Recent advances in the synthesis of pyrrolo[1,2-a]indoles and their derivatives

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The pyrrolo[1,2-a]indole unit is a privileged heterocycle found in numerous natural products and has been shown to exhibit diverse pharmacological properties. Thus, recent years have witnessed immense interest from the synthesis community on the synthesis of this scaffold. In light of the ever-increasing demand for pyrrolo[1,2-a]indoles in drug discovery, this review provides an overview of recent synthesis methods for the preparation of pyrrolo[1,2-a]indoles and their derivatives. The mechanistic pathway and stereo-electronic factors affecting the yield and selectivity of the product are briefly explained. Furthermore, we have attempted to demonstrate the utility of the developed methods in the synthesis of bioactive molecules and natural products, wherever offered.

1. Introduction

Indoles are versatile structures and are present in many naturally occurring and synthetic compounds having various biological and pharmacological activities. Annulated indoles are commonly found in a large number of heterocyclic compounds having medicinal properties. Among these, the pyrrolo[1,2-a]indole family is highly pursued synthetically as they are present in biologically important molecules, such as mitomycin C (1) (Fig. 1). Mitomycins show extraordinary ability to cross-link DNA and are used as antitumor and chemotherapeutic agents. The analogue of mitomycins, 7-methoxymitosene (2), lacking the aziridine ring, has shown to be effective against Gram-positive bacteria. Melatonin analogue (3) demonstrates interesting anti-inflammatory and antinociceptive activities. Indolo-sesquiterpene alkaloids, such as polyavolensin (4) and polyavolensinol (5), are used for treating blackwater fever and stomach disorders, while isatisine (6) exhibits antimalarial properties.

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Since the 1960s, many synthesis approaches to pyrrolo[1,2-α]indoles, driven by their interesting biological activity and structural diversity, have been described. These strategies have been reviewed by Makarov,7 Voituriez,8 and Plieva.9 Makarov’s review has covered the literature on the synthesis of pyrrolo[1,2-α]indole core structures up to April 2014, while reviews by Voituriez and Plieva are dedicated to one specific isomer. Despite extensive progress in the synthesis of the pyrrolo[1,2-α]indole core (especially after 2014), no recent reviews covering the entire topic are available. Thus, a systematic review covering the synthesis strategies for pyrrolo[1,2-α]indoles, mechanistic studies, and their applications is timely and desirable.

2. Scope and organization of review

This review highlights work published since April 2014, covering up to April 2021. For earlier work on pyrrolo[1,2-α]indole analogs, we direct readers to the review by Makarov.7

The organization of this review intends to introduce themes that incorporate methods for the synthesis of pyrrolo[1,2-α]indole analogs. Based on the observed product, the review is divided into four topics, (i) 1H-pyrrolo[1,2-α]indole (10) and 10H-indolo[1,2-α]indole (11); (ii) 3H-pyrrolo[1,2-α]indole (12), 6H-isoidolo[2,1-a]indole (13), 10b,11-dihydro-6H-isoidolo[2,1-a]indole (14), 2,3-dihydro-1H-pyrrolo[1,2-α]indole (15), and 9H-pyrrolo[1,2-α]indole (16) (Fig. 2). However, the synthesis of other reduced analogs, such as 9,9a-dihydro-3H-pyrrolo[1,2-α]indoles, 9,9a-dihydro-1H-pyrrolo[1,2-α]indoles, 2,9-dihydro-3H-pyrrolo[1,2-α]indoles, and 2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-α]indoles, are not included.

Fig. 2 Structures of pyrrolo indole derivatives covered in this review.

Hence, we strive to update the reader with recent advancements in this research area.

This review article covers recent literature on the synthesis of pyrrolo[1,2-α]indole analogs, such as 1H-pyrrolo[1,2-α]indole (10), 10H-indolo[1,2-α]indole (11), 3H-pyrrolo[1,2-α]indole (12), 6H-isoidolo[2,1-a]indole (13), 10b,11-dihydro-6H-isoidolo[2,1-a]indole (14), 2,3-dihydro-1H-pyrrolo[1,2-α]indole (15), and 9H-pyrrolo[1,2-α]indole (16) (Fig. 2). However, the synthesis of other reduced analogs, such as 9,9a-dihydro-3H-pyrrolo[1,2-α]indoles, 9,9a-dihydro-1H-pyrrolo[1,2-α]indoles, 2,9-dihydro-3H-pyrrolo[1,2-α]indoles, and 2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-α]indoles, are not included.

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3. 1H-Pyrrolo[1,2-α]indole (10) and 10H-indolo[1,2-α]indole (11)

The discussion in this section will focus on the synthesis methods for derivatives of 1H-pyrrolo[1,2-α]indole (10) and 10H-indolo[1,2-α]indole (11) (Fig. 3).
3.1. Acid mediated reactions

Arylative cyclisation using diaryliodonium salts, under metal-free or metal-catalysed reactions, has emerged as a powerful technique for the construction of fused heterocycles. Copper-catalysed intramolecular arylative cyclisation of (2-cyanophenyl)indoles 17 with diaryliodonium salts 18 for the synthesis of pyrrole indole derivatives 19 has been reported by Hua and co-workers (Scheme 1).10 A plausible mechanism for this cyclisation is outlined in Scheme 1. Cu(i) species generated after reduction or disproportion of Cu(OTf)₂ undergo oxidative addition to iodonium salts 18 and generate Ph–Cu(III) intermediate 20. The cyano group of substrate 17 attacks Ph–Cu(III) species 20 to form carbocation 21, which is then trapped by indole at the 2 position to provide delocalized carbocation 22. Finally, deprotonation of 22 furnishes pyrrolo indole 19. Based on a similar idea, Zou et al. used MeOTf instead of diaryliodonium salts for alkylative cyclisation to access pyrrolo indoles.11 A metal-free variant of the intramolecular Friedel–Crafts reaction of indole–alkyl acid chloride 23 was demonstrated by Aubé and co-workers.12 Simply, dissolution of indole–alkyl acid chloride 23 in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) promoted an intramolecular Friedel–Crafts aeylation to furnish N-fused polycyclic scaffold 24 (Scheme 2). Mechanistically, in situ ionization of the acid chloride promoted by HFIP is responsible for charge separation and hence for the Friedel–Crafts reaction.

Covalently merging two bioactive pharmacophores to generate hybrid molecules proved to be a viable route to improve the bioactivity and the pharmacokinetics. Thus, hybrid molecules comprised of benzimidazole and indole/indole pharmacophores were synthesized by Lee et al. (Scheme 3).13 Pictet–Spengler-type condensation of (o-aminobenzyl)benzimidazole 25 with 2-phthalaldehydic acid (26) using catalytic AcOH under microwave irradiation delivered tetracyclic pyrrolo indole derivative 27 in good yield. The proposed mechanism for the formation of pyrrolo indole 27 is outlined in Scheme 3. At first, the addition of amine 25 to aldehyde 26 under acidic conditions gives intermediate 28, which upon dehydration provides iminium ion 29. Furthermore, protonation and proton transfer deliver intermediate 30, which undergoes tautomerisation to produce iminium ion 31. After intramolecular Pictet–Spengler reaction of iminium ion 31 and subsequent EDC mediated amide bond formation delivers pyrrolo indole 27. Zhao et al. reported a single example of pyrrolo indole synthesis using the electrophilic gold catalysed intramolecular cyclisation of indole to in situ generated allene (Scheme 4).14

![Scheme 1](image1.png)

**Scheme 1** Cu-catalysed arylative cyclisation of (2-cyanophenyl)indoles. OTf = trifluoromethanesulfonate.

![Scheme 2](image2.png)

**Scheme 2** Metal-free intramolecular Friedel–Crafts reaction of acid chloride. HFIP = hexafluoro-2-propanol.

![Scheme 3](image3.png)

**Scheme 3** Pictet–Spengler-type condensation of (o-aminobenzyl)benzimidazole with 2-phthalaldehydic acid. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodimide.

![Scheme 4](image4.png)

**Scheme 4** Gold catalysed intramolecular cyclisation. XPhos = 2-dicyclohexylphosphino-2',4',6'-trisopropylbiphenyl.

![Fig. 3](image5.png)

**Fig. 3** 1H-Pyrrolo[1,2-a]indole and 10H-indolo[1,2-a]indole.
In the presence of a gold catalyst, indole derivative 32 underwent generation of the allene (not shown) followed by its trapping with indole to give pyrrolo indole 33 in 88% yield.

3.2. Radical cyclisation

The first example of a radical Smiles rearrangement based on ynamides for the synthesis of pyrrolo indole derivatives 34 was disclosed by Ye and co-workers (Scheme 5). The photoredox-catalysed reaction of styryl-tethered ynamides 35 with Togni’s reagent (36) (source of CF₃ radicals) initiates the Smiles rearrangement and delivers trifluoromethylated pyrrolo indole derivatives 34 in moderate to good yields. Several control experiments were conducted to elucidate the mechanism of the reaction. A standard radical clock experiment suggested the involvement of benzyl radical 37. As expected, the Smiles rearrangement was not observed after changing the protecting group on nitrogen from tosylate to mesylate. Based on these experimental observations, the mechanism was proposed, as shown in Scheme 5. In the presence of a light source, the Ir-catalyst generates CF₃ radicals from Togni’s reagent (36). The addition of a CF₃ radical to styryl-tethered ynamide 35 gives benzyl radical 37, which subsequently undergoes addition to the alkyne to deliver vinyl radical 38. Furthermore, a desulfinative Smiles rearrangement gives N-centered radical 39, which upon intramolecular cyclisation of the aromatic ring followed by oxidation furnishes pyrrolo indole 34 via intermediate 40.

A silver-catalysed two-fold C–H activation strategy for the synthesis of pyrrolo indole was described by Rao and co-workers (Scheme 6). The intramolecular oxidative coupling of the aldehyde C–H and the C–H at the 2 position of the indole moiety of N-(2-formylaryl)indoles 41 in the presence of AgOMs and oxone in dioxane:DCE at 100 °C delivered pyrrolo indole derivatives 42 in moderate to excellent yield. A radical trapping experiment using TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) indicates the involvement of a radical intermediate.

3.3. Transition metal-catalysed reactions

In this section, transition metal-catalysed transformations, involving non-radical intermediates, for the synthesis of pyrrolo[1,2-a]indoles have been collated.

