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ADVANCES IN THE SYNTHESIS AND BIOLOGICAL PERSPECTIVES OF BENZANNULATED MEDIUM RING HETEROCYCLES

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Abstract – Benzannulated medium ring heterocycles represent a class of compounds, capable of binding to multiple receptors with high affinity and act as good antagonist. Exploration of these types of compounds in drug discovery is a rapidly emerging area in synthetic chemistry and exploitation of these molecules will help researchers to discover biologically active compounds with a broad range of medicinal values.

CONTENTS

1. INTRODUCTION

Benzofused cyclic molecules are often referred to as ‘privileged structures’ and their appearance in natural products and modern pharmaceuticals are well-known.[1] These structures represent a class of molecules capable of binding to multiple receptors with high affinity.[2a-b] In this respect benzofused medium ring

heterocycles incorporating one or more heteroatoms have received considerable attention in chemical, medicinal and pharmaceutical research. The term 'medium ring',[3] introduced by Prelog and Brown, is usually applied to cyclic molecules having ring size in the range of eight to twelve atoms. Currently available synthetic methodologies for the preparation of this class of compounds still remain very specific and there are only few general and useful strategies.[4] It is mainly due to the fact that their formation is usually hampered by entropic/enthalpic factors and transannular interactions between methylene groups.[5a-c] These are serious limitations, which have usually resulted in low chemical yield of the desired products.[6a-c] Although some solutions to this formidable challenge have been advanced using cycloaddition or annulation strategies,[7a-b] the cyclization approach for the synthesis of these structures still remains an important challenge to synthetic organic chemists.

In this review, synthetic methods for benzofused medium ring heterocycles are classified into two major categories depending on whether the cyclization of acyclic precursors bearing an aromatic moiety is effected either through a C-C bond formation (Type 1) or a C-X (X = N, O) bond formation (Type-2) (Figure 1). The former method involves radical reaction, olefin metathesis or palladium induced intramolecular C-C bond formation. Type 2 involves palladium induced aryl amination or intramolecular etherification of aryl halides in the presence of suitable ligands. This has been the more developed route and offers a highly efficient method for the synthesis of seven- or eight-membered cyclic amines, ethers or their analogues. Development of optically active molecules using chiral ligands or catalyst, or even 'chiron approach' has also been discussed in this review. As we did not encounter any major review covering benzofused medium ring heterocycles, we focused on the literature dealing with the synthesis of benzofused seven- to twelve-membered rings with one or more heteroatoms. Publications appearing during the past decade (1996-) are mainly covered. Any omissions on this wide topic are unintentional and should be brought to the attention of the authors.

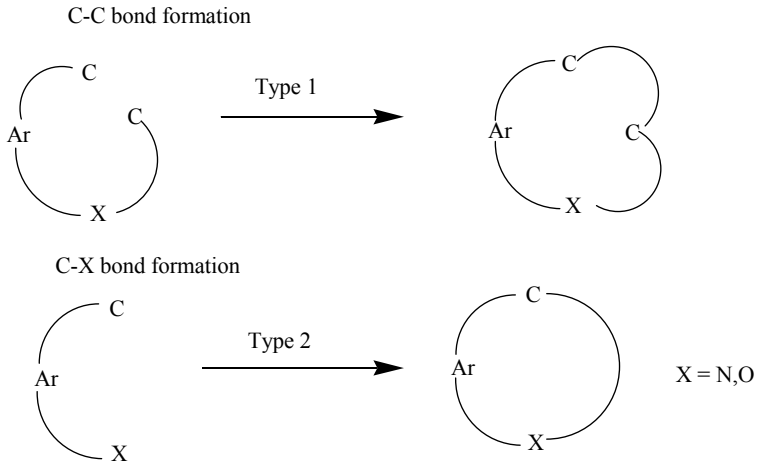


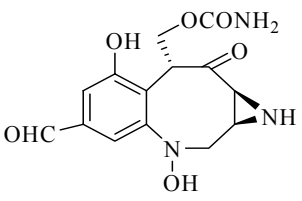
Figure 1

2. BENZOFUSED HETEROCYCLES WITH ONE NITROGEN ATOM

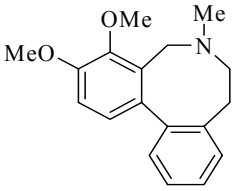
(a) Important structural types

Benzofused seven- or eight-membered cyclic amines, referred to as benzazepine or benzazocine, exhibit important pharmacological properties and are currently under intense scrutiny due to their physiological activity. For example, 1-benzazepine system[8a-c] has shown significant antimicrobial and analgesic activity. 2-Benzazepines have been reported[9] to be used as non-peptide mimics for the well-known tripeptide sequence Arg-Gly-Asp (RGD), which interacts with $\alpha_v\beta_3$ integrin, a pivotal protein that plays a key role in cell-cell signaling and acts as its antagonist. 3-Benzazepines have been of interest due to their dopaminergic and antidopaminergic activities,[10a] and the inhibitory effect[10b] on reverse transcriptase. Substituted dihydrobenzazocine displays anti-exploratory behavior in mice.[11a] 1-Benzazocine derivatives and their analogues are described as CCR-5 antagonist and used against HIV infection and other diseases.[11b]

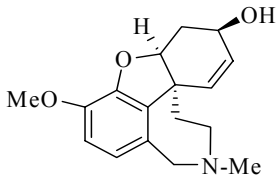
Recent discoveries of some selected systems (Figure 2) include the antitumor antibiotic[12a-b] (+)-FR900482, appears as a mixture of diastereoisomers in equilibrium through the intermediate **1**, the Amaryllidaceae alkaloid buflavine (**2**) isolated from *Boophana flava*,[13] the anti Alzheimer drug (-)- galanthamine (**3**) having benzannulated furobenzazepine moiety,[14] the benzopyran benzazepine class of alkaloids[15] exemplified by clavizepine (**4**), another Amaryllidacae alkaloid (-)-pancracine (**5**) having weak hypotensive and anti-convulsive activities,[16] substituted dihydrobenzazocine **6** displaying anti-exploratory behavior in mice,[11a] isoindolobenzazepine alkaloids lennoxamine (**7**) and chilenine (**8**),[17] cephalotaxine (**9**),[18] and dysazecine (**10**)[19]-the first alkaloid having hexahydrodibenz[*d,f*]azecine skeleton and possessing bioactivity against mollusks and agriculturally important insect pests.



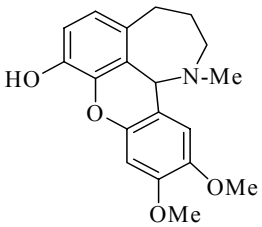
1



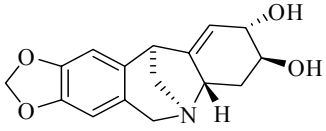
buflavine (**2**)



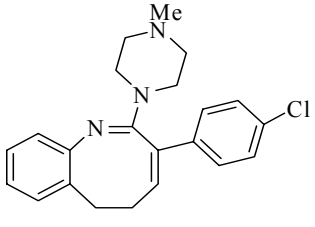
(-)-galanthamine (**3**)



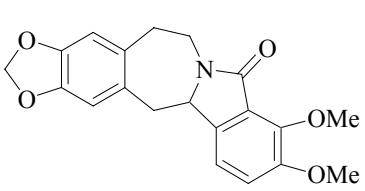
clavizepine(**4**)



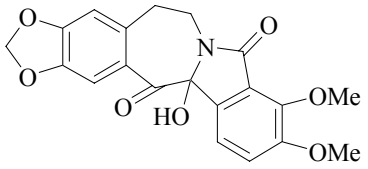
(-) -pancracine (**5**)



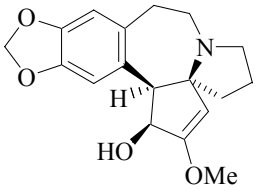
dihydrobenzazocine (**6**)



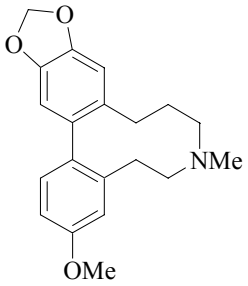
lennoxamine (**7**)



chilenine (**8**)



cephalotaxine (**9**)

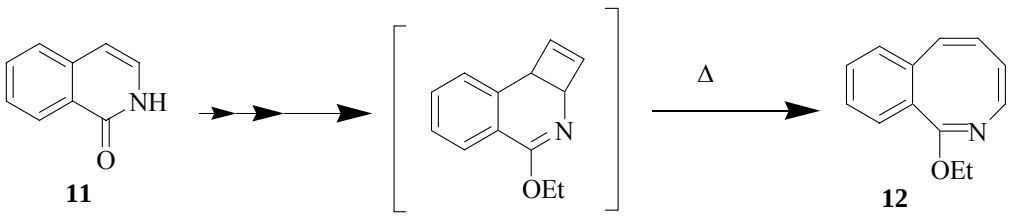


dysazecine (**10**)

Figure 2

(b) Synthetic approaches

Seven- and eight-membered cyclic amines have been traditionally prepared mainly by Beckmann rearrangement, Friedel Crafts reaction and Schmidt reaction.[20a-d] Recent reports based on intramolecular cyclization[21a-g] offer attractive routes for the synthesis of medium ring compounds under milder reaction conditions. 1-Ethoxy-2-benzazocine **12**, the first example of a 2-benzazocine, was synthesized from 1-isoquinolone **11** *via* photocyclization methodology (Scheme 1).[22]

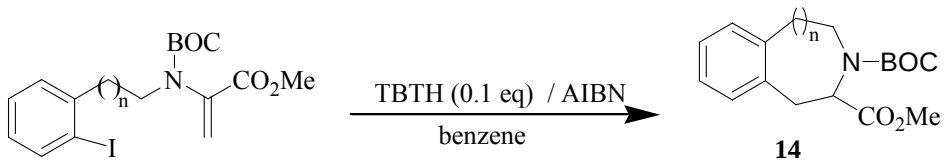


11 **12**

Scheme 1

These cyclization processes mainly involve free-radical reaction, ring closing metathesis and metal catalyzed reactions etc.

(i) Radical methods: *n*-Tributyltin hydride (TBTH) mediated radical cyclization has been used in few cases for the synthesis of medium ring heterocycles. A highly regioselective *endo-trig*-aryl radical cyclization has been developed by Gibson *et al.*,[23] which led to the synthesis of benzofused seven-, eight- and nine-membered cyclic amines **14a-c** from iodoolefins **13a-c** (Scheme 2).



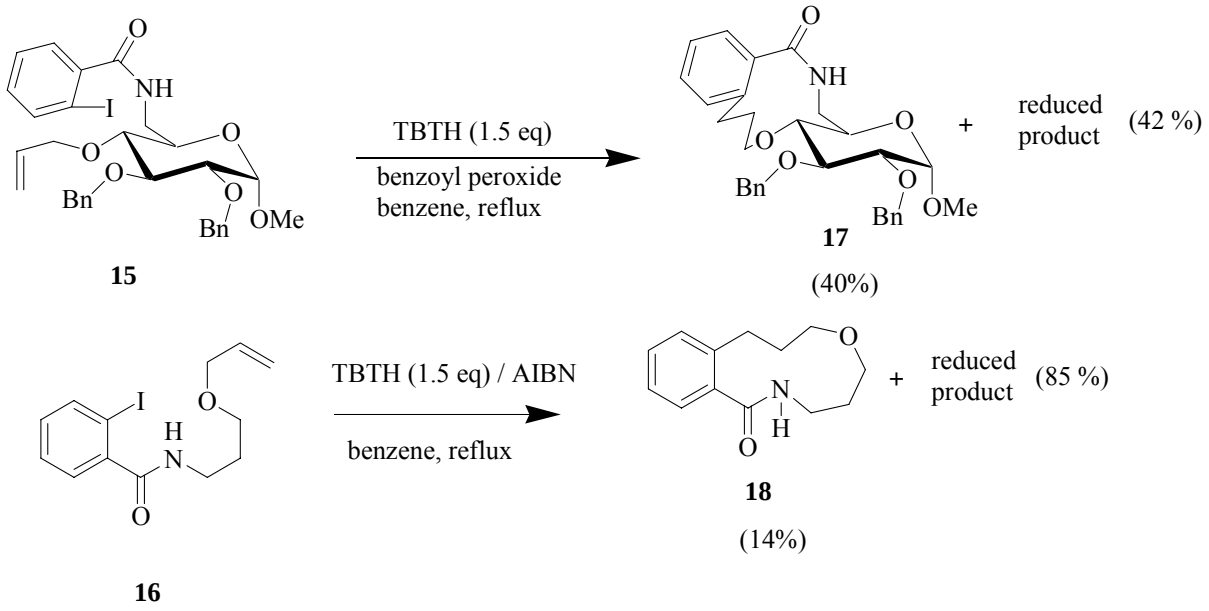
13 **14**

AIBN = azobisisobutyronitrile

a: n = 1 73%
b: n = 2 71%
c: n = 3 52%

Scheme 2

Regioselective 11-*endo* aryl radical cyclization of methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-glucopyranoside **15** and *N*-(3-allyloxypropyl)-2-iodobenzamide **16** with TBTH provided the benzolactams **17** and **18** respectively with major amounts of reduced products (Scheme 3).[24]

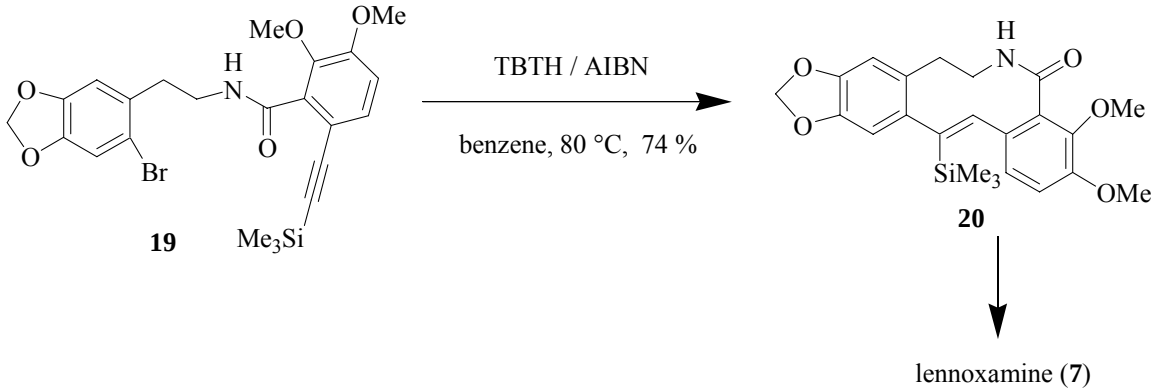


15 **17** (40%)

16 **18** (14%)

Scheme 3

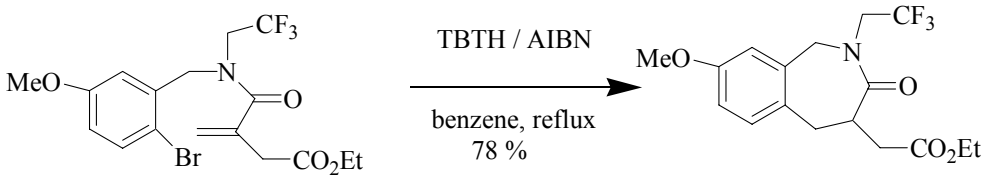
In studies towards the synthesis of the isoindolobenzazepine group of alkaloid, lennoxamine (**7**), a ten-membered ring lactam **20** was obtained by intramolecular cyclization of an aryl radical (generated from the bromobenzene **19**) onto a trimethyl silyl alkyne group (Scheme 4).[25] The unusual large ring cyclization tests the limit of ring size in radical reaction.



19 **20**

Scheme 4

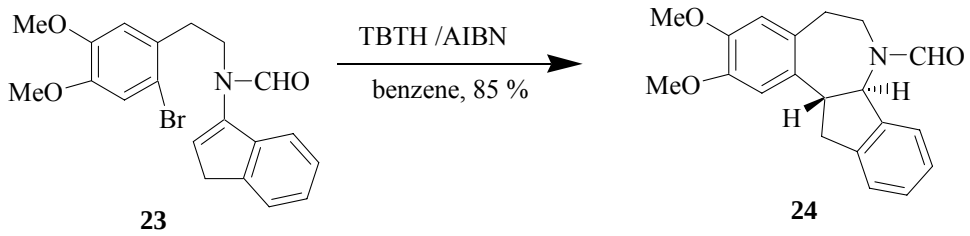
Recently, Kamimura *et al.* [26] reported the synthesis of 2-benzazepine analogues like **22** using 7-*endo-trig* aryl radical cyclization of the easily accessible bromobenzyl amide **21** (Scheme 5).



21 **22**

Scheme 5

Castedo and co-workers[27a-b] developed an exclusive stereoselective 7-*endo-trig* cyclization method towards the synthesis of the *trans*-3-benzazepine system **24** from bromoenamide **23** (Scheme 6). To prevent byproduct formation, an excess of TBTH in benzene was added very rapidly to the substrate **23**. The radical cyclization reaction was very fast because no reaction product from hydrogen transfer to the aryl radical was formed, even at a high concentration of TBTH.

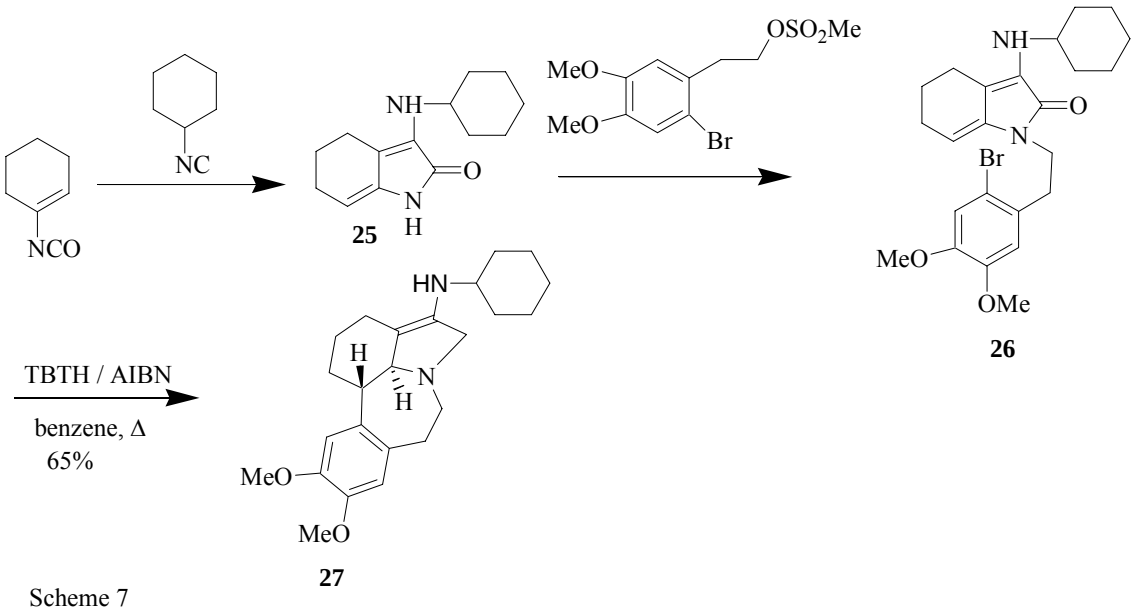


23 **24**

Scheme 6

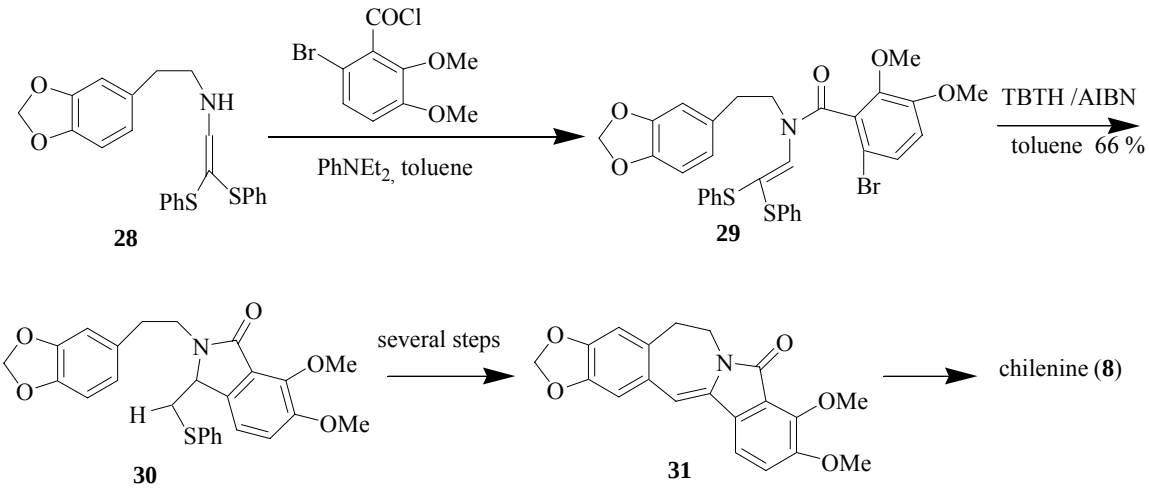
A few other reports of TBTH mediated radical cyclization in the preparation of medium and large ring nitrogen heterocycles and their analogues have appeared in the literature.[28a] General guidelines for the radical cyclization of medium ring heterocycles have been found to be similar to that of carbocycles, favoring the *endo* processes.[28b]

Rigby and Qabar[29] demonstrated an elegant approach towards the synthesis of apoerysopine, a structurally complex and biologically active *Erythrina* alkaloid. They synthesized the starting material **25** by applying a (1+4) cyclization of vinyl isocyanate with alkyl isocyanide. The radical precursor **26** was generated by base catalyzed alkylation reaction and was treated with TBTH. Surprisingly only the hydroapoerysopine derivative **27**, arising from a 7-*endo-trig* cyclization route, was obtained from the reaction mixture in 65% yield; no *exo*-product was detected in the reaction (Scheme 7). Ishibashi *et al.* [30a] reported a facile sulfur directed 5-*exo-trig* aryl radical cyclization towords the projected synthesis of chilenine (**8**) using **28** as the starting material, prepared from the condensation of 2-(3,4-methylenedioxyphenyl)ethylamine with bis(phenyl-thio)acetaldehyde. Compound **28** on subsequent acylation and treatment with excess TBTH



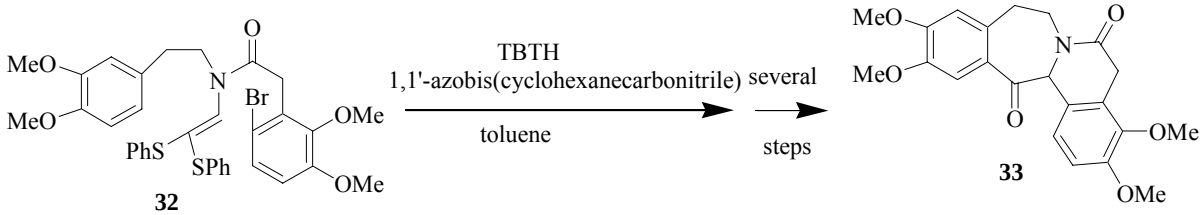
Scheme 7

(Scheme 8) furnished a five-membered cyclic amide through (**28**-**30**), which was then transformed *via* **31** to chilenine (**8**).



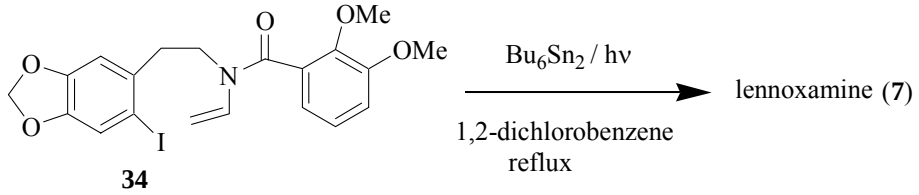
Scheme 8

An extension of this method was used to synthesize the isoquinolinobenzazepine alkaloid saulatine (**33**) through the intermediate **32** (Scheme 9).[30b]



Scheme 9

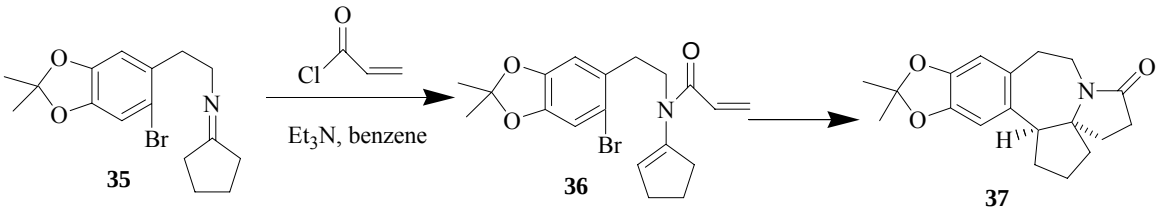
Recently, Ishibashi and co-workers[30c] reported another synthesis of lennoxamine (**7**) from the enamide **34**, using a radical cascade involving 7-*endo*-trig cyclization and homolytic aromatic substitution onto the dimethoxyphenyl ring (Scheme 10).



34

Scheme 10

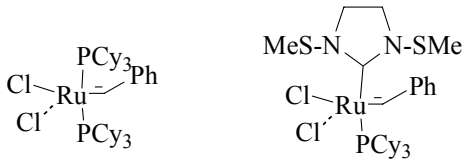
This 7-*endo*-cyclization methodology[30d] was applied for a concise construction of the cephalotaxine skeleton **37** using the sequence **35→36→37** (Scheme 11).



35 **36** **37**

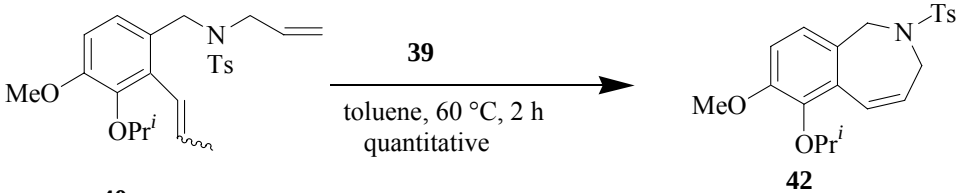
Scheme 11

(*ii) Ring closing metathesis:* In recent years the ring closing metathesis reaction strategy has been extensively used in the synthesis of benzofused heterocyclic systems.[4, 21b, 21d-e] The versatility of Grubbs' catalysts **38** (first generation) and **39** (second generation) in cyclization to olefinic rings of different sizes is well documented. These catalysts have proved to be compatible in presence of many sensitive functional groups including esters, amides, acetals, silyl ethers, ammonium salts etc. Selective examples of the synthesis of benzofused medium ring systems are described below.

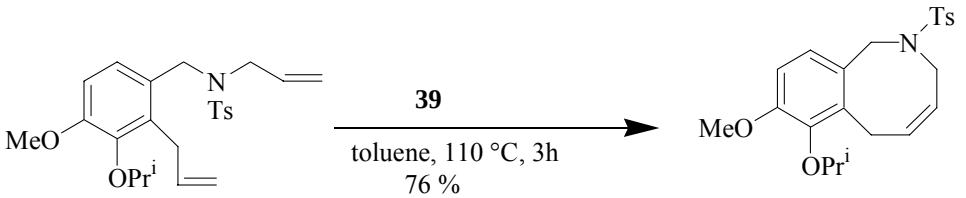


38 **39**

An expedient approach[31] to the synthesis of 2-benzazepine and benzazocine derivatives **42** and **43** involved ruthenium mediated metathesis from the respective dienes **40** and **41** (Scheme 12).



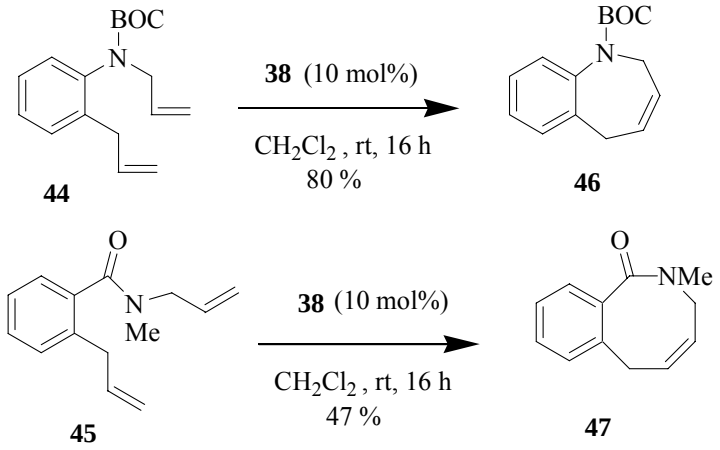
40 **42**



41 **43**

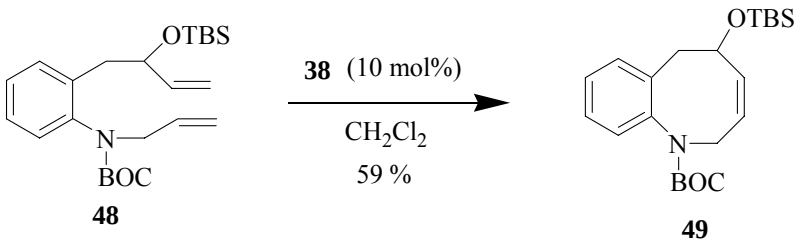
Scheme 12

Rapid construction of biologically active 1-benzazepine and 2-benzazocinone derivatives **46** and **47** has been reported by Lane and Snieckus,[32] utilizing ring closing metathesis sequences from the parent dienes **44** and **45** (Scheme 13).



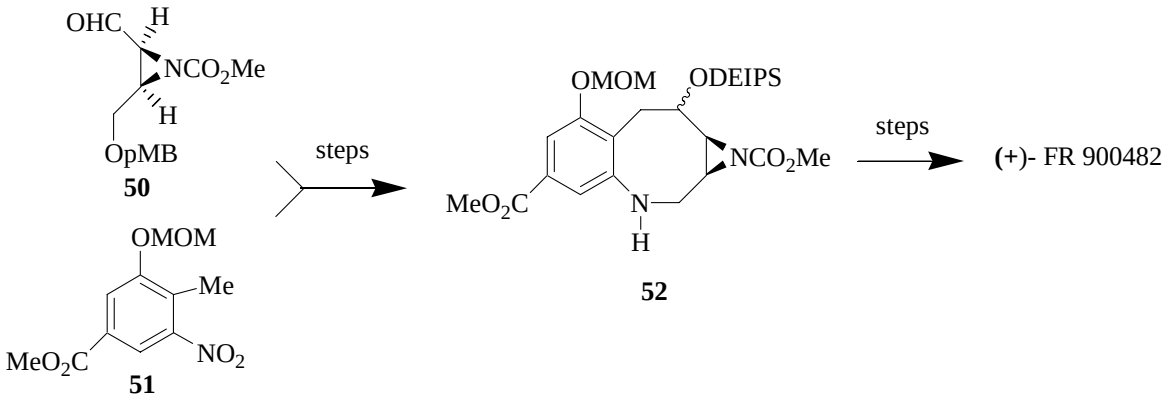
Scheme 13

Grubbs and co-workers[33] employed a similar intermediate **48** and used the ruthenium catalyst **38** to obtain 1-benzazocine **49** (Scheme 14).



Scheme 14

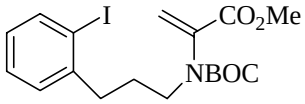
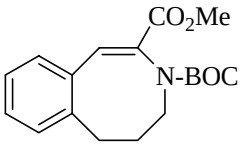
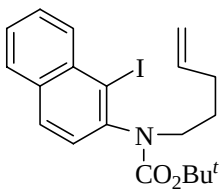
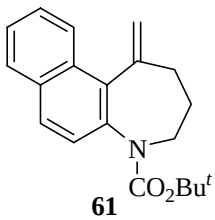
Judd and Williams[34] reported a concise enantioselective synthesis of FR 900482 and FK 66979. Both these drugs possess highly promising antitumor activity and can replace the widely used anti tumor drug mitomycin C. The benzazocine ring scaffold **52**, prepared from the precursors **50** and **51**, has been utilized as a key intermediate for the synthesis of FR 900482 (Scheme 15).

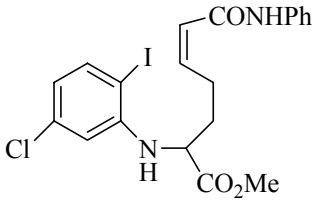


Scheme 15

(iii) Intramolecular palladium promoted reactions: The intramolecular palladium catalyzed reaction of alkenes (**13c**, **53-59**), with or without ligands (**L**), has emerged as a powerful tool for the construction of benzannulated cyclic amines or derivatives (**60-68**).[16,23,35a-f] An overwhelming preference[35d] for the *exo*-mode of cyclization has been noted in most cases. There are, however, few examples where *endo*-mode cyclization has occurred depending on the nature of the catalyst and the electronic effect of the substitution in the precursors as presented (Table 1).

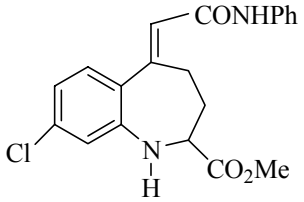
Table 1 Intramolecular palladium promoted cyclization

Entry	Substrate	Reagents	Product Yield	Refs
1.	 **13c**	$Pd(OAc)_2$, $NaHCO_3$, Bu^n_4NCl , 3A°, MS, DMF	 **60** 73%	23
2.	 **53**	$Pd(PPh_3)_4$ (0.5 eq), TEA, MeCN	 **61** 89%	35a

3. 

54

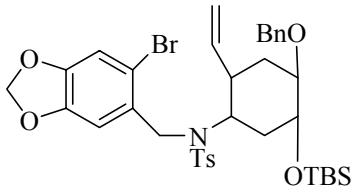
$Pd(PPh_3)_4$ (0.5 eq), Et_3N, DMF



62

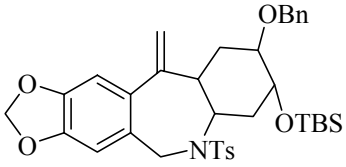
60%

35b

4. 

55

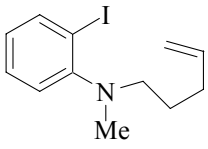
$Pd(PPh_3)_4$ (0.5 eq), Me_3NBnCl Et_3N, MeCN



63

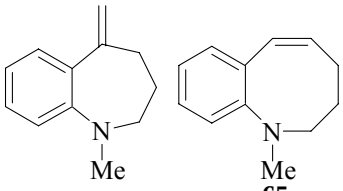
48%

16

5. 

56

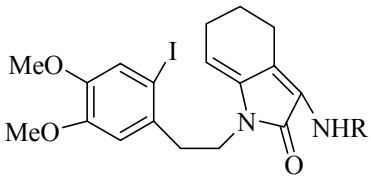
$PdCl_2$, TPPTS, Pr^i_2NEt, MeCN, H_2O, reflux



64 7-exo 55%

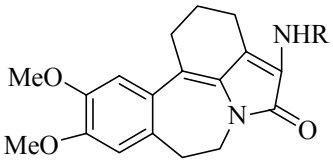
65 8-endo 22%

35c

6. 

57

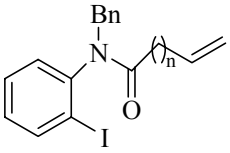
$Pd(OAc)_2$ (10 mol%) Bu^n_4NCl (2eq), KOAc, DMF



66

48%

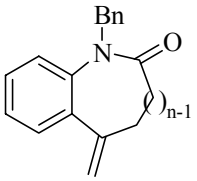
35d

7. 

n = 2 or 3

58

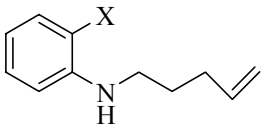
$Pd_2dba_3.CHCl_3$ (5 mol%) PPh_3 (4 eq), LiCl, Et_3N, DMF



67

n = 2 85%
n = 3 72%

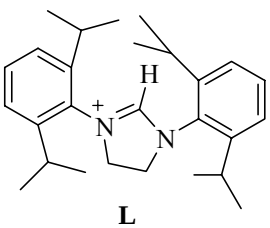
35e

8. 

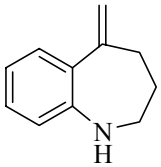
X = I, Br or Cl

59

Pd_2dba_3 (1%), Cs_2CO_3 (1.5 eq) DMA



L

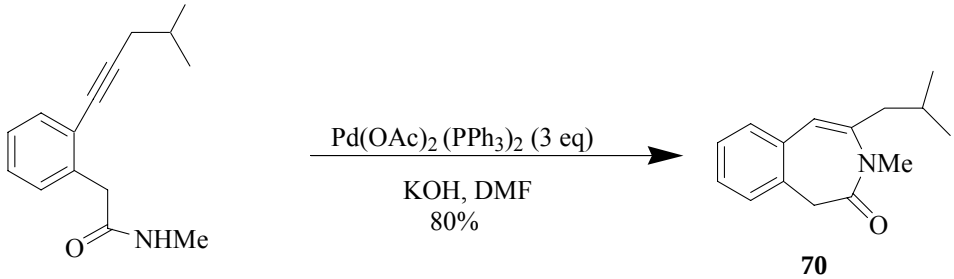


68

X = I 82%
X = Br 60%
X = Cl 28-32%

35f

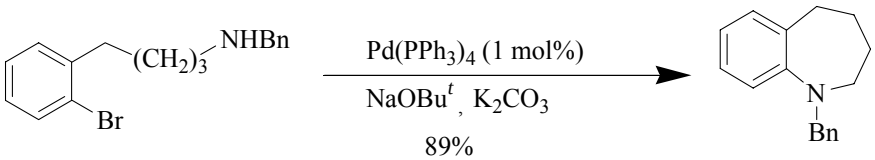
Very recently, Mitchell and co-workers[36] reported the synthesis of 3-benzazepine **70** in excellent yield using palladium catalyzed intramolecular cyclization of phenyl acetylenes **69** substituted in the ortho-position with tethered amide functionality (Scheme 16).



69 **70**

Scheme 16

A series of intramolecular palladium catalyzed aryl amination reactions of aromatic amines **71** were reported by Buchwald and co-workers[37] leading to the synthesis of 1-benzazepine derivatives **72** (Scheme 17).

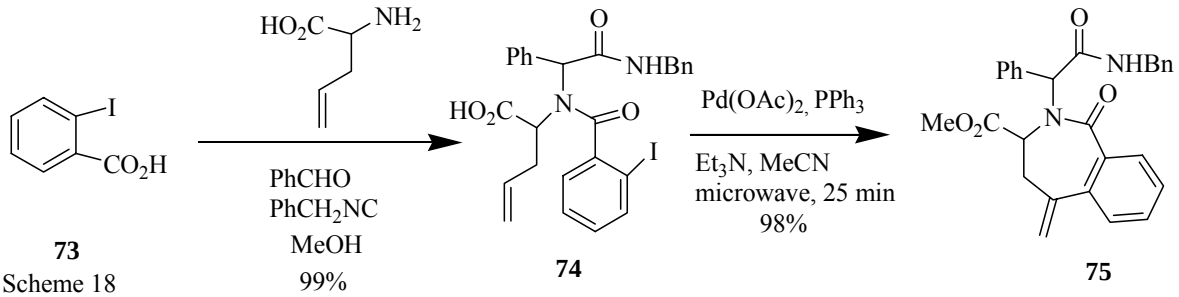


71 **72**

Scheme 17

A few other examples of palladium catalyzed aryl amination reaction used $Pd(dba)_2$-PPh_3 mixture in presence of the bases $NaOBu^t$-K_2CO_3, furnishing 1-benzazepine in good yield.[38]

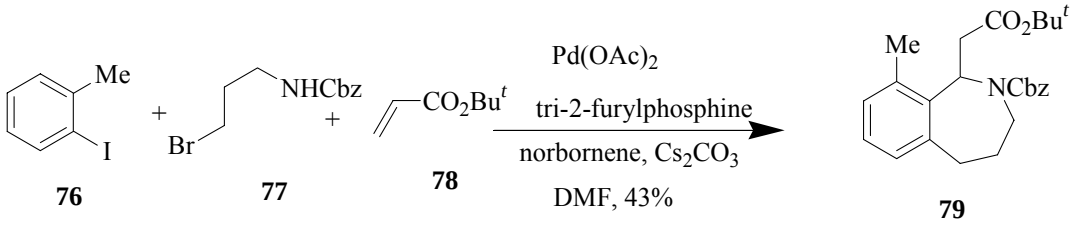
A new strategy has been published employing sequential Ugi reaction and microwave assisted intramolecular Heck cyclization[39] to access an array of benzofused *N*-containing heterocyclic scaffold **75** from easily accessible starting materials **73**. It proceeds *via* the intermediate iodoolefin **74** with excellent yield (Scheme 18).



73 **74** **75**

Scheme 18

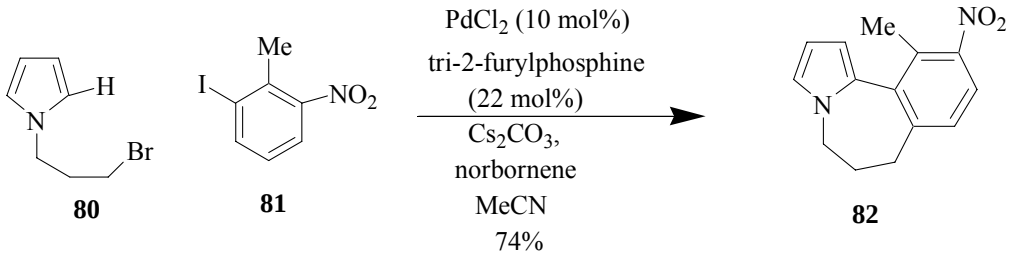
1-Substituted tetrahydro-1*H*-2-benzazepines **79** were synthesized similarly from *ortho*-iodotoluene **76**, *N*-substituted bromoalkyl amine **77** and an electron poor olefin **78** through a one-pot palladium-catalyzed sequence involving *ortho*-alkylation, alkenylation and intramolecular aza-Michael reaction[40] (Scheme 19).



76 **77** **78** **79**

Scheme 19

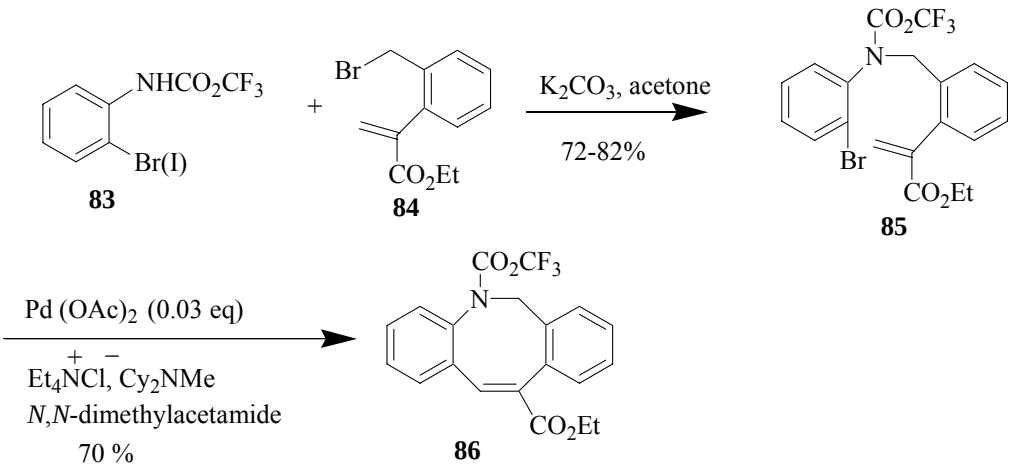
Lautens and co-workers[41] reported a palladium catalyzed norbornene mediated sequential coupling reaction involving an aromatic sp^2 functionalization as the key step, in which an alkyl-aryl bond and an aryl-heteroaryl bond are formed in one pot. A variety of highly functionalized seven-membered benzannulated heterocycles, e.g. **82** were synthesized in one step in good yield from the readily accessible 1-(3-bromopropyl)-1*H*-pyrrole **80** and aryl iodides **81** (Scheme 20).



80 **81** **82**

Scheme 20

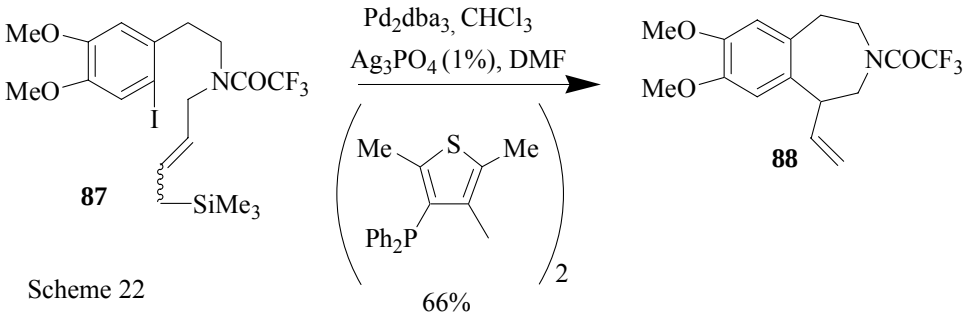
Guy and co-workers[42] reported a convergent synthesis of dibenzofused medium ring heterocycles incorporating seven- or eight-membered ring by using the highly selective intramolecular Heck arylation reaction. With **85** (obtained from **83** and a substituted benzyl bromide **84**) as the substrate, the cyclization proceeded exclusively in the 8-*endo* mode, providing **86** in 70% yield (Scheme 21). They have used a similar procedure for the synthesis of oxygen and sulfur heterocycles.



83 **84** **85** **86**

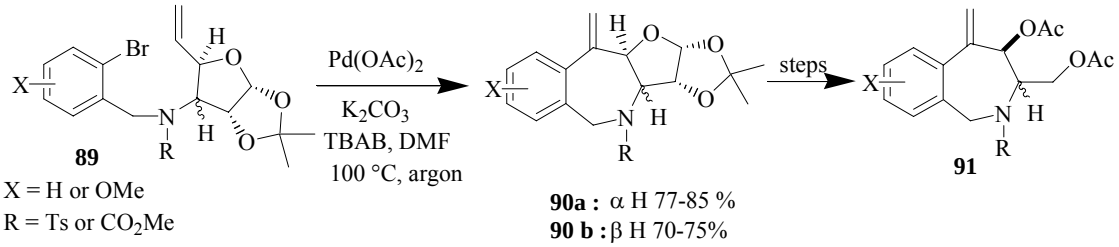
Scheme 21

The intramolecular Heck reaction of the iodoaryl compound **87** having an *N*-allylsilane moiety was carried out in presence of the chiral ligand (+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene leading to the chiral synthesis of 3-benzazepine **88** with 92% ee (Scheme 22).[43]



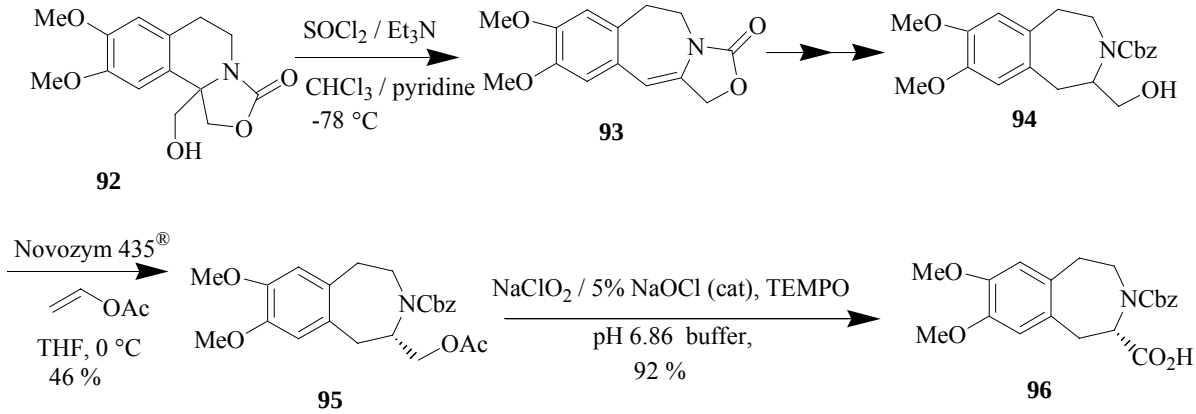
Scheme 22

Facile annulation to obtain benzazepines fused to a furano-sugar has been achieved on various aryl bromide tethered to a sugar nucleus **89**, through intramolecular Pd-catalyzed cyclization. Cleavage of the sugar ring of the tricyclic derivative **90** provided a convenient route for entry into chiral functionalized 2-benzazepines **91** (Scheme 23).[44]



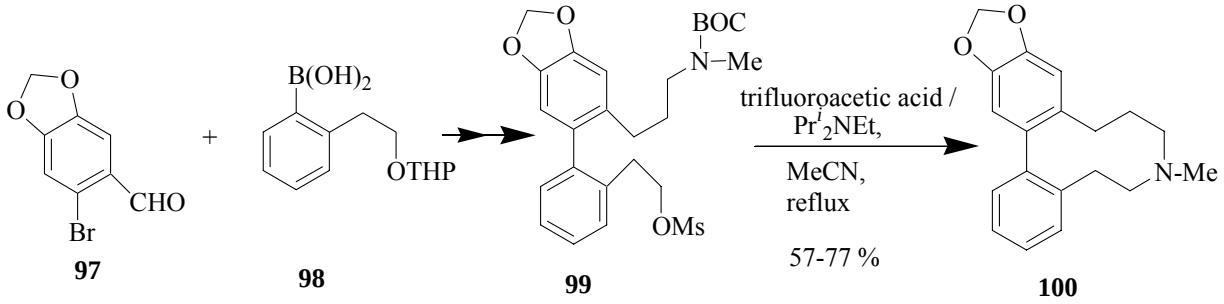
Scheme 23

(iv) Other methods: A chiral synthesis of (-)-(*S*)-*N*-Cbz-3-benzazepine-2-carboxylic acid derivative **96** was carried out by using sequential ring expansion reaction of oxazoloisoquinoline (**92→93**) and enzyme-catalyzed acylation of alcohol **94**. Removal of the acetyl group on **95** followed by Zao's oxidation afforded (-)-(*S*)-**96** in 92% yield (Scheme 24).[45]



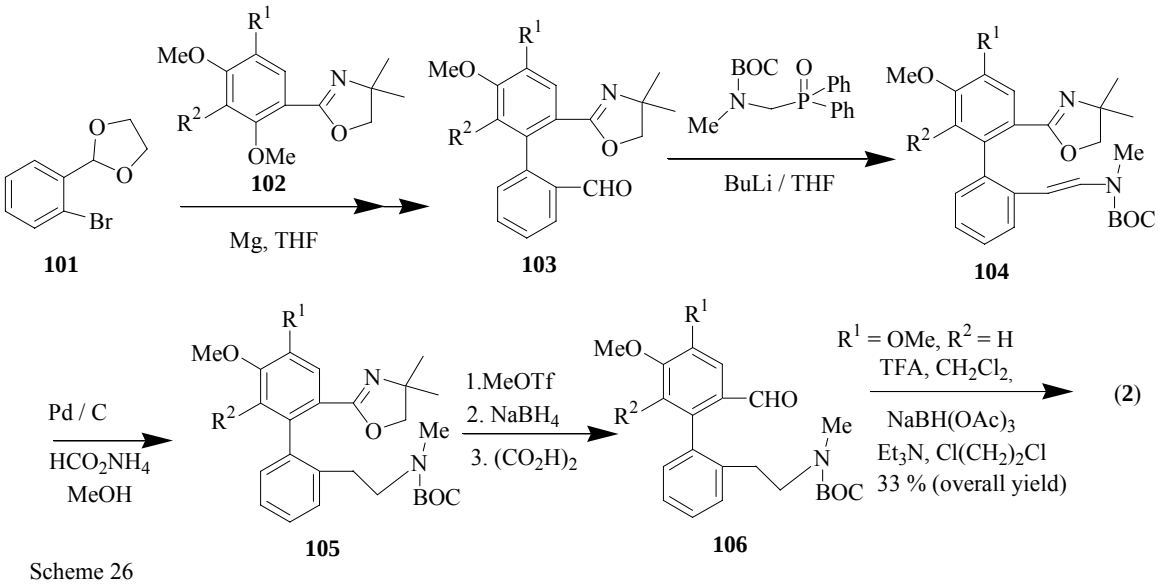
Scheme 24

Suzuki coupling procedure[46] was used to make appropriate biphenyl derivatives **99** obtained from bromo-aldehyde **97** and boronic acid **98**, which yielded the analogues of dysazecine **100** through intramolecular mesyloxy displacement (Scheme 25).



Scheme 25

A concise synthesis of the Amaryllidaceae alkaloid buflavine (**2**) and its regioisomer have been reported involving sequential Meyer's biaryl coupling, enecarbamate formation and hydrogenation followed by ultimate intramolecular reductive amination (**101** +**102**→**103**→**106**) (Scheme 26).[47]



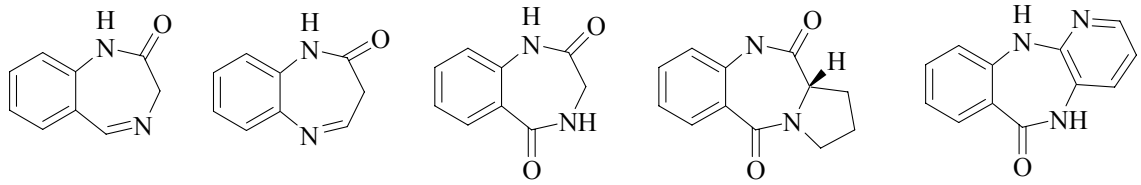
Scheme 26

3. BENZOFUSED HETEROCYCLES WITH TWO NITROGEN ATOMS

(a) Important structural types

Due to the ability of 1,4-benzodiazepin-2-one **107** to bind to cholecystokinin (CCK), gastrin and central benzodiazepine receptors,[48a] different types of benzodiazepines have been synthesized and their pharmacological activities were reported. The biological activity of **107** on central nervous system such as sedation, hypnosis, decreased anxiety, muscle relaxation and anticonvulsant activity have been well established.[48b] Presently, there are numerous types of benzodiazepines (Figure 3) including **107**, 1,5-benzodiazepin-2-one **108**, 1,4-benzodiazepin-2,5-dione **109**, pyrrolo[2,1-*c*][1,4]benzodiazepin-

5,11-dione **110** and 5,11-dihydro-benzo[*e*]pyrido[3,2-*b*][1,4] diazepin-6-one **111**. These compounds may be substituted on either ring to produce derivatives with a variety of biological effects. All types of benzodiazepines have been synthesized. Among these, a few approaches have been selected for this review.

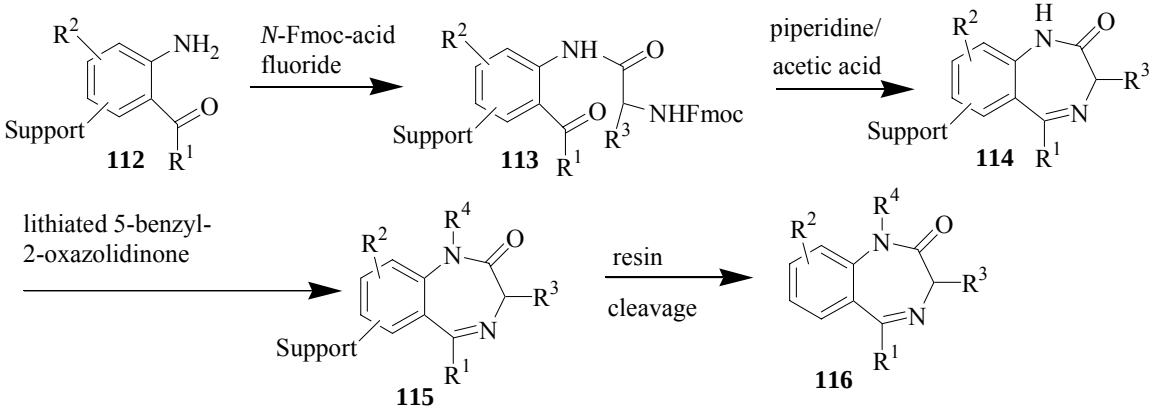


107 **108** **109** **110** **111**

Figure 3

(b) Synthetic approaches:

(i) 1,4-Benzodiazepin-2-one derivatives: A solution phase synthesis of 1,4-benzodiazepin-2-one derivatives was reported by Evans and co-workers.[48a] Bunin *et al.* [48c] utilized the reaction of Fmoc protected aminoacid fluorides with substituted 2-aminobenzyl ketones **112** to yield **113**. After removal of the Fmoc group the compound is treated with 5% acetic acid to effect ring closure yielding **114**. Following treatment with lithiated 5-benzyl-2-oxazolidinone, the alkylating agent was added, allowing substitution at N_1 atom to furnish **115**. Cleavage from resin yielded the benzodiazepine derivatives **116** (Scheme 27).

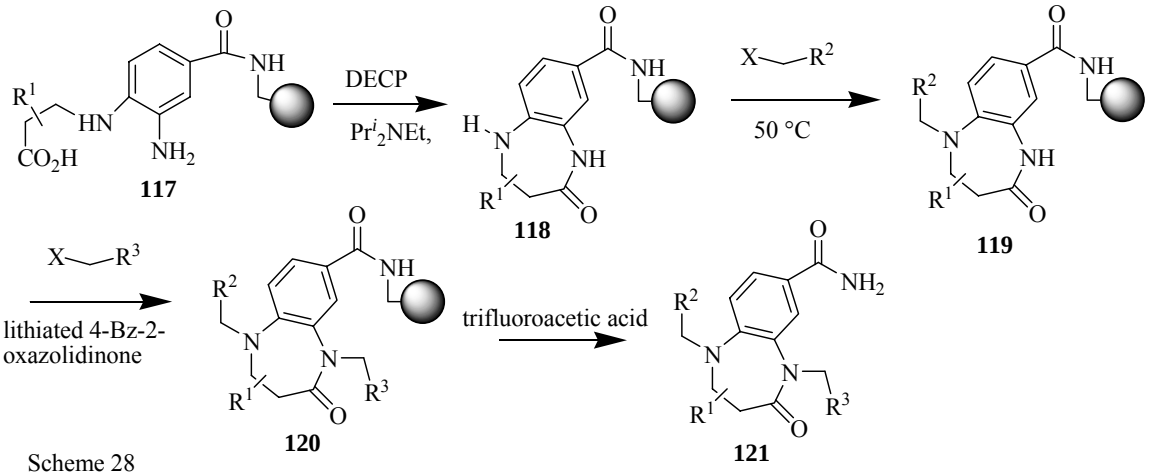


112 **113** **114** **115** **116**

Scheme 27

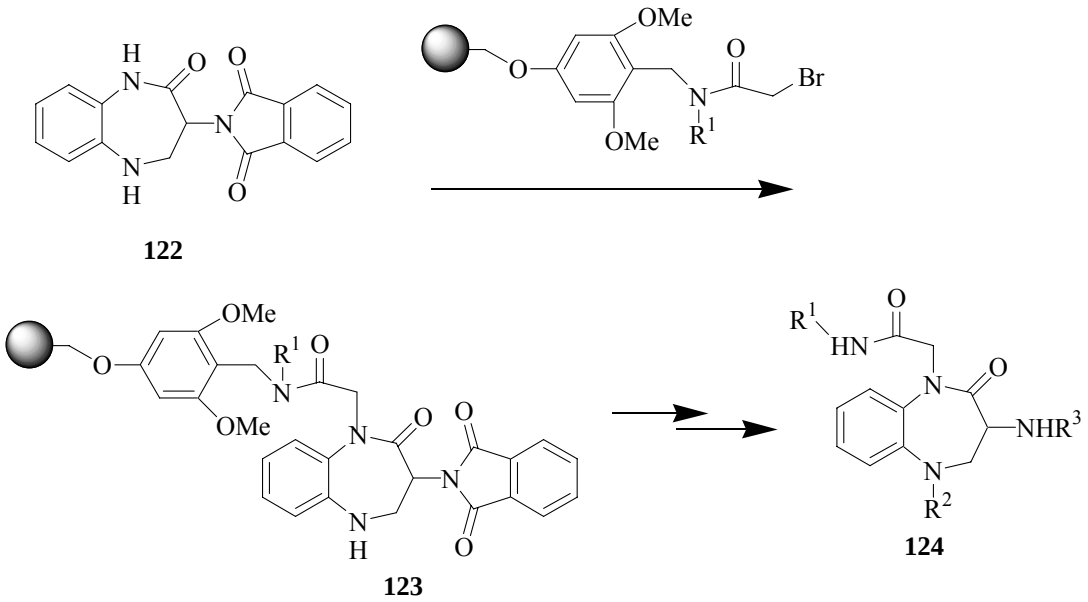
Bhalay *et al.*[48d] have synthesized tetrahydro-1,4-benzodiazepin-2-one on solid phase using Wang resin and utilized 7-*exo-trig* cyclization during the cleavage of resin.

(ii) 1,5-Benzodiazepin-2-one derivatives: Molecules with 1,5-benzodiazepin-2-one scaffold exhibits a range of biological activity including interleukin-1β converting enzyme (ICE) inhibition and delayed potassium current blocking (I_k).[49a] Schwarz *et al.* [49b] reported a synthetic strategy on solid support using **117** as the precursor. Treatment of **117** with diethyl cyanophosphonate (DECP) and diisopropylethylamine (DIEA) afforded **118**. Regioselective N_5 alkylation with alkyl halides furnished **119** in about 85% purity. A final alkylation was then accomplished at N_1 using lithiated 4-benzyl-2-oxazolidinone as a base yielding **120**. Subsequent cleavage from the resin led to 1,5-benzodiazepin-2-one derivatives **121** (Scheme 28).



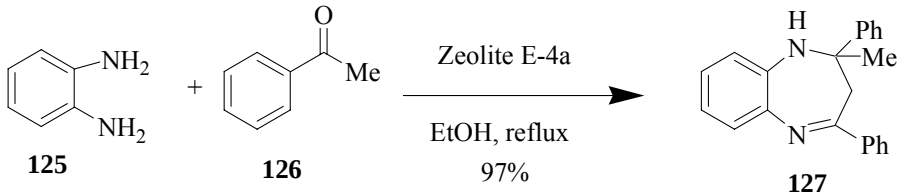
Scheme 28

Herpin *et al.*[49a] reported a different combinatorial approach to synthesize a library of 1,5-benzodiazepin-2-ones. In this synthesis, 3-phthalyl-1,5-benzodiazepin-2-one **122** was attached to the resin through the amide nitrogen to afford **123**, derivatized and then subjected to cleavage from resin to yield **124** (Scheme 29).



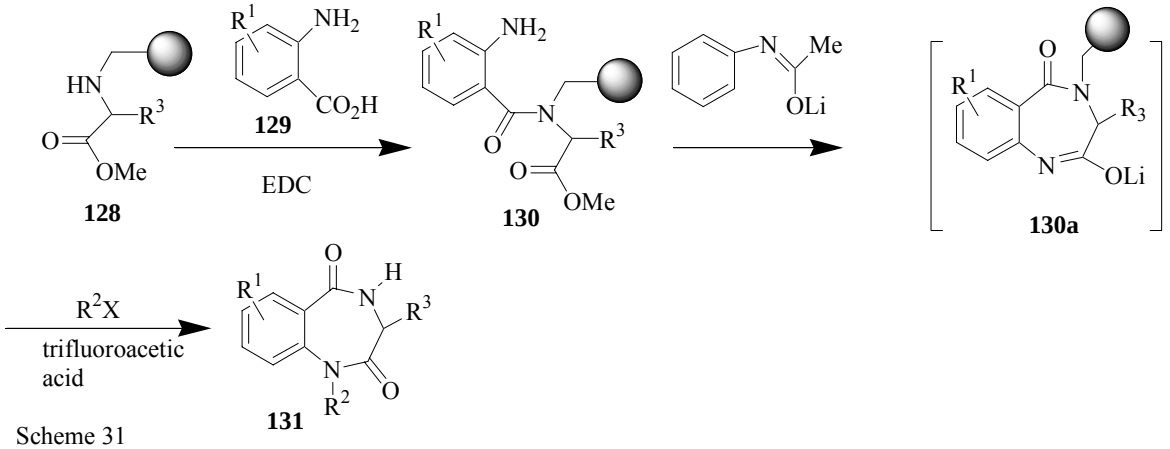
Scheme 29

Modified small pore size Zeolite E-4a was found to be an efficient catalyst for the regioselective synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepine **127** from *ortho*-phenylene diamine **125** and an aromatic ketone **126** (Scheme 30).[50] The method, described as simple, cheap and environment friendly, gave the benzodiazepine in high yield.



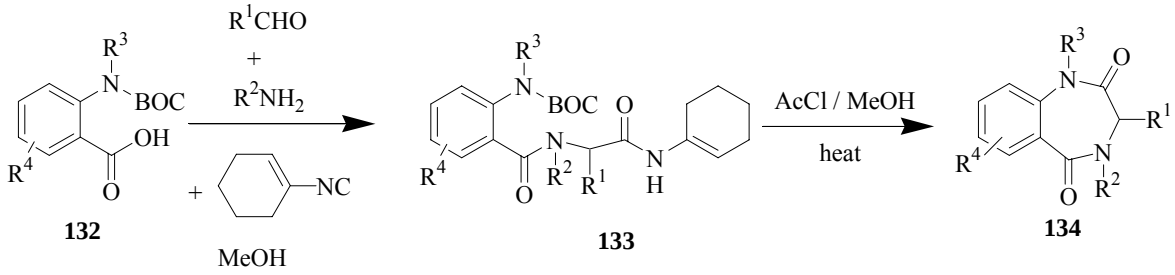
Scheme 30

(iii) 1,4-Benzodiazepin-2,5-dione derivatives: 1,4-Benzodiazepin-2,5-diones have been reported to possess anticonvulsant, anxiolytic and antitumor properties, as well as being antagonists for cholecystokinin receptor (CCK), opiate receptor and have been identified as platelet aggression inhibiting mimics of the RGD peptide sequence.[51a] There are two major combinatorial strategies for the synthesis of these compounds. The first is based on the use of amino acid derivatives **128**. The condensation of Merrifield resin linked **128** and variously substituted anthranilic acid **129** in the presence of EDC (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide) provided the resin bound tertiary amides **130**. Treatment with the lithium salt of acetanilide then brought about a base-catalyzed cyclization to produce **130a**, which on subsequent treatment with an alkylating agent followed by cleavage from resin furnished **131** (Scheme 31).[51b]



Scheme 31

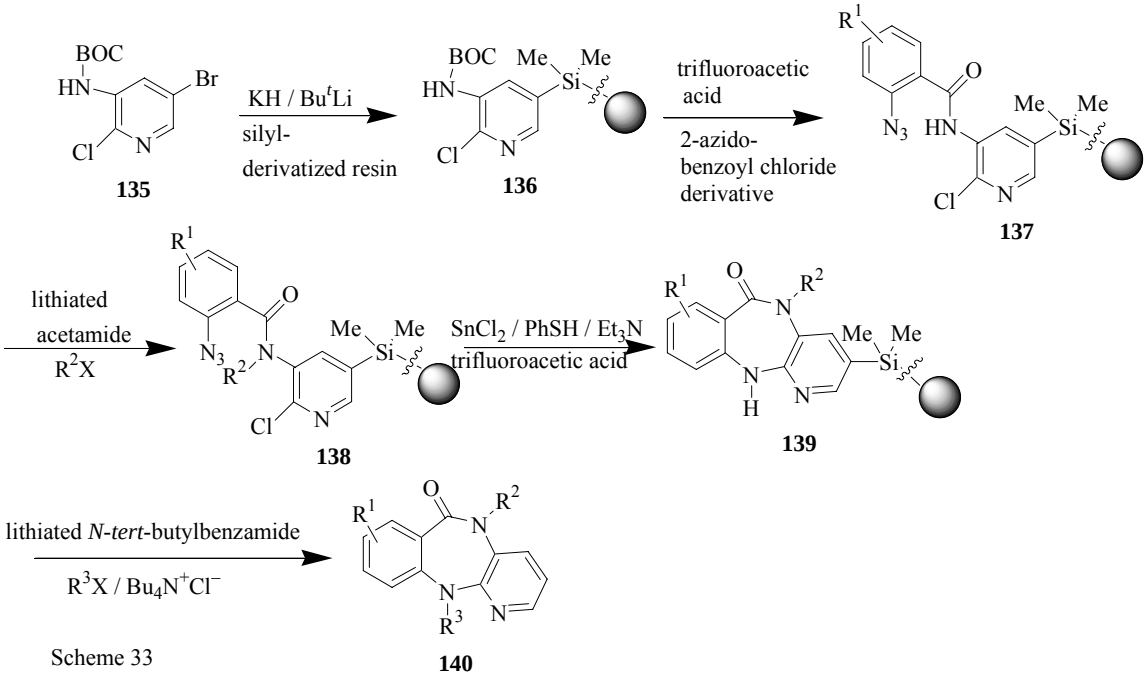
The second approach is the potentially more versatile four-component Ugi reaction, accomplishing the entire synthesis in fewer steps and circumventing many drawbacks. An example of this strategy (**132**→**134**) is displayed in Scheme 32.[51c]



Scheme 32

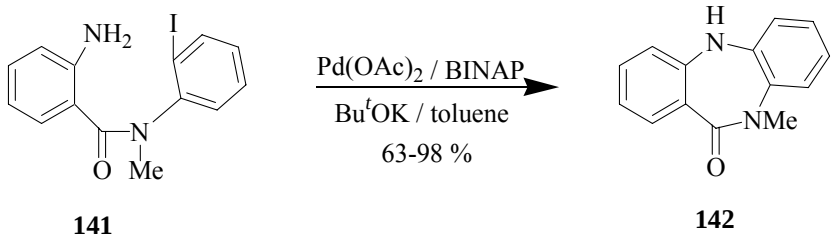
Pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones **110** have also been synthesized by the reduction of aromatic nitro- and azido-compounds using indium-NH_4Cl on solid support.[52]

(iv) Benzo[e]pyrido[3,2-b][1,4]diazepin-6-ones: Benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-one derivatives posses anti-HIV activities[53a] and inhibit muscarinic receptor (used for ulcer treatment).[53b] Ellman and co-workers[53c] reported a combinatorial synthesis (**135**→**140**) as outlined in Scheme 33.



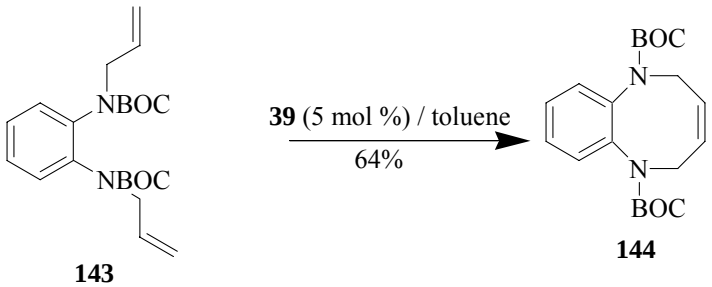
Scheme 33

(v) Other benzofused diazaheterocycles: Beccalli *et al.*[54a] reported an efficient synthetic route for dibenzo[*b*,*e*][1,4]diazepin-11-one **142** and its analogues, having antidepressant, antihistamin, anti-inflammatory, antiarrhythmic, antitumor or anticonvulsant properties. They used intramolecular arylamination reaction starting from amide **141** (Scheme 34). A further synthesis of 1,4-benzodiazepine-5-ones in high yield was reported[54b] by the same group using similar methodology.



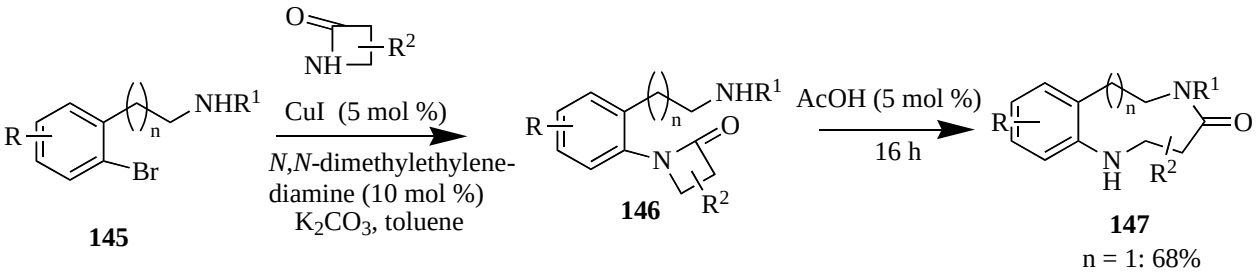
Scheme 34

Van Otterlo *et al.*[55] have studied the versatile olefin metathesis reaction with Grubbs' catalyst **39**. Utilizing this strategy they reported the synthesis of benzofused eight-membered heterocycle **144** from the diene **143** (Scheme 35).



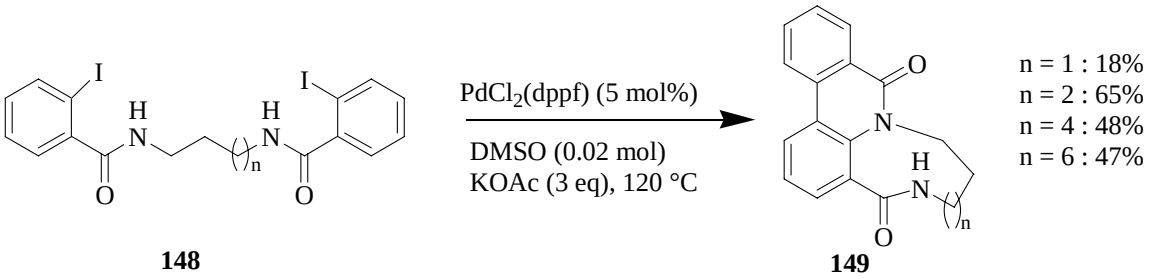
Scheme 35

Buchwald and co-workers[56] have developed a synthesis of medium ring benzofused heterocycles incorporating 7-10 membered rings. For example, **147** were obtained in good yield utilizing sequential Cu-catalyzed coupling of a β-lactam with bromo- or iodo-aryl amine **145**, intramolecular attack of the amino group, and ring expansion (**145→147**) (Scheme 36). Acetic acid was found to be a superior catalyst for the ring expansion.



Scheme 36

Recently, a palladium promoted synthesis of dihydroazaphenanthrene fused medium to large ring heterocycles **149** was developed by Zhu and co-workers[57] involving aryl-aryl bond coupling from linear amide scaffold **148** (Scheme 37).



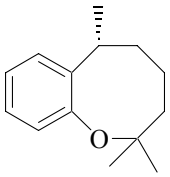
Scheme 37

4. BENZOFUSED MEDIUM RING OXYGEN HETEROCYCLES

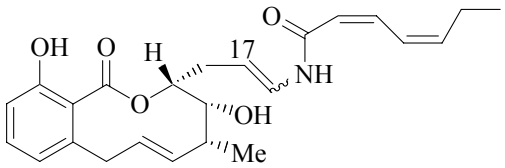
(a) Important structural types

A large number of natural products endowed with diverse biological activities are found to incorporate oxygen heterocycles of varying ring sizes, linearly fused with aromatic moiety (Figure 4). Recent discoveries of some selected systems include heliannuols A-L[58a-b] belonging to a new group of phenolic allelochemicals, these were isolated from the cultivated sunflowers *Helianthus annuus* which exhibit their activity against dicotyledon plant species.[58b] The significant bio-activity and the hitherto unknown benzofused seven- and eight-membered cyclic ether skeleta enshrined in their structural network made them attractive synthetic targets. Very recently, the structures of heliannuols G and H were revised to incorporate dihydrobenzofuran ring[58c] instead of eight-membered benzannulated ether ring. The analogous eight-membered benzannulated ether helianane (**150**)[58d] has been isolated from marine sponge. Novel twelve-membered cyclic lactones salicylihalamides A and B (**151**, **152**) were reported by Boyd *et al.*[59] as

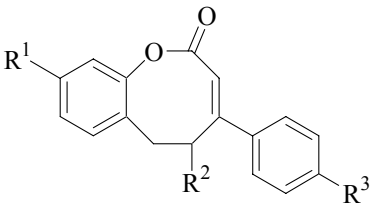
novel cytotoxic macrolides possessing growth inhibitory activities against cultured human tumor cell. Puerosides A and B (**153**, **154**), natural glycosides bearing benzoxocine ring framework and isolated from the roots of *Pueraria lobata*, constitute one of the most important oriental drugs.[60a] Penicillides (**155**, **156**), metabolites of the fungus *Penicillium*, were found to be root-growth stimulant;[60b] their analogue dehydroisopenicillide **157** was isolated from another fungus, *Talaromyces derxi*, cultivated on rice.[60c] These products (**150**-**157**) incorporate benzannulated oxo or dioxocinone ring skeleton. The fungal metabolite pterulinic acid (**158** and **159**) having monochlorinated 2,3-dihydro-1-benzoxepene ring, existing as a mixture of geometric isomers was isolated from the fermentation broth of a *Pterula* species[61a] and acts as an antitumor agent.[61b]



helianane (**150**)

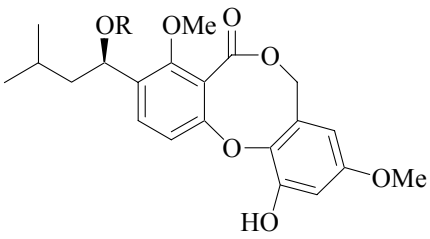


salicylihalamide A(**151**) 17-E
salicylihalamide B(**152**) 17-Z

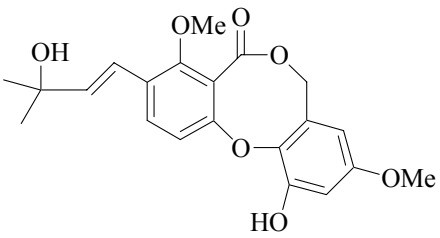


R^1 = OH; R^2 = α-L-rhamno-pyranosyl-(1→6)-β-glucopyranosyloxy
R^3 = OH
pueroside A (**153**)

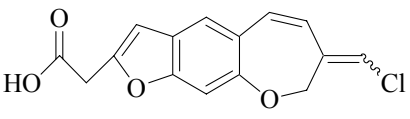
R^1 = OMe;
R^2 = R^3 = β-D-glucopyranosyloxy
pueroside B (**154**)



R = H, penicillide A (**155**)
R = Ac, penicillide B (**156**)



dehydroisopenicillide (**157**)



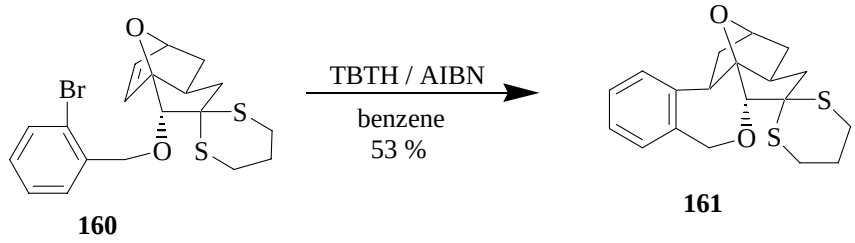
Z-pterulinic acid (**158**)
E-pterulinic acid (**159**)

Figure 4

(b) Synthetic approaches

A few selected synthetic approaches are described here for medium ring benzofused oxacycles incorporating seven- to ten-membered rings.

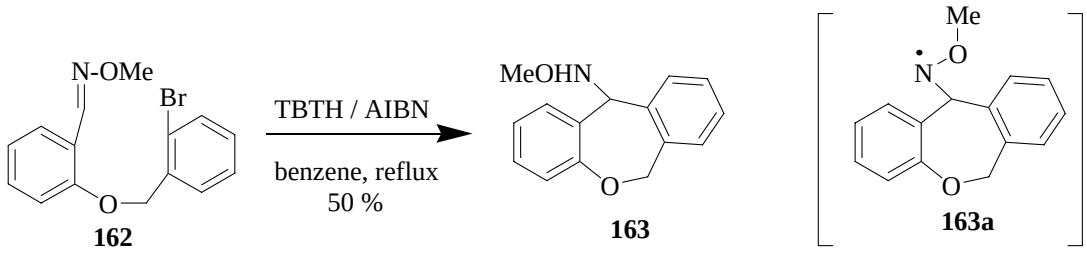
(i) Radical approach: Organo-tinhydride mediated intramolecular free radical cyclization has received enhanced prominence in organic synthesis, particularly for oxacyclic rings. Five- and six-membered ring formation is facile in the aryl-/alkyl- radical mediated cyclization and the formation of the ring is known to proceed via *exo*-cyclization.[62] But *endo*-mode of cyclization pathway is mostly favoured for medium or higher membered rings.[63] Synthesis of the highly substituted seven-membered ring ether **161** from the parent bromo-olefin **160** was reported by Ghosh and Hart [64] using regioselective 7-*exo*-aryl radical cyclization (Scheme 38). The seven-membered benzoxepine was formed with complete stereocontrol in the cyclization process.



160 **161**

Scheme 38

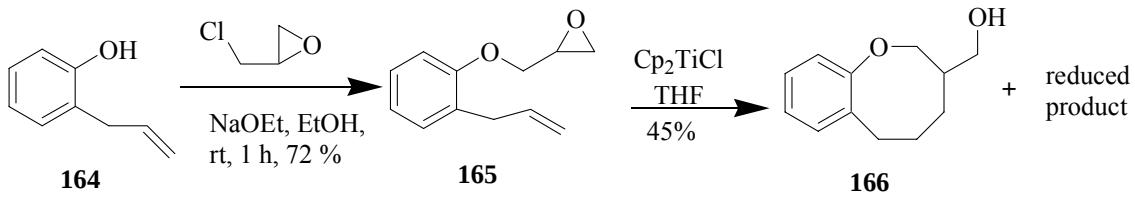
Jenkins and co-workers[65] explored aryl radical addition to the oxime ether **162**, to synthesize seven-membered oxacycles. The radical was generated by TBTH in the presence of AIBN and cyclized to afford the lower membered ring system, dibenzofused oxepine **163**, along with the reduced product (Scheme 39). The phenomenon was explained by the stabilizing effect on the aminyl radical **163a** by the lone pair of electrons on the oxime ether.



162 **163** **163a**

Scheme 39

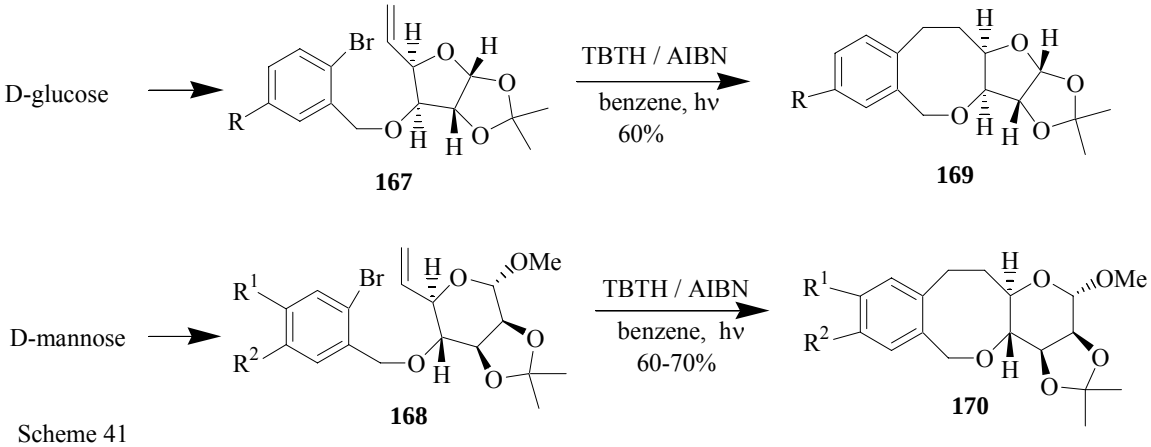
A titanocene (III) chloride (Cp_2TiCl) mediated 8-*endo*- radical cyclization towards the synthesis of eight-membered cyclic ether **166** from the epoxide **165** (obtained in a single step using 2-allylphenol **164** and epichlorohydrine), in moderate yield along with the reduced product (9-11%) and other unidentified materials was reported by Mandal and Roy[66] (Scheme 40).



164 **165** **166**

Scheme 40

Free radical cyclizations to a carbohydrate-derived scaffold to give medium sized rings in chiral form were relatively uncommon. Studies in this laboratory established that the reactions shown in Scheme 41 using carbohydrates as chiral precursors take place in good yield, affording enantiopure eight-membered benzoethers **169** and **170** [67a-b] from the respective bromo-olefins **167** and **168**. Formation of the *trans*-ring junction using a furanose sugar derivative is much less efficient.[67c]

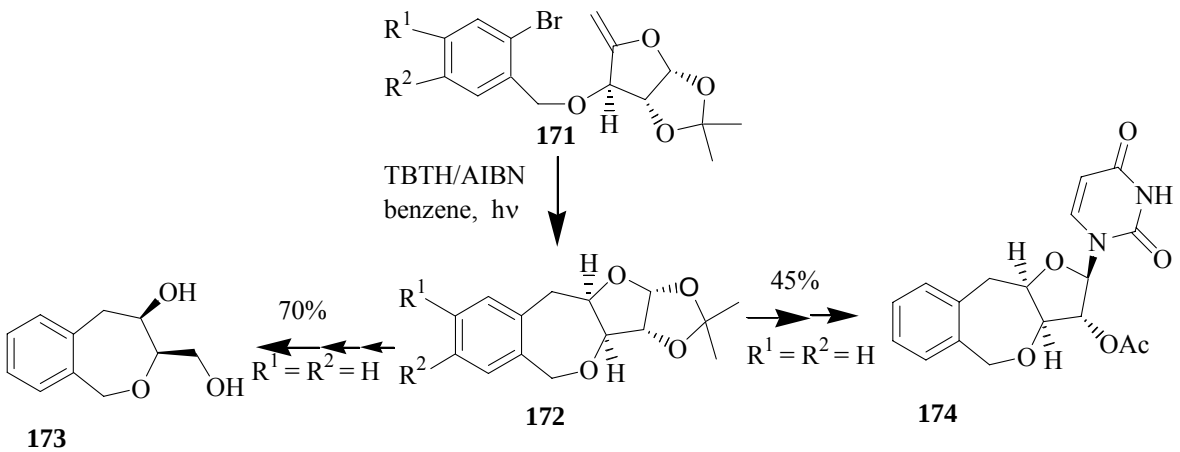


167 **169**

168 **170**

Scheme 41

Subsequently we reported the successful preparation of the furobenzoxepine derivatives **172**, obtained from the intramolecular radical cyclization of *exo*-furanose derivatives **171**. **172** is a potential synthetic intermediate and was transformed to the chiral benzannulated oxepine **173** and the tricyclic nucleoside analogue **174** (Scheme 42). [67d]

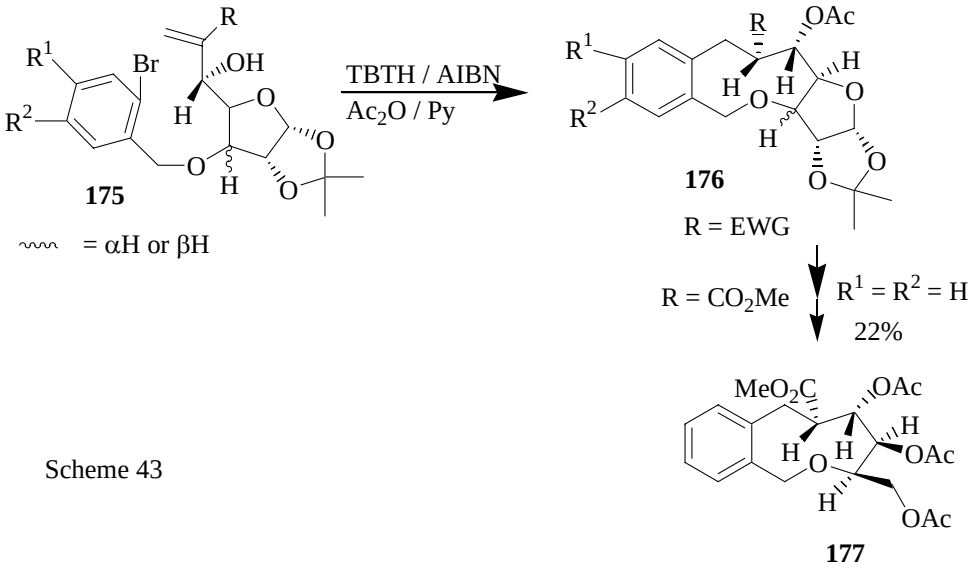


171

173 **172** **174**

Scheme 42

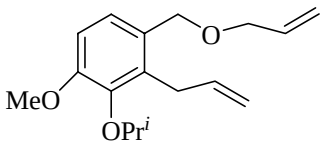
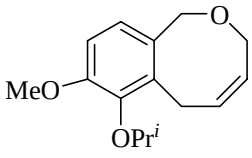
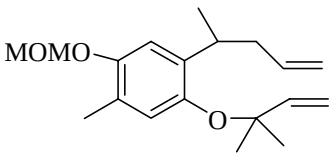
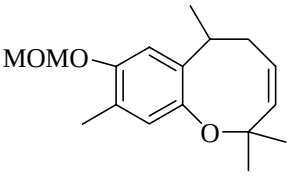
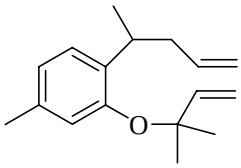
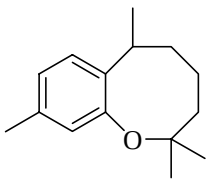
Recently, we have reported a straightforward and an efficient synthetic route to chiral benzannulated nine-membered oxygen heterocycles **176**[67e] (Scheme 43) using sequential Baylis-Hillman reaction and radical cyclization on appropiate furanose derivatives (**175**→**177**).

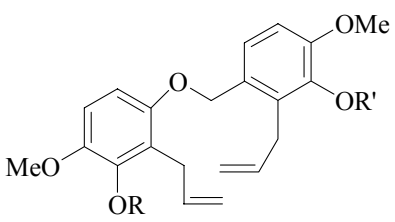


Scheme 43

(ii) Ring closing metathesis: Ring closing metathesis approach with ruthenium catalyst has been utilized as a key step for the synthesis of various benzofused medium ring heterocycles (**184-186**, **188**), helianane (**150**) and heliannuols (**187**) from the respective dienes (**178-183**). Few selected examples[31,68a-d] are described in Table 2.

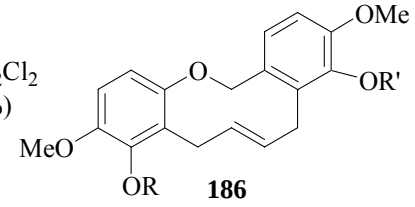
Table 2 Cyclization *via* ring closing metathesis

Entry	Substrate	Reagents (yield)	Product	Refs
1.	 **178**	**39** benzene (52%)	 **184**	31
2.	 **179**	**39** CH_2Cl_2 (88%)	 **185**	68a
3.	 **180**	1. **38** / CH_2Cl_2 2. H_2 / Pd 30%	 **(150)**	68b

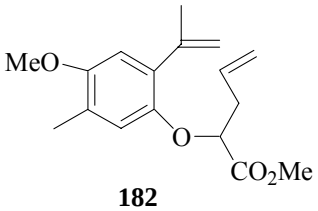
4. 

181

38 / CH_2Cl_2
(41-50%)



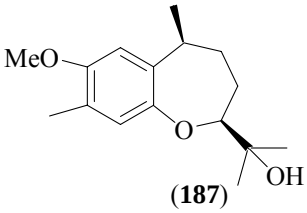
186 68c

5. 

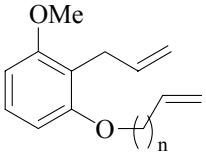
182

1. **39** / CH_2Cl_2
2. H_2 / Pd
3. MeMgI

overall yield 90%

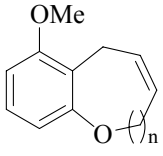


(**187**) 68d

6. 

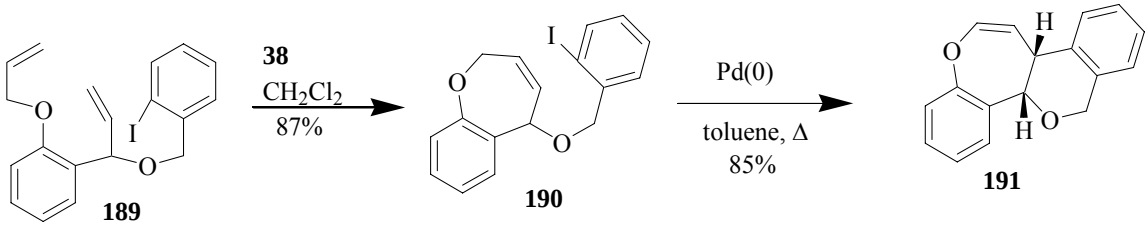
n = 3, 6, 9
183

38 / CH_2Cl_2
n = 3 (45%)
n = 6 (30%)
n = 9 (20%)



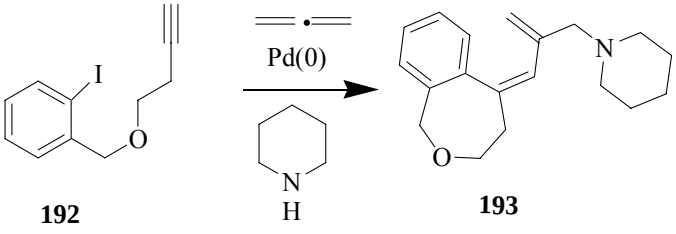
188 68b

A sequential ring closing metathesis and intramolecular Heck reaction was developed by Grigg *et al.*[69] with comparable yield in each step (**189**→**191**) (Scheme 44). The sequence can be carried out as one-pot process.



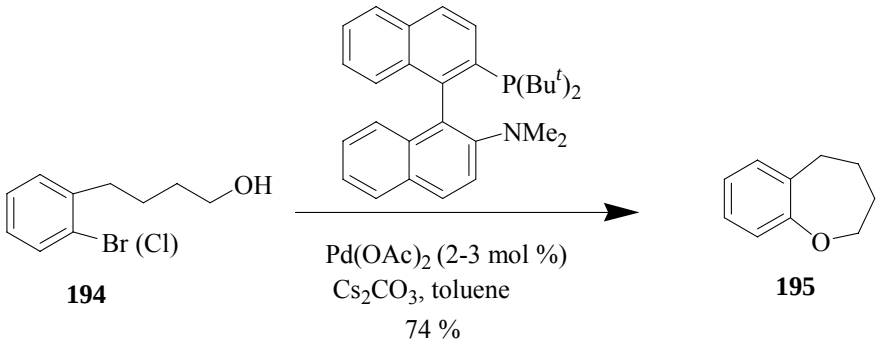
Scheme 44

(iii) *Intramolecular palladium promoted reactions:* Pd(0) catalyzed intramolecular cyclization of aryl iodides on to a proximate alkyne **192** followed by allene insertion and capture of the resulting π-complex by secondary amine afforded the benzannulated seven-membered ether **193** in substantial yield (Scheme 45). However the formation of eight-membered rings is less efficient.[70]



Scheme 45

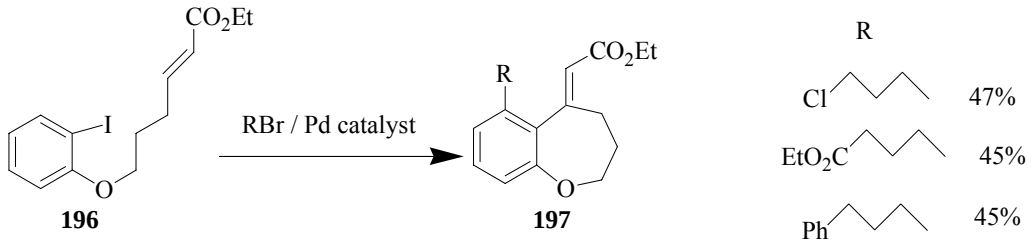
Buchwald and co-workers[71] synthesized a large number of oxygen heterocycles, *e.g.* **195** using palladium catalyzed intramolecular etherification of aryl halide **194** in the presence of di-*tert*-butylphosphinobiaryl as ligand. The reaction proceeds under mild condition using a weak base such as Cs_2CO_3 or K_3PO_4 (Scheme 46).



194 **195**

Scheme 46

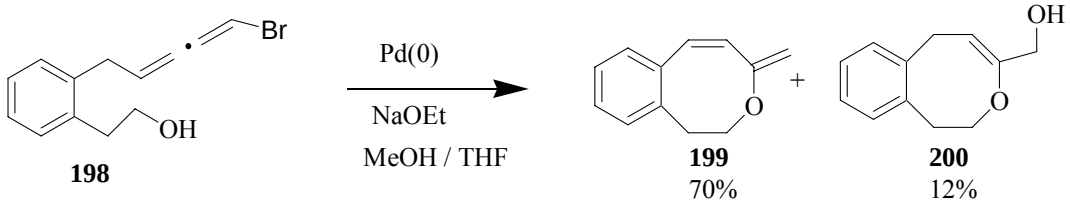
Lautens and co-workers[72] reported the synthesis of various alkylidene benzoxepines *via* domino palladium catalyzed *ortho*-alkylation / intramolecular Heck reaction (Scheme 47). Under the optimized condition [$Pd(OAc)_2$ (10 mol%), P(2-furyl)$_3$ (20 mol%), norbornane (4 eq), Cs_2CO_3 (2 eq) in CH_3CN at 80 °C], aryl iodides **196** bearing an oxygen-tethered Heck acceptor coupled with alkyl bromides (5 eq) to generate seven membered annulated oxacycles **197**.



196 **197**

Scheme 47

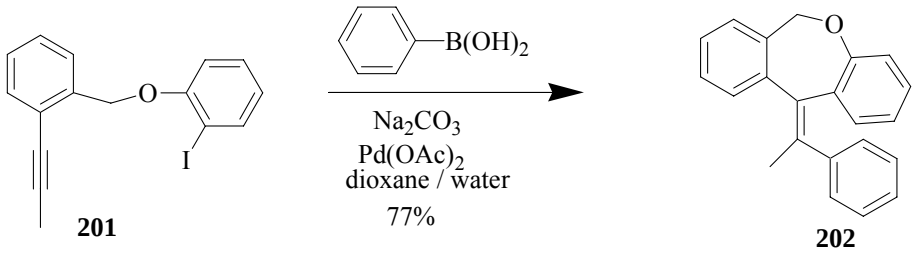
Palladium catalyzed reaction of bromoallenes **198** afforded eight-membered benzannulated oxacycles **199** in good yield along with minor alcohol **200** (Scheme 48).[73]



198 **199** 70% **200** 12%

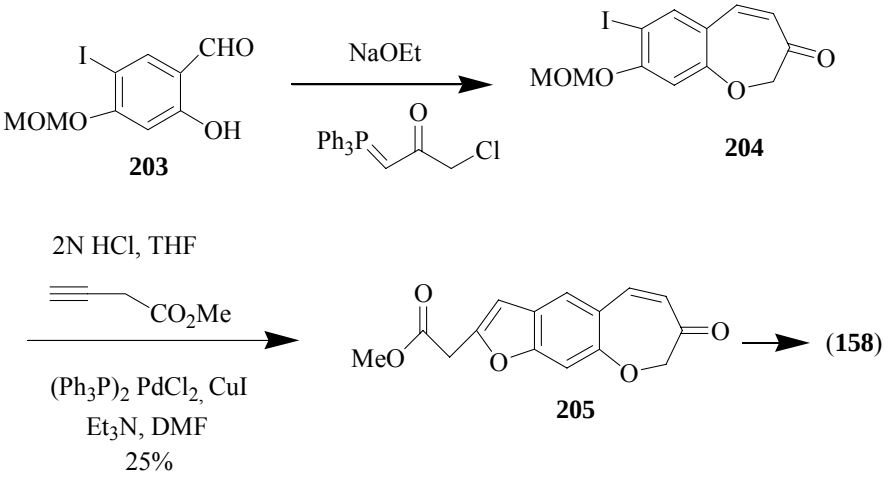
Scheme 48

Palladium-catalyzed intramolecular alkyne carbometalation reaction[74] was developed for the preparation of tetrasubstituted exocyclic alkene **202** from alkyne **201** with high stereo- and regio-control (Scheme 49).



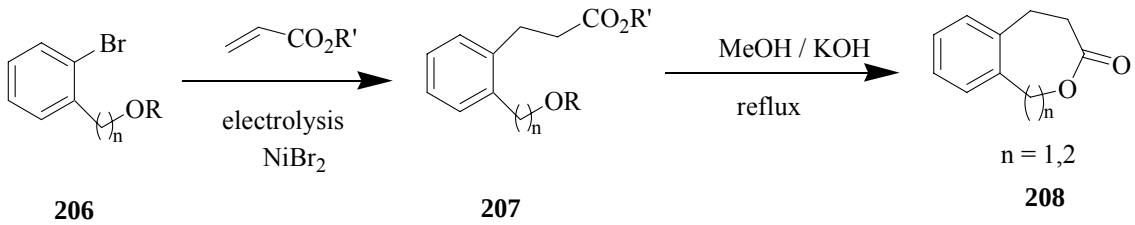
Scheme 49

1-Benzoxepine ring skeleton **204**, the key architectural framework of the antagonist pterulinic acid (**158**), was smoothly prepared from a salicylaldehyde derivative **203** and a phosphorane *via* tandem S_N2 / Wittig reaction in 53% yield (Scheme 50).[75] Compound **204** was smoothly converted to a tricyclic pterulinic acid analogue **205** *via* palladium-catalyzed heteroannulation reaction.



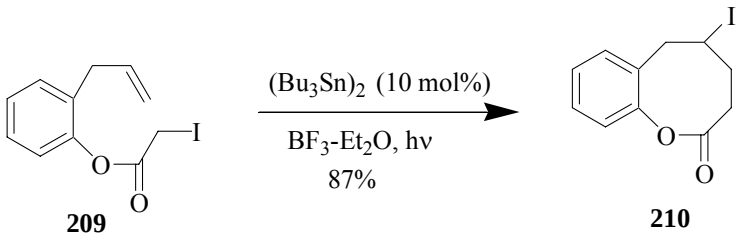
Scheme 50

(iv) Benzofused medium ring lactones: Nédélec and co-workers[76] reported the synthesis of benzannulated medium ring lactones **208** from ester **207**, itself obtained by $NiBr_2$ catalyzed electrochemical arylation of activated olefins and substituted aryl bromides **206** (Scheme 51).



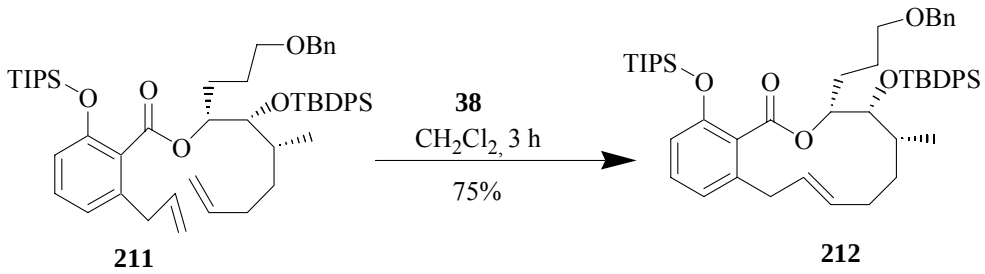
Scheme 51

Bis(tributyltin)-initiated atom transfer photostimulation of benzannulated 4-phenyl iodoacetate **209** with BF_3-Et_2O at room temperature afforded the corresponding benzoxocinone **210** (Scheme 52).[77]



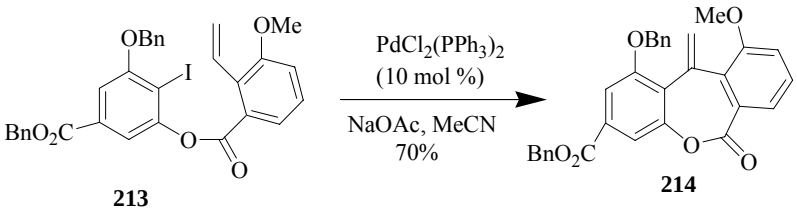
Scheme 52

The key step for the total synthesis of salicylihalamides, the cytotoxic twelve-membered lactones, has been accomplished utilizing ring closing metathesis strategy (Scheme 53).[78] The selectively favored *E*-olefin **212** was obtained in the ratio 9:1 with minor Z-isomer from the respective diene **211**.



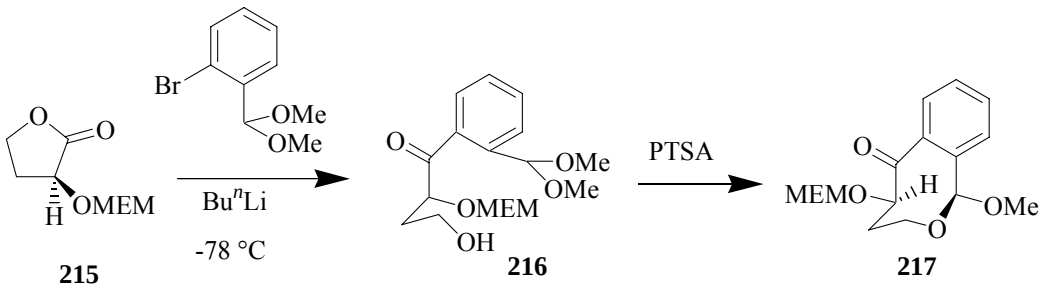
Scheme 53

Aryl iodide **213** was employed in the intramolecular Heck coupling of two functionalized aryl subunits affording regioselectively a biaryl seven-membered lactone with the *exo*-cyclic alkenes **214** as the major component. This intramolecular *exo*-cyclization reaction was used as a key step for the construction of the benzophenone fragment of biologically active balanol (Scheme 54).[79]



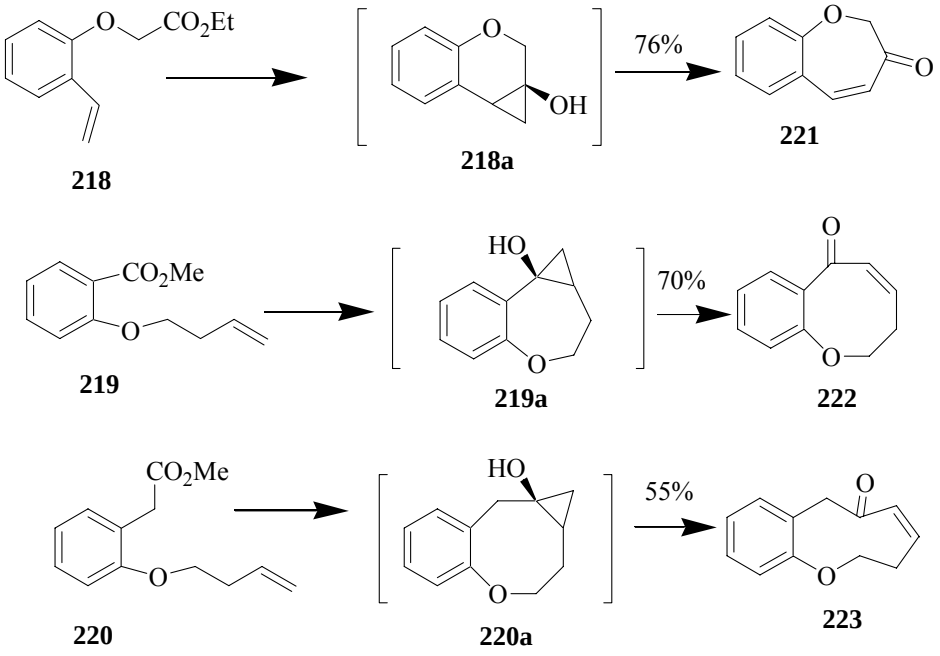
Scheme 54

(v) Benzoxocinone derivatives: A two-step chiron approach was adopted for the synthesis of the benzoxocinone derivative **217** from the *S*-malic acid derivative **215** through the intermediate, **216** (Scheme 55).[80]



Scheme 55

For the synthesis of different oxacycloalkenones **221**-**223** bearing seven-, eight- and nine-membered rings, the synthetic protocol consists of an intramolecular Kulinkovich cyclopropanation on oxa-ω-alkenoic esters **218**-**220**, followed by oxidative cleavage of the cyclopropanol moiety (**218a**-**220a**) with ferric chloride, and subsequent base induced dehydrochlorination (Scheme 56).[81]

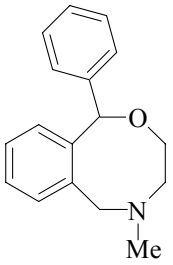


Scheme 56

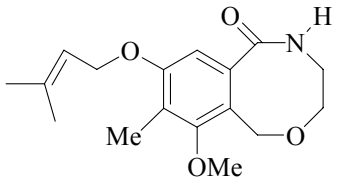
5. BENZOFUSED HETEROCYCLES WITH OXYGEN AND NITROGEN

(a) Important structural types

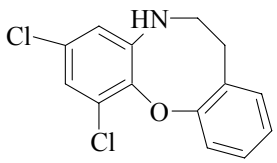
Benzoxazocines or benzoxazepines are often present in pharmaceutical agents as core structural motifs. Numerous important therapeutic agents, including those with antiarrhythmic, angiogenic, antispasmodic or CNS activity contain these core structures. Recent discoveries of some selected systems (Figure 5) include Nefopam (NEF) (**224**) (potent analgesic),[82] porritoxin (**225**) (phytotoxin produced by the fungus *Alternaria porri*),[83] dibenzo[*b*,*g*]1,4- and 1,5-oxazocines **226**, **227** (CNS active and also used in pain and inflammation)[84,85] and benzoxazepine-3-acetic acid derivative **228** (potent inhibitor on squalene synthesis).[86]



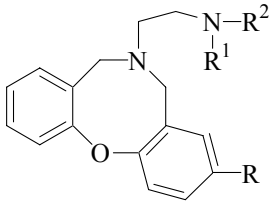
nefopum (NEF) (**224**)



porritoxin (**225**)



226



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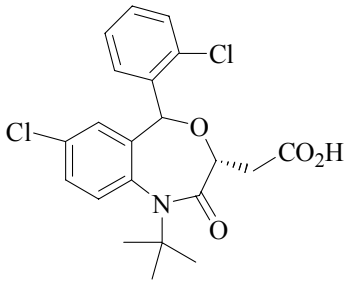
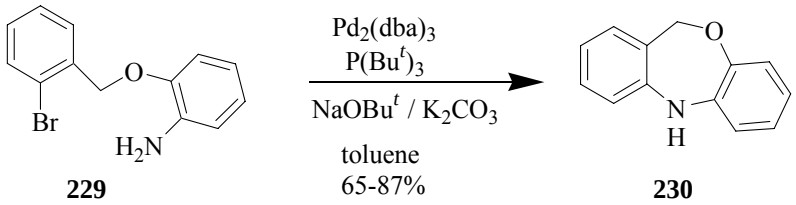


228

Figure 5

(b) Synthetic approach

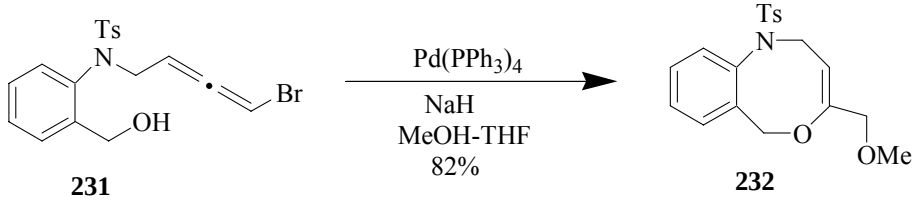
Rogers and co-workers[87] reported an improved palladium catalyzed aryl amination reaction for the synthesis of dibenzoxazepine **230** in good yield from aryl amine tethered bromoarylether **229** using $P(Bu^t)_3$ as ligands in the presence of bases (Scheme 57).



229 **230**

Scheme 57

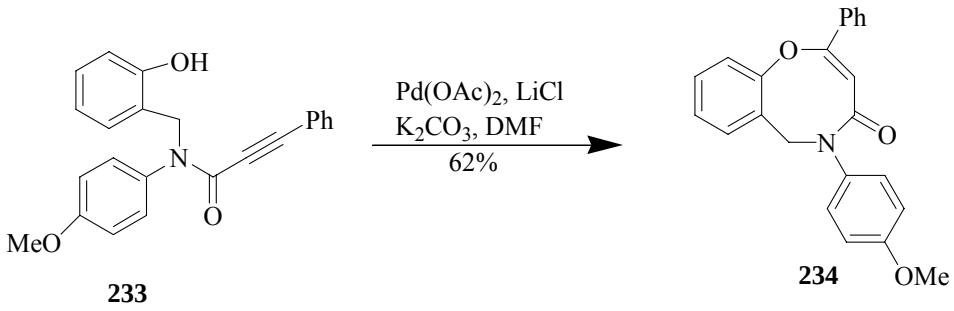
Recently, Ohno *et al* [88] achieved the construction of the benzoxazocine ring in **232** based on the Pd(0) catalyzed cyclization of bromoallenes **231** bearing a nucleophilic functionality (Scheme 58).



231 **232**

Scheme 58

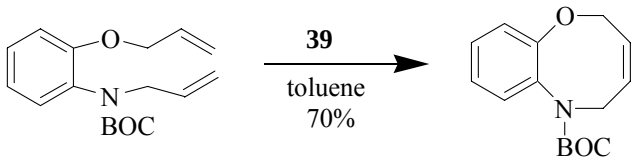
N-Aryl-*N*-(2-hydroxybenzyl)-3-phenylpropynamide **233** afforded the eight-membered framework 5-(4-substituted-aryl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]-oxazocin-4-one **234** in the presence of a palladium catalyst and base (Scheme 59) in moderate yield.[89]



233 **234**

Scheme 59

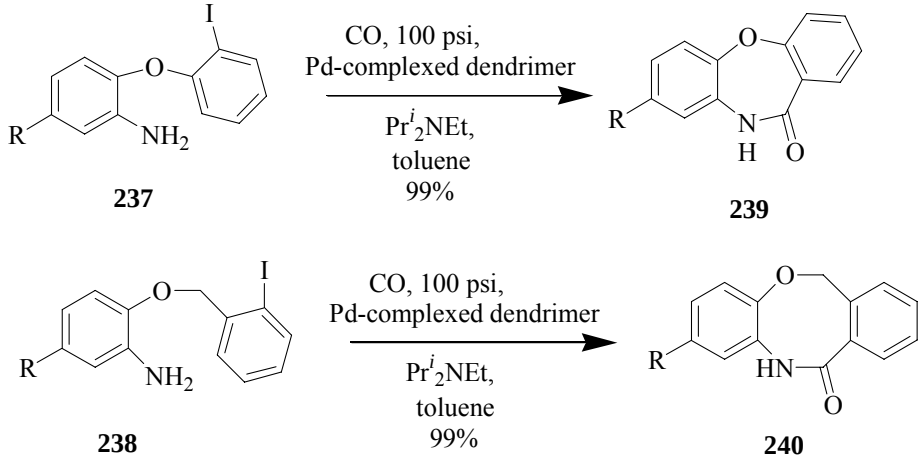
A ring-closing metathesis strategy was developed by van Otterlo *et al.*[55] to afford Boc-protected benzoxazocines **236** in 70% yield (Scheme 60) from dienes **235** using second generation Grubbs' catalyst **39**.



235 **236**

Scheme 60

Lu and Alper[90] developed a palladium complexed dendrimer supported on silica, and used it on 2-(2-iodophenyloxy or benzyloxy)anilines **237** and **238** for intramolecular carbonylation reaction affording excellent yield of dibenzoxazepinones **239** and oxazocinones **240** (Scheme 61). They applied the same methodology for the synthesis of dibenzothiazocinone derivatives and dibenzodiazepinone analogues.

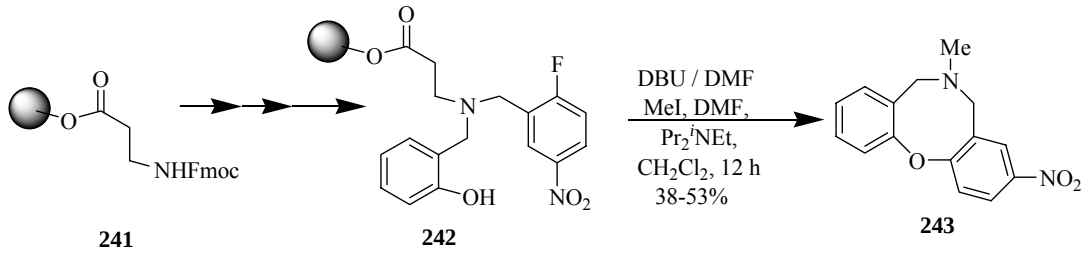


237 **239**

238 **240**

Scheme 61

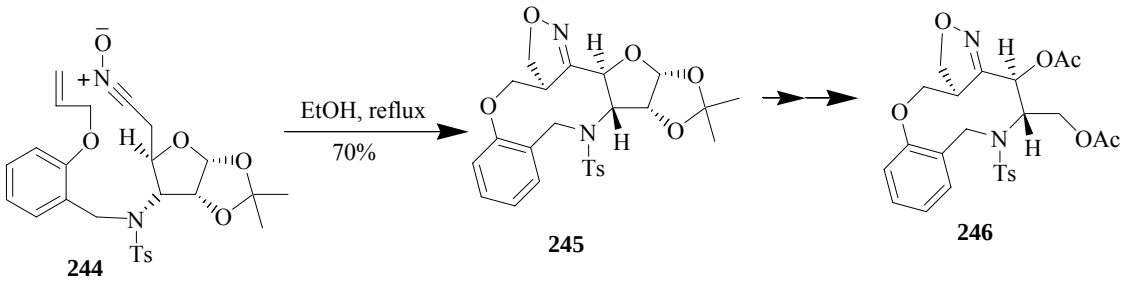
Ouyang and Kiselyov[85] have reported an efficient synthesis of dibenz[*b,g*]1,5-oxazocines **243** on β-alanine immobilized Wang resin. β-Alanine resin **241** was selected as the solid support for this synthesis. The procedure is based on the intramolecular nucleophilic aromatic substitution of fluorine atom of 2-fluoro-5-nitrobenzaldehyde derivative **242** with the OH function of the immobilized phenols (Scheme 62).



241 **242** **243**

Scheme 62

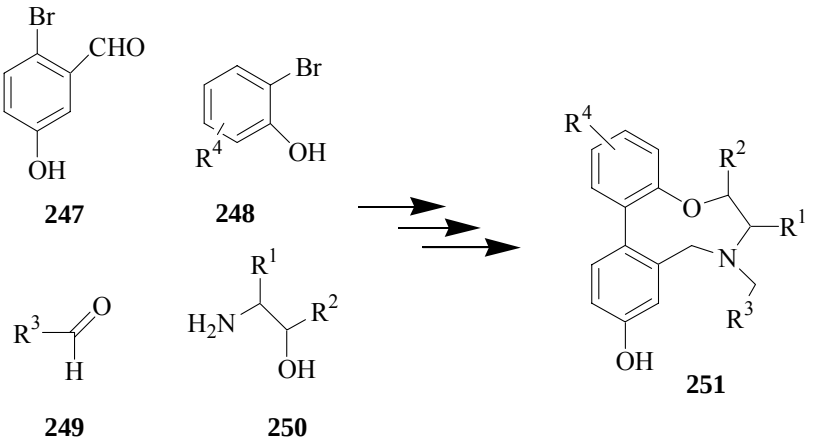
Bhattacharjya and co-workers[91] carried out the synthesis of optically active ten-membered benzannulated heterocycles fused to isoxazoline rings **246** in a highly stereo- and regio-selective manner by intramolecular nitrile oxide cycloaddition of tethered *O*-allyl carbohydrate derivatives **244** *via* the sugar annulated intermediate **245** (Scheme 63).



244 **245** **246**

Scheme 63

A parallel synthesis of a library of nine-membered, biaryl-based heterocyclic rings **251** has been accomplished on polystyrene macrobeads utilizing the substrates **247**-**250**. Dimeric medium rings were shown to be accessible *via* a regio- and stereoselective double cyclization (Scheme 64).[92]

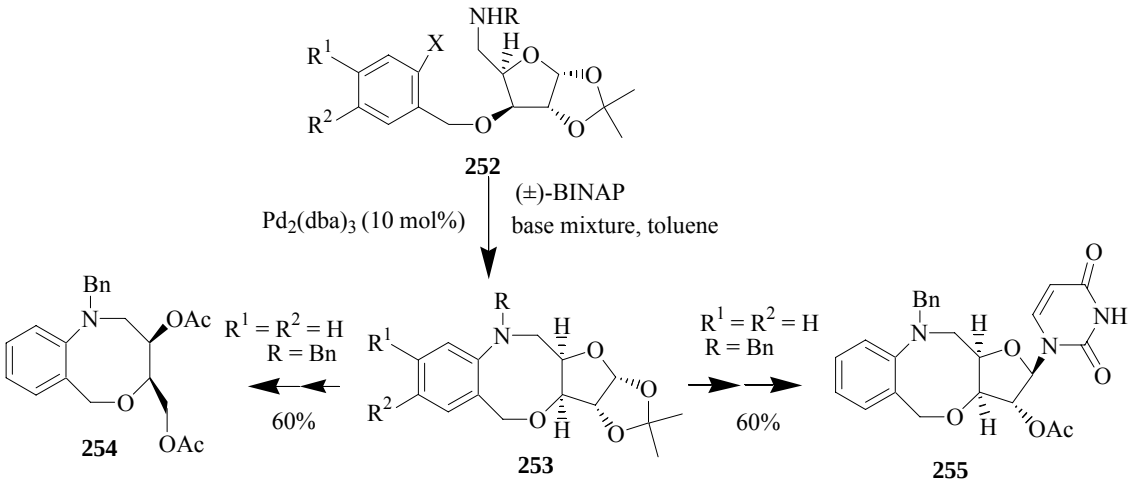


247 **248** **249** **250** **251**

Scheme 64

Pd-catalyzed intramolecular arylamination of sugar derivatives has been accomplished in our laboratory by using bulky biaryl phosphine ligands. An application of this methodology to a variety of D-glucose derived substrates **252** led to the synthesis of enantiopure benzoxazocines **254** and conformationally restricted tricyclic nucleoside **255**. Evaluation of ligands and palladium sources showed that the best condition for the

reaction was $Pd_2(dba)_3$ as the palladium source, (±)-BINAP as the ligand, $KOBu^t$-K_2CO_3 mixture as the base and toluene as the solvent. The tricyclic product **253** could subsequently be transformed to optically active benzoxazocine derivative **254** and nucleoside **255** (Scheme 65).[93]



Scheme 65

6. BENZANNULATED HETEROCYCLES WITH SULFUR ATOM

(a) Important structural types

Medium ring heterocycles incorporating sulfur atoms with or without nitrogen have important biological properties. Benzothiazepins **256** behave as angiotensin converting enzyme inhibitor and a calcium channel blocker, and also acts as anticancer agent.[94] Analogues of dihydro[*b*,*f*]thiocine **257** can be used as antiepileptic drug[95]and pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTD) **258** are sulfonamide analogues of the antitumor antibiotic pyrrolobenzodiazepines (PBDs)[96] (Figure 6).

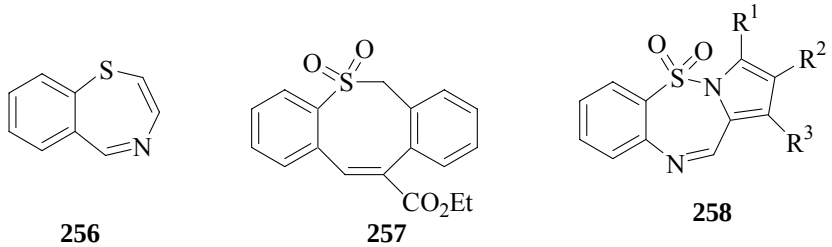
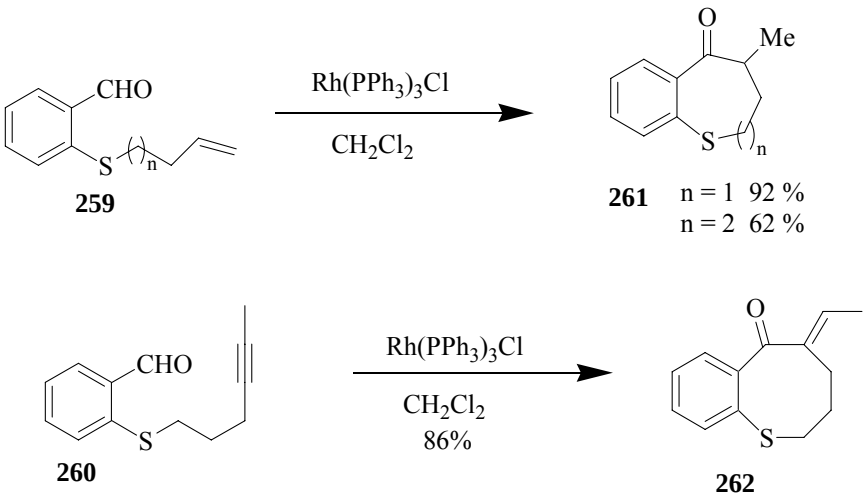


Figure 6

(b) Synthetic approaches

Benzannulated medium ring thiolactones (**261**, **262**) were prepared in high yields from ω-alkenals **259** and alkynals **260**, utilizing novel chelation assisted intramolecular hydroacylation catalyzed by rhodium (Scheme 65).[97]

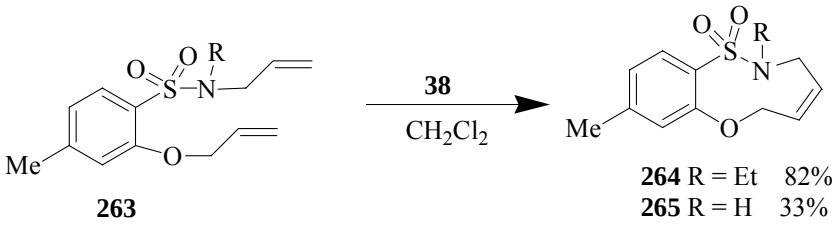


259 **261** n = 1 92 %
n = 2 62 %

260 **262**

Scheme 66

Lane and Snieckus[32] succeeded in the synthesis of 2-benzoxothiazonines **264**, **265** using ortho-metalation-Grubbs' metathesis tactics (Scheme 67) from the respective dienes **263**. They have prepared 15-membered sulfonamide-bearing heterocycles also utilizing similar approach.

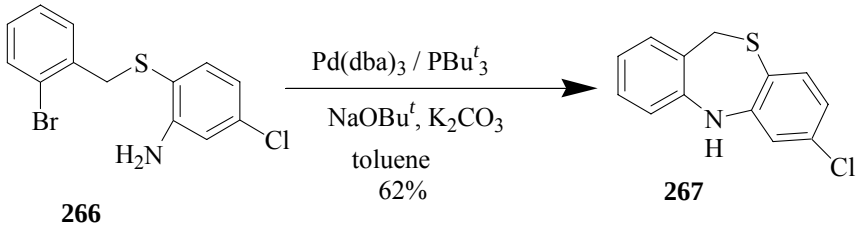


263

264 R = Et 82%
265 R = H 33%

Scheme 67

Margolis *et al.*[87] disclosed an improved synthesis of seven-membered thiazepine ring system **267** from bromo aniline **266** utilizing palladium catalyzed aryl amination reaction (Scheme 68). This reaction has been shown to be effective with a variety of substrates.

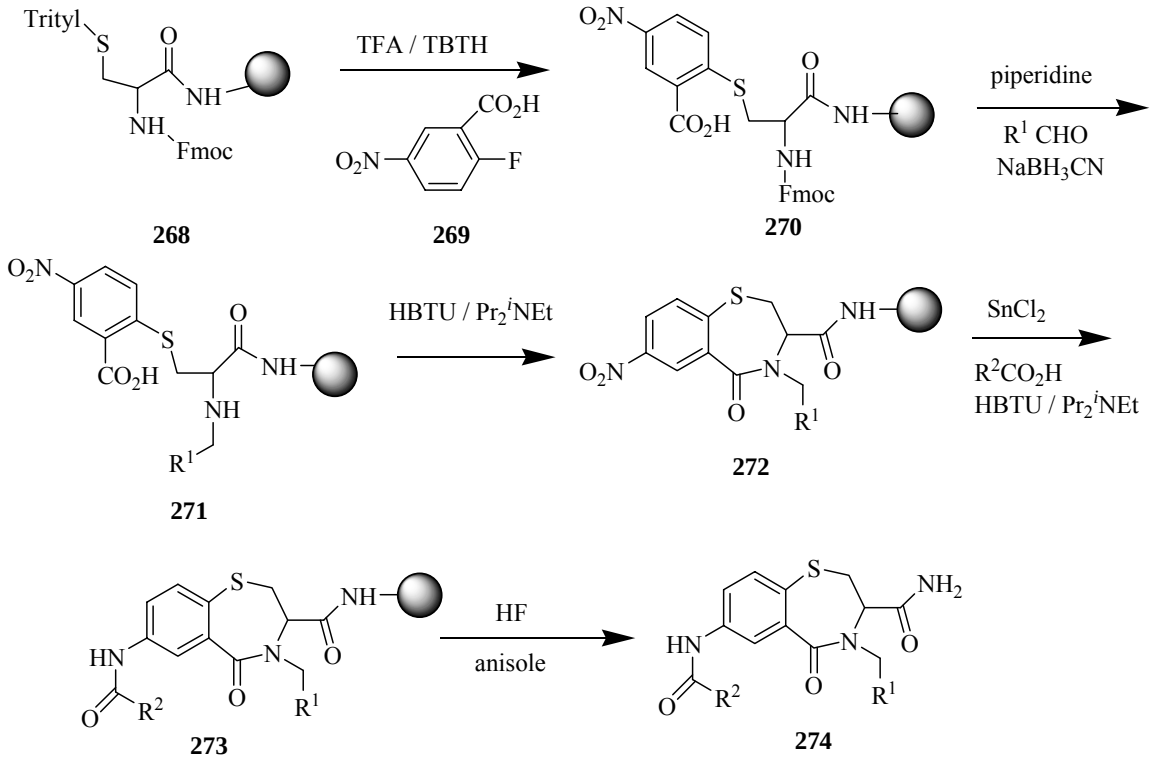


266 **267**

Scheme 68

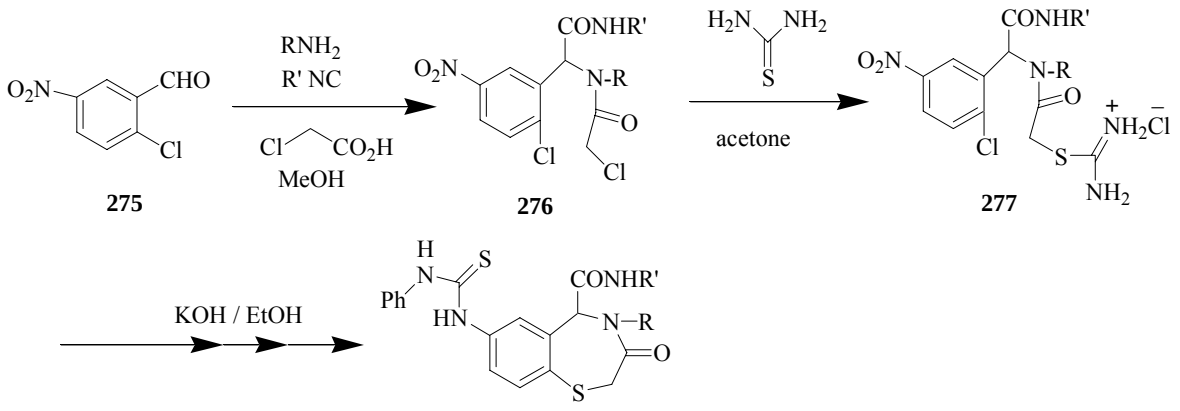
Nefzi *et al.*[94] reported a combinatorial synthesis of 1,4-benzothiazepin-5-one derivatives. Cleavage of the trityl group from the resin protected *N*-α-Fmoc-S-trityl-L-cystein **268** and coupling with 2-fluoro-5-nitrobenzoic acid **269**, yielded the intermediate **270**, which on removal of the Fmoc group, alkylation and treatment with *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and diisopropylethylamine (DIEA) yielded the nitrolactam (**270**→**272**). Reduction with $SnCl_2$ and

coupling with an acid using HBTU/DIEA led to the resin bound lactam-amide **273**, which could be cleaved from the resin using HF-anisole to afford the 1,4-benzothiazepin-5-one scaffold **274** (Scheme 69).



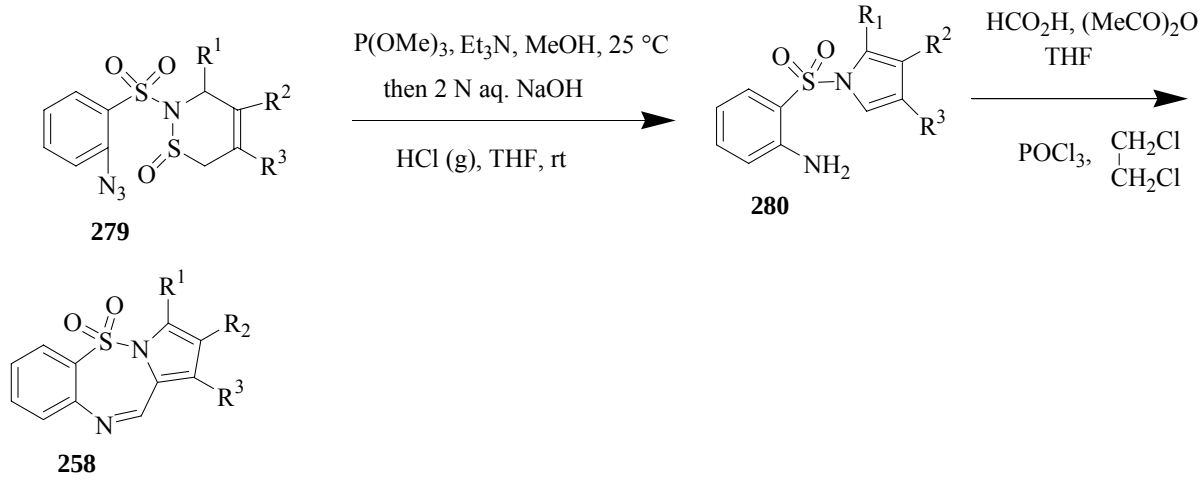
Scheme 69

Marcaccini and co-workers[98] reported the preparation of a series of 4,5-dihydro-benzothiazepin -3(2*H*)-ones **278**, used for the treatment for cardiovascular diseases,[99] by exploiting the Ugi four component condensation reaction. 2-Chloro-5-nitrobenzaldehyde **275** was smoothly converted to the adduct **276** by 4-component Ugi reaction. The adduct **276** was converted quantitatively to the isothiouronium salt **277**, followed by subsequent cyclization, reduction of the nitro-group and reaction with phenyl isothiocyanate afforded **278** in excellent yield (Scheme 70).



Scheme 70

A concise synthetic route to the antitumor antibiotics pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTD) **258** has been reported.[100] It involves an one pot conversion of 2-(*ortho*-azidobenzenesulfonyl)-1,2-thiazen-1-oxide **279** into 1-(*ortho*-aminobenzenesulfonyl)pyrrols **280** followed by formylation and Bischler-Napieralski ring closure (Scheme 71).



Scheme 71

7. CONCLUSION

Benzