REVIEW

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Recent advances in the synthesis of 3,4-fused tricyclic indoles

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The 3,4-fused tricyclic indole framework is a key structural motif in numerous bioactive natural products and pharmaceuticals, thus, it has drawn much attention in synthetic organic chemistry. Synthetic organic chemists have expended substantial effort in developing efficient methods for constructing this privileged molecular framework. In this review, we highlight the advances made in this area, particularly since 2018.

1. Introduction

Tryptophan-derived indole alkaloids contain numerous bioactive compounds that are valuable in medicinal chemistry research, rendering them an important class of compounds for drug discovery. Monoterpene indole alkaloids have diverse molecular structures. These alkaloids are biosynthesized from strictosidine, which bears a tetrahydro-β-carboline framework constructed *via* the Pictet–Spengler reaction between trypta-

mine and secologanin. Consequently, many indole alkaloids have fused molecular structures at the C2 and C3 positions of the indole.[1] By contrast, ergot alkaloids, such as lysergic acid, feature a functionalized six-membered ring bridging the C3 and C4 positions of the indole (Fig. 1).[2] Numerous natural products and derivatives containing this framework exhibit remarkable biological activities, including ergotamine, which is used to treat migraines by constricting blood vessels, and ergometrine, a uterine contraction agent. The structure of the fused ring moiety is modified *via* various molecular transformations during the biosynthetic process, leading to a diverse range of natural products such as chanoclavine and cycloclavine. The tetracyclic structure of lysergic acid is biosynthesized from 4-dimethylallyltryptophan, which also serves as an inter-

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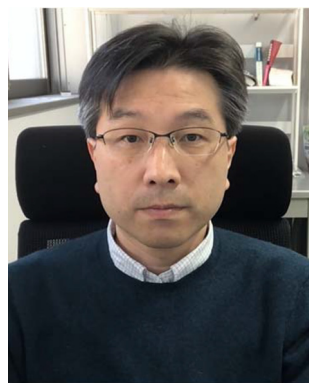
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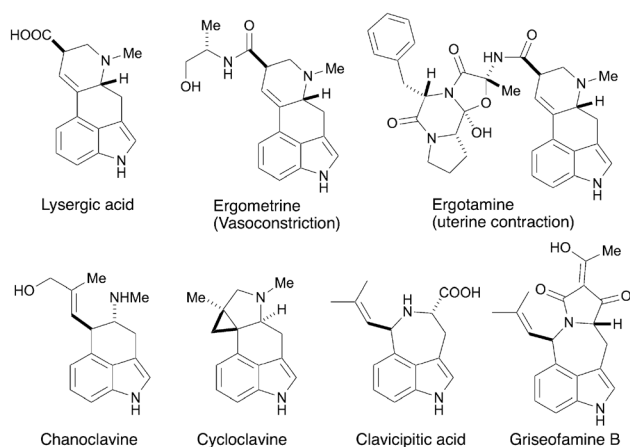
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Fig. 1 Representative 3,4-fused indole alkaloids biosynthesized from 4-dimethylallyl tryptophan.

Fig. 2 Representative 3,4-fused indole alkaloids bearing an oxygen substituent on the benzenoid ring of the indole.

mediate in the biosynthesis of clavicipitic acid and its derivatives such as griseofamine B, which are natural products featuring a fused seven-membered ring bridging the C3 and C4 positions of the indole.

On the other hand, there are 3,4-fused indole natural products that contain an oxygen functional group at the C5 or C7 positions of the indole. Because of the electron density distribution of the indole ring, the C4 position is less reactive than the C2, C3, and C5 positions, making it challenging to introduce a substituent at the C4 position *via* Friedel–Crafts-type reactions. The oxygen functional group on the benzene ring is believed to facilitate substitution at the C4 position, leading to the biosynthesis of various natural products with 3,4-seven- or eight-membered ring-fused indole structures. Examples include hyrtimomines A and F, which exhibit antimicrobial activity; dragmacidin E, which acts as a serine-threonine protein phosphatase inhibitor; decursivine, which possesses antimalarial activity; and serotobenine, as shown in Fig. 2.
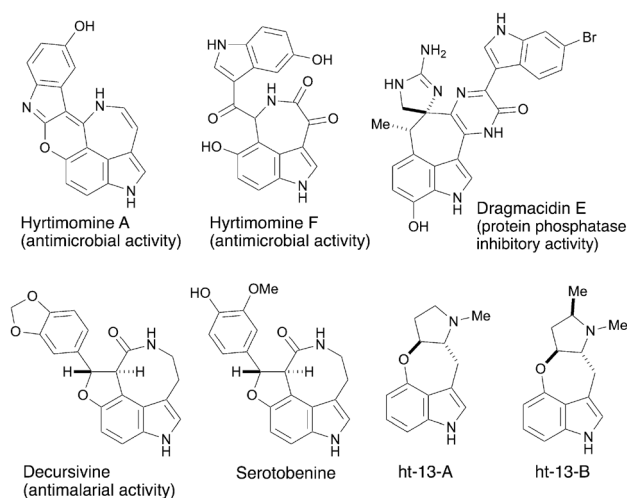
Additionally, 3,4-fused indole natural products, such as ht-13-A and ht-13-B, which feature a seven-membered ring bridged *via* an ether oxygen, are known.

Recently, new 3,4-fused indole natural products have been isolated and their structures elucidated (Fig. 3). In 2020, Klein-Júnior *et al.* isolated nemorosines A and B and nemorosinoside A and its derivatives, from the leaves of *Psychotria nemorosa*; the compounds comprise a hydroxyl group at the C6 position of the indole core.[3] Nemorosinoside A and its derivatives have a distinctive structure with a secologanin unit connected to a seven-membered ring. Notably, nemorosine A reportedly inhibits MAO-A activity with an IC_{50} value of 0.9 μM. In 2021, Wu *et al.* reported the isolation and identification of clonorosin A, a 3,4-six-membered ring-fused indole with a 2,5-diketomorpholine motif, isolated from the soil-derived fungus *Clonostachys rosea* YRS-06.[4] This alkaloid exhibited anti-

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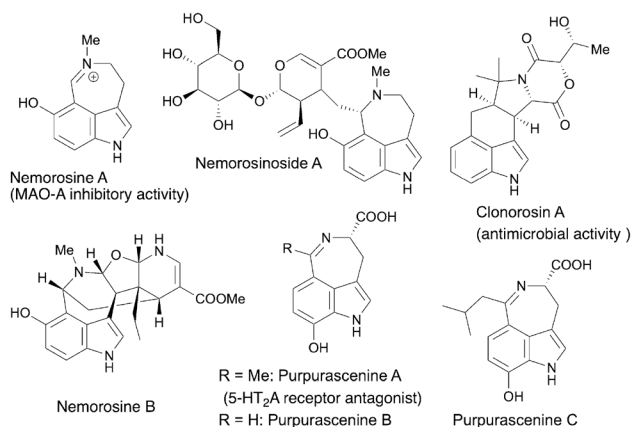
Fig. 3 Recently isolated and structurally elucidated 3,4-fused indole alkaloids.

microbial activity against *Fusarium oxysporum* with a minimum inhibitory concentration value of 50 µg mL^{-1}. More recently, Arnold *et al.* isolated 7-hydroxytryptophan-derived azepinoindole alkaloids, purpurascenines A–C, from the fruiting bodies of *Cortinarius purpurascens* Fr. (Cortinariaceae).[5] Purpurascenine A binds to the 5-HT$_2$A serotonin receptor and potentially exerts antagonistic effects.

Building on this structural and biological background, considerable effort has been directed toward the development of synthetic methods for 3,4-fused tricyclic indole derivatives. The synthetic approaches to this molecular framework have been reviewed several times. Wipf,[6] Shibata,[7] and Jia[8] have independently published comprehensive reviews on the synthesis of ergot alkaloids. Additionally, Guiry reviewed synthetic methods that utilize one-pot or multi-step synthesis,[9] and Fan, Xu, and Yang reviewed synthetic approaches that use domino reactions with Pd catalysis.[10] In 2018, we published a review of this topic, focusing on the synthetic methods for constructing 3,4-fused tricyclic indole skeletons *via* indole ring formation.[11] In that review, we classified the types of reactions used for the synthesis of this framework into two categories. Category **I** involves methods that use functionalized indole derivatives as starting materials to construct fused medium-sized rings, whereas category **II** involves the construction of a 3,4-fused tricyclic indole skeleton *via* indole ring formation. In this review, we summarize the recent advances in this field of research since 2018 based on this classification. Each category is further subdivided as shown in Scheme 1. The use of 3,4-difunctionalized indoles as substrates to construct medium-sized rings (Type A) is the most typical strategy in category **I**. Another conventional approach is the construction of medium-sized rings using substrates with a leaving group at the C4 position of the indole (Type B). Reaction systems using 4-substituted indoles (Type C) or 3-substituted indoles (Type D) as starting materials have also been reported, wherein medium-sized rings were constructed *via* Friedel–Crafts-type reactions. However, some reaction systems that appear to follow Type C
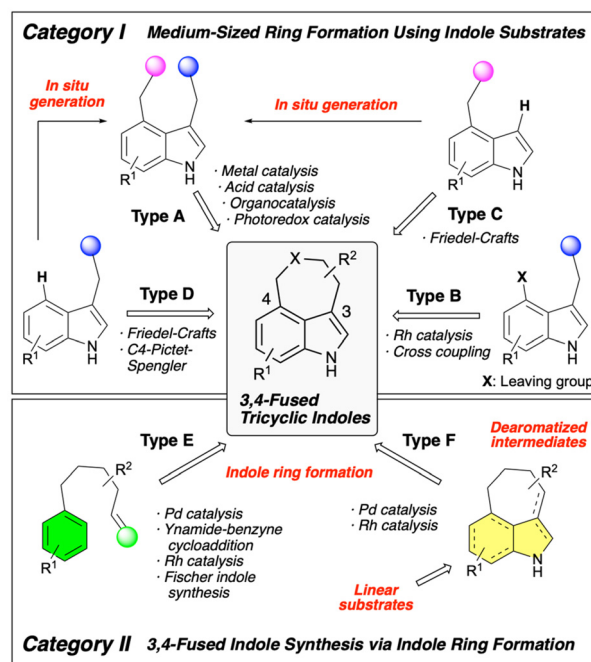
Scheme 1 Classification of synthetic methods for 3,4-fused tricyclic indoles discussed in this review.

or Type D mechanisms generate a Type A substrate *in situ* by introducing a substituent at the C4 or C3 position, resulting in the formation of a target skeleton. We categorize these reactions as "*In situ* generation of substrates for Type A reaction" in this review. The synthetic processes in category **II** are subdivided into two. Type E reactions involve the synthesis of target tricyclic skeletons from linear substrates or intermediates *via* direct indole ring formation. By contrast, Type F reactions first generate fused-ring molecules with a dearomatized indole framework, followed by a rearomatization step to construct the target 3,4-fused tricyclic indole skeleton. Although many of the synthetic methods discussed in this review have demonstrated broad substrate generality, we have minimized the discussion on the substrate scope to focus on strategies for constructing the target 3,4-fused tricyclic indole framework and explore their mechanistic insights. Please refer to the original research articles for more detailed information on substrate generality.

2.   Type A synthetic methods

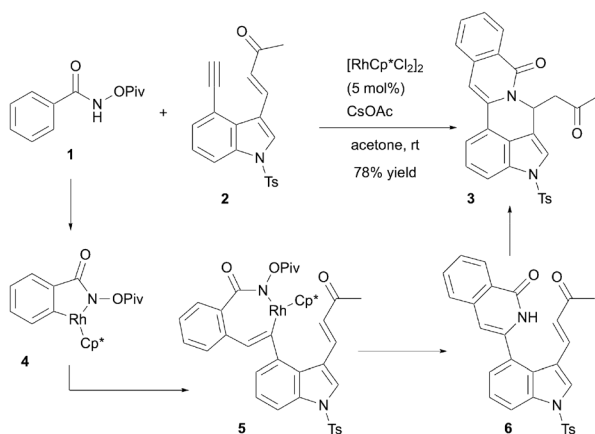### 2.1.   Fused medium-sized ring formation *via* transition metal catalysis

N-(Pivaloyloxy)arylamide derivatives such as **1** react with 1,5-enynes or 1,6-enynes in the presence of a Rh(III) catalyst, yielding fused polycyclic compounds.[12] Building on these previous findings, in 2020, Reddy *et al.* reported the construction of polycyclic 3,4-fused indole skeletons *via* a Rh(III)-catalyzed domino reaction using 4-alkynyl 3-alkenyl indoles, such as **2**,
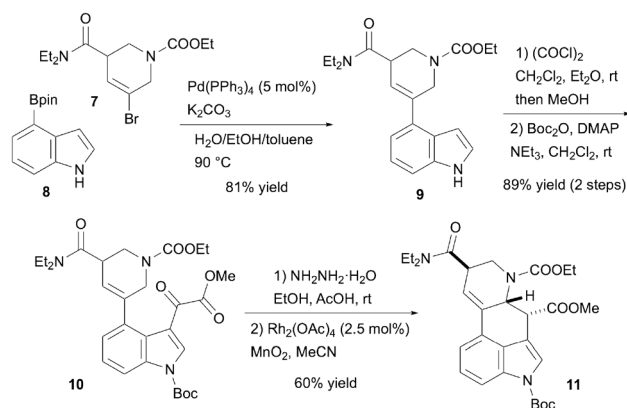
as their 1,6-enyne counterparts (Scheme 2).[13] When **1** and **2** were treated with 5 mol% of [RhCp*Cl$_2$]$_2$ and CsOAc in acetone at room temperature, the 3,4-fused polycyclic indole derivative **3** was obtained in 78% yield. The reaction occurs *via* the following mechanism: the reaction between **1** and [RhCp*Cl$_2$]$_2$ activates the *ortho* C–H bond, forming the rhodacycle intermediate **4**. Subsequent insertion of the alkyne in **2** into the Rh–C bond of **4** generates intermediate **5**. The reductive elimination of **5** followed by protonation, produces cyclized product **6**. Finally, the intramolecular aza-Michael reaction proceeds in the presence of CsOAc as the base, yielding **3**. Regarding substrate generality, the catalytic domino reaction system was applicable to various substituted *N*-(pivaloyloxy)benzamides and to *N*-(pivaloyloxy)thiophene-2-carboxamide and indole-2-carboxamide derivatives. Additionally, methyl ketones, phenyl ketones, and nitrile groups are suitable for alkene terminal substitutions.

In 2023, Olson *et al.* reported synthetic strategies for lysergic acid diethylamide derivatives based on transition metal catalysis for the construction of the fused six-membered rings. Although several strategies have been examined using Cu and Ir catalysis, these methods are impractical because of product stability. The researchers discovered that a method utilizing Rh-catalyzed C–H insertion (Scheme 3) was the most efficient for constructing the target framework.[14] After the Suzuki–Miyaura cross-coupling between compound **7** and 4-Bpin indole **8**, an α-keto ester unit was introduced at the C3 position of the resulting indole derivative **9**, yielding **10**. After condensation with hydrazine, oxidation using MnO$_2$ in the presence of Rh$_2$(OAc)$_4$ generates the Rh carbene *in situ*. This facilitates the desired C–H insertion reaction to produce **11** with the target molecular framework as a single diastereomer in 60% yield over both steps.

Another example of the synthesis of a lysergic acid framework using a Type A reaction with a transition metal-catalyst was reported by Garner *et al.*[15] The researchers uesd an intramolecular azomethine ylide cycloaddition reaction to con-
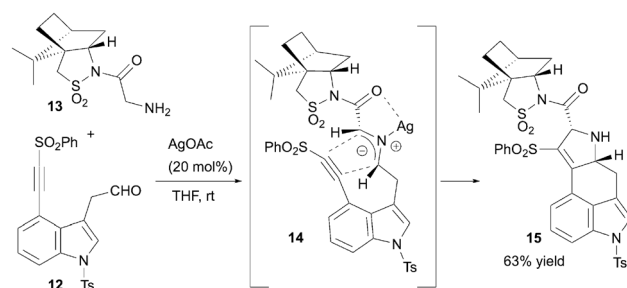
Scheme 3 Olson's synthetic method based on the Rh-catalyzed C–H insertion.

struct a fused six-membered ring. 3,4-Disubstituted indole derivative **12** and chiral glycylsultam **13** were treated with 20 mol% of AgOAc in THF at room temperature to produce **15** in 63% yield. This reaction was expected to proceed *via* concerted transition state **14** (Scheme 4). The resulting product, **15**, was successfully transformed into a lysergic acid framework *via* ring expansion process of the functionalized pyrroline moiety.
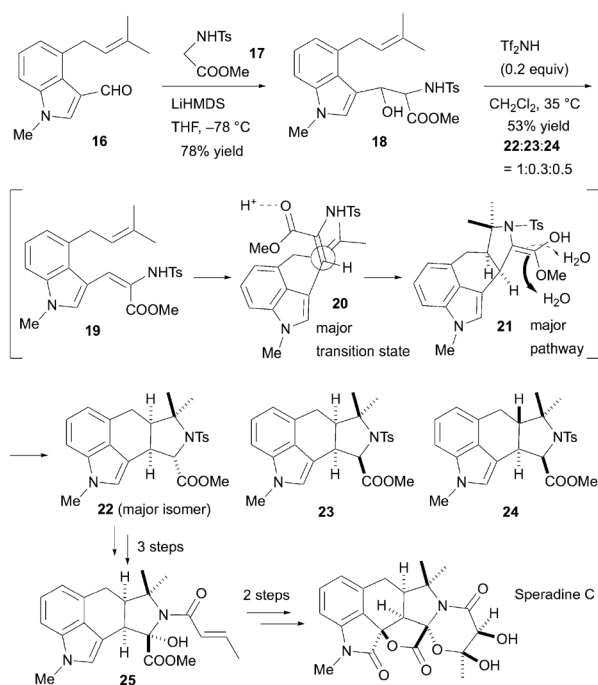
In addition to these examples, Pan, Liu, and co-workers reported the asymmetric total synthesis of griseofamine B,[16] which utilized a Pd-catalyzed cyclization reaction as an application of the Type A synthetic method previously developed by Park *et al.*[17] and Jia *et al.*[18]

2.2. Fused medium-sized ring formation *via* acid-promoted reactions

In 2019, Jia *et al.* accomplished the total synthesis of speradine C using a bioinspired method for constructing the 3,4-fused indole framework based on an Brønsted acid-catalyzed intramolecular [3 + 2]-annulation (Scheme 5).[19] The reaction of aldehyde **16** with glycine derivative **17** was performed in the presence of LiHMDS at −78 °C, yielding **18** as a mixture of diastereomers. Subsequent treatment of **18** with 0.2 equivalent of Tf$_2$NH in CH$_2$Cl$_2$ produced **22**, **23**, and **24** in 53% yield, with a diastereomeric ratio of 1 : 0.3 : 0.5. The mechanism for the for-
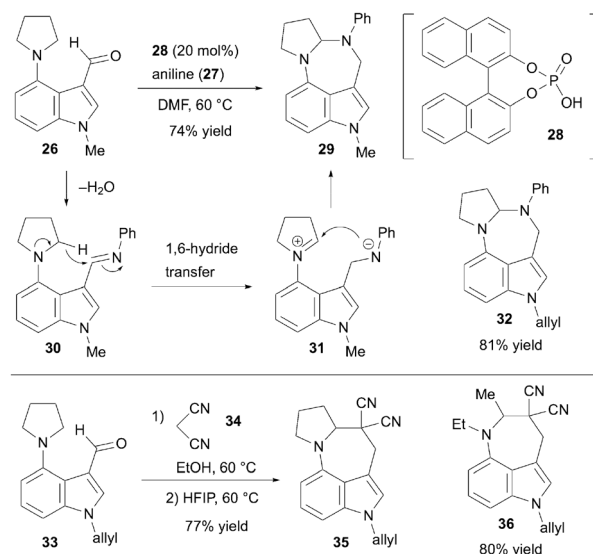
Scheme 2 Reddy's synthetic method based on the Rh-catalyzed domino reaction.

Scheme 4 Garner's synthetic method based on the Ag-catalyzed intramolecular azomethine ylide cycloaddition.

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Scheme 5 Jia's synthetic method demonstrated in the total synthesis of speradine C.

Scheme 6 Qiu and Xiao's synthetic method based on the phosphoric acid-catalyzed 1,6-hydride transfer/cyclization cascade.

mation of major product **22** is believed to occur as follows: the dehydration of **18** generates intermediate **19**, which is activated by an acidic proton, promoting intramolecular [3 + 2]-annulation. This annulation proceeds through transition state **20** to minimize the steric repulsion between the indole ring and the dimethyl groups of the prenyl unit, leading to the predominant formation of intermediate **21**. Owing to the influence of the tosyl group on the nitrogen and hydrogen atoms on the fused ring, the concave face of intermediate **21** is less sterically hindered than the convex face. Consequently, the protonation of the enol occurs preferentially from the concave face, forming **22** as the major diastereomer. Jia *et al.* successfully accomplished the total synthesis of speradine C *via* a five-step transformation from **22** *via* **25**.

In 2023, Qiu *et al.* developed an acid-catalyzed [6 + 1]-annulation reaction to synthesize 3,4-fused azepinoindoles *via* a 1,6-hydride transfer/cyclization cascade (Scheme 6).[20] Sequential intramolecular hydride transfer/cyclization is an effective strategy for rapid construction of fused cyclic molecules. The researchers hypothesized that a 3,4-azepine ring-fused indole skeleton could be constructed using the 4-aminoindole-3-carbaldehyde derivatives as six-atom synthons in a 1,6-hydride transfer/cyclization reaction. The designed reaction cascade was first examined using the indole derivative **26** with aniline **27** as a one-atom synthon. Detailed optimization revealed that the postulated transformation proceeded in the presence of 20 mol% of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **28** in DMF at 60 °C, producing the diazepinoindole derivative **29** in 74% yield. The reaction begins with the formation of imine **30** between compounds **26** and **27**. The

vicinal hydrogen on the nitrogen atom of the pyrrolidine ring in **30** undergoes 1,6-hydride transfer to the internal imine, yielding the iminium intermediate **31**. Finally, cyclization occurs, producing **29**. The highest yield was obtained when the substituent on the indole nitrogen was an allyl group, as observed in **32**. In addition, malononitrile **34** can be used as a one-atom synthon. Specifically, the Knoevenagel condensation in ethanol between **33** and **34** produced the corresponding indole derivative with an electron-deficient alkene moiety. The 1,6-hydride transfer/cyclization cascade of the obtained product proceeded after replacing the solvent with hexafluoro-isopropanol (HFIP), producing the azepinoindole derivative **35** in 77% yield. Moreover, as shown for **36**, indole substrates containing a diethylamine unit were applicable when malononitrile was used as the one-carbon synthon.

In addition to this example, the construction of the fused-ring system *via* an acid-catalyzed intramolecular addition of a nitrogen nucleophile to imine has also been utilized in the 3,4-fused indole synthesis method developed by Link *et al.*[21]

In 2024, Trushkov *et al.* developed a synthetic method for tropane-fused indole derivatives based on Yb(OTf)$_3$-catalyzed intramolecular [3 + 2]-cross-cycloaddition between an imine and a donor–acceptor cyclopropane to afford bridged bicyclic compounds (Scheme 7).[22] To accomplish this transformation, the researchers designed **37** as a substrate. By heating **37** with aniline **27** in the presence of 10 mol% of Yb(OTf)$_3$, **38**, which has a bridged bicyclic structure, was obtained in 85% yield. The reaction mechanism begins with the formation of imine **39** *via* a reaction between **37** and **27**. Subsequently, the donor–acceptor cyclopropane unit is activated by Yb(OTf)$_3$, which facilitates an intramolecular nucleophilic attack by the imine nitrogen (**40**), leading to the formation of intermediate **41**. Finally, the intramolecular cyclization of **41** occurs, resulting in the formation of **38**. This reaction can accommodate
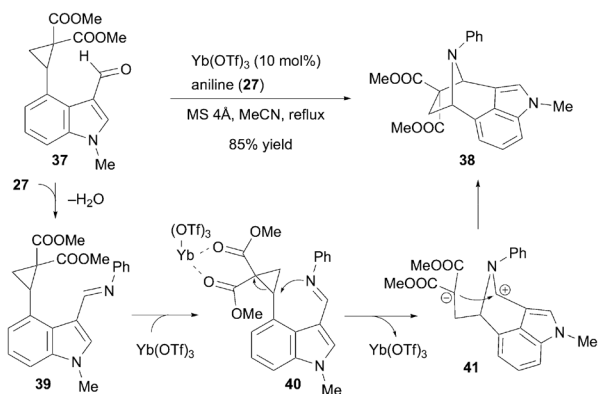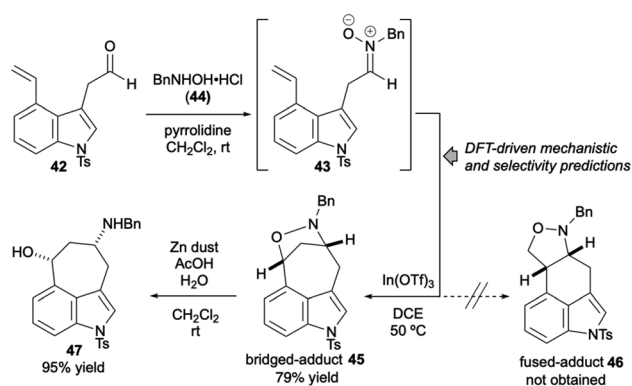
Scheme 7 Trushkov's synthetic method based on the Yb(OTf)$_3$-catalyzed intramolecular [3 + 2]-cross-cycloaddition.

various aromatic amine derivatives as substrates; however, the reactivity is significantly influenced by the steric factors of aromatic amines.