Similar to Rao’s report (cf. Scheme 6), a double C–H bond activation strategy based on a palladium-catalysed intramolecular CDC (cross dehydrogenative coupling) reaction was explored by Roy and co-workers (Scheme 7). Exposure of oxime derivatives 43 to Pd(OAc)₂ and K₂S₂O₈ in refluxing toluene led to good yields of pyrrolo indole derivatives 44.

In 2016, Ramana and co-workers disclosed an efficient synthesis of pyrrolo indole 45 using a copper-catalysed, one-pot, three C–N bond formation methodology (Scheme 8). The tetracyclic pyrrolo indolone core of 45 could be accessed from 2,2′-bis-bromochalcones 46 using a Cu-catalysed process involving the formation of a C–N bond by SNAr with an azide, azide to nitrene conversion and its insertion into the C–H bond to give the indole and finally the third C–N bond is formed by an intramolecular Ullmann reaction, thus leading to the formation of 45. Starting precursors, 2,2′-bis-bromochalcones 46,
were obtained in excellent yields through the aldol reaction of 1-(2-bromophenyl)ethan-1-ones 47 and bromo benzaldehyde derivatives 48.

Palladium-catalysed annulation reactions featuring the construction of C-N and C-C bonds in one-pot for the synthesis of pyrrolo[1,2-a]indoles 49 was reported by Dethe and co-workers (Scheme 9).19 In this approach, the treatment of 2-acyl indoles 50 with internal alkyne esters 51 in the presence of a palladium catalyst led to good yields of pyrrolo[1,2-a]indoles 49. This method is quite general with a broad substrate scope. Additionally, it was noticed that in CDCl 3, pyrrolo indole derivatives 49 were converted into the corresponding more stable derivatives 52 via dehydration. A plausible mechanism for this annulation is outlined in Scheme 9. The authors proposed two reaction pathways for the generation of vinyl Pd complex 53, an intermediate in the reaction mechanism. In path A, initial activation of alkyne ester 51 with the Pd catalyst triggers attack of the acyl indole on Pd-bound alkyne ester 54, to generate vinyl-palladium complex 53. Alternatively, palladium intermediate 55 with a N-Pd bond is formed from acyl indoles 50 in the presence of Cs2CO3 and Pd(OAc)2 (path B). This palladium intermediate 55 undergoes syn addition to alkyne ester 51 to produce vinyl-palladium complex 53. Intramolecular insertion of vinyl-palladium complex 53 into the carbonyl group furnishes intermediate 56, which upon protodepalladation gives pyrrolo indole derivative 49.

A single example of pyrrolo indole synthesis based on a “rollover” pathway is described by Shibata et al. (Scheme 10).20 Rollover reactions are observed with cyclometalated complexes, where rotation of a single bond induces a change in coordination from the metal–nitrogen bond to a metal–carbon bond.

The reaction of 3-alkynyl-2-indolylpyridine 57 with Rh(III) catalyst and sodium pivalate (cat.) in xylene at 120 °C led to tetracyclic pyrrolo indole derivative 58 in good yield. Mechanistically, it was speculated that the reaction involved steps like Rh(III) catalysed C–H bond activation, rollover, alkyne insertion, and protonation. The Ru–carbene catalysed ring-closing metathesis reaction was also used in the synthesis of 1H-pyrrolo[1,2-a]indoles derivatives.21

An elegant synthesis of pyrrolo indole derivatives 59 based on the Rh-catalysed [4 + 1] annulation reaction between aroyl sulfoxonium ylides 60 and anthranils 61 was described (Scheme 11).22 Electron donating substituents on aroyl sulfoxonium ylides 60 gave the corresponding products in good yield, while electron-deficient ones failed to give the required product. To better understand the reaction mechanism, a
variety of control experiments were carried out. 2,6-Dimethylbenzoyl sulfoxonium ylide did not give the corresponding product under optimized conditions. A deuterium labelling experiment proved that cleavage of the C–H bond was reversible. No D-incorporation was observed after using CH₃CO₂D instead of CH₃CO₂H under optimized conditions. Based on these experimental observations, the proposed mechanism is delineated in Scheme 11. First, generation of an active catalyst, followed by directed C–H activation furnishes five-membered rhodacycle 62. Binding and insertion of anthranils 61 into rhodacycle 62, generates metal nitrene complex 63. Migratory insertion with the formation of a C-N bond results in equilibrated six-membered rhodacycles 64 and 65. The release of DMSO produces Rh–carbenoid species 66, which then undergoes N–H bond insertion to give intermediate 67. Furthermore, protonation with AcOH releases intermediate 68 and the Rh catalyst for the next catalytic cycle. Finally, product 59 is liberated by an intramolecular aldol condensation reaction of 68 via intermediates 69 and 70.

4. 3H-Pyrrolo[1,2-a]indole (12), 6H-isooindolo[2,1-a]indole (13), and 10b,11-dihydro-6H-isooindolo[2,1-a]indole (14)

In this section, strategies for the preparation of derivatives of 3H-pyrrolo[1,2-a]indole (12), 6H-isooindolo[2,1-a]indole (13), and 10b,11-dihydro-6H-isooindolo[2,1-a]indole (14) are covered (Fig. 4).

4.1. Radical cyclisation

In 2018, Shan et al. reported an elegant approach based on a transition metal-free intramolecular C–H arylation reaction (Scheme 12). The reaction of N-(2-iodobenzyl)indoles 71 with t-BuOK and 1,10-phenanthroline in chlorobenzene at 90 °C

![Scheme 12](Image)

provided rapid and versatile access to pyrrolo indoles 72 in moderate to excellent yields. The reaction showed that a broad substrate scope and variety of substituents having different electric and steric properties were compatible. Especially, chloride, fluoride, and bromide substituents are tolerable, though a competing dehydrohalogenation reaction was also observed to some extent. Radical trapping experiments with TEMPO revealed a radical pathway.

In 2018, Gharpure and co-workers disclosed an efficient, cascade thyl radical cyclisation of N-propargyl indoles 73a and 73b for the synthesis of N-fused indoles 74 and indoline derivatives 75 (Scheme 13).24 Primary and secondary propargyl indole derivatives 73a delivered N-fused indoles 75, while tertiary propargyl indoles 73b provided access to pyrrolo[1,2-a]indole derivatives 74. The substituents present at the carbon next to the nitrogen of indole have a profound effect on the efficiency of the reaction. The observed order of N-propargyl indoles for the reaction rate and yield of the corresponding products is tertiary > secondary > primary. Thus, the “Thorpe–Ingold effect” was observed in this cascade radical cyclisation. Elaboration of the products on the core of the putative structure of yuremamine 76 and indoline 77 bearing five contiguous stereocenters highlights the synthetic utility of the method.

Along similar lines, Qing and co-workers reported a AgSCF₃ mediated trifluoromethylthiolation and cyclisation of N-[3-aryl]propioylo]indoles to construct pyrrolo indoles bearing –SCF₃ groups.25

4.2. Transition metal-catalysed reactions

An efficient and general strategy for the synthesis of pyrrolo indolones 78 using a Cp*Co(Ⅲ) catalysed alkenenylation/annulation sequence was described by Kanai and co-workers (Scheme 14).26 When carbamoyl indoles 79 were reacted with alkenes 80 in the presence of the Cp*Co(Ⅲ)-catalyst, they underwent C-2-selective indole alkenenylation, followed by annulation to furnish N-fused indoles 78 in good yields. Interestingly, the concentration of the reaction mixture and N-carbamoyl moiety are critical for obtaining the desired alkenenylation/annulation product over the undesired alkenenylation/protonation product. Various alkenes including those
with aryl/alkyl, diaryl, ester, and silyl ether substituents were tolerated, and corresponding annulation products 78 were obtained in good yields. However, terminal alkynes and dialkyl-substituted alkynes gave only alkenylation products. A plausible mechanism is outlined in Scheme 14. Initially, active monocationic species 81 is generated from [Cp*RhCl2(C6H6)]−(PF6)2 by thermal dissociation and ligand exchange to acetate. Then, N-carbamoyl directed C–H functionalization at the C-2 position of indole gives intermediate 82, which upon alkyne insertion produces Co-alkenyl complex 83. Finally, annulation with the release of morpholine furnishes product 78, and active catalyst 81 enters the next catalytic cycle. Another example of the alkenylation/annulation approach, employing [RuCl2(p-cymene)]2 as the catalyst and N-ethoxycarbamoyl as a directing group, was developed by Liu and co-workers.27

In 2017, Park and co-workers reported a regiodivergent intramolecular hydroarylation of N-alkynyldihaloindoles 84 for the synthesis of polycyclic N-fused indoles 85 (Scheme 15).28 In the presence of Pd(OAc)2, N-alkynyldihaloindoles 84 underwent cross dehydrogenative coupling (CDC) of the C–H bond of olefin and the N–H bond of indole to afford N-fused indoles 87. Interestingly, using [Cp*RhCl2]2 as the catalyst gave C-fused indoles (not shown) via the CDC reaction of the C–H bond of olefin and the C–H bond at the indole 3 position. A variety of substituents, such as alkyl, halides, and OMe, on the indole and phenyl ring, were tolerated under standard reaction conditions. With respect to the olefin partner, various acrylates and phosphonates underwent the C–H/N–H CDC reaction smoothly to provide the corresponding products in good yields. However, nonactivated alkenes, such as styrene, failed to give the required product.

In 2018, the same group reported the Rh-catalysed cascade C–H activation/aza-Michael reaction of 2-aryl-1H-indoles and acrylates to access pyrrolo indole derivatives.30

In 2017, Zhang et al. described a Pd-catalysed intramolecular oxidative aminooarylation of alkenes 88 for the enantioselective synthesis of fused indoles 89 bearing a quaternary stereocenter (Scheme 16).31 Here, quinoline–oxazoline ligand 90 was used as a chiral ligand for asymmetric induction (Scheme 17).32 Interestingly, using [Cp*RhCl2]2 as the catalyst gave 5-fused indoles (not shown) via the CDC reaction of the C–H bond of olefin and the C–H bond at the indole 3 position. A variety of substituents, such as alkyl, halides, and OMe, on the indole and phenyl ring, were tolerated under standard reaction conditions. With respect to the olefin partner, various acrylates and phosphonates underwent the C–H/N–H CDC reaction smoothly to provide the corresponding products in good yields. However, nonactivated alkenes, such as styrene, failed to give the required product.

