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RECENT ADVANCES IN THE CHEMISTRY OF AZAAZULENES AND RELATED COMPOUNDS[†]

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Abstract – In this review, the synthetic methods and about the biological and physical properties of mono- and poly-azaazulenes including some of their *dihydro*-, *tetrahydro*-, *oxo*-derivatives and *aromatics- and heterocycles-fused* derivatives and related compounds, such as *pyrrolobenzazepines, azepinoindole* derivatives, and so on, published from end of 2017 to April 2019, are surveyed.

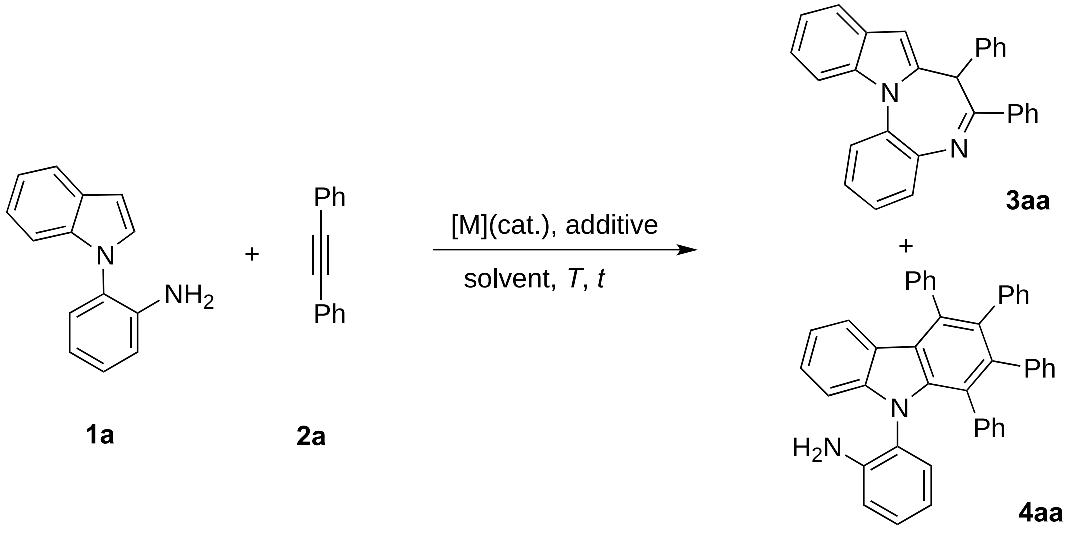
Azaazulenes are a class of the compounds that have been receiving attention for their relationship with the chemistry of azulenes and for remarkable characters about physical and chemical properties as well as biological activities.[1] After being previously reviewed last year,[1a] many significant researches were developed in this field, especially, polycyclic and /or polyaza-compounds containing azaazulene skeleton, such as pyrrolobenzazepines, azepinoindole derivatives, and so on, were directed attention from their biological activities and potentialities of drug use. As a consequence, some reviews appeared about the synthesis for 3,4-fused tricyclic indoles,[2a,b] 1,7-fused tricyclic indoles,[3] azepinoindole alkaloids,[4] and cyclo[*b*]fused indoles,[5] and construction of seven-membered ring.[6] This review covers the recent progress in the chemistry of azaazulenes including some of their *dihydro*-, *tetrahydro*-, *oxo*-derivatives and *aromatics-fused derivatives* and related compounds such as *pyrrolobenzazepines,* and *azepinoindole derivatives* published from end of 2017 to April 2019.

[†] Dedicated to Prof. Dr. Kaoru Fuji on the occasion of his 80th birthday

I. SYNTHESES OF AZAAZULENES

For construction of azaazulene skeletons, cyclization strategies are frequently used and conspicuous methods.[2,5-7] Cycloaddition reactions are the important tools for synthesis of the complex cyclic skeletons. Annulation of seven-membered ring onto pyrrole, diazole, triazole or indole rings are frequently used synthetic methodology. As building blocks, alkynyl compounds, such as skipped diynes (1,4-diynes), propargyl derivatives, and arylacetylenes, have been used extensively. Among cycloadditions, the [5+2]cycloaddition is an excellent method for construct seven-membered ring systems.[8] The [3+2+2]cycloaddition is also important synthetic tool for the functionalized seven-membered ring systems.[9] Varieties of transition metals such as Ni, In, Rh, Pd, Co, Au, or Ru were used as catalyst for various cycloadditions. Recently, an interesting review about palladium-catalyzed cascade cyclization appeared.[10] Mechanistic elucidations of [Rh(NHC)]-catalyzed intramolecular [5+2]cycloaddition of vinyloxiranes and vinylcyclopropanes by DFT calculations with alkynes were carried out.[11]

Unprecedented Pd-catalyzed highly regio- and chemoselective alkyne insertion/cyclization of the C2-H bond with *o*-indoloanilines was reported (Scheme 1).[12]

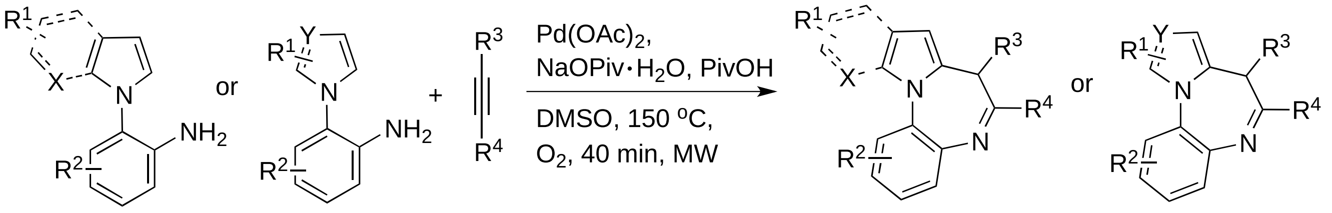


Optimization of reaction conditions

	Catalyst/Additive	Solvent	T (°C)	t	Yield (%)
1)	Pd(OAc)$_2$/LiOAc,	DMA	100	5 h	**3aa** (0), **4aa** (62)
2)	Pd(OAc)$_2$/NaOPiv.H$_2$O, PivOH	DMSO	150	40 min, MW	**3aa** (83), **4aa** (0)

Scheme 1

The reaction is applicable for electron-deficient systems such as *o*-indolopyrroles and *o*-indoloimidazoles to afford the respective products in good to excellent yield (Scheme 2).[12] The mechanistic pathway shows pivalic acid and molecular oxygen to play crucial roles for the regeneration of highly active electrophilic palladium species in the catalytic cycle.



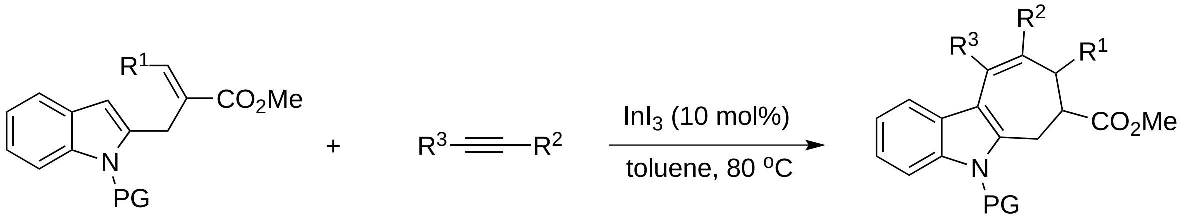
1a-j **1'a-d** **2a-c** **3** **3'**

X = C, N Y = C, N

1 : R^1 = H, 4-OMe, 5-OMe, 5-CN; R^2 = H, 4-Me, 4-CO_2Me, 4-CF_3
1' : R^1 = H, 3-Me, 3-Et; R^2 = H, 4-Me
2 : R^3 = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4; R^4 = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4

Scheme 2

The cyclohepta[*b*]indole skeleton (**7**) was synthesized through an InI_3-catalyzed [5+2]cycloaddition (Scheme 3).[13] The reaction proceeded under catalysis by an indium(III) salt as both a *π*- and *σ*-Lewis acid, which enabled two types of carbon-carbon bond-formation under a single catalytic system. Using this reaction, cyclohepta[*cd*]indoles (**9**, **10**) were obtained in excellent yields (Scheme 4).[13]

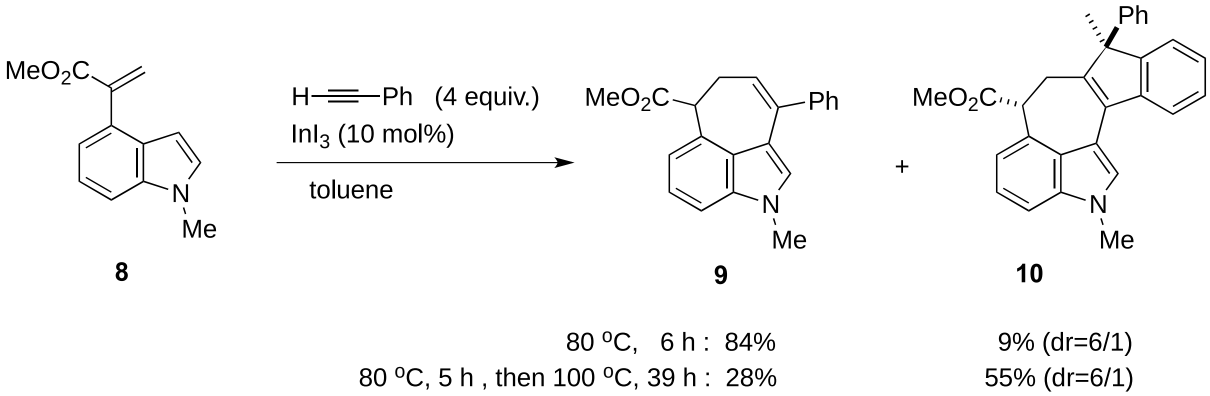


5 **6** **7**

PG = H, Me, Bn
R^1 = H, 4-$MeOC_6H_4$, 2-furyl, ^{n}Pr

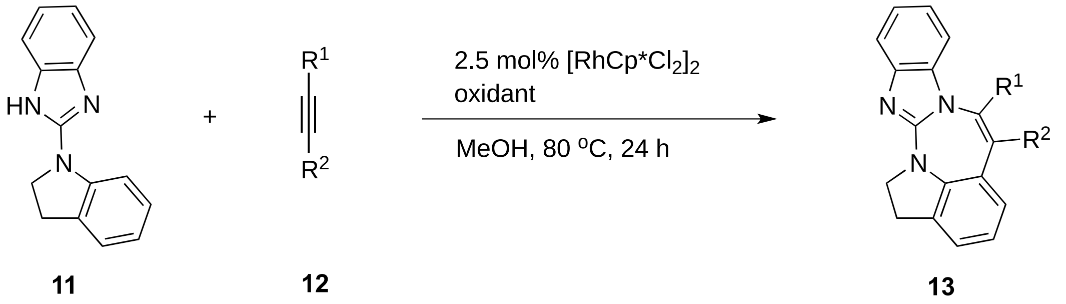
R^2 = H
R^3 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$

Scheme 3



Scheme 4

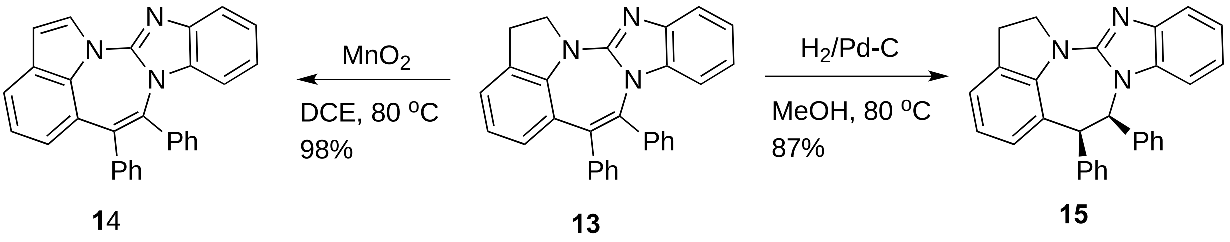
A novel and mild Rh(III)-catalyzed [5+2] oxidative annulation between cyclic arylguanidines (**11**) and alkynes gave 1,3-benzodiazepines (**13**) (Scheme 5). A striking mechanistic proposal for the [5+2] oxidative annulation was supported by DFT calculations.[14]



R^1 = R^2 : Et, *n*-Pr, *n*-Bu, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-thiophen-2-yl, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$
R^1 = Me, R^2 = Ph

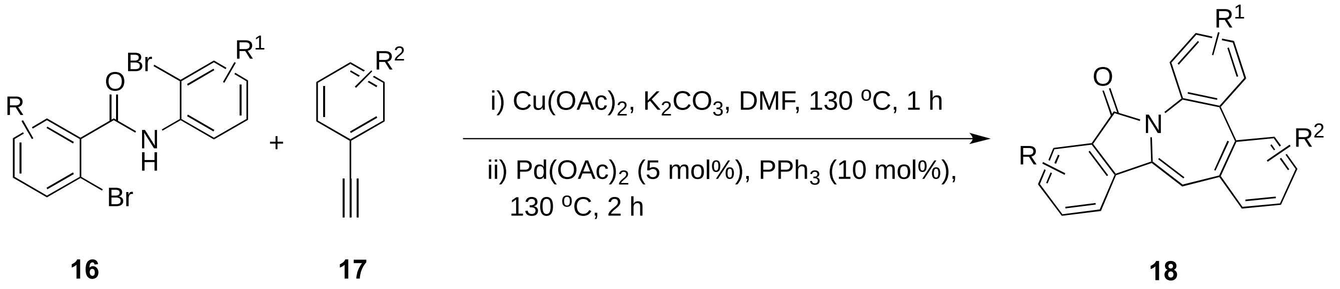
Scheme 5

Oxidation of **13** with MnO$_2$ gave indolo-1,3-benzodiazepine (**14**) in excellent yield, and careful hydrogenation of **13** gave dihydro-1,3-benzodiazepine (**15**) in fairly good yield (Scheme 6).[14]



Scheme 6

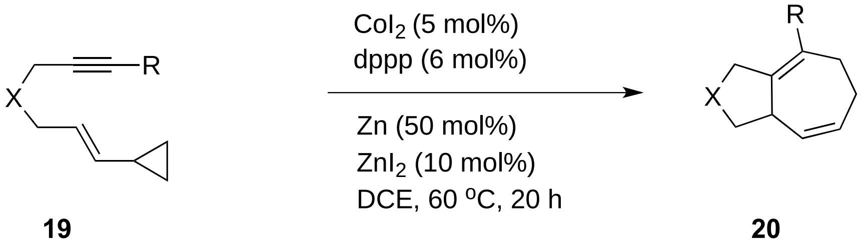
A sequential copper-catalyzed Sonogashira coupling followed by an intramolecular hydroamination and palladium-catalyzed intramolecular direct arylation reaction in one-pot was reported, where a convenient and modular approach for the synthesis of useful azepino-fused indolinones were generated (Scheme 7).[15]



R = H, 3-MeO, 4-F
R^1 = H, 4-Me, 4-F
R^2 = H, 4-Me, 4-*n*-Pr, 4-^{t}BuC_6H_4, 4-MeO

Scheme 7

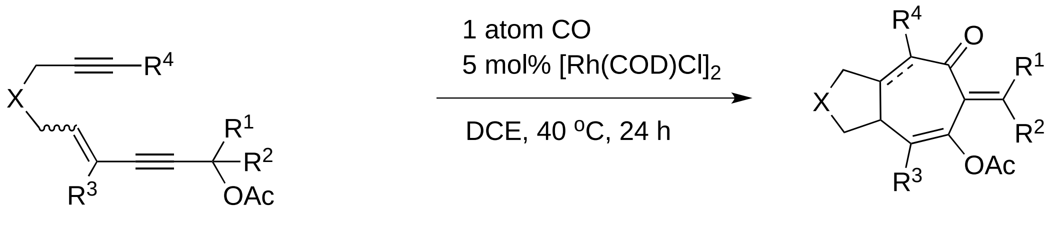
Yoshikai *et al*. investigated the ability of cobalt to promote intramolecular reaction between vinylcyclopropane (VCP) and alkynes, where enabling either [5+2]cycloaddition or homo-ene reaction by appropriate choice of the solvent and other reaction conditions (Scheme 8).[16] Chemodivergence was achieved for a broad range of substrates. DFT calculations provided qualitative insight into the reaction mechanism and influence of coordinating solvents on the chemoselectivity.



X = O, R = Ph : 85%
X = NTs, R = Ph : 94%
X = $C(CO_2Me)_2$, R = Ph : 85%

Scheme 8

Yu *et al*. reported that first Rh(I)-catalyzed [4+2+1]cycloaddition of *in situ* generated ene/yne-ene-allenes (**21**) with CO afforded seven-membered carbocycles fused with five membered rings (heteroazulene skeletons) (**22**) (Scheme 9).[17] The reaction features easily prepared substrate and broad scope to reach a 5/7 skeleton.

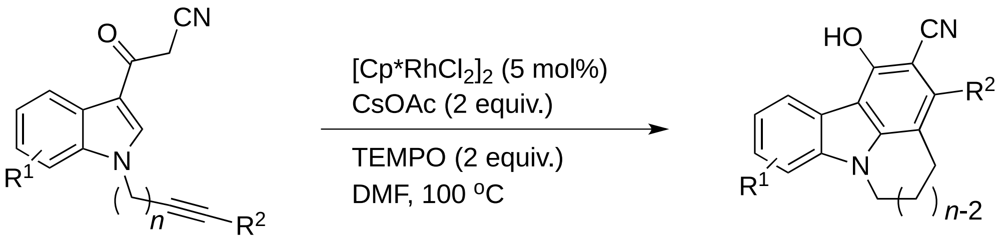


21 **22**

X = NTs, $C(CO_2Me)_2$, O
R^1 = Me, Et, $-CH_2(CH_2)_2CH_2-$, $-CH_2(CH_2)_3CH_2-$
R^2 = Me, Et, $-CH_2(CH_2)_2CH_2-$, $-CH_2(CH_2)_3CH_2-$, H

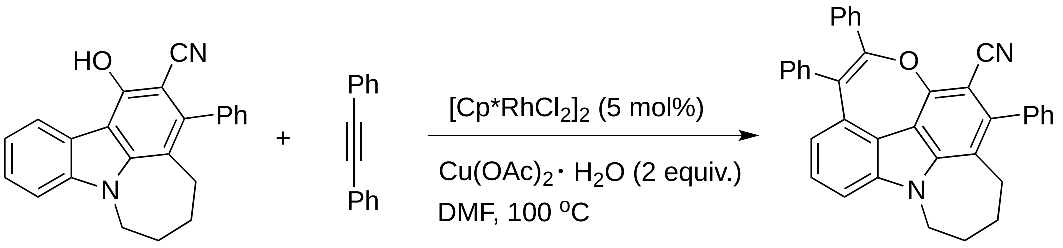
Scheme 9

A mild and efficient method for the synthesis of azaheterocyclo[3,2,1-*jk*]carbazoles (**24**) was reported (Scheme 10), being based on rhodium(III)-catalyzed C-H bond activation and subsequent intramolecular oxidative annulation of alkyne tethered 3-(indol-3-yl)-3-oxopropanennitrile (**23**) by cleavage of $C(sp^2)$-H/$C(sp^3)$-H bonds.[18] The hydroxy group of **24a** (R^1 = H, R^2 = Ph) can act as an efficient directing group for further rhodium(III)-catalyzed C-H functionalization at the 9-position of the fused carbazole derivatives. Thus the reaction of **24a** (n = 2, R^1 = H, R^2 = Ph) with diphenylacetylene gave fused carbazole (**25**) in 87% yield (Scheme 11).[18]



23 (n = 2,3,4) **24**

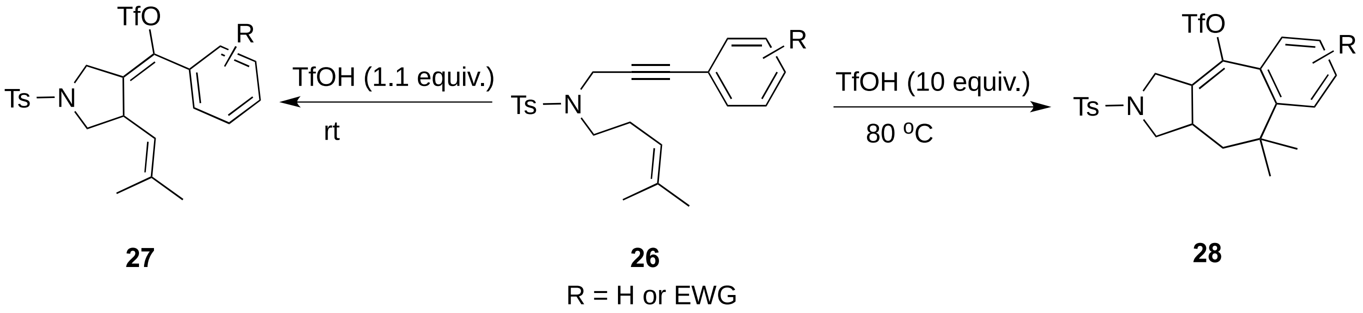
Scheme 10



24a (n - 4) **25**

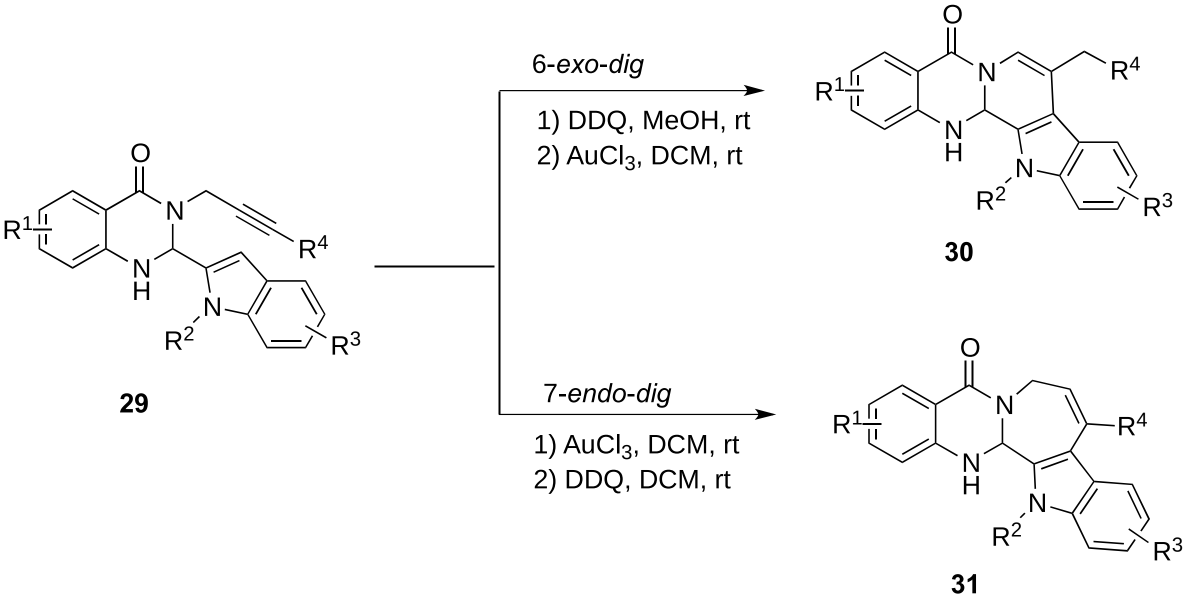
Scheme 11

A metal-free TfOH (1.1 equiv.)-mediated formal cycloisomerization of allene-alkynylbenzenes (**26**) was appeared, and pyrrolidine derivatives (**27**) was investigated. This cycloisomerization can be further tuned to become an acid-mediated intramolecular formal [4+3]cycloaddition by using 10 equiv. of TfOH, and hydroazaazulene derivatives (**28**) were obtained (Scheme 12).[19] The excess acid would be used to promote the Friedel-Crafts reaction of the acid-mediated cycloisomerization products (**27**).



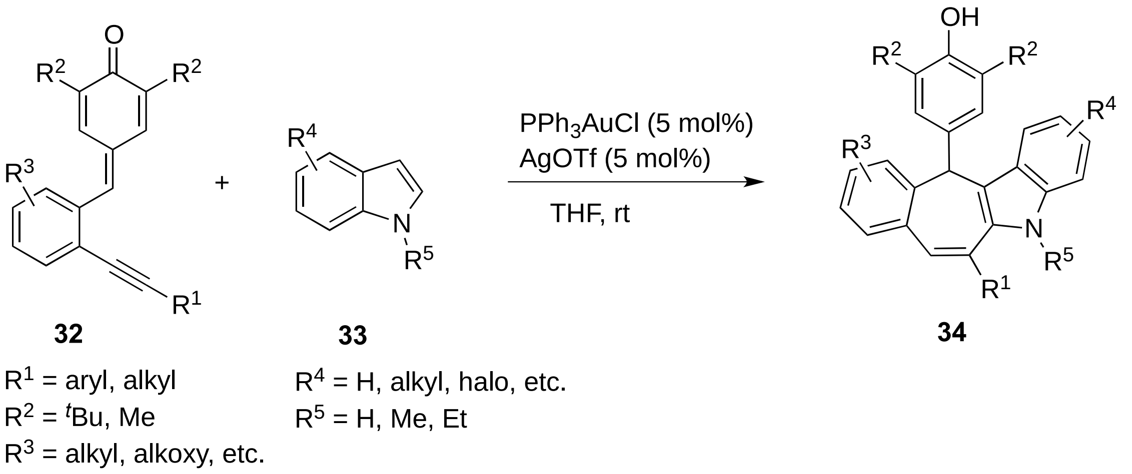
Scheme 12

A report about gold-catalyzed selective 6-*exo-dig* and 7-*endo-dig* cyclizations of alkyne-tethered indoles (**29**) to give two types of rutaecarpine derivatives appeared. When the reaction performed in order of oxidation and sequential gold-catalysis, 6-*exo-dig* cyclization occurred and gave **30**. Whereas the reaction performed in order of gold catalysis and sequential oxidation, 7-*endo-dig* cyclization occurred and gave **31** (Scheme 13).[20]



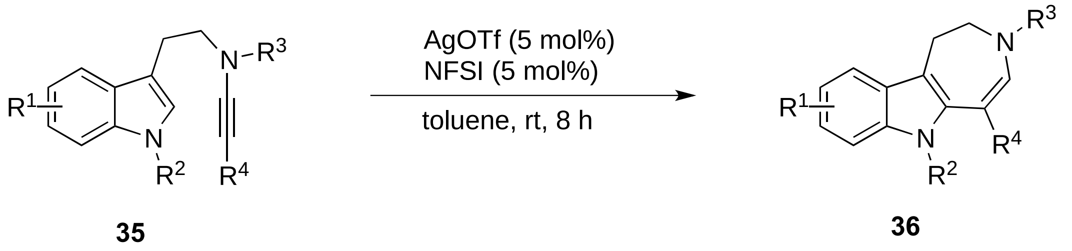
Scheme 13

The complex fused cyclohepta[*b*]indoles (**34**) were synthesized through the gold-catalyzed intramolecular 1,6-conjugate addition of indoles (**33**) to 2-alkynyl *p*-benzoquinone methides (**32**) followed by an intramolecular electrophilic cyclization (Scheme 14).[21]



Scheme 14

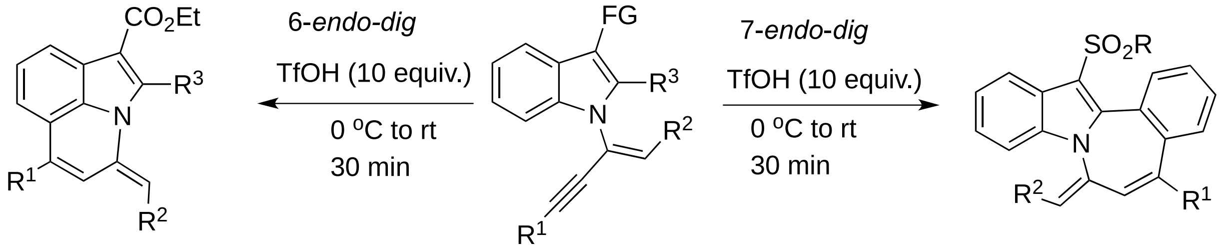
To synthesize azepino[4,5-*d*]indole derivatives (**36**), it was reported that *N*-fluorobenzenesulfonimide (NFSI) was a highly effective Ag(I)-catalyst attenuator in the annulation of a tryptamine-derived ynesulfonamide (**35**) at first time. Liu *et al*. advanced the reaction and performed thoroughly substrate tolerances (Scheme 15) and a mechanistic study by DFT caluculations.[22]



R^1 = H, 6-Me, 7-Me, 5-MeO, 5-F, 5-Cl, 5-Br
R^2 = H, Me, Bn, PMB
R^3 = Ts, Ns, Ms
R^4 = Ph, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, etc.

Scheme 15

Park *et al*. reported regiodivergent cyclization of indole ynenamines for the synthesis of multi-fused *N*-heterocycles. TfOH-mediated cycloisomerizations were controlled through the choice of the electron-withdrawing functional group at C-3 of indoles to provide pyrrolo[3,2,1-*ij*]quinolones (**38**) and benzo[3,4]azepino[1,2-*a*]indoles (**39**) *via* 6-*endo*-*dig* and 7-*endo*-*dig* cyclizations, respectively (Scheme 16).[23] The selectivity of TfOH-mediated cycloisomerization was depended on the effects of indole C-3 substituents. The weaker electron-withdrawing ester group facilitated 6-*endo-dig* cyclization while strongly electron-withdrawing sulfonyl group favored 7-*endo-dig* cyclization.