Recently, Harada, Nemoto, and co-workers developed a novel approach for the synthesis of oxazabicyclo ring-fused indoles *via* a regioselective intramolecular nitrone-alkene cycloaddition (Scheme 8).[23] The researchers conducted a computational analysis of previously reported nitrone-alkene cycloadditions using density functional theory (DFT) calculations.[24] A minimal energy difference was observed between the transition states corresponding to the two possible regioisomers (bridged *vs.* fused adducts, 1.0 kcal mol^{-1}), indicating the inherent difficulty in controlling the regioselectivity. Computational predictions identified the addition of an acid as a potentially effective strategy to induce an energy difference of more than 20 kcal mol^{-1} between transition states leading to bridged *vs.* fused products, strongly favoring the former. Therefore, the reaction conditions were optimized using nitrone **43** prepared *via* the condensation of the indole derivative **42** and hydroxylamine **44**. The regioselective cycloaddition proceeded in the presence of In(OTf)$_3$, enabling the synthesis

of the complex polycyclic compound **45** in a single step without generating fused compound **46**. A gram-scale reaction was performed involving a series of transformations, including N–O bond cleavage, to yield amino alcohol **47**. This work represents an elegant example of how modern computational methods can be applied to solve challenging selectivity problems in complex heterocyclic synthesis.

2.3. Formation of fused medium-sized rings *via* NHC-catalysis

In 2024, Suresh *et al.* developed an N-heterocyclic carbene (NHC)-catalyzed umpolung-driven intramolecular cyclization to construct 3,4-cycloheptanone annulated indoles.[25] As shown in Scheme 9, compound **48**, which bears an aldehyde and a 1,6-conjugate acceptor, was transformed into the α-aryl-3,4-fused tetracyclic indole **50** in 96% yield in the presence of 20 mol% of thiazolium-based NHC precatalyst **49** and 60 mol% of K$_2$CO$_3$ in acetonitrile at 80 °C. The reaction occurs based on the intramolecular vinylogous Stetter reaction: treatment of **50** with a base generates a free NHC catalyst, which reacts with the aldehyde moiety in **48**; subsequent proton transfer affords Breslow intermediate **51**. Thereafter, the intramolecular 1,6-conjugate addition of **51** produces **50** *via* intermediate **52**, while generating a free NHC catalyst. When methanol was used as the solvent, **48** was transformed into the oxidized product **53** in 93% yield because of the dissolved oxygen in methanol. The NHC-catalyzed method was applied to a substrate bearing a 1,4-conjugate acceptor to afford the α-alkyl-3,4-fused tetracyclic indole **54** in 95% yield. In addition, intramolecular benzoin condensation of a dialdehyde-containing substrate yielded the hydroxy cycloheptanone-annulated indole **55** in 90% yield.
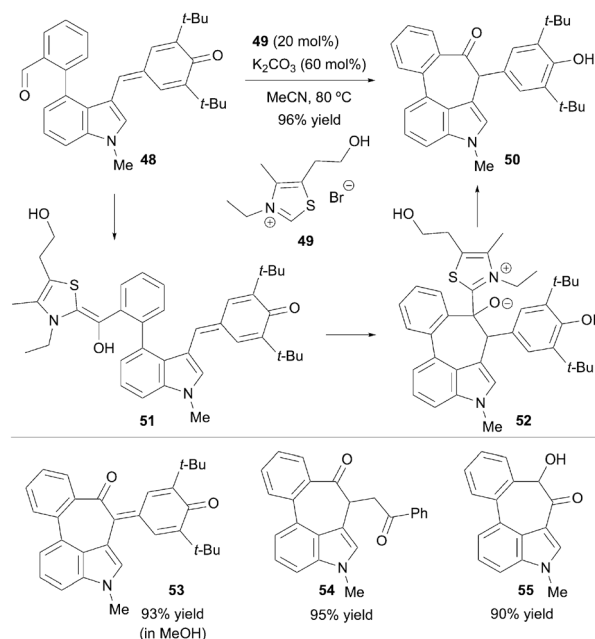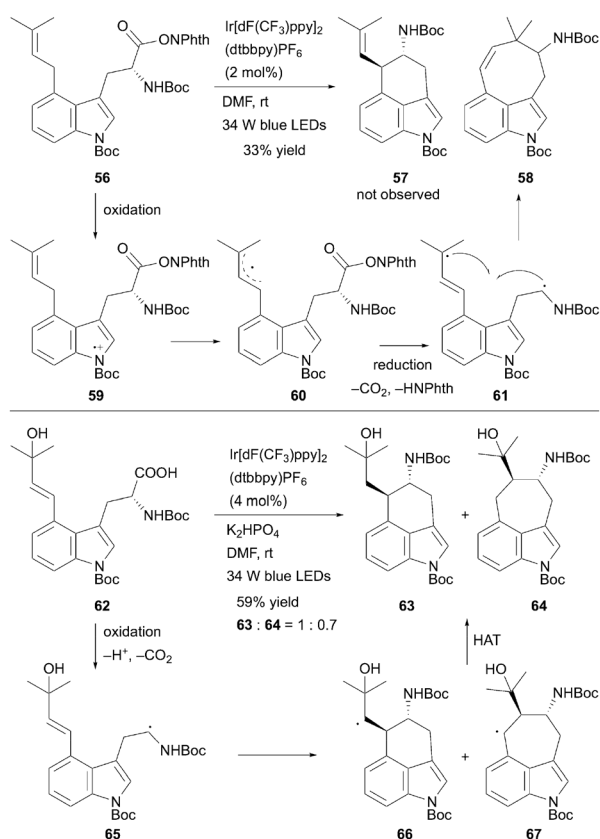

Scheme 8 Harada and Nemoto's synthetic method based on the regioselective intramolecular nitrone-alkene cycloaddition inspired by computational chemistry.

Scheme 9 Suresh's synthetic method based on the NHC-catalyzed intramolecular cyclization.

2.4. Fused medium-sized ring formation *via* photoredox catalysis

In 2023, Piersanti *et al.* reported an Ir photoredox catalyst-enabled decarboxylative radical cyclization of γ,γ-dimethylallyltriptophane derivatives **56** and **62** for access to 3,4-six-, seven-, and eight-membered ring-fused tricyclic indoles (Scheme 10).[26] The researchers examined two decarboxylation strategies: reductive single-electron transfer (SET) of redox-active esters and oxidative SET of carboxylic acids. In the former, the reaction of the *N*-hydroxyphthalimide-derived redox-active ester **56** with 2 mol% of an Ir photoredox catalyst produced 3,4-eight-membered ring-fused tricyclic indole **58** in 33% yield at room temperature under light irradiation with 34 W blue LEDs. The reaction starts with the single-electron oxidation of the indole ring to generate the indole radical cation **59**. Subsequent sequential electron and proton transfers afford intermediate **60** with an allyl radical at the C4 side chain. Thereafter, the single electron reduction of the redox-active ester produces the α-amino radical **61**, which traps the resonance-stabilized allyl radical, yielding product **58**. When **62** was treated with 4 mol% of an Ir photoredox catalyst and K_2HPO_4 under the same light irradiation conditions, 3,4-six- and seven-membered ring-fused tricyclic indole derivatives **63** and **64** were obtained in 59% yield, with a ratio of 1 : 0.7. T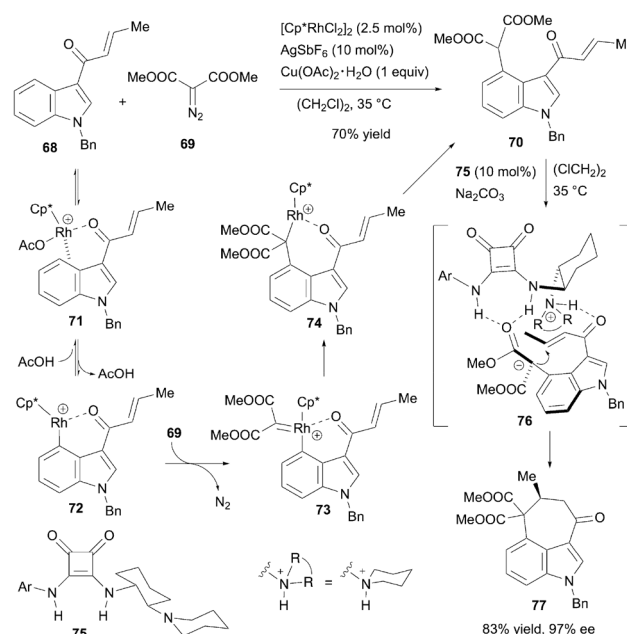he reaction most probably begins with the single electron oxidation of carboxylic acid, generating α-amino radical **65**. Subsequently, 6-*exo*-trig and 7-*endo*-trig radical cyclizations yield secondary radicals **66** and **67**, respectively. Finally, hydrogen atom transfer from DMF to intermediates **66** and **67** affords products **63** and **64**, respectively, as confirmed by deuterium experiments using DMF-d_7 as a hydrogen atom donor.

2.5. Synthetic methods based on C–H activation at the C4 position of the indole derivatives

In 2020, Harada, Nemoto, and co-workers reported a Rh-catalyzed, site-selective C–H functionalization of indoles at the C4 position utilizing α,β-unsaturated enones (Scheme 11).[27] Their mechanistic analysis, based on experimental and computational investigations, indicated that the enone-directed C–H metalation process is reversible (**71** ⇌ **72**) and that C–H activation at the C2 position of the indoles can also occur. Nevertheless, the subsequent generation of the Rh–carbene species **73** was irreversible, controlling the overall site selectivity. Subsequent migratory carbene insertion and demetallation *via* intermediate **74** afforded **70**, which could serve as a versatile scaffold for the synthesis of 3,4-fused tricyclic indoles. Additional mechanistic studies indicated that Cu(OAc)₂ plays two important roles in this transformation. First, it provides the source of the acetate anion necessary for C–H bond cleavage. Second, it forms a complex with the C–H insertion product, regenerating the active Rh catalyst. Furthermore, chiral squaramide **75** promoted the intramolecular C–C bond formation of **70** *via* transition state **76**, furnishing 3,4-seven-membered ring-fused indole **77** with 97% ee.

Scheme 10 Piersanti's synthetic method based on the photoredox-catalyzed decarboxylative strategy.


Scheme 11 Harada and Nemoto's synthetic method based on the site-selective C–H activation followed by catalytic enantioselective C–C bond formation. Ar: *p*-trifluoromethylphenyl group.

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In 2021, Ge, Chen, and co-workers successfully accomplished the total synthesis of (±)-festuclavine and (±)-pyroclavine *via* a biomimetic synthetic strategy (Scheme 12).[28] One of the key steps was the 4-nitrobenzenesulfonyl (Ns) group-directed C–H activation of the L-tryptophan derivative **78**. This Pd-catalyzed transformation was performed on a gram scale, affording **80** in 67% yield. The researchers converted **80** to **81** in several steps of the Giese coupling reaction. After preparing the *N*-hydroxyphthalimide ester **82**, decarboxylative cyclization was examined under nickel catalysis in *N,N*-dimethylacetamide (DMA). The desired product **83** was obtained in good yield with good diastereoselectivity (72% yield, 5.5 : 1 dr); however, racemization was observed, which is a common occurrence in radical coupling reactions. Finally, (±)-festuclavine and (±)-pyroclavine were synthesized from (±)-**83** *via* functional group interconversions and piperidine formation. In a related approach, Prabhu reported Rh-catalyzed C–H bond activation using a simple substrate set comprising indole-3-carbaldehyde derivatives such as **85** and allyl alcohol derivatives such as **84**.[29] Product **86**, bearing two carbonyl groups, is a versatile precursor for the synthesis of 3,4-fused indoles. Specifically, **86** was treated with a base and a fused six-membered ring was constructed in **87**, which is a core structure found in the frameworks of ergot and hapalindole alkaloids.
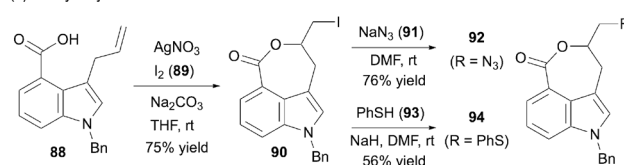
2.6.   Other synthetic methods in this category

In 2021, Thiery *et al.* reported the construction of a 3,4-fused tricyclic indole skeleton *via* an intramolecular iodolactoniza-
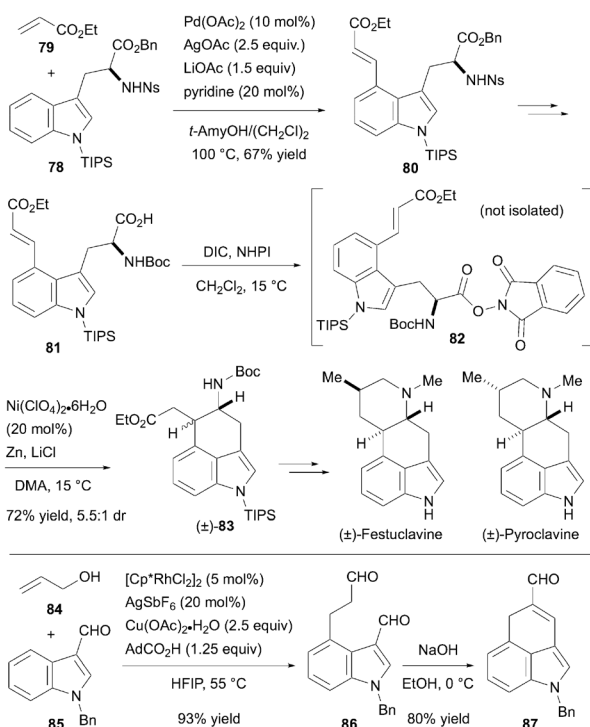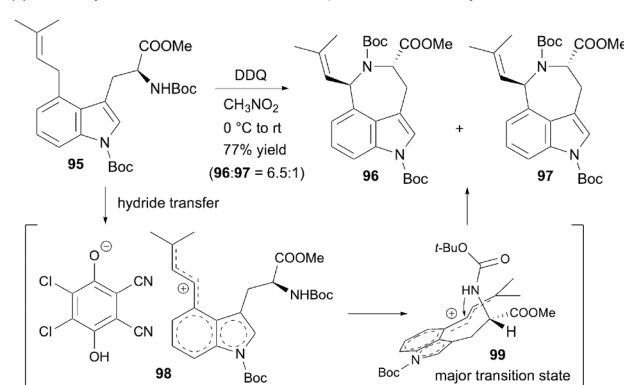

Scheme 12   Ge, Chen, and Prabhu's synthetic method based on the site-selective C–H activation followed by the ring closure. DIC: *N,N*-diisopropylcarbodiimide. NHPI: *N*-hydroxyphthalimide.

Scheme 13   Synthesis of 3,4-seven-membered ring-fused tricyclic indoles *via* iodolactonization and oxidative cyclization.

tion reaction (Scheme 13a).[30] The reaction of carboxylic acid derivative **88** with iodine **89** in the presence of a stoichiometric amount of $AgNO_3$ afforded the iodinated lactone-fused indole product **90** in 75% yield. The iodine moiety of **90** was functionalized *via* nucleophilic substitution with sodium azide **91** or thiophenol **93**, producing the corresponding products **92** and **94** in 76% and 56% yields, respectively. Notably, the azide-substituted derivative **92** enabled effective side-chain diversification through click chemistry. The potential utility of this approach in medicinal chemistry was demonstrated by evaluating the antibacterial activity of the synthesized derivatives.

In 2023, Chein *et al.* accomplished the biomimetic total synthesis of clavicipitic acid using a DDQ-mediated cross-dehydrogenative coupling reaction to construct the 3,4-fused indole skeleton. (Scheme 13b).[31] After the preparation of L-tryptophan derivative **95** from 4-bromoindole, prenyl chloride, and L-serine, compound **95** was reacted with DDQ in nitromethane at 0 °C and then warmed to room temperature. Azepinoindole derivatives **96** and **97** were obtained in 77% yield at a 6.5 : 1 ratio. These products were separable using column chromatography, and the *trans*-isomer **96** could be converted into clavicipitic acid *via* sequential deprotection of the two Boc groups. From a mechanistic point of view, DDQ first interacts with **95**, inducing hydride transfer through charge transfer complex formation, thereby generating ion pair intermediate **98**. The subsequent diastereoselective construction of the seven-membered ring proceeded *via* transition state **99**, in which the carbamate nitrogen was more likely to attack the benzylic position from the upper side of the resonance plane because of the reduced steric interactions between the Boc and prenyl groups. Compound **96** was also utilized in the synthesis of griseofa-

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mine B by Pan *et al.*,[32] wherein the researchers used a Pd-catalyzed aminocyclization reaction developed by Jia *et al.*[33]

# 3. *In situ* generation of substrates for Type A reaction

Substrates for Type A reactions can be synthesized by introducing a substituent at the C3 position of appropriately modified C4-substituted indole derivatives. Therefore, reaction systems have been developed in which substrates for Type A reactions are generated *in situ* from those used for Type C reactions, enabling a sequential cyclization process that leads to the formation of 3,4-fused indoles. Although these reactions may appear to be Type C reactions, they can be classified as Type A reactions based on the reaction mode used to construct the fused ring structure.

3.1. Introduction of C3 substituent *via* a 1,4-addition of indole derivatives to α,β-unsaturated carbonyl compounds

In 2019, Guiry *et al.* reported the synthesis of six-membered ring-bridged 3,4-fused indoles through tandem asymmetric Friedel–Crafts alkylation/Michael addition (Scheme 14). Although the synthetic methods for constructing the target framework using this strategy had already been reported,[34] the researchers further explored the reaction by using indole derivatives with an α,β-unsaturated ketone at the C4 position and *trans*-β-nitrostyrene derivatives.[35] The treatment of **100** and **102** with 10 mol% of Zn(OTf)$_2$ in toluene led to a highly diastereoselective reaction (dr = 49 : 1), where a Friedel–Crafts-type 1,4-addition to nitrostyrene was followed by an intramolecular Michael addition, yielding **101**. When **103** was used as the chiral ligand, the tricyclic product **101** was obtained in 95% yield with 90% ee.

On the other hand, Xie and Guo *et al.* developed an asymmetric synthetic method for seven-membered ring-bridged 3,4-fused tricyclic indoles *via* regio- and *enantio*-selective Friedel–Crafts alkylation/*N*-hemiacetalization and dehydration cascades (Scheme 15).[36] The researchers used 4-aminoindole derivative **104** as a bis-nucleophile and aimed to synthesize 3,4-disubstituted indole derivatives *in situ via* conjugate addition to compound **105**. The target conjugate addition proceeded in the presence of 5 mol% of Ni(OTf)$_2$ and 5 mol% of chiral tridentate ligand **107**, yielding compound **109**.
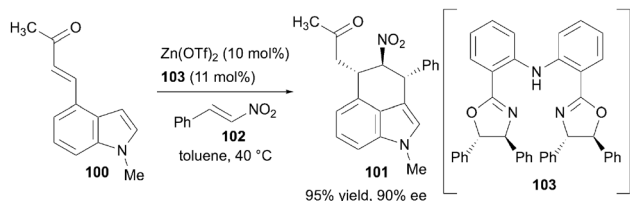
Scheme 14 Guiry's synthetic method based on the tandem asymmetric Friedel–Crafts alkylation/Michael addition.
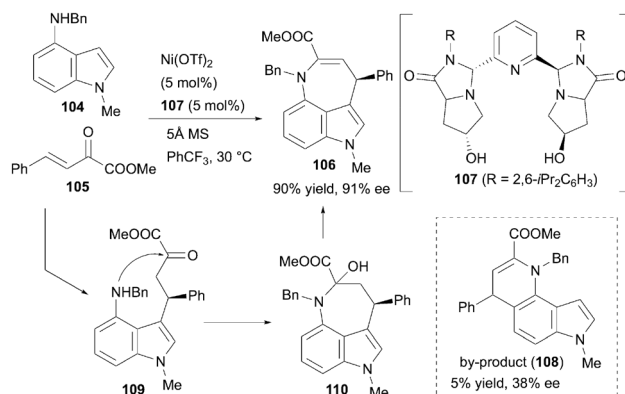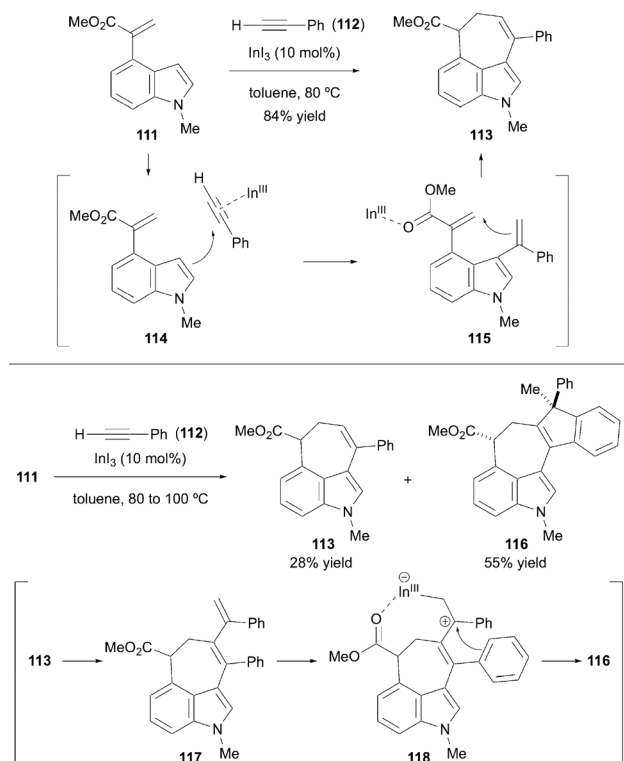

Scheme 15 Xie and Guo's synthetic method based on the regio- and enantioselective Friedel–Crafts alkylation/*N*-hemiacetalization and dehydration cascade.

Subsequent intramolecular *N*-hemiacetalization, followed by the dehydration of **110** afforded the 3,4-seven-membered ring-fused tricyclic indole **106** in 90% yield and 91% ee. Compound **108** was obtained as a by-product in only 5% yield, indicating that high regioselectivity between the C3 and C5 positions was accomplished in the initial Friedel–Crafts-type reaction step.

## 3.2. Introduction of C3 substituent *via* a metal-catalyzed process

In 2018, Harada and Nishida *et al.* reported the synthesis of seven-membered carbocycles *via* the [5 + 2]-cycloaddition of indoles and alkynes (Scheme 16).[37] This method utilizes In(III) as a bifunctional catalyst, activating both the alkyne and α,β-unsaturated ester moieties of indoles to form two new carbon–carbon bonds in a single step. The authors demonstrated that their methodology could be extended to the synthesis of 3,4-fused tricyclic indoles. The desired cyclohepta[*c,d*] indole product **113** was obtained in 84% yield using 4-substituted indole substrate **111** and phenylacetylene **112** under optimized reaction conditions. In this transformation, the indium salt activates the triple bond owing to its π-Lewis acidity (**114**). Hence, Friedel–Crafts alkenylation proceeded and subsequent rearomatization/protonation afforded the alkenylated indole **115**. In(III) activated the ester moiety as a σ-Lewis acid, and a second C–C bond was formed to construct a seven-membered ring. Pentacyclic compound **116** was synthesized at higher reaction temperatures, probably *via* the following mechanism: compound **116** was generated from **113** *via* compound **117** followed by intramolecular cyclization (**118**).

Yu *et al.* recently developed an efficient synthetic route for azepino[5,4,3-*cd*]indoles *via* Rh-catalyzed [4 + 3]-annulation of *N*-sulfonyl-1,2,3-triazoles with 4-vinyl indoles (Scheme 17).[38] Using triazoles as aza-[3C] synthons and their ability to generate Rh carbenes has been reported previously. Based on this precedent, Yu *et al.* hypothesized that incorporating a Michael acceptor into the indole skeleton would facilitate intra-

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Scheme 16 Harada and Nishida's cyclohepta[c,d]indole synthesis by bifunctional In(III) catalyst.
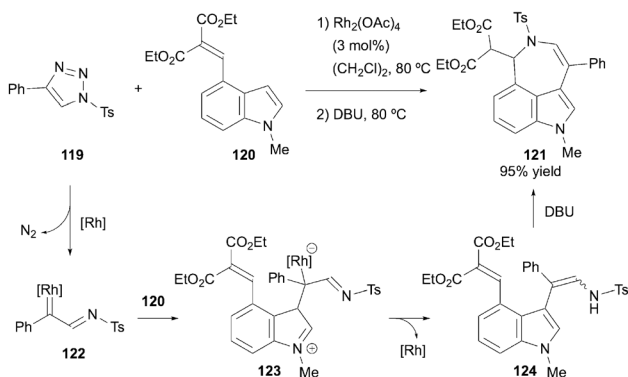
**Scheme 17** Yu's azepinoindole synthesis by the Rh-catalyzed [4 + 3]-annulation.

molecular amino cyclization. Using Rh$_2$(OAc)$_4$ as the catalyst in the presence of DBU as a base, the reaction between triazole derivative **119** and indole derivative **120** proceeds to afford the desired azepino[5,4,3-cd]indole **121** in 95% yield. Additionally, several transformations were performed to modify the azepinoindole framework. This method involves a reaction cascade. First, indole **120** attacked the α-imino Rh(II) carbene **122**, leading to intermediate **123**. Thereafter, catalyst dissociation afforded enamine **124**. Subsequently, an intramolecular aza-Michael addition led to the formation of the product. Additionally, Yu et al. demonstrated a one-pot synthesis of **121**

from phenylacetylene and tosyl azide via Cu–Rh sequential catalysis.

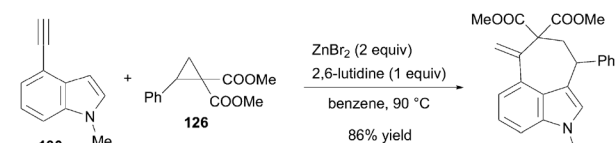### 3.3. Construction of medium-sized rings using donor–acceptor cyclopropanes/aziridines

Donor–acceptor cyclopropanes have been utilized as versatile 1,3-zwitterion precursors in organic synthesis.[39] In 2020, Zhang, Xu and their co-workers demonstrated that [4 + 3]-cyclization between indole derivatives bearing a Michael acceptor at the C4 position and a donor–acceptor cyclopropane is effective for synthesizing 3,4-seven-membered ring-fused indole derivatives.[40] As shown in Scheme 18, **125** reacted with donor–acceptor cyclopropane **126** in dichloroethane at 60 °C in the presence of 10 mol% of Yb(OTf)$_3$, yielding **127** in 95% yield with 13 : 1 diastereoselectivity. After alkylation at the C3 position of the indole to generate **128**, Michael addition subsequently proceeds via transition state **129** to avoid steric hindrance between the diester units, resulting in high diastereoselectivity. Various substitution patterns on the aromatic ring of the donor–acceptor cyclopropane are applicable.

The synthesis of 3,4-fused tricyclic indoles using donor–acceptor cyclopropanes was also reported by Kerr et al. in 2022,[41] who utilized 4-ethynyl indole **130** as a coupling partner with donor–acceptor cyclopropane **126** to achieve the target synthesis. C3 alkylation of **130** with **126**, followed by an intramolecular Conia-ene reaction, proceeded in the presence of 2 equiv. of ZnBr$_2$ and 1 equiv. of 2,6-lutidine in benzene under reflux, producing **131** in 86% yield (Scheme 19a). Punniyamurthy and Trivedi also reported the synthesis of 3,4-fused azepinoindoles via a C3-alkylation–aza-Michael reaction cascade using 2-aryl 1-sulfoxyaziridines as 1,3-zwitterion precursors.[42] As shown in Scheme 19b, the reaction between **125** and 2-phenyl 1-tosylaziridine **132** in the presence of 5 mol% Cu(OTf)$_2$, followed by the addition of K$_2$CO$_3$ as a base to promote an intramolecular aza-Michael reaction, yielded the 3,4-seven-membered ring-fused tricyclic indole **133** in 75% yield with high diastereoselectivity.
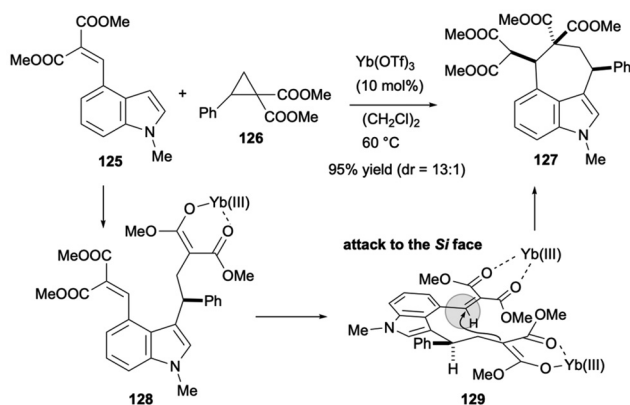
Scheme 18 Zhang, Xu's method based on the [4 + 3]-cyclization between C4-substituted indole derivatives and a donor–acceptor cyclopropane.

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(a) C3-alkylation–Conia-ene reaction cascade reported by Kerr et al.

(b) C3-alkylation–aza-Michael reaction cascade reported by Punniyamurthy and Trivedi et al.
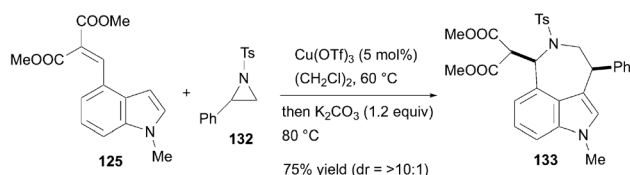
Scheme 19 Synthesis of 3,4-seven-membered ring-fused tricyclic indoles using 1,3-zwitterion precursors.

4. Type B synthetic methods

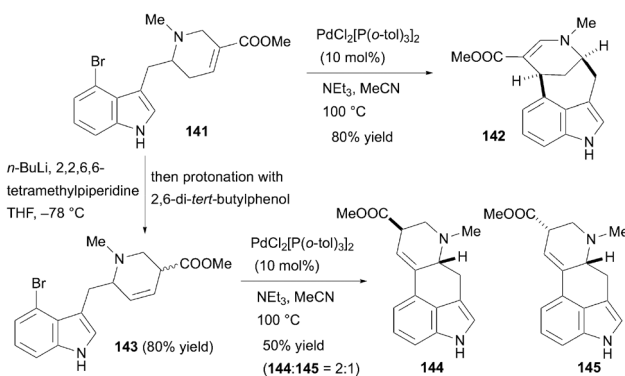## 4.1. Synthetic methods using intramolecular nucleophilic addition of arylrhodium(I) species

Optically active 4-amino-5-oxo-1,3,4,5-tetrhydrobenz[*cd*]indole, also known as 4-amino Uhle's ketone, is a valuable intermediate in the synthesis of 3,4-six-membered ring-fused ergot alkaloid derivatives.[43] However, owing to facile racemization through enolization under both acidic and basic conditions,[44] an efficient method for synthesizing this compound in its optically active form is highly desirable. To overcome this challenge, Piersanti *et al.* developed an efficient conversion method in 2021 using optically active 4-substituted tryptophan derivatives as starting materials (Scheme 20).[45] The researchers first examined transition-metal-catalyzed carbonyl-arylation/acylation using the bromoindole derivative **134**. However, extensive examination revealed that the desired six-membered
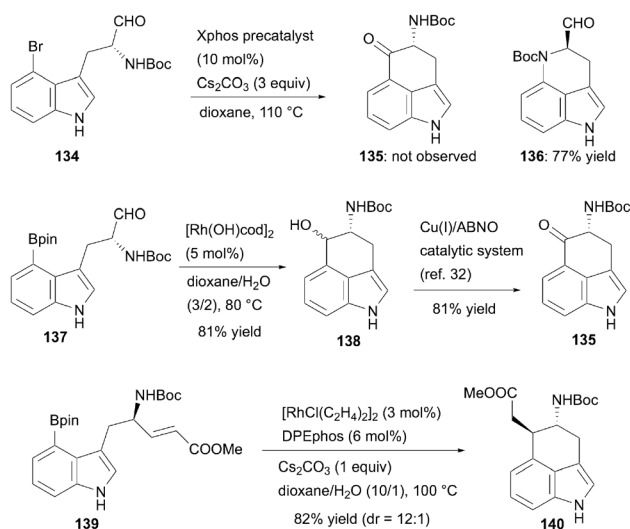
ring-fused product **135** was not obtained, and an unexpected six-membered NH carbamate-arylated cyclization product **136** formed in 77% yield when 10 mol% (2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride (Xphos precatalyst) was used. Piersanti *et al.* overcame this challenge by generating a more nucleophilic aryl rhodium(I) species. When pinacolboronic acid derivative **137** was treated with 5 mol% of [Rh(OH)cod]$_2$ in a dioxane/H$_2$O mixed media at 80 °C, the cyclization reaction afforded the corresponding alcohol adduct **138** in 81% yield as a diastereomixture (*cis*:*trans* = 1:2.6). Oxidation of this alcohol proceeded smoothly using the Cu(I)/ABNO catalytic system developed by Stahl *et al.*,[46] yielding the 4-amino Uhle's ketone derivative **135** in 81% yield without any loss of optical purity. The developed approach provides a solution for synthesizing the desired 4-amino Uhle's ketone derivatives in an optically active form, which can be successfully applied to the asymmetric total synthesis of all rugulovasine stereoisomers[47] and (−)-6,7-secoagroclavine.[48] Furthermore, Piersanti and Bartoccini *et al.* recently developed a diastereoselective synthetic method for 3,4-six-membered ring-fused indole derivatives, such as **140**, by harnessing the conjugate addition of an arylrhodium(I) species generated from pinacolboronic acid derivative **139** to an internal α,β-unsaturated ester.[49]

4.2. Construction of the medium-sized ring based on the Pd- or Ni-catalyzed cross coupling strategy

The construction of medium-sized rings using an intramolecular Heck reaction with substrates bearing a leaving group at the C4 position of the indole is a representative method for building ergoline frameworks. A recent example is the work of Wipf *et al.*, who utilized the Heck reaction as a key step in the short synthesis of ergot alkaloids (Scheme 21).[50] Using compound **141**, which can be synthesized in two steps from commercially available materials, as a substrate, Wipf *et al.* performed the Heck reaction in the presence of a 10 mol% Pd catalyst. The 3,4-seven-membered ring-fused indole derivative **142** was obtained in 80% yield. However, after isomerization of the double bond, the resulting com-

Scheme 20 Piersanti and Bartoccini's synthetic method based on the intramolecular nucleophilic addition of arylrhodium(I) species.

Scheme 21 Wipf's synthetic method based on the intramolecular Heck coupling.

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pound **143** was treated under Heck reaction conditions to produce a mixture of compounds **144** and **145** in 50% yield (**144** : **145** = 2 : 1). These compounds were possibly formed *via* a Heck coupling–alkene isomerization sequence. In addition to this work, Smith *et al.* reported the synthesis of lysergic acid, utilizing a Heck reaction as the key step for constructing the fused six-membered ring.[51] More recently, Opatz *et al.* successfully constructed a lysergic acid framework using a Ni-catalyzed cross-coupling process.[52]

5. Type C synthetic methods

5.1. Fused medium-sized ring formation *via* enantioselective [4 + 3]-cycloaddition with azomethine ylides

Azomethine ylides are valuable building blocks in the synthesis of optically active azaheterocycles. However, achieving catalytic asymmetric [4 + 3]-cycloadditions presents challenges owing to unfavorable entropic factors, transannular interactions, and the presence of multiple stereocenters. In 2021, Deng *et al.* reported an Ir-catalyzed asymmetric [4 + 3]-cycloaddition for the synthesis of azepino[3,4,5-cd]indole derivatives (Scheme 22).[53] The researchers used racemic 4-indolyl allylic alcohol (±)-**146** and an azomethine ylide precursor **147** to produce 3,4-fused indole **149** in 83% yield, exhibiting excellent enantioselectivity and diastereoselectivity (>99% ee and >20 : 1 dr) in the presence of [Ir(cod)Cl]$_2$, Carreira's P/olefin ligand (*S*)-**148**, and Zn(OTf)$_2$. The proposed reaction mechanism for the [4 + 3]-cycloaddition is described below. The Zn(II)-stabilized azomethine ylide species **150** enantioselectively attacks the cationic π-allyl iridium(III) intermediate **151**, which is generated in the presence of Zn(OTf)$_2$ as an acid promoter. Subsequently, the addition of the C3 position of indole **152** to the electrophilic imine, activated by coordination with Zn(II), forms product **149**. The diastereoselectivity may be attributed to steric repulsion between the aryl imine and diester moiety. Deng *et al.* focused on the required amount of indole (2

equiv.) and explored the kinetic resolution of compound **146**, yielding (*R*)-**146** with an enantiomeric excess greater than 99%.

In addition, Dang, Dong, Wang, and their coworkers reported a stereodivergent synthetic method that uses a cooperative Ir- and Cu-catalyzed formal asymmetric [4 + 3]-cycloaddition (Scheme 23).[54] By combining Ir(I)/(*S*$_a$,*S*,*S*)-**155** and Cu(I)/(*S*,*S*$_p$)-**156** catalysts, the reaction of (*E*)-4-indolyl allyl carbonate **153** with an alanine-derived aldimine ester **154** formed the first coupling intermediate **157**. The subsequent intramolecular Friedel–Crafts reaction, catalyzed by Zn(OTf)$_2$, furnished the final product **158** in 67% overall yield with 99% ee and 18 : 1 dr. In this reaction, the π-allyl iridium(III) complex generated from **153** determined the C6 stereochemistry: using Ir(I)/(*S*$_a$,*S*,*S*)-**155** led to the formation of the 6*S* stereocenter, while Ir(I)/(*R*$_a$,*R*,*R*)-**155** produced the 6*R* stereocenter. Similarly, the Cu(I)-stabilized azomethine ylide formed from **154** controlled the C7 stereochemistry: Cu(I)/(*S*,*S*$_p$)-**156** generated a 7*S* stereocenter and Cu(I)/(*R*,*R*$_p$)-**156** yielded a 7*R* stereocenter. Moreover, C9 epimerization of **158** was accomplished *via* a trifluoroacetic acid (TFA)-promoted ring-opening-cyclization reaction to yield product **159** in 95% yield and 99% ee. Therefore, the synergistic effect of the Ir/Cu catalysts, along with TFA-promoted epimerization, facilitated the stereodivergent synthesis at the C6, C7, and C9 positions of the azepino[3,4,5-cd]indole derivatives.

