

An Update on Cyclohepta[b]indoles

Jan Gierok,^[a] Lars Benedix,^{*[a]} and Martin Hiersemann^[a]

The cyclohepta[b]indole scaffold constitutes a salient structural motif in natural products as well as in man-made pharmaceutically active ingredients. Cyclohepta[b]indoles consist of an indole nucleus fused to a seven-membered carbocycle. Interest in cyclohepta[b]indole chemistry originates from natural product chemistry and medicinal chemistry. The chemistry of

cyclohepta[b]indole-based organic functional materials may be a research area with some potential. The state of the art of cyclohepta[b]indoloid chemism has been comprehensively and scholarly summarized by the leading review article of Stempel and Gaich in 2016. Following this lead, our Minireview covers the literature from 2016 to 2021.

1. Introduction

The cyclohepta[b]indole scaffold has been recognized as an architectural motif of natural products as well as of man-made active pharmaceutical ingredients.^[1] Cyclohepta[b]indole-derived natural products (cyclohepta[b]indoloids) constitute a subfamily of the widespread family of indole alkaloids. Cyclohepta[b]indoloids feature various biological effects, e.g., cytotoxicity,^[2] anti-inflammatory activity,^[3] or interference with ion channel function.^[4] Intricate architecture paired with specific function distinguish meaningful targets for synthetic endeavors. Method awareness guides synthetic planning and defines goals for method development. In the first part of this minireview, recently isolated cyclohepta[b]indoloids are introduced to the reader interested in architecture and function. In the second part, newly developed methods for cyclohepta[b]indoloid synthesis are revealed to readers interested in synthesis. The scientific content is categorized by underlying chemical concepts, and then presented in chronological order.

2. Alkaloids

Originally discovered 1931^[5] from a probe of *Rauwolfia serpentina*, (+)-ajmaline (**1**) can be considered as a prototype for natural products featuring the cyclohepta[b]indole scaffold (Figure 1). The intricate molecular architecture of **1** emanates from a bicyclo[4.2.1]nonane-derived carbon core structure, and the cyclohepta[b]indole scaffold is tangled within.

In 1965, Woodward proposed the correct constitution of ajmaline based on the results of degradation studies and on visionary biosynthetic considerations.^[6] Chemical correlation

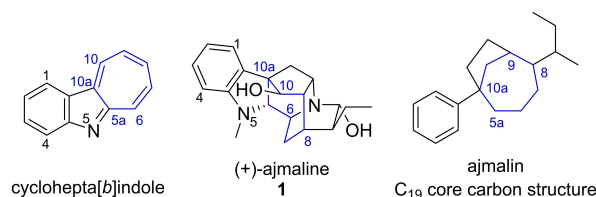


Figure 1. Categorization and deconstruction of (+)-ajmaline: cyclohepta[b]indole structural motif and bicyclo[4.2.1]nonane-derived core carbon structure. Cyclohepta[b]indole numbering is used throughout the review.

enabled assignment of the absolute configuration of ajmaline (**1**) by Wenkert et al. in 1962.^[7] In 1967, the first total synthesis of (\pm)-ajmaline was disclosed by Masamune et al.^[8] Besides its intricate molecular architecture, **1** features strong antiarrhythmic properties^[9] and is an approved in Germany under the name Gilurytma[®].^[10] Since the discovery of (+)-ajmaline, indole alkaloids with a related core structure have been isolated and are categorized as ajmaline-type alkaloids.

In 2018, Kam et al. reported the isolation of octahydrocyclohepta[b]indoles **2** and **3** from *Alstonia penangiana* (Figure 2).^[11] Vincamaginine A and B share the vincamaginine core carbon structure and possess significant cytotoxicity against human cancer cell lines.^[12] Within in the compound family, structural diversity originates from *N*- and *O*-acylation with eudesmic acid (**2**) or *N*-acylation with eudesmic acid and *O*-acylated with syringic acid (**3**). In comparison to **1**, **2** and **3** are equipped with an exocyclic carbon/carbon double bond but are missing the hemiaminal function. The *Alstonia* alkaloids **2** and **3** are distinguished from the *Rauwolfia* alkaloid **1** by an opposite absolute configuration at carbon atom 5a.

The octahydrocyclohepta[b]indole alkaloid **4** was isolated by Hu et al. in 2018 from the leaves *Alstonia scholaris*. Methoxalstiphyllanine H is structurally characterized by the vincamaginine core structure.^[13]

In 2016, Zhao et al. disclosed the isolation of the hexahydrocyclohepta[b]indole alkaloids **5**, **6** and **7** from *Vinca major*.^[14] The vinorine-type cyclohepta[b]indole alkaloids are structurally characterized by the ajmaline core carbon structure.

In 2017, the acetylcholinesterase inhibiting octahydrocyclohepta[b]indole alkaloid **8** was isolated by Rukachaisirikula et al.

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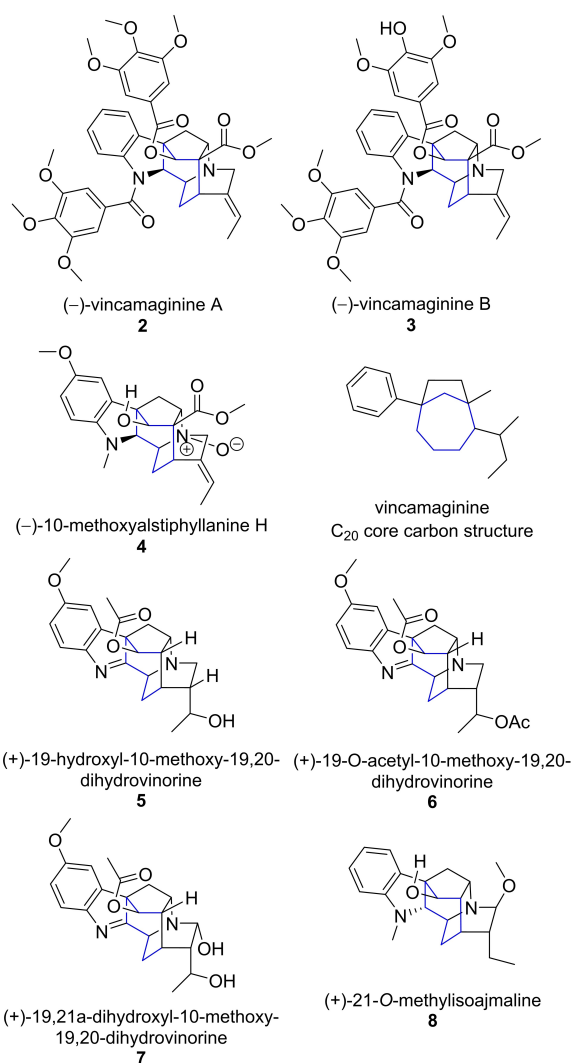


Figure 2. Ajmaline-type cyclohepta[b]indole alkaloids.

from *Rauwolfia serpentina* (Figure 3).^[15] 21-O-Methylisoajmaline (**8**) is derived from the vincamaginine core carbon structure.

