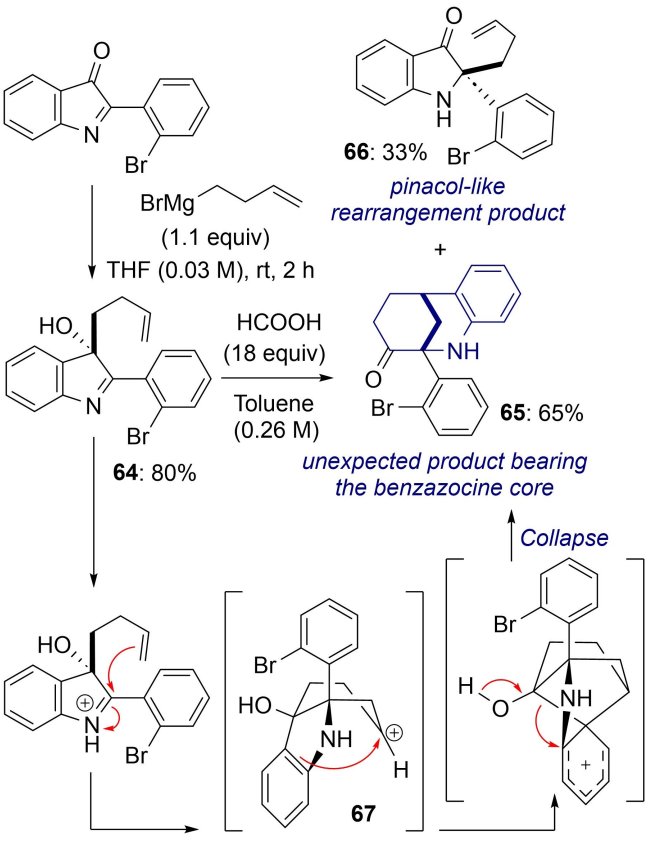
dines was studied. When treating nitrone **62**, which had allyl and 3-buten-1-yl substituents at the benzylic position, the cyclization selectively took place on the butenyl fragment to provide benzazocine **63** in 91% yield. Alternatively, the process was conducted in a one-pot fashion by treating **61** in methanol at 65 °C for 24 hours to give **63** in 50% yield.

3.2. Strategy 2: Incorporation of 2-azabicyclo[3.3.1]nonane

McWhorter *et al.* utilized 2-aryl indole-type precursors for the total synthesis of 8-desbromohinckdentine A.[61] In this approach, 3-butylmagnesium bromide was added to 2-(2-bromophenyl)-3*H*-indol-3-one to furnish 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**64**) by means of a Grignard



Scheme 14. Nitrone formation followed by 1,3-dipolar cycloaddition by Yokoshima *et al.*



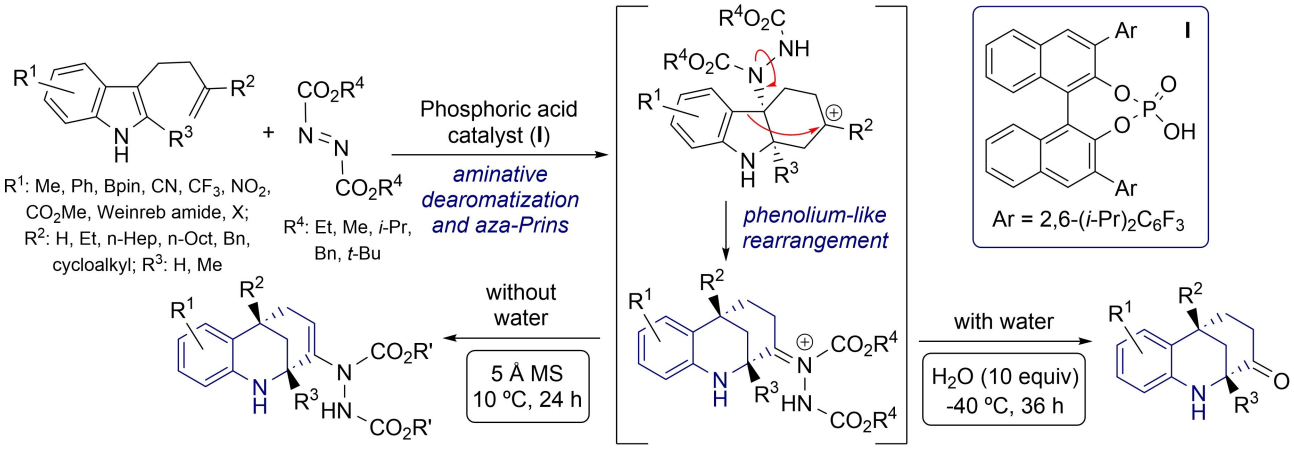
Scheme 15. Novel rearrangement of 2-aryl-indoles by Hadden *et al.*

reaction. Upon treatment of **64** with formic acid at reflux, a novel aza-Prins cyclization/phenolium-like rearrangement product containing the benzazocine core (**65**) was formed together with the pinacol-like rearrangement product **66** (Scheme 15).[20]

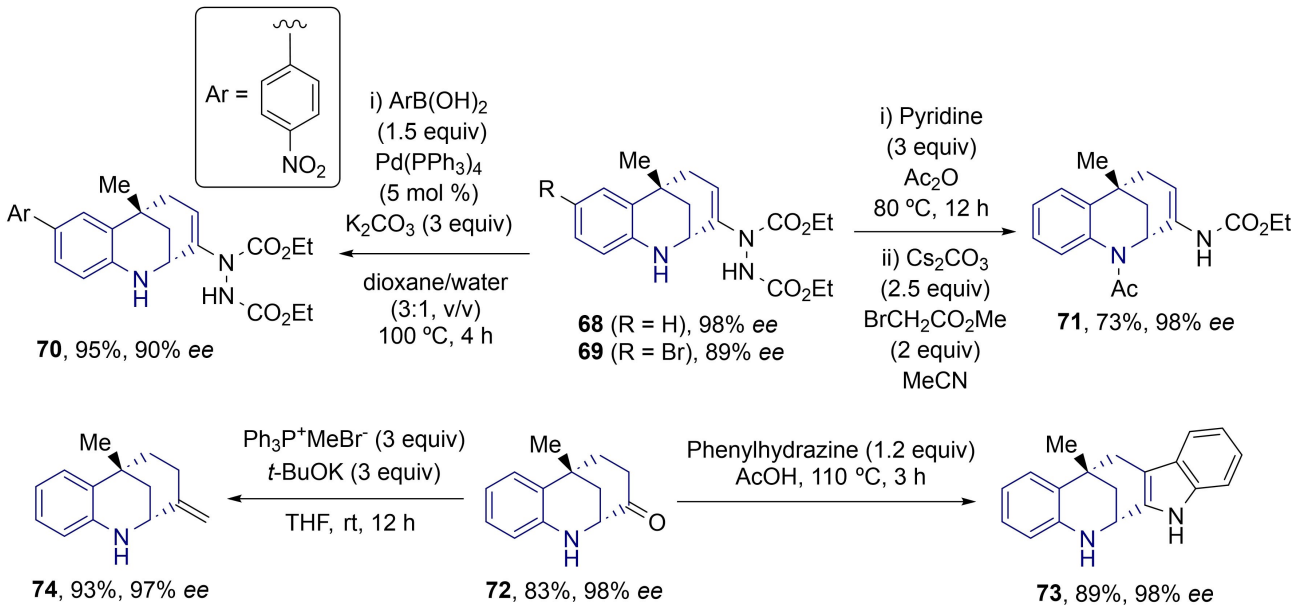
This enabled the skeletal relationship between anominine and aspernomine to be established.[62] The rearrangement was believed to start with the Markovnikov addition of the protonated imine to the double bond to give intermediate **67**. The steric hindrance generated by the bromophenyl group forced the double bond and the imine functionalities to approach one another to form a boat-like conformation. A subsequent electrophilic attack of the secondary carbocation on the π-bond of the electron-rich aromatic ring followed by collapse provided the benzazocine scaffold.

Relying on an analogous electrophilic amination/aza-Prins cyclization/phenolium-like cascade, You *et al.* have recently published an enantioselective strategy to access aza-[3.3.1]-bicyclic enamines and ketones (Scheme 16).[63] The cascade reaction is promoted by the presence of a newly designed fluorine-containing chiral phosphoric acid catalyst, which provides the targeted products with good to excellent yields and enantioselectivities. To demonstrate the synthetic utility of the method, the authors performed a series of additional transformations. The N–N bond in enamine **68** was subjected to reductive cleavage with methyl bromoacetate under basic conditions to give carbamate **71** in 73% yield. Moreover, enamine **69** underwent a Suzuki coupling with (4-nitrophenyl)boronic acid to form **70** in 95% yield. Finally, ketone **72** was subjected to Fischer indolization with phenylhydrazine and to a Wittig reaction with $Ph_3P^+MeBr^-$ to access benzazocines **73** and **74**, respectively (Scheme 17).