5.2. Other catalytic synthetic methods in this category

In 2019, Gu *et al.* reported the synthesis of 3,4-seven-membered ring-fused indole derivatives using 4-aminoindole **160** as the 1,4-bisnucleophile (Scheme 24).[55] Their approach involved initial formation of a nucleophilic enamine between **160** and diethyl acetylenedicarboxylate **161**, generating the 1,6-bisnucleophile intermediate **164**. Subsequent condensation with aldehydes such as **162** facilitates the formation of a seven-membered ring structure. Detailed optimization of the reaction conditions revealed that using 5 mol% of Cu(OTf)$_2$ as the catalyst, with ethanol as the solvent, afforded product **163** in
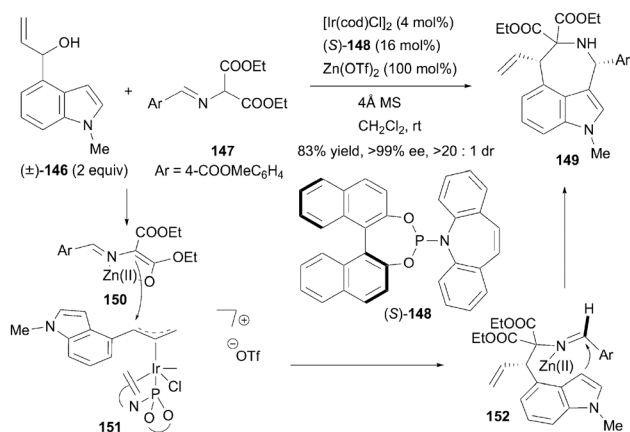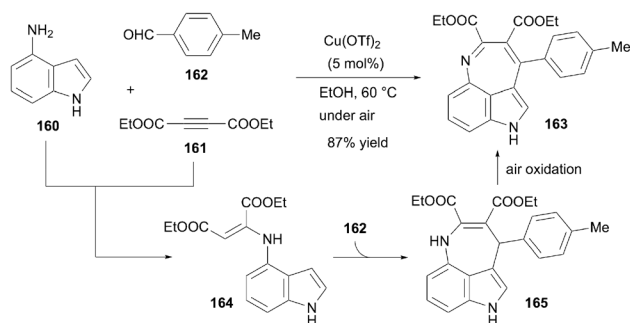

Scheme 22 Deng's synthetic method based on the Ir-catalyzed [4 + 3] cycloaddition reaction.
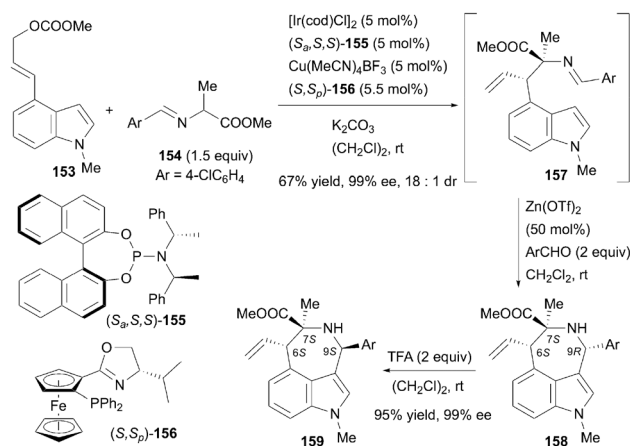
Scheme 23 Dang, Dong, and Wang's synthetic method based on cooperative Cu(I)/Ir(I)-catalyzed [4 + 3] cycloaddition reaction.

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Scheme 24 Gu's synthetic method based on the Cu-catalyzed three-component condensation.

87% yield under air. When the reaction was performed under an argon atmosphere, a mixture of enamine-type compounds **165** and **163** was obtained (**163** : **165** = 1 : 4). Therefore, compound **163** was formed *via* air oxidation of **165**. Additionally, because the conversion of **164** to **163** was not observed in the absence of Cu(OTf)$_2$, the Cu catalyst probably played a key role in the condensation step between **164** and **162**. In addition to aromatic aldehydes, aliphatic aldehydes could be used as the aldehyde components, demonstrating the broad substrate generality of the reaction.

In 2019, Stokes *et al.* developed an efficient acid-catalyzed method for the synthesis of tetrahydrobenzo[*cd*]indoles *via* the intramolecular hydroindolation of *cis*-configured methindolylstyrenes (Scheme 25a).[56] The researchers used *cis*-β-(α′,α′-dimethyl)-4′-methindolylstyrene **166** as a substrate and benzenesulfonic acid as a catalyst, in toluene, at 130 °C. This setup facilitated selective cyclization at the C3 position of the indole, yielding the desired tetrahydrobenzo[*cd*]indole **167**, although some substrates underwent a competitive minor cyclization

pathway at the C5 position, producing regioisomer **168**. The observed regioselectivity was attributed to the dispersive interactions between the indole and styrene moieties, which pre-organized the substrate structure to that of **169** for efficient six-membered ring formation. Notably, the *cis*-alkene configuration and geminal dimethyl substitution were critical for controlling the regioselectivity and reaction efficiency, as *trans*-configured substrates favored undesired oligomerization.

Recently, Das *et al.* reported a similar reaction system using 1,1-diarylalkanols as starting materials.[57] As shown in Scheme 25b, **170** reacted with 10 mol% of *p*-TsOH·H$_2$O in HFIP at room temperature, forming the corresponding cationic intermediate, which was then trapped by an indole nucleophile to afford **171** in 82% yield. Additionally, alkene **172** was generated *via* a formal E1 elimination of the tertiary alcohol. Construction of the 3,4-fused tricyclic indole framework *via* cation formation from **172** under reflux conditions highlighs the advantage of the cyclization reaction of **170**, which proceeds at room temperature.

In 2020, Li, Van der Eycken, and co-workers developed an Au-catalyzed method for synthesizing polycyclic azepino[5,4,3-*cd*]indoles *via* a post-Ugi dearomatization cascade (Scheme 26).[58] This process begins with the formation of Ugi adducts using indole-4-carboxaldehyde **173**, 4-aminophenol **174**, isocyanide **175**, and alkyne carboxylic acid **176**, producing versatile substrate **177**. The key reaction was initiated by activating the triple bond with a cationic Au catalyst, generated *in situ* from IPrAuCl and AgOTf, which underwent dearomative *ipso*-cyclization in a 5-*endo-dig* manner to yield spiro compound **178**. Subsequently, Michael addition at the C3 position of the indole selectively formed the azepino[5,4,3-*cd*]indole core **179**. The substrate design was crucial because terminal alkynes proved to be unsuitable for the reaction. Furthermore, substituents on the indole nitrogen influenced the pathway, with electron-withdrawing groups on the nitrogen reducing the nucleophilicity at C3, thereby hindering Michael addition.
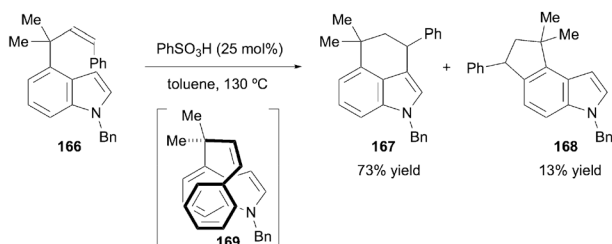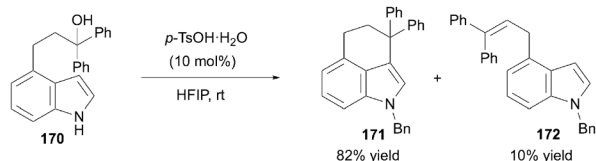
Scheme 25 Synthesis of 3,4-seven-membered ring-fused tricyclic indoles using Brønsted acid-catalyzed intramolecular Friedel-Craft reaction.
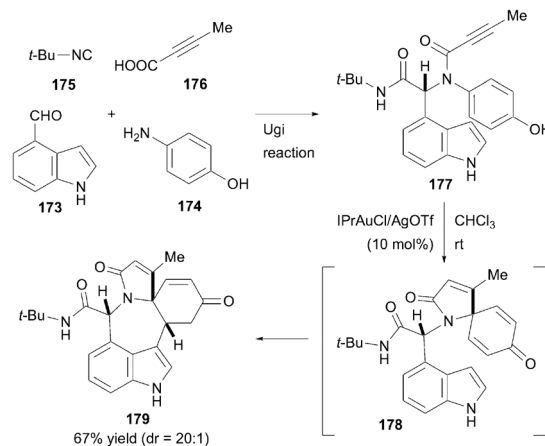
Scheme 26 Li and Van der Eycken's synthetic method based on the Au-catalyzed post-Ugi cyclization.

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6. Type D synthetic methods

Type D reactions are less common than the other types of reactions. In our previous review, we categorized the reactions listed in Section 2–6 as Type D reactions. However, in this review, we classified them as Type A reactions based on the reaction mode of the medium-sized ring formation step.

A recently reported synthetic method in this category involves the construction of azepinoindole frameworks *via* a C4-Pictet–Spengler reaction. This methodology was designed to mimic the proposed biosynthetic pathway of hyrtiazepine-type alkaloids, such as hyrtimomine A, which feature a hydroxy group at the C5 position of the indole ring. Accordingly, it represents a goal-oriented strategy for the synthesis of related natural products and their derivatives. In 2017, Abe and Yamada reported the total synthesis of hyrtioreticulins C and D *via* a C4-Pictet–Spengler reaction (Scheme 27a).[59] They aimed to construct a 3,4-fused tricyclic indole framework *via* a C4-Pictet–Spengler reaction between a 5-hydroxytryptophan derivative **180** and acetaldehyde **181**. However, controlling the chemoselectivity was crucial, as competitive reaction at the C2-position could lead to the formation of undesired β-carboline-type products. Optimization of the reaction conditions revealed that conducting the reaction under microwave irradiation effectively suppressed the formation of β-carboline-type byproducts. Furthermore, when the reaction was carried out in a solvent mixture of *N,N*-diisopropylethylamine (DIPEA) and methanol (1 : 1), the 3,4-fused

tricyclic indole derivative *trans*-**182** was obtained in 59% yield with a 15 : 1 trans-selectivity. The observed trans-selectivity was attributed to the steric bias between two plausible post-cyclization intermediates **183** and **184**, with intermediate **184** being favored due to reduced steric hindrance in the transition state. Hydrolysis of *trans*-**182** afforded (–)-hyrtioreticulin C in 72% yield.

Abe, Yamada *et al.* also applied this strategy to the synthesis of the core structure of hyrtiazepine alkaloids (Scheme 27b).[60] In the C4-Pictet–Spengler reaction between compound **180** and an aldehyde derivative **185**, the use of trifluoroethanol (TFE) as the solvent and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base enabled the trans-selective formation of **186** in 85% yield.

A similar transformation was demonstrated by Yu and Liu *et al.* in 2021 (Scheme 27c).[61] Following C2-selective arylation of a tryptamine derivative using palladium catalysis to afford compound **187**, the subsequent C4-Pictet–Spengler reaction with isatin **188** in the presence of TFA in HFIP furnished the 3,4-fused tricyclic indole derivative **189** in 77% yield.

In addition to the C4-Pictet–Spengler reactions, the key step in the synthesis of (±)-decursivine, as reported by Manetsch *et al.* in 2021, can be categorized under this reaction type.[62] To accomplish an efficient synthesis of (±)-decursivine, the researchers investigated the conversion from **190** to (±)-decursivine (Scheme 28). After screening the oxidative transformation conditions, they discovered that the desired reaction proceeded in 47% yield using [bis(trifluoroacetoxy)iodo]benzene (PIFA) in HFIP. Furthermore, the addition of 5 mol% BINOL phosphoric acid **28** improved the yield, successfully synthesizing (±)-decursivine in 74% yield. The reaction initially proceeds with the oxidation of the 5-hydroxyindole unit by PIFA to afford the dearomatized intermediate **191**. Subsequent eight-membered ring formation is facilitated by the involvement of BINOL phosphoric acid, which is converted into intermediate **192**. Finally, an intramolecular C–O bond formation results in the formation of the furan ring, effectively affording (±)-decursivine.
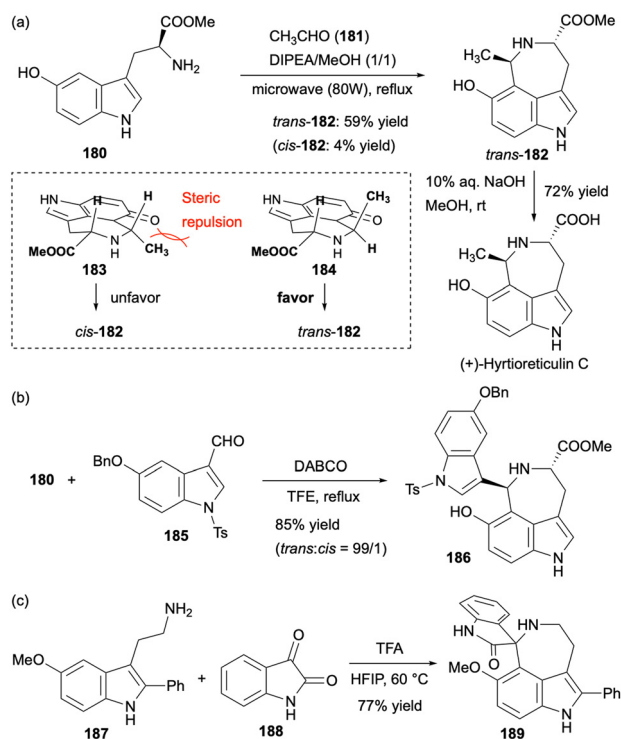
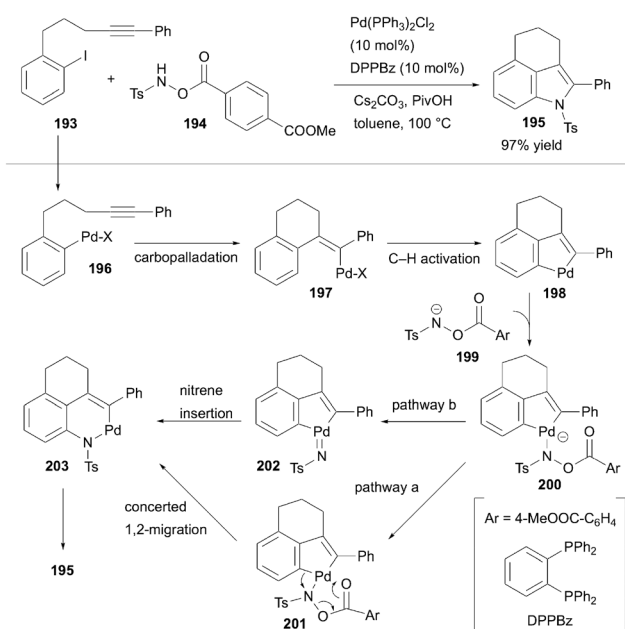**Scheme 27** Synthesis of azepinoindole frameworks *via* a C4-Pictet–Spengler reaction.
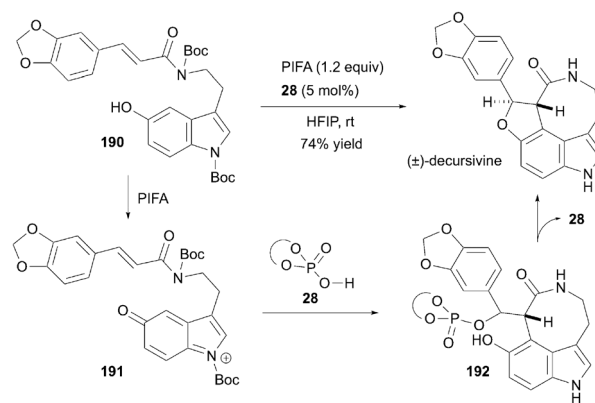
Scheme 28 Manetsch's synthetic method demonstrated in the total synthesis of (±)-decursivine.

7. Type E synthetic methods
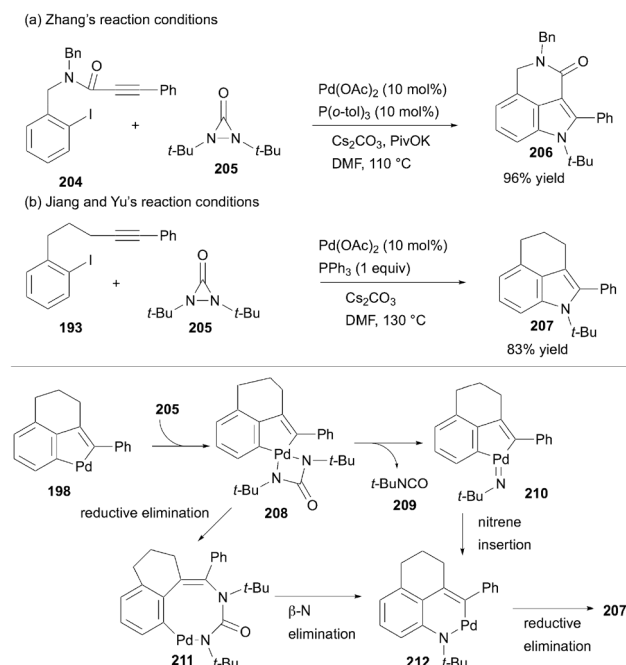
7.1. Synthetic method based on Pd Catalysis

In 2020, Luan *et al.* developed a one-step synthetic method to produce diverse 3,4-fused tricyclic indole derivatives using secondary hydroxylamines as bifunctional nitrogen sources in a Pd-catalyzed reaction.[63] Their strategy for constructing the indole ring relied on the hypothesis that fine-tuned hydroxylamine derivatives could enable two sequential C–N bond formations. The first step involves electrophilic amination of a palladacycle intermediate, and the second step proceeds *via* reductive elimination. This design leverages the bifunctional nature of hydroxylamine derivatives in a sequential Pd-catalyzed process, facilitating the streamlined one-step synthesis of diverse 3,4-fused tricyclic indole derivatives. Luan *et al.* successfully obtained **195** by heating an iodobenzene derivative with an alkyne side chain **193** and a hydroxylamine derivative, using 10 mol% of a Pd catalyst, Cs_2CO_3 as a base, and PivOH as an additive, in toluene. After optimizing the structure, hydroxylamine **194**, comprising a Ts group on nitrogen and benzoate derivative on oxygen, performed best, affording **195** in 97% yield (Scheme 29). Using this reaction system, 3, 4-fused tricyclic indole derivatives with six-, seven-, and eight-membered rings were synthesized. Additionally, 3,5-fused and 3,6-fused tricyclic indole derivatives were synthesized using the same catalytic system. This reaction system demonstrated high substrate generality and enabled the construction of the desired framework in a single step from simple 2-substituted iodobenzene and hydroxylamine derivatives *via* Pd-catalyzed C–H activation. Given its efficiency and simplicity, it can be regarded as a state-of-the-art methodology among the reported synthetic approaches. The reaction mechanism begins with the reaction of the Pd(0) catalyst with **193**, generating intermediate **196**. This was followed by carbopalladation to yield intermediate **197**. Subsequent C–H activation then forms palladacycle intermediate **198**. Following the formation of intermediate **200** from the reaction between **199**, derived from **194** with a base, and palladacycle intermediate **198**, two possible reaction pathways were proposed. In pathway a, the electron flow, as shown in intermediate **201** triggers concerted 1,2-migration, yielding intermediate **203**. In pathway b, insertion of the Pd-nitrene intermediate **202** also led to the formation of intermediate **203**. Finally, the reductive elimination afforded **195**. This method is limited to the synthesis of indole derivatives with a Ts protecting group on nitrogen. In 2022, Bai, Luan, and co-workers expanded their approach to include the synthesis of 3,4-fused tricyclic indoles featuring a removable alkyl group on the nitrogen.[64] The researchers used hydroxylamines with bulky alkyl substituents as the nitrogen source. This process relies on the selective cleavage of large *t*-butyl or benzyl groups during palladacycle formation *via* an S_N1 mechanism, which allows the incorporation of smaller alkyl groups into the product.

After the Luan's report, Zhang *et al.*, and Jiang and Yu *et al.* independently reported the synthesis of 3,4-fused tricyclic indoles in 2020, following the same concept, using *N,N*-di-*t*-butyldiaziridinone **205** as the nitrogen source (Scheme 30). Zhang *et al.* successfully synthesized the desired 3,4-fused tricyclic indole **206** in 96% yield by reacting iodobenzene deriva-

Scheme 29 Luan's synthetic method based on the Pd-catalyzed sequential carbopalladation, C–H activation, and two C–N bonds formation using a bifunctional secondary hydroxylamine derivative as the nitrogen source.

Scheme 30 Zhang's, and Jiang and Yu's synthetic methods based on the Pd-catalyzed sequential carbopalladation, C–H activation, and two C–N bonds formation using *N,N*-di-*t*-butyldiaziridinone as the nitrogen source.

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tive **204** with **205** under conditions in which Pd(OAc)$_2$ was used as the catalyst and P(o-tol)$_3$ served as the ligand.[65] By contrast, Jiang and Yu et al. used 10 mol% Pd(OAc)$_2$ and 1 equivalent of PPh$_3$ as the ligand, and successfully produced **207** in 83% yield from **205** and **193**.[66] Mechanistically similar to that of the system developed by Luan et al., the reaction proceeded with the formation of palladacycle intermediate **198**. Subsequently, the oxidative addition of **205** to palladacycle intermediate **198** occurred, resulting in the formation of Pd(IV) intermediate **208**. The transformation of intermediate **208** to **212** involves two pathways. One route proceeds via the formation of the Pd-nitrene intermediate **210**, which is generated by the release of t-butyl isocyanate **209**. The other pathway suggests that intermediate **208** undergoes reductive elimination to form eight-membered palladacycle intermediate **211**, which then undergoes subsequent β-N elimination to yield the key palladacycle intermediate **212**.

Furthermore, Zhang, Liang, Li, and Quan, and their co-workers reported a synthetic method for 3,4-fused tricyclic indoles via an ortho-C–H activation using the palladium/norbornene chemistry.[67,68] The researchers discovered that after ortho-C–H activation of iodoaniline derivative **213**, facilitated by a Pd catalyst and norbornene **216**, incorporation of **214** as an ortho-C–H alkylating agent triggered cyclization involving N–S bond cleavage, yielding the corresponding tricyclic indole derivative **215** in 63% yield (Scheme 31). The reaction proceeds according to the following mechanism. First, the three-component reaction of the Pd catalyst, **213**, and norbornene **216** forms intermediate **217**. This intermediate then undergoes ortho-C–H activation, transforming into **218**. The subsequent reaction of **218** with **214** facilitates ortho-alkylation, resulting in intermediate **219**. The following β-carbon elimination leads to the extrusion of norbornene, forming intermediate **220**. This intermediate undergoes an intra-

molecular migratory insertion reaction with an alkyne to afford intermediate **221**. Subsequent C–N bond coupling, accompanied by N–S bond cleavage to liberate **222**, afforded the corresponding 3,4-six-membered ring-fused indole derivative **215**. This reaction mechanism is supported by control experiments and DFT calculations. This reaction system could also be applied to the synthesis of 3,4-seven-membered ring-fused indoles using one-carbon unit-extended alkylating reagents.

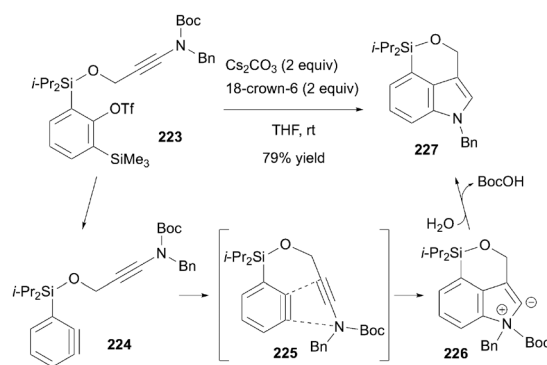### 7.2. Synthetic method based on the intramolecular ynamide-benzyne cycloaddition

In 2023, ynamide-benzyne [3 + 2]-cycloaddition reactions were developed by Takasu, Takikawa, and co-workers to synthesize silicon-containing 3,4-fused tricyclic indoles (Scheme 32).[69] The proposed reaction mechanisms and unique intermediates are of particular interest. The authors proposed that the intramolecular [3 + 2]-cycloaddition of **223** proceeds through transition state **225** via benzyne intermediate **224**, generating indolium ylide **226**. The subsequent hydrolysis of **226** affords **227** in 79% yield. Deuterium labeling experiments indicate that residual water contaminated with 18-crown-6 and/or Cs$_2$CO$_3$ serves as a potential proton source at the C2 position of the indole variants. Notably, no literature precedent exists for using ynamides as three-atom components in [3 + 2]-cyclo-addition reactions. Computational studies have suggested that simple combinations of ynamides and benzynes preferentially undergo intermolecular [2 + 2]-cycloaddition reactions over [3 + 2]-cycloaddition reactions. The transformation had a broad substrate scope and afforded various fused products in good yields. Furthermore, the synthesized product could be converted into potentially useful 3,4-fused indole derivatives via C–H functionalization and into indoles with functionalities at the C4-positions through ring-opening.

7.3. Application of the previously developed Type E methods

Reddy et al. applied 3,4-fused tricyclic indole synthesis, based on acetyl-amide-directed Rh-catalyzed C–H activation developed by Xu and Liu et al.,[70] as the key step in the synthesis of
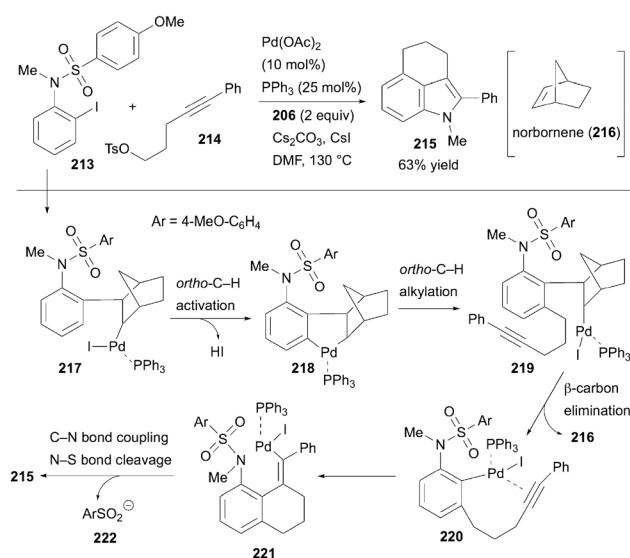
Scheme 31 Zhang, Liang, Li, and Quan's synthetic method via an ortho-C−H activation using the palladium/norbornene chemistry.

Scheme 32 Takasu and Takikawa's synthetic method based on the intramolecular [3 + 2]-cycloaddition reactions between ynamides and benzynes.
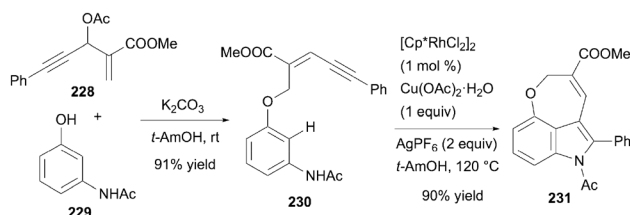
Scheme 33 Application of the Xu and Liu's synthetic method to the synthesis of 3,4-oxepino-fused indole by Reddy and co-workers.

3,4-oxepino-fused indole derivatives (Scheme 33).[71] As part of their efforts to develop synthetic methods using Morita-Baylis–Hillman (MBH) products, the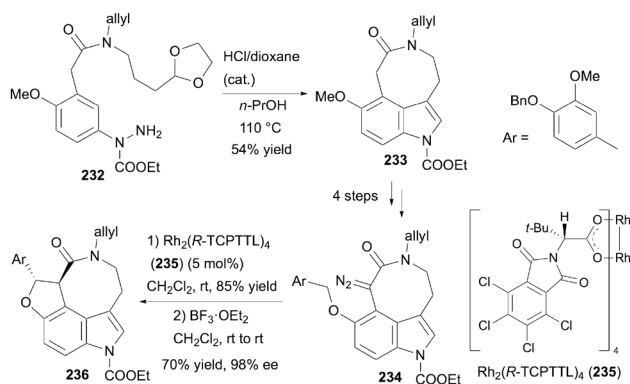 researchers investigated the Rh-catalyzed cyclization reaction of linear substrate **230** derived from MBH adduct **228** and 3-acetoamido phenol **229**. The subsequent intramolecular annulation reaction proceeded in the presence of 2 mol% of Rh catalyst in *t*-amyl alcohol at 120 °C, producing the corresponding 3,4-oxepino-fused indole **231** in 90% yield. In addition to various aryl groups, alkyl groups are applicable as substituents at the alkyne terminal, demonstrating that this reaction system has wide substrate generality.

In 2022, Cho *et al.* succeeded in accomplishing the total synthesis of (+)-decursivine and (+)-serotobenine based on a previously developed method using intramolecular Fisher indole synthesis (Scheme 34).[72] Starting from compound **232**, intramolecular Fisher indolization was performed in *n*-PrOH at 110 °C in the presence of a catalytic amount of HCl, resulting in the formation of 3,4-eight-membered ring-fused tricyclic indole derivative **233** in 54% yield. After a 4-step transformation to obtain diazoamide **234**, an intramolecular C–H insertion reaction was performed using chiral Rh catalyst **235**, successfully constructing the dihydrofuran ring in 85% yield. At this stage, the *cis*-isomer was favored (*cis*:*trans* = 27:1), but treatment with BF₃ enabled isomerization to the *trans*-isomer in 70% yield. Intermediate **236** with 98% ee was subsequently transformed in three steps to yield (+)-serotobenine. Compound **233** was also used in the enantioselective total synthesis of (+)-decursivine using a similar strategy.[73]
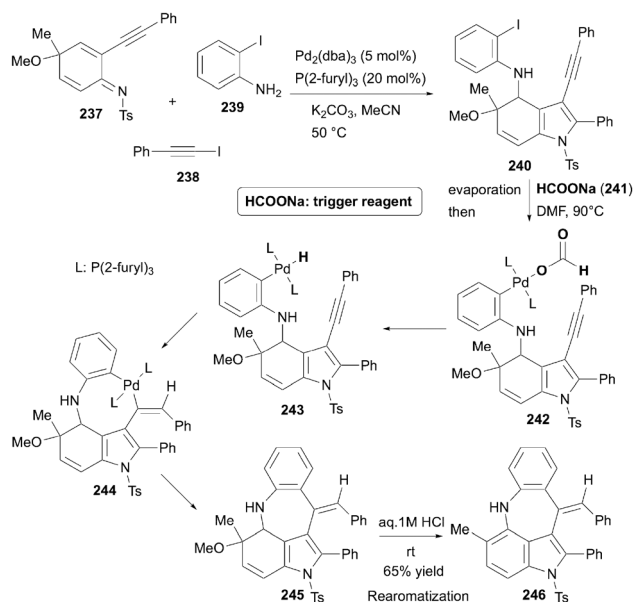
8. Type F synthetic methods

8.1. Synthetic method based on the tandem palladium catalysis strategy

Assisted tandem catalysis is defined as a reaction system in which the catalytic cycle switches to another catalytic cycle upon the addition of a trigger reagent. This approach enables sequential transformations within the same reaction vessel, allowing efficient synthesis by shifting the reaction pathways as needed. In 2020, He, Fan and their co-workers succeeded in the rapid construction of 3,4-fused tricyclic indoles based on this strategy (Scheme 35).[74] The reaction began with a three-component coupling reaction involving 2-alkynylcyclohexadienimine derivative **237**, alkynyl iodide **238**, and 2-iodoaniline **239** in the presence of a Pd catalyst and K₂CO₃ at 50 °C, which initially produced compound **240**. After removing acetonitrile, the solvent was replaced with DMF, and sodium formate **241** was added as the trigger reagent. Upon heating to 90 °C, the catalytic cycle switched to the next stage. The reaction proceeds *via* the oxidative addition of iodoarene to the Pd catalyst, followed by a reaction with sodium formate, which generates palladium hydride species **243** *via* intermediate **242**. Next, insertion of the Pd–H bond into the internal alkyne unit yields palladacycle intermediate **244**, which undergoes reductive elimination to afford tricyclic intermediate **245**. Finally, rearomatization of intermediate **245** furnished 3,4-fused tricyclic indole derivative **246** in 65% yield. In a control experiment, when the reaction was conducted without the addition of sodium formate, **240** was obtained in 74% yield, demonstrating that sodium formate acts as a trigger reagent for this process.

Scheme 34 Cho's synthetic method demonstrated in the enentioselective toral synthesis of (+)-serotobenine and (+)-decursivine.

Scheme 35 He and Fan's synthetic method based on the tandem Pd catalysis.

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8.2. Application of the previously developed Type F methods

Zong, Wang and co-workers applied the Rh-catalyzed 3,4-fused tricyclic indole synthesis developed by Miura and Murakami *et al.*[75] as a key step in the synthesis of (+)-isolysergol (Scheme 36a).[76] Compound **248**, featuring a tetracyclic ergot alkaloid framework, was obtained in 64% yield by heating chiral intermediate **247** in the presence of 1 mol% of $Rh_2(OCOt\text{-Bu})_4$, followed by the addition of MnO_2. Compound **248** was then converted into (+)-isolysergol *via* a three-step transformation.

On the other hand, Harada, Nemoto and their collaborators conducted a synthetic study on dragmacidin E, utilizing their previously developed method.[77] Nemoto *et al.* introduced a Pd-catalyzed cascade process for the synthesis of 3,4-fused tricyclic indoles (Scheme 36b).[78] This methodology was successfully applied to linear substrate **249** for the construction of the 3,4-fused tricyclic indole framework. Treatment of **249** with 30 mol% of Pd catalyst in DMSO at 80 °C yielded tricyclic 3-alkylideneindoline derivative **250** in 60% yield. This intermediate was successfully transformed into synthetic intermediate **251**, which comprised contiguous stereocenters on the fused seven-membered ring, through a seven-step process that included isomerization of the double bond to form the indole skeleton. The utility of synthesizing 3,4-fused indoles *via* the acid-promoted isomerization of 3-alkylideneindoline

Scheme 36 Application of the previously developed Type F methods to synthetic studies of natural products.

Fig. 4 Examples of synthetic pharmaceuticals with 3,4-fused tricyclic indole frameworks.

derivatives was also demonstrated by Rawal in 2022.[79] In addition, Nakajima, Nemoto and co-workers conducted a detailed mechanistic study of their Pt-catalyzed reaction system for the synthesis of 3,4-fused tricyclic indoles, which were initially developed by the Nemoto group.[80] By combining DFT calculations with experimental validation, the researchers obtained an in-depth understanding of the reaction pathways.[81]

9. Conclusions

This review highlights the advances made in the synthesis of 3,4-fused tricyclic indoles, particularly the advances published since 2018. We had previously[11] classified the method of constructing a tricyclic framework based on the sequential building of the indole ring as Type G. To the best of our knowledge, no reports of Type G reactions have been published since 2018. This suggests a shift toward more direct approaches for constructing the target framework, moving away from stepwise synthetic methods.

Many of the reported reactions were designed to synthesize natural product frameworks, and future studies should explore the synthesis of natural products using these methods. Additionally, given the wide range of bioactive natural products containing the 3,4-fused tricyclic indole framework, these reactions have immense potential for application in medicinal chemistry. Representative examples of synthetic pharmaceuticals based on a 3,4-fused tricyclic indole framework include rucaparib and pergolide (Fig. 4). Rucaparib, a poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor,[82] has been approved by the FDA as Rubraca for the treatment of ovarian cancer in 2016. Pergolide, a dopamine receptor agonist, is used to treat Parkinson's disease, and mimics the action of dopamine, helping to compensate for the dopamine deficiency characteristic of Parkinson's disease.[83] The development of molecules with significant biological activity from such relatively simple molecular structures underscores the potential of 3,4-fused tricyclic indole frameworks for drug discovery. To fully harness the drug discovery potential of this core structure, interdisciplinary research must be promoted alongside synthetic chemistry, including the investigation of the biological activities of synthetic derivatives. In addition, the development of more refined and environmentally friendly synthetic methods that can be scaled up for large-scale industrial production is crucial.

Additionally, reaction development based on reactivity predictions using DFT calculations has been reported.[23] While further improvements in predictive accuracy remain a challenge, the approach of virtually designing reactions and validating them through experimental verification is expected to gain increasing attention as a research strategy.

The 3,4-fused tricyclic indole framework is a key structural motif in numerous bioactive natural products and pharmaceuticals and has garnered significant interest from synthetic organic chemists. The development of practical synthetic
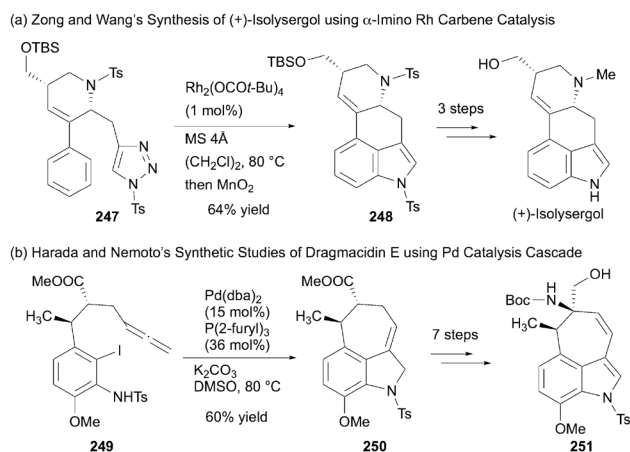
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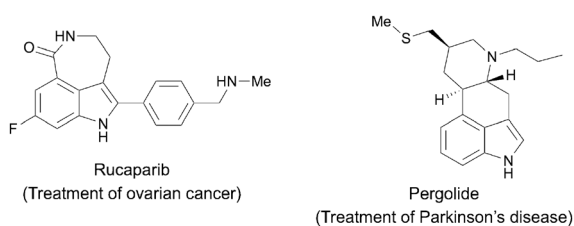
methods targeting this structure has the potential to contribute significantly to advances in both organic synthesis and medicinal chemistry. We anticipate further progress will be made in this area.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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