In 2004, the isolation and structural characterization of kopsifolines A–F from *Kopsia fruticosa* was reported by Kam and Choo.^[16] Kopsifolines G–K were isolated from the same species by Chen et al (Figure 3).^[17] Kopsifoline-type hexahydrocyclohepta[b]indole alkaloids are characterized by a bridged hexacyclic ring system and by the kopsifoline core carbon structure. The kopsifoline core carbon structure is shaped from a bicyclo[3.2.1]octane and features three all-carbon atom-substituted quaternary chirality centers. The structural diversity of the kopsifolines arises from various degrees of oxyfunctionalization of the bridged hexacyclic ring system. It was found that the kopsifolines G–K exert noticeable inhibitory activities against 12 microorganisms as well as cytotoxicity against human cancer cell lines on a micromolar scale.^[17]

A very recent report on the isolation and structural elucidation of alstonarsine A (**20**) from *Alstonia scholaris* emphasizes the fascinating constitutional diversity within the cyclohepta[b]indole class of alkaloids (Figure 4).^[18] The hexahydrocyclohepta[b]indole alkaloid alstonarsine A is characterized by the alstonarsine core carbon structure. The alstonarsine core carbon structure arises from the bicyclo[3.2.2]nonane scaffold. It was revealed that **20** possesses inhibitory activity against the serine/threonine kinase DRK2.

The core carbon structures of the vincamaginine type, the kopsifoline type and of the alstonarsine type differ fundamentally (Figure 5). The intricate architecture of these cyclohepta[b]indole alkaloids is paired with different biological activities. Thus, vincamaginine, kopsifoline and alstonarsine cyclohepta[b]indole alkaloids represent meaningful targets for natural product total synthesis. Synthetic planning may require specifically elaborated cyclohepta[b]indole building blocks. Hence, a deep and rich toolbox for the construction of cyclohepta[b]indole building blocks is essential. Thus, method development to supplement synthetic design constitutes a worthwhile contemporary endeavor of prime relevance. The ingenious



Jan Gierok was born in Wickede, Germany in 1993. He started to study chemistry at the Technical University of Dortmund in 2013 and completed his master studies in 2018 supervised by Martin Hiersemann and is currently carrying out his Ph.D. studies about the total synthesis of daphniphyllum alkaloids within the same workgroup.



Lars Benedix was born in Castrop-Rauxel, Germany in 1996. After graduation from high school in 2014 he began his studies in chemistry at the Technical University of Dortmund. He earned his masters degree in 2019 in the working group of Martin Hiersemann. Since then, he has started his Ph.D. studies on the usage of the Alkyne-Aza-de Mayo reaction for the synthesis of material molecules such as helicenes in the same working group.



Martin Hiersemann was born in Berlin-Steglitz, Germany. He studied chemistry at the FU Berlin. He went on to study organic chemistry with Johann Mulzer (Berlin), Gary Molander (Boulder), and Hans-Ullrich Reißig (Dresden). His research group is active in the development of synthetic methods as well as the synthesis of functional molecules of intricate architecture.

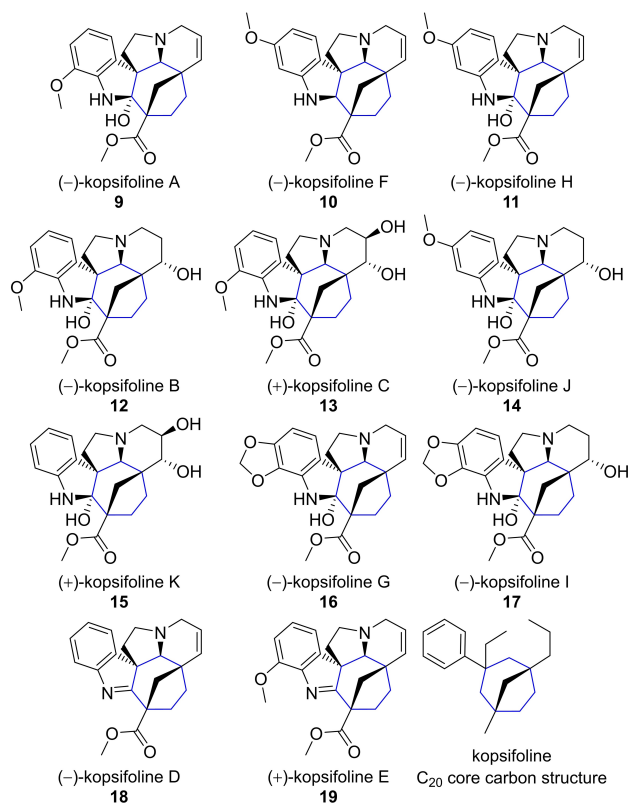


Figure 3. Kopsifoline-type cyclohepta[b]indole alkaloids.

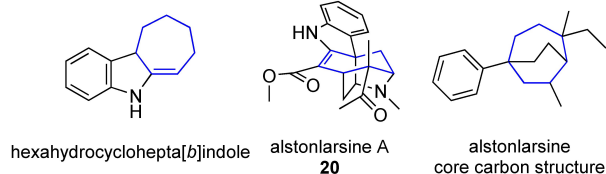


Figure 4. (+)-Alstonlarsine A, a hexahydrocyclohepta[b]indole alkaloid with bicyclo[3.2.2]nonane-derived core carbon structure.

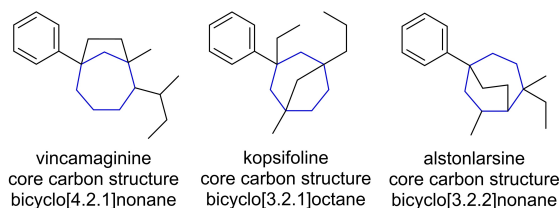


Figure 5. Core carbon structures of cyclohepta[b]indole alkaloids.

methods for cyclohepta[b]indole building block synthesis developed within the last few years mirror the persistent need for novel tools of ever-increasing efficiency and generality. Existing shortcomings will guide future developments.

3. Cyclohepta[b]indoles from Indoles

We consider an intermolecular ($m+n$) cycloaddition as a ring-forming bond reorganization.^[19] Two molecules contribute units of m and n linearly connected atoms. These units become connected at their respective termini by two new σ -bonds. Hence, a new cycle is formed containing ($m+n$) atoms. Importantly, this classification scheme will be valid regardless of the nature of the bond reorganization (pericyclic, concerted, non-concerted via transient intermediates).

3.1. (4+3) Cycloadditions

In 2016, Shi et al. reported the synthesis of racemic cyclohepta[b]indoles **23** by intermolecular (4+3) cycloaddition (Figure 6).^[20] When subjected to aqueous HBr in acetonitrile at elevated temperature, indolyl methanol **21** and γ,δ -unsaturated β -keto ester **22** underwent a diastereoselective (4+3) cycloaddition to afford racemic spirocyclic indolinones **23**. Notably, several Brønsted and Lewis acids were screened, however, cyclohepta[b]indoles were formed only in the presence of HBr.

In 2016, Xiao et al. revealed an ingenious synthetic access to bridged racemic cyclohepta[b]indoles **26** from substituted indolyl methanols **24** and cyclopentadiene (**25**) by intermolecular (4+3) cycloaddition (Figure 7).^[21] Cycloadditions were performed in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at room temperature. Solvent screening revealed that product formation is also possible in more cost-efficient 2,2,2-trifluoroethanol (TFE) or even aqueous acetic acid, although with inferior yields. Notably, the accessible core carbon structure of **26** features a bicyclo[3.2.1]octane segment and, therefore, is related to the kopsifoline core carbon structure (Figure 5).