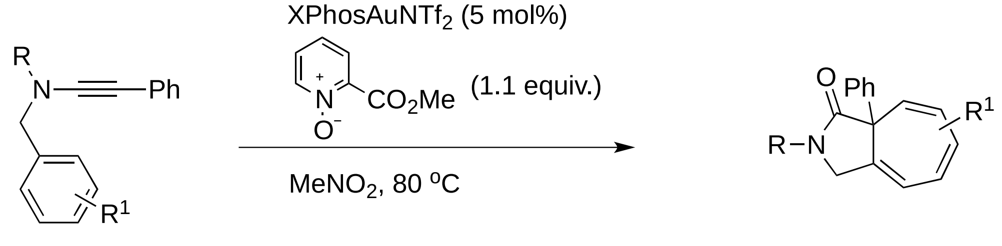
38 **37** **39**

FG = CO_2Et
R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4
R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 3-ClC_6H_4
R^3 = H, Ph

FG = Ts, Ms
R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4
R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 2-$CF_3C_6H_4$
R^3 = Ph

Scheme 16

New and efficient methods for the synthesis of cyclohepta[*c*]pyrrol-1-one derivatives (2-azaazulene derivatives) (**41**) by gold catalyzed oxidative cyclization reaction of ynamides (**40**) was reported (Scheme 17).[24]

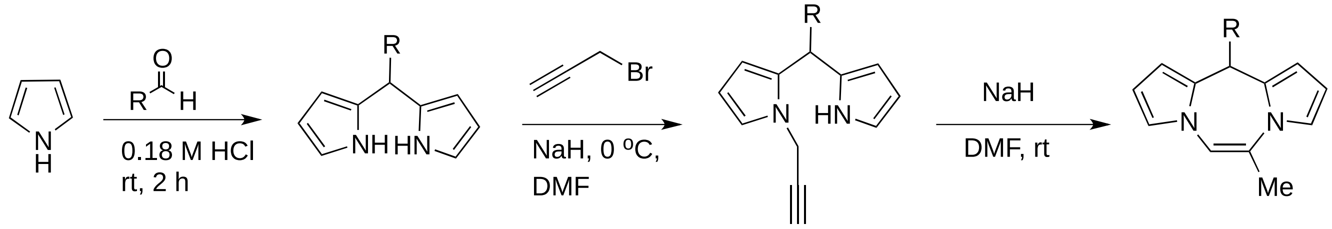


40 **41**

R = Ms, Ts
R^1 = 4-Me, 4-O-allyl, 2-MeO, 2-Me, 2,4,6-tri-Me

Scheme 17

The investigation for the synthesis of dipyrrolo-diazepine derivatives was appeared. The methodology starts with the synthesis of dipyrrolylmethanes (**43**) from pyrrole (**42**). Incorporation of a propargyl group to dipyrrolylmethanes (**44**) followed by NaH-supported cyclization resulted in dipyrrolo-diazepine derivatives (**45**) (Scheme 18).[25] The formation of 8-*endo-dig* or 7-*exo-dig* cyclization products using AuCl, $AuCl_3$, or other metal catalysts did not proceed.



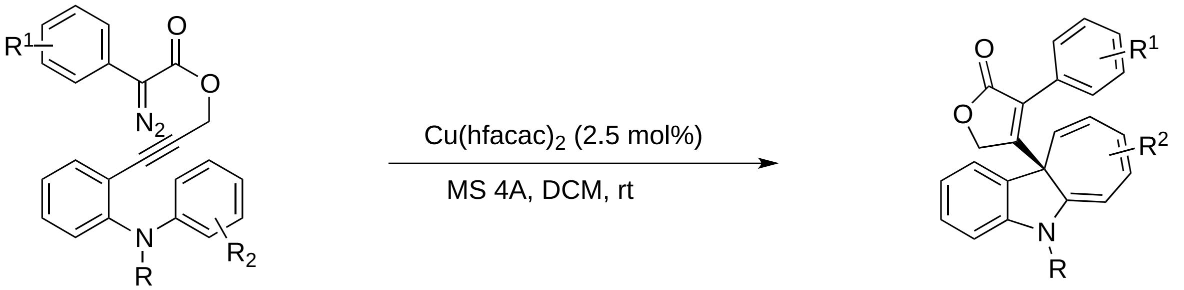
42 **43** **44** **45**

R = H, Me, Ph, 2-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-pyrrolyl

Scheme 18

For construction of seven-membered rings, [4+3]cycloadditions are frequently used synthetic methodology, and variable investigations were put into practice.

The reaction of carbenes provides a powerful tool to construct synthetically and biologically important organic compounds *via* intramolecular insertion. A copper-catalyzed selective cascade reaction of propargyl diazoacetate (**46**) to afford the dihydrocyclohepta[*b*]indole derivatives (**47**) was reported by Xu *et al*. (Scheme 19).[26] The reaction was initiated *via* a copper-catalyzed carbene/alkyne metathesis (CAM), and terminated by the selective Buchner reaction with donor/donor type metal carbenes.



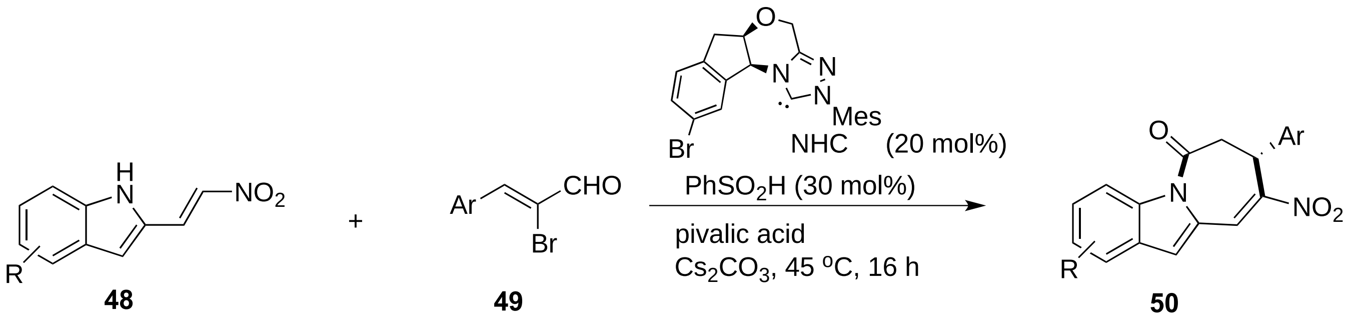
46 **47**

R = Me, Et, ^{i}Pr, Bn, 2-BrBn
R^1 = H, 4-F, 4-Cl, 4-Br, 4-Me, 4-CF$_3$, 4-MeO, 3-MeO, 2-MeO
R^2 = H, 4-F, 4-Cl, 4-Br, 4-Me, 3-Me, 4-CF$_3$, 4-MeO

R^2 = H, 6-Me, 7-Me, 8-Me, 9-Me, 8-MeO

Scheme 19

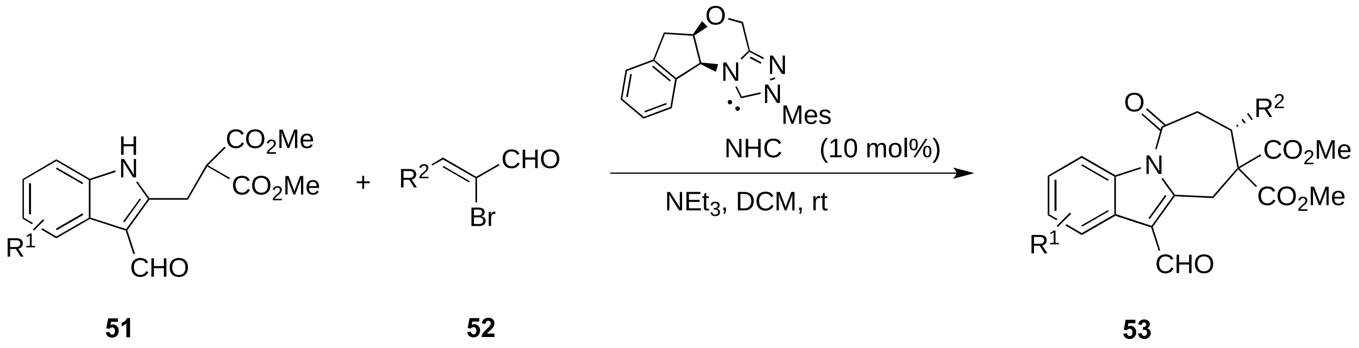
The merging of a sulfonate and an *N*-heterocyclic carbene (NHC) catalyst readily enables intermolecular Rauhut-Currier reactions to generate azepino[1,2-*a*]indole scaffolds with high enantioselectivity. Treatment of 2-(nitroviny)lindole (**48**) with α-bromoenal (**49**) under the conditions afforded azepino[1,2-*a*]indoles (**50**) (Scheme 20).[27]



Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$,4-FC$_6$H$_4$,
3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$,
4-MeCO$_2$C$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, etc.

Scheme 20

Similar investigation for the synthesis of functionalized azepino[1,2-*a*]indoles (**53**) by the treatment of 2-((3-formy-1*H*-indol-2-yl)methyl)malonate (**51**) with 2-bromoenals (**52**) through NHC-catalyzed [4+3]annulation was reported by Hu *et al.* (Scheme 21).[28] The reaction proceeded with high enantioselectivities. This method, in which the 3-formyl group in indoles act as a necessary mediating group, provided cycloaddition products under the mild conditions.

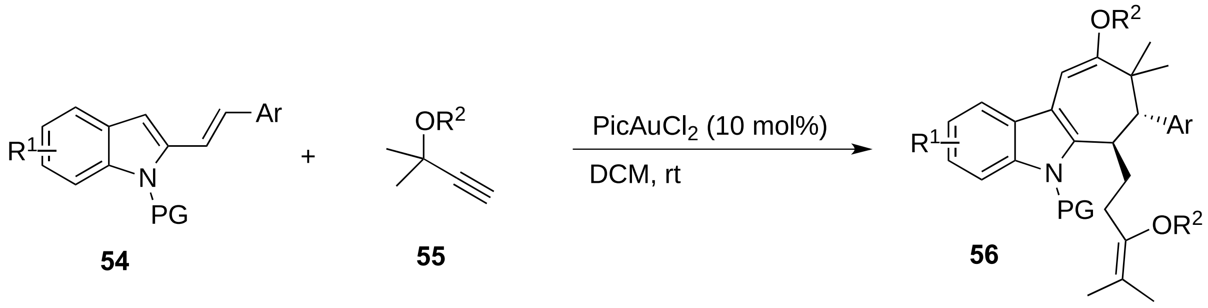


R^1 = H, 5-Cl, 5-Me

R^2 = Ph, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$,
4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-ClC$_6$H$_4$,
4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, etc.

Scheme 21

Synthesis of the densely functionalized cyclohepta[*b*]indole derivatives (**56**), in which a second propargylic ester is incorporated as the pendent function group, through gold-catalyzed [4+3]annulations of 2-vinylindoles (**54**) with propargylic ester (**55**) in one pot was reported (Scheme 22).[29]

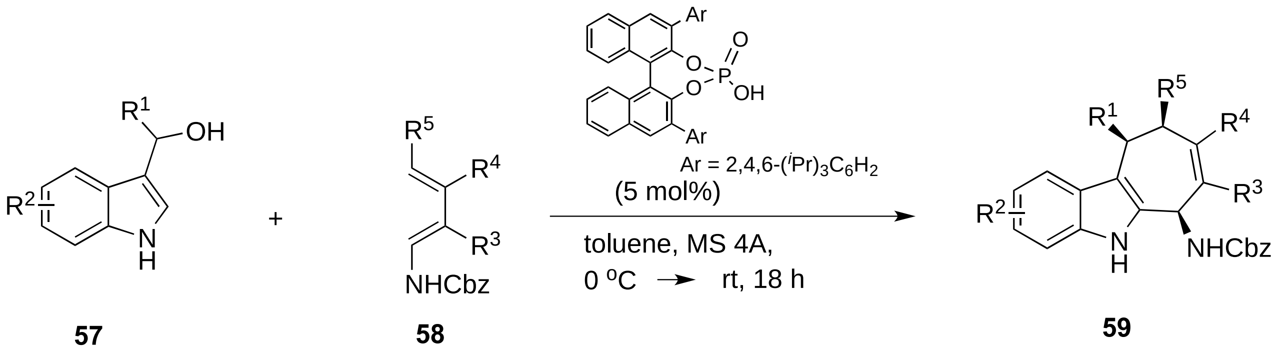


PG = CO_2Et, Ts, Boc
R^1 = H, 4-MeO, 5-Me, 6-MeO
Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-EtC_6H_4,
4-${}^tBuC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, etc.

R^2 = Ac, Bz, Piv

Scheme 22

Masson *et al*. reported the formation of cyclohepta[*b*]indole derivatives (**59**) through a highly enantio- and diastreoselective formal [4+3]cycloaddition of 1,3-diene-1-carbonate (**58**) with 3-indolylmethanols (**57**) in the presence of a chiral phosphoric acid catalyst (Scheme 23).[30] A mechanistic study suggested that cycloaddition occurred in a stepwise fashion, after the formation an ion pair between the chiral catalytic phosphate and the intermediate carbocation.

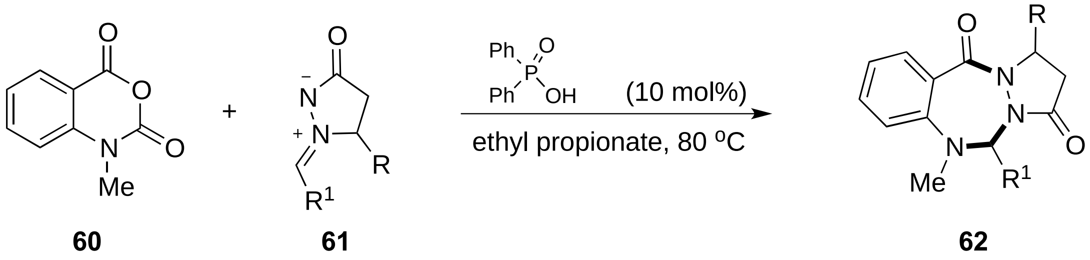


R^1 = Ph, 4-BrC_6H_4, 4-$CF_3C_6H_4$,
4-$MeOC_6H_4$, 3-$MeOC_6H_4$,
3-FC_6H_4
R^2 = H, 5-MeO, etc.

R^3 = H, Me
R^4 = H, Me
R^5 = H, Me

Scheme 23

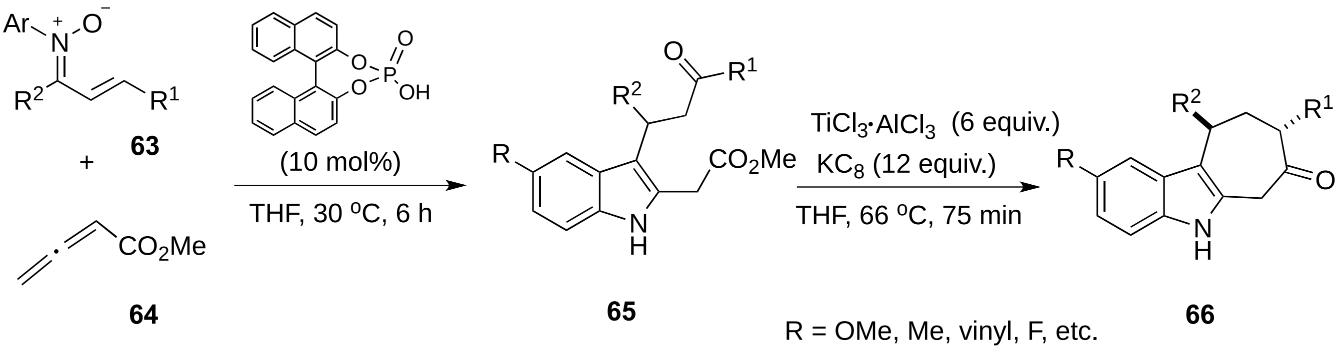
Construction of 3a,9,10a-triazabenzazulene skeleton (containing seven-membered nitrogenous heterocyclic frameworks) (**62**) through a Brønsted acid-catalyzed [4+3]cyclization of *N*,*N'*-cyclic azomethine imines (**61**) with isatoic anhydride (**60**), involving the reassembly of a C-N bond, was reported by Shi *et al*. (Scheme 24).[31]



R = H, Ph
R^1 = 2-MeOC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-FC$_6$H$_4$, 4-MeC$_6$H$_4$,
4-MeOC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-FC$_6$H$_4$, 2-naphthyl, 2-thienyl
Bn, cyclohxyl, ^{i}Bu, Ph

Scheme 24

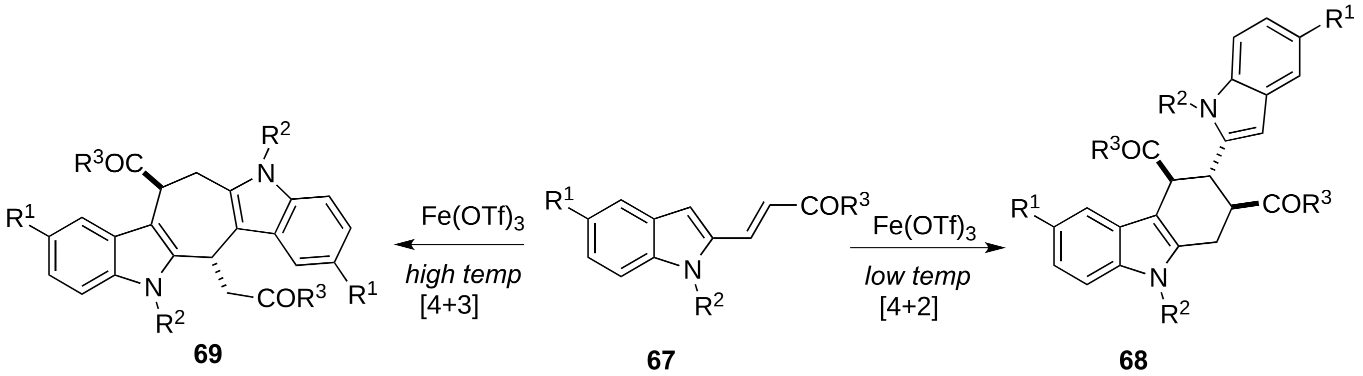
Treatment of a mixture of nitrones (**63**) and electron-deficient allenes (**64**) proceeded a cascade reaction for the synthesis of functionalized indoles (**65**) in the presence of phosphoric acid catalyst. A McMurry coupling afforded azabenz[*b*]azulene skeleton (cycloheptanone-fused indoles) (**66**) (Scheme 25).[32]



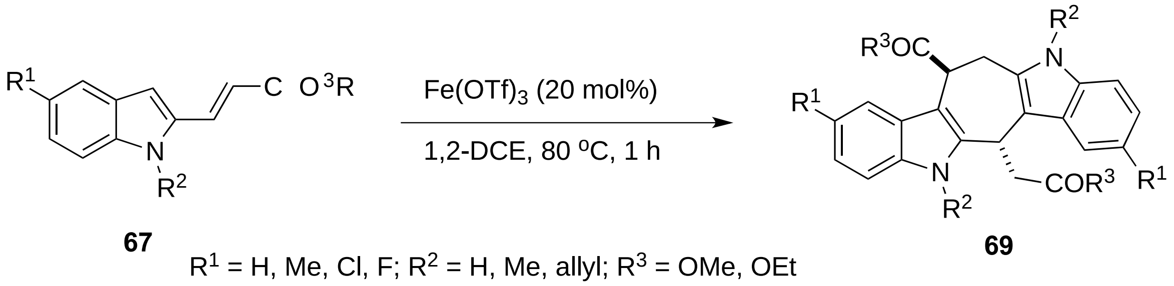
R = OMe, Me, vinyl, F, etc.
R^1 = Ph
R^2 = Ph, 4-FC$_6$H$_4$, 2-thienyl, stylyl

Scheme 25

Direct and expedient access to densely substituted carbazole derivatives (**68**) and cycloheptadiindole derivatives (**69**) was achieved *via* a two-fold divergent diastereoselective transformation of 2-vinylindoles (**67**) (Scheme 26).[33] The conversions proceeded through Lewis acid-catalyzed [4+2] and [4+3]cyclization-aromatization cascade reactions, respectively. The two synthetic routes are effortlessly transposable into each other by modulating the temperature to furnish the corresponding products in a selective and exclusive fashion. Under the conditions as shown in Scheme 27, the sole formation was performed in excellent yield and as a single diastreomer.[33]



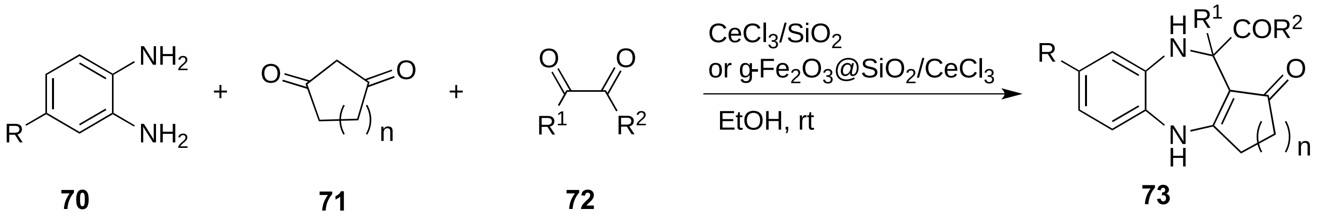
Scheme 26



R^1 = H, Me, Cl, F; R^2 = H, Me, allyl; R^3 = OMe, OEt

Scheme 27

Multi-component or domino reactions enable a variety of unique heterocyclic scaffolds through carbon-carbon and carbon-nitrogen bond formations. Wang *et al.* reported the synthesis of benzodiazepine derivatives (**73**) from 1,2-phenylenediamine (**70**), β-cyclodione (**71**), and aldehyde derivatives (**72**) by using a mild catalyst (γ-Fe_2O_3@SiO_2/$CeCl_3$) in one-pot (Scheme 28).[34]



R = H, F, Cl, Me

n = 1,2

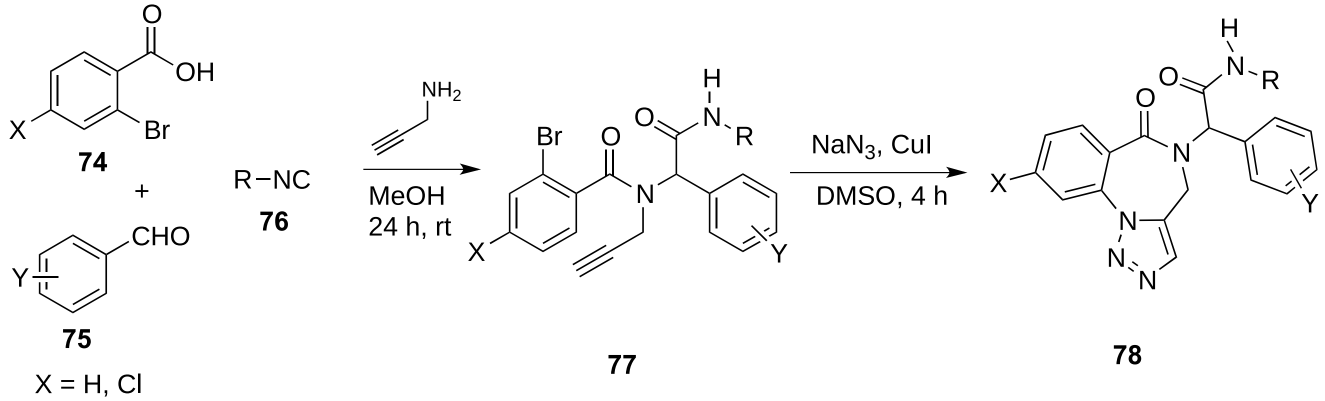
R^1 = H, Me
R^2 = OEt, OH, Me

Scheme 28

The 1,4-benzodiazepine core is a common structure to a number of biologically active products and pharmaceutically interesting compounds. Diazole- and triazole-fused benzodiazepine rings have also gained popularity due to their potent biological activity. Therefore, considerable interest has been generated in the development of many efficient synthetic routes to a diverse range fused benzodiazepines.

In addition, individual reports about the construction of polyaza-containing azulene skeletons occurred passim.

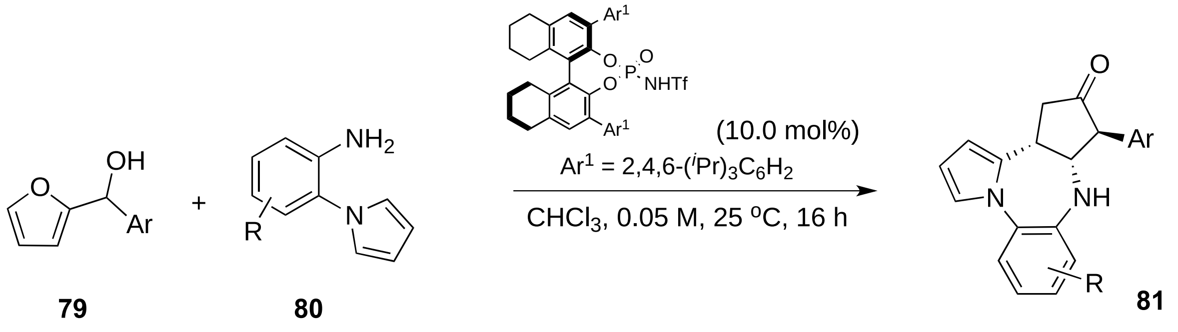
Ugi multi-component reaction based route is excellent strategy for the synthesis of structurally varied and complex intermediates or scaffolds. The protocol (**78**) involves Ugi four-component reaction of 2-bromobenzoic acid (**74**), benzaldehydes (**75**), isocyanides (**76**), and propargylamine followed by *in situ* sequential click reaction of azide ion with triple bond and *N*-arylation reaction afforded triazolobenzodiazepine analogues in good to excellent yields (Scheme 29).[35]



X = H, Cl
Y = 4-OMe, 3,4-OMe, 4-Cl, 4-Me, 2-Me, 4-Br, 2-F, 4-F
R = cyclohexyl, ^{t}Bu, 1,1,3,3-tetramethyl-butyl

Scheme 29

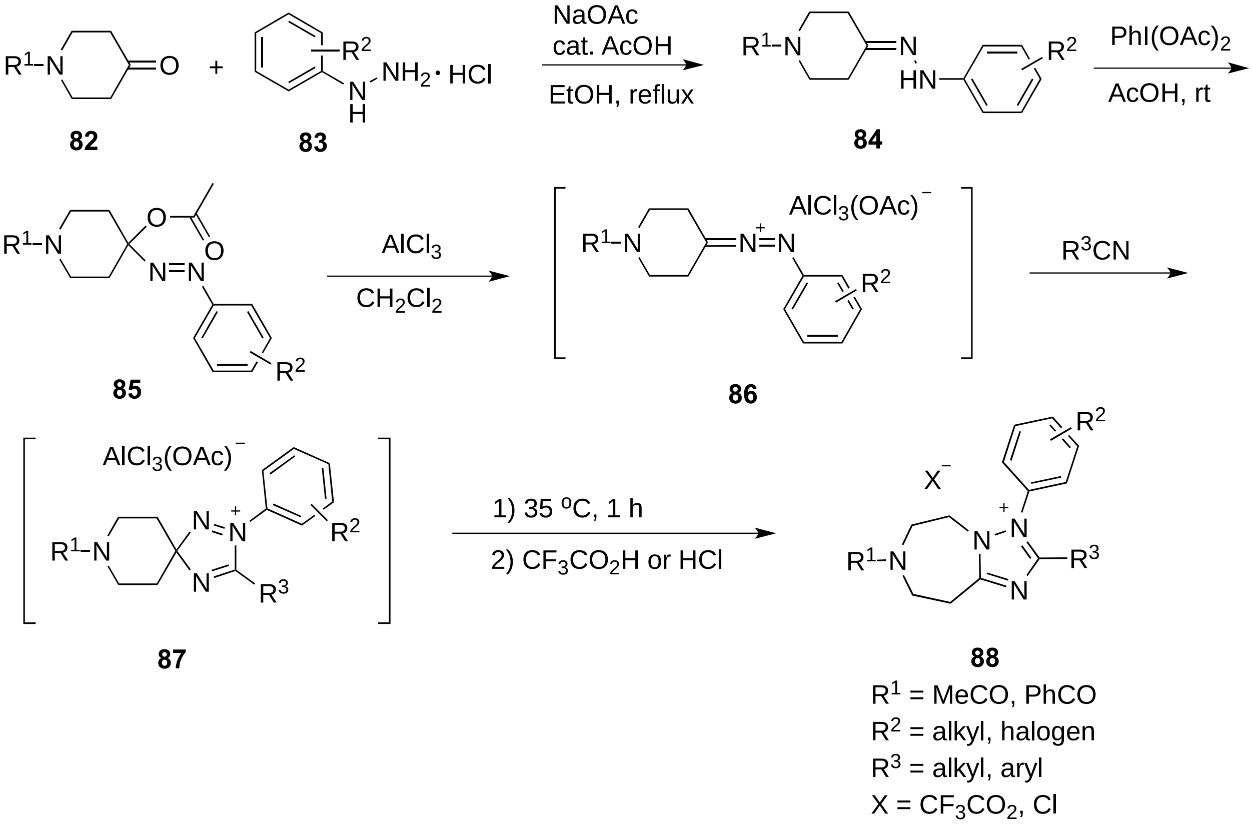
A highly enantio- and diastereoselective cascade cyclization by chiral Brønsted acid (CBA) catalysis, which streamlines the synthesis of enantio-enriched cyclohepta[*f*]pyrrolo[1,2-*d*][1,4]diazepinones (**81**) from a wide range of 2-furylcarbinols (**79**) and (1*H*-pyrrol-1-yl)anilines (**80**) (Scheme 30), which represents the first asymmetric intramolecular conjugate addition of α,β-unsaturated cycloketones with inert *N*-substituted pyrroles as well as the first enantioselective aza-Piancatelli rearrangement/Friedel-Crafts alkylation cascade reaction.[36]



Ar = H, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 1-naphthyl, 2-naphthyl, etc.
R = H, etc.

