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RECENT ADVANCES IN SYNTHETIC STRATEGIES FOR THE C4a,C9a-FUSED TETRACYCLIC HYDROCARBAZOLE CORE STRUCTURE OF MINFIENSINE AND RELATED AKUAMMILINE ALKALOIDS

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Abstract – The *Strychnos* alkaloid minfiensine and its analogs among the akuammiline alkaloids have a variety of biological activities, including anti-tumor and analgesic activities, and have therefore attracted considerable synthetic interest. Here we provide an overview of recent advances in methodologies for the construction of the characteristic tetracyclic hydrocarbazole core structure containing a fused pyrrolidine ring at C4a and C9a.

INTRODUCTION

The tetrahydrocarbazole **1** bearing a fused pyrrolidine ring at C4a and C9a forms the core structure of the *Strychnos* alkaloid minfiensine (**2**)[1-4] and its analogs among the akuammiline alkaloids, such as vincorine (**3**),[5-7] echitamine (**4**)[8] and corymine (**5**) (Figure 1).[9,10] These alkaloids have various biological activities, including anti-tumor[11] and analgesic activities.[12-14] These activities, together with the complex structures including a characteristic cage-like motif, have attracted the interest of synthetic chemists.[15]

In 2005, Overman and co-workers reported the first total synthesis of minfiensine (**2**) with tetracyclic hydrocarbazole **9** as a key intermediate (Scheme 1).[1] They employed an enantioselective intramolecular Heck reaction of **6** followed by iminium ion mediated intramolecular cyclization of amine to construct the corresponding tetracyclic hydrocarbazole **9**, which lead them to the synthesis of **2**. In the report, Overman mentioned about the utility of the tetracyclic hydrocarbazole **9** for constructing those types of alkaloids. Since then, most synthetic works on **2** and the structurally related akuammiline alkaloids have been focused on the construction of the characteristic tetracyclic hydrocarbazole core, such as **9**.[16-18]

Here, we review recent advances in methodologies for the construction of the C4a,C9a-fused tetracyclic hydrocarbazole skeleton (**1**).

The core structure **1** possesses an all-carbon quaternary stereogenic center at C4a and an *N*,*N*-aminal at C9a (Figure 2), and synthetic approaches reported so far can be categorized into three main types: 1) intramolecular alkylation, 2) [3+2] cycloaddition, and 3) dearomatization of phenols. The intramolecular alkylation approach is straightforward and has been widely explored by utilizing tryptamine derivatives **10** with a side chain bearing an electrophilic moiety at C2 in the indole for cascade construction of the quaternary carbon center at C4a and the *N*,*N*-aminal moiety at C9a. In the case of the [3+2] cycloaddition approach, the new bond at C4a and C9a can be constructed in a single step by the reaction of tricyclic indole derivatives **11** with three-atom components such as aziridine **12**. In the third approach, researchers have focused on dearomatization of diarylamine **13** with phenols and subsequent intramolecular nucleophilic conjugate addition to the resulting enone. In the following sections, we review advances in each of these three main approaches, as well as some additional strategies.

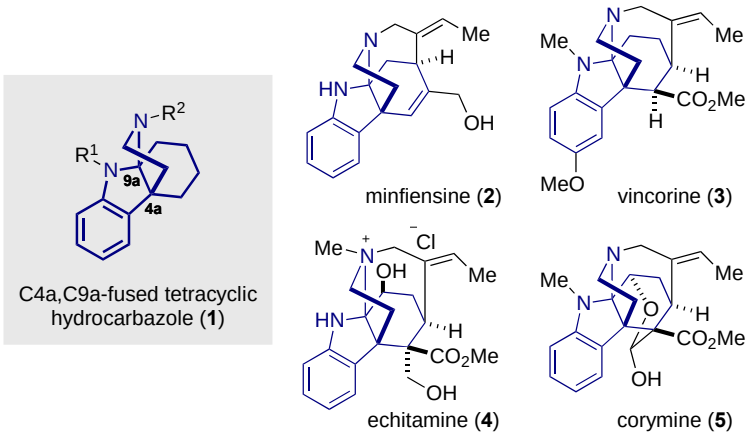
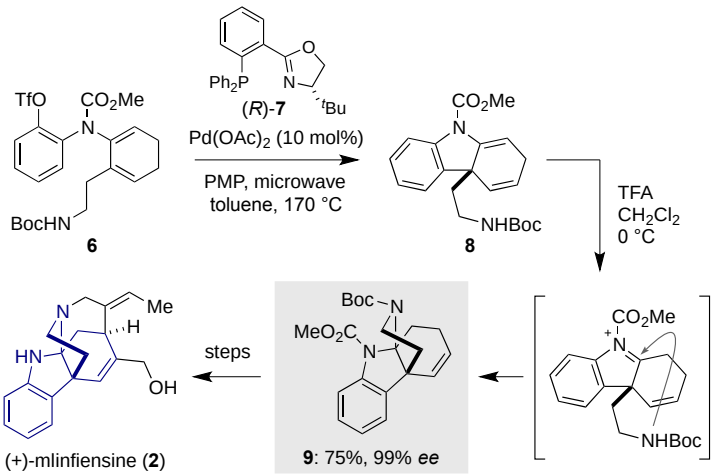


Figure 1. Structures of the *Strychnos* alkaloid minfiensine (**2**) and analogous akuammiline alkaloids having a C4a,C9a-fused tetracyclic hydrocarbazole motif



Scheme 1. First total synthesis of (+)-minfiensine (**2**) through a construction of tetracyclic carbazole **9** by Overman's group

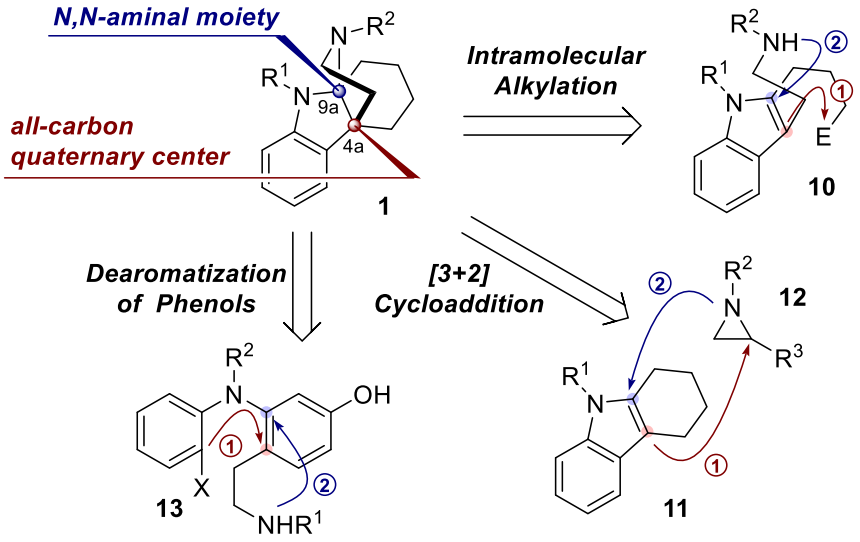


Figure 2. Main synthetic strategies for the construction of C4a,C9a-fused tetracyclic hydrocarbazoles