In general, based on the proposed mechanism for the intramolecular arylation of indole, the intermediates involved in the catalytic cycle are shown in Scheme 18. Initially, the oxidative addition of Pd(0) to the aryl halide affords aryl–Pd complex 91, which upon coordination with the indole double bond followed by migratory insertion generates benzylic Pd(n)-

**Scheme 14** Co-catalysed alkenenylation/annulation reaction of carbamoyl indoles and alkynes.

**Scheme 15** Pd-catalysed intramolecular hydroarylation of N-alkynyl-2-phenyl indoles.

A catalyst-controlled, regioselective C–H functionalization of ortho-alkenyldihaloindoles 86 was described by Huang and co-workers (Scheme 16).33 In the presence of Pd(OAc)2, ortho-alkenyldihaloindoles 86 underwent cross dehydrogenative coupling (CDC) of the C–H bond of olefin and the N–H bond of indole to afford N-fused indoles 87. Interestingly, using [Cp*RhCl2]2 as the catalyst gave C-fused indoles (not shown) via the CDC reaction of the C–H bond of olefin and the C–H bond at the indole 3 position. A variety of substituents, such as alkyl, halides, and OMe, on the indole and phenyl ring, were tolerated under standard reaction conditions. With respect to the olefin partner, various acrylates and phosphonates underwent the C–H/N–H CDC reaction smoothly to provide the corresponding products in good yields. However, nonactivated alkenes, such as styrene, failed to give the required product.

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**Scheme 16** Pd-catalysed C–H/N–H functionalization of ortho-alkenyldihaloindoles. DMAP = 4-dimethylaminopyridine.
This intermediate 92 contains synthetically useful stereochemical information. The fate of benzylic Pd(II)-complex 92 is pivotal in determining the outcome of the reaction, which can be broadly divided into three types. In the first type, re-aromatization gives indole 93, which is called the C–H arylation of indole (or Heck type cyclisation). In the second type, intermediate 92 undergoes protonation or hydrogen migration followed by reductive elimination to produce indoline 94. In general, this transformation is referred to as a reductive Heck type cyclisation. In the third type, the stereochemical information of intermediate 92 is retained by using it in a further transformation, leading to indoline 95.

Intramolecular Heck-type cyclisation has proved to be a powerful method for the synthesis of N-fused indoles. In 2014, Laha and co-workers demonstrated a Pd-catalysed domino N-benzylation/intramolecular C–H arylation of indoles with 2-bromobenzyl bromide to access the N-fused indole derivatives in good yields. Moreover, Signori et al. used Pd nanoparticles in an aqueous medium for the intramolecular C–H arylation of aryl iodide. A single example of Pd-catalysed C(sp2)–H arylation for the synthesis of N-fused indole, using tri(cyclohexylmethyl) acetic acid as an efficient ligand, was described by Tanji et al.

In 2017, Gu and co-workers reported a Pd-catalysed, atroposelective C–H arylation reaction employing TADDOL derived phosphoramidite ligand 96 (Scheme 19). Various iodoindoles 97 having substituents on the indole ring, an aryl ring bearing iodide, and substituents on the naphthalenol ring were examined, with the reaction giving products 98 in excellent yields with good enantioselectivities, irrespective of substituent present. However, substrates with an electron-rich indole ring provided the corresponding products in comparatively low yields. Based on X-ray crystal structure analysis and thermal racemization studies, it was concluded that the indole-based atropoisomers had relatively low rotation barriers (energy barrier for racemization = 31.3 kcal, half-life = 67 h at 90 °C, for compound 99).

The one-step synthesis of substituted N-fused indole derivatives 100 via the sequential intramolecular Heck reaction of dihalo N-allyl N-arylbenzamide derivatives 101 was reported by Pal and co-workers (Scheme 20). The reactivity difference between the two halides present in dihalide precursor 101 was the key to the success of this reaction. Promising antiproliferative properties shown by the synthesized N-fused indoles 100 against several cancer cell lines indicated the expediency of this method.

In 2015, Laha and co-workers demonstrated an efficient synthesis of heterobiaryl sultams 102a (X = SO2) and isoindolo[2,1-a]indoles 102b (X = CO, CH2), employing a Pd-catalysed intramolecular oxidative coupling reaction (Scheme 21). Under standard reaction conditions, N-arylsulfonyl indoles 103a (X = SO2) and N-benzoyl/N-benzylindoles 103b (X = CO, CH2) were obtained.
CH$_3$) underwent the oxidative coupling involving double C(sp$^2$)–H bond activation to deliver heterobiaryl sultams 102a ($X = SO_2$) and isoindolo[2,1-$a$]indoles 102b ($X = CO, CH_2$), respectively. Similarly, Gao et al. used a Pd(II)-catalysed intramolecular oxidative Heck reaction of N-indolylole thiazole to produce a thiazole-fused pyrrolo indole derivatives bearing C-2aza quaternary centre and C-3 exo double bond.$^{40}$

In 2016, Douki et al. achieved the first enantioselective total synthesis of (+)-hinckdentine A (104), employing the Pd-catalysed intramolecular dearomative Heck reaction as a key step (Scheme 22).$^{41}$ The reaction of tetrahydrocarbazole derivative 105 having a tethered phenyl iodide under Pd-catalysis, in the presence of Feringa’s phosphoramidite ligand 106, delivered product 107 in excellent yield and enantioselectivity. Furthermore, the pentacyclic scaffold was transformed into (+)-hinckdentine A (104). The scope of this Pd-catalysed intramolecular dearomative Heck reaction was extended by Jia and co-workers, to aryl iodides/triflates bearing the C–C double bond of indoles, benzofurans, pyrroles, and furans to access spiro- and benzo-fused heterocycles with quaternary stereocenters.$^{42}$

Recently, Jia’s group also demonstrated the Pd-catalysed domino Larock cyclisation/dearomative Heck reaction to afford pyrrolo indoline derivatives 108 (Scheme 23).$^{43}$ First, the Larock annulation of N-(2-bromo-aroyl)-indoles 109 with alkynes 110 under optimized reaction conditions, gave indole derivatives 111, which subsequently, in the same pot, underwent the intramolecular Heck reaction to provide indolines 108 in moderate to excellent yields.

Despite several reports on the Heck reaction at the C2 position of indole developed over the last decade, the enantioselective variant has been comparatively underexplored.

In 2015, Jia and co-workers used [R]-BINAP (112) as a chiral ligand for the Pd-catalysed enantioselective reductive Heck reaction of N-(2-bromo-aroyl)-indoles 113, delivering chiral pyrrolo indoles 114 in good yields and enantioselectivities (Scheme 24).$^{44}$ The substrate scope of the transformation was investigated by varying the substituents on indole (R/R1) and the bromo bearing phenyl ring (R2). The substrates with alkyl, ester, and para-substituted aryl groups efficiently underwent the reductive Heck reaction to afford the corresponding products in good yields and enantioselectivities. However, substrates with meta/ortho-substituted aryl groups at the C2 indole delivered the corresponding products in low yields and enantioselectivities, indicating the negative effect of steric hindrance.

The first Ni-catalysed enantioselective intramolecular reductive Heck cyclisation of N-(o-chloroaryl)-indole 115 to access chiral pyrrolo indolines 116 in the presence of chiral Pfaltz’s semicorrin ligand 117 was reported by Zhou and co-workers (Scheme 25).$^{45}$ Mechanistically, the authors proposed that in
the last step of the catalytic cycle, direct protonation converts the C–Ni bond into a C–H bond, while in Jia’s approach (cf. Scheme 24), hydride donation followed by reductive elimination is responsible for the same result.

The stereochemical information carried by benzylic Pd(II) complex 92 (cf. Scheme 18) was retained by trapping it with various groups such as cyanide, alkyne, vinyl, aryl, heteroaryl, iodide, and cyano olefins in an intramolecular fashion to access bis-functionalized indole derivatives.

In 2015, Lautens and co-workers demonstrated the Pd-catalysed diastereoselective bis-functionalization of the indole double bond via an arlycyanation reaction of N-(o-bromobenzoyl)indoles 118 to deliver cyanated indolines 119 (Scheme 26). Here, Zn(CN)₂ and D₂I were used as a cyanide source and ligand, respectively. The choice of solvent and concentration of the reaction mixture are critical to avoid epimerization at the carbon-bearing CN group. Recently, the same group also described the Ni-catalysed diastereoselective dearomative carboiodination reaction of N-(o-iodobenzoyl) indoles to gain access to N-fused indolines bearing benzylic iodide.

Furthermore, the authors studied Pd-catalysed diastereomeric syn-selective 1,2-diarylation using the arylation/Suzuki reaction of N-(o-bromobenzoyl)indoles with aryl boroxines as an aryl group source. The arylation/heteroarylation sequence was also utilized for the diastereoselective bis-functionalization of indoles.

Termination of benzylic Pd-complex 92 (cf. Scheme 18) by a decarboxylative alkylation reaction was reported by Chen et al. (Scheme 27). When N-(o-bromobenzoyl)indoles 120 were reacted with alkynyl carboxylic acids 121 under standard reaction conditions, intramolecular arylation of the indole followed by decarboxylative alkylation delivered N-fused indolines 122 in moderate to excellent yields and diastereoselectivities. The scope and limitation of the reaction were investigated by varying substituents at the indole ring and the alkynyl carboxylic acids. Electron rich alkynyl carboxylic acids gave a better yield of the product compared with electron-deficient ones. Like Lautens’s method (cf. Scheme 26), the substrate without the C-2 substituent at the indole ring provided a low yield of the product.

In 2016, Jia and co-workers reported the bis-functionalization of indole via a domino Heck/Sonogashira sequence for the diastereoselective synthesis of 2,3-disubstituted indolines bearing vicinal tertiary and aza-quaternary centers. Furthermore, the enantioselective variant of this reaction was developed by employing BINOL based chiral phosphoramidite ligand 123 (Scheme 28). Under optimized conditions, a range of N-(o-bromobenzoyl)indole derivatives 124 were reacted with terminal alkynes 125 to provide 2,3-disubstituted indolines 126 in excellent enantio- and diastereoselectivities.

Recently, the same group achieved a Pd-catalysed dearylation arylyphosphorylation reaction, in which the benzyl-Pd complex 92 (cf. Scheme 18) was trapped with dialkyl phosphate to access the phosphorylated indolines. Termination of benzyl-Pd complex 92 (cf. Scheme 18) with a carbene precursor, such as N-arylsulfonylhydrazones 127, to synthesize N-fused indolines 128 bearing a 1,1-disubstituted alkene at the 3 position was reported (Scheme 29). A variety of N-(o-iodobenzoyl)indoles 129 and N-tosylhydrazones 127 were tested under optimized conditions to deliver vinylated products 128 in good to excellent yields. Interestingly, contrary to other arylation bis-functionalizations of indoles, steric hindrance around the aryl iodide has not significantly affected the yield of the product.
Pd–benzyl complex 92 (cf. Scheme 18) generated after intramolecular arylation of 130 was carbonylated using CO and nucleophiles 131 (alcohols and anilines) and a series of N-fused indolines 132 having an ester/amide functionality at the 3 position were prepared in moderate to good yields and diastereoselectivities (Scheme 30). 56 Several side reactions, leading to by-products such as 133–135, were responsible for the moderate yield of the products. Hence, the choice of ligand, base, CO pressure, and temperature is critical for good yields. The authors proposed that the reaction proceeded via acyl–palladium intermediate 136 generated after coordination and insertion of CO with Pd–benzyl complex 92 (cf. Scheme 18). Furthermore, the attack of nucleophiles 131 on acyl–palladium intermediate 136 led to products 132.

In 2019, Guo, Fan, and co-workers described a Rh-catalysed oxidative spiroannulation of 2-arylindoles 137 with benzoquinones 138 for the efficient synthesis of spirocyclic pyrrolo indolones 139 (Scheme 31). 57 Under optimized reaction conditions, substrates 137 with methyl or aryl substituents at the 3 position of indole underwent spiroannulation smoothly to deliver the corresponding products 139 in good yields.

The Pd-catalysed carbynylative reaction employing carbon monoxide (CO) as a cheap and abundant C1 source denotes an efficient and economical strategy for the introduction of a carbonyl group into the product. 58 Similarly, the synthesis of pyrrolo indolone derivatives having a lactam functional group was commonly achieved using a cyclocarbonylative reaction involving the formation of C–C and C–N bonds.

In 2016, Cho and co-workers demonstrated the Pd-catalysed carbonylative cyclisation of 2-(2-bromoaryl)-1H-indoles 140 under CO pressure to afford pyrrolo indolone derivatives 141 in good yields (Scheme 32). 59 Interestingly, it was observed that the product yield was increased after increasing the CO pressure from 5 atm to 10 atm. However, substrate scope studies revealed that the yield was not significantly affected by the sterical and electronic nature of substituents on the indole ring.

Along similar lines, Fan and co-workers also studied the palladium-catalysed cyclocarbonylation of 2-(2-bromoaryl) indoles 140 under atmospheric CO pressure. Both N- and C-fused indoles were regioselectively synthesized using N-unsubstituted indoles and N-substituted indoles as starting precursors, respectively. 60 A very similar approach, by changing the halide coupling partner from bromide to iodide, was further explored by Huang and co-workers. 61 This method displays a broad substrate scope compared with Fan’s approach. Aryl tosylates could also be used as electrophiles in the Pd-catalysed cyclocarbonylative reaction to access 6H-isoidolo[2,1-a] indol-6-ones. 62 In 2016, Huang et al. published a carbonylative cyclisation involving Rh-catalysed indole NH directed C–H bond activation for the efficient synthesis of 6H-isoidolo[2,1-a]indol-6-ones. 63 Under similar reaction conditions, glyoxylic acid was used as a CO source for the synthesis of N-fused indole derivatives. 64

Zhu and co-workers demonstrated the synthesis of pyrrolo indolones 142, employing tert-butyl isocyanide 143 as a C1 building block, like carbon monoxide (CO). 65 As shown in Scheme 33, under optimized conditions, the treatment of 2-(2-bromophenyl)-1H-indoles 144 with tert-butyl isocyanide (143) produced imines 145, which upon acid hydrolysis furnished...
pyrrolo indolones 142. Various aryl bromides bearing electron-donating and withdrawing groups were tested, resulting in moderate to excellent yield of the corresponding products.

4.3. Miscellaneous transformation

Domino intramolecular hypervalent iodine(III) catalysed C–N and C–C bond formation in a single step for the synthesis of N-fused indoles 146 was reported by Dev et al. (Scheme 34).66 Intramolecular oxidative cyclisation of 2-(1-arylethynyl)benzamides 147 in the presence of PIDA (phenyliodonium diacetate) furnished pyrrolo indole derivatives 146 in good yields.

5. 2,3-Dihydro-1H-pyrrolo[1,2-a]indole (15)

In this section, the synthesis of 2,3-dihydro-1H-pyrrolo[1,2-a]indole (15) and its derivatives are discussed (Fig. 5).

5.1. Acid mediated reactions

The Lewis acid-catalysed highly stereo- and regioselective formal [3 + 2] cycloaddition reaction between tertiary alcohol 148 and olefin 149 for the synthesis of pyrrolo[1,2-a]indole 150 was reported by Dethe and co-workers (Scheme 35).67 Tertiary alcohol 148 upon treatment with Cu(OTf)2/BF3·OEt2, underwent dehydration to form intermediate 151, which upon formal [3 + 2] cycloaddition with olefin 149 delivered N-fused indole 150 in good yields. Interestingly, Cu(OTf)2 provided products with excellent diastereoselectivity, favouring the cis-isomer, presumably due to transition state 151 with coordination of copper to the –SO2Ph group of one indole unit and nitrogen of the other unit. The authors did not observe any [4 + 2] cycloaddition products. The potential of the method was highlighted in the first total synthesis of isomeric natural products flinderoles B (8) and C (9).

May and co-workers demonstrated that similar intermediates 149 and 151 could be generated by acid-mediated ring-opening of borerine derivative 153 (cf. Scheme 36) and furthermore, these intermediates were used in the total synthesis of flindersial alkaloids.68

Similarly, in 2014, Dethe’s group used the dimerization of borerine derivative 153 to achieve an efficient total synthesis of flinderole A (7) and desmethyl flinderole C (154) (Scheme 36).69 TFA mediated opening of the dihydropyridine ring of compound 153 generated an extended iminium ion (not shown), which upon formal [3 + 2] cycloaddition reaction with another molecule afforded a chromatographically separable mixture of diastereomers 155 and 156 (dr = 4 : 5).
Diastereomers 155 and 156 were separately subjected to LAH reduction to furnish flinderole A (7) and desmethyl flinderole C (154) in good overall yields. Here, products 155 and 156 are easily separated by column chromatography, while, in the case of May’s approach, HPLC purification is required.

Based on the approach shown in Scheme 36, the same group developed a Cu(OTf)$_2$ catalysed [6 + 2] cycloaddition reaction to access pyrrolo[1,2-$a$]indole derivatives 157 bearing three contiguous stereocenters (Scheme 37).$^{70}$ Substituted indolyl alcohols 158 in the presence of catalytic Cu(OTf)$_2$ generated 2H-methide-2H-indoles 159, which upon [6 + 2] cycloaddition reaction with $\alpha,\beta$-unsaturated esters/nitriles 160 furnished N-fused indole derivatives 157 in good yields and excellent diastereoselectivities. The reaction showed a broad substrate scope and a variety of substituents having different steric and electronics were tolerated under optimized reaction conditions. The method was extended to the synthesis of optically active pyrrolo indoles using $\alpha,\beta$-unsaturated esters/nitriles 160 ($R^3 = \text{CO}_2X; X = \text{chiral auxiliary}$) having a chiral auxiliary. Out of the chiral auxiliaries screened, (−)-$\epsilon$-ethyl lactate gave the corresponding product in the highest diastereomeric excess (de > 96%).

An asymmetric variant of this cycloaddition reaction for accessing chiral N-fused indole derivatives 161 and 162 was developed by Schneider and co-workers (Scheme 38).$^{71}$ Chiral BINOL–phosphoric acids 163 and 164 were used as Brønsted acids for the in situ generation of 2H-methide-2H-indoles 159 (cf. Scheme 37). The cycloaddition reaction of 2H-methide-2H-indoles 159 with 2-vinyl indoles 165 as well as with cyclic enamides 166 afforded $N$-fused indole derivatives 162 and 161, respectively, with three contiguous stereocenters in good diastereoselectivity and enantioselectivity. Here, alkyl-substituted indol-2-yl carbinols 167 ($R^2 = \text{alkyl}$) gave lower yields of the products compared with those with aryl substituents. This was attributed to the lack of extra $\pi$-conjugation, resulting in the decomposition of the 2H-methide-2H-indole intermediate. Based on control experiments, it was proposed that a well-organized transition state through hydrogen bonding of substrates with the catalyst was responsible for chiral induction. Free N–H groups within 2-styryl indoles 165 and cyclic enamides 166 play a pivotal role in successful activation through hydrogen bonding.

In 2016, Rodríguez and co-workers reported an enantioselective synthesis of pyrrolo[1,2-$a$]indoles 168 by employing chiral sulfonamide ($R$)-169 catalysed coupling of indole-2-carbaldehydes 170, amines 171, and enol ethers 172 (Scheme 39).$^{72}$ The chiral Brønsted acid-catalysed formal [3 + 2] cycloaddition reaction of the imines formed in situ from aldehydes 170 and amines 171, with enol ethers 172, gave various pyrrolo[1,2-$a$]indole derivatives 168 in moderate to good yields and enantioselectivities. Enol ethers, other than dihydrouran 172, like butyl vinyl ether or dihydropyran, were not compatible with the reaction.

Shi and co-workers revealed the Bronsted acid catalysed [3 + 2] cyclodimerization of 3-alkyl-2-vinyl indoles 173, which led to the diastereoselective synthesis of pyrrolo indole frameworks 174 in high yields (Scheme 40).$^{73}$ The authors also developed an asymmetric variant of this reaction, using...
chiral BINOL–phosphoric acid as a catalyst, and a series of pyrrolo indoles were synthesized in a highly diastereoselective and enantioselective fashion (dr > 95:5, er = 98:2).74

The diastereoselective synthesis of tricyclic indole derivative 175 using the [3 + 2] cycloaddition reaction of metal-containing azomethine ylide 176 with activated alkene 177 was described by Iwasawa and co-workers (Scheme 41).75 When N-(o-alkynylphenyl) imine derivative 178 was reacted with PtCl2, intramolecular cyclisation of the imine with the activated alkyne generated azomethine ylide 176. Cycloaddition of metal-containing azomethine ylide 176 with vinyl ether 177 gave tricyclic metal carbenoid 179, which upon 1,2-alkyl migration furnished pyrrolo[1,2-a]indole 175 in good yield. The synthetic utility of the method was demonstrated in the 14-step total synthesis of the putative structure of yuremamine (180).76

Along similar lines, the regioselective intermolecular [3 + 2] annulation of platinum-bound azomethine ylide 176 (cf. Scheme 41) with N-allenamides 181 for the synthesis of pyrrolo[1,2-a]indoles 182 was studied by Patil and co-workers (Scheme 42).77 The distal C–C bond of N-allenamides 181 participated in cyclisation, leaving the proximal C–C bond intact. The reaction showed a broad substrate scope with respect to N-allenamides 181 and imino alkynes 183 having an aromatic ring attached to the alkyne (R1 = aryl) and gave desired products 182 in good yields. It was found that the strategy was not viable for substrates bearing a terminal alkyne (R2 = H) and an alkyl-substituted alkyne (R1 = alkyl).

Zhang and co-workers developed the Pt-catalysed cycloisomerization of N-(2-alkynylphenyl) lactams 184 to form N-fused indoles 185 (Scheme 43).78 From a mechanistic point of view, it was proposed that this reaction involved three major steps: i. intramolecular attack of the tertiary nitrogen of lactam 184 on the activated alkyne to generate Pt-containing azomethine ylide 186; ii. 1,2-acyl migration in azomethine ylide 186 to generate metallocarbenoid moiety 187; and iii. 1,2-migration of the R1 group to the metallo-carbene, resulting in the formation of N-fused indole derivative 185. The developed strategy was further used to synthesize analogues of mitomycin A and C.79

Intramolecular C–H insertion of in situ generated gold carbenoid for the synthesis of pyrrolo indolone derivatives 188 was described (Scheme 44).80 A series of terminal propargyl indoles 189 were reacted with the Au-catalyst in the presence of N-oxide 190 in DCE at 60 °C to furnish pyrrolo indolones 188. The reaction scope is quite broad and a variety of electron-donating and withdrawing substituents, and halides are tolerated under the reaction conditions.

In 2019, Liu and co-workers revealed an efficient approach based on organocatalytic conjugate addition and intramolecular trapping of an oxocarbenium ion (Scheme 45).81 In the presence of TMS protected prolinol 191 and benzoic acid, conjugate addition of hemiacetal 192 on an indole containing nitroolefin (193) delivered an indole having a hemiacetal (194) in a highly enantio- and diastereoselective manner. p-Toluenesulfonic acid (p-TsOH) mediated generation of oxo-
carbenium ion 195 and its N-alkylation, provided access to polycyclic pyrrolo indole derivatives 196. One-pot N-alkylation with an oxonium ion and indole C-3 functionalization (when \( R^1 = H \)) was also explored.

The reactivity of the N-acyliminium ion in the ring-forming reaction using alkynes as a nucleophile is underdeveloped but highly desirable for accessing novel heterocyclic compounds. In 2015, Gharpure and co-workers reported counter anion dependent alkyne iminium ion cyclisation for the stereo-selective synthesis of N-fused indolylidine triflates 197 and pyrrolo[1,2-\( a \)]indoles 198a–b (Scheme 46).\(^7\) When \( \gamma \)-hydroxy lactam 199 was treated with neat formic acid, a series of reactions, such as alkyne–iminium ion cyclisation, trapping of the vinyl cation with formate anion, and aromatization, ensued to deliver pyrrolo[1,2-\( a \)]indole 198a in excellent yield. Interestingly, when \( \gamma \)-hydroxy lactams 200 bearing an olefin were treated with TMSOTf, the reaction exclusively provided pyrrolo[1,2-\( a \)]indoles 198b with isomerization of the double bond. It was observed that substitution on the alkynyl partner had a profound effect on the stability of the product. In general, electron-deficient and aliphatic alkynes gave poor yields of the corresponding products.

In 2017, the same group reported a Lewis/Brønsted acid-mediated, cascade Friedel–Crafts/alkyne indol-2-yl cation cyclisation/vinyl cation trapping sequence for the efficient and divergent synthesis of pyrrolo[1,2-\( a \)]indole derivatives 201 (Scheme 47).\(^8\) In the presence of TMSOTf, intermolecular condensation of \( N \)-propargyl indoles 202 and aldehydes 203 generated indol-2-yl cations, which upon cyclisation with alkynes followed by trapping of vinyl cations with OTf anions provided triflate derivatives 204. Furthermore, unstable triflates 204 were hydrolysed to ketone derivatives 201 in a diastereoselective manner. This method was found to be general with a broad substrate scope and substituents like halides, CN, heteroaryl, and free OH were compatible with the reaction conditions. However, \( N \)-propargyl indole with the OMe group at the 5 position of indole gave the product in trace amounts. Additionally, trapping of the vinyl cation with a nucleophilic group attached to the aldehyde was also explored.

The microwave-assisted intramolecular 1,3-dipolar cycloaddition reaction of azomethine imine with a tethered alkene, for an efficient synthesis of pyrazolopyrroloindoles 205 was reported (Scheme 48).\(^9\) The reaction of \( N \)-allylated indole-2-carboxaldehydes 206 with phenyl hydrazine (207) in the presence of conc. HCl and microwave irradiation provided access to a library of the pyrazolopyrroloindoles 205.

An elegant approach based on TiCl\(_4\) catalysed multiple hydrogen transfers was reported by Mori and co-workers (Scheme 49).\(^8\) The reaction of \( o \)-amino ketoesters 208, where \( R^2 = H \), with TiCl\(_4\) (cat.) in the presence of DMC (2-chloro-1,3-dimethylimidazolium chloride) (209), provided access to pyrrolo indoles 210a. DMC acts as a dehydrating agent. This process involves three hydrogen transfer events. In the case of...
o-amino ketoesters 208, where $R^2 = alkyl$, two hydrogen shifts and one alkyl group transfer with decarboxylation were observed and delivered pyrrolo indoles 210b in good yields. Here, a stoichiometric amount of TiCl4 is needed for complete conversion of the starting material. Mechanistically, the initial complexation of TiCl4 with the keto group gives intermediate 211, which upon a [1,5]-hydride shift furnishes iminium ion 212. The stability of iminium ion 212 is a key factor in determining the regioselectivity of the hydride shift. Furthermore, proton transfer delivers intermediate 213 having both electrophilic and nucleophilic sites tethered. Trapping of the iminium ion followed by the elimination of water gives extended iminium ion 214. Finally, a [1,2]-hydride shift and aromatization (when $R^2 = H$) or a [1,2]-alkyl shift, decarboxylation, and aromatization (when $R^2 = alkyl$) provided pyrrolo indoles 210a or 210b, respectively.

Strategies based on the acid or metal-catalysed Michael addition of indole to an $\alpha,\beta$-unsaturated acid, ester, or amide, followed by condensation with the nitrogen of indole are extensively used for the synthesis of pyrrolo indoles.86 One example of the organocatalytic conjugate addition of 3-methyl indole (215) and methacrylaldehyde (216), followed by Brønsted acid-mediated aminal formation with another molecule of 3-methyl indole (215) for the diastereoselective synthesis of pyrrolo indole 217 was demonstrated (Scheme 50).87

5.2. Base mediated cyclisation

In 2014, Buzard and co-workers discovered compound 218 as a novel S1P1 functional antagonist.88 The synthesis of compound 218 was achieved using the key steps shown in Scheme 51. When indole derivative 219 was heated with butyl acrylate in the presence of sodium hydride, it resulted in diester 220, which further underwent decarboxylative Dieckmann cyclisation to deliver pyrrolo indolone derivative 221.89 This pyrrolo indolone 221 was transformed into compound 218, which acts as a S1P1 functional antagonist, with favourable pharmacological properties.

5.3. Radical cyclisation

In 2017, Song and co-workers published the Ag-catalysed cascade radical cyclisation of N-cinnamamide indoles 222 with diphenylphosphine oxides 223 to produce phosphinoyl pyrrolo [1,2-α]indoles 224 (Scheme 52).90 Various N-cinnamamide indoles 222 having different substituents on the indole ring were examined, with electron-rich cinnamamides giving higher yields than electron-deficient ones. Interestingly, no desired product was detected when $R^1 = Hi n$ 222, presumably due to lower stability of the radical intermediate.

Scheme 49 TiCl4 mediated multiple hydrogen transfers of o-amino ketoesters.

Scheme 50 Domino conjugate addition/amination of 3-methyl indole and methacrylaldehyde.

Scheme 51 Synthesis of an S1P1 functional antagonist.

Scheme 52 Ag-catalysed cascade radical cyclisation of N-cinnamamide indoles with diphenylphosphine oxide.
Another efficient approach to phosphinoyl pyrrolo[1,2-\(a\)]indoles, using Eosin Y catalysed, visible light-mediated radical cyclisation of \(N\)-cinnamamide indoles with diphenylphosphine oxide, was developed by Gorre et al.\(^91\) In 2018, Cui et al. described a similar protocol using the Fe-catalysed decarboxylative radical addition/cyclisation of alkyl peresters or peroxides to \(N\)-cinnamamide indoles.\(^92\) Similar substrates, such as \(N\)-acrylamide indoles, were used in visible light-mediated 5-exo-trig radical cyclisation reactions (Scheme 53).\(^93\) In the presence of visible light and an iridium(III) sensitizer, \(N\)-acrylamides undergo singlet-to-triplet excitation to give diradicals. The 5-exo-trig cyclisation of diradical on indole followed by intersystem crossing (ISC) provides zwitterionic intermediate, which upon proton transfer produces product. Under similar reaction conditions, decarboxylative 5-exo-trig radical cyclisation was also studied for the synthesis of pyrroloindoles.\(^94\)

A novel copper(I) promoted trifluoromethylation of a tethered olefin followed by cyclisation on indole to access trifluoromethylated \(N\)-fused indoles was reported by Zhang and co-workers (Scheme 54).\(^95\) The indole derivatives with tethered olefin, upon treatment with Togni’s reagent, in the presence of catalytic amounts of copper, afforded trifluoromethylated \(N\)-fused indole derivatives. In the presence of Cu(II) salt, Togni’s reagent generates the CF\(_3\) radical species via single electron transfer (SET). This CF\(_3\) radical undergoes addition across olefin to provide trifluoromethylated radical, which upon oxidation with either Cu(II) or Togni’s reagent, furnishes carbocationic species. Finally, intramolecular trapping of the carbocation with indole followed by aromatization delivered product. Along similar lines, very recently Pagire et al. described visible-light-mediated cascade sulfonyl radical cyclisation for the synthesis of tosylated \(N\)-fused indoles.\(^96\)

Gold-catalysed, photoredox initiated free-radical cyclisation on indole was reported by Barriault and co-workers (Scheme 55).\(^97\) Excitation of the dimeric Au(I) photocatalyst was used to generate carbon-centred radicals from unactivated bromoalkanes/arenes, which further underwent cyclisation on indole to give \(N\)-fused indoles in good yields.