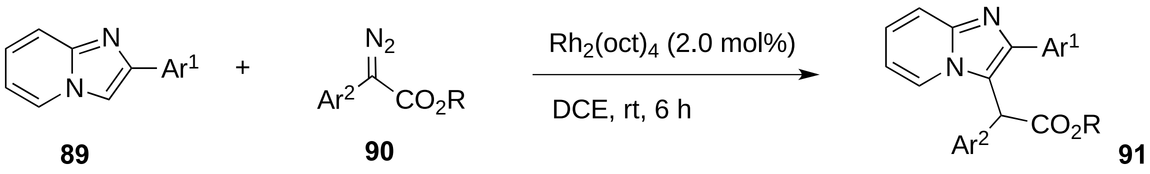
Scheme 30

A facial pathway for construction of 6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]diazepine derivatives (**88**) through sequential [3$^+$+2]cycloaddition/rearrangement reactions of 1-aza-2-azoniaallenium cation intermediates (**86**) which are generated from piperidin-4-one arylhydrazones (**84**) was reported (Scheme 31).[37]

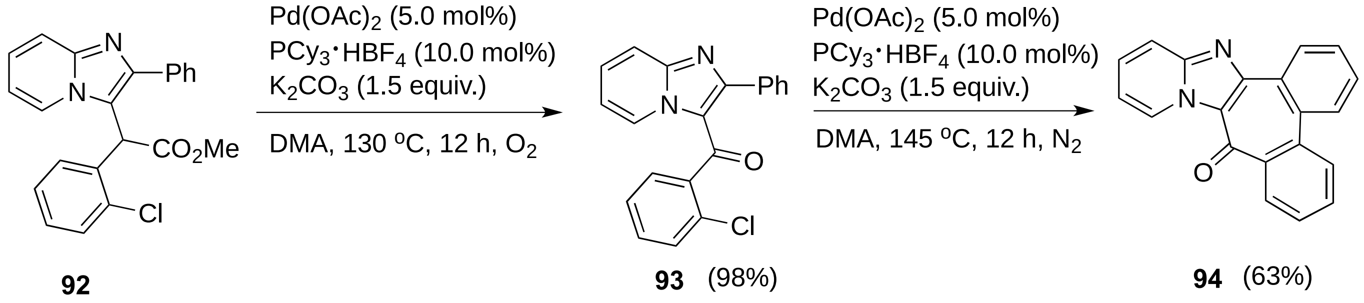


Scheme 31

An effective and wide range of regioselective C3-alkylation of arylimidazo[1,2-*a*]pyridines (**89**) with aryl α-diazoesters (**90**) in the presence of Rh(II)-catalyst to give **91** was reported (Scheme 32).[38] The C3-alkylated compound were easily converted to benzimidazoquinolizinone and cycloheptaimidazopyridinone. The C3-alkylated compounds (**92**) provided *o*-chlorobenzoyl imidazopyridine (**93**) in 98% yield under the conditions. Compound (**93**) cyclized to cycloheptaimidazopyridinone (**94**) in 63% yield (Scheme 33).[38]

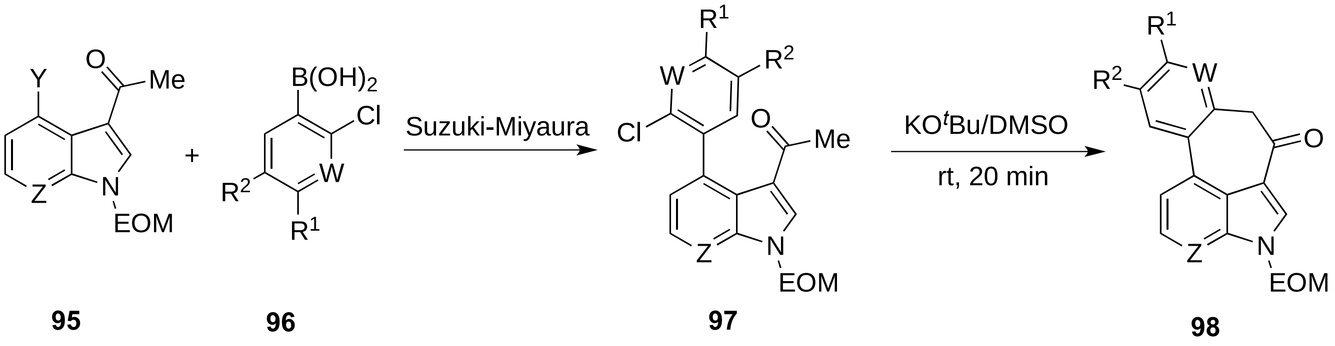


Scheme 32



Scheme 33

A transition-metal-free α-arylation of ketone methodology for the synthesis of 3,4-fused tetracyclic indoles and 7-azaindoles (**98**) was reported.[39] The synthetic strategy involves, as the first step, the construction of **97** by Suzuki-Miyaura coupling of 3-acetyl-4-bromoindoles or 3-acetyl-4-chloro-7-azaindoles (**95**) with **96**. Successive an intramolecular α-arylation of **97** furnishes **98** (Scheme 34).[39]

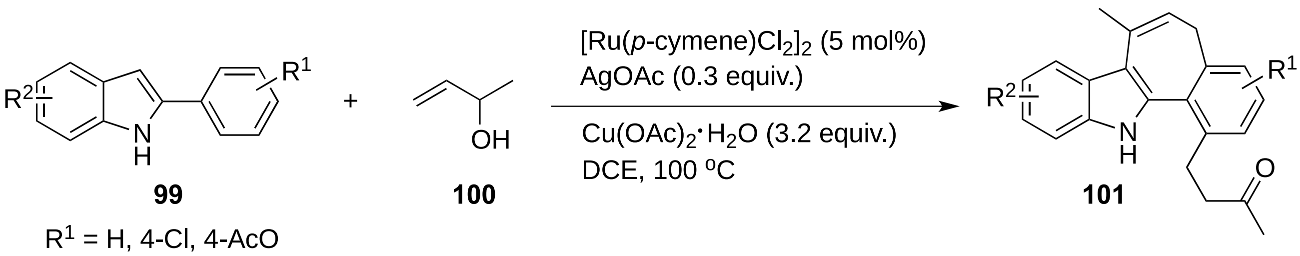


Y = Br, Cl
Z = CH, N

W = CH, C-Cl, N
R^1 = H, CF_3, F, Me
R^2 = H, OMe, CF_3

Scheme 34

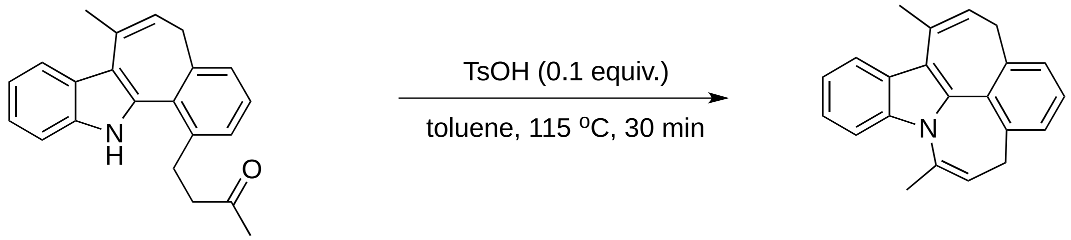
Synthesis of 5,12-dihydrobenzo[6,7]cyclohepta[1,2-*b*]indoles (**101**) by [Ru(*p*-cymene)Cl_2]$_2$-catalyzed selective C-C coupling of indoles (**99**) with allylic alcohols (**100**) was reported (Scheme 35).[40]



R^1 = H, 4-Cl, 4-AcO
R^2 = H, 5-Cl, 5-Me, 5-AcO, 6-F

Scheme 35

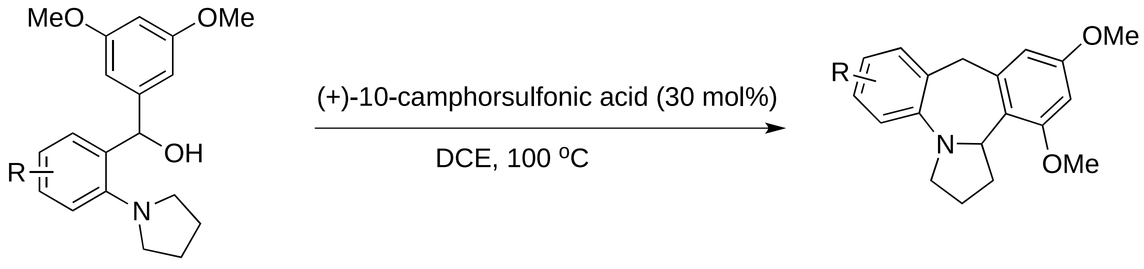
The cyclization product (**101**: R^2 = R^3 = H) was further converted into unique heterocyclic compound (**102**) in 83% yield via nucleophilic addition and cyclization (Scheme 36).[40]



101 (R^2 = R^3 = H) **102**

Scheme 36

Construction of dihydrodibenzo[*b*,*e*]azepine skeletons (**104**) by a carbocation-initiated cascade [1,5]hydride transfer/cyclization from (3,5-dimethoxyphenyl)(2-(pyrrolidin-1-yl)phenyl)methanol (**103**) was reported (Scheme 37).[41]

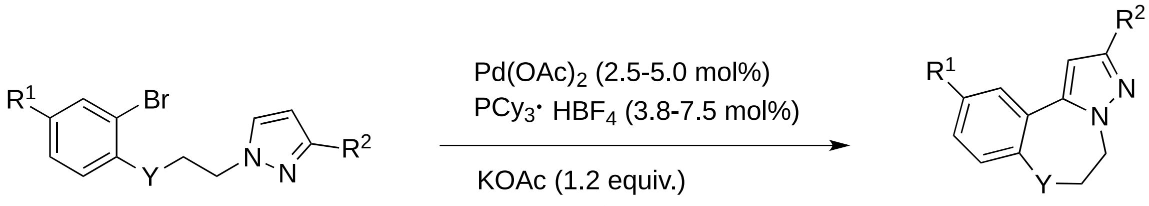


103 **104**

R = H, 3-Cl, 4-Cl, 5-Cl, 5-Br, 5-CF$_3$, 5-Me, etc.

Scheme 37

Heterocyclic fused 2-benzazepines (**106**) were synthesized from **105** by Pd-catalyzed C-H activation strategy (Scheme 38).[42] The strategy is wide substrate scope including various azepines, benzoxazepines, thiazepines, and even benzodiazepines.

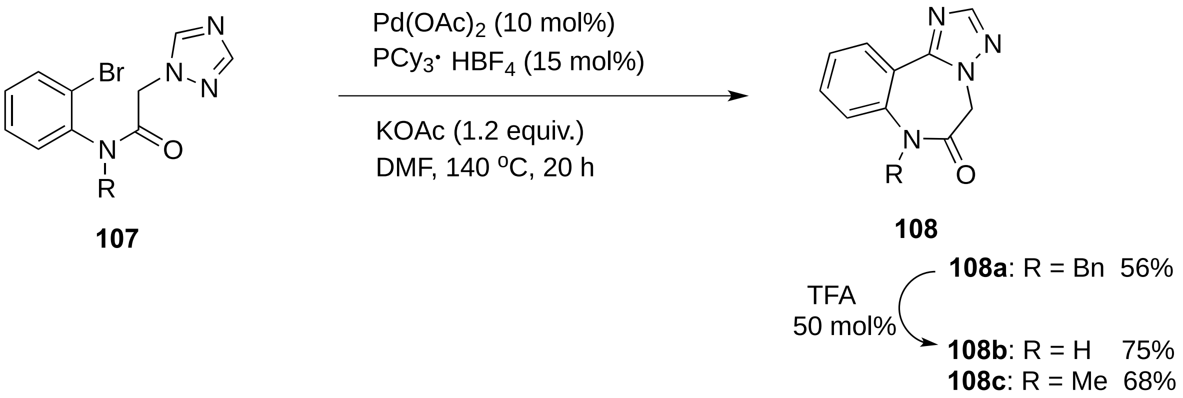


105 **106**

Y = CH$_2$, O, S
R^1 = H, Me, Et, Cl, etc.
R^2 = H, Ph, C$_6$H$_3$(OMe)$_2$

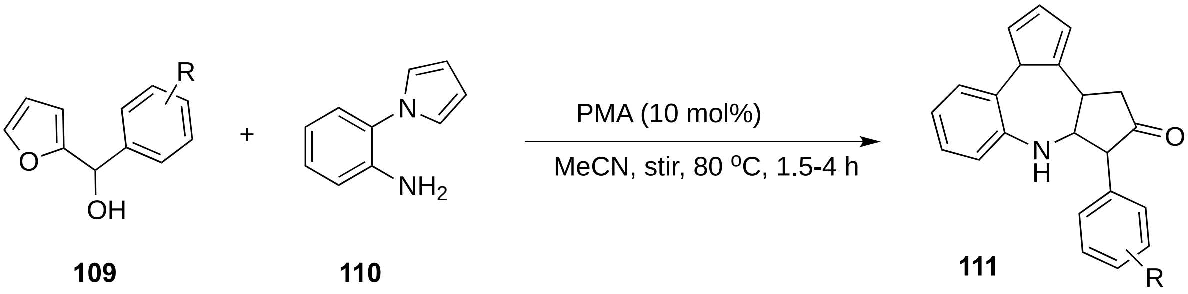
Scheme 38

Starting from easily accessible 2-bromoaniline derivatives (**107**), diversely decollated benzotriazolodiazepinones (**108**) were obtained under otherwise identical conditions (Scheme 39).[42] The benzotriazolodiazepinones (**108**) were identified as new heat shock protein 90 (Hsp90) inhibiting lead compounds.[42]



Scheme 39

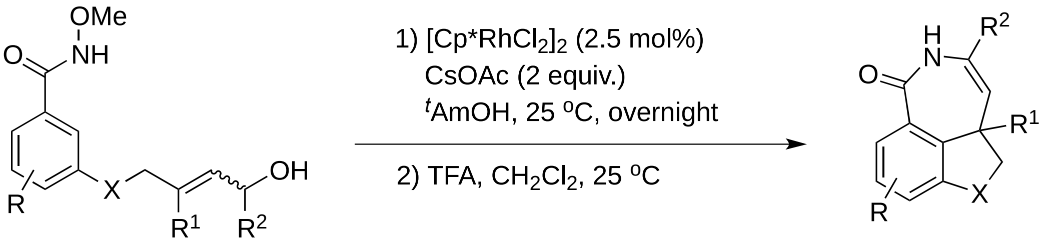
Tetrahydrobenzo[*b*]cyclopenta[*f*]pyrrolo[1,2-*d*]diazepinone derivatives (**111**) were derived through domino coupling of (furan-2-yl)methanol (**109**) with 2-(1*H*-pyrrol-1-yl)aniline (**110**) in the presence of phosphomolybdic acid (PMA) in MeCN under reflux (Scheme 40).[43]



R = H, Ph, 4-Me, 4-Br, 4-^{i}Pr, 4-^{t}Bu, 4-OMe, 2-Cl, 4-F, 2,3,4-(OMe)$_3$

Scheme 40

Azepinone derivatives (**113**) were synthesized by a Rh(III)-catalyzed aryl-CH activation intramolecular Heck-type reaction of benzamide-tethered allylic alcohols (**112**) followed by elimination under acidic conditions. (Scheme 41).[44] The reported two-steps, one-pot procedure is operationally simple and proceeds under mild conditions to provide a variety of tricyclic benzazepinones.

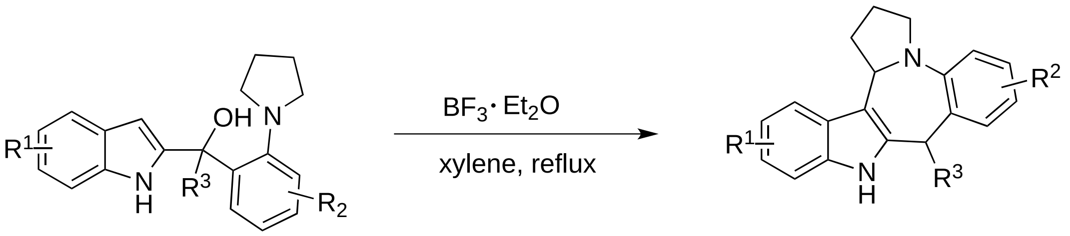


112 **113**

X = O, NMe
R = H, 4-OMe, 4-F, 4-NO_2, etc.
R^1 = H, Me, Ph, 4-$MeOC_6H_4$, etc.
R^2 = H

Scheme 41

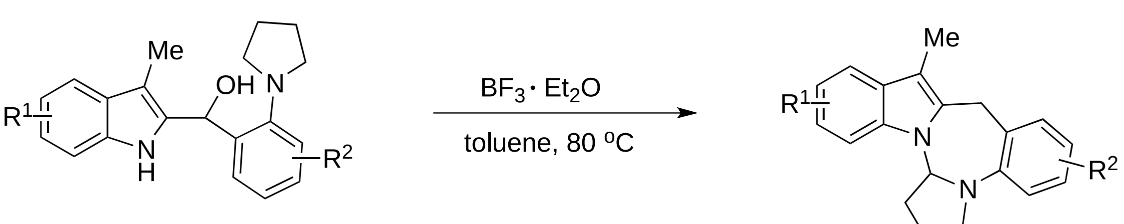
Wang *et al*. reported a new and efficient strategy for synthesis of indoloazepines (**115**) and indolodiazepines (**117**) from indolyl aryl carbinols (**114** and **116**), respectively, through dehydration/[1,5]-hydride shift/7-cyclization sequences, by appropriate control of the conditions and substrates (Scheme 42 and 43).[45]



114 **115**

R^1 = H, 5-Cl, 5-Me, 5-MeO, 6-Cl
R^2 = H, 5-Me, 5-F
R^3 = H, Ph

Scheme 42

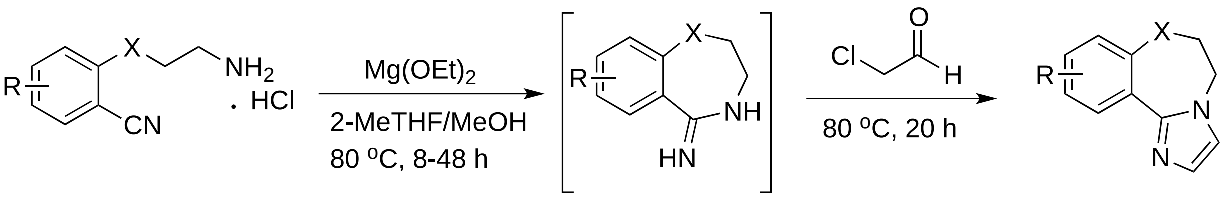


116 **117**

R^1 = H, 5-Cl, 5-Me
R^2 = H, 5-Me, 5-F

Scheme 43

For the construction of aza-cycles, the strategy by intramolecular direct attacks of amines to aryl nitriles or aryl esters often used. Dalziel *et al.* reported the synthesis of imidazobenzoxazepines and imidazobenzodiazepines (**120**) *via* intramolecular cyclization of **118** using magnesium ethoxide to access cyclic amidines (**119**) and successive reaction with chloroacetaldehyde (Scheme 44).[46]



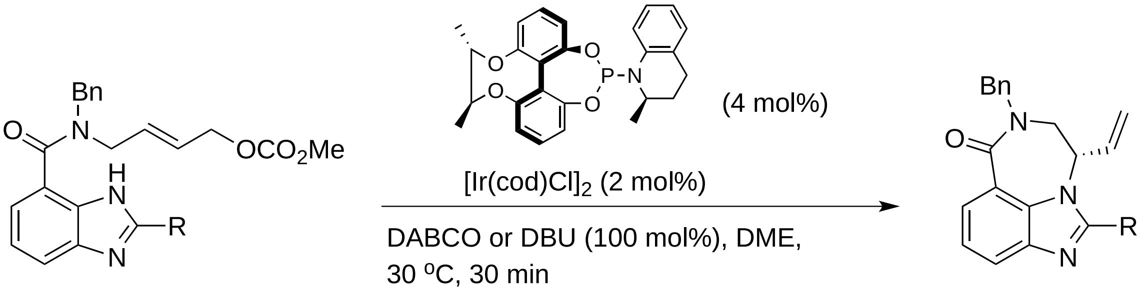
118 **119** **120**

X = O, S, NH

R = H, 5-Me, 5-OMe, 5-CF_3, 5-CN, 5-Cl, 4-MeO, 6-Me, etc.

Scheme 44

The interesting and efficient iridium-catalyzed enantioselective intramolecular allylation of benzimidazole-tethered allylic carbonate was reported by Qiu and co-workers. The methods enables access to synthetically valuable tricyclic benzimidazoles. Under the conditions, compounds (**121**) cyclized to benzimidazole-fused diazepanone derivatives (**122**) in excellent yields (Scheme 45).[47]

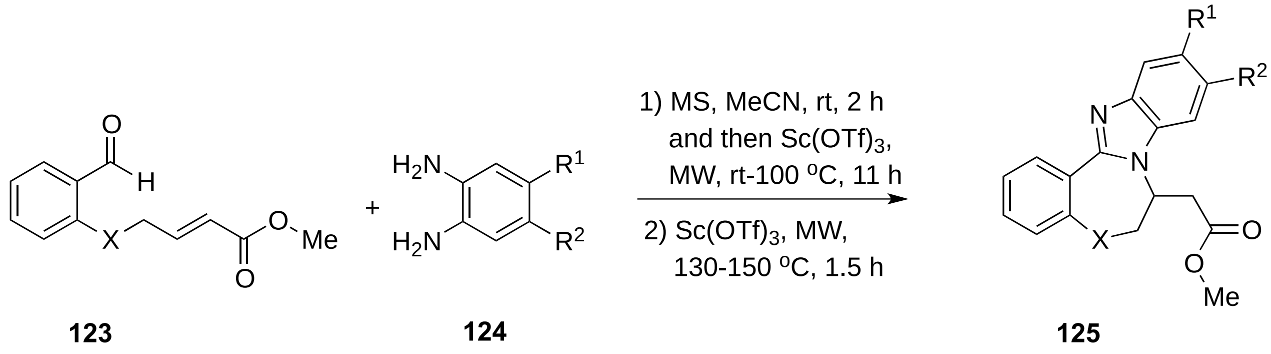


121 **122**

R = H, Me, CF_3, ${}^{i}Pr$, cyclopropyl, cyclohexyl, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-CNC_6H_4, 3-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, naphthyl, etc.

Scheme 45

A one-step build/couple/pair strategy that allows to diversely functionalized benzoxazepine, benzodiazepine, and indolopyrazine scaffolds was reported. The methodology featured a one-pot combination of condensation, Mannich oxidation, and aza-Michael addition reactions employing a variety of functionalized anilines and aldehydes. Thus, treatment of aryl aldehydes (**123**) with phenylenediamine (**124**) under the conditions afforded benzimidazole-fused benzodiazepines (**125**) in fairly good yields (Scheme 46).[48]

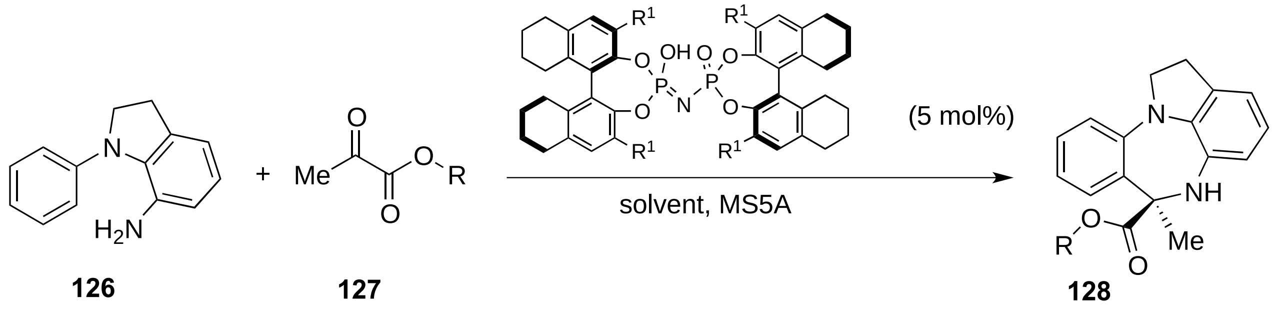


X = O, NTs

$R^1 = R^2 = H$
$R^1 = R^2 = Me$
$R^1 = R^2 = Cl$
$R^1 = Cl, R^2 = H$

Scheme 46

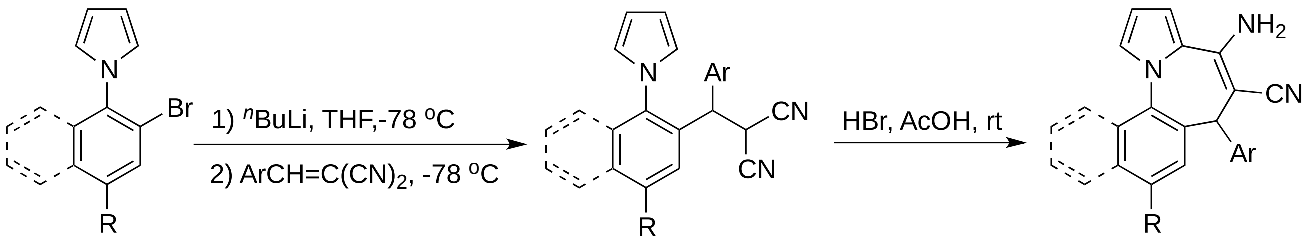
Chiral indoline-benzodiazepine scaffolds (**128**) were constructed from 7-aminoindolines (**126**) with pyruvate derivatives (**127**) by the Pictet-Spengler reaction using H_8-BINOL type chiral imidodiphosphoric acid catalysts (Scheme 47).[49]



R = Et, ^{t}Bu, Bn, 2-naphthyl; R^1 = 2-naphthyl

Scheme 47

An efficient procedure for the preparation of pyrrolo[1,2-*a*][1]benzazepine derivatives (**131**), *via* the formation of compounds (**130**), being produced by the reaction of arylidenemalononitriles with 2-(1*H*-pyrrol-1-yl)phenyllithiums (prepared form 1-(2-bromophenyl)-1*H*-pyrroles (**129**) and ^{n}BuLi) and successive HBr-mediated cyclization, was reported (Scheme 48).[50] The method was applicable to the construction of naphthalene-fused azaazulene system.

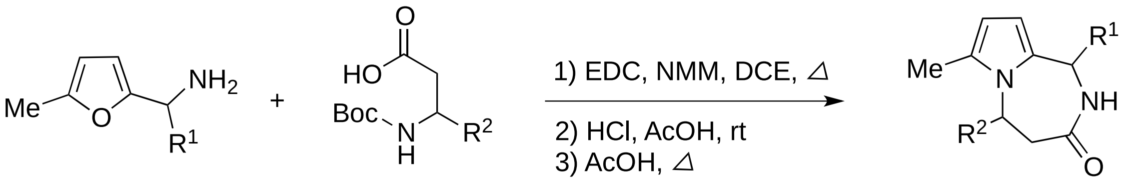


129 **130** **131**

R = H, Me, Cl
Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 3,4-(MeO)$_2$C$_6$H$_3$

Scheme 48

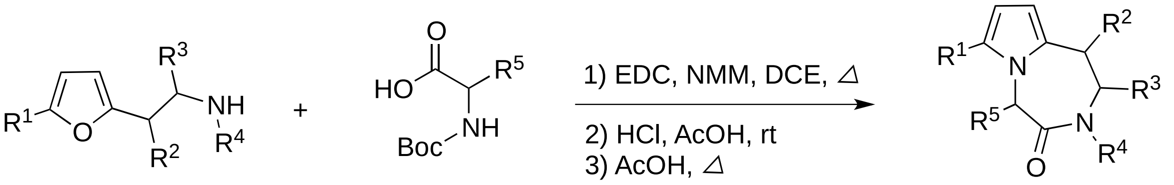
A simple one-pot method for the synthesis of isomeric pyrrolo[1,2-*x*][1,4]diazepinones (**134** and **137**) was reported.[51] The method is based on the condensation of *N*-Boc amino acids with furans containing aminoalkyl groups followed by deprotection, furan ring opening, and Paal-Knorr cyclization. By employing this method, the reaction of furfurylamines (**132**) with β-amino acids (**133**) gave pyrrolo[1,2-*a*][1,4]diazepin-3(2*H*)-ones (**134**) (Scheme 49) and the reaction of 2-(2-furyl)ethylamines (**135**) with α-amino acids (**136**) gave pyrrolo[1,2-*d*][1,4]diazepin-4(5*H*)-ones (**137**) (Scheme 50).[51] The investigations of cytotoxicity of the compounds (**134**, **137**) against HEK293T, VA13, MCF7, and A549 were performed. Compounds (**137**) demonstrated low-to-moderate cytotoxicity, but **134** was inactive.[51]



132 **133** **134**

R^1 = H, 4-CF$_3$C$_6$H$_4$ R^2 = Ph, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeOC$_6$H$_4$

Scheme 49

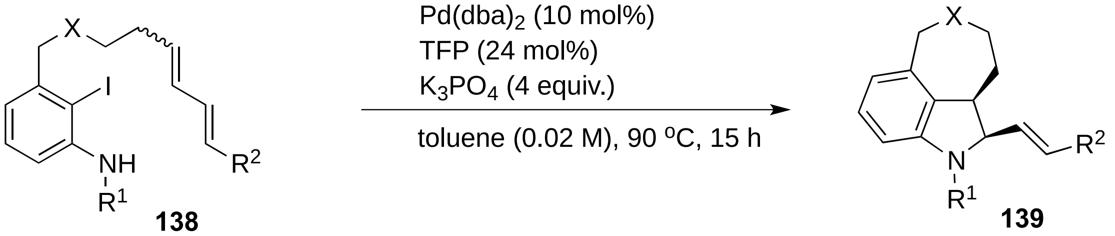


135 **136** **137**

R^1 = Me, Et, ^{t}Bu R^5 = H, Me, ^{i}Pr, ^{n}Bu, Bn, etc.
R^2 = H, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$
R^3 = H, 3,4-(MeO)$_2$C$_6$H$_3$
R^4 = H, Bn

Scheme 50

Cascade reactions of palladium catalyzed seven-membered fused indole derivatives from iodoanilines bearing a diene side chain at 3-positon was reported. In the reaction, the compounds (**138**) cyclized to cyclohepta-fused tricyclic indolines (**139**) (Scheme 51).[52] By DFT calculations, it is suggested that the sequence reaction proceeded *via* an intramolecular Heck insertion of diene, followed by nucleophilic attack to η^3 π-allylpalladium species.



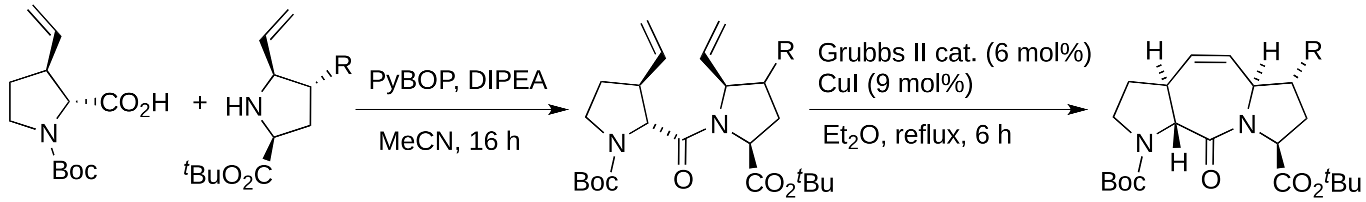
138

139

R^1 = Ts, 4-$CF_3C_6H_4SO_2$
R^2 = Me, Pn
X = NTs, $C(CO_2Me)_2$

Scheme 51

For the synthesis of scaffolds (**143**), a mimicking a diproline unit in a PPII (polyproline type II) helix conformation, a useful methodology for the preparation of 4-substituted 5-vinylprolines (**140**, **141**) was elaborated. The bilding blocks (**140**, **141**) were employed to the synthesis of the tricyclic structures (**143**) through peptide coupling and successive Ru-catalyzed ring closing metathesis (Scheme 52).[53]

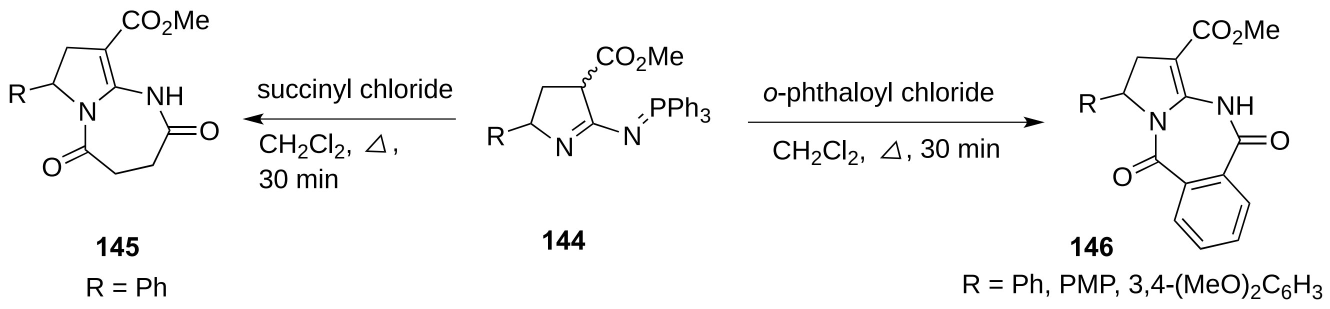


140 **141** **142** **143**

R = H, Me, Et

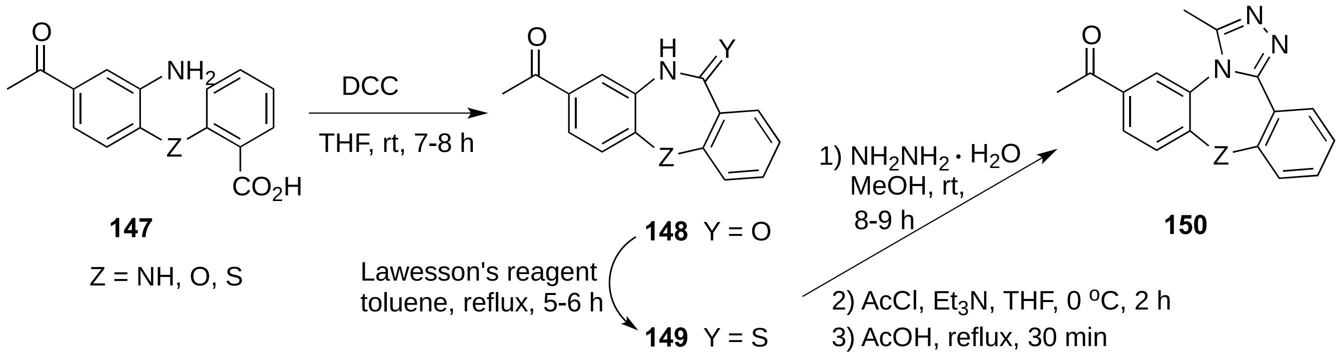
Scheme 52

Aza-Wittig reaction of iminophosphazenes (**144**), which were produced from γ-azidonitriles and triphenylphosphine, with succinyl and *o*-phthaloyl chlorides afforded pyrrolo[1,2-*a*][1,3]diazepines (**145**) and pyrrolo[1,2-*b*][2,4]benzodiazepines (**146**), respectively (Scheme 53).[54]



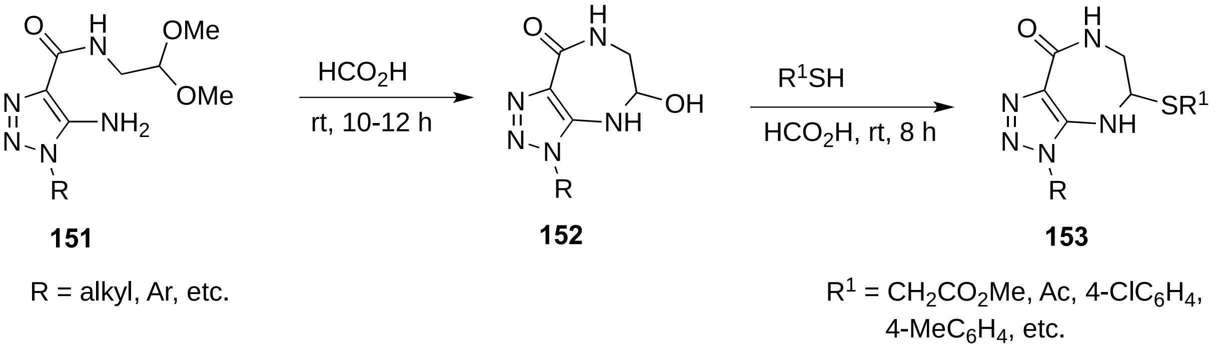
Scheme 53

An expedient method for the synthesis 1,2,3-triazolo-fused 1,5-benzodiazepine and related compounds (**150**) from benzodiazepinone and related compounds (**148**) *via* **149** was reported (Scheme 54).[55] Where, compounds (**148**) were produced by cyclization of **147** using *N,N'*-dicyclohexylcarbodiimide (DCC). The obtained compounds (**148**, **149**, and **150**) were screened for antibacterial, antifungal, and antioxidant activities.



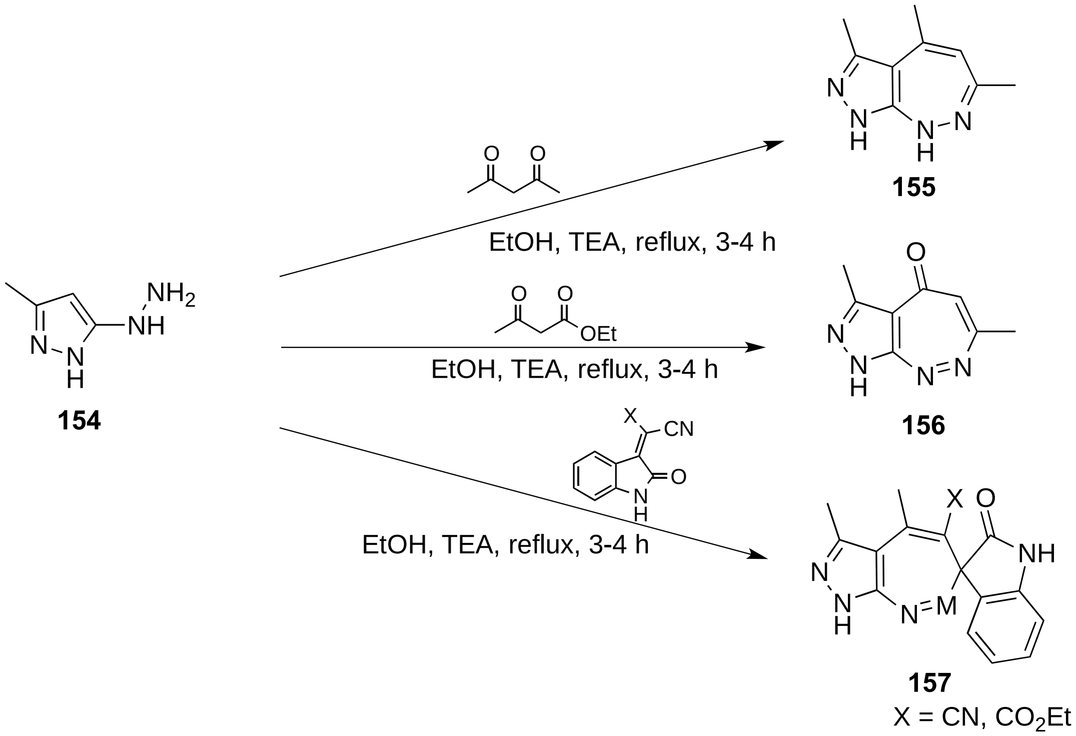
Scheme 54

Intramolecular cyclization of 5-amino-*N*-(2,2-dimethoxyethyl)-1*H*-1,2,3-triazole-4-carboxamides (**151**) in formic acid provided a convenient method for the synthesis of isomeric 5-hydroxy[1,2,3]triazolo[4,5-*e*][1,4]diaepine derivatives (**152**), which were converted by *S*-nucleophiles to 5-thio-functionalized derivatives (**153**) (Scheme 55).[56]



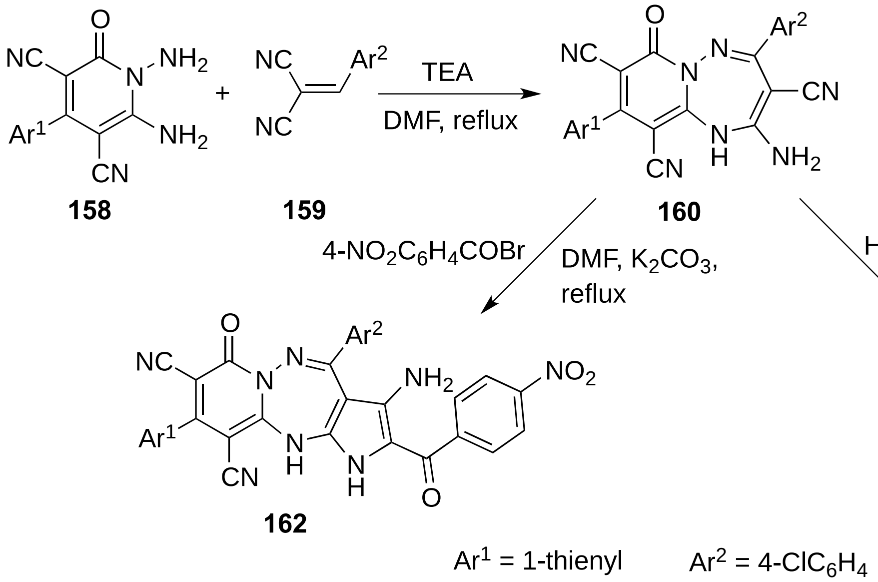
Scheme 55

Simple and efficient method for the synthesis of pyrazolo[3,4-*c*][1,2]diazepine derivatives (**155**, **156**, and **157**) by the reaction of 5-hydrazinyl-3-methyl-1*H*-pyrazole (**154**) with acetylacetone, ethyl acetoacetate, and isatylidene derivatives, respectively, was appeared (Scheme 56).[57] The newly synthesized compounds were screened for their antioxidant activities, and compound (**155**) showed higher radical-scavenging activities.[57]



Scheme 56

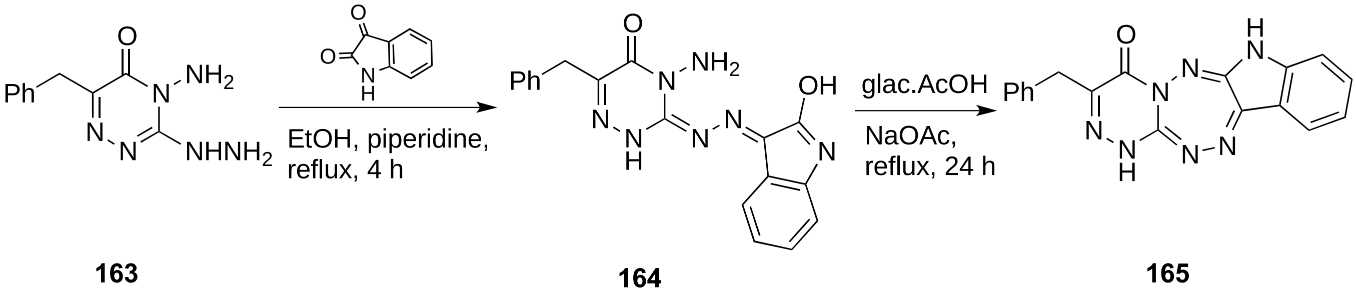
The pyrido[1,2-*b*][1,2,4]triazepine moiety (**160**) was utilized as a building unit to synthesize of various fused pyridotriazepine analogues, such as pyrido[1,2-*b*]pyrimido[4,5-*e*][1,2,4]triazepines (**161**), pyrido[1,2-*b*]pyrido[2,3-*e*][1,2,4]triazepines, pyrido[1,2-*b*]pyrrolo[2,3-*e*][1,2,4]triazepines, and so on. Compound (**160**) was synthesized by heating an equimolar mixture of 1,2-dihydropyridine-3,5-dicarbonitrile derivative (**158**) and 2-(4-chlorobenzylidene)malononitrile (**159**) in DMF containing Et_3N as a catalyst. Compound (**162**) was synthesized *via* equimolar mixture of **160** and *p*-nitrophenacyl bromide in DMF containing K_2CO_3 as a base (Scheme 57).[58] The newly synthesized compounds were subjected to *in vitro* anticancer screening against mammalian colon carcinoma HCT-116 cell line. Some compounds exhibited moderate to strong anticancer activity against mammalian colon carcinoma HCT-116 cell line, but the compound (**162**) did not show the activity.[58]



Ar^1 = 1-thienyl   Ar^2 = 4-ClC$_6$H$_4$

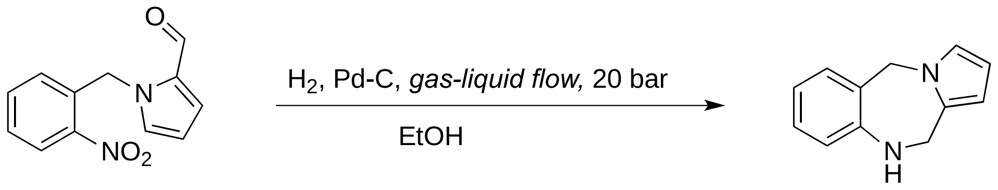
Scheme 57

Synthesis of 4*H*-[1,2,4]triazino[3’,4’:3,4][1,2,4,5]tetrazepino[6,7]indol-4-one derivative (**165**) was achieved *via* treatment of 3-hydrazinyl-1,2,4-triazin-5(4*H*)-one derivative (**163**) with isatine in dry EtOH in the presence of few drops of piperidine, and successive ring closure of obtained **164** in boiling AcOH in the presence of NaOAc (Scheme 58).[59] Compound **165** exhibit good antifungal activity against *A. fumigatus* and *C. albicans* fungal strains.[59]



Scheme 58

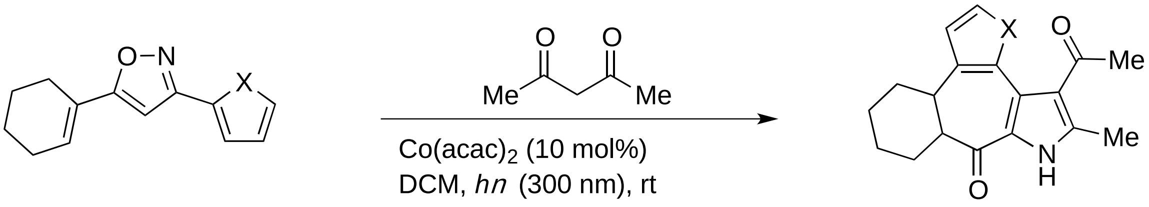
The construction of a pyrrolobenzo[1,4]diazepine (**167**) scaffold was achieved, by gas-liquid flow hydrogenation using Tube-in-Tube device based on amorphous Teflon AF-2400 fluoropolymer, from 1-(2-nitrobenzyl)pyrrole-2-carbaldehyde (**166**) through a tandem hydrogenation-condensation-hydrogenation sequence (Scheme 59).[60]



166 **167**

Scheme 59

Vinylogous Nazarov-type cyclization yielded seven-membered rings from butadienyl vinyl ketones via a photochemical [6π]-photocyclization followed by subsequent isomerization steps (photoisomerization/pyrrole synthesis/[6π]-photocyclization). Thus, isoxazole derivatives (**168**) reacted under the conditions to give 1-azaazulene skeletons (**169**) (Scheme 60).[61] The mechanism was investigated using unrestricted DFT, SF-TDDFT, and CASSCF/NEVPT2 calculations.[61]



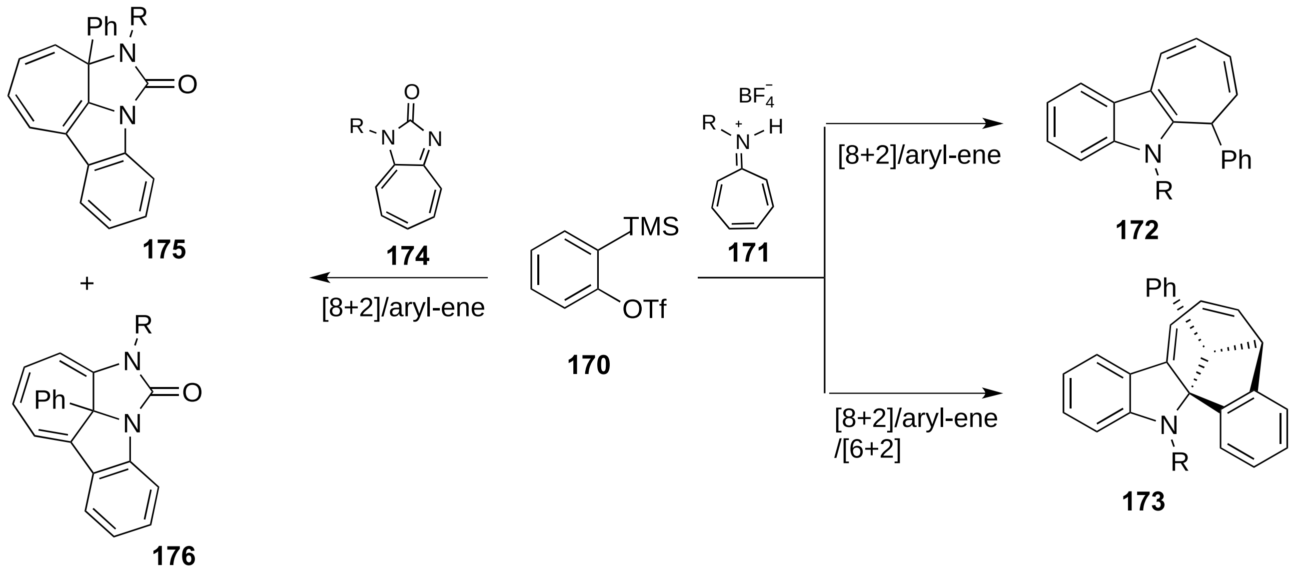
168
X = CHCH, O, S

169

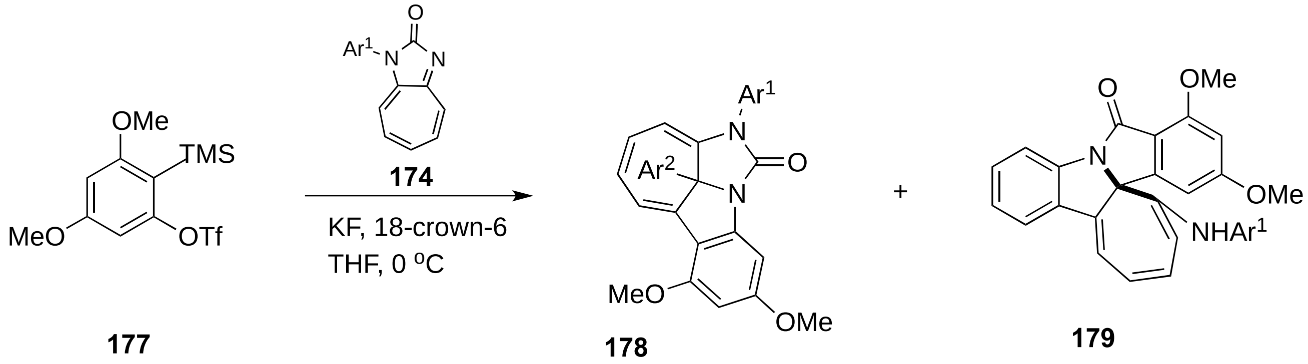
Scheme 60

II. REACTIONS AND SOME PROPERTIES

[8+2]Cycloaddition of 8-azaheptafulvenes with electron-deficient olefins was frequently used to construction of azaazulene skeleton.[1] For the synthesis of 5-azabenzazulene (cyclohepta[*b*]indoles) skeletons, an efficient [8+2]/aryl-ene tandem reaction between azaheptafulvenes and arynes was reported.[62] When excess arynes were used, [8+2]aryl-ene/[6+2] tandem reaction occurred, and polycyclic oxacyclohepta[*b*]indoles were provided.[62] Thus, treatment of **170** (2.5 equiv.) and **171** in the presence of KF and 18-crown-6 in MeCN at 25 °C for 2 h afforded **172** in high yields, whereas treatment of **170** (5.0 equiv.) and **171** in the presence of KF/Cs_2CO_3 and 18-crown-6 in MeCN/toluene at 25 °C for 2 h afforded **173** in high yields (Scheme 61).[62] Treatment of **170** (2.5 equiv.) and **174** in the presence of KF and 18-crown-6 in THF at 0 °C afforded indole derivatives (**175**) and indoline derivatives (**176**) at a ratio of 1:1 (Scheme 61).[62] When unsymmetrical aryne precursor (**177**) was used, another unexpected [8+2]/aryl-ene/ring opening tandem reaction occurred, and **178** and **179** were provided (Scheme 62).[62]



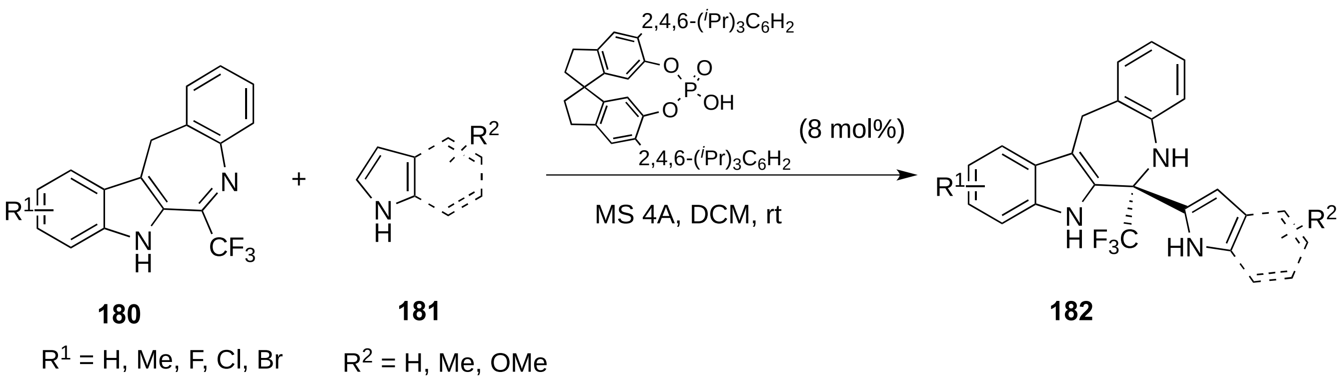
Scheme 61



Ar^1 = 4-ClC_6H_4 Ar^2 = 2,5-$(MeO)_2C_6H_3$ **178**/**179** = 1 : 1

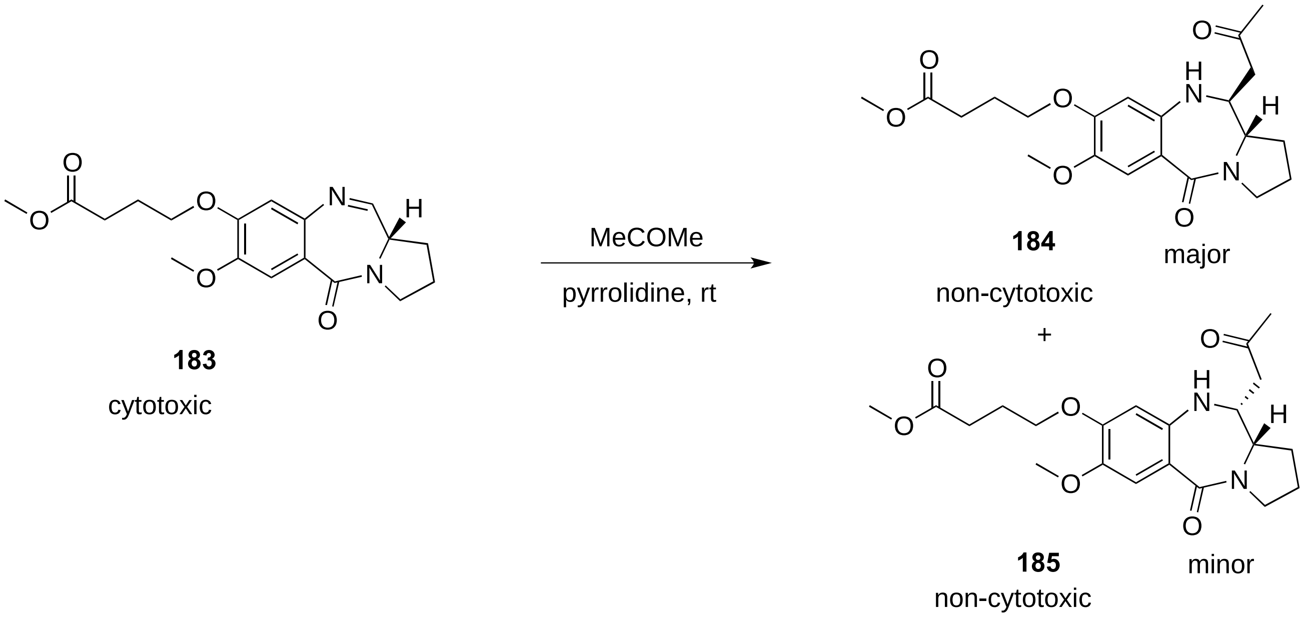
Scheme 62

An enantioselective chiral spirocyclic phosphoric acid (SPA) catalyzed aza-Friedel-Crafts reaction of trifluoromethyl-benzoazepinoindoles (**180**) with pyrroles (or indoles) (**181**) under mild conditions afforded CF_3- and pyrrole-containing benzazepinoindoles (**182**) bearing quaternary stereocenters in good yields (Scheme 63).[63]



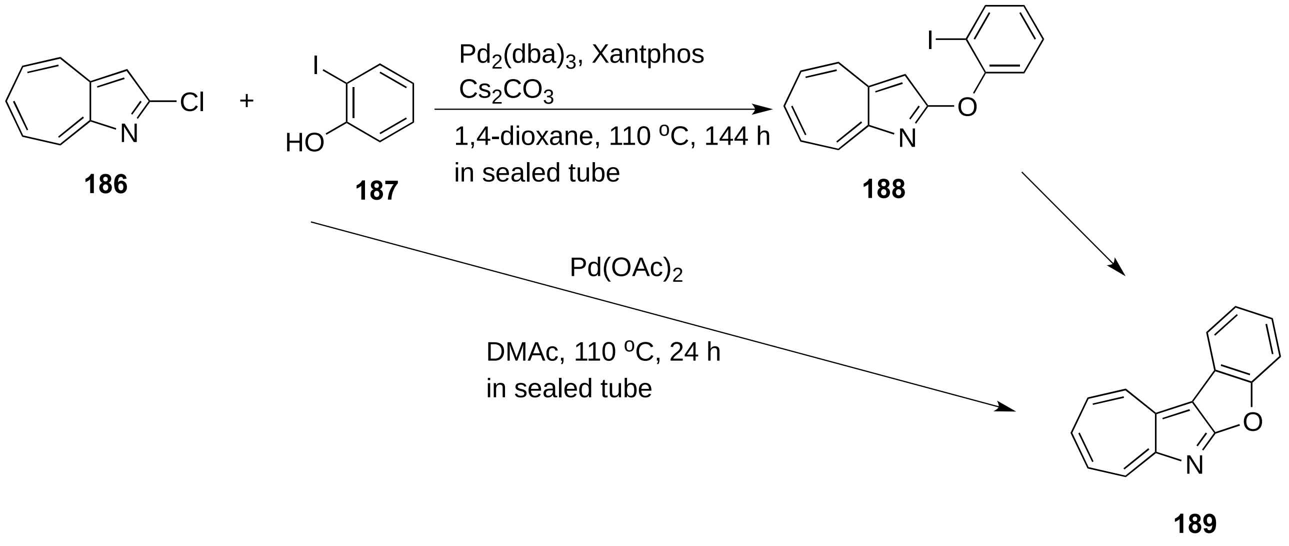
Scheme 63

Pyrrolidine-catalyzed diastereomeric addition on C11 of pyrrolobenzodiazepine (PBD) compounds (**183**) occurred during the chromatographic purification in the presence of acetone, and C11-adducts (**184** and **185**) were obtained (Scheme 64).[64] A cellular cytotoxicity of the modified PBD confirmed their lack of cytotoxicity, consistent with loss of the DNA-interactive N10-C11 imine functionality. Awareness of the possibility of the reaction may allow its prevention by using alternative amines to protecting group removal during the final synthetic step.



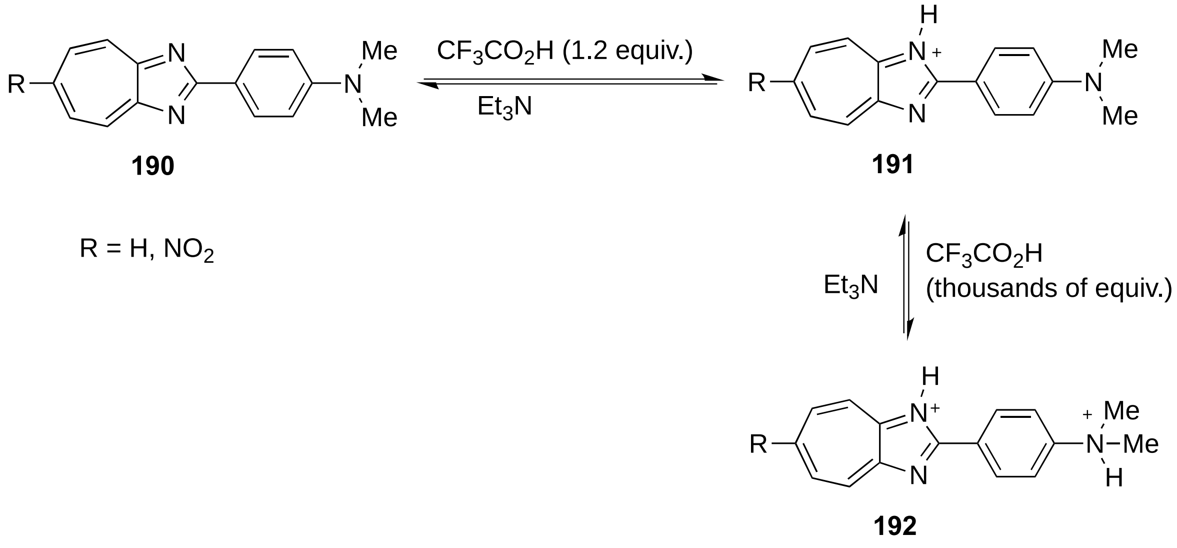
Scheme 64

Benzofuran-fused 1-azaazulene (**189**) was obtained by stepwise treatment of **186** with **187** under the conditions of Hartwig-Buchwald type hetroarylation *via* compound (**188**). Compound (**189**) was also obtained domino Suzuki coupling/Hartwig-Buchwald coupling reaction of **186** with **187** in the presence of Pd(OAc)$_2$ in one-pot (Scheme 65).[65] In the reaction, the intermediate (**188**) was not isolated.[65]



Scheme 65

Guo *et al*. reported systematically investigation about the protonation behaviors on 1,3-diazaazulene derivatives by UV-vis absorption titration and ^{1}H NMR titration, as well as theoretical calculations.[66] 2-Dimethylamino-1,3-diazaazulenes (**190**) displayed prominent halochromic deprotonation responses (Scheme 66).[66] Upon protonation of 2-phenyl-1,3-diazaazulene derivatives, the co-planarity and conjugation of the 16-π backbones were well sustained, while electronic structures were controllably adjusted.



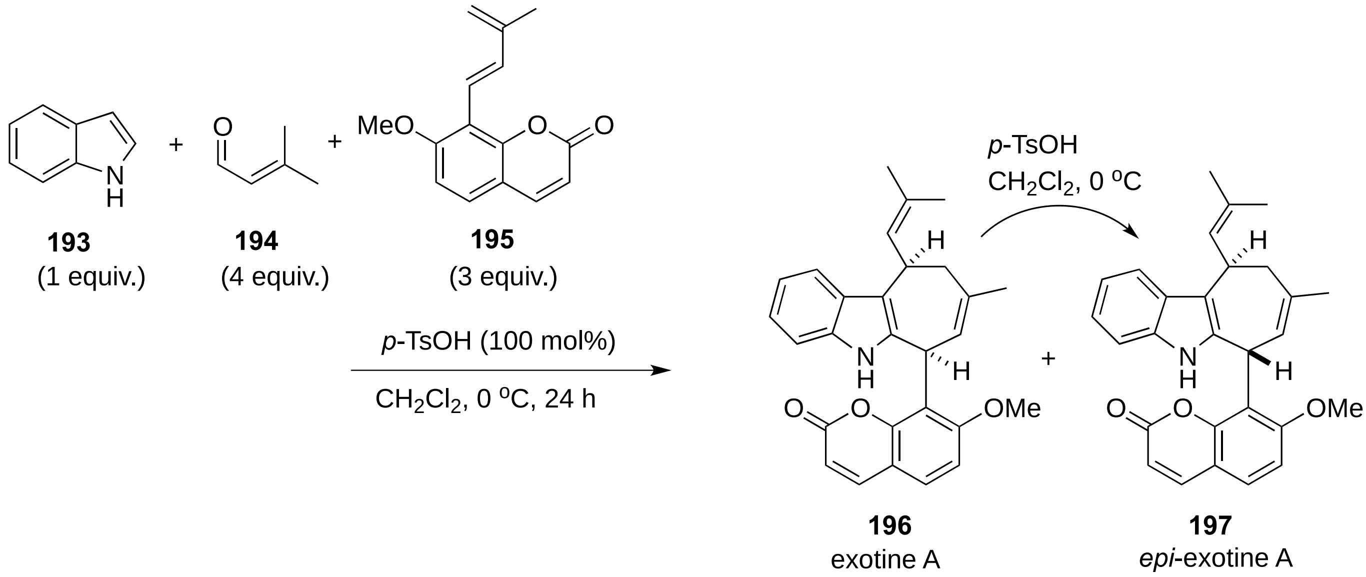
Scheme 66

III. NATURAL PRODUCTS AND TOTAL SYNTHESIS

For the synthesis of numerous natural products and bioactive molecules containing an indole core motif, indolylvinyl ketones are investigated as valuable building blocks for some alkaloids and their analogues, and reviwed.[67] For construct fused indole skeletons, recently some reviews published.[3,5] Nemoto *et al*. investigated vigorously and reviewed about 3,4-fused tricyclic indoles.[2] Alkaloids containing azaazulene skeletons (azepinoindoles, pyrroloazepines, pyrrolobenzazepines, etc.) are especially interesting, and the review about non-monoterpenoid azepinoindole alkaloids appeared.[4]

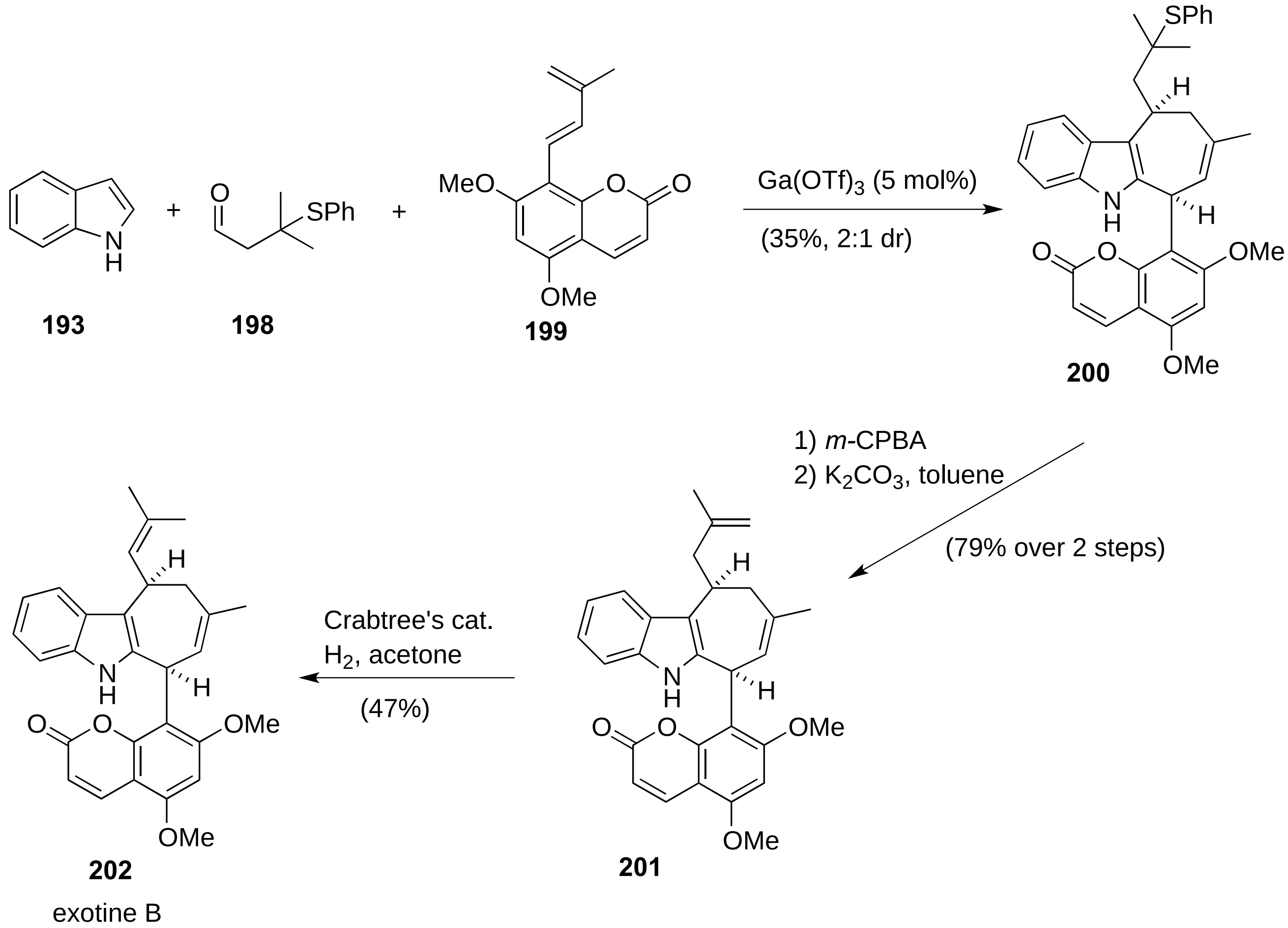
Syntheses of exotine A and B, which were isolated from roots of *Murraya exotica* (commonly known as orange jasmine), were reported by two research groups.

Martin and co-worker reported the first total synthesis (±)-exotine A (**196**) by a biomimetic process that features a one-pot, formal [4+3]cycloaddition involving three starting materials (**193**, **194**, and **195**) (Scheme 67).[68] Some mechanistic aspects of the reaction were discussed.



Scheme 67

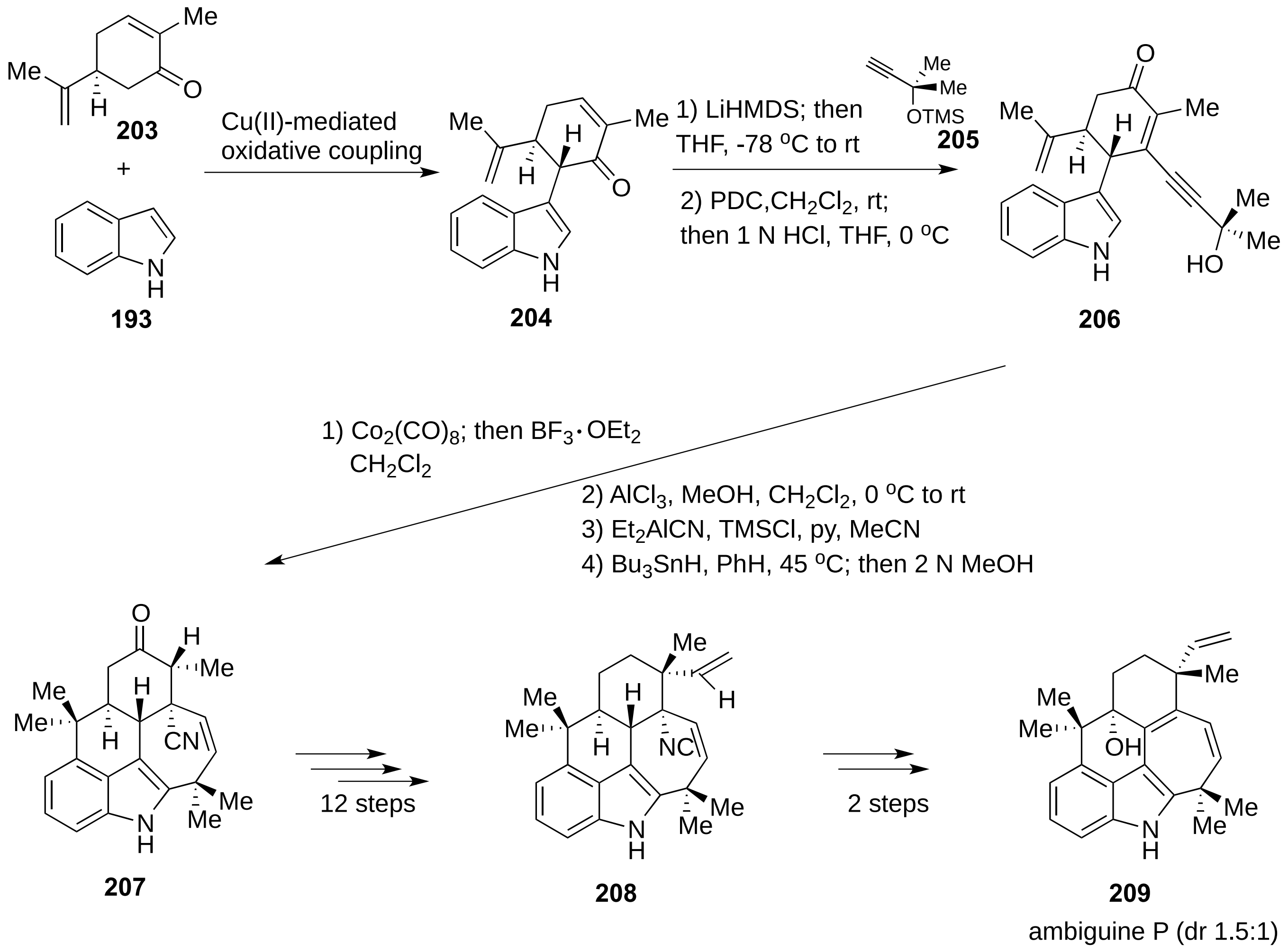
Cheng and co-workers reported the total synthesis (±)-exotine B (**202**) through a gallium-catalyzed three component [4+3]cycloaddition reaction (Scheme 68).[69]



Scheme 68

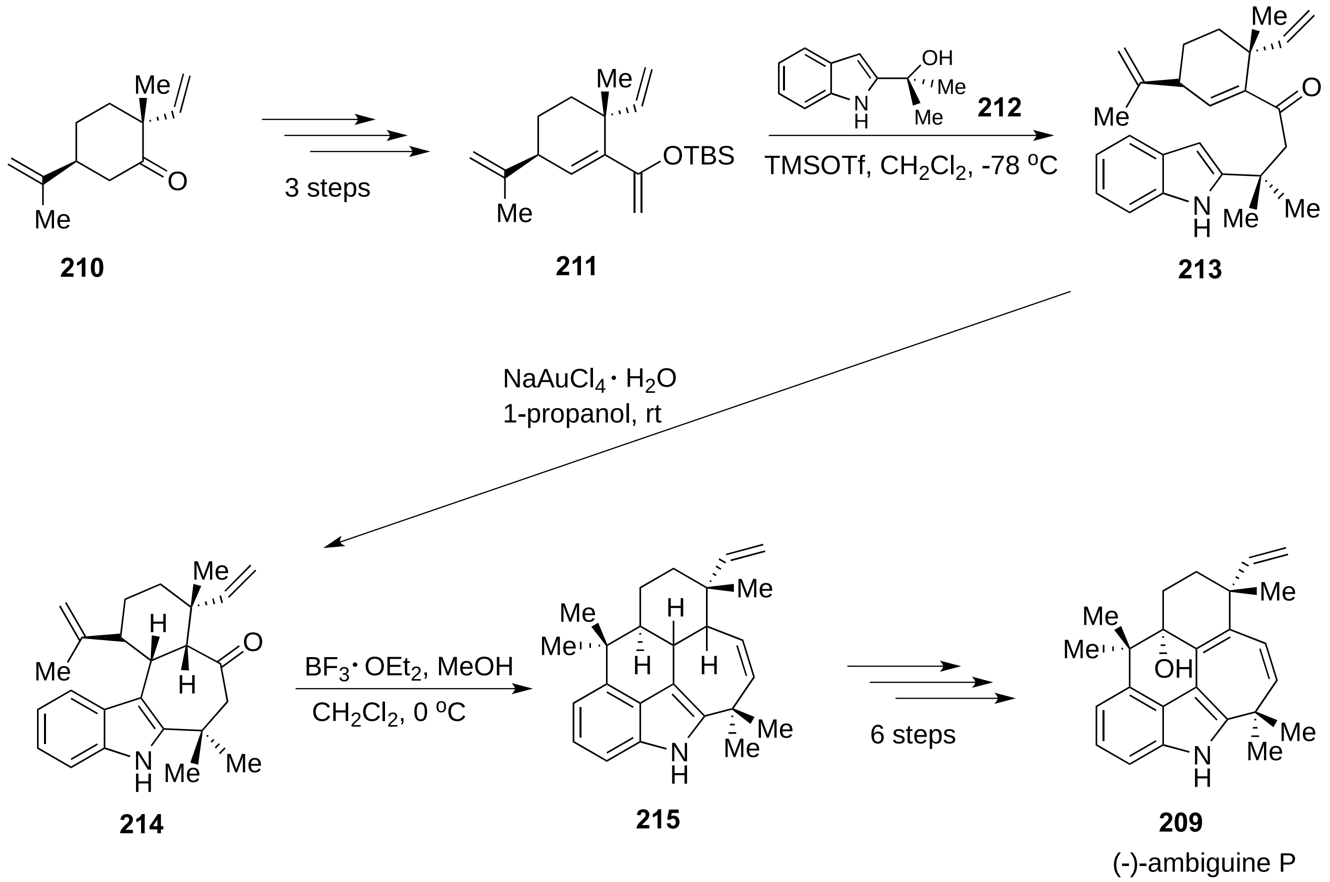
The ambiguine natural products, isolated from *Fischerella ambigae* - a blue-green algae - are a subset of larger family of indole secondary metabolites known as hapalindoles. Recently, two research groups reported total synthesis of (-)-ambiguine P.

Sapong *et al*. achieved synthesis of (-)-ambiguine P in 20 steps from C3-functionalized indole (**204**) (readily prepared from commercially available **193** and **203**), where rapid construction of the pentacyclic skeleton through sequential alkylations of indole using robust C-C bond forming reactions as well as novel application of an amide group to accomplish a stereoselective C12-functionalization (Scheme 69).[70] With ready access to pentacyclic isonitrile (**208**), the results would direct toward the late-stage derivatization to access other pentacyclic members of ambiguine family that retain the isonitrile group.



Scheme 69

Rawal and co-workers reported the concise total synthesis of (-)-ambiguine P (Scheme 70).[71] The construction of pentacyclic framework of the natural product was assembled rapidly via [4+3]cycloaddition reaction-inspired strategy, and the tertiary hydroxy group was introduced by an NBS-mediated bromination-nucleophilic substitution sequence.

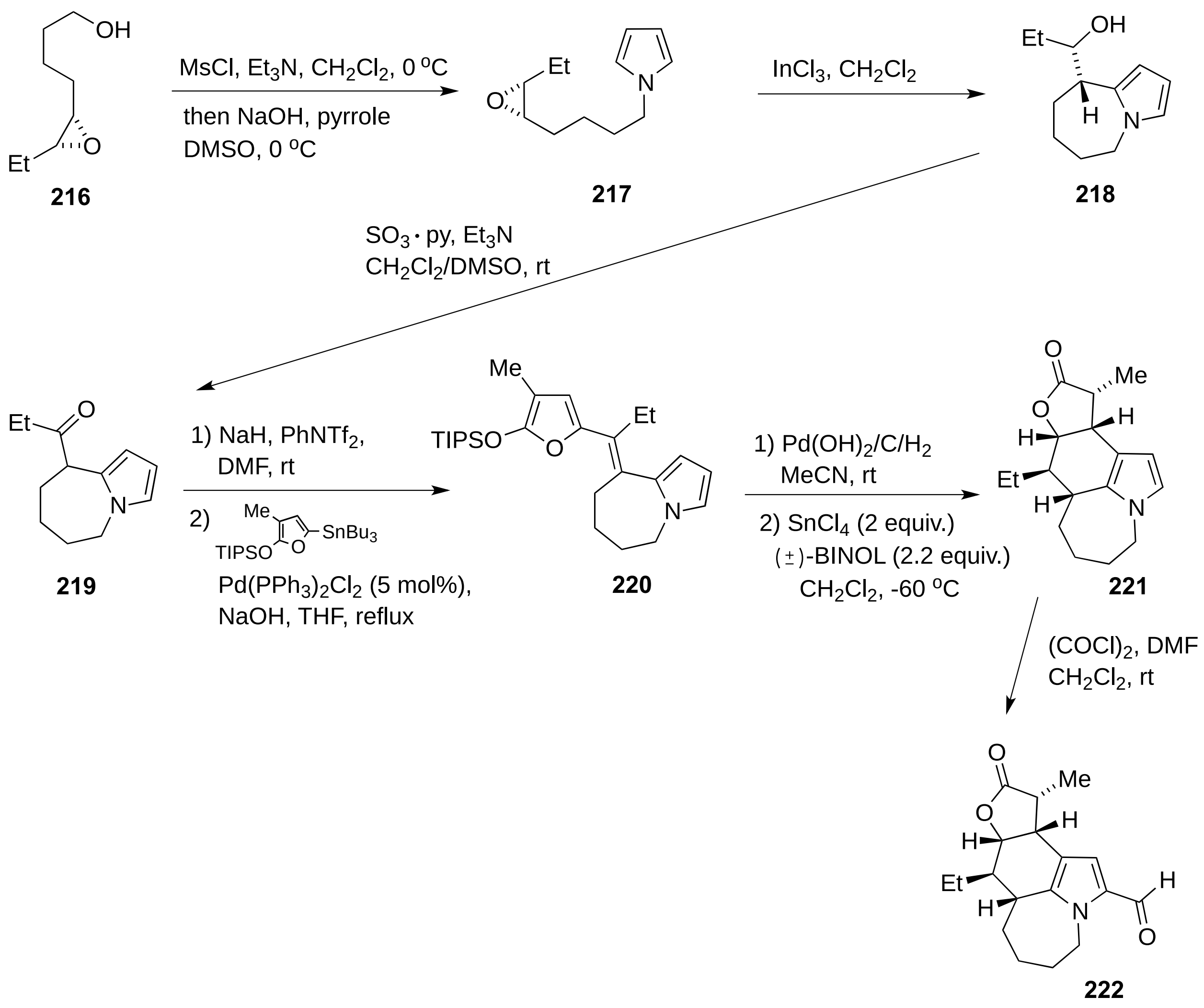


Scheme 70

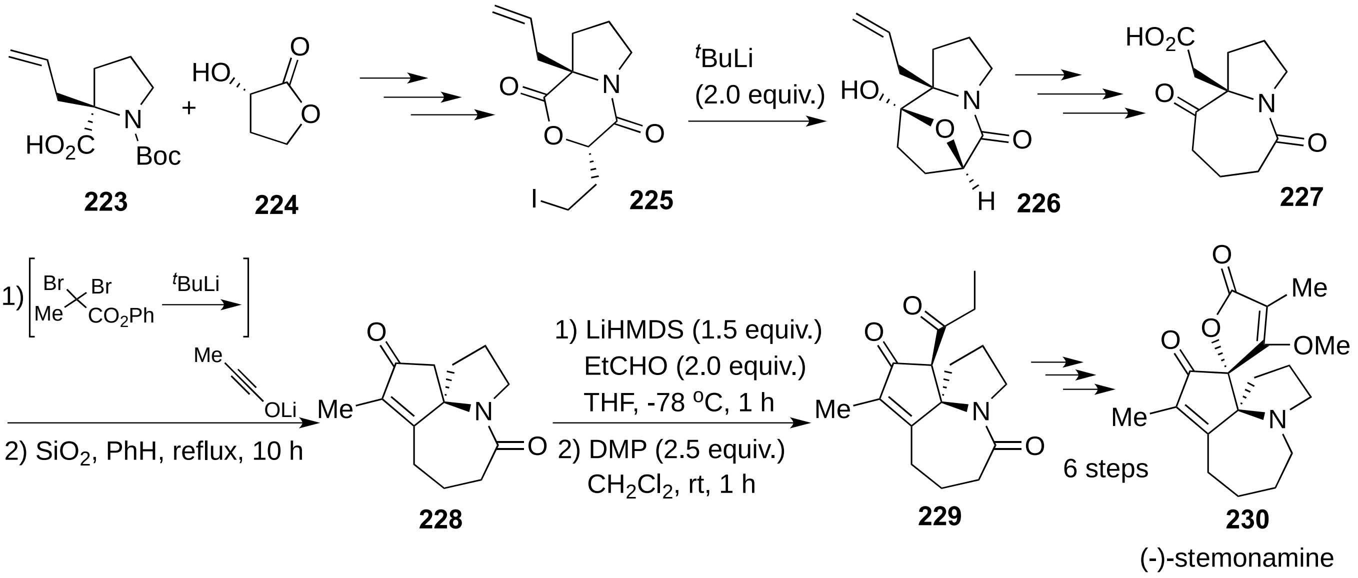
The *Stemona* alkaloids, being isolated from *Stenoma* plants of the *Stemonaceae* species, are a large class of natural products, possessing a wealth complex stereochemistry as well as potent bioactivity, and attract many interests. Recently, an interesting review was published by Shindo and co-worker.[72]

Booker-Milburn *et al*. reported the stereoselective formation of the tetracyclic *Stemona* alkaloid skeleton (**222**) through a Lewis acid-Brønsted acid cascade reaction in five steps from epoxide (**216**) (Scheme 71).[73] This tetracyclic product can be accessed as either C13 epimer, potentially serving as intermediates for the synthesis of a range of *Stemona* alkaloids.