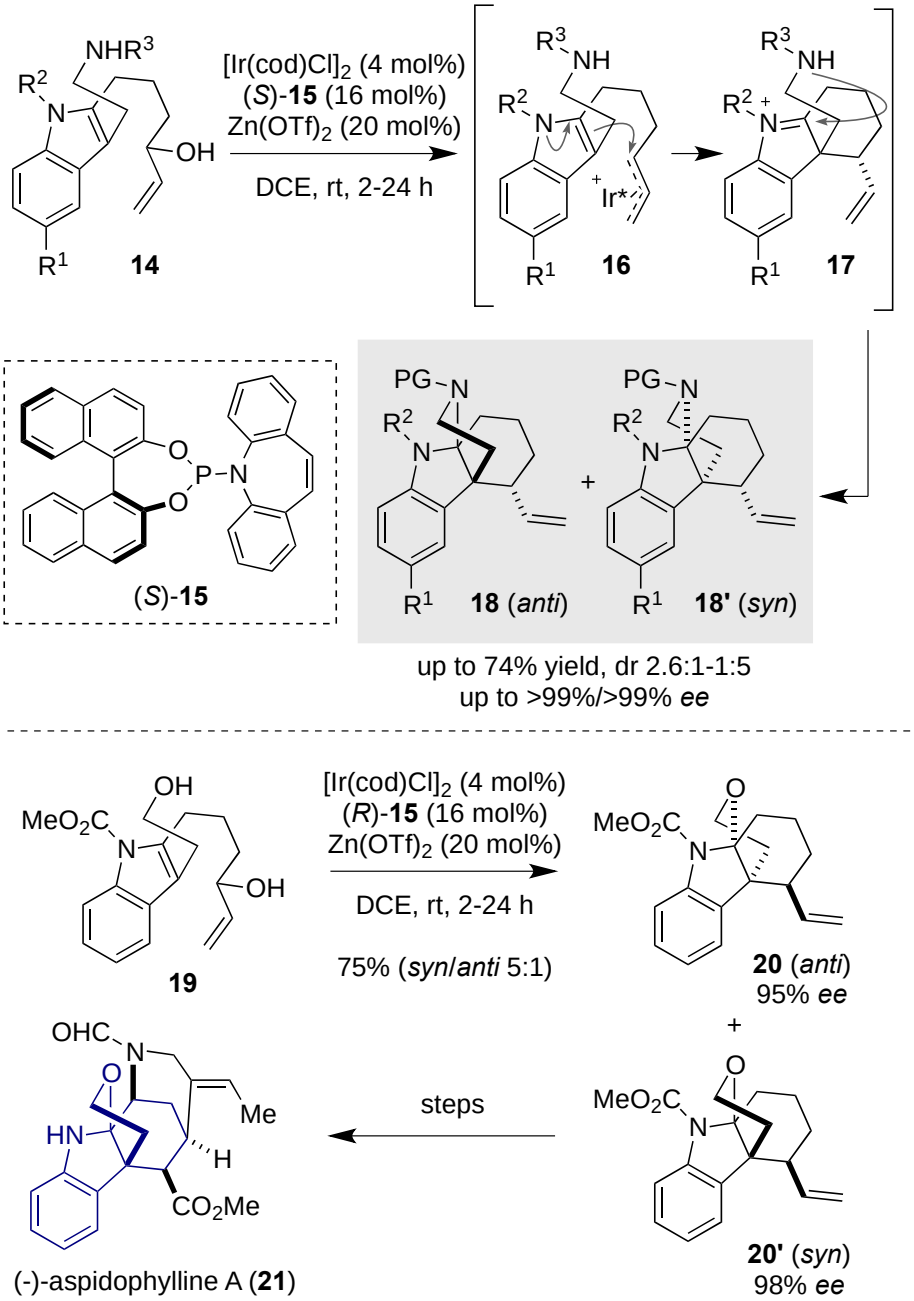
INTRAMOLECULAR ALKYLATION

The C3 position in indoles is strongly nucleophilic.[19] In the case of indoles substituted at this position, dearomatization of the pyrrole ring occurs by nucleophilic reaction at C3, generating a highly electrophilic iminium cation. By applying this strategy to tryptamine derivatives, a multiple ring system can be constructed via a cascade reaction,[20] and this is a powerful approach for construction of the tetracyclic hydrocarbazole skeleton.

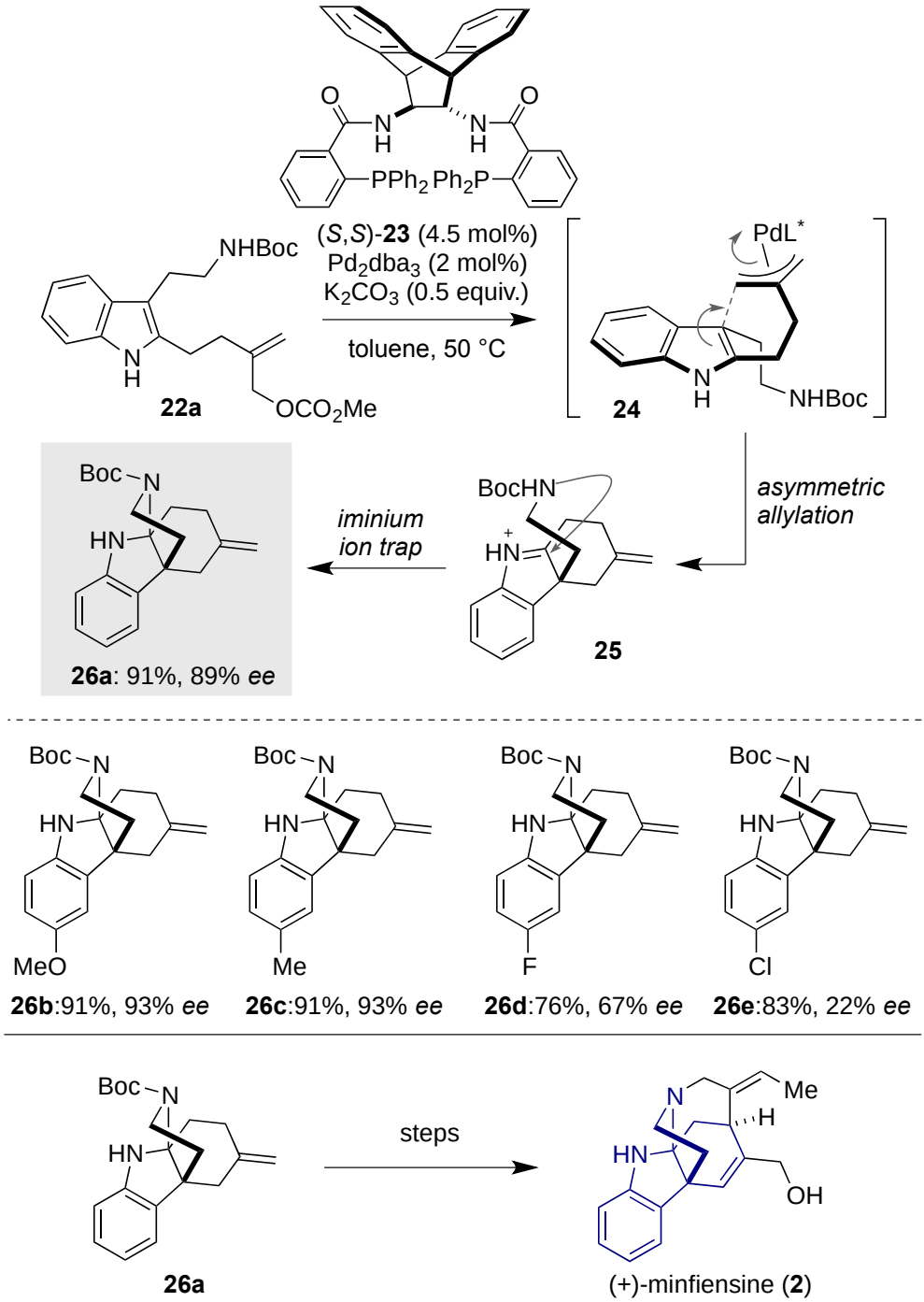
Yang and co-workers synthesized tetracyclic hydrocarbazoles from tryptamine derivative **14** bearing an allylic alcohol moiety by employing an iridium catalyst.[21] They employed Carreira's chiral phosphoramidite ligand (*S*)-**15**[22] with $Zn(OTf)_2$ as a promoter in the presence of the iridium catalyst, resulting in nucleophilic attack at C3 to generate the π-allyl cation **16**, followed by nucleophilic addition of the amine to the subsequently formed iminium cation **17** (Scheme 2). The reaction affords a mixture of *anti* and *syn* products in good yield with high enantioselectivity. This reaction was applied to the synthesis of tetrahydrofuran-fused tetracyclic hydrocarbazole **20'**, leading to the first total synthesis of the akuammiline alkaloid (-)-aspidophylline A (**21**) by the same group.