In 2009, Yao *et al.* used stable isochromenilium tetrafluoroborate (ICTB) precursors[64] to access two different types of



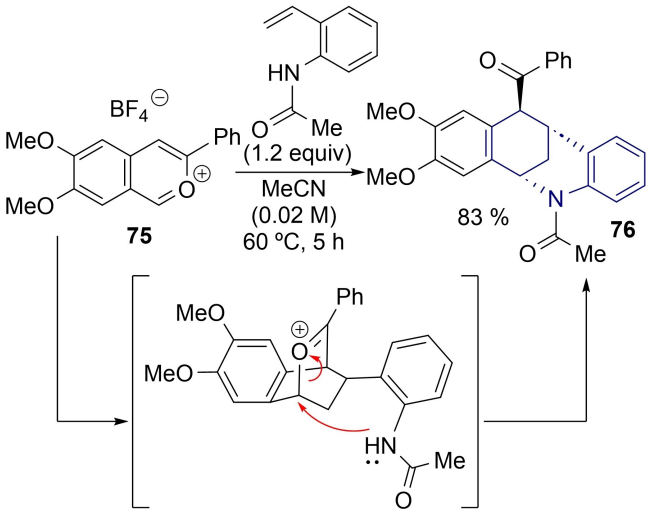
Scheme 16. Asymmetric dearomatization of indoles with azodicarboxylates by You *et al.*



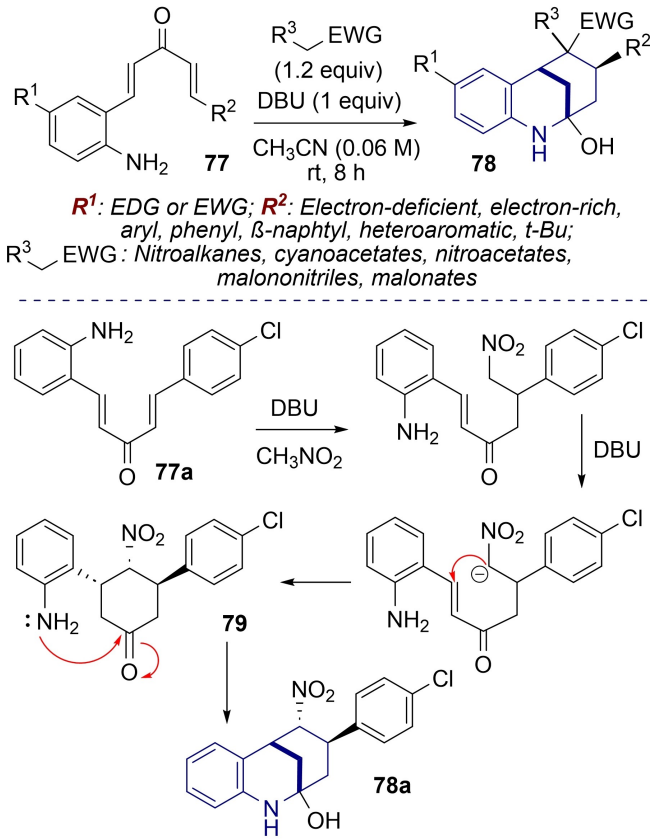
Scheme 17. Asymmetric dearomatization of indoles with azodicarboxylates by You *et al.*

polycyclic frameworks bearing the benzazocine core through a metal-free cascade reaction (Scheme 18).[65] Although efficient transformations involving ICTBs are described in the literature,[66] this was the first study to report a prolonged cationic cascade involving the entrapment of cationic intermediates to access complex polycyclic scaffolds of natural products. The transformation proceeded *via* a [4+2] cycloaddition between the ICTB precursor **75** and an engineered styrene or allyl bearing *N*- or *O*-based functionalities or Friedel-Crafts donors. This set the stage for a subsequent intramolecular entrapment of the generated oxonium intermediate to obtain the targeted cyclized products in yields ranging from 57% to 84%.

A domino strategy to access 3,4-benzomorphan derivatives was proposed by Li *et al.*[67] The transformation proceeded through a general [5+1]/hemiaminalization sequence of (2-aminoaryl) divinyl derivatives with a series of nitroalkanes and activated methylene compounds under mild conditions and with high regio- and stereoselectivity. Four stereocenters were set in the 3,4-benzomorphan framework without isolating any intermediates (Scheme 19). Mechanistically, the overall process begins with a DBU-promoted Michael addition of the (2-aminoaryl) divinyl ketone (**77a**) and the nucleophile (e.g., nitromethane). Upon deprotonation, an intramolecular Michael addition by a selective attack at the less hindered face generates the anti-diastereomer of cyclohexanone **79**.[68] Eventually, an intramolecular semiaminalization of **79** furnishes benzazocine **78a**. To emphasize the synthetic potential of the previously outlined tandem process, the group carried out two additional transformations for benzazocine **78a** (Scheme 20). Firstly, the hydroxyl group was smoothly removed when treating **78a** with triethylsilane and $TiCl_4$. Then, in the presence of allyltrimethylsilane and $TiCl_4$, the substrate was converted into the allylic 3,4-benzomorphan **81**, thereby introducing a new tetrasubstituted tertiary carbon center.



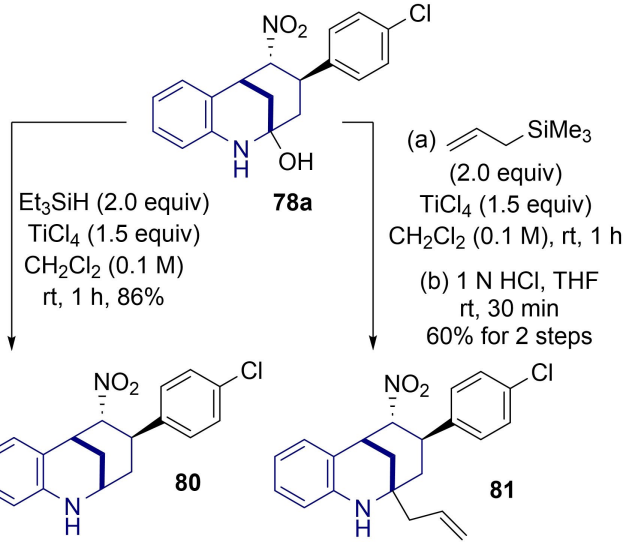
Scheme 18. Metal-free cascade cyclization by Yao *et al.*



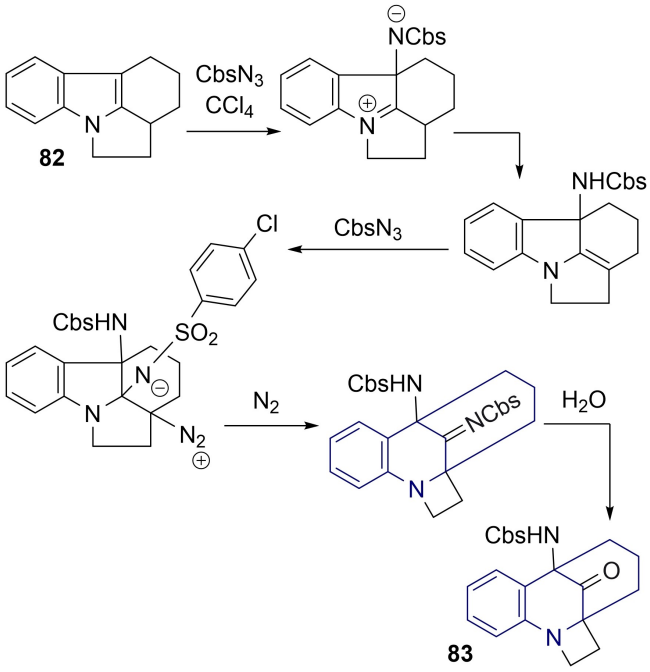
Scheme 19. Tandem [5+1]/hemiaminalization reaction by Li *et al.*

3.3. Strategy 3: Formation of the nitrogenated ring

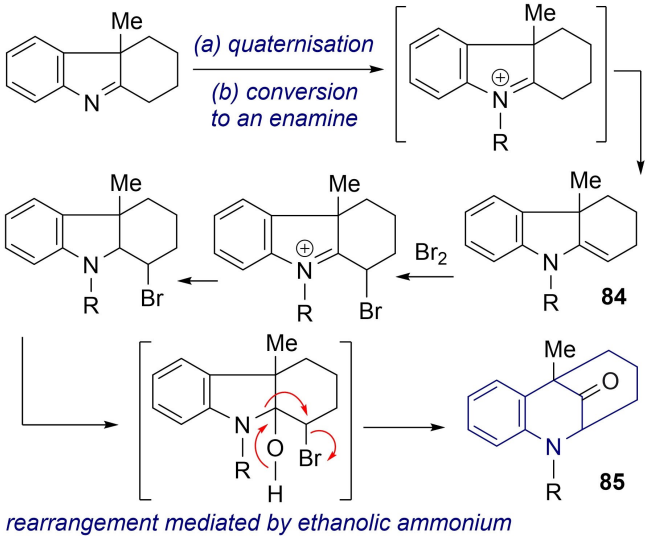
For clarity, this section is divided into four categories according to the type of transformation that gives access to the targeted benzazocine core: rearrangement-type reac-



Scheme 20. Additional reactivity of the 3,4-benzomorphan framework.



Scheme 21. Reaction of an indole with 4-chlorobenzenesulphonyl azide by Couldwell *et al.*

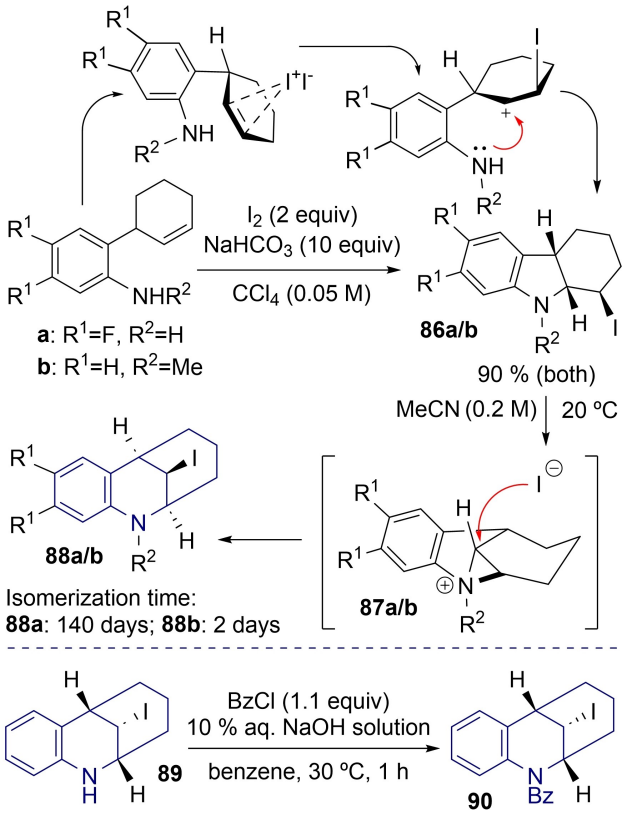


Scheme 22. Formation of the benzazocine core via ethanolic ammonium-mediated rearrangement by Joule *et al.*

tions, photochemical transformations, palladium-catalyzed reactions, and redox cyclizations.

3.3.1. Rearrangement-type reactions

Up to now, three approaches toward the azatricyclic structure through a rearrangement of indole-type precursors have been published. In 1980, Couldwell *et al.* reported a strategy to access the benzazocine core from simple indolenines.[69] After the reaction of tetracyclic indole **82** with 4-chlorobenzenesulphonyl azide, hydrolysis of the generated imine with water gave tetracycle **83**, among other compounds (Scheme 21).[70]



Scheme 23. Use of carbazole derivatives as intermediates for the synthesis of the benzazocine core and *N*-protection by Abdrakhmanov *et al.*

A second approach toward the benzomorphan framework using indolenine-type precursors was published shortly afterwards by Joule *et al.* (Scheme 22).[71] The synthesis started with the quaternization of the starting imine, followed by conversion to the enamine species **84** upon treatment with aqueous sodium hydroxide. A subsequent reaction with bromine produced bromo iminium salt, which underwent a rearrangement mediated by ethanolic aqueous ammonium carbonate, leading to the desired bridged scaffold **85**.

The third rearrangement strategy was proposed by Abdrakhmanov *et al.*, again employing indole-type precursors (Scheme 23). The group demonstrated that 2-(cyclohex-2-enyl)-4,5-difluoroaniline and *N*-methyl-2-(cyclohex-2-enyl) aniline reacted with I_2 in CCl_4 in the presence of sodium hydrogen carbonate to exclusively give 1-iodo-1,2,3,4,4a,9a-hexahydrocarbazoles **86a/b** in 90% yield. Subsequent isomerization in acetonitrile at room temperature proceeded through an intramolecular attack of the nitrogen atom on the highlighted carbon atom to give aziridinium salts **87a/b**, which were in turn attacked by an iodide anion to form the targeted azatricyclic compounds **88a/b**. It is noteworthy that substrate **88b**, bearing no fluorine atoms, isomerized to the benzazocine structure within two days, whereas the isomerization of compound **88a** took about 140 days to complete.

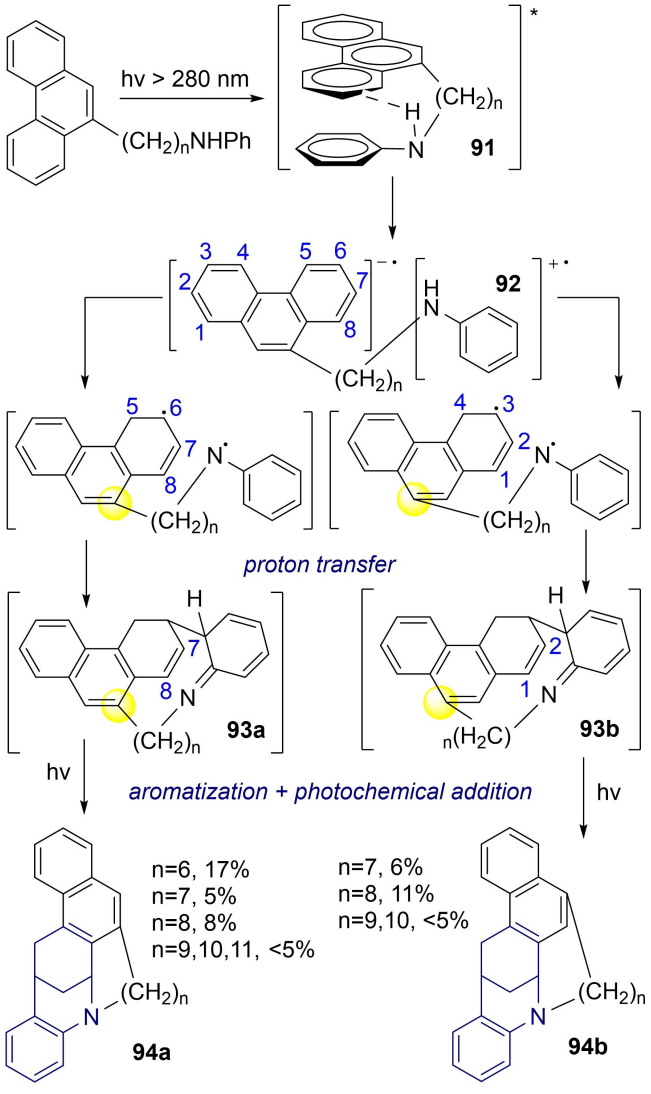
In later work, the nitrogen atom was successfully protected with a benzoyl group using the simpler substrate **89**,[72–73] the first incident-free example of such a protection on a benzazocine scaffold. It should be stressed that this is not always the case; the outcome depends on the substituents located around the nitrogen atom (see Section 3.3.4).

3.3.2. Photochemical transformations

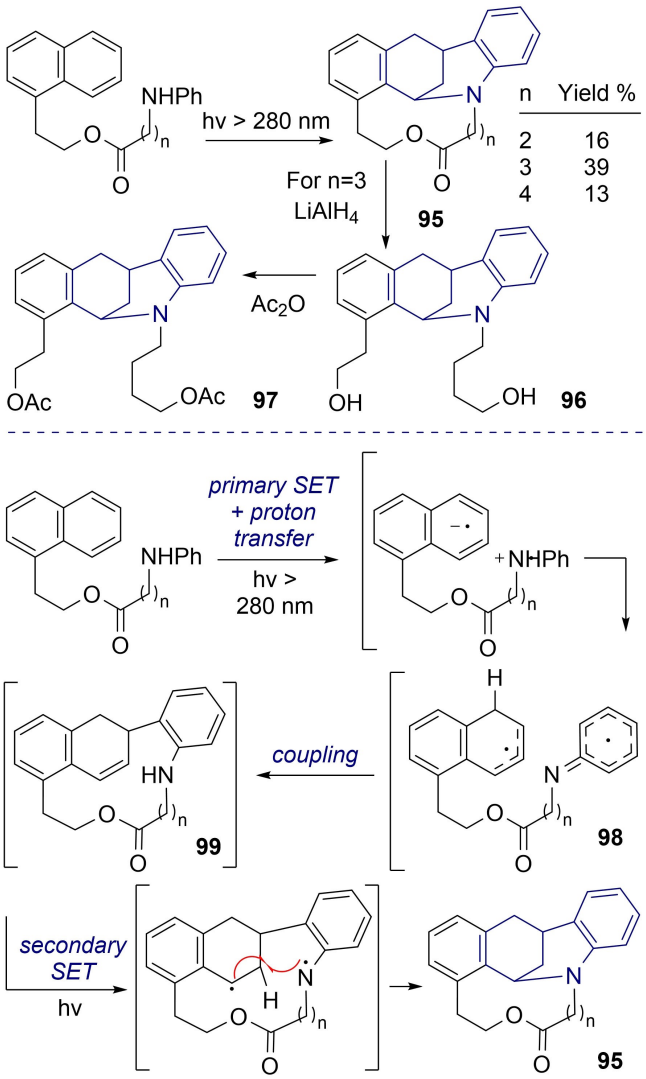
The first two reported syntheses of the targeted core using photoirradiation gave access to complex polycyclic structures bearing the benzazocine motif. In 1995, Sugimoto *et al.* described that photoirradiation of 9-(ω-anilinoalkyl)phenanthrenes in benzene under anaerobic conditions furnished polycyclic compounds bearing the 2-azabicyclo[3.3.1]nonane skeleton after cyclization at the 6,8-positions of the phenanthrene ring (Scheme 24).[74] The reaction was thought to proceed *via* exciplex **91**, which showed a π-π stacking structure with the NH/π interaction, leading to the radical anion-radical cation pair **92**. A subsequent proton transfer from the radical cation of **92** to the 5- and 4-positions of the phenanthryl radical anion would give intermediates **93 a** and **93 b**, respectively. An aromatization of the intermediates followed by the photochemical addition of the NH group to the C7—C8/C1—C2 double bond would provide the benzazocine scaffold **94 a** and **94 b**, respectively.

Shortly after their work on the photoirradiation of 9-(ω-anilinoalkyl)phenantrenes, Sugimoto *et al.* designed a similar strategy for the formation of tricyclic lactones from 2-(1-naphtyl)ethyl ω-anilinoalkanoates, which were subjected to further reduction and acetylation (Scheme 25).[75]

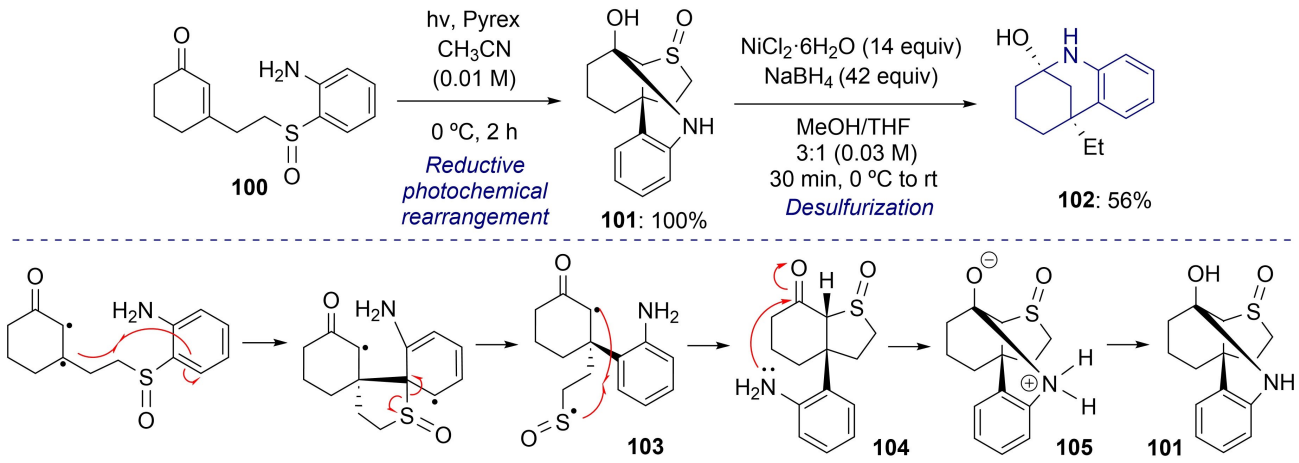
The photoreaction proceeded *via* a tandem photoinduced electron-transfer mechanism. The primary SET step from the anilino to the naphthyl group was followed by a proton transfer that produced diradical **98**, which in turn coupled to give bicyclic lactone **99**. The secondary electron transfer from the anilino group to the 1,2-dihydronaphthyl group led to



Scheme 24. Photoirradiation of 9-(ω-anilinoalkyl)phenantrenes under anaerobic conditions by Sugimoto *et al.*



Scheme 25. Photoinduced synthesis of tricyclic lactones by Sugimoto *et al.*



Scheme 26. Photochemically mediated route for the construction of thiolane heterocycles by Lee *et al.*

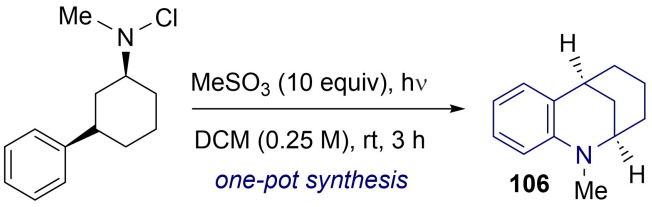
the formation of the benzazocine core **95**. The chemical yields of the 2-azabicyclo[3.3.1]nonane derivatives depended on the length and functionalization of the chain. The $-(CH_2)_2-OCO-(CH_2)_3-$ ester-containing side chain (n = 7) proved suitable for the reaction, but when polymethylene chains were tested, the best result was obtained for n = 6, which suggests that the ester-containing chain is more flexible than the methylene chain. Interestingly, the C–O bond of the ether-containing chain broke during the reaction, giving several unexpected products.[76]

More recent approaches toward the benzomorphan scaffold involve the photoirradiation of simpler substrates, and more useful tricyclic products have been obtained. In studies on a second-generation synthesis of ingenol,[77] a novel photochemical cyclization of aromatic sulfides was used by Lee *et al.* to access a variety of thiolane heterocycles (Scheme 26).[78]

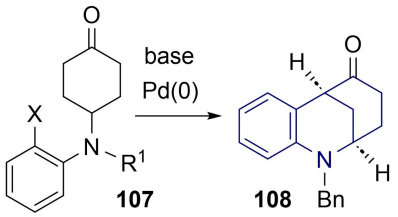
The photochemical rearrangement of an ortho-amino substrate was examined to expand the scope of substrates able to undergo the transformation. The irradiation of *ortho*-amino substrate **100** led to the formation of **101** as a mixture of sulfoxide epimers in quantitative yield. The removal of the sulfur group was then investigated. Desulfurization of **101** using Raney nickel afforded hemiaminal **102** in a modest 31% yield, which was consistent with the work of Simpkins *et al.*[79] In the search for alternative desulfurization protocols, exposure of **101** to nickel boride was found to provide hemiaminal in a more satisfactory 56% yield.

Mechanistically, the reaction proceeded through the addition of the β-radical of the enone to the aromatic ring, followed by fragmentation and concomitant rearomatization to furnish **103**, which, upon radical recombination, led to the cyclized aromatic sulfide **104**. The subsequent hemiaminalization of the product took place through the conventional mechanism.

In a recent study, Marsden *et al.* described a metal-free radical-based strategy for the direct amination of aromatic C–H bonds employing UV photolysis of simple secondary *N*-chloroamine precursors (Scheme 27).[80] In addition, the homogeneous reaction conditions allowed for a one-pot conversion of the amines to their arylated derivatives.



Scheme 27. Metal-free radical-based strategy for the direct amination of aromatic C–H bonds with simple alkylamine precursors by Marsden *et al.*

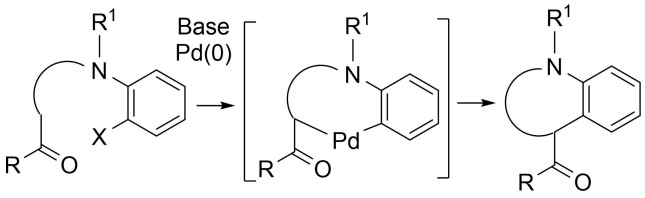


Method A: $Pd(PPh_3)_4$ (0.2 equiv), KO*t*-Bu (3 equiv), THF (0.020 M),reflux, 3.5 h

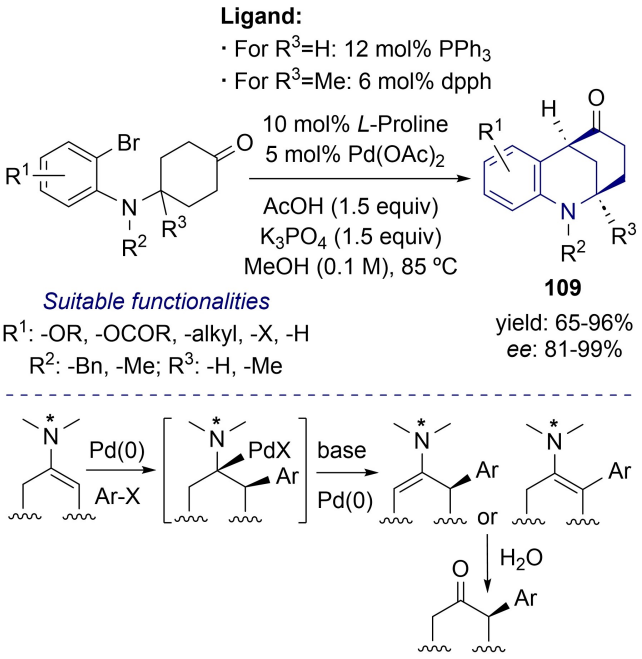
Method B: $PdCl_2(PPh_3)_2$ (0.2 equiv), Cs_2CO_3 (3 equiv), THF (0.028 M), 100-110 °C, sealed tube, 24 h

Method C: $Pd(PPh_3)_4$ (0.2 equiv), K_3PO_4 (3 equiv), THF (0.025 M), 100-110 °C, sealed tube, 24 h

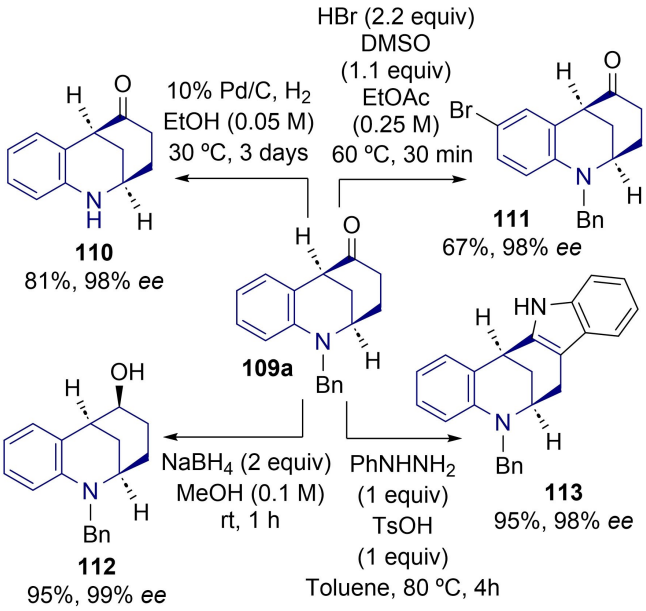
a: X=I, R^1=Bn	**a**: R^1=Bn	A: 84	B: 68	C: 76 (%)
b: X=Br, R^1=Bn		A: 67	B: 60	C: 78 (%)
c: X=I, R^1=Ac	**b**: R^1=Ac	A: -	B: 33	C: 38 (%)
d: X=I, R^1=CO_2Me	**c**: R^1=CO_2Me	A: 48	B: 92	C: 35 (%)



Scheme 28. Intramolecular Pd-catalyzed coupling of aryl halides and ketone enolates by our group.

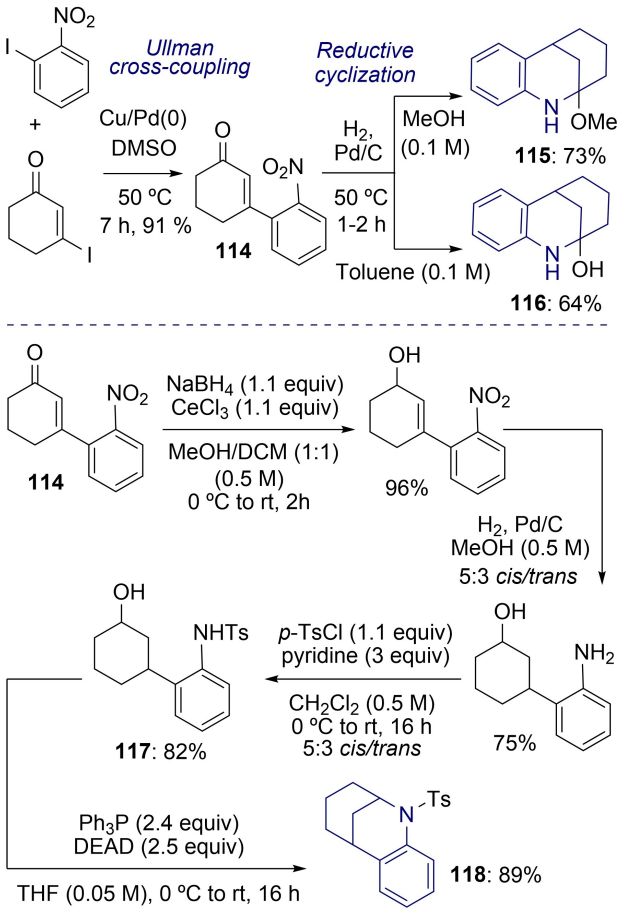


Scheme 29. Palladium/L-proline-catalyzed intramolecular α-arylative desymmetrization by Jia *et al.*



Scheme 30. Expanded reactivity of the azatricyclic products by Jia *et al.*

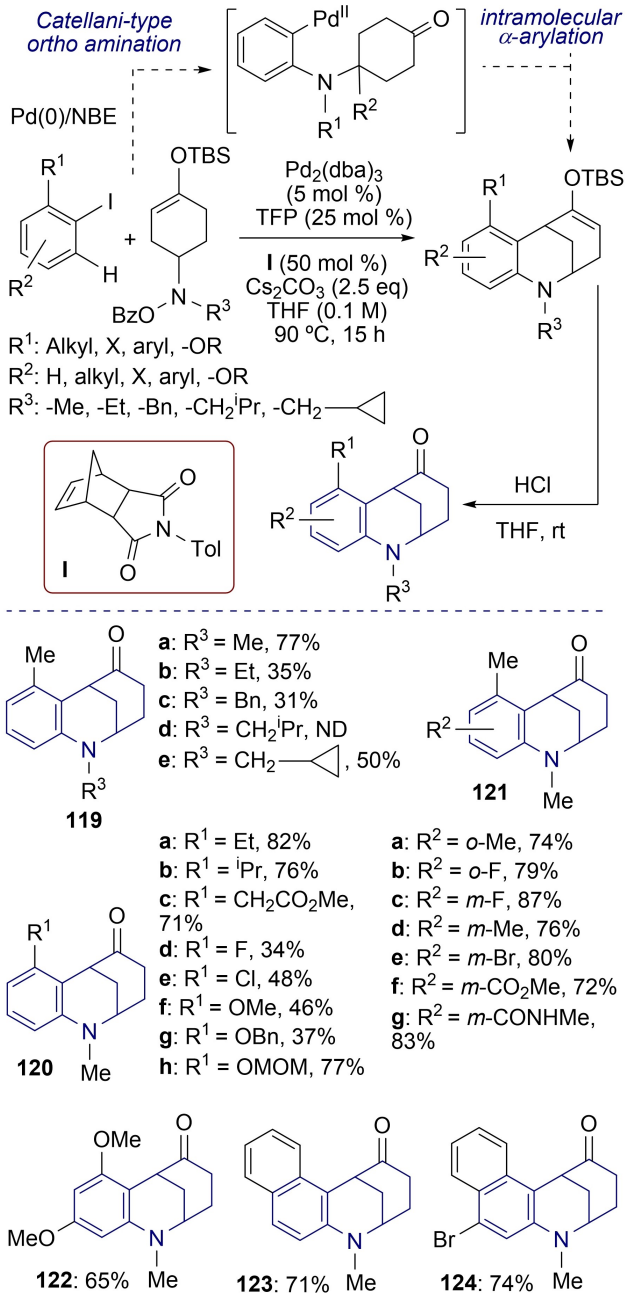
Studies on the potential of direct amination for the preparation of several polycyclic scaffolds revealed that the *N*-chloroamine of 3-phenylcyclohexylamine underwent cyclization to give the bridged azatricyclic skeleton **106**, despite the requirement for a highly disfavored 1,3-diaxial disposition of the reacting moieties in the substrate. Mechanistically, the reaction proceeded through the UV-light-induced formation of a protonated aminium radical[81] followed by an ortho-cyclization, which provided access to the bridged polycyclic structure.[82]



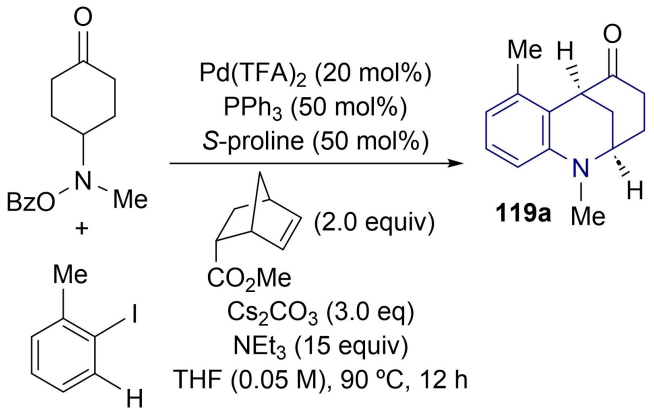
Scheme 31. Palladium-catalyzed cross-coupling reaction of a β-iodoenone and an *o*-halonitroarene followed by reductive cyclization by Banwell *et al.*

3.3.3. Palladium-catalyzed reactions

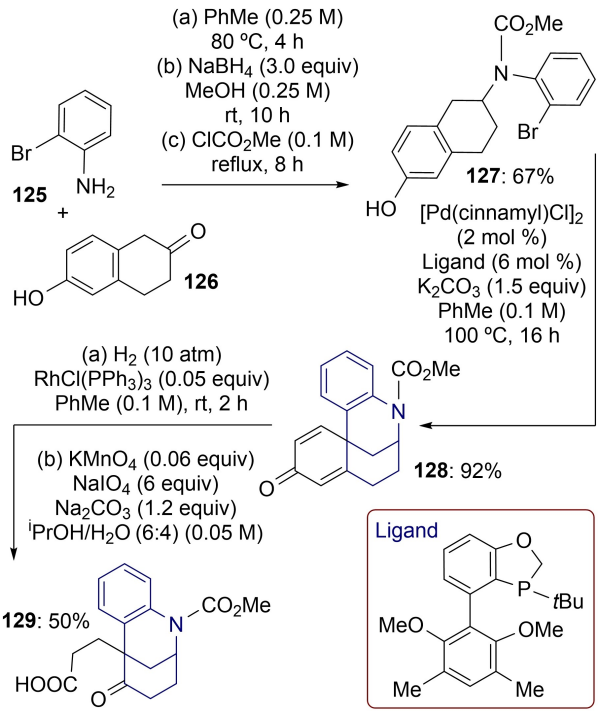
The palladium-catalyzed intermolecular coupling of aryl halides and ketone enolates has been widely used to access α-aryl ketones.[83] However, despite being a promising procedure to synthesize complex polycyclic compounds, examples of the intramolecular version of the transformation are scarce.[84] In 2001, our group designed a Pd-catalyzed intramolecular coupling of 2-haloanilines and ketone enolates to furnish 2,6-methano-1-benzazocine derivatives (Scheme 28).[85] A thorough optimization of the reaction conditions led to three general reaction procedures for the cyclization. In general, changing the halide from iodide to bromide had no significant effect on the reaction, whereas varying the substituent at the nitrogen had a marked impact on the cyclization performance, depending on the reaction conditions. For instance, when KO*t*-Bu was used as the base, acetamide **107 c** gave a complex reaction mixture, and no cyclization product was obtained. In comparison, carbamate **107 d** gave azatricyclic ketone **108 c** as the only isolable product in moderate yield. The Pd-catalyzed cyclization of amide **107 c** was achieved by using Cs_2CO_3 or K_3PO_4 as the base, although the yield was moderate, and small amounts of the dehalogenated amide were isolated.



Scheme 32. Modular and convergent strategy to access the benzazocine core based on the Catellani annulation by Zhou *et al.*



Scheme 33. Preliminary studies of the asymmetric Catellani-type annulation by Zhou *et al.*



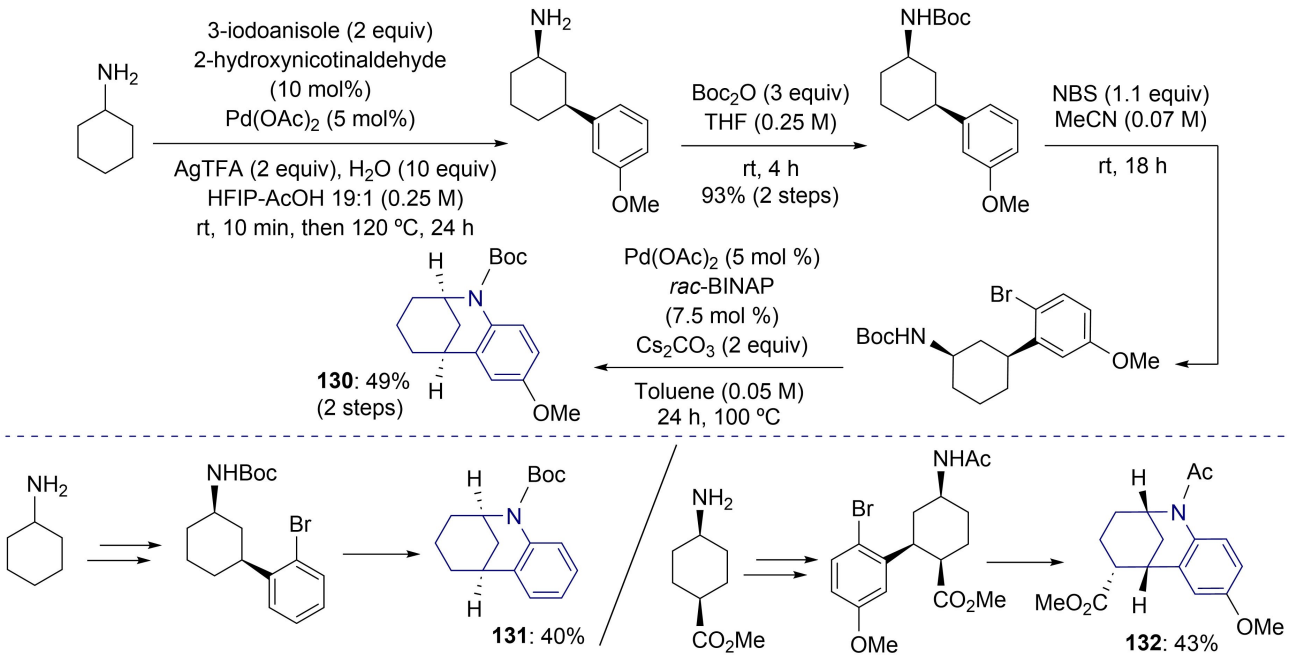
Scheme 34. Palladium-catalyzed dearomative cyclization strategy to access a variety of polycyclic skeletons by Tang *et al.*

Adding to the array of strategies for the enantioselective α-arylation of ketones,[86] Jia *et al.* reported an enantioselective version of the intramolecular coupling of 2-haloanilines and ketone enolates published by our group.[85a]

Palladium/*L*-proline catalysis was employed to obtain a variety of optically active compounds containing the targeted benzazocine moiety.[87] Incorporating an α-carbonyl stereogenic center, achieved through the formation of enamine intermediates followed by Heck arylation, prevented racemization due to the rigidity of the bridged framework (Scheme 29). After an exhaustive screening of the reaction conditions, including variations in the base, additive, solvent, and catalyst, the conditions shown in Scheme 29 were established as optimal and used to study the scope of the α-arylation.

Regarding the nature of the halogen, in contrast with the bromo substrate, yields, and *ee* were negatively affected when iodinated precursors were employed. Moreover, no reaction was observed for chloro substrates under the standard conditions.

Analysis of the substitution at the C4-C6 positions in the aromatic ring revealed that electron-withdrawing and -donating groups were well-tolerated, furnishing benzazocines bearing alkyl, halide, alkoxyl, ester, and carboxylic acid functionalities. Furthermore, the study of different *N*-protect-



Scheme 35. Regio- and stereoselective directed C–H arylation followed by cyclization to access a variety of three-dimensional scaffolds by Nelson *et al.*

ing groups revealed that methyl and benzyl substituted groups were suitable for the reaction. In contrast, the introduction of N-benzoyl and N-ethoxycarbonyl groups disfavored the process. To further extend the reaction scope, three additional products containing a tetrasubstituted carbon center were synthesized. However, due to enantioselectivity issues, 1,6-bis(diphenylphosphino)hexane (dpph) was employed as a ligand instead of PPh_3. Once the scope of the products had been established, their reactivity was tested under a series of conditions (Scheme 30).