Shindo *et al*. reported asymmetric total synthesis of (-)-stemonamine, in which the reaction proceeded through construction of the seven-membered ring by intramolecular acylation and successive tandem [2+2]cycloaddition-Dieckmann condensation reaction using an ynolate to form the fully substituted cyclopentenone moiety (Scheme 72).[74]

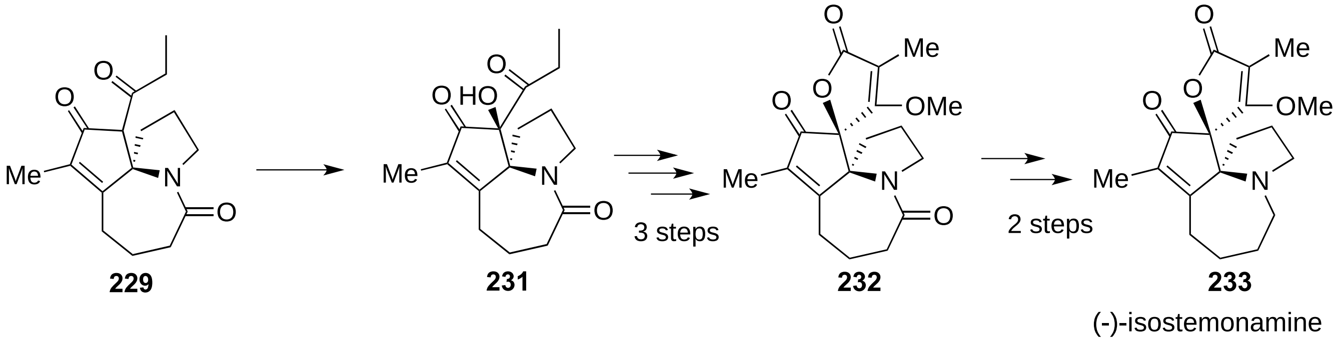


Scheme 71



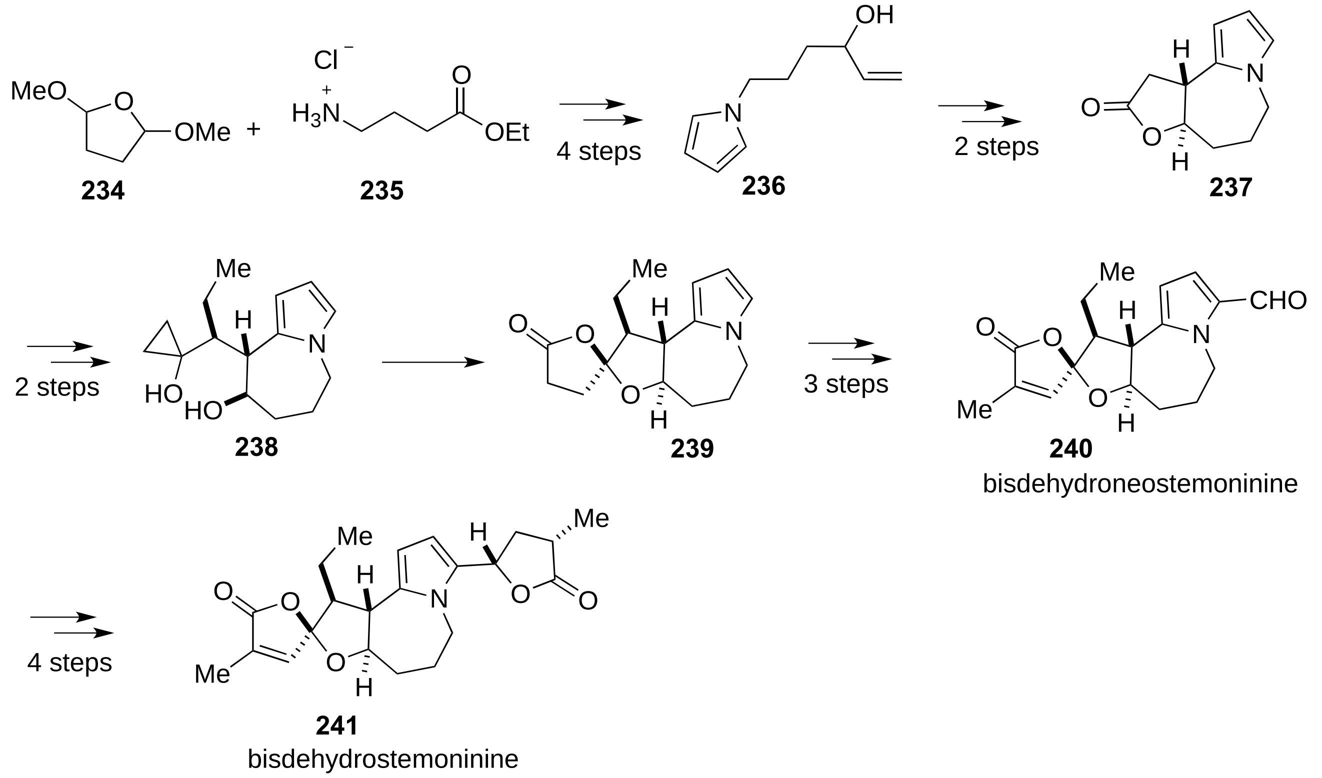
Scheme 72

Shindo *et al*. also reported asymmetric total synthesis of (-)-isotemonamine (**233**), from the diketone intermediate (**229**) (Scheme 73).[75]



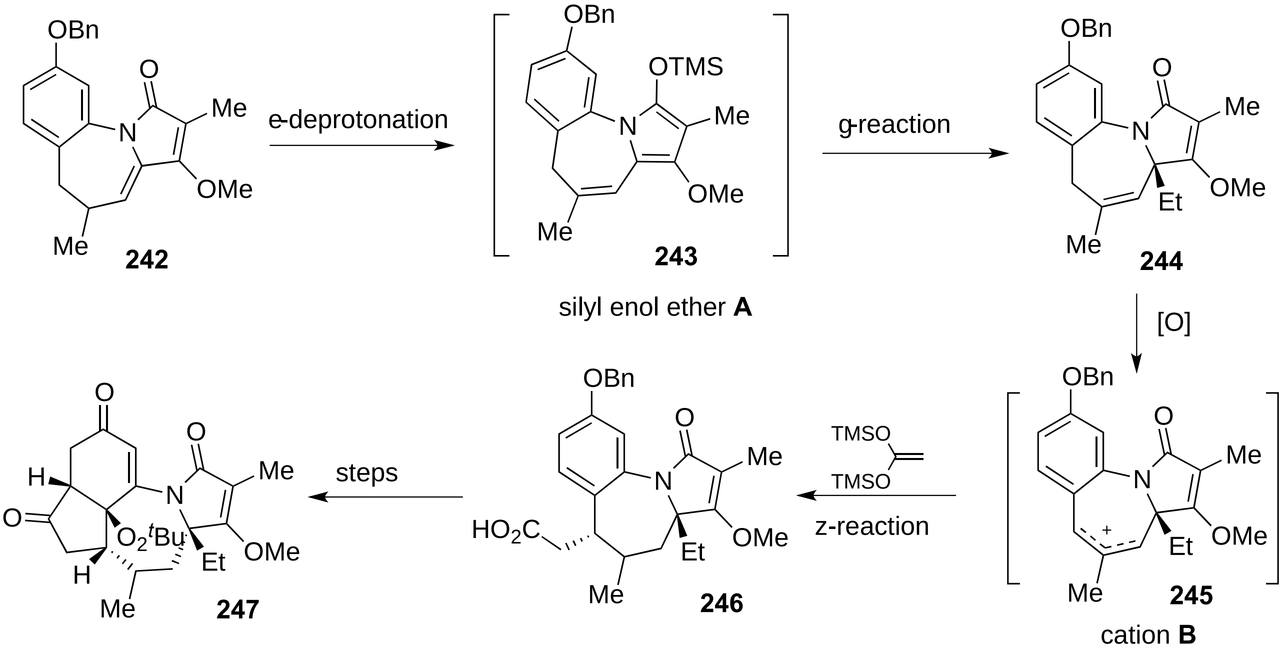
Scheme 73

Dai *et al*. completed the total syntheses of the *Stemona* alkaloids bisdehydroneostemoninine (**240**) and bisdehydrostemoninine (**241**) using a palladium-catalyzed carbonylactive spirolactonization as the key step to constructing the oxaspirolactone moiety (**239**) (Scheme 74).[76]



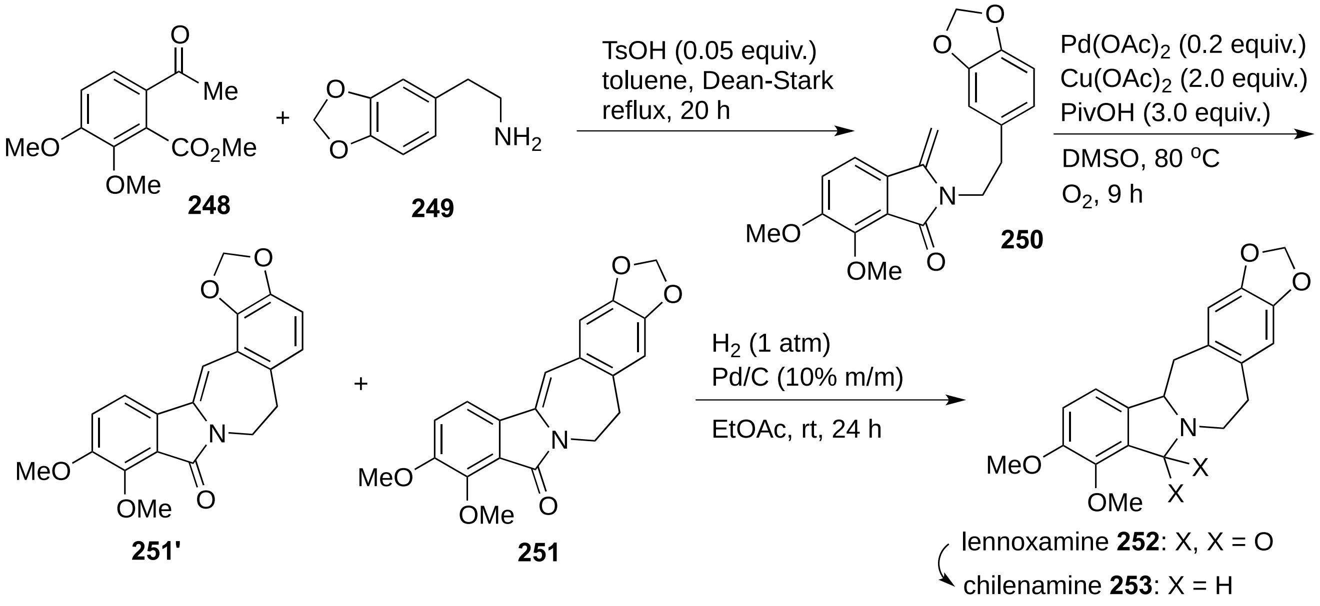
Scheme 74

Tetrapetalone A was isolated from *Streptomyces* sp. USF-4727. For approach to total synthesis of tetrapetalones, Pettus and co-worker investigated the synthesis of tetracyclic product (**247**). The reaction proceeded *via* a site-selective ethylenation of the silyl enol ether **A** (**243**), the oxidative formation of cation **B** (**245**), which included subsequent selective formation of either C-O or C-C bonds at the δ or ζ position on the seven-membered ring. The fourth ring was formed using a Stetter reaction (Scheme 75).[77]

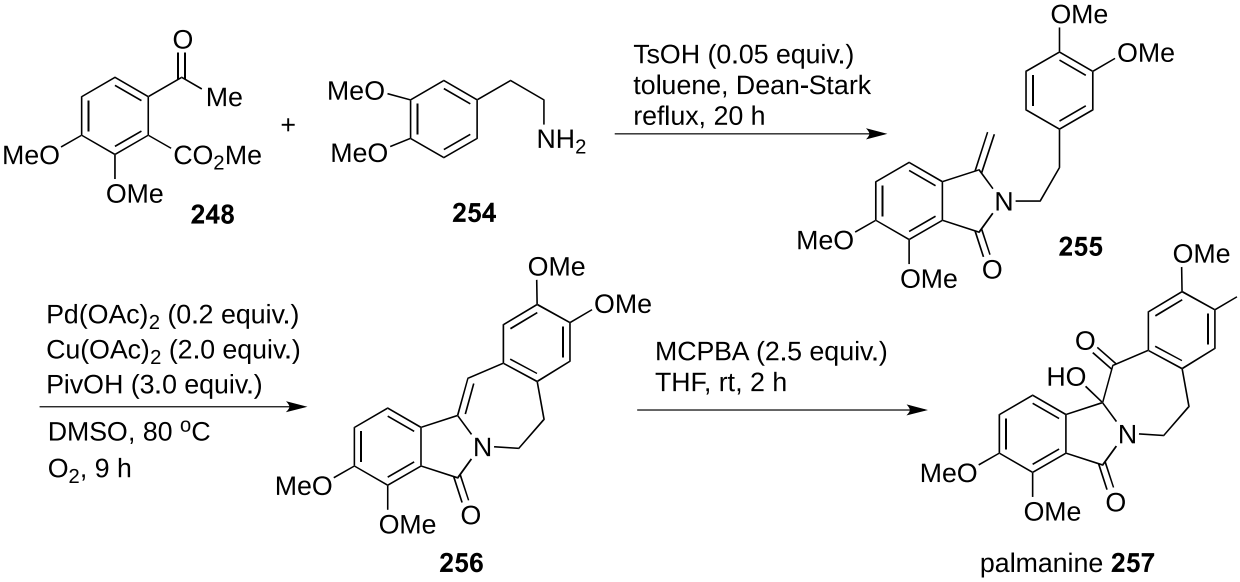


Scheme 75

Construction of benzo[4,5]azepino[2,1-*a*]isoindol-5(5*H*)-one derivative was accomplished by Pd(OAc)$_2$-catalyzed intramolecular dehydrogenative cross-coupling reaction between tertiary enamides, which were derived from the condensation of 2-arylethylamines and methyl *o*-acetylbenzoate. The synthetic method was applied in the total synthesis of aporhoeadane alkaloids palmanine (**257**), lennoxamine (**252**), and chilenamine (**253**) in only three steps (Scheme 76, 77).[78]

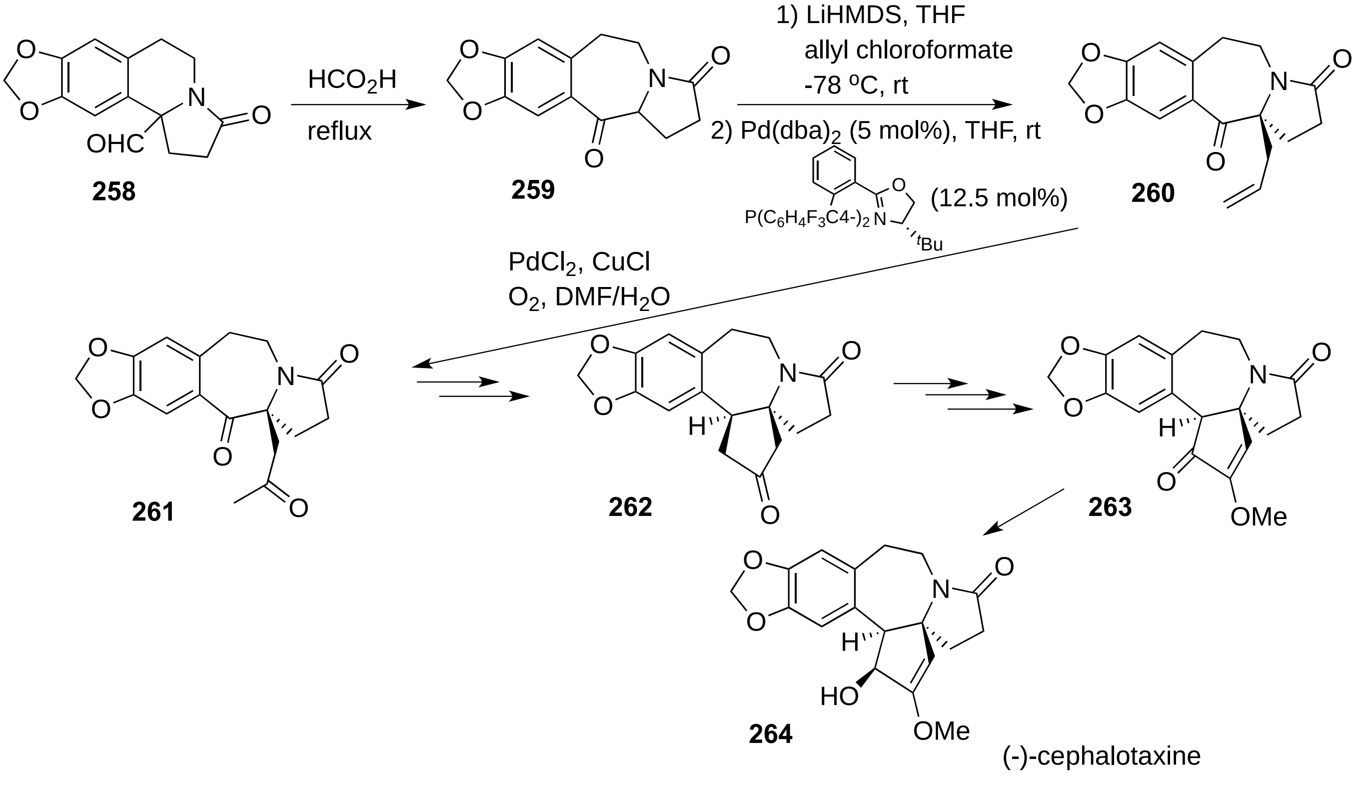


Scheme 76



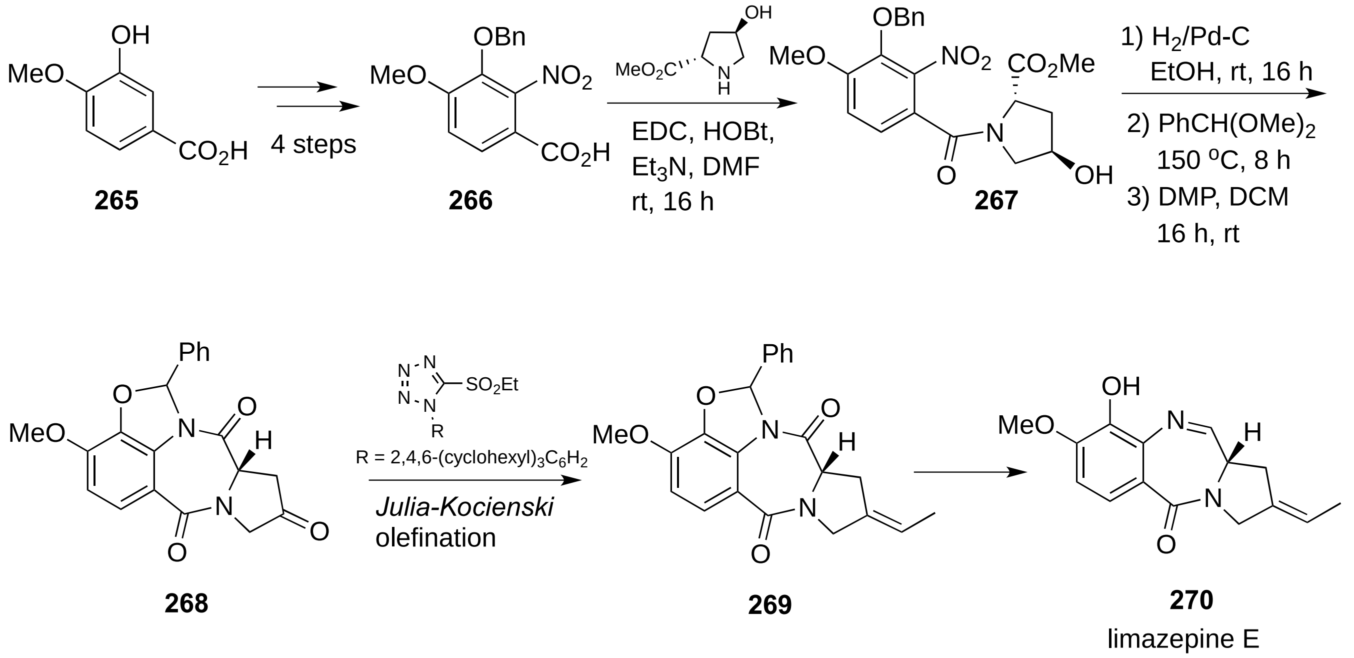
Scheme 77

Asymmetric synthesis of the pentacyclic alkaloid (-)-cephalotaxine from homopiperonylamine in 15 steps was accomplished *via* palladium-catalyzed enantioselective Tsuji allylation for construction of tetrasubstituted stereogenic center. The allyl enol carbonate precursor was prepared from Hanaoka's pyrrolobenzazepine intermediate, which was synthesized *via* novel formic acid-promoted ring-expansion reaction (Scheme 78).[79]



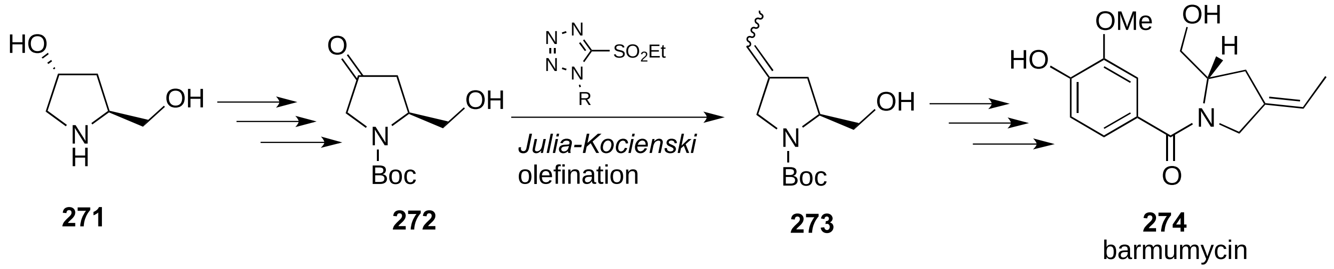
Scheme 78

Limazepine E (**270**) was isolated from a culture broth of *Micrococus* sp. strain ICBB 8177 and belong to the PBD class of natural products. Barmumycin (**274**) was isolated from the marine actinomycete *Streptomyces* sp. BOSC-022A. Total synthesis of limazepine E (**270**) was achieved as shown in the Scheme 79 by Smits and co-worker.[80] The synthesis started with conversion of isovanilic acid (**265**) into **266**. The compound (**266**) was coupled with *trans*-4-hydroxy-L-ploline to give **267**. Hydrogenation of **267**, followed by treatment with benzaldehyde dimethyl acetal achieved cyclization, and successive oxidation gave the ketone (**268**). Julia-Kocienski olefination of **268** gave **269**.



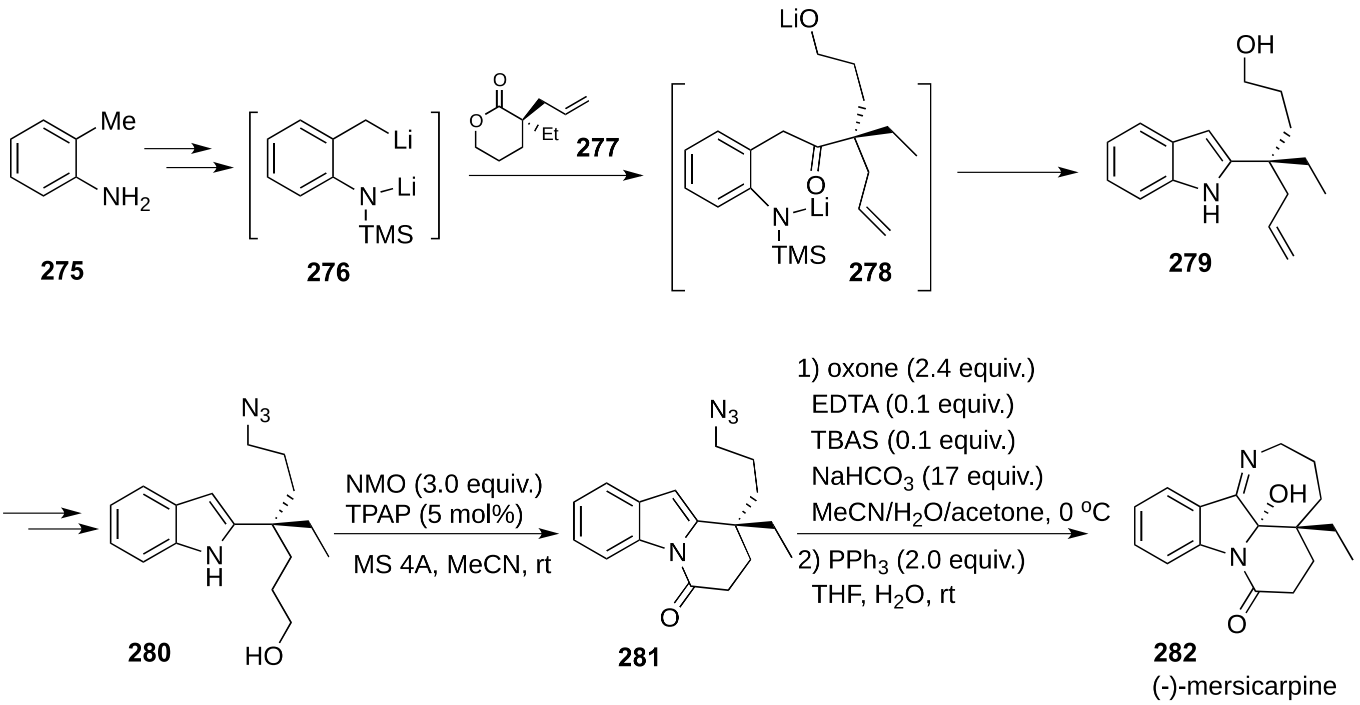
Scheme 79

Smits and co-worker also reported the formal total synthesis of barmumycin (**274**) was started with an oxidation of the known prolinol derivative (**272**) and successive reaction gave **273** using newly developed reagents (Scheme 80).[80] The obtained **273** can be further converted into barmumycin (**274**) by a known sequence.



Scheme 80

The leuconolam-leuconoxine-mersicarpine triads are structurally complex and biologically interesting Aspidosperma-derived monoterpene indol alkaloids. Wang and co-worker reported the total syntheses (-)-mersicarpine (**282**) and other this class compounds from a common 2-alkylated indole intermediate by a unified strategy. Synthetic scheme of (-)-mersicarpine (**282**) is shown in the Scheme 81.[81] The Smith-modified Madelung indole synthesis was used to couple simple *o*-toluidine (**275**) with chiral lactone (**277**), and successive cascade acylation/heteroatom Peterson olefination/isomerization achieved substituted indole (**279**).

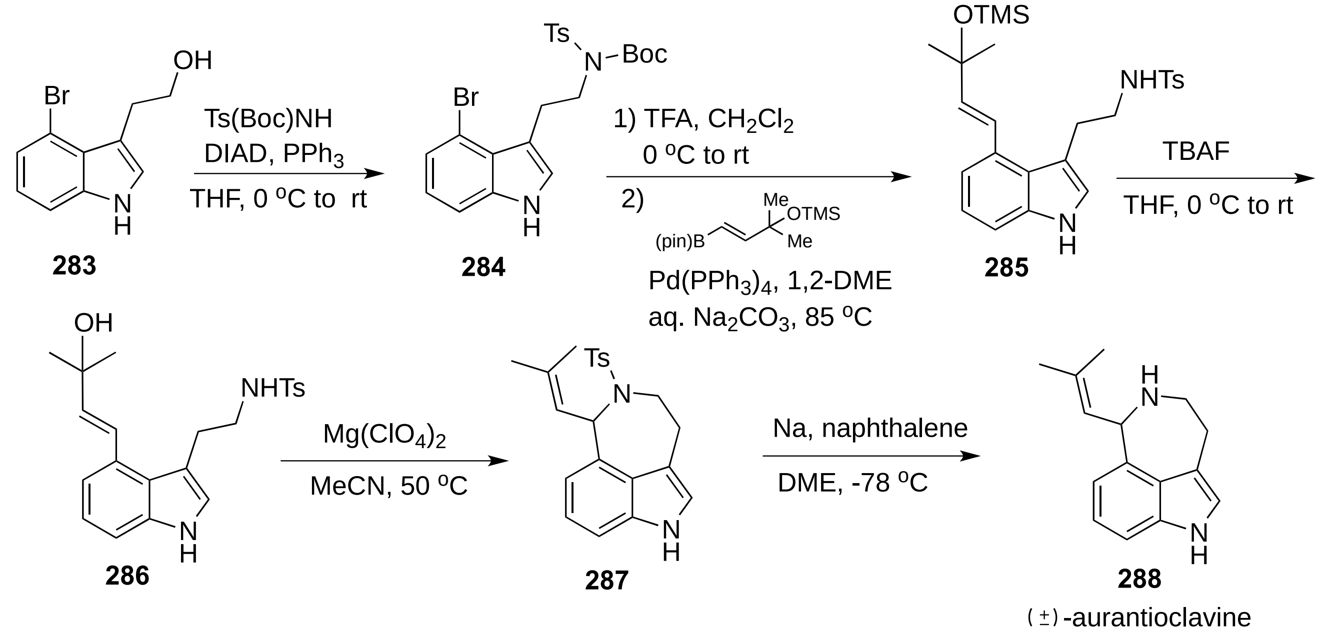


Scheme 81

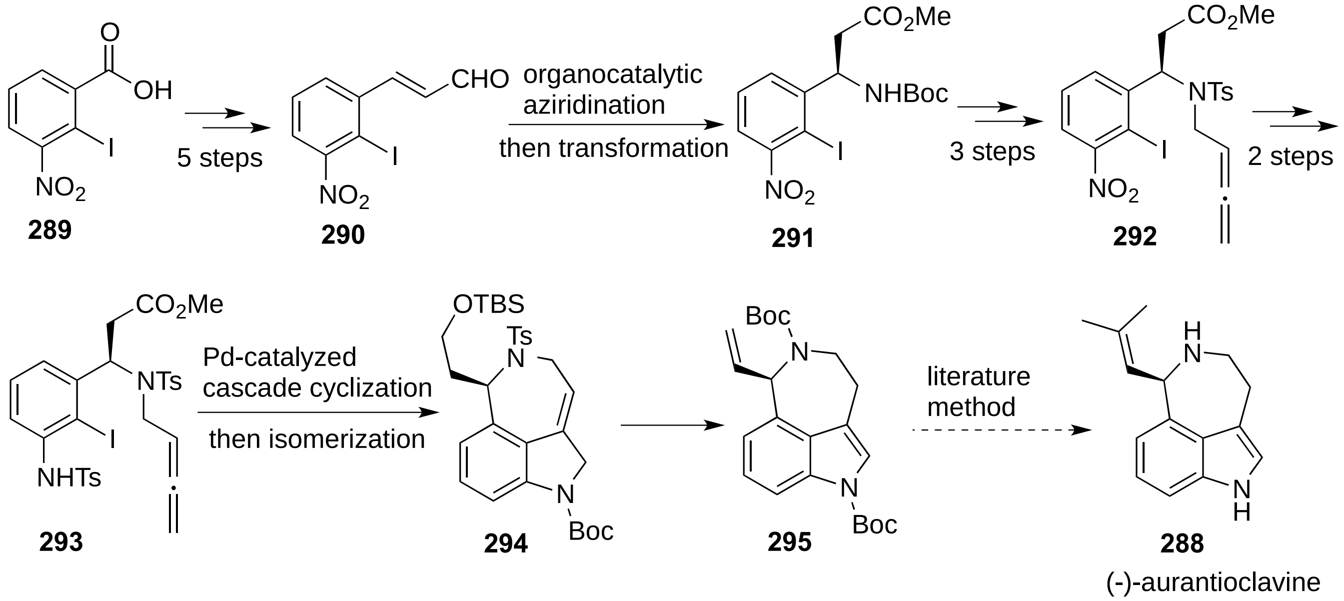
The ergot alkaloid (-)-aurantioclavine was isolated from *Penicillium aurantiovirens*, and many groups have focused on aurantioclavine as a synthetic target. Recently, two research groups reported synthesis of aurantioclavine.