A similar type of dearomative cyclization of tryptamine derivatives with allyl carbonate **22a** was reported by Jiao and co-workers, who utilized the diphosphine ligand (*S*,*S*)-**23** with a dihydro-9,10-ethanoanthracene backbone[23] in the presence of a palladium catalyst to obtain tetracyclic hydrocarbazole **26a** via π-allylpalladium cation **24** (Scheme 3).[24] In this reaction, the intramolecular nucleophilic addition of the amine to the iminium cation intermediate **25** gave **26a** in 91% yield with 89%

ee. Substituents on the aromatic ring in the indole affect the enantioselectivity of the reaction. High enantioselectivity was obtained when an electron-donating group was present on the aromatic ring, such as in **26b** and **26c**, while the enantioselectivity was decreased to 22-76% ee in the case of an electron-withdrawing group on the aromatic ring, such as in **26d** and **26e**. The same group reported the total synthesis of (+)-minfiensine (**2**) from the tetracyclic hydrocarbazole **26a**.



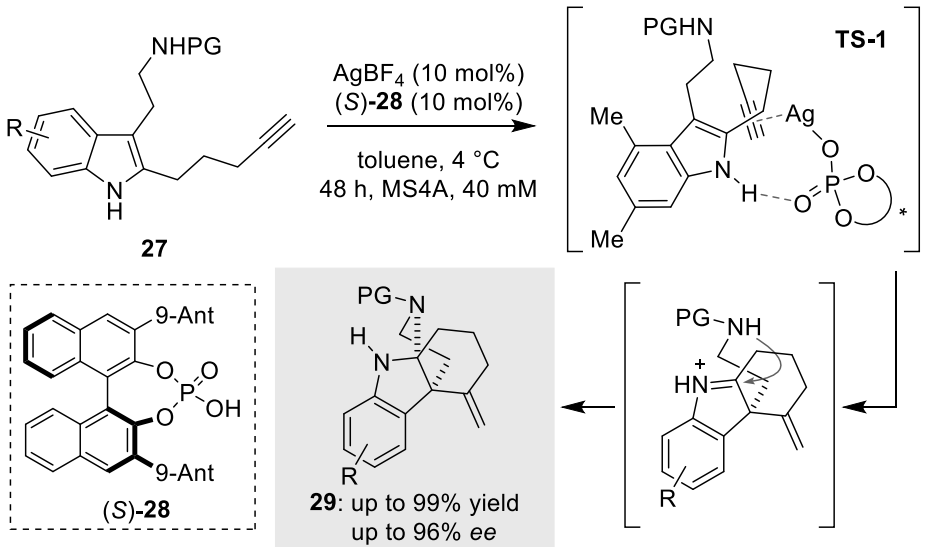
Scheme 2. Enantioselective construction of tetracyclic hydrocarbazole **18** via iridium-catalyzed enantioselective cyclization of indole **14**, leading to a total synthesis of (-)-aspidophylline A (**21**) (Yang's group)



Scheme 3. Enantioselective construction of tetracyclic hydrocarbazoles **26** via palladium-catalyzed enantioselective cyclization of indole **22**, leading to a total synthesis of (+)-minfiensine (**2**) (Jiao's group)

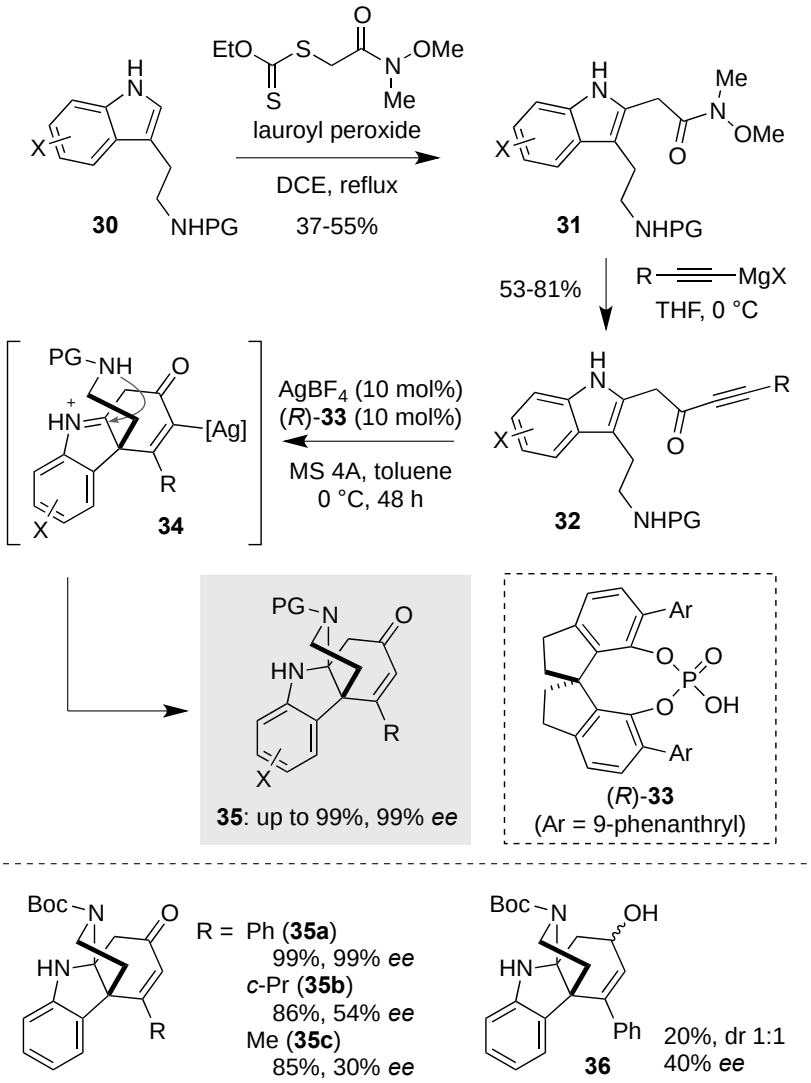
In 2017, Wang and co-workers reported a synthesis of tetracyclic hydrocarbazoles **29** from tryptamine derivatives **27** bearing an alkynyl group via 6-*exo*-*dig* cyclization of an iminium cation by utilizing chiral phosphoric acid (*S*)-**28** bearing a 9-anthryl group at the 3,3' position together with a complex of Ag(I) and phosphoric acid (Scheme 4).[25] In this reaction, tetracyclic hydrocarbazoles **29** were obtained in up to 99% yield with 96% ee. DFT calculations suggested that hydrogen-bonding interaction between oxygen of phosphoric acid and NH of indole is crucial to stabilize the transition state (**TS-1**).

A similar type of activation of alkynes using Ag(I) for the construction of the tetracyclic hydrocarbazole skeleton was reported by Unsworth and co-workers (Scheme 5).[26,27] The 6-*endo-dig* cyclization of ynone **32** proceeded under similar conditions to those reported by Wang, and various tetracyclic hydrocarbazoles **35** were obtained in high yield with high enantioselectivity. The enantioselectivity of the products increased as the bulkiness of the R group was increased (**35a**-**35c**). An ynone moiety in the substrate **32** is crucial to obtain the product in high yield with high enantioselectivity. The cyclized product **36**, obtained from the corresponding propargyl alcohol, was produced in a low yield of 20%, and with only 40% ee. The ynones **32** was prepared from the tryptamine derivatives **30** by radical alkylation followed by treatment with alkynyl Grignard agents. With the three-steps simple manipulation, a variety of tetracyclic hydrocarbazoles were synthesized.