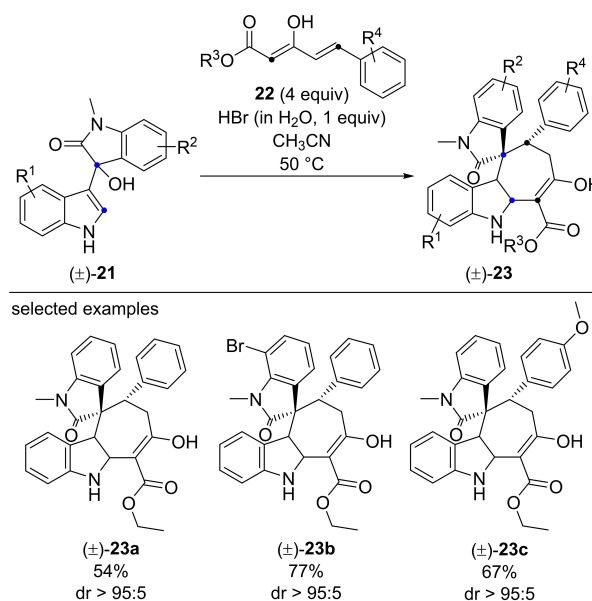


Figure 6. Racemic spiro-cyclohepta[b]indoles by Brønsted acid-mediated (4+3) cycloaddition.

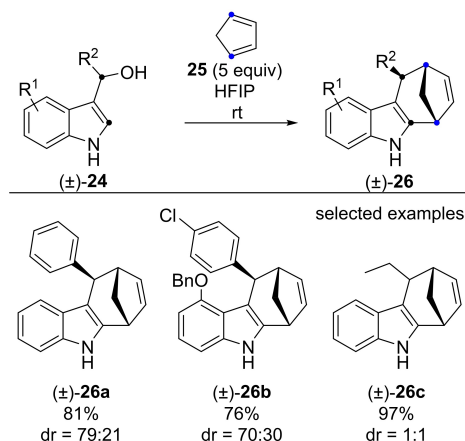


Figure 7. Synthesis of bridged racemic cyclohepta[b]indoles featuring the bicyclo[3.2.1]octane-derived core carbon structure related to the kopsifoline core.

In 2017, Zhang et al. published the synthesis of racemic tetrahydrocyclohepta[b]indoles **29** by intermolecular (4+3) cycloaddition of 2-vinylindoles **27** with 2-methylbut-3-yn-2-yl acetate **28** in the presence of catalytic amounts of dichloro(2-pyridinecarboxylato)gold (Figure 8).^[22] The authors used a modification of the original (4+3) cycloaddition reaction protocol to gain access to the methano-bridged cyclohepta[b]indol **29d**. Formation of **29d** results from consecutive (4+3) and (4+1) cycloadditions. The building block **29d** features a bicyclo[3.2.1]octane segment and is vaguely related to the kopsifoline core carbon structure (Figure 5).

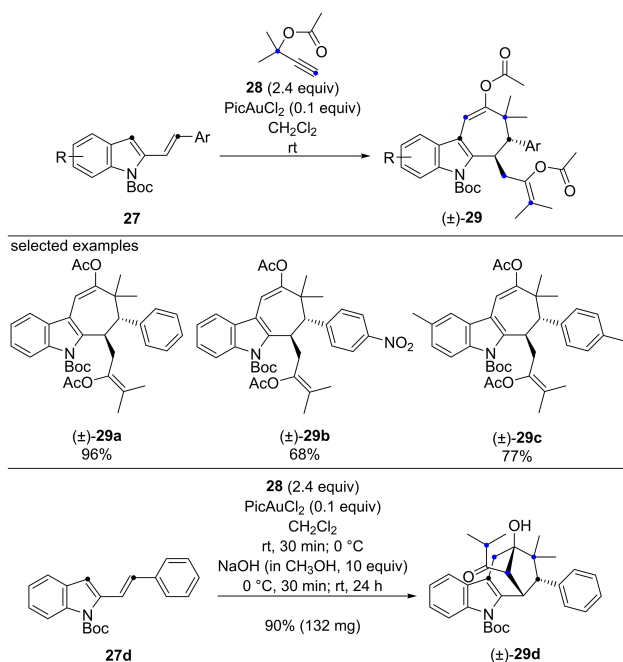


Figure 8. Racemic cyclohepta[b]indoles by Au-catalyzed diastereoselective intermolecular (4+3) cycloaddition

In 2018, Sun et al. disclosed the synthesis of non-racemic tetrahydrocyclohepta[b]indoles **32** from 2-vinyl indoles **30** and methyl 2-diazobut-3-enoates **31** in the presence of a chiral Davies dirhodium complex (Figure 9).^[23] The cascading annulation^[24] is probably initiated by a cyclopropanation with asymmetric induction by the chiral catalyst, and proceeds by a diastereospecific Cope rearrangement of the intermediate *cis*-divinyl cyclopropane to afford the highly substituted non-racemic tetrahydrocyclohepta[b]indoles **32**.

The protocol of Sun et al. was extended and adapted to convert 3-vinyl indoles **33** to tetrahydrocyclohepta[b]indoles **35** by catalytic asymmetric (4+3) cycloaddition (Figure 10).^[23]

In 2018, Masson et al. reported the synthesis of substituted non-racemic cyclohepta[b]indoles **39** by organocatalytic inter-

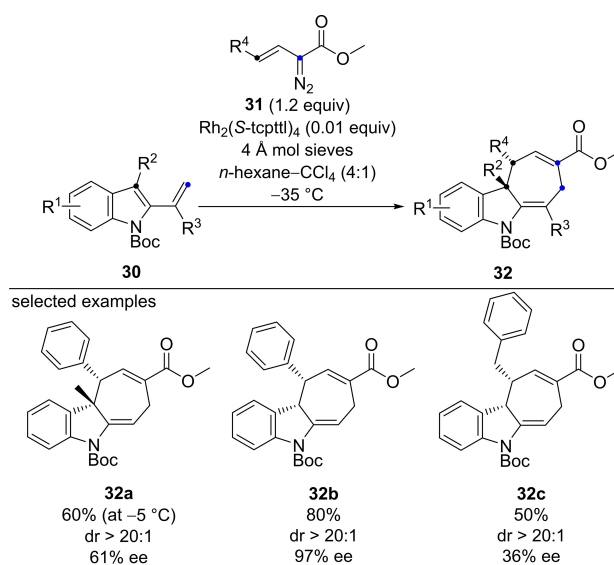


Figure 9. Non-racemic tetrahydrocyclohepta[b]indoles **35** by Rh-catalyzed diastereoselective intermolecular (4+3) cycloaddition

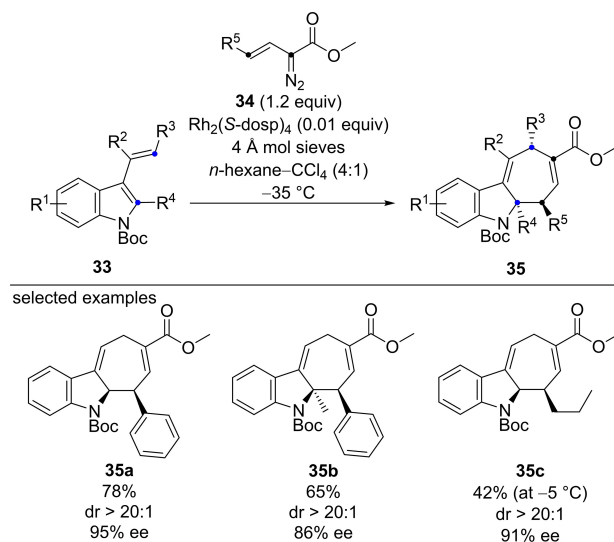


Figure 10. Non-racemic tetrahydrocyclohepta[b]indoles by catalytic asymmetric (4+3) intermolecular cycloaddition

molecular (4 + 3) cycloaddition (Figure 11).^[25] In the event, substituted indolyl methanols **36** reacted with Cbz-protected dienamines **37** in the presence of the chiral phosphoric acid TRIP (–)-**38**.

In 2020, Deng et al. disclosed the synthesis of substituted non-racemic cyclohepta[b]indoles by Pd(0)-catalyzed intermolecular (4 + 3) cycloaddition (Figure 12).^[26] Substituted 2,3-dimethyleneindolines **40** and the trimethylene methane zwitterion precursor **41** were subjected to a chiral catalyst complex generated in situ from Pd₂(dba)₃ and the BINOL-based phosphoramidite ligand **42**. Substituted cyclohepta[b]indoles **43** were thus accessible in good yields and with mostly high enantio- and diastereoselectivities. Palladium(II) pre-catalyst complexes Pd(PPh₃)₂Cl₂ and [Pd(allyl)Cl]₂ were ineffective.

In 2020, Rossi et al. described the synthesis of racemic ethano-bridged cyclohepta[b]indoles **46** by intermolecular (4 + 3) cycloaddition (Figure 13).^[27] Product formation was accomplished by reacting 2-vinylindoles **44** and α-bromocyclopentanone **45** in the presence of 2,2,2-trifluoroethanol and Hünig's base in toluene. Constitutionally, the accessible bicyclo[4.2.1]nonane-derived building block is loosely related to the bicyclo[4.2.1]nonane-derived core carbon structure of the vincamaginine alkaloids (Figure 5).

When using acyclic α-bromoketones **47**, racemic cyclohepta[b]indoles **48** were made accessible by diastereoselective (4 + 3) cycloaddition (Figure 14).^[27] Subjecting furo[3,2-b]indoles **49** and 2-bromo cyclopentanone **45** to the (4 + 3) cycloaddition protocol afforded racemic ethano- and oxo-bridged cyclohepta[b]indoles **50** as single diastereomers (Figure 15).^[27]

Racemic cyclohepta[b]indoles **51** highlighting a 8-oxabicyclo[3.2.1]octane core structure were synthesized by diastereoselective (4 + 3)-cycloaddition between furo[3,2-b]indole-derived dienes **49** and acyclic α-bromo ketones **47** (Figure 16).^[27]

3-(4-Methylstyryl)-substituted indole **52** was also susceptible to (4 + 3) cycloaddition with 2-bromo cyclopentanone **45** under previously optimized conditions (Figure 17).^[27] The substituent pattern of the bicyclo[4.2.1]nonane core of the ethano-bridged cyclohepta[b]indole **53** loosely related to the bicyclo[4.2.1]nonane segment of the vincamaginine core carbon structure (Figure 5).

In 2020, Lepovitz and Martin published a total synthesis of racemic exotines A ((±)-**57**) and B ((±)-**58**) by (4 + 3) cycloaddition of an in situ formed allyl indolyl carbenium ion.^[28]

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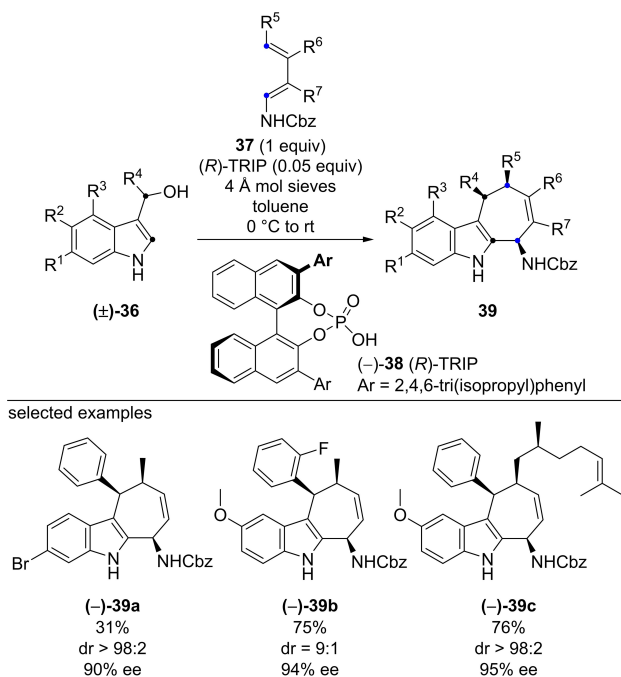


Figure 11. Non-racemic cyclohepta[b]indoles by asymmetric organocatalytic (4 + 3)-cycloaddition.

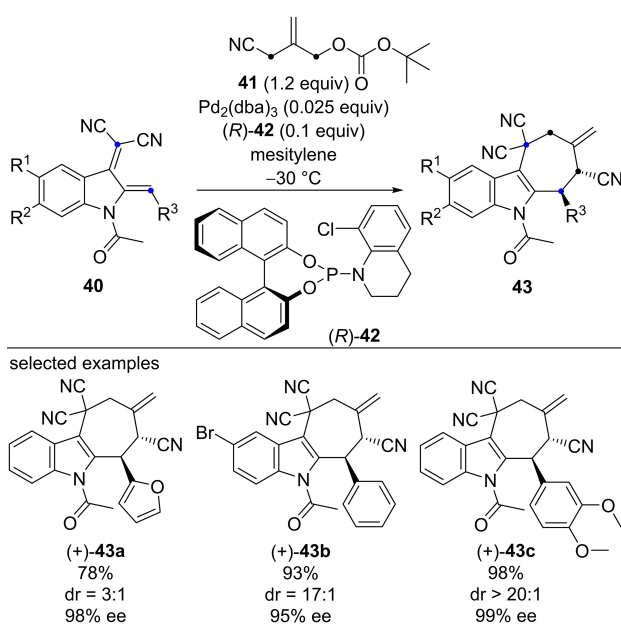


Figure 12. Non-racemic cyclohepta[b]indoles by asymmetric Pd(0) catalyzed (4 + 3) cycloaddition

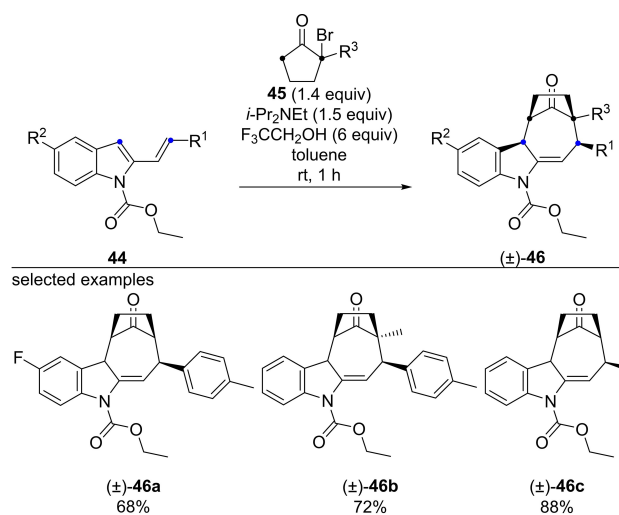


Figure 13. Racemic bicyclo[4.2.1]nonane-derived cyclohepta[b]indoles by intermolecular (4 + 3) cycloaddition using a cyclic oxalyl cation precursor.

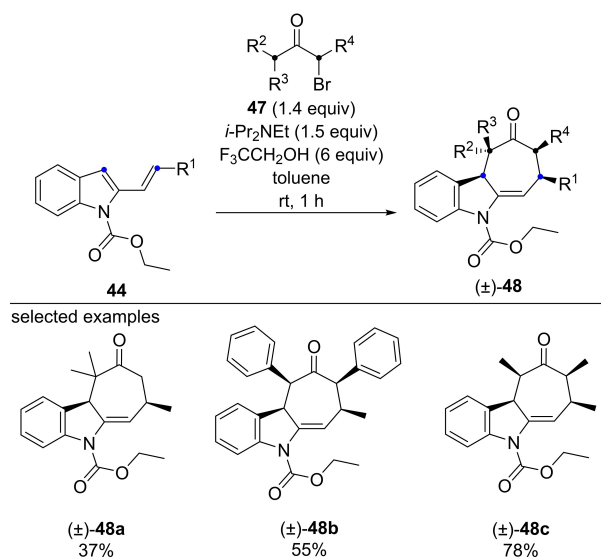


Figure 14. Racemic cyclohepta[b]indoles by intermolecular (4 + 3)-cycloaddition using an acyclic oxyallyl cation precursor.

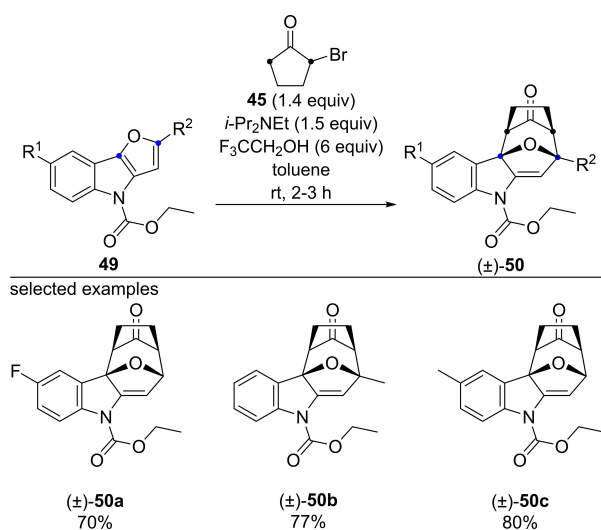


Figure 15. Racemic bridged cyclohepta[b]indoles by intermolecular (4 + 3) cycloaddition using furo[3,2-*b*]indole-derived dienes.

Inspired by the possible biosynthetic pathway proposed by Jiang *et al.* in 2015,^[29] they developed a one-pot procedure using indole (**56**), prenal (**55**) and an appropriately substituted coumarin derivative **54** in the presence of *p*-TsOH·H₂O to obtain (±)-**57** or (±)-**58** (Figure 18).

Notably, Trauner *et al.* used a similar approach to access the advanced building block (±)-**59** for their total synthesis of (±)-**58** (Figure 19).^[30]

In 2020, Deng *et al.* reported the synthesis of non-racemic cyclohepta[b]indoles **63** by organocatalytic intermolecular (4 + 3)-cycloaddition.^[31] 2-Nitrovinylindoles **60** were reacted with four-membered β-ketoamides **61** in an intermolecular Michael addition in presence of the chiral organocatalyst **62**. Subse-

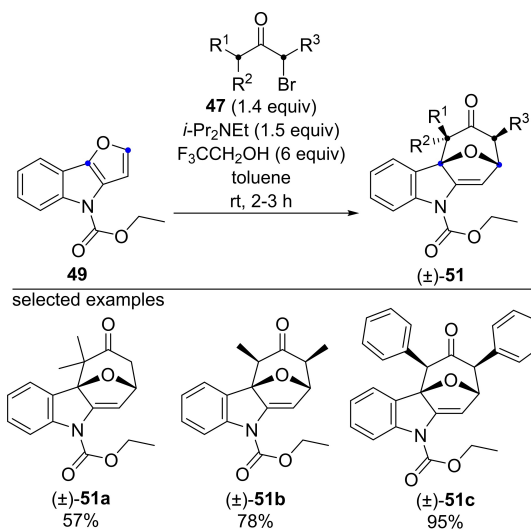


Figure 16. Racemic oxo-bridged cyclohepta[b]indoles by diastereoselective (4 + 3) cycloaddition of furo[3,2-*b*]indole-derived dienes and acyclic oxyallyl cation precursors.

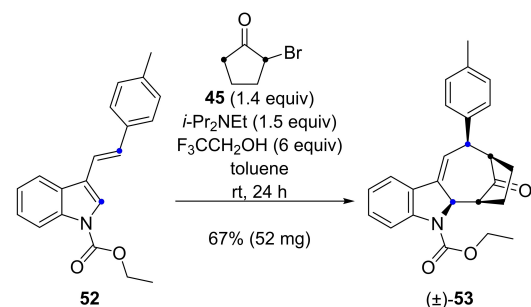


Figure 17. Racemic bicyclo[4.2.1]nonane-derived cyclohepta[b]indole by diastereoselective (4 + 3) cycloaddition.

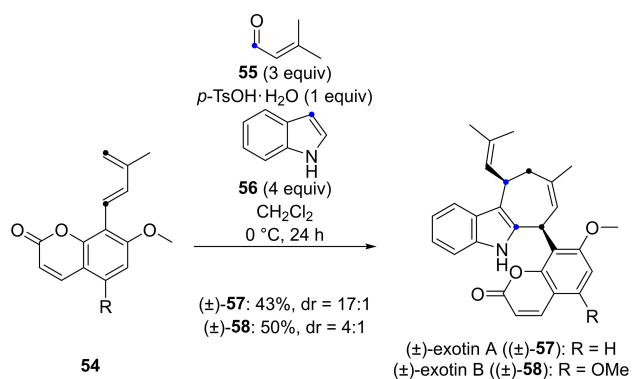


Figure 18. Racemic exotin A ((±)-**57**) and B ((±)-**58**) by (4 + 3) cycloaddition.

quent retro-aldol-type ring-expansion delivered the enantio-merically enriched cyclohepta[b]indoles **63** (Figure 20).

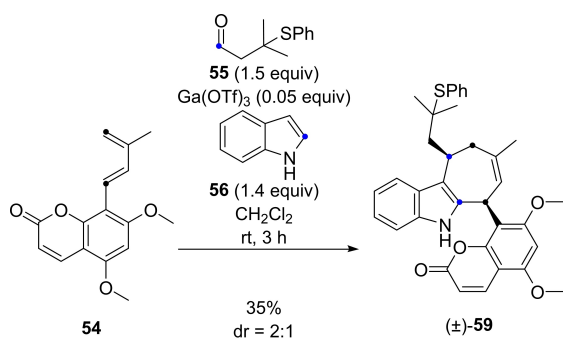


Figure 19. Toward racemic exotin A ((±)-57) and B ((±)-58) by (4+3) cycloaddition.

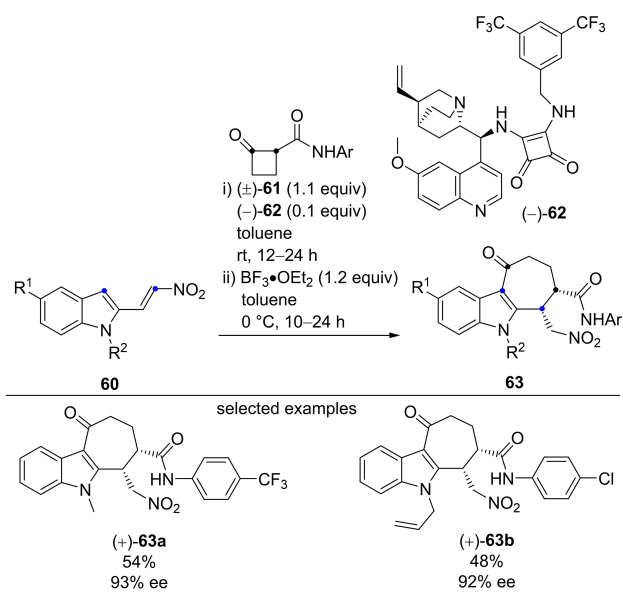


Figure 20. Enantiomerically enriched tetrahydrocyclohepta[b]indoles by ring-expansive (4+3)-cycloaddition exploiting asymmetric organocatalysis.

3.2. (5+2) Cycloadditions

In 2017, Ohno et al. described the synthesis of dihydrocyclohepta[b]indoles **66** by Au(I)-catalyzed intermolecular (5+2) cycloaddition of 1,5-diphenylpenta-1,4-diyne **64** and 5-substituted indoles **65** (Figure 21).^[32]

In 2018, Nishida et al. disclosed the synthesis of racemic tetrahydrocyclohepta[b]indoles **69** by intermolecular (5+2) cycloaddition of methyl 2-((1*H*-indol-2-yl)methyl)acrylates **67** and terminal or internal alkynes **68** in the presence of catalytic amounts indium(III)iodide (Figure 22).^[33] When applicable, the In(III)-catalyzed (5+2) cycloaddition proceeded with excellent 7,8-*trans* diastereoselectivity.

In 2018, Haak et al. revealed the synthesis of racemic hexahydrocyclohepta[b]indol **72** from indole (**56**) and pent-1-en-4-yn-3-ol **70** by (5+2) cycloaddition in the presence of catalytic amounts of the Ru(0) complex **71** (Figure 23).^[34] Two additional lower-yielding examples were reported.

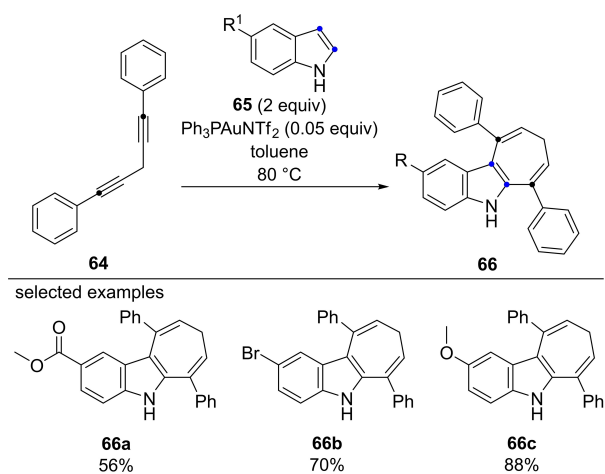


Figure 21. Dihydrocyclohepta[b]indoles **66** by Au(I)-catalyzed intermolecular (5+2) cycloaddition.

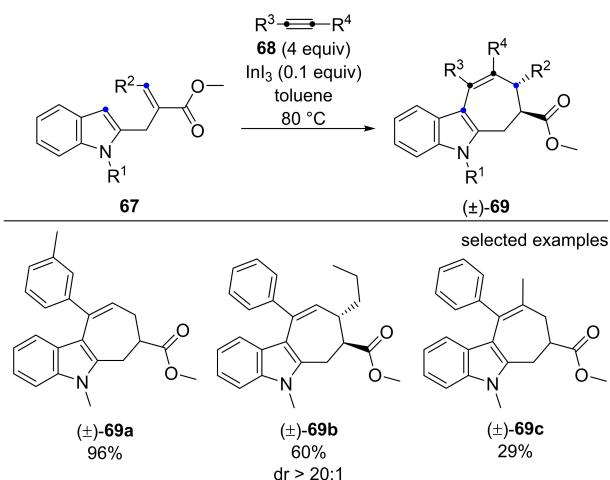


Figure 22. Racemic tetrahydrocyclohepta[b]indoles by In(III)-catalyzed intermolecular (5+2) cycloaddition.

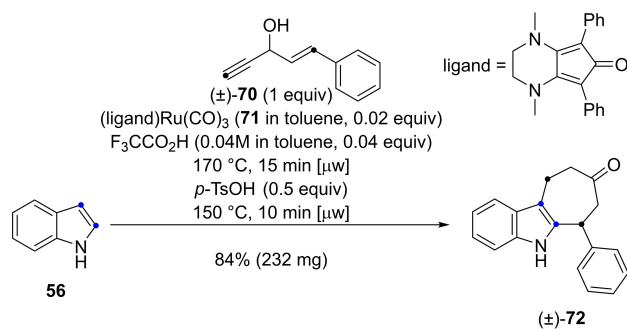


Figure 23. Racemic hexahydrocyclohepta[b]indoles by Ru(0)-catalyzed intermolecular (5+2) cycloaddition.

In 2018, Anand et al. reported the synthesis of cyclohepta[b]indole-derived tetra- and pentacycles **75** by Au-catalyzed intermolecular (5+2) cycloaddition of indoles **73** and 2-alkynyl

p-quinone methides **74** (Figure 24).^[35] The method could be useful in accessing rather exotic cyclohepta[b]indole-based azaacenes.

In 2019, France et al. reported the synthesis of racemic tetrahydrocyclohepta[b]indoles **78** by intermolecular (5 + 2) cycloaddition (Figure 25).^[36] The catalytically active species is formed in situ from calcium triflimide and tetrabutylammonium hexafluorophosphate. Notably, triflimide (HNTf₂) catalyzed the formation of **78b** in 64% yield. Substituent effects profoundly

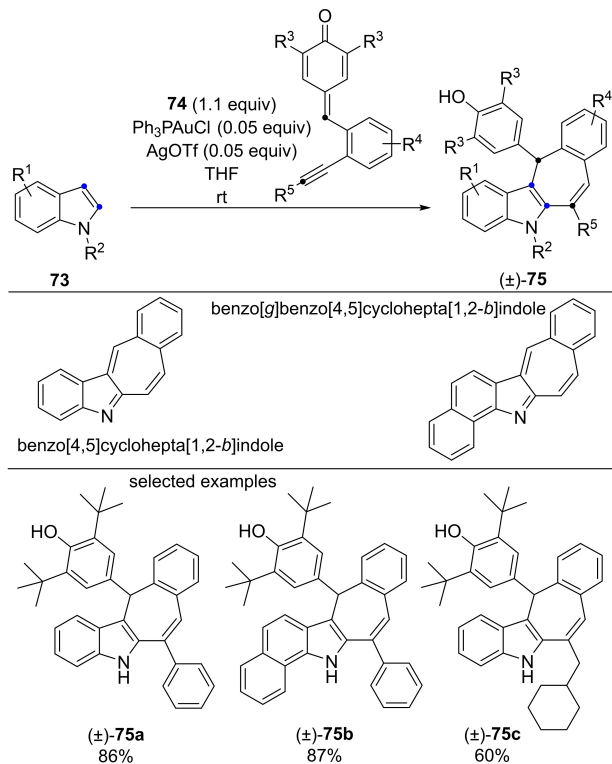


Figure 24. Racemic cyclohepta[b]indole-derived azaacene precursors by Au(I)-catalyzed intermolecular (5 + 2) cycloaddition.

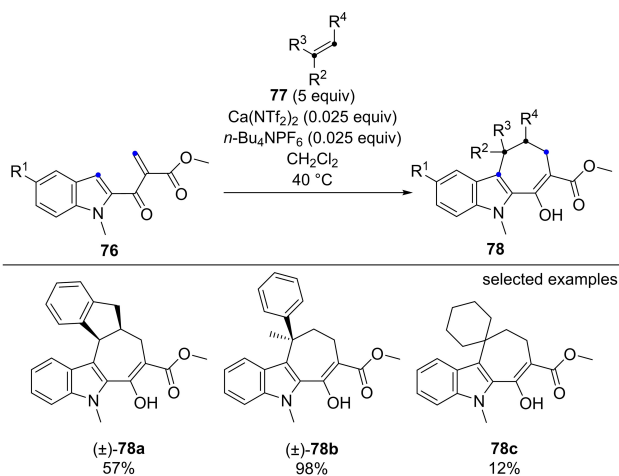


Figure 25. Racemic tetrahydrocyclohepta[b]indoles by catalyzed intermolecular (5 + 2) cycloaddition.

determine reactivity and chemoselectivity. Subjecting the initially formed keto/enol mixtures of **78** to the forcing conditions of a nucleophilic alkoxydecarbonylation delivered the corresponding tetrahydrocyclohepta[b]indolones (not depicted).

Intriguingly, the racemic bicyclo[3.2.2]nonane-derived cyclohepta[b]indole **79** was obtained by two consecutive non-concerted (5 + 2) cycloadditions of **76** with phenyl vinyl thioether **77** (Figure 26).^[36] The core carbon structure of the bicyclo[3.2.2]nonane-derived cyclohepta[b]indole **79** resembles the core carbon structure of astolarsine **20** (Figure 5).

3.3. Miscellaneous cyclizations

In 2020 Huang et al. published the Rh-catalyzed synthesis of racemic benzo[6,7]-cyclohepta[1,2-*b*]indoles from indoles **80** and diazo compounds **81** by formal (6 + 1) cycloaddition. (Figure 27).^[37]

In 2021, Yang et al. reported the synthesis of substituted hexahydrocyclohepta[b]indoles **85** by photocatalyzed cyclization of tryptamine-derived vinylogous amides **83** (Figure 28).^[38] The Ir(III) complex **84** served as the photocatalyst and operated under irradiation with visible light. It was demonstrated that the photocatalytic two-carbon ring-expansion is triggered by a

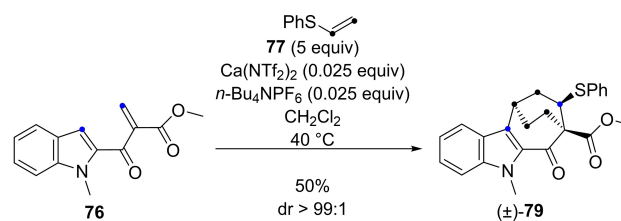


Figure 26. Racemic bicyclo[3.2.2]nonane-derived cyclohepta[b]indole by consecutive intermolecular (5 + 2) cycloadditions.

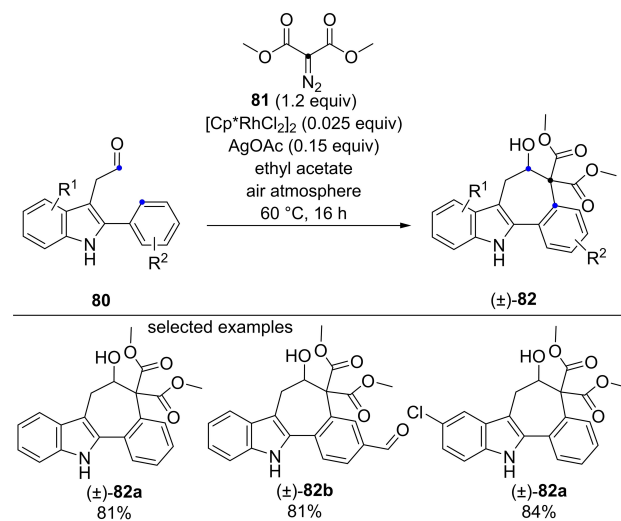


Figure 27. Racemic tetrahydrobenzo[6,7]cyclohepta[1,2-*b*]indoles by Rh-catalyzed (6 + 1) cycloaddition.

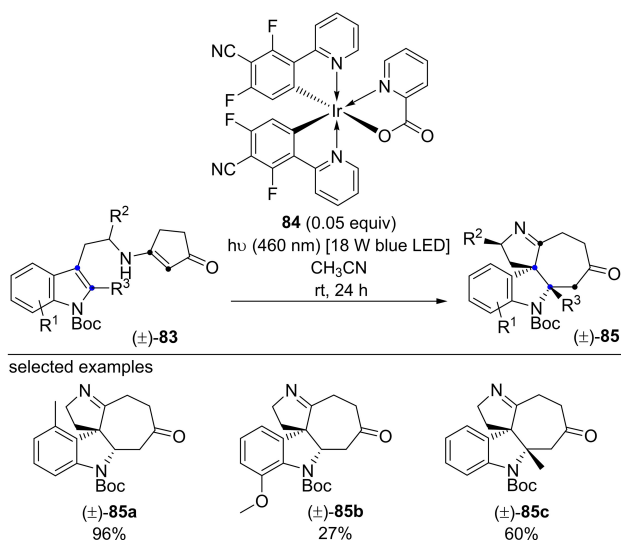


Figure 28. Racemic hexahydrocyclohepta[b]indoles by photocatalyzed cyclization.

single electron oxidation of the substrate molecule and subsequently proceeds along a reaction coordinate shaped by transient radical intermediates.

In 2021, Ackermann et al. revealed the synthesis of hexahydrocyclohepta[b]indoles **88** by Ru(II)-catalyzed aromatic C–H activation. The chiral carbonic acid (–)-**87** was utilized to achieve moderate external asymmetric induction (Figure 29).^[39]

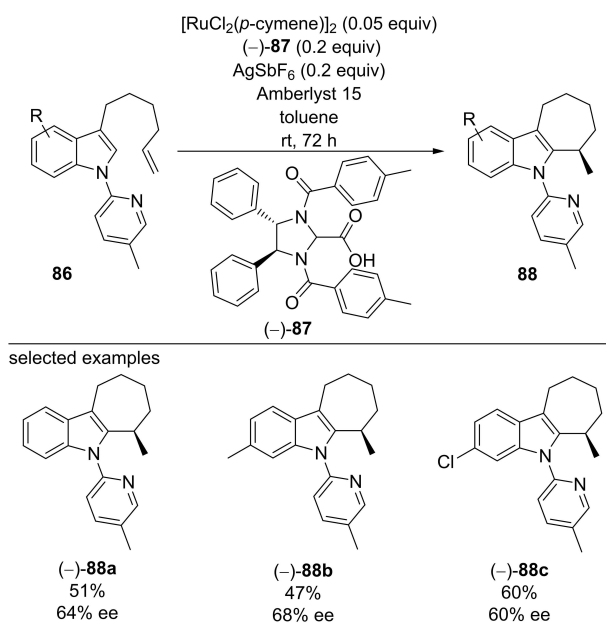


Figure 29. Enantiomerically enriched hexahydrocyclohepta[b]indoles by Ru(II)-catalyzed cyclization.

4. Cyclohepta[b]indoles by Indole Synthesis

Ingenious (4 + 3) and (5 + 2) cycloadditions as well as cyclizations that exploit a wide variety of indole derivatives have been developed recently to access the cyclohepta[b]indole scaffold. The assembling of the cyclohepta[b]indole scaffold by de novo synthesis of the indole nucleus represents a logic alternative to well established synthetic designs based on cycloaddition and cyclization.

In 2018, He et al. reported the synthesis of racemic cyclohepta[b]indoles **91** by (3 + 2) cycloaddition of the *N*-aryliminium tetrafluoroborate of tropone **90** with the benzyne precursor **89** (Figure 30).^[40] In situ formation of benzynes from **89** required a large excess of fluoride and crown ether. Notably, a second benzyne moiety is attached to the product cyclohepta[b]indole. The authors propose a sequence consisting of intermolecular [8 + 2] cycloaddition and intermolecular ammonium ene-type reaction to explain indole nucleus formation and benzyne addition.

By varying stoichiometry and conditions, the theme could be diversified to provide even more intricate condensation products from *N*-aryliminium tetrafluoroborates of tropone and benzyne precursors, for instance **92** (Figure 31).^[40]

In 2018, Tymann et al. made an initial report on a photochemical synthesis of the cyclohepta[b]indole scaffold.^[41] Originally designed for tropolone synthesis is the context of terpenoid total synthesis,^[42] the photochemically triggered two-carbon ring expansion was adapted and expanded for cyclohepta[b]indole synthesis. In 2020, Tymann et al. disclosed in more detail the synthesis of 6,7-dihydrocyclohepta[b]indol-8(5*H*)-ones **94** by irradiation of *N*-Boc protected vinylogous amides **93** (Figure 32).^[43] The two-carbon ring-expansion exploits the inherent atom economy of a photochemically triggered cycloisomerization.

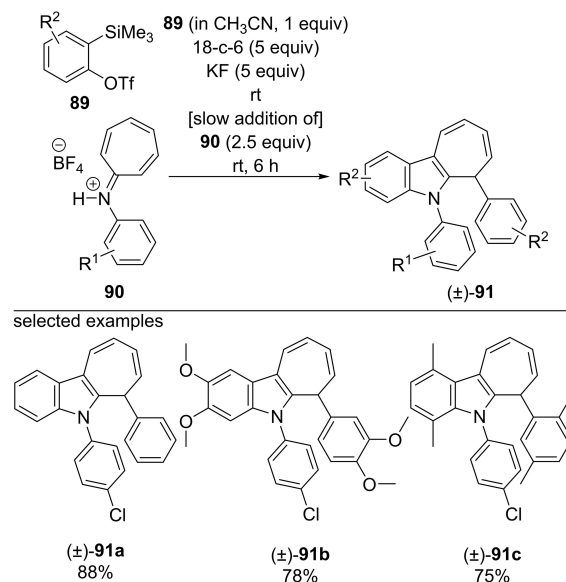


Figure 30. Racemic dihydrocyclohepta[b]indoles by benzyne chemistry.

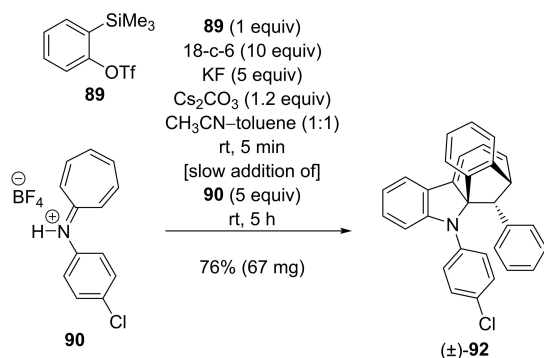


Figure 31. Exploiting benzyne for the synthesis of racemic bridged cyclohepta[b]indoles.

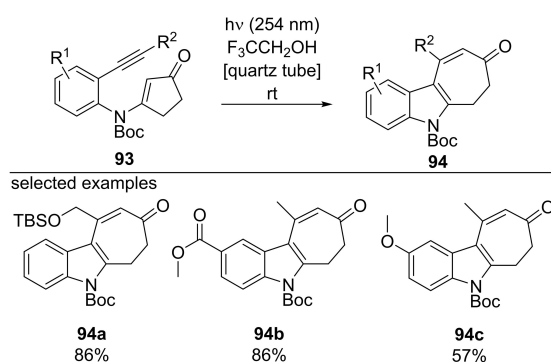


Figure 32. Synthesis of the tetrahydrocyclohepta[b]indole scaffold by photochemically triggered intramolecular two-carbon ring expansion.

In 2019, Xu et al. disclosed the intramolecular cascade cyclization of α -diazo phenyl acetates **95** in the presence of copper(II)hexafluoroacetylacetonate to deliver racemic dihydrocyclohepta[b]indoles **96** (Figure 33).^[44] One-carbon ring-expansion

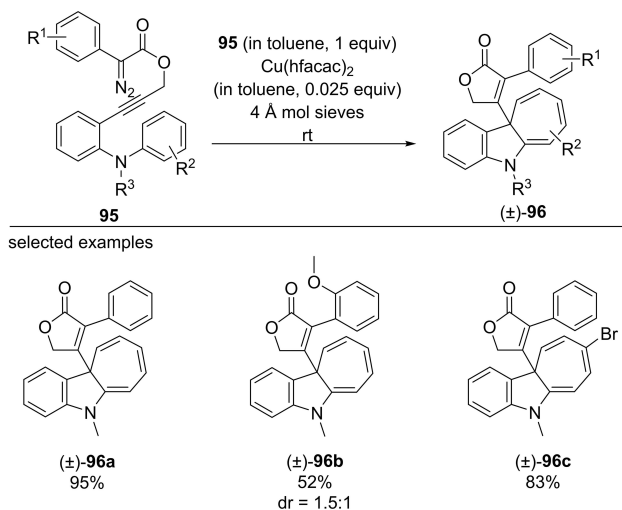


Figure 33. Racemic dihydrocyclohepta[b]indoles by Cu-catalyzed cascade cyclization.

by intramolecular Buchner reaction is considered to be accountable for the assembling of the cyclohepta[b]indole scaffold.

5. Summary

Since 2016, advancement in the chemistry of the cyclohepta[b]indole class of compounds was propelled by newly discovered natural products and recently developed synthetic methods. Intricate polycyclic cyclohepta[b]indole alkaloids have been introduced lately. The vincamaginine, the kopsifoline, and the alstonlarsine type core carbon structures are derived from bicyclo[4.2.1]nonane, bicyclo[3.2.1]octane and bicyclo[3.2.2]nonane structural motifs. The cyclohepta[b]indole scaffold may be accessed from indoles or by indole synthesis from anilines. Exploiting accessible indole building blocks, innovative (4 + 3) and (5 + 2) cycloadditions have been developed to access the cyclohepta[b]indole scaffold. Catalysis and asymmetric catalysis play a prominent role in perhydrocyclohepta[b]indole synthesis. Cyclohepta[b]indole-by-indole syntheses from aniline building blocks showcase the ability to direct the reactivity of metal carbenes, benzyne, and photochemically accessed radicals. We encourage the application of the available methodology for the synthesis of cyclohepta[b]indole-derived target molecules.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkaloids · Biological activity · Cycloaddition · Photochemistry · Synthetic methods

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