The Mn(III)-catalysed aerobic dehydrogenative cyclisation coupled with Yb(III) catalysed opening of donor–acceptor cyclopropane was explored by Kerr and co-workers (Scheme 56).\(^98\) The nucleophilic ring-opening of donor–acceptor cyclopropanes by nucleophilic indolines followed by oxidative radical cyclisation of the resulting pendant malonyl moiety on indole provided access to \(N\)-fused indoles. The utility of the method was highlighted by the preparation of the core structure of flinderole natural products.

In 2015, Alexanian and co-workers reported Pd-catalysed alkylative cyclisation using unactivated alkyl halides having a tethered arene or heteroarene ring (Scheme 57).\(^99\) The

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**Scheme 53** Visible light mediated 5-exo-trig radical cyclisation of \(N\)-acrylamide indoles.

**Scheme 54** Cu-catalysed trifluoromethylation reaction of \(n\)-butenyl indoles.

**Scheme 55** Au-catalysed photoredox radical cyclisation of unactivated bromoalkanes/arenes. dppm = 1,1-bis(diphenylphosphino)methane.

**Scheme 56** Mn-catalysed intramolecular aerobic dehydrogenative cyclisation.
reaction of primary and secondary N-alkyl iodides 238 with Pd (PPh3)2 and K3PO4 in dioxane at 100 °C afforded pyrrolo indoles 239 in moderate to good yields. Under standard reaction conditions with the addition of TEMPO, no C–H alkylation products 239 were detected. An enantioenriched alkyl iodide gave the racemic cyclized product. These observations suggested the involvement of radical intermediates. A kinetic isotopic study suggested that C–H bond cleavage was not the rate-determining step of the reaction. Based on these experiments, the mechanism for this alkylative cyclisation was proposed. Firstly, the single-electron oxidative addition of alkyl iodides 238 generates radical species 240, which undergo 5-exo-trig cyclisation on indole to provide delocalized radicals 241. Finally, oxidation of the radical and loss of proton affords product 239.

In 2016, Morandi and co-workers demonstrated the cobalt-catalysed intramolecular opening of epoxides and aziridines with alkenes to access homoallylic alcohols and amines, respectively.100 This developed method was applied to the synthesis of pyrrolo indole 242 (Scheme 58). The reaction of epoxy indole 243 with Co-catalyst and KOT-Bu (cat.) in MeOH under white LED irradiation provided straightforward entry to pyrrolo indole core 242. Similarly, a very efficient approach based on the Ti(III) mediated reductive epoxide opening reaction of N-tethered epoxy-indoles followed by intramolecular cyclisation was also explored.101

In 2016, Norton and co-workers studied both CpCr(CO)3H and Co(dmgBF2)2(H2O)2 complexes as a donor/acceptor of hydrogen radicals under H2 pressure (Scheme 59).102 The authors applied the Co(dmgBF2)2(H2O)2 (244) catalysed hydrogen radical transfer reaction to the synthesis of pyrrolo indoles 245 from substrate 246, in good yield. Based on control experiments, kinetic studies, and precedence from the literature, the mechanism of Co-catalysed cycloisomerization was proposed, as depicted in Scheme 59. Under the pressure of H2, the Co (dmgBF2)2(H2O)2 complex is in equilibrium with [Co–H] species, which act as a hydrogen radical source. The addition of a hydrogen radical to Michael acceptor 246 generates radical intermediate 247, which, regioselectively, in 5-exo-trig fashion attacks the tethered olefin to deliver radical species 248. Subsequent hydrogen radical elimination gives pyrrolo indole 245.

Another elegant approach to difluoroalkylated pyrrolo[1,2-a] indoles 249, utilizing an Ir-catalysed photoredox difluoroalkylation and cyclisation cascade was reported by Li and co-workers (Scheme 60).103 A mixture of N-(but-2-enoyl)indole derivatives 250 and BrCF2R3 (251) in the presence of fac-Ir (ppy)3 (photocatalyst) and Na2HPO4 (base) was irradiated to deliver difluoroalkylated pyrrolo[1,2-a]indoles 249 in moderate to good yields. Research into the [3 + 2] cycloaddition of an in situ generated azomethine ylide with an alkene has explored the synthesis of pyrrolo indole derivatives. In 2019, Casado-Sánchez et al. reported the synthesis of pyrrolo indoles 252 using dual photo- and Lewis acid catalysed diastereoselective [3 + 2] cycloaddition between silyl indoles 253 and α,β-unsaturated N-acyl oxazolidinones 254 in the presence of 255 and 256 (Scheme 61).104 Here, photocatalyst 257 is used for the gene-

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**Scheme 57** Pd-catalysed alkylative cyclisation of unactivated alkyl halides having tethered arene or heteroarene rings.

**Scheme 58** Co-catalysed intramolecular opening of epoxides with indoles. dmg = dimethylglyoxime.

**Scheme 59** The radical cyclisation of bis-olefinic indole using Co (dmgBF2)2(H2O)2 complex as a donor/acceptor of hydrogen radicals.

**Scheme 60** Ir-catalysed photoredox difluoroalkylation/cyclisation cascade.
rational of the α-amino radical from silyl indoles 253 and the Lewis acid, Yb(OTf)₃, activates α,β-unsaturated N-acyl oxazolidinones 254.

Zhang et al. reported the iridium(III) catalysed visible light photoredox generation and cyclisation of α-amino alkyl radicals 258 for the synthesis of 3-acyl N-fused indole derivatives 259 (Scheme 62). Mechanistically, it was hypothesized that α-amino alkyl radicals 258 generated from tertiary amines 260 underwent intramolecular radical addition to the C-C triple bond to produce vinyl radical 261. Subsequently, vinyl radical 261 is captured by molecular oxygen or a superoxide radical to provide vinyl peroxide 262, which upon intramolecular hydrogen abstraction furnishes 3-acyl N-fused indole derivatives 259.

Patel and co-workers also developed the metal-free domino reaction of α-alkynyl amines 263 by employing TBAI/TBHP to access 3-aryl N-fused indoles 264 (Scheme 63). When the reaction was performed under standard reaction conditions with the addition of H₂¹⁸O, the product without any ¹⁸O enriched at its carbonyl group was detected, implying that TBHP was the oxygen source for the ketone in the product.

Scheme 61. Dual photo- and Lewis acid catalysis for the [3 + 2] cycloaddition of azomethine ylide with an alkene.

Scheme 62. Ir-catalysed visible light-mediated generation and cyclisation of α-amino alkyl radicals.

Scheme 63. Metal-free, TBAI catalysed cyclisation of α-alkynyl amine. TBAI = tetrabutylammonium iodide.

5.4. Organocatalytic transformations

An intramolecular hydroacylation of α-substituted acrylates 265 on indole for the synthesis of fused indole derivatives 266 having a quaternary carbon was discovered by Xu and co-workers (Scheme 64). This transformation was facilitated by the combination of a nucleophilic tertiary amine for N-allylation and N-heterocyclic carbene (NHC) catalyst 267 for hydroacylation to afford pyrrolo indolones 266 with high levels of enantioselectivity. The reaction of indole-2-carbaldehydes 268 and MBH carbonates 269 in the presence of (DHQD)₂PHAL gave N-allylated products 265, which upon reaction with NHC catalyst 267 afforded N-fused indole derivatives 266 in good yields. The N-allylation/acylation reaction of indole-2-carbaldehyde 268 having deuterium at the aldehyde carbon with MBH carbonate 269 delivered the product, with the deuterium atom in the methyl group. Based on this experiment, the reaction mechanism was proposed as depicted in Scheme 64. Initially, the reaction of a tertiary amine with MBH carbonate 269 affords intermediate 270, which upon Sₙ₂' reaction with the anion of indole-2-carbaldehyde 268 generates allylated product 265. The reaction of free NHC 271 (generated in situ by deprotonation of 267) with intermediate 265 produces Breslow intermediate 272. Intramolecular cyclisation of Breslow intermediate 272 via 273 provides tetrahedral intermediate 274. Furthermore, tetrahedral intermediate 274 gives product 266 and catalyst 271 for the next catalytic cycle. Along similar lines, Glorius and co-workers reported one example of a chiral N-heterocyclic carbene (NHC)-catalysed, enantioselective intramolecular hydroacylation reaction of unactivated olefin substituted aldehydes to access chiral pyrrolo indoles.

In 2017, Hui and co-workers published an enantioselective synthesis of pyrrolo indole derivatives 275, employing chiral NHC catalysed Michael/aldol/lactamization cascade of enals 276 and enones 277 (Scheme 65). After testing various enals 276 and indole derived enones 277, it was observed that enals 276 with substituents at the para position of the phenyl ring gave higher diastereoselectivities compared with substituents at the meta position. A plausible mechanism for this cascade cyclisation is depicted in Scheme 65. Initially, free NHC 278, generated by deprotonation of NHC precursor 279, reacts with enal 276 to generate Breslow intermediate 280. Next, Michael addition of intermediate 280 to enone 277 delivers intermediate 281, which, after proton transfer, undergoes an intramolecular aldol reaction to produce inter-
Lastly, intramolecular lactamization with the indole nitrogen as a nucleophile furnishes product 275 and free NHC 278.

Electrophilic bromocyclisation of polyenyl indole derivative 283 for the efficient synthesis of polycyclic fused indole derivative 284 was demonstrated by Hennecke and co-workers (Scheme 66). Various electrophilic brominating agents were screened and sterically demanding bromiranium ion salt 285 with the weakly coordinating counterion BArF\(^-\), delivered required product 284 in moderate yield and excellent diastereoselectivity.

In 2016, Pavlova et al. reported a triphenylphosphine mediated domino Staudinger/aza-Wittig/Mannich reaction. The scope of this reaction was extended to the synthesis of polycyclic pyrrolo indole derivative 286 (Scheme 67).

Scheme 64  N-Allylation/hydroacylation reaction of indole-2-carbaldehydes and MBH carbonates. (DHQD)\(_2\)PHAL = hydroquinidine 1,4-phthalazinediyldiether.

Scheme 65  NHC catalysed Michael/aldol/lactamization cascade of enals and enones.

Scheme 66  Electrophilic bromocyclisation of polyenyl indole derivatives. HMDS = bis(trimethylsilyl)amine.