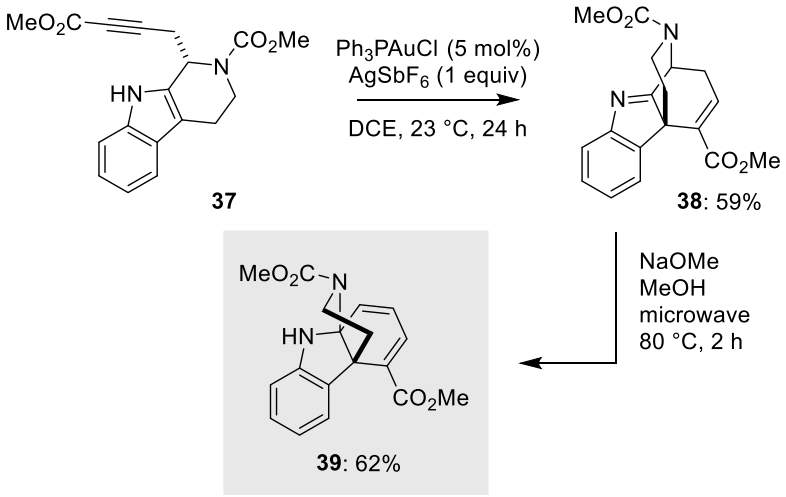


Scheme 4. Enantioselective construction of tetracyclic hydrocarbazole **29** via Ag(I) promoted 6-*exo-dig* cyclization of **27** (Wang's group)

In 2017, Snyder and co-workers synthesized tetracyclic hydrocarbazole **39** from tetrahydro-β-carboline **37** (Scheme 6).[28] They employed 6-*endo-dig* cyclization of the alkyne moiety in **37** by utilizing a catalytic amount of $AuPPh_3Cl$ and a stoichiometric amount of $AgSbF_6$, and obtained the cyclized product **38** in 59% yield. Skeletal rearrangement of **38** under microwave irradiation in the presence of a base furnished tetracyclic hydrocarbazole **39** in 62% yield.



Scheme 5. Enantioselective construction of tetracyclic hydrocarbazole **35** from ynones **32** via Ag(I) promoted cyclization (Unsworth's group)

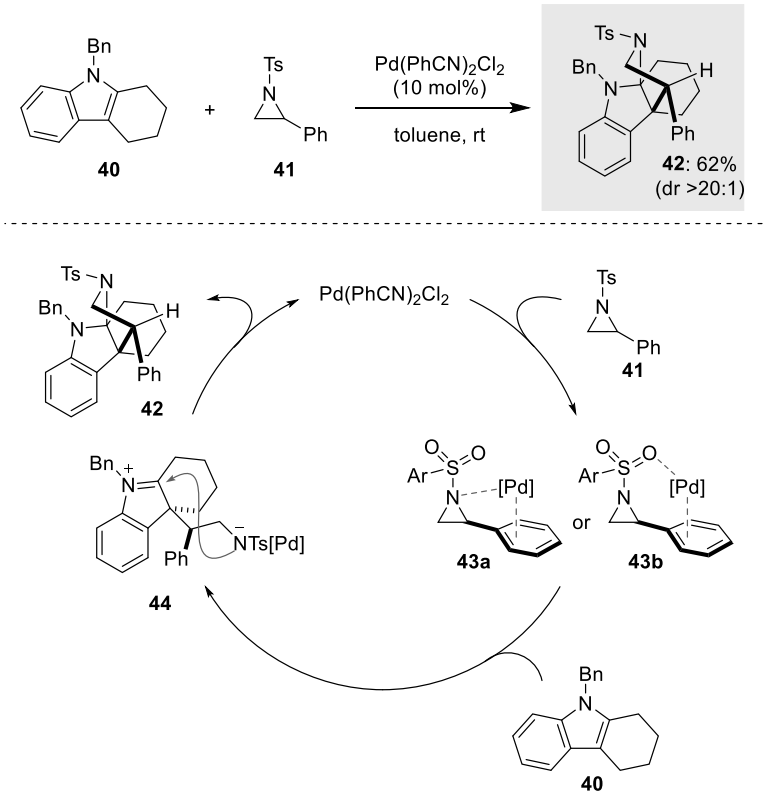


Scheme 6. Construction of tetracyclic hydrocarbazole **39** using Ag(I)-catalyzed cyclization followed by skeletal rearrangement (Snyder's group)

[3+2] CYCLOADDITION

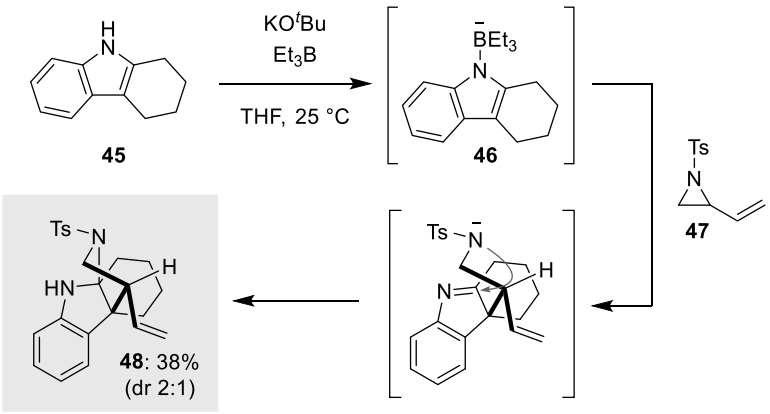
The double bond at C2-C3 in indoles can undergo cycloaddition reaction, and indole derivatives with fused ring structures can be synthesized by applying a cycloaddition reaction strategy using C3-substituted indoles.[29-31] For example, tetracyclic hydrocarbazoles can be constructed by employing [3+2] cycloaddition reaction of tricyclic indole derivatives with appropriate ethylamine units. Aziridines, aza-oxyallyl cations, and acetamide acrylates have been applied as ethylamine units for this purpose.

Aziridine is a synthetically useful aminoethyl group equivalent, which is introduced by means of nucleophilic ring-opening reaction.[32-34] In 2015, Zhao and co-workers developed a formal [3+2] cycloaddition of indole with aziridines to construct tetracyclic hydrocarbazole (Scheme 7).[35] The formal [3+2] cycloaddition reaction of tricyclic indole **40** and aziridine **41** was carried out in the presence of $Pd(PhCN)_2Cl_2$ to generate tetracyclic hydrocarbazole **42** in 62% yield. In this reaction, Pd(II), which has a Lewis-acidic nature, activates aziridine by interacting with nitrogen (intermediate **43a** or **43b**) to promote the nucleophilic addition of indole at C3 to aziridine with ring-opening to generate iminium cation intermediate **44**. Then, intramolecular cyclization of the amino group in **44** affords **42**.



Scheme 7. Construction of tetracyclic hydrocarbazole **42** via formal [3+2] cycloaddition reaction of **40** with aziridine **41** in the presence of Pd(II) catalyst (Zhao's group)

A similar formal [3+2] cycloaddition of tricyclic indole **45** with aziridine **47** was reported by Xiao and co-workers (Scheme 8).[36] In this reaction, indole **45** was activated with triethylborane and potassium *tert*-butoxide, and the resulting borate **46** underwent nucleophilic addition at C3 with allylaziridine **47**, followed by cyclization to furnish tetracyclic hydrocarbazole **48** in 38% yield with 2:1 dr.