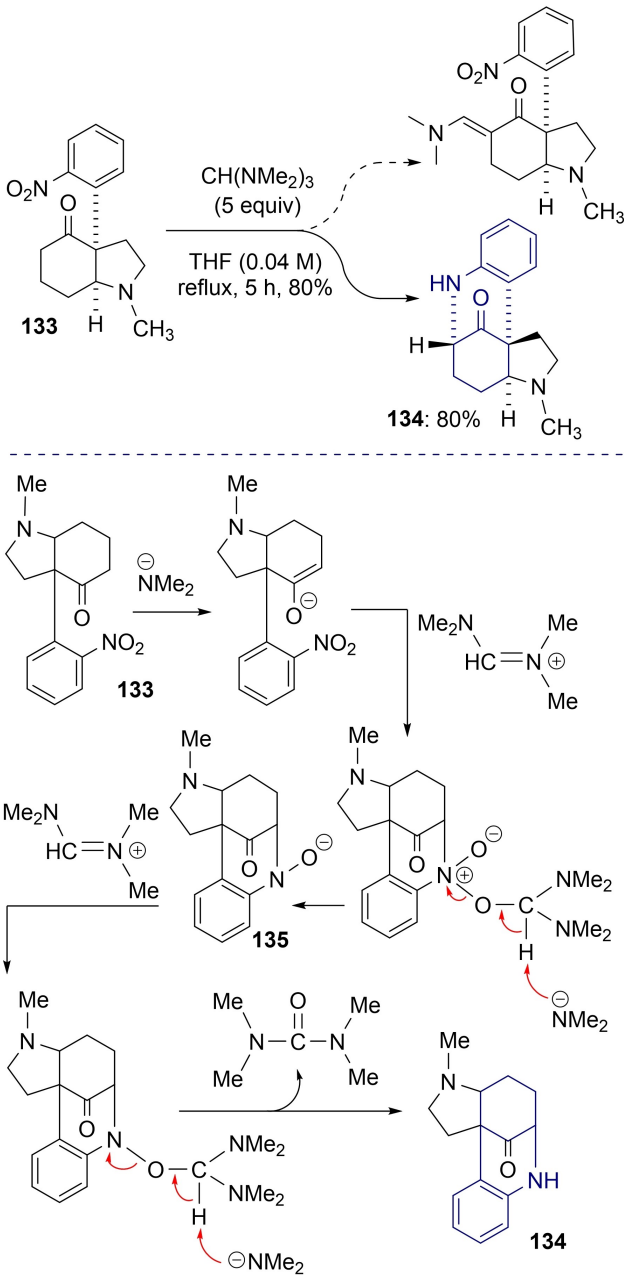
Conveniently, Pd/C-catalyzed hydrogenation of **109a** furnished free amine **110** in 81% yield with 98% *ee*. Moreover, bromination employing HBr/DMSO in ethyl acetate gave benzazocine **111** in 67% yield with 98% *ee*. A reduction using $NaBH_4$ in methanol proceeded smoothly to access alcohol **112** in an excellent 95% yield with 99% *ee*. Finally, an acid-catalyzed Fischer indolization afforded indole derivative **113** in 95% yield with 98% *ee*.

In 2018, Banwell *et al.* developed a palladium-catalyzed Ullman cross-coupling of β-iodoenones and β-iodoacrylates with *o*-halonitroarenes and *o*-iodobenzonitriles, which, upon reductive cyclization generated various heterocyclic scaffolds, including benzomorphan derivatives.[88]

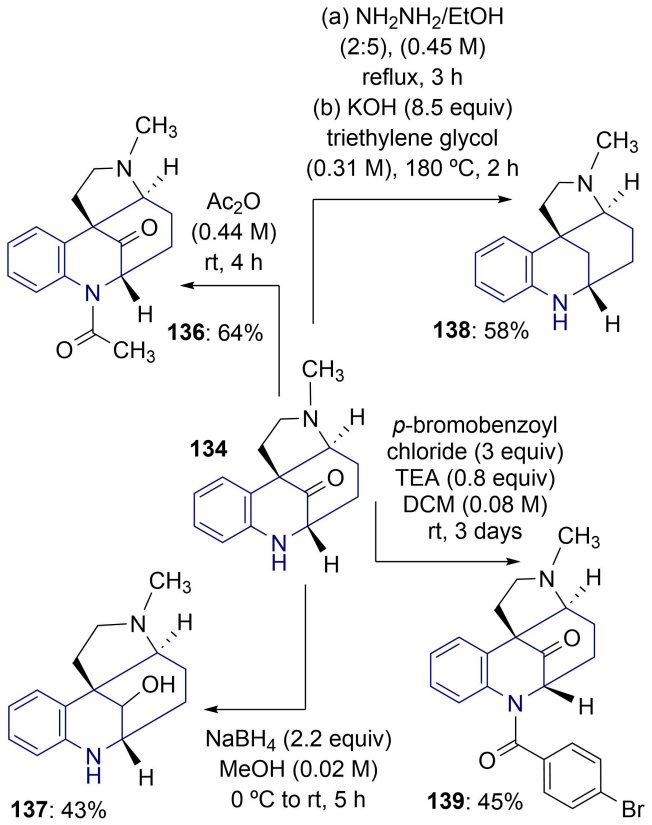
Studies on the scope of the transformation revealed that a broad spectrum of β-iodoenones, including β-halo 2-cyclohexen-1-ones, β-iodinated-2-cyclopenten-1-ones, bromonitropyridines, and β-iodoalkenones, could easily engage in cross-coupling reactions with *o*-halonitrobenzene.[89] However, iodinated forms of the coupling partners proceeded with better yields than brominated species. In addition, β-iodoacrylate and β-iodocinnamate coupled with *o*-halonitrobenzene. When nitroarenes were substituted with *o*-iodobenzonitriles, the reaction still proceeded adequately, albeit with poorer yields, which were likely attributable to the weaker electron-withdrawing capacities of the nitrile group compared with the nitro group.

Many of the cross-coupling products outlined previously were engaged in reductive cyclization processes. For instance, exposure of a methanolic solution of β-aryl-2-cycloalkene-1-one **114** to hydrogen in the presence of Pd/C led to the formation of 3,4-benzomorphan **115**. Interestingly, compound 116 bearing a bridgehead hydroxyl group was obtained when the same substrate was treated with toluene instead. By means of further elaboration of substrate **114**, it was possible to convert the protected aniline **117** to benzazocine **118** through a Mitsunobu reaction and exposure to Ph_3P/DEAD (Scheme 31).

In 2019, Zhou *et al.* developed a palladium/norbornene-catalyzed Catellani-type annulation involving an *ortho*-C–H amination followed by an intramolecular α-arylation cascade between aryl iodides and functionalized amination reagents.[90–91] Even though the strategy relied on cyclization precursors similar to those used in our[85a] and Jia's work,[87] it offered a modular and convergent approach toward the bridged scaffold relying on simpler substrates. When studying the scope of the reaction, the annulation was found to be very sensitive to the steric hindrance of *N*-substitution at the amination reagent (see **119b–e**). Therefore, a methyl group was used in all cases. Gratifyingly, in comparison with aryl iodides, the scope was broader (see **120**–**121**). All the substrates, whether bearing electron-donating or withdrawing groups, proved to be competent. Moreover, the transformation was highly chemoselective, showing good tolerance to fluorides, chlorides, bromides, methoxy, benzyloxy, MOM-protected hydroxy, methyl ester, and amide groups. Conveniently, bicyclic aryl iodides **123** and **124** smoothly



Scheme 36. Reductive cyclization mediated by tris(dimethylamino)methane by Bonjoch *et al.*



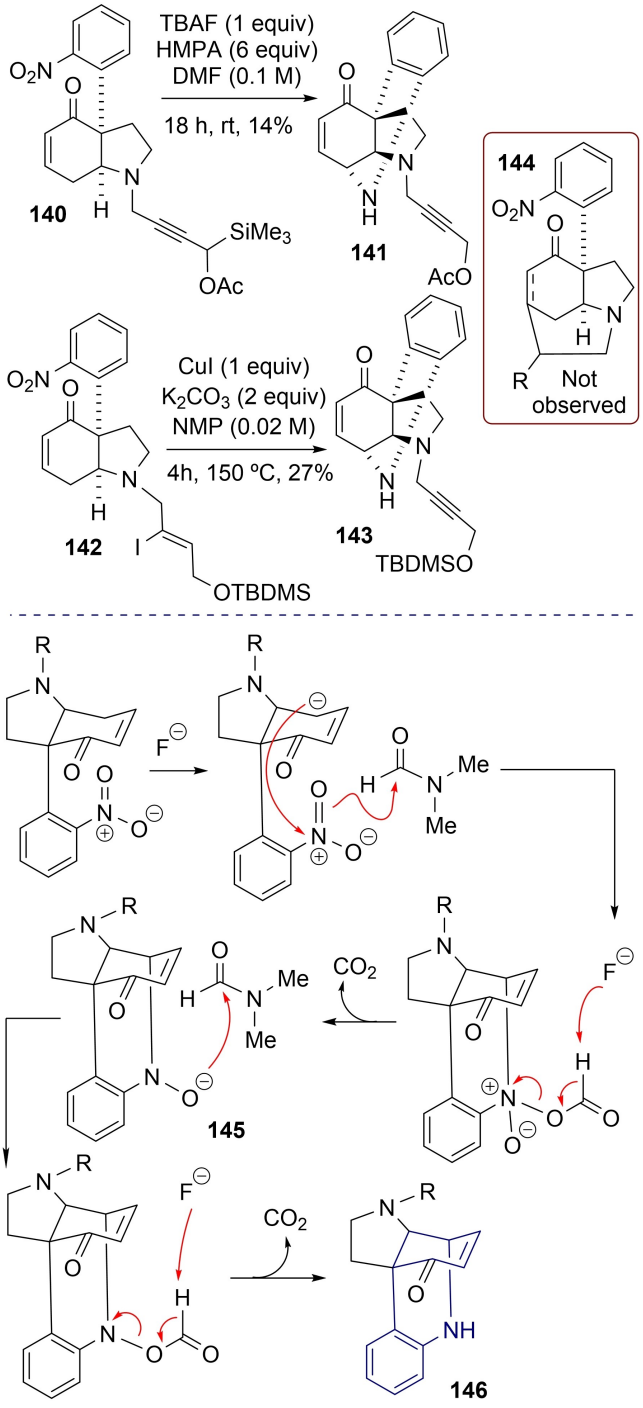
Scheme 37. Expanded reactivity of azatricyclic products by Bonjoch *et al.*

engaged in the annulation reaction (Scheme 32). The study also focused on the asymmetric version of the reaction cascade. Preliminary investigations revealed that under the conditions depicted in Scheme 33, the desired product could be obtained in 38% yield and 24% *ee*. As *S*-proline was the only chiral source, it was postulated that the transformation may proceed through an intramolecular Heck reaction of an *in situ* formed chiral enamine from *S*-proline and the cyclohexanone motif.[87]

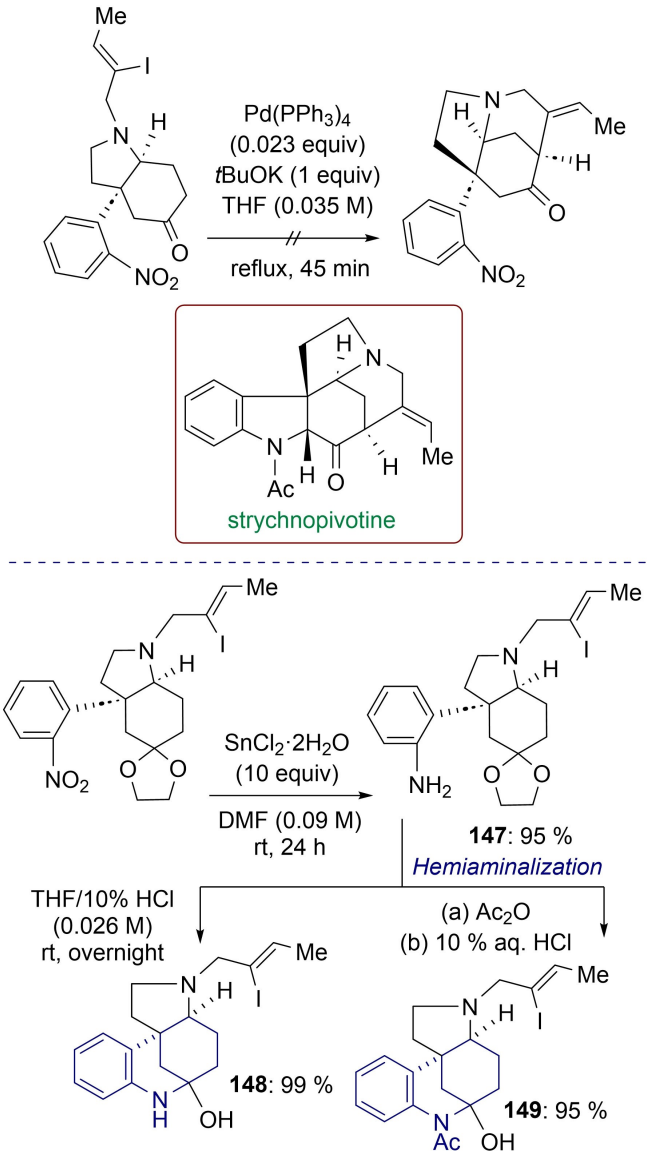
Tang *et al.* designed a palladium-catalyzed dearomative cyclization to access eight bridged tetracyclic skeletons, including two benzazocine core examples.[92] The strategy featured a site-specific cross-coupling between an aryl halide and a phenol moiety, with high yields and excellent regio- and chemoselectivities. Furthermore, using a chiral palladium catalyst enabled the formation of a series of enantiomerically enriched bridged systems with up to 99% *ee*.

As shown in Scheme 34, the preparation of the benzomorphan core began with the reductive amination between ketone **126** and *o*-bromoaniline, followed by carbamylation with ClCOOMe to furnish **127**. Then, in the presence of a sterically hindered and electron-rich palladium catalyst, the cyclization took place in toluene to form **128**, representing an advanced intermediate toward the total synthesis of aspernomine. The scaffold was further elaborated to obtain another intermediate for the total synthesis of strychnochromine. Hence, one carbocycle of compound **128** was cleaved by oxidation with $KMnO_4/NaIO_4$ to form carboxylic acid **129**, which constitutes the bridged tricyclic core of the natural product.

In 2021, Nelson *et al.* envisaged a strategy toward 30 diverse three-dimensional scaffolds[93] containing both a nitrogen atom and an aromatic ring. The transformation proceeded through an amine-directed C–H (het)arylation of mono- or bicyclic amines, which provided a *syn*-relationship between the amine and the (het)aryl group, followed by a Pd-catalyzed cyclization process. The reaction scope was examined by varying the amine substrate and the (het)aryl ring (Scheme 35). Hence, after a Buchwald-Hartwig reaction,



Scheme 38. Reductive cyclization of hexahydroindolones by Bonjoch *et al.*



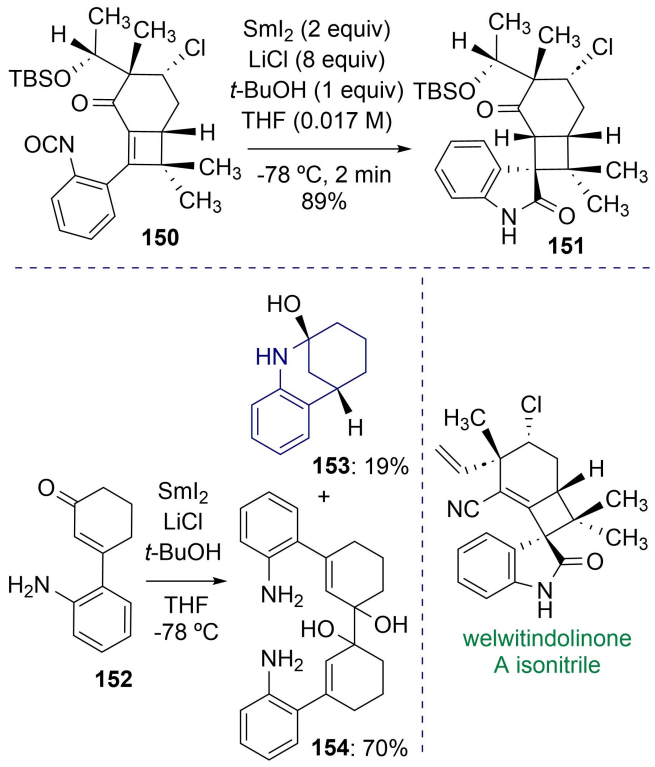
Scheme 39. Hemiaminalization of anilines to furnish the benzazocine core by Bonjoch *et al.*

the palladium-catalyzed cyclization of products **130**–**132** bearing the benzomorphan framework was completed.

3.3.4. Redox cyclizations

The first reduction-based routes to access the benzazocine scaffold were accidentally discovered by our group when treating a variety of nitrophenylketones with diverse bases. During our studies on the synthesis of curan-type *Strychnos* indole alkaloids,[94] attempts at an α-formylation of the nitrophenyl scaffold **133** resulted in the fortuitous formation of the azatricyclic product **134** bearing a pyrrolobenzazocine framework obtained via a reductive cyclization (Scheme 36).[95]

The transformation started with the base-mediated deprotonation of the α-carbon of nitrophenylketone **133**. A subsequent intramolecular nucleophilic attack of the enolate on the nitro moiety occurred simultaneously with the reduction of the nitro group, furnishing deprotonated hydroxylamine **135**. A further reduction mediated by the amidinium cation led to the formation of the benzomorphan structure in 80% yield.



Scheme 40. SmI_2/LiCl-mediated cyclization affording the benzazocine core by Wood *et al.*

In addition, compound **134** was transformed using standard procedures into several derivatives, including amides **136** and **139**, alcohol **137**, and diamine **138** (Scheme 37).

In the context of the total synthesis of strychnine,[96] efforts by our group to form the piperidine ring in **144** using propargylic and vinyl iodide precursors resulted in the unexpected generation of bridged tetrahydroquinoline scaffolds under two different reaction conditions. When treating hexahydroindolone **140** with TBAF in DMF-HMPA, benzazocine **141** was isolated in 14% yield. Moreover, when **142** was heated in *N*-methylpyrrolidinone in the presence of copper iodide and potassium carbonate, tetracyclic benzazocine **143** was obtained in 27% yield (Scheme 38).[97]

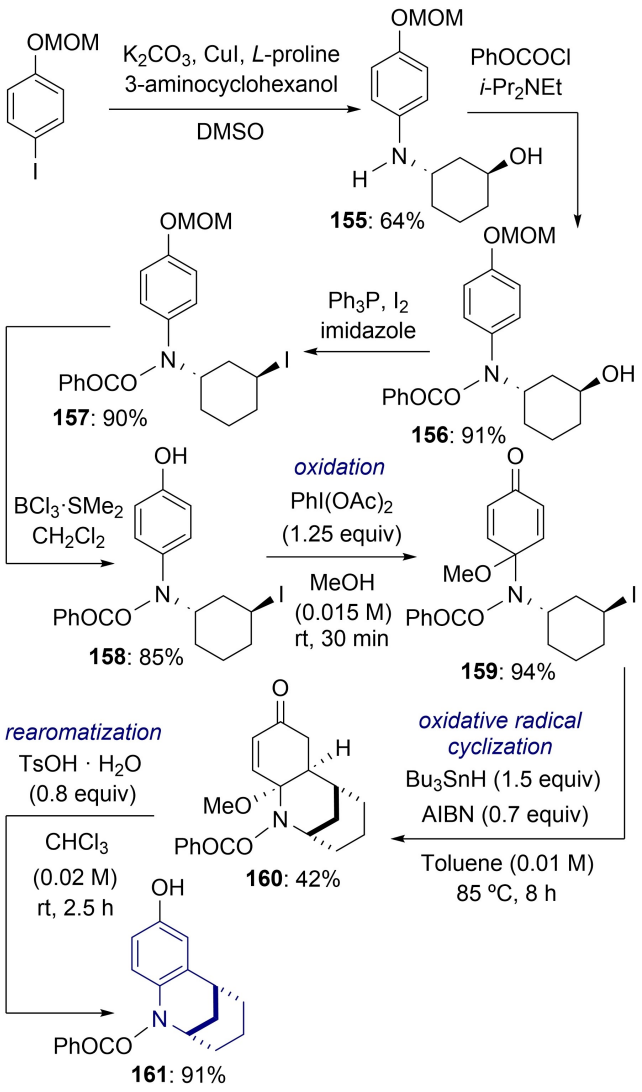
The TBAF in the DMF-HMPA cyclization process began with the intramolecular nucleophilic attack of the enolate on the nitro group, followed by formylation of the generated intermediate. Subsequent reduction with loss of carbon dioxide afforded hydroxylamine **145**, which may undergo an additional reduction consisting of a formylation/CO_2 elimination sequence to give the final cyclization product. An analogous mechanism for the CuI-promoted reaction employing Cu^+ as the reducing agent was proposed by our group.

In studies on the synthesis of the bridged azatricyclic fragment of strychnopivotine using a Pd(0)-promoted α-alkenation of ketone enolates, it was concluded that *o*-nitrophenyl derivatives were not suitable substrates due to incompatibilities with the basic reaction medium. Therefore, a simpler alternative with a reduced group was required. Surprisingly, once aniline **147** was obtained, hydrolysis under acidic conditions furnished hemiaminal **148** bearing the benzazocine core instead of the deprotected 3a-aryloctahydroindole framework, ready for further elaboration toward the natural product. Analogously, when aniline **147** was acetylated, it also formed a hemiaminal species (**149**) upon hydrolysis with hydrochloric acid (Scheme 39).[98]

In the context of the first total synthesis of (+)-welwitindolinone A isonitrile by Wood *et al*,[99] a substrate containing the benzazocine ring system was isolated during the elucidation of the mechanism underlying the SmI_2/LiCl-mediated preparation of the spiro-oxindole moiety in **151**.[100] As indicated in Scheme 40, substrate **150** possessed two potential electron acceptors: the α,β-unsaturated ketone, and isocyanate fragments. Aiming to distinguish which functional group was reduced by Kagan's reagent, aniline **152** was exposed to identical reaction conditions and furnished pinacol dimerization product **154** alongside benzomorphan **153** in 19% yield as a result of net-1,4-reduction of the enone. In contrast, the subjection of phenyl isocyanate, which lacked a reactive enone, to identical conditions resulted in no reaction. It was therefore concluded that the formation of spiro-oxindole **151** proceeded through the reduction of the enone functionality followed by cyclization into the isocyanate fragment.

In 2008, Clive *et al.* proposed a strategy toward linearly fused, angularly fused, and bridged nitrogen heterocyclic systems through an oxidative radical cyclization of an sp^3-hybridized carbon onto a benzene ring.[101] *p*-Iodophenols, particularly those with the phenolic oxygen protected with a MOM group, were smoothly coupled with amino alcohols to yield *N*-aryl amino alcohols, which were then converted into the corresponding iodide derivatives upon protection of the nitrogen with a carbamate group. Subsequent removal of the phenolic protecting group followed by oxidation with $PhI(OAc)_2$ in the presence of methanol afforded cross-conjugated ketones (**159**). These were subjected to 5-, 6- or 7-*exo*-trigonal oxidative radical cyclization (**160**) and exposed to acidic conditions to effect rearomatization, leading to the nitrogen heterocyclic systems (**161**). This strategy efficiently generated 5-, 6- and 7-membered carbon rings in the radical closure step, with one example bearing the benzazocine core (Scheme 41).

In the context of studies on the total synthesis of aspernomine, we recently reported a K_2CO_3/NMP reductive cyclization of nitrophenylketones to access the hexahydro-2,6-methano-1-benzazocine ring system with yields of up to 87%.[102] The scope of the reaction was explored with eight different analogs (see **162a–h**). Based on the observed reactivity, a Grob fragmentation reaction mechanism was proposed, as outlined in Scheme 42.[103] After the initial enolate-nitrophenyl coupling, the overall process could include a ring-opening nucleophilic attack on the carbonyl group of NMP, which would generate the five-atom scaffold required for the concerted fragmentation of **167**.



Scheme 41. Oxidative radical cyclization of a sp^3-hybridized carbon onto a benzene ring to furnish the benzazocine core by Clive *et al.*

The cleavage of the indicated bonds would cause the reduction of the nitro to a deprotonated hydroxylamine **168**, which, through an iterative sequence, would enable a second reduction process, and the resulting amide **170** could render the targeted benzazocine product by protonation. To improve the handleability of the cyclized products, the protection of the nitrogen atom was attempted to prevent benzomorphan degradation during prolonged storage. However, the task proved less straightforward than envisaged due to the poor nucleophilicity of the nitrogen caused by the neighboring electron-withdrawing group. Therefore, efforts at protection with various groups such as methyl chloroformate, *p*-TsCl, CbzCl, Ac_2O, and Boc_2O in the presence of a range of bases (TEA, DIPEA, K_2CO_3, NaOH, and NaH) did not result in any reaction. Interestingly, the use of LiHMDS and Boc anhydride provided **164** with excellent yield, even though the protection of the carbonyl group was required to avoid *O-tert*-butoxycarbonylation of the substrate (**165**) as well as to enhance the nucleophilicity of the nitrogen atom.

The synthesized benzazocines were screened for their cytotoxic activity against the human breast cancer MCF7 cell line, revealing that most of the products were less active than aspernomine ($44\ \mu M < IC_{50} < 182\ \mu M$). These results suggest that the cytotoxicity might not depend only on the presence of the benzazocine core but that other structural elements could be required. The racemic nature of the synthesis or the presence of an ester moiety could also have contributed to the lower activities. However, substrate **162h** bearing an enone functionality exhibited a higher activity than the natural product aspernomine ($IC_{50,\ aspernomine} = 11.7\ \mu M$). Hence, the study was expanded to seven additional cell lines, and satisfactory IC_{50} values between 2.40 and 4.66 μM were obtained.

4. Summary and Outlook

We have provided an overview of the reported biogenesis as well as the biosynthetic and synthetic approaches to access the hexahydro-2,6-methano-1-benzazocine framework, which is present in several natural products with cytotoxic, antibiotic, and antiviral properties.

Even though the study of nature's chemical diversity allows the discovery of bioactive entities and serves as an inspiration for the design of effective synthetic routes, so far the only published total synthesis of an alkaloid bearing the benzazocine framework is that of sespenine. Nevertheless, with the advances in natural product synthesis, synthetic strategies toward the azatricyclic core have evolved to achieve higher efficiency and applicability. Some of the most sophisticated and recent methodologies include Jia's enantioselective Pd-catalyzed intramolecular coupling of 2-haloanilines and ketone enolates and Zhou's Catellani-type annulation between aryl iodides and functionalized amination reagents. These approaches, among others, give modular and convergent access to the benzazocine framework relying on readily available substrates.

Interestingly, studies by Riva and, more recently, by our group have focused on the biological testing of several simple analogs bearing the benzazocine core, confirming the antibiotic and cytotoxic properties of the ring system. However, despite the promising results obtained to date, the scarcity of precedents in this field indicates the necessity for further research in the future.

Acknowledgements

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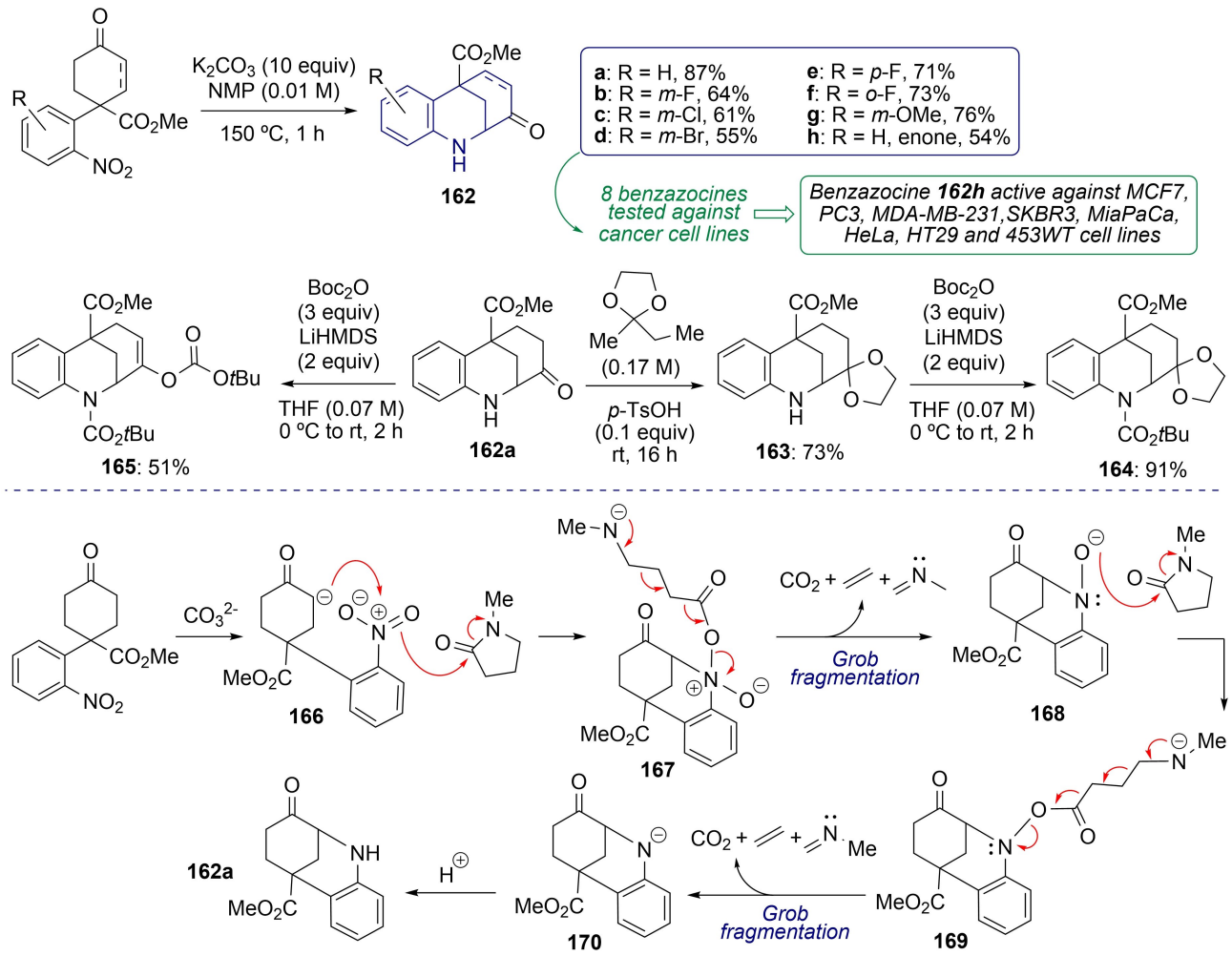

Scheme 42. Base-mediated reductive cyclization of nitrophenylketones by Bradshaw *et al.*

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: alkaloids · benzomorphan · morphinan · natural products · total synthesis

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