Scheme 67  Triphenylphosphine mediated domino Staudinger/aza-Wittig/Mannich reaction.
upon the reaction of 2-indolecarbaldehyde 287 with azide 288, in the presence of triphenylphosphine, a series of domino reactions, such as Staudinger/aza-Wittig/Mannich, followed by amideative cyclisation occurred and corresponding polycyclic N-fused indole 286 was obtained in moderate yield and diastereoselectivity.

### 5.5. Transition metal-catalysed reactions

An efficient approach to spirocyclic N-fused indoles 289, based on a Pd(0)-catalysed Heck-type carbopalladation/C–H activation cascade, was described (Scheme 68). A series of (Z)-1-iodo-1,6-dienes 290 bearing an indole ring, under optimized reaction conditions, underwent intramolecular carbopalladation followed by indole C–H activation to deliver pyrrolo indoles 289 in moderate to excellent yields. Particularly, electron-rich substrates gave better yields of the products. Furthermore, the asymmetric variant of this cascade reaction using PHOX ligands was investigated. Under optimal conditions using the (R)-p-MeO-PhHOX ligand, the corresponding product was delivered in 39% yield and 27% ee.

In 2019, Lui and co-workers described a Pd-catalysed annulation/acyl migration reaction for the efficient synthesis of N-fused indoles 291. Various enamiones 292 were heated with Pd(OAc)2 in DMSO without any ligand to afford N-fused indoles 291. Principally, the optimized reaction conditions were applied to the synthesis of pyrido[1,2-a]indoles. A single example of the synthesis of pyrido[1,2-a]indole in moderate yield was reported under microwave irradiation. The authors also developed a catalytic system based on CuI and 8-HQ (293) for achieving this annulation/acyl migration cascade (Scheme 69). A series of enamiones 292, upon heating with CuI, 8-HQ (293), and K2CO3 in DMSO, underwent intramolecular α-arylation followed by C- to N-acyl migration to provide access to N-fused indole derivatives 291. Interestingly, Cu-catalysed conditions delivered pyrrolo[1,2-a]indoles in good yields compared with Pd-catalysed conditions.

![Scheme 68 Pd-catalyzed Heck-type carbopalladation/C–H activation cascade of (Z)-1-iodo-1,6-dienes bearing an indole ring. dba = dibenzylideneacetone.](image)

![Scheme 69 Cu-catalysed annulation/acyl migration reaction of iodo aryl enamiones.](image)

In 2016, Petit and co-workers utilized a low-valent cobalt catalyst [Co(PMe3)4] for inter- and intramolecular imine-directed C-2-alkylation and alkenylation of indoles (Scheme 70). When N-homoallylic indoles 294 were reacted with the cobalt catalyst under microwave irradiation, intramolecular C-2-alkenylation of indoles proceeded to furnish pyrrolo indoles 295 in high yields and regioselectivity. Kinetic isotopic studies indicated that C–H bond cleavage was not the rate-determining step.

The amide directed, Rh(m)-catalysed indole C–H activation/ intramolecular Heck-type reaction for the synthesis of spirocyclic N-fused indoles was exhibited by Chabaud et al. Among similar lines, in 2016, Rit, Sahoo, and co-workers described a Ru-catalysed, amide directed C–H activation/ hydroarylation strategy to produce dihydrobenzofuran, indoline, chroman, and pyrrolo indole scaffolds. The Ir-catalysed, aryl directed C–H activation/alkylation sequence to access pyrrolo indoles was also explored.

A unique example of the synthesis of pyrrolo indole 296, employing a Rh-catalysed amide directed C–H activation/cyclisation of N-homoallyl indole derivative 297 was described by Glorius and co-workers (Scheme 71). Out of two possible C–H bonds, regioselectively one was activated and cyclized, suggesting equilibrium in the C–H activation step.

Recently, Guo et al. developed a Pd-catalysed cascade alkyne insertion/C–H functionalization/[4 + 2] carboannulation of alkynes to produce the tri/tetraacyclic compounds. The developed method was applied to the synthesis of pyrrolo indole derivatives 298, using N-homoallyl-3-iodo indole derivatives 299 and alkyne 300 (Scheme 72). To gain an insight into the reaction mechanism, several control experiments were conducted. Deuterium labelling studies suggested that C–H bond activation was a reversible and rate-determining step. Based on control experiments and previous reports in the literature, the mechanism was proposed, as shown in Scheme 72. Initially, the oxidative addition of Pd(0) to aryl iodide 299 produces intermediate 301, which upon coordination and insertion of...

An efficient synthesis of pyrrolo indoles 306 using a Ru-catalysed two-fold C–H activation reaction was described (Scheme 73). Under the optimized reaction conditions, when a mixture of N-acyl indole 307 and acrylate 308 was heated, activation of two C–H bonds with the formation of two C–C bonds ensued to afford pyrrolo indoles 306 in good yields and moderate diastereoselectivities. The developed method was further extended to triple C–H activation of substrates 309 for synthesizing pentacyclic N-fused indoles 310.

In 2017, Fernández et al. developed a carboxamide-assisted olefinic C–H bond activation/cyclisation sequence using a cationic Ir^I–bisphosphine catalyst (Scheme 74). Under Ir-catalysis, α,β-unsaturated amides 311 having a tethered N-allylic, exocyclic olefin underwent initial C–H activation, then exo-cyclisation to provide pyrrolo indoles 312 in excellent yields, albeit in poor E/Z ratio.

Recently, Grover and co-workers published an efficient synthesis of pyrrolo indoles 313 using the tandem C–H functionalization/Conia ene reaction of N-propargylic indoles 314 and α-diazomalonates 315 (Scheme 75). A dual catalytic system based on Rh_2(OAc)_4, for the formation a metal carbeneoid with α-diazomalonates 315 and ZnBr_2, for the Conia–ene reaction of intermediate 316 was developed. Various propargylic indole derivatives 314 were examined, with electron-rich propargylic indoles giving higher yields than electron-deficient ones. Substrates without C-3 substituents on indole delivered only C-3 functionalized products.

Stanley and co-workers described the catalytic, enantioselective intramolecular hydroacylation of N-vinyl-indole-2-carboxaldehydes 317 for the enantioselective synthesis of pyrrolo [1,2-α]indoles 318 (Scheme 76). When N-vinyl-indole-2-carboxaldehydes 317 were subjected to the hydroacylation reaction in the presence of a readily accessible rhodium catalyst in combination with axially chiral (S)-MeO-BIPHEP catalyst 319,
pyrrolo indole derivatives 318 were obtained in high yields with excellent enantioselectivities. Furthermore, the developed hydroacylation protocol was used for the construction of the chiral pyrrolo[1,2-a]indole core of the putative structure of yur-emamine.125 The same group also demonstrated the Ni-catalysed exo-selective hydroacylation reaction of N-homoallyl indole-2-carboxaldehydes to access N-fused indoles.126

In 2017, the Cu(OAc)₂ catalysed radical [1,3]-nitrogen shift via 4-exo-trig cyclisation of the N-radical for the synthesis of indole derivatives was reported by Wang and co-workers.127 By using this strategy, a single example of the synthesis of pyrrolo indole 320 from 2,2-diphenylpyrrolidine 321 was described (Scheme 77). Oxygen as a green oxidant, water as the only by-product, and one-pot cleavage of five bonds with the construction of two C–N bonds and one C–C double bond are some attractive features of this procedure. Inhibition of the reaction with radical scavenging reagents suggested intermediate radical species. Radical clock experiments proved the involvement of N-centred radicals, while in a cross-over experiment only an intramolecular radical [1,3]-nitrogen shift was observed. Based on these experiments and reports in the literature, the proposed mechanism is depicted in Scheme 77. The copper-catalysed oxidation of secondary amine 321 generates aminal radical 322, which undergoes 4-exo-trig cyclisation on the phenyl ring to produce aryl radical 323. Furthermore, oxidation of aryl radical 323, followed by aromatization, affords tertiary amine 324. Then, retro-[4π] ring-opening of tertiary amine 324 gives seven-membered amino quinone methide 325, which upon [1,5]H-shift delivers intermediate 326. Finally, the intramolecular cyclisation of N-centred radical 327, followed by oxidation and aromatization of benzyl radical 328 furnishes pyrrolo indole 320.

Reddy et al. have developed the cobalt(u)-porphyrin catalysed intramolecular cyclopropanation reaction of indoles for the synthesis of cyclopropane-fused indolines 329 (Scheme 78).128 When N-tosylhydrazones 330 were reacted with cobalt(u)-porphyrin complex 331, alkyl diazomethanes generated in situ underwent intramolecular cyclopropanation to furnish corresponding tetracyclic cyclopropane fused indolines 329 in moderate to high yields. Elaboration of the obtained products 332 and 333 via ring-opening of cyclopropane provided straightforward access to pyrrolo indole derivatives 334 and 335, respectively.

In 2017, two groups independently reported a Mn-catalysed hydroarylation/cyclisation cascade involving C–N bond cleavage with an aryl shift. Rueping and co-workers discovered that the reaction of N-pyrimidinyl indole 336 with di-substituted allenyl ester 337 in the presence of catalytic MnBr(CO)₅ provided C-2 alkenylated indoles (not shown) in excellent yields. Interestingly, tri-substituted allenyl ester 337 under similar reaction conditions gave pyrroloindolone scaffolds 338.129 At the same time, Chen et al. also revealed a similar MnBr(CO)₅ catalysed transformation for the synthesis of pyrroloindolone derivatives 338 (Scheme 79).130 Both groups independently prepared Mn-complex 339 and subjected it to the respective optimized reaction conditions to deliver products 338; this indicates that Mn-complex 339 is an intermediate in the reaction mechanism. Kinetic isotopic studies indicated that C–H activation is not a rate-determining step. Based on these experiments, the mechanism is proposed as depicted in Scheme 79. At first, Mn-catalysed directed C–H functionalization gives manganese complex 339, which upon coordination to allene 337 followed by migratory insertion generates

Scheme 76 Rh-catalysed enantioselective intramolecular hydroacylation of N-vinyl-indole-2-carboxaldehydes. (S)-MeO-BIPHEP = (S)-(−)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl.

Scheme 77 Cu-catalysed nitrogen radical generation and cascade cyclisation of 2,2-diphenylpyrrolidine.

Scheme 78 Co-catalysed intramolecular cyclopropanation of N-tosylhydrazone indoles.
intermediate 340. Furthermore, N- to C-migration of the pyrimidine group and amide formation delivered cyclized product 338.

In 2019, Takai and co-workers reported the Mo(CO)\textsubscript{6} mediated deoxygenative intramolecular insertion of carbonyl carbon into the C(sp\textsubscript{3})–H bond (Scheme 80).\textsuperscript{131} The strategy employs Mo(CO)\textsubscript{6} with ortho-quinone 341 for the in situ generation of a low valent molybdenum(II) complex, which upon reaction with (pyrrolidinyl)arylketone 342 provided pyrroloindole 343 in 58% yield. Based on experimental results and previous reports in the literature, two mechanistic pathways for Mo-mediated cyclisation were proposed. In the first pathway, an intramolecular [1,5]H-shift from the pyrrolidine ring to the activated carbonyl group generates iminium ion 344, which upon deoxygenative cyclisation provides pyrroloindole 343. However, in the second pathway, the formation of metal carbenden 345 followed by insertion into a C(sp\textsubscript{3})–H bond is proposed.

**Scheme 79** Mn-catalysed hydroarylation/cyclisation cascade reaction of N-pyrimidinyl indole and di-substituted allenyl ester.

**Scheme 80** Mo(CO)\textsubscript{6} mediated deoxygenative intramolecular insertion of carbonyl carbon into the C(sp\textsubscript{3})–H bond.

6. **9H-Pyrrolo[1,2-a]indole (16)**

The methods for the construction of 9H-pyrrolo[1,2-a]indole (16) and its derivatives are discussed in this section (Fig. 6).

**Fig. 6** 9H-Pyrrolo[1,2-a]indole.

6.1. Acid mediated reactions

Lewis/Brensted acid-catalysed formal [3 + 2] annihilation reactions of indoles with α,β-unsaturated ketones or alkylens are commonly exploited for the efficient synthesis of 9H-pyrroloindoles.\textsuperscript{112} This reaction involves two steps in one pot: i. Friedel–Crafts alkylation via conjugate addition of the indole 2 position to the α,β-unsaturated ketone, and ii. condensation of the carbonyl group with indole nitrogen followed by migration of the double bond.\textsuperscript{133} Zu and co-workers used P-TsOH·H\textsubscript{2}O,\textsuperscript{134} while CuBr\textsubscript{2} was employed by Jin et al.,\textsuperscript{135} to achieve a formal [3 + 2] annihilation reaction and a variety of 9H-pyrrolo indole derivatives were synthesized. In 2016, Chen and co-workers disclosed the Cu(OTf)\textsubscript{2} catalysed synthesis of pyrroloindoles 346 using a formal [3 + 2] annihilation reaction between substituted indoles 347 and 1,2-dicarbonyl-3-enes 348 (Scheme 81).\textsuperscript{136} Isolation of reaction intermediate proves the proposed mechanism based on Friedel–Crafts alkylation and condensation reaction.

The low reactivity of amides has hindered their utilization in the acylation of aromatic rings. However, the activation of amides with Tf\textsubscript{2}O has emerged as a valuable method for their functionalization. Tf\textsubscript{2}O-mediated intramolecular dehydrative cyclisation of 1-arylpyrrole-derived tertiary amides 349 was reported by Mátravölgyi and co-workers (Scheme 82).\textsuperscript{137} Initial activation of tertiary amides 349 by Tf\textsubscript{2}O generated electrophilic α-triflyliminium triflates 350, which were trapped by the tethered pyrrole ring to provide iminium ions 351. Finally, aqueous NaOH workup produced 9H-pyrrolo[1,2-a]indoles 352 in excellent yields.
6.2. Base mediated reactions

Base mediated transformations for the synthesis of pyrroloindoles are uncommon. In 2019, Song and co-workers reported the Cs$_2$CO$_3$ mediated C–N bond formation of 2-bromophenyl pyrrole/indol-2-yl ketones for the straightforward synthesis of 9H-pyrrolo indole derivatives (Scheme 83). Control experiments verify the absence of a benzine intermediate. Based on a radical quenching experiment with TEMPO, it was proposed that C–N bond formation might proceed via SNAr, as well as a radical pathway.

6.3. Radical cyclisation

A Cu(OTf)$_2$ catalysed tandem radical process involving the oxidative functionalization of C–H bonds of arenes and acetonitrile is disclosed (Scheme 84). The author employed MeCN as a single reagent, serving as the solvent, and CH$_2$CN radical source. Under optimized reaction conditions, various 1,1-disubstituted styryls having tethered pyrrole or indole rings provided access to cyanoethylated pyrrolo indole derivatives in moderate to good yield.

Tang and co-workers reported a silver-mediated oxidative phosphinoylation of N-propargylic indoles using various phosphate oxides for the construction of a variety of 2-phosphinoyl-9H-pyrrolo[1,2-a]indoles under mild conditions (Scheme 85). This transformation permits the introduction of a phosphonyl group into the pyrrolo[1,2-a]indole motif with the formation of C–P and C–C bonds in one pot. Here, secondary propargylic indole (R$_2^2$ = Et) gave a poor yield of corresponding pyrrolo[1,2-a]indole and other phosphorus reagents, such as Ph$_2$P(S)H or Ph$_2$PH, are incompatible. At the same time, Zhu and co-workers also described the CuSO$_4$ catalysed phosphorylation of N-propargylic indoles for the synthesis of 2-phosphorylated-pyrrolo[1,2-a]indoles by activating both P–H and C–H bonds.

A similar substrate, N-propargylic indole, was used in a sulfonyl-radical cyclisation–isomerization process for the efficient synthesis of 2-sulfonated pyrrolo[1,2-a]indoles. Subsequently, the copper-catalysed generation of sulfonyl radicals from aryl sulfonylhydrazides and their oxidative cyclisation for the production of 2-sulfonated 9H-pyrrolo[1,2-a]indoles was also developed. The arylsulfonyl hydrazides also serve as thioarylation reagents and are employed in the synthesis of 2-thiolated 3H-pyrrolo[1,2-a]indoles. In 2019, Xie et al. reported the silver-catalysed synthesis of 2-sulfonated 9H-pyrrolo[1,2-a]indoles using arylsulfinic acids as a source of sulfonyl radicals. Liu et al. also disclosed a Ru-catalysed visible light-mediated sulfonation/cyclisation strategy, by changing the source of the aryl sulfonic radical.

The first report on the cascade radical cyclisation of N-propargylic indoles was described by Reddy and co-workers (Scheme 86). Here, an
acetyl radical is generated in situ by decarboxylation of α-keto acid 362a-b in the presence of Ag₂CO₃ and K₂S₂O₈. Interestingly, the amount of oxidant (K₂S₂O₈) has a profound effect on the ratio of mono- and bis-acylated products. Under standard reaction conditions, 2 equiv. of K₂S₂O₈ gave mono-acylated product 361a, while, bis-acylated product 361b was observed with 8 equiv. of K₂S₂O₈.

Another approach to 2-acyl-pyrrolo indoles 363 using Ir-catalysed visible light-mediated acyl radical cyclisation of acyl chlorides 364 with N-propargylic indoles 365 was reported (Scheme 87). Steric hindrance around the alkyne has a negative influence on the yield of the product. Aliphatic or terminal alkynes were not tolerant of the reaction conditions. The yields of the products were also very responsive to the electronic and steric nature of substituents on benzyl chlorides. Radical quenching experiments indicated the involvement of an acyl radical in the catalytic cycle.

### 6.4. Transition metal-catalysed reactions

The Pd-catalysed formal [4 + 1] annulation reaction between 1-(2-bromophenyl)-1H-pyrrole derivatives 366 and (trimethylsilyl)diazomethane 367 for the synthesis of pyrrolo indoles 368, was revealed by Wang and co-workers (Scheme 88). Measurement of the kinetic isotopic effect was carried out and it was found that $K_{H}/K_{D} = 2.3$, indicating that C–H bond functionalization was the rate-determining step. A single example of a similar transformation using 1-(2-iodophenyl)-1H-pyrrole and α-diazoester as starting precursors was also described, but it delivered the corresponding product in lower yield.

In 2017, Perumal and co-workers demonstrated a Pd(0)-catalysed domino cyclisation for the efficient synthesis of pyrrolo indoles 369 (Scheme 89). Here, 2-bromoaryl alkynyl biaryls/heteroaryls 370 upon reaction with norbornene (371) in the presence of a Pd catalyst underwent double carbopalladation followed by C–H bond activation to furnish pyrrolo indoles 369 in excellent yields. An intramolecular competition experiment between C–D and C–H bonds ($K_{H}/K_{D} = 4$) suggested that cleavage of the C–H bond was the product determining step. Mechanistically, at first, the oxidative addition of Pd(0) to 2-bromoaryl alkynyl biaryls/heteroaryls 370 generates intermediate 372, which upon carbopalladation with norbornene (371) delivers intermediate 373. Strong intramolecular coordination of palladium with an alkyne favours syn-carbopalladation to furnish vinyl palladium species 374. Finally, intramolecular C–H bond activation, followed by reductive elimination through intermediates 375 and 376, provides pyrrolo indoles 369.

### 6.5. Organocatalytic transformation

In 2016, Voituriez and co-workers reported the reaction between indole-2-carboxaldehydes 377 and dialkylacetylene dicarboxylates 378, employing a catalytic amount of phosphine 379, by in situ salvaging the phosphine oxide using the silane as a reducing agent (Scheme 90). Mechanistically, the addition of trivalent phosphine 380 to dialkylacetylene dicarboxylate 378 generates zwitterionic species 381. Furthermore, protonation of 381 with the NH proton of indole 377, followed by the addition of generated conjugate base 382 to salt 383, delivers ylide intermediate 384. Isolation and characterization of this stable ylide 384, in the case of one substrate, supported it being an intermediate. An intramolecular Wittig reaction followed by migration of the double bond provided 9H-pyrrole [1,2-α]-indoles 385 through intermediate 386. In situ reduction of phosphine oxide 379 by phenyl silane provided corres-
Casing their application to the synthesis of bioactive molecules is highly desirable. Some competent methods are shown in developed methods for the synthesis of bioactive molecules, including the total synthesis of flinderols, mitomycins, and hinckdentine A. Recent developments in electro- and photochemical methods might provide a mild, green, and atom economical route to pyrrolo[1,2-a]indoles. Moreover, enantioselective methods for the generation of stereocenters on the pyrrolo indole core are significantly underexplored and advancement in this area will certainly be beneficial. Overall, pyrrolo[1,2-a]indoles constitute a vibrant and evolving research area that is expected to see considerable attention in the future, and we hope that this review will inspire the synthesis community for that.

Conflicts of interest

There are no conflicts to declare.

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