Takemoto *et al*. reported a concise total synthesis of (±)-aurantioclavine (**288**) from substituted indole (**283**) (Scheme 82).[82]

Nemoto *et al*. reported enatioselective formal synthesis of (-)-aurantioclavine (**288**).[83] The core tricyclic skeleton was synthesized using Pd-catalyzed Heck insertion-allylic amination cascade as the key step. The stereocenter was constructed by enantioselective organocatalytic asymmetric aziridination reaction (Scheme 83).[83]



Scheme 82

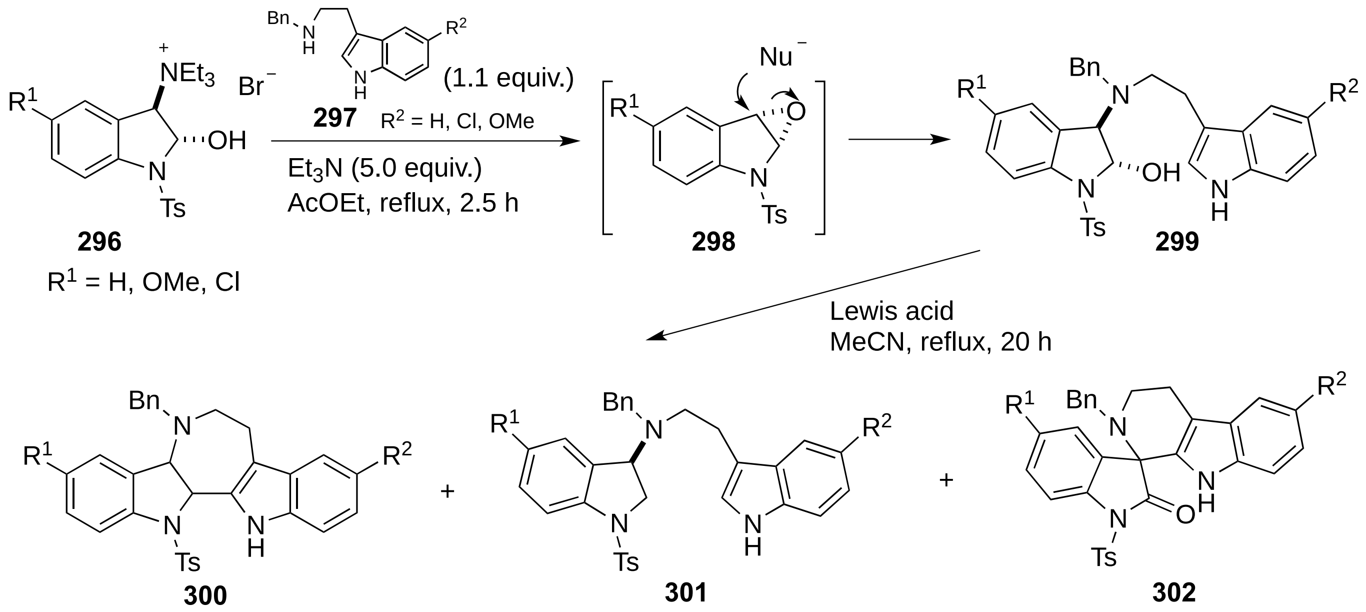


Scheme 83

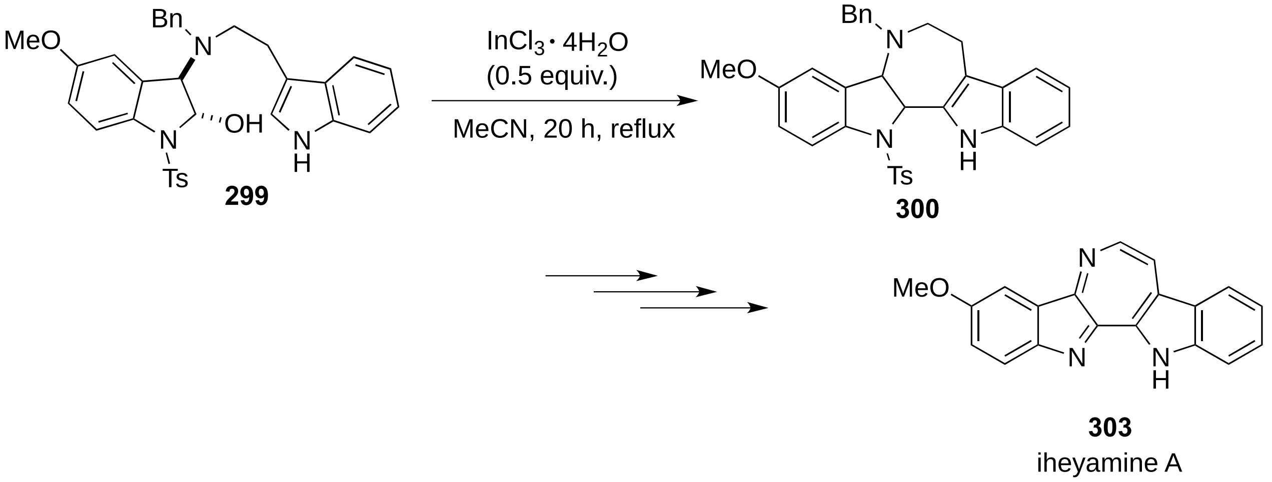
Azepinobisindole alkaloids iheyamine A (**303**) and B were isolated from a colonial ascidian *Polycitorella* sp. collected off the coast of Iheya island in Japan. These alkaloids have attracted considerable interest for their intriguing structural features and cytotoxicity against tumor cells.

Abe *et al*. reported a concise synthesis of iheyamine A (**303**).[84,85] Construction of iheyamine A (**303**) was achieved by a formal C3 electrophilic reaction of an indole-2,3-epoxide equivalent (**296**) with tryptamine (**297**) to form a 3-aminoindoline (**299**) (Scheme 84) and indium-mediated dehydrative Mannich-type reaction of hemiaminal (Scheme 85).[84] A key feature of the strategy is the use of stable hemiaminals for the construction of azepinobisindole skeleton.

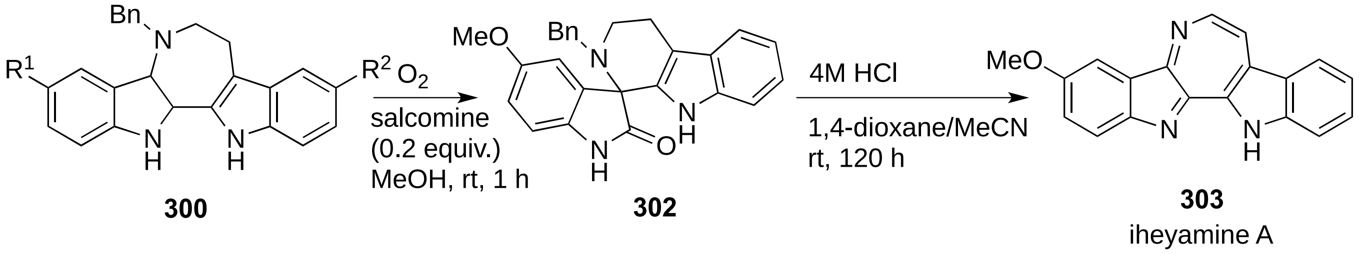
Abe *et al*. also reported the biomimetic synthesis of iheyamine A (**303**) from a spirocyclic oxindole (**302**) through the oxidative rearrangement in one-pot (Scheme 86).[85] Furthermore, they found unprecedented method for construction of 2,1'-spirocyclic oxindoles (**302**) from azepinobisindoles (**300**) through alternative oxidative rearrangement (Scheme 86).[85]



Scheme 84

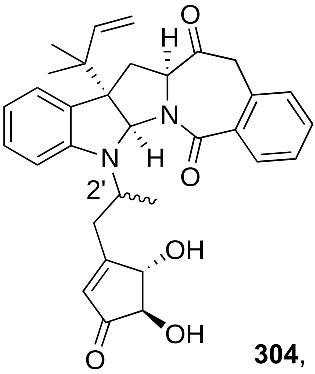


Scheme 85



Scheme 86

Hosoe *et al*. isolated four new cyclodipeptides asnovolenins A (**304**) and B (**305**) (Figure 1) as new products from the fungus *Aspergillus novofumigatus* CBS 117520. Compounds **304** and **305** are 2'-epimers each other.[86] None of the isolated compounds exhibited antifungal activity.[86]



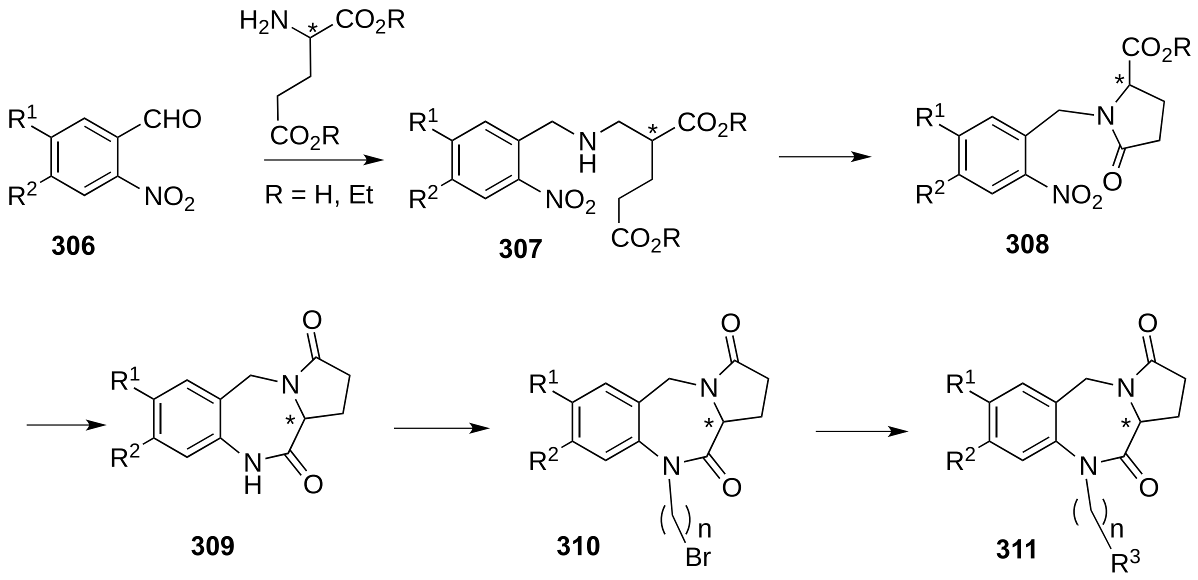
304, **305**

Figure 1

IV. BIOLOGICAL ACTIVITIES AND PHARMACOROGY

Azaazulenes and polycyclic compounds containing azaazulene and/or azepine skeleton, such as pyrrolobenzazepines, azepinoindole-derivatives, and so on, were directed attention from their biological activities and potentialities of drug use, especially antitumor antibiotics. Pyrrolobenzodiazepines (PBDs) have been investigated as potential anticancer agents.

Compounds of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD)-3,11-diones were discovered as potent neuroprotective agents against Cd-induced toxicity in SH-SY5Y cells for the first time. Cheng *et al*. synthesized twenty-six PBD-3,11-dione (Scheme 87) and evaluated for their neuroprotective activity against Cd-induced toxicity by CCK-8 assay. Among the compounds, compound (**311)** (R^1 = OBn, R^2 = OMe, R^3 = 4-(2-pyridyl)piperazinyl, n = 4) exhibited the best activity (cell viability = 68.6%, 25 μM).[87] An initial SARs (structure activity relationships) revealed that various subsequents were tolerated on C7 and alkyl heterocycles group at N10-position of the PBD scaffold could improve the potency.

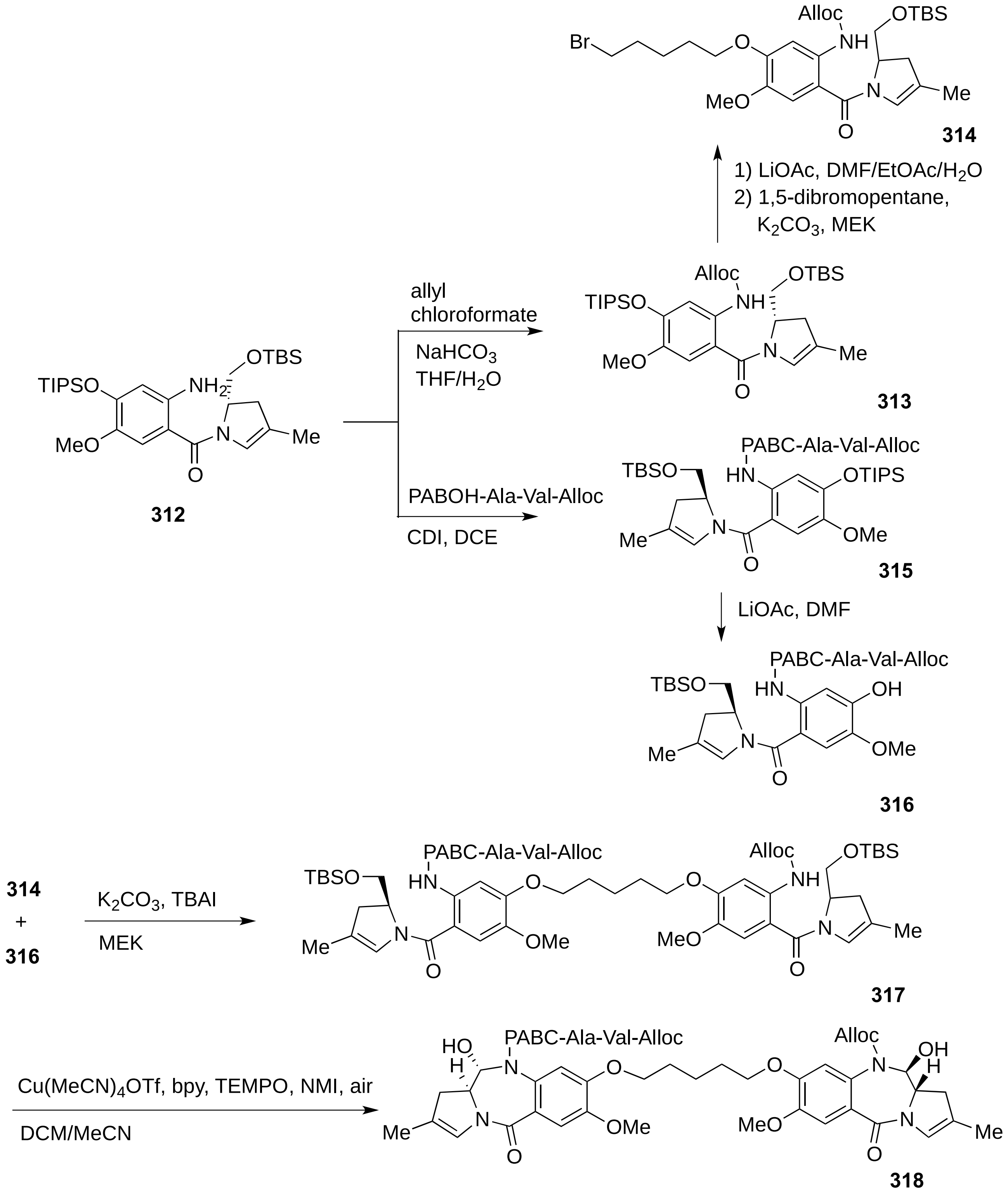


Scheme 87

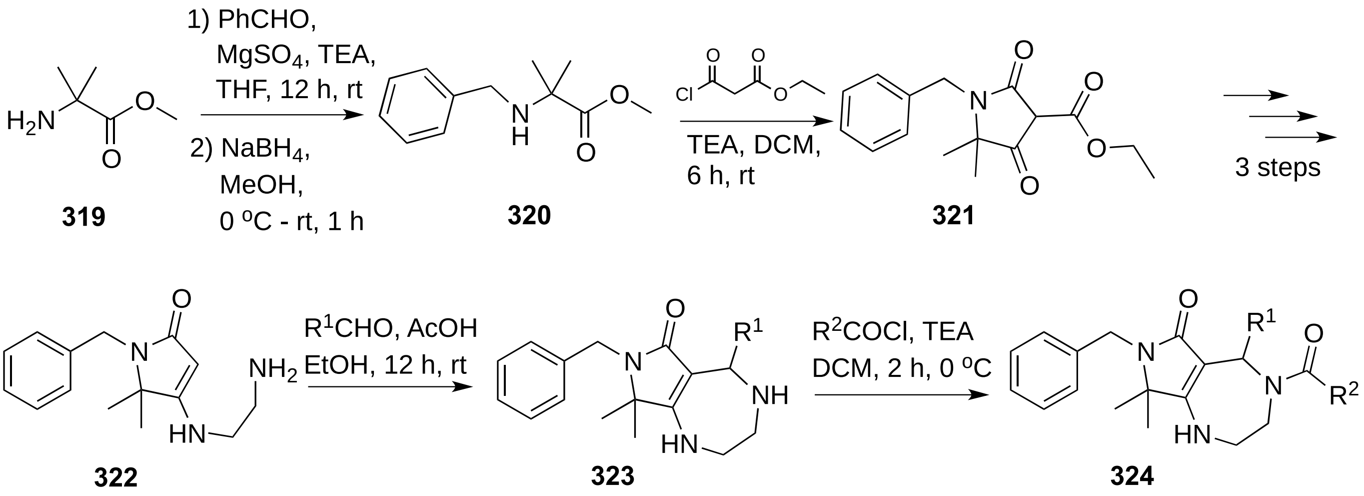
Parker *et al.* presented a new approach to route design for the synthesis of cytotoxic drugs (payloads) which focused on the reduction in the number of synthetic steps requiring high-containment facilities. They showed an improved synthesis of the ADC (antibody-drug conjugates) linker-payload tesirine (Scheme 88).[88]

Schlitz *et al.* reported the synthesis of a library of fused heterobicyclic molecules based on the pyrrolo[3,4-*b*][1,4]diazepine scaffolds (**324**) (Scheme 89).[89] Key chemical transformations included a Mannich-type condensation and chemoselective *N*-acylation reactions. Screening showed anti-cancer activity of several library compounds.

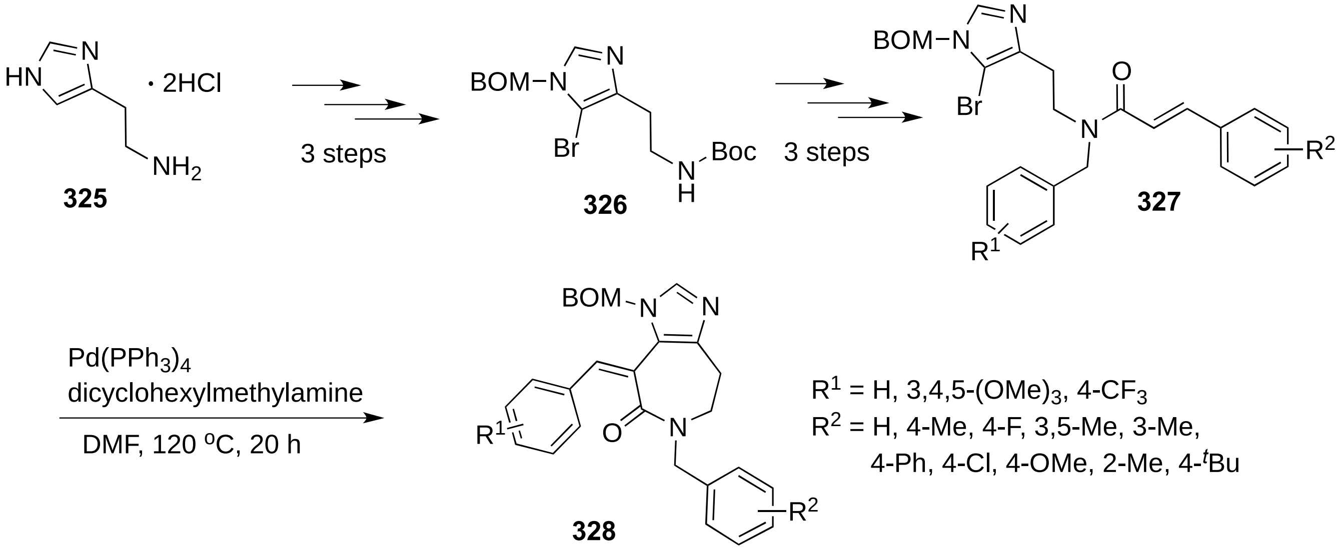
Liu *et al.* derived a series of ceratamine A simplified possessing imidazo[4,5-*d*]azepine core (**328**), being designed and synthesized from histamine dihydrochloride (**325**) in 7 steps (Scheme 90).[90] The synthesized compounds exhibited comparable cytotoxicity to ceratamine A. Compound (**328** : R^1 = 3,4,5-OMe, R^2 = H) showed better cytotoxicity than ceratamine A.[90]


314
1) LiOAc, DMF/EtOAc/H2O
2) 1,5-dibromopentane, K2CO3, MEK
allyl chloroformate
NaHCO3
THF/H2O
313
312
PABOH-Ala-Val-Alloc
CDI, DCE
315
LiOAc, DMF
316
314 + 316
K2CO3, TBAI
MEK
317
Cu(MeCN)4OTf, bpy, TEMPO, NMI, air
DCM/MeCN
318

Scheme 88



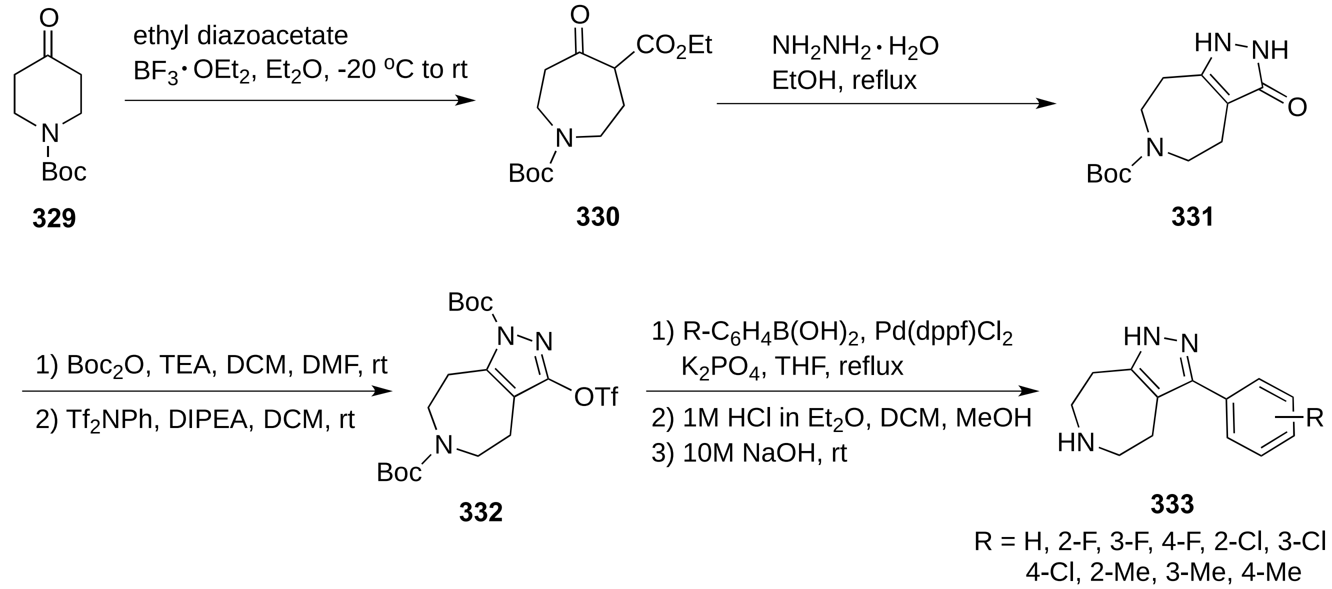
Scheme 89



R^1 = H, 3,4,5-(OMe)$_3$, 4-CF$_3$
R^2 = H, 4-Me, 4-F, 3,5-Me, 3-Me, 4-Ph, 4-Cl, 4-OMe, 2-Me, 4-^{t}Bu

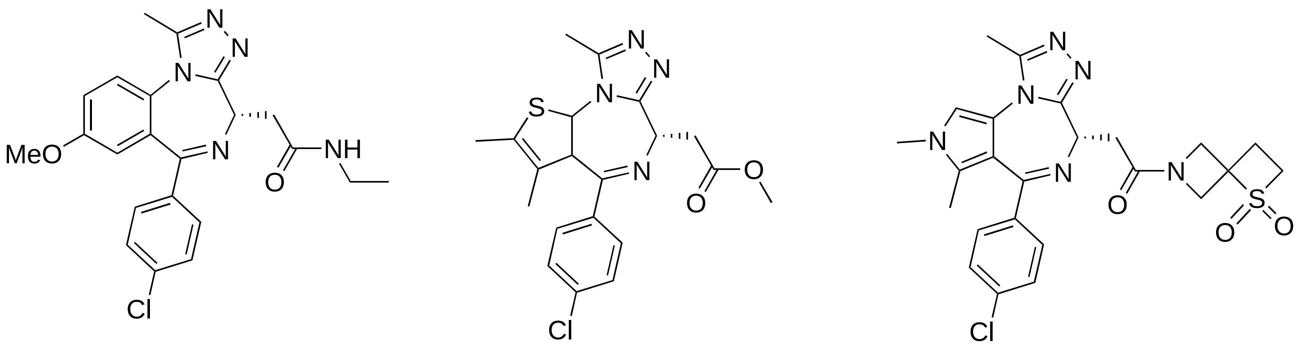
Scheme 90

Choo and co-workers designed and synthesized a series of arylpyrazolo[3,4-*d*]azepines (**333**) and arylisoxazolo[3,4-*d*]azepines (Scheme 91), and proceeded biological evaluations such as binding affinity, selectivity profile, and functions in G protein/β-arrestin signaling pathway.[91] SAR studies of **333** revealed that compounds having a *para*-substituent in phenyl group more strongly bind to 5-HT7R.



Scheme 91

The 1,4-benzodiazepine scaffold has attracted attention in the field of epigenetics, with the discovery of a class of potent small molecule inhibitors of the interaction between Bromo and Extra-Terminal (BET) bromodomain proteins and their acetylated histone substrates. Rapid success has been achieved with the BET family of bromodomains, and a number of potent and selective probes has been reported. These compounds have enabled linking of the BET bromodomains with diseases, including cancer and inflammation, suggesting that bromodomains are druggable targets. Bromodomein-containing protein 4 (Brd4) plays an important role in mediating the expression of genes involved in cancers and non-cancer diseases such as inflammatory diseases and acute heart failure. Numerous Brd4 inhibitors have been studied in recent years and some of them are currently in various phases of clinical trials. Recently, a review was reported by Liu and co-workers.[92] The optimized lead compound I-BET762 (**334**) is currently being evaluated in Phase I/II clinical trial for treatment of human cancer (Figure 2). Thienodiazepine derivatives (**335**) showed impressive Brd4(1) inhibitory activity with an IC_{50} value of 34 nM, and pyrrolodiazepine derivatives (**336**) were potent against Brd4(1) (IC_{50} = 20 nM) (Figure 2).



334 I-BET762 (GSK525762A)

Brd4 pIC_{50}: 6.2

335

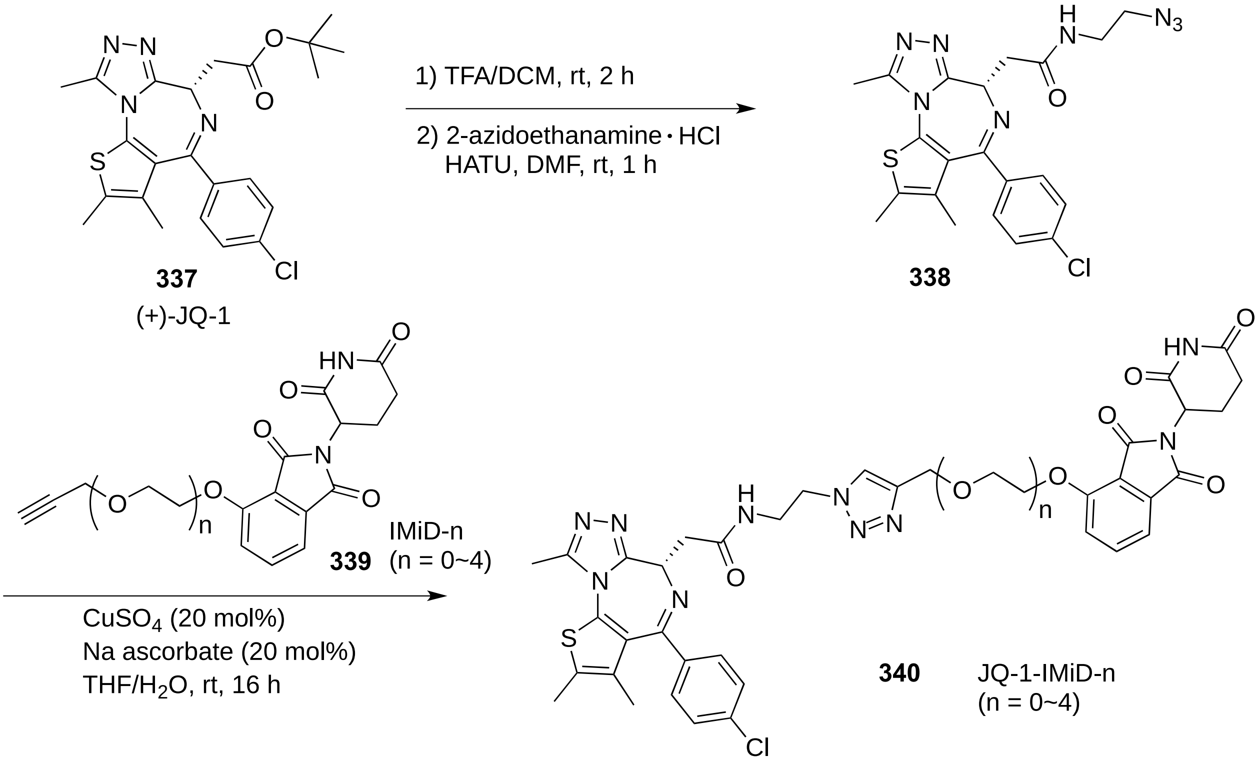
Brd4(1) IC_{50}: 34 nM

336

Brd4(1) IC_{50}: 20 nM

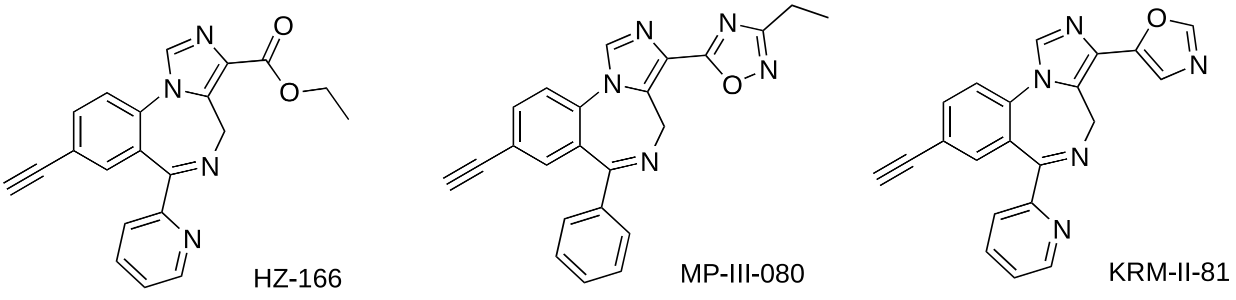
Figure 2

Wurz and co-workers reported the use of a "click chemistry" platform to prepare a 10-membered library of PROTACs (proteolysis-targeting chimmeras) using both cereblon and von Hippel-Lindau (VHL) ligase ligands (Scheme 92) and evaluated these molecules in their ability to form ternary complexes between the ligase/PROTAC/Brd4 protein as well as their activity in the targeted degradation of Brd4 protein in two lung carcinoma cell lines.[93]



Scheme 92

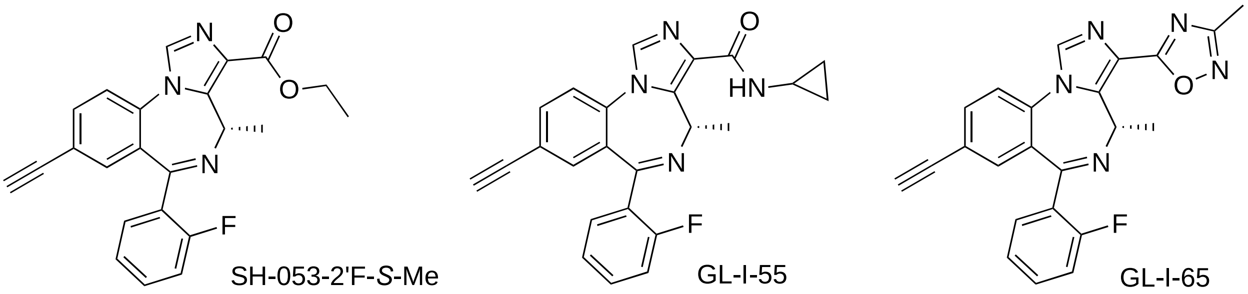
The gamma-amino butyric acid A ($GABA_A$) receptor is a heteropentameric chloride ion channel in the central nervous system (CNS). The $GABA_A$ receptors ($GABA_AR$) are responsible for a myriad of brain functions. Cook *et al*. reported improved synthesis of anxiolytic, anticonvulsant, and antinociceptive compounds: HZ-166 (**341**), and its bioisoesters, 1,2,4-oxadiazole MP-III-080 (**342**), and 1,3-oxazole KRM-II-81 (**343**) in high yields and with more facile purification methods in multigram quantities (Figure 3).[94]



341 **342** **343**

Figure 3

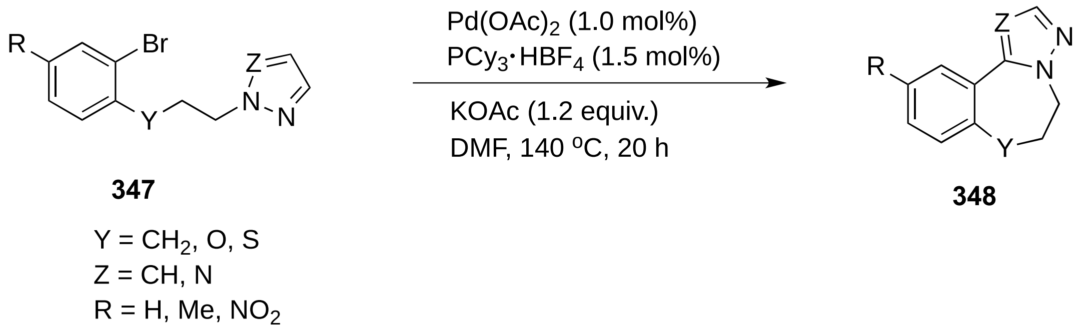
Cook and co-workers reported the synthesis of a series of novel imidazobenzodiazepine analogs of the lead chiral ligand SH-053-2’F-*S*-Me (**344**), an α2/α3/α5(Bz)GABA$_A$-ergic receptor subtype selective ligand, which reverses PCP-induced prepulse inhibition (PPI) of acoustic startle. The synthesized new ligands were designed by modifying the labile ester functionality in **344** to improve the metabolic stability, cytotoxicity, and activity as compared **344**. Based on the data, the most promising ligands are the *N*-cyclopropylamide GL-I-55 (**345**) and methyl bioisostere GL-I-65 (**346**) (Figure 4).[95]



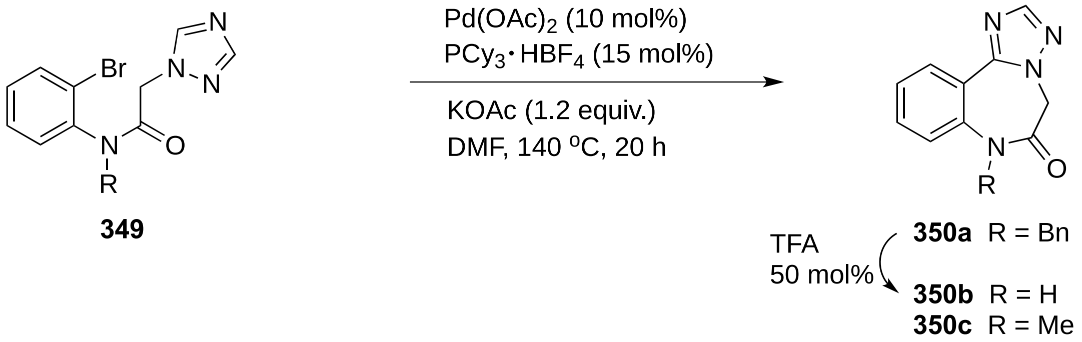
344 **345** **346**

Figure 4

Zanoni and co-workers reported on an unprecedented palladium-catalyzed C-H activation strategy to provide step-economical access to heterocyclic fused 2-benzazepines (Scheme 93, 94).[96] The obtained compounds were identified as new low molecular weight inhibitors heat shock protein 90 (Hsp) low molecular weight inhibitors. Triazolobenzodiazepinone (**350b**) exhibited an affinity that was even higher than the one of NVP-AUY922.[96]



Scheme 93



Scheme 94

Ballet *et al*. reported the synthesis of non-cationic and amphipathic indoloazepinone-constrained (Aia) oligomers (**351**) (Figure 5) as new vectors for intracellular delivery.[97] In MDA-MB-231 human breast cancer cell lines, oligomers were non-toxic and higher *in vitro* cell internalization efficiency. The Aia (aminoindoloazepinone)-based oligomers could represent a new family of cell-penetrating peptides and blood-brain barrier (BBB) shuttles.[97]

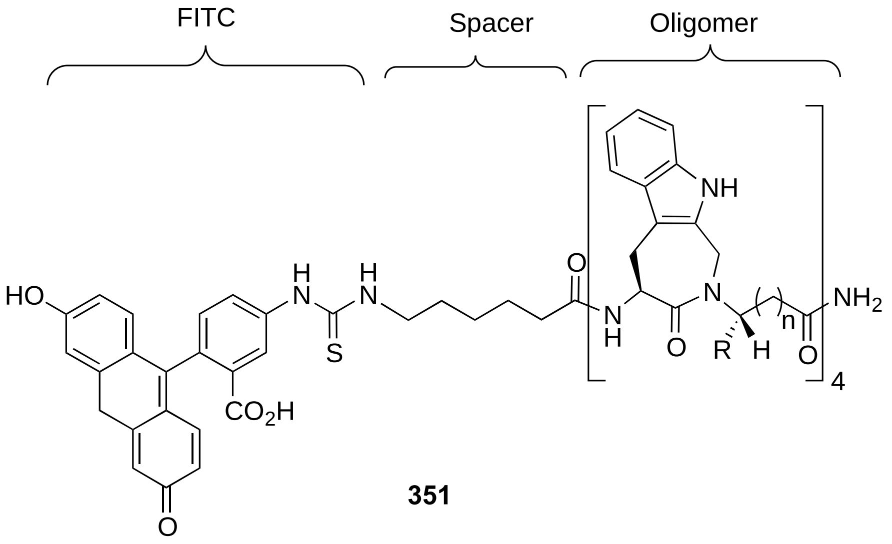
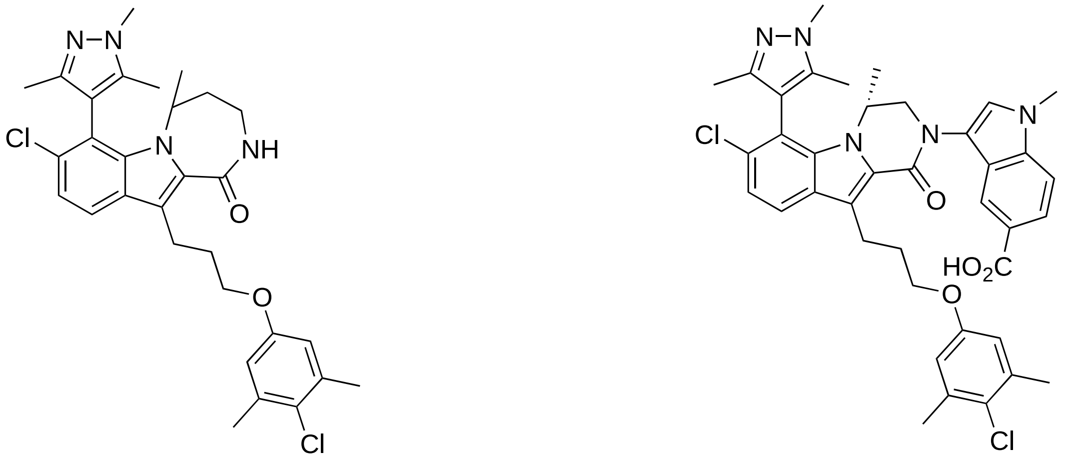


Figure 5

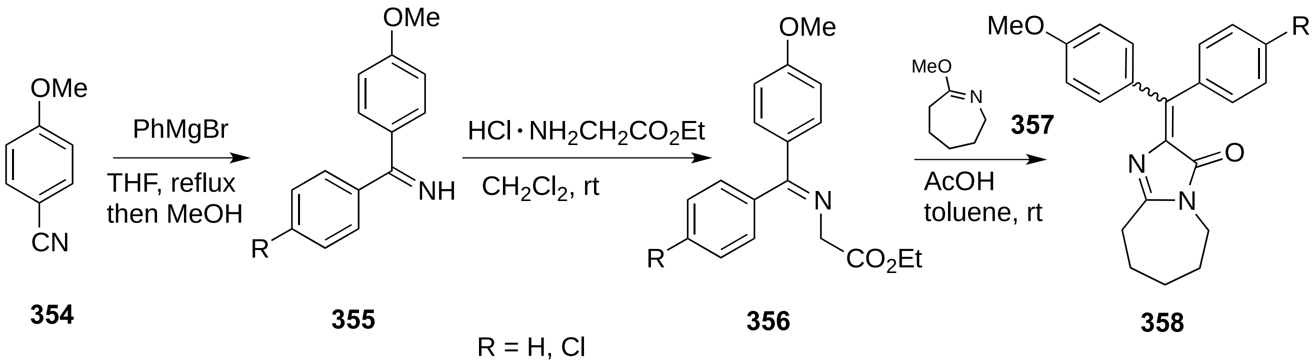
Myeloid cell leukemia 1 (Mcl-1) inhibitors are potentially useful in a wide range of cancers, both as a single agent and in combination therapies. Diazepinone is known as Mcl-1 inhibitor. To improve upon the potency and pharmacokinetic profile of tricyclic diazepinone series, Fesik *et al.* optimized the three-carbon linker portion of the diazepinone. It is found that methylation at the 5-position (**352**) led to a binding affinity in the NH lactam core, and the increased steric hindrance at this diazepinone position resulted in a low chemical yield. To improve the binding affinity, replaced the diazepinone ring to six-membered piperazinone tricyclic core. They discovered a novel compound (**353**) that robustly and specially inhibits Mcl-1 cell culture and animal xenograft models.[98]



352 **353**

Figure 6

Miyashita *et al.* developed a new analog of the GFP chromophore: geo-DAIN (4-(diarylmethylene)imidazolinone) (**358**), which has an *E*/*Z*-photoisomerizable geometrical diarylmethylene moiety. They synthesized geo-DAINs (**358**) by condensation with imino-glycinates (**356**) and methyl imidate (**357**) (Scheme 95).[99] The emission from geo-DAIN to be different from that of benzylidene-type analogs; in the powder state, the *E*- and *Z*-isomers of geo-DAIN emitted different fluorescence colors.[99]



Scheme 95

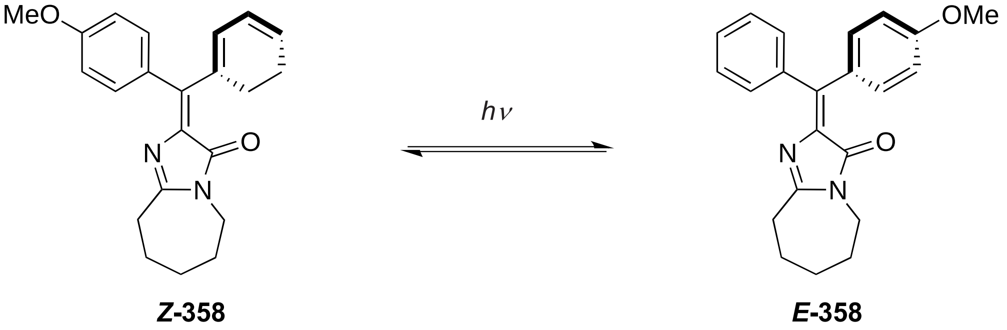


Figure 7

CONCLUSION

In the recent advances of the investigations about azaazulenes, pyrrolobenzazepines (PBDs), azepinoindole-derivatives, and so on, some new synthetic methods were evolved, and a lot of novel compounds having various patterns of the azaazulene, pyrrolobenzazepine, and their analogous skeletons were provided. In addition, their biological activities and pharmaceutical pursuits are prominent. I wish that the investigations of these region develop and go far towards the evolvement of medicinal researches.

REFERENCES AND NOTES

1. For reviews see: a) N. Abe, *Heterocycles*, 2018, **97**, 43; b) N. Abe and T. Gunji, *Heterocycles*, 2010, **82**, 201; c) N. Abe, 'Recent Research Developments in Organic and Bioorganic Chemistry', 2001, **4**, 14, Transworld Research Network; d) N. Abe, 'Trends in Heterocyclic Chemistry', 2001, **7**, 25, Research Trends; e) T. Nishiwaki and N. Abe, *Heterocycles*, 1981, **15**, 547; f) M. Kimura, *J. Synth. Org. Chem. Jpn.*, 1981, **39**, 690.
2. a) T. Nemoto, *Chem. Rec.*, 2019, **19**, 320; b) T. Nemoto, S. Harada, and M. Nakajima, *Asian J. Org. Chem.*, 2018, **7**, 1730.
3. D. V. Vorobyeva and S. N. Osipov, *Synthesis*, 2018, **50**, 227.
4. A. C. Lindsay, S. H. Kim, and J. Sperry, *Nat. Prod. Rep.*, 2018, **35**, 1347.
5. E. Haak, *Synlett*, 2019, **30**, 245.
6. K. Gao, Y.-G. Zhang, Z. Wang, and H. Ding, *Chem. Commun.*, 2019, **55**, 1859.
7. W. J. Olivier, J. A. Smith, and A. C. Bissember, *Org. Biomol. Chem.*, 2018, **16**, 1216.
8. H. Pellissier, *Adv. Synth. Catal.*, 2018, **360**, 1551.
9. B. Kulia, M. Kaur, P. Singh, and G. Bhargava, *Eur. J. Org. Chem.*, 2018, 853.
10. J. Biemolt and E. Ruijter, *Adv. Synth. Catal.*, 2018, **360**, 3821.
11. H. Zhou, B. Wu, J.-A. Ma, and Y. Dang, *Org. Biomol. Chem.*, 2018, **16**, 4295.
12. T. U. Thikekar and C.-M. Sun, *Adv. Synth. Catal.*, 2017, **359**, 3388.

13. T. Takeda, S. Harada, A. Okabe, and A. Nishida, *J. Org. Chem.*, 2018, **83**, 11541.
14. N. Martinez-Yanez, J. Suarez, A. Cajaraville, J. A. Varela, and C. Saa, *Org. Lett.*, 2019, **21**, 1779.
15. H. K. Saini, N. K. Nandwana, S. Dhiman, K. Rangan, and A. Kumar, *Eur. J. Org. Chem.*, 2017, 7277.
16. C. Wu and N. Yoshikai, *Angew. Chem. Int. Ed.*, 2018, **57**, 6558.
17. Z.-Y. Tian, Q. Cui, C.-H. Liu, and Z.-X. Yu, *Angew. Chem. Int. Ed.*, 2018, **57**, 15544.
18. Q. Li, B. Li, and B. Wang, *Chem. Commun.*, 2018, **54**, 9147.
19. Y. Xiang, Z. Li, L.-N. Wang, and Z.-X. Yu, *J. Org. Chem.*, 2018, **83**, 7633.
20. X.-F. Kong, F. Zhan, G.-X. He, C.-X. Pan, C.-X. Gu, K. Lu, D.-L. Mo, and G.-F. Su, *J. Org. Chem.*, 2018, **83**, 2006.
21. A. S. Jadhav, Y. A. Pankhade, and R. V. Anand, *J. Org. Chem.*, 2018, **83**, 8615.
22. Y. Pang, G. Liang, F. Xie, H. Hu, C. Du, X. Zhang, M. Cheng, B. Lin, and Y. Liu, *Org. Biomol. Chem.*, 2019, **17**, 2247.
23. K. Alam, J. G. Kim, D. Y. Kang, and J. K. Park, *Adv. Synth. Catal.*, 2019, **361**, 1683.
24. F. Sanchez-Cantalejo, J. D. Priest, and P. W. Davies, *Chem. Eur. J.*, 2018, **24**, 17215.
25. D. Baskin, Y. Cetinkaya, and M. Balci, *Tetrahedron*, 2018, **74**, 4062.
26. Q. Zeng, K. Dong, J. Huang, L. Qie, and X. Xu, *Org. Biomol. Chem.*, 2019, **17**, 2326.
27. X. Wu, L. Zhou, R. Maiti, C. Mou, L. Pan, and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2019, **58**, 477.
28. S.-Y. Zhu, Y. Zhang, X.-F. Chen, J. Huang, S.-H. Shi, and, X.-P. Hui, *Chem. Commun.*, 2019, **55**, 4363.
29. Y. Li, C.-Z. Zhu, and J. Zhang, *Eur. J. Org. Chem.*, 2017, 6609.
30. C. Gelis, G. Levitre, J, Merad, P. Retailleau, L. Neuville, and G. Masson, *Angew. Chem. Int. Ed.*, 2018, **57**, 12121.
31. C. Li, C.-S. Wang, T.-Z. Li, G.-J. Mei, and F. Shi, *Org. Lett.*, 2019, **21**, 598.
32. M. A. Kroc, A. Prajapati, D. J. Wink, and L. L. Anderson, *J. Org. Chem.*, 2018, **83**, 1085.
33. I. A. Wani, A. Bhattacharyya, M. Sayyad, and M. K. Ghorai, *Org. Biomol. Chem.*, 2018, **16**, 2910.
34. Y.-W. Sun and L.-Z Wang, *New J. Chem.*, 2018, **42**, 20032.
35. M. S. Asgari, M. Soheilizad, P. R. Ranjbar, B. Larijani, R. Rahimi, and M. Mahdavi, *Tetrahedron Lett.*, 2019, **60**, 583.
36. Z. Wei, J. Zhang, H. Yang, and G. Jiang, *Org. Lett.*, 2019, **21**, 2790.
37. L.-B. Song, Z.-M. Li, Q.-r. Wang, and J.-m. Wang, *J. Org. Chem.*, 2018, **83**, 3441.
38. H. Kim, M. Byeon, E. Jeong, Y. Baek, S. J. Jeong, K. Um, S. H. Han, G. U. Han, G. H. Ko, C. Maeng, J.-Y. Son, D. Kim, S. H. Kim, K. Lee, and P. H. Lee, *Adv. Synth. Catal.*, 2019, **361**, 2094.
39. C. Adouma, M. E. Buden, W. D. Guerra, M. Puiatti, B. Joseph, S. M. Barolo, R. A. Rossi, and M.

Medebielle, *Org. Lett.*, 2019, **21**, 320.

40. Y.-Q. Xia, C. Li, M. Liu, and L. Dong, *Chem. Eur. J.*, 2018, **24**, 5474.
41. S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu, and J. Xiao, *Org. Lett.*, 2018, **20**, 138.
42. M. Virelli, E. Maroni, G. Colombo, L. Fiengo, A. Porta, L. Ackermann, and G. Zanoni, *Chem. Eur. J.*, 2018, **24**, 16516.
43. Y. P. Sarnikar, D. O. Biradar, Y. D. Mane, and B. C. Khade, *J. Heterocycl. Chem.*, 2019, **56**, 1111.
44. A. Peneau, Q. Tricart, C. Gutherine, and L. Chabaud, *Chem. Commun.*, 2018, **54**, 5891.
45. S. Liu, J. Qu, and B. Wang, *Chem. Commun.*, 2018, **54**, 7928.
46. M. E. Dalziel, J. A. Deihert, D. E. Carrera, D. Beaudry, C. Han, and H. Zhang, *Org. Lett.*, 2018, **20**, 2624.
47. X. Jiang, X. Chen, Y. Li, Y. Zhang, X. He, B. Chen, W. T. K. Chan, A. S. C. Chan, and L. Qiu, *Org. Lett.*, 2019, **21**, 608.
48. V. Srinivasulu, I. Shehadeh, M. A. Khanfar, O. G. Malik, H. Tarazi, I. A. Abu-Yousef, A. Sebastian, N. Baniowda, M. J. O'Connor, and T. H. Al-Tel, *J. Org. Chem.*, 2019, **84**, 934.
49. J. Gao, Y. Chen, T. Zhou, G. Liu, D. An, M. Zhuo, G. Zhang, and S. Zhang, *Asian J. Org. Chem.*, 2018, **7**, 697.
50. K. Kobayashi, A. Nakajima, T. Nogi, and T. Ueyama, *Heterocycles*, 2018, **96**, 2143.
51. E. Y. Zelina, T. A. Nevolina, L. N. Sorotskaja, D. A. Skvortscov, I. V. Trushkov, and M. G. Uchuskin, *J. Org. Chem.*, 2018, **83**, 11747.
52. T. Kuribara, J. Ueda, Y. Tanaka, M. Nakajima, S. Harada, and T. Nemoto, *Heterocycles*, 2018, **97**, 1175.
53. S. Chiha, A. Soicke, M. Barone, M. Muller, J. Bruns, R. Opiz, J.-M. Neudorfl, R. Kuhne, and H.-G. Schmalz, *Eur. J. Org. Chem.*, 2018, 455.
54. H. B. Tukhtaev, K. L. Ivnov, S. I. Bezzubov, D. A. Cheshkov, M. Y. Melnikov, and E. M. Budynina, *Org. Lett.*, 2019, **21**, 1087.
55. A. Sharma, D. Kishore, and B. Singh, *J. Heterocycl. Chem.*, 2018, **55**, 586.
56. S. V. Kemskiy, N. A. Syrota, A. V. Bol'but, V. I. Dorokhov, and M. V. Vovk, *Chem. Heterocycl. Compd.*, 2018, **54**, 789.
57. K. S. Mohammed, E. E. Elbeily, F. M. El-Taweel, and A. A. Fadda, *J. Heterocycl. Chem.*, 2019, **56**, 493.
58. M. A. El-Deeb and M. S. El-Zoghbi, *J. Heterocycl. Chem.*, 2019, **56**, 676.
59. W. S. Hamama, G. G. El-bana, S. Shaaban, and H. H. Zoorob, *J. Heterocycl. Chem.*, 2018, **55**, 971.
60. E. Dimitriou, R. H. Jones, R. G. Pritchard, G. J. Miller, and M. O'Brien, *Tetrahedron*, 2018, **74**, 6795.

61. S. Pusch, A. Troster, D. Lefrancois, P. Farahani, A. Dreuw, T. Bach, and T. Opatz, *J. Org. Chem.*, 2018, **83**, 964.

62. Z. Wang, Y. Addepalli, and Y. He, *Org. Lett.*, 2018, **20**, 644.

63. A. Rahman, E. Xie, and X. Lin, *Org. Biomol. Chem.*, 2018, **16**, 1367.

64. D. B. Corcoran, P. Picconi, C. K. Khui, G. Procopiou, I. Pysz, K. M. Rahman, and D. E. Thurton, *Synlett*, 2018, **29**, 1112.

65. H. Fujii, Y. Hironaka, and N. Abe, *Heterocycles*, 2019, **99**, 1361.

66. P. Sun, D. Rao, P. Zhang, Y. Qin, and Z.-X. Guo, *Tetrahedron*, 2018, **74**, 731.

67. I. V. Trushkov, M. G. Uchuskin, V. T. Abaev, and O. V. Serdyuk, *Synthesis*, 2019, **51**, 787.

68. L. T. Lepoviz and S. F. Martin, *Org. Lett.*, 2018, **20**, 7875.

69. B. Cheng, G. Volpin, J. Morstein, and D. Trauner, *Org. Lett.*, 2018, **20**, 4358.

70. R. E. Johnson, H. Ree, M. Hartmann, L. Lang, S. Sawano, and R. Sarpong, *J. Am. Chem. Soc.*, 2019, **141**, 2233.

71. J. Xu and V. H. Rawal, *J. Am. Chem. Soc.*, 2019, **141**, 4820.

72. T. Iwata and M. Shindo, *Heterocycles*, 2019, **98**, 349.

73. R. L. Connelly, J. P. Knowles, and K. I. Booker-Milburn, *Org. Lett.*, 2019, **21**, 18.

74. S. Fujita, K. Nishikawa, T. Iwata, T. Tomiyama, H. Ikenaga, K. Matsumoto, and M. Shindo, *Chem. Eur. J.*, 2018, **24**, 1539.

75. T. Iwata, T. Tomiyama, S. Fujita, and M. Shindo, *Heterocycles*, 2018, **97**, 712.

76. K. Ma, X. Yin, and M. Dai, *Angew. Chem. Int. Ed.*, 2018, **57**, 15209.

77. W.-J. Bai and T. R. R. Pettus, *Org. Lett.*, 2018, **20**, 901.

78. W. Zhu, S. Tong, J. Zhu, and M.-X. Wang, *J. Org. Chem.*, 2019, **84**, 2870.

79. Z.-W. Zhang, C.-C. Wang, H. Xue, Y. Dong, J.-H. Yang, S. Liu, W.-Q. Liu, and W.-D. Z. Li, *Org. Lett.*, 2018, **20**, 1050.

80. G. Sakaine and G. Smits, *J. Org. Chem.*, 2018, **83**, 5323.

81. Y. Liu and H. Wang, *Chem. Commun.*, 2019, **55**, 3544.

82. H. Ikota, C. Tsukano, and Y. Takemoto, *Heterocycles*, 2018, **97**, 621.

83. S.-i. Nakano, Y. Hamada, and T. Nemoto, *Tetrahedron Lett.*, 2018, **59**, 760.

84. T. Abe and K. Yamada, *Org. Lett.*, 2018, **20**, 1469.

85. T. Abe, S. Satake, and K. Yamada, *Heterocycles*, 2019, **99**, 379.

86. K. Ishikawa, D. Wakana, T. Itabashi, H. Takeda, T. Yaguchi, K.-i. Kawai, and T. Hosoe, *Heterocycles*, 2018, **96**, 1053.

87. C. Ma, K. Du, Y. Zhao, L. Zhang, B. Hu, and M. Cheng, *Bioorg. Med. Chem.*, 2018, **26**, 5151.

88. A. C. Tiberghien, P. W. Hawared, W. R. F. Goundry, M. McCormick, and J. S. Parker, *J. Org.*

Chem., 2019, **84**, 4830.

89. N. Malik, I. D. Iyamu, K. A. Scheidt, and G. E. Schiltz, *Tetrahedron Lett.*, 2018, **59**, 1513.
90. X. Pan, L. Tao, M. Ji, X. Chen, and Z. Liu, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 866.
91. Y. Kim, H. Kim, J. Lee, J. K. Lee, S.-J. Min, J. Seong, H. Rhim, J. Tae, H. J. Lee, and H. Choo, *J. Med. Chem.*, 2018, **61**, 7218.
92. Y. Duan, Y. Guan, W. Qin, X. Zhai, B. Yu, and H. Liu, *Med. Chem. Commun.*, 2018, **9**, 1779.
93. R. P. Wurz, K. Dellamaggiore, H. Dou, N. Javier, M.-C. Lo, J. D. McCarter, D. Mohl, C. Sastri, J. R. Lipford, and V. J. Cee, *J. Med. Chem.*, 2018, **61**, 453.
94. G. Li, L. K. Golani, R. Jahan, F. Rashid, and J. M. Cook, *Synthesis*, 2018, **50**, 4124.
95. G. Li, M. R. Stephen, R. Kodali, N. M. Zahn, M. M. Poe, V. V. N. P. B. Tiruveedhula, A. T. Huber, M. K. Schussman, K. Qualmann, C. M. Panhans, N. J. Raddatz, D. A. Baker, T. D. Prevot, M. Banasr, E. Sibille, L. A. Arnold, and J. M. Cook, *ARKIVOC*, 2018, **iv**, 158.
96. M. Virelli, E. Moroni, G. Colombo, L. Fiengo, A. Porta, L. Ackermann, and G. Zanoni, *Chem. Eur. J.*, 2018, **24**, 16516.
97. O. Van der Poorten, B. Legrand, L. L. Vezenkov, J. Garcia-Pindado, N. Bettache, A. Knuhtsen, D. S. Pedersen, M. Sanchez-Navarro, J. Martinez, M. Teixido, M. Garcia, D. Tourwe, M. Amblard, and S. Ballet, *ChemBioChem*, 2018, **19**, 696.
98. T. Lee, P. P. Christov, S. Shaw, J. C. Tarr, B. Zhao, N. Veerasamy, K. O. Jeon, J. J. Mills, Z. Bian, J. L. Sensintaffer, A. L. Arnold, S. A. Fogarty, E. Perry, H. E. Ramsey, R. S. Cook, M. Hollingshead, M. D. Millin, K.-m. Lee, B. Koss, A. Budhraja, J. T. Opferman, K. Kim, C. L. Arteaga, W. J. Moore, E. T. Olejniczak, M. R. Savona, and S. W. Fesik, *J. Med. Chem.*, 2019, **62**, 3971.
99. M. Ikejiri, H. Kojima, Y. Fugono, A. Fujisaka, Y. Chihara, and K. Miyashita, *Org. Biomol. Chem.*, 2018, **16**, 2397.

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