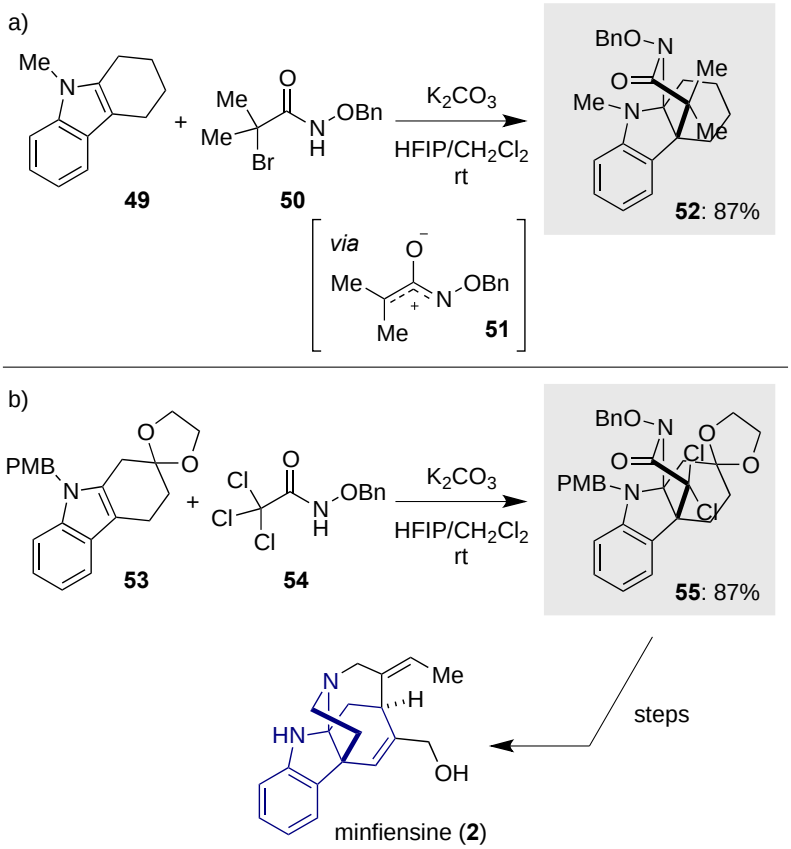
Scheme 8. Construction of tetracyclic hydrocarbazole **48** via formal [3+2] cycloaddition, using indole **45** and allylaziridine **47** (Xiao's group)

Liao and co-workers reported a formal [3+2] cycloaddition of tricyclic indole **49** with aza-oxyallyl cation **51**, generated *in situ* from α-bromo amide **50** by reaction with potassium carbonate, to construct tetracyclic hydrocarbazole **52** (Scheme 9a).[37] This led to a total synthesis of minfiensine (**2**) from tricyclic indole **53** via tetracyclic hydrocarbazole **55** (Scheme 9b).[38]

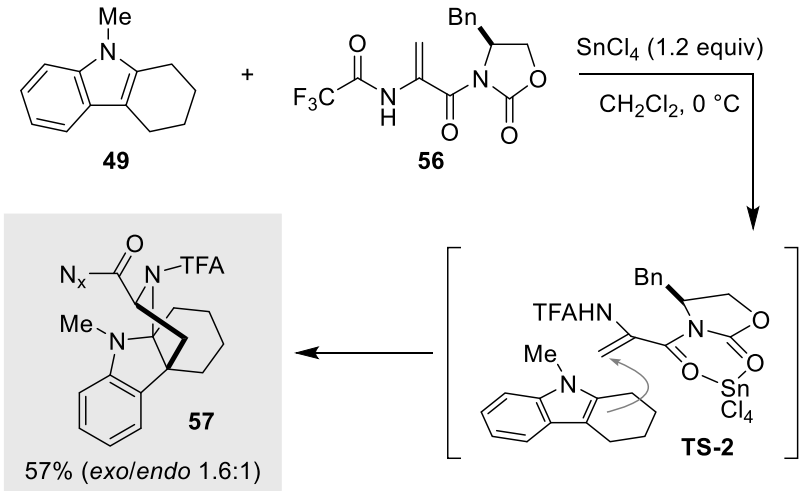
Andrus and co-workers developed a synthesis of tetracyclic hydrocarbazole **57** from tricyclic indole **49** and acetamide acrylate **56** with an isoxazolidinone-type chiral auxiliary via an *exo*-selective formal [3+2] cycloaddition in the presence of the Lewis acid $SnCl_4$ (Scheme 10).[39] In this reaction, acetamide acrylate is activated by tin chloride through bidentate coordination, and nucleophilic attack of indole proceeds from the less hindered side (**TS-2**). However, the regioselectivity was low (1.6:1 *exo*/*endo*).

DEAROMATIZATION OF PHENOLS

Dearomatization of *para*-substituted phenols provides 2,5-cyclohexadienones, which are reactive electrophiles that have been applied widely in the synthesis of natural products, as well as pharmaceuticals.[40-43] This approach was successfully adopted to synthesize tetracyclic hydrocarbazole by utilizing diarylamine derivatives bearing a phenol group. Dearomatization of the diarylamines was performed with palladium catalysts or hypervalent iodine reagents.



Scheme 9. a) Construction of tetracyclic hydrocarbazole **52** via formal [3+2] cycloaddition reaction of tricyclic indole **49** and aza-oxyallyl cation **51** (Liao's group). b) Total synthesis of minfiensine (**2**) based on the formal [3+2] cycloaddition reaction by the same group



Scheme 10. Construction of tetracyclic hydrocarbazole **57** from tricyclic indole **49** and acetamide acrylate **56** via formal [3+2] cycloaddition reaction (Andrus' group)

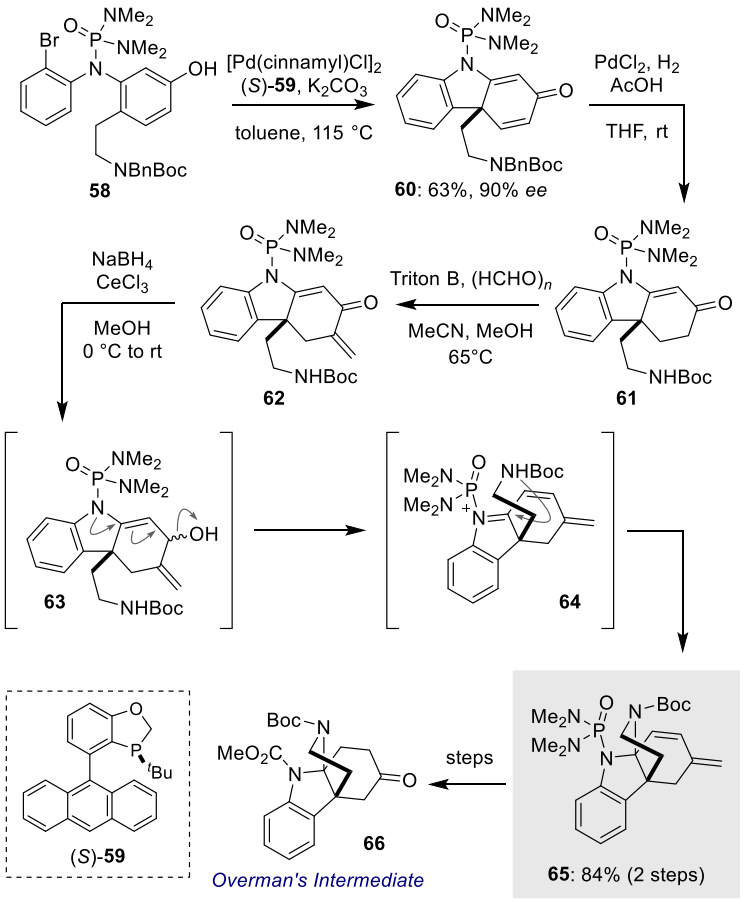
Tang and co-workers reported a synthesis of tetracyclic hydrocarbazole **65** via palladium-catalyzed asymmetric dearomative cyclization of diarylamine **58** followed by intramolecular cyclization of allylic alcohol **63** derived from dienone **60** (Scheme 11).[44] Specifically, they performed palladium-catalyzed asymmetric dearomative cyclization of diarylamine of **58** to obtain dienone **60** in 63% yield with 90% ee. The less hindered olefin in **60** was selectively reduced under hydrogenolysis conditions in the presence of $PdCl_2$ catalyst and the *exo*-olefin was installed by aldol condensation using paraformaldehyde with Triton B. Upon conversion of **60** into allyl alcohol **63**, intramolecular cyclization took place simultaneously to generate tetracyclic hydrocarbazole **65**. Several further steps afforded **66**, which is identical to Overman's intermediate for their group's synthesis of minfiensine (**2**).[2]

In 2020, our group reported a synthesis of tetracyclic hydrocarbazole **70** from dienone **68**, which was obtained from oxidative dearomative cyclization of diarylamine **67** with hypervalent iodine agent (Scheme 12).[45] Specifically, oxidative dearomative cyclization of diarylamine **67** bearing an ethylamino group using diacetoxy iodobenzene (PIDA) in hexafluoro-2-propanol (HFIP) afforded dienone **68** in 40% yield. The aza-Michael reaction products at C9a **71** and C4 **72** were each selectively obtained from **68** under different acidic conditions (TFA and HCl, respectively). The product **72** corresponds to the core structure of *Aspidosperma* monoterpene indole alkaloids such as aspidospermidine (**73**).[46-48]

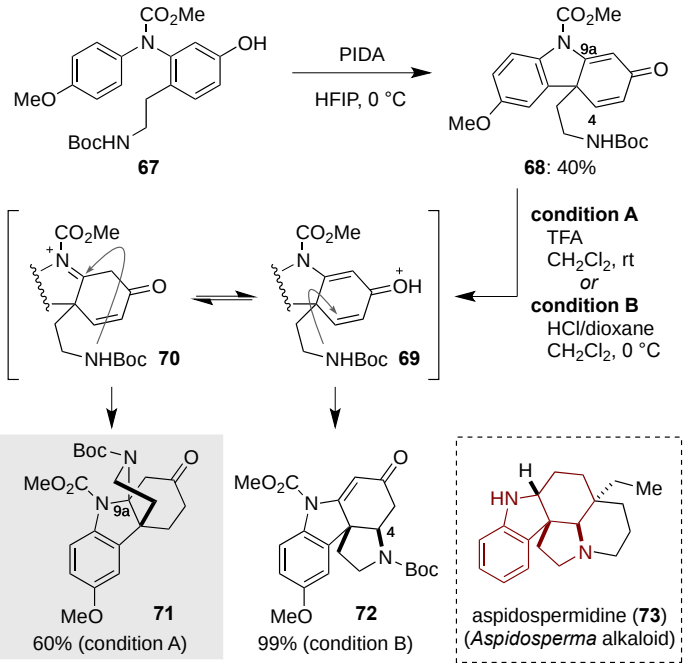
OTHER APPROACHES

In addition to the above three synthetic approaches to tetracyclic carbazoles, some other strategies, i.e., aza-pinacol rearrangement, photo-redox catalyst-mediated reaction, and asymmetric addition reaction with a copper catalyst, have also been developed.

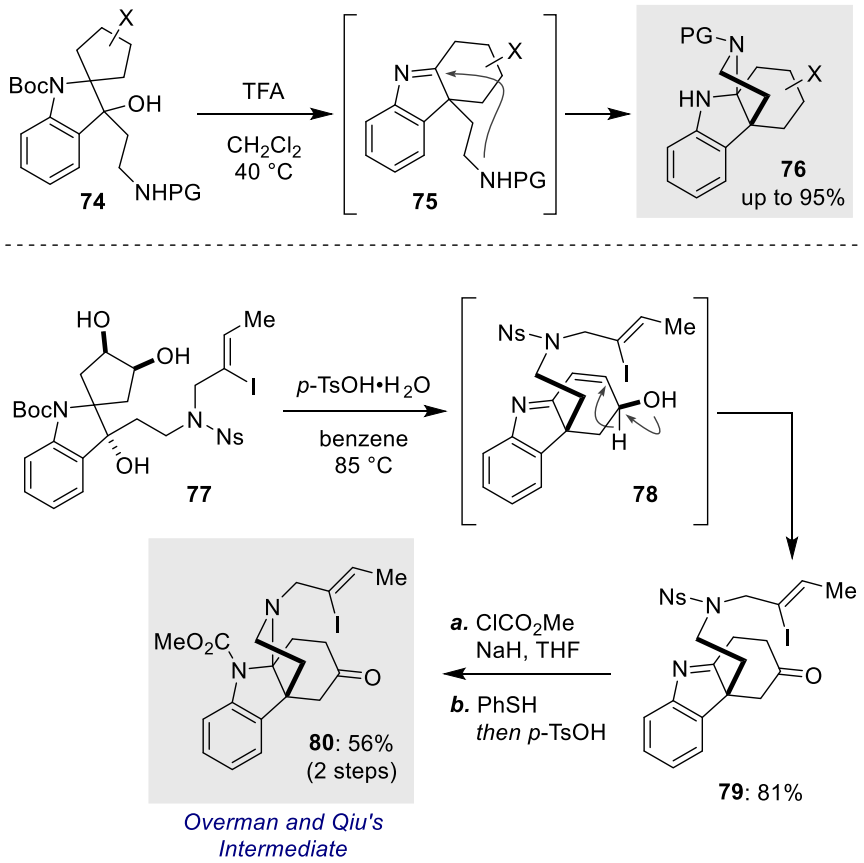
Zu and co-workers reported the synthesis of tetracyclic hydrocarbazole **76** by means of aza-pinacol rearrangement of spiroindoline **74** (Scheme 13).[49] They subjected the tertiary alcohol **74** bearing an aminoethyl group to aza-pinacol rearrangement in the presence of trifluoroacetic acid. The resulting tricyclic indolenines **75** cyclized immediately to afford the tetracyclic hydrocarbazoles **76** in up to 95% yield. This strategy was successfully applied for the synthesis of Overman and Qiu's intermediate **80** for minfiensine (**2**)[2,50] from **77** via indolenine **79**.



Scheme 11. Enantioselective synthesis of tetracyclic hydrocarbazole **65** via dearomative cyclization of diarylamine with phenols, leading to a formal total synthesis of (-)-minfiensine (**2**) (Tang's group)



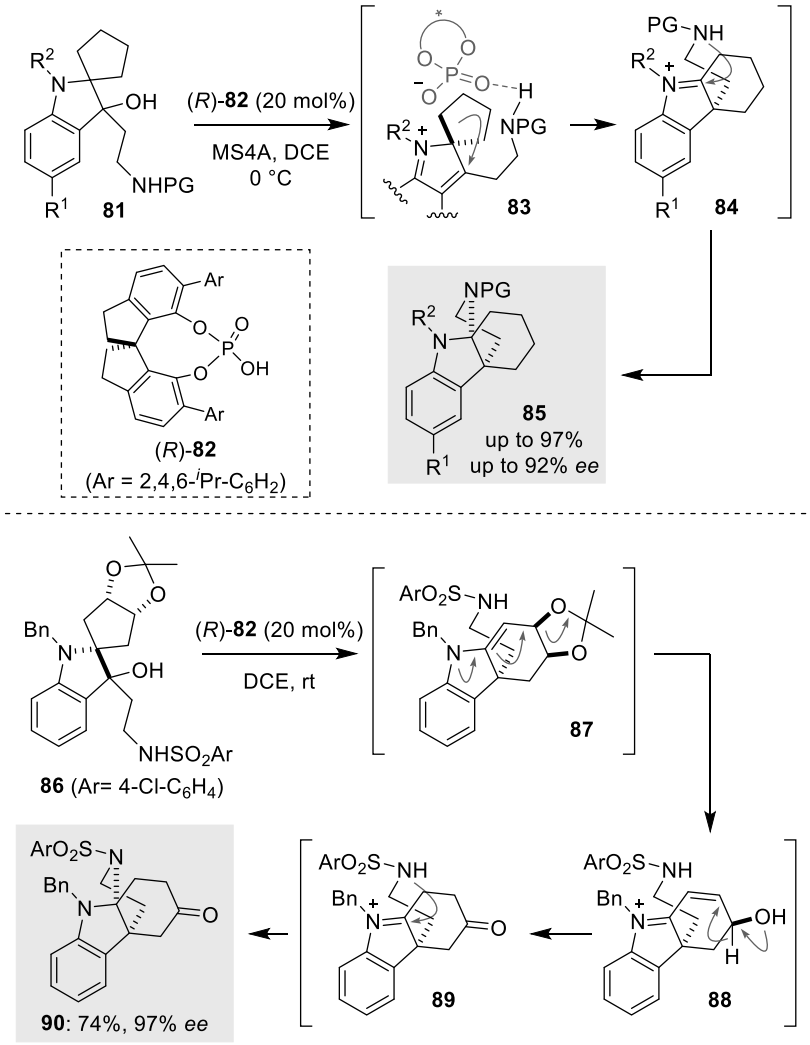
Scheme 12. Synthesis of tetracyclic hydrocarbazoles **71** and **72** by regioselective aza-Michael reaction of dienone **68** obtained via oxidative dearomative cyclization of diarylamine **67** (Nagasawa's group)



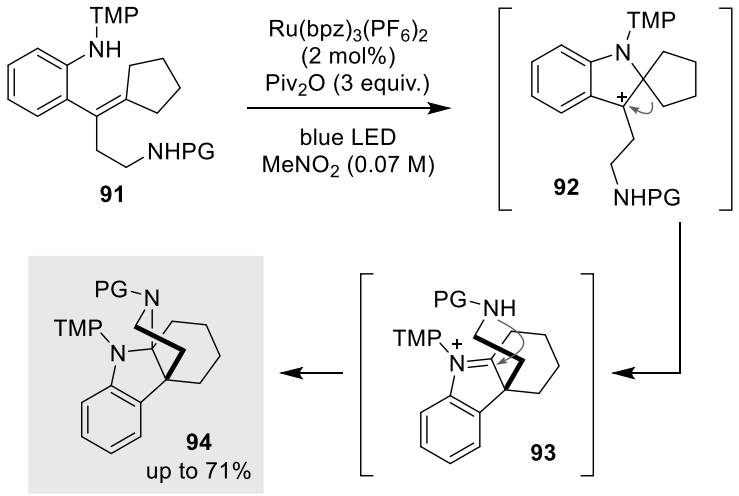
Scheme 13. a) Synthesis of tetracyclic hydrocarbazole **76** through aza-pinacol rearrangement, leading to a formal total synthesis of minfiensine (**2**) (Zu's group)

The same authors reported an asymmetric version of the aza-pinacol rearrangement by using chiral phosphoric acid (*R*)-**82**, derived from a SPINOL, and obtained tetracyclic hydrocarbazoles **85** with high enantioselectivity (Scheme 14).[51] The reaction proceeds via an aza-*ortho*-xylylene intermediate **83**, and the catalyst presumably coordinates with NH and iminium cation through electrostatic interaction to control the transition state of the reaction. Application of this reaction to a substrate containing acetonide **86** afforded tetracyclic hydrocarbazole **90** in 74% yield with 97% ee through the aza-pinacol rearrangement product **87** via isomerization and 1,2-hydride transfer.

Zheng and co-workers reported a photo-redox catalyst-mediated cascade reaction for the synthesis of tetracyclic hydrocarbazole **94** (Scheme 15).[52] The ruthenium photo-redox catalyst-mediated reaction of **91** afforded tetracyclic hydrocarbazole **94** in up to 71% yield under blue LED irradiation conditions via formation of a benzyl cation intermediate **92**, followed by a 1,2-alkyl shift in intermediate **93**. Pivalic anhydride is mandatory for the reaction to trap generated water, as well as to keep the medium acidic.

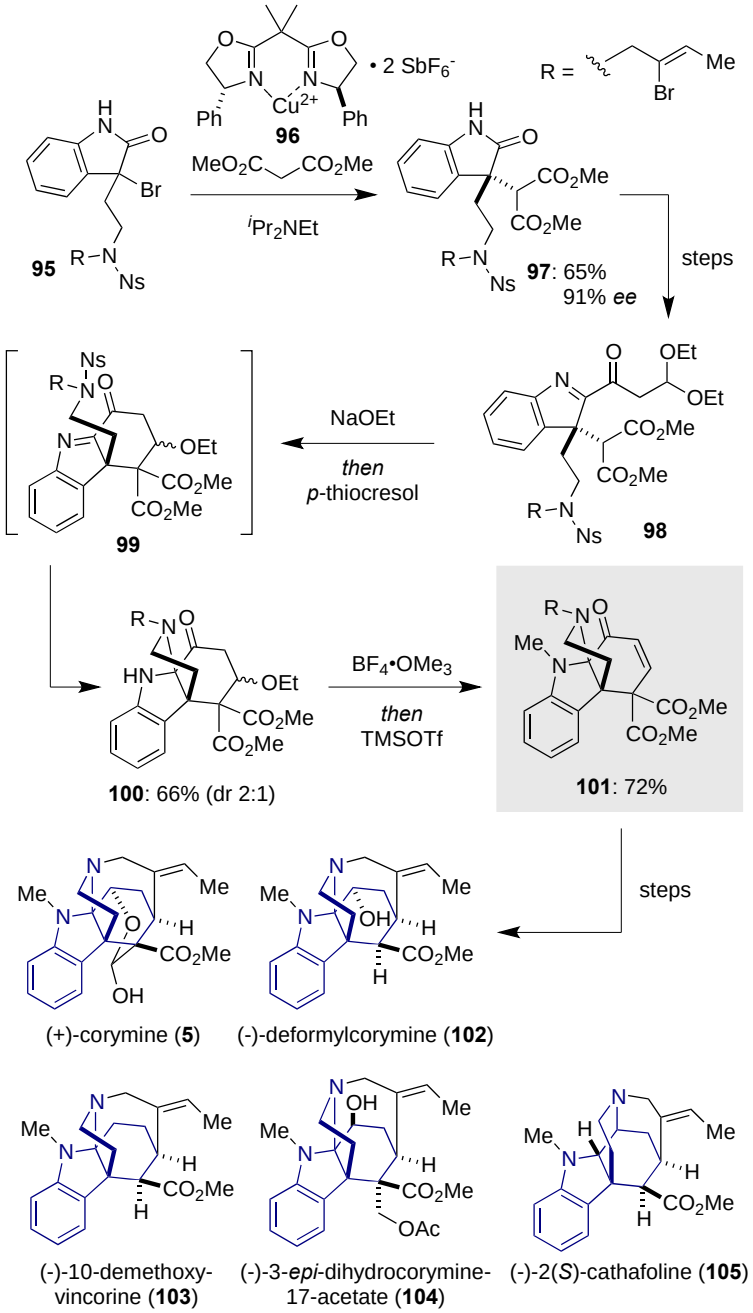


Scheme 14. Enantioselective synthesis of tetracyclic hydrocarbazoles **85** and **90** via asymmetric aza-pinacol rearrangement in the presence of the chiral phosphoric acid catalyst (*R*)-**82** (Zu's group)



Scheme 15. Synthesis of tetracyclic hydrocarbazole **94** from **91** via photoredox catalyst-mediated spiro-cyclization followed by 1,2-alkyl rearrangement (Zheng's group)

In 2020, Li and co-workers achieved total syntheses of five kinds of akuammiline alkaloids, including (+)-corymine (**5**) and (-)-deformylcorymine (**102**), from tetracyclic hydrocarbazole **101** as a common key intermediate (Scheme 16).[10] They employed Stoltz's enantioselective alkylation[53,54] of bromooxindole **95** to introduce malonic diester, obtaining oxindole **97** bearing the all-carbon quaternary stereogenic center at C3 in 65% yield with 91% ee. After single recrystallization of **97**, the resulting enantiomerically pure **97** (>99% ee) was converted to **98**, which was cyclized with sodium ethoxide. In this reaction, *p*-thiocresol was added successively in one pot to deprotect the Ns group, affording aminal **100** in 66% yield.



Scheme 16. Total syntheses of (+)-corymine (**5**), (-)-deformylcorymine (**102**), and other akuammiline alkaloids from tetracyclic hydrocarbazole **101** as a common key intermediate (Li's group)

Then, syntheses of (+)-corymine (**5**) and (-)-deformylcorymine (**102**) were accomplished via tetracyclic hydrocarbazole **101**. This strategy was extended to the synthesis of other akuammiline alkaloids: (-)-10-demethoxyvincorine (**103**), (-)-3-*epi*-dihydrocorymine-17-acetate (**104**), and (-)-2(*S*)-cathafoline (**105**).

SUMMARY AND OUTLOOK

In this review, we cover recent advances in synthetic strategies for C4a,C9a-fused tetracyclic hydrocarbazole, which is the core structure of akuammiline alkaloids and the *Strychnos* alkaloid minfiensine. These strategies are grouped according to the context of the construction of the all-carbon quaternary stereogenic center at C4a and *N*,*N*-aminal moiety at C9a. All the methodologies are still being actively investigated with the aim of synthesizing tetracyclic hydrocarbazoles on a multi-gram scale, in order to investigate the potential of compounds containing this structure as drug candidates.

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REFERENCES

1. B. Dounay, L. E. Overman, and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2005, **127**, 10186.
2. B. Dounay, P. G. Humphreys, L. E. Overman, and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2008, **130**, 5368.
3. L. Shen, M. Zhang, Y. Wu, and Y. Qin, *Angew. Chem. Int. Ed.*, 2008, **47**, 3618.
4. S. B. Jones, B. Simmons, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 13606.
5. M. Zhang, X. Huang, L. Shen, and Y. Qin, *J. Am. Chem. Soc.*, 2009, **131**, 6013.
6. D. Horning and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 6442.
7. W. Zi, W. Xie, and D. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9126.
8. X. Zhang, B. N. Kakde, R. Guo, S. Yadav, Y. Gu, and A. Li, *Angew. Chem. Int. Ed.*, 2019, **58**, 6053.
9. B. Zhang, X. Wang, C. Cheng, D. Sun, and C. Li, *Angew. Chem. Int. Ed.*, 2017, **56**, 7484.
10. B. Zhang, X. Wang, and C. Li, *J. Am. Chem. Soc.*, 2020, **142**, 3269.
11. G. C. Jagetia, M. S. Baliga, P. Venkatesh, J. N. Ulloor, S. K. Mantena, J. Genebriera, and V.

Mathuram, *J. Pharm. Pharmacol.*, 2005, **57**, 1213.
12. M. Duwiejua, E. Woode, and D. D. Obiri, *J. Ethnopharmacol.*, 2002, **81**, 73.
13. J. H. Shang, X. H. Cai, T. Feng, Y. L. Zhao, J. K. Wang, L. Y. Zhang, M. Yan, and X. D. Luo, *J. Ethnopharmacol.*, 2010, **129**, 174.
14. W. Wang, M. H. Cheng, and X. H. Wang, *Molecules*, 2013, **18**, 7309.
15. A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, 2003, **10**, 1891.
16. R. Eckermann and T. Gaich, *Synthesis*, 2013, **45**, 2813.
17. G. L. Adams and A. B. Smith, 'Alkaloids: Chemistry and Biology', Vol. 76, ed. by H.-J. Knölker, Elsevier Inc., Amsterdam, 2016, pp. 171–257.
18. J. M. Smith, J. Moreno, B. W. Boal, and N. K. Garg, *Angew. Chem. Int. Ed.*, 2015, **54**, 400.
19. S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, and H. Mayr, *J. Org. Chem.*, 2006, **71**, 9088.
20. C. Zheng and S. L. You, *Nat. Prod. Rep.*, 2019, **36**, 1589.
21. S. Z. Jiang, X. Y. Zeng, X. Liang, T. Lei, K. Wei, and Y. R. Yang, *Angew. Chem. Int. Ed.*, 2016, **55**, 4044.
22. C. Defieber, M. A. Ariger, P. Moriel, and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2007, **46**, 3139.
23. B. M. Trost, D. L. Van Vranken, and C. Bingel, *J. Am. Chem. Soc.*, 1992, **114**, 9327.
24. Z. X. Zhang, S. C. Chen, and L. Jiao, *Angew. Chem. Int. Ed.*, 2016, **55**, 8090.
25. Y. Zhu, W. He, W. Wang, C. E. Pitsch, X. Wang, and X. Wang, *Angew. Chem. Int. Ed.*, 2017, **56**, 12206.
26. J. A. Rossi-Ashton, A. K. Clarke, R. J. K. Taylor, and W. P. Unsworth, *Org. Lett.*, 2020, **22**, 1175.
27. A. K. Clarke, J. A. Rossi-Ashton, R. J. K. Taylor, and W. P. Unsworth, *Tetrahedron*, 2020, **76**, 131392.
28. M. W. Smith, Z. Zhou, A. X. Gao, T. Shimbayashi, and S. A. Snyder, *Org. Lett.*, 2017, **19**, 1004.
29. L. M. Repka, J. Ni, and S. E. Reisman, *J. Am. Chem. Soc.*, 2010, **132**, 14418.
30. H. Li, R. P. Hughes, and J. Wu, *J. Am. Chem. Soc.*, 2014, **136**, 6288.
31. R. F. Kester, S. J. Berthel, and F. Firooznia, 'Topics in Heterocyclic Chemistry', Vol. 26, ed. by G. W. Gribble, Springer, Berlin, 2010, pp. 327–396.
32. Z. Chai, *Synthesis*, 2020, **52**, 1738.
33. G. S. Singh, S. Sudheesh, and N. Keroletswe, *ARKIVOC*, 2018, **i**, 50.
34. A. S. Pankova and M. A. Kuznetsov, *Synthesis*, 2017, **49**, 5093.
35. Y. M. Huang, C. W. Zheng, L. Pan, Q. W. Jin, and G. Zhao, *J. Org. Chem.*, 2015, **80**, 10710.
36. Y. N. Wang, T. R. Li, M. M. Zhang, B. Y. Cheng, L. Q. Lu, and W. J. Xiao, *J. Org. Chem.*, 2016, **81**, 10491.

37. W. Ji, L. Yao, and X. Liao, *Org. Lett.*, 2016, **18**, 628.
38. C. Zhang, W. Ji, Y. A. Liu, C. Song, and X. Liao, *J. Nat. Prod.*, 2018, **81**, 1065.
39. T. Smith, J. B. Neeley, T. D. Brinley, P. R. Fullmer, and M. B. Andrus, *Tetrahedron Lett.*, 2020, **61**, 151947.
40. L. Pouységu, D. Deffieux, and S. Quideau, *Tetrahedron*, 2010, **66**, 2235.
41. Q. Ding, Y. Ye, and R. Fan, *Synthesis*, 2013, **45**, 1.
42. G. Maertens, C. L'Homme, and S. Canesi, *Front. Chem.*, 2015, **2**, 115.
43. M. A. Ciufolini, N. A. Braun, S. Canesi, M. Ousmer, J. Chang, and D. Chai, *Synthesis*, 2007, 3759.
44. K. Du, H. Yang, P. Guo, L. Feng, G. Xu, Q. Zhou, L. W. Chung, and W. Tang, *Chem. Sci.*, 2017, **8**, 6247.
45. K. Hosoya, K. Iida, M. Odagi, and K. Nagasawa, *J. Org. Chem.*, 2020, **85**, 11980.
46. B. P. Pritchett and B. M. Stoltz, *Nat. Prod. Rep.*, 2018, **35**, 559.
47. Y. Wang, F. Xie, B. Lin, M. Cheng, and Y. Liu, *Chem. Eur. J.*, 2018, **24**, 14302.
48. J. M. Saya, E. Ruijter, and R. V. A. Orru, *Chem. Eur. J.*, 2019, **25**, 8916.
49. Y. Yu, G. Li, L. Jiang, and L. Zu, *Angew. Chem. Int. Ed.*, 2015, **54**, 12627.
50. P. Liu, J. Wang, J. Zhang, and F. G. Qiu, *Org. Lett.*, 2011, **13**, 6426.
51. Y. Yu, J. Li, L. Jiang, J. R. Zhang, and L. Zu, *Angew. Chem. Int. Ed.*, 2017, **56**, 9217.
52. Q. Wang, J. Hu, and N. Zheng, *Org. Lett.*, 2019, **21**, 614.
53. S. Ma, X. Han, S. Krishnan, S. C. Virgil, and B. M. Stoltz, *Angew. Chem. Int. Ed.*, 2009, **48**, 8037.
54. C. W. Lee, S. J. Han, S. C. Virgil, and B. M. Stoltz, *Tetrahedron*, 2015, **71**, 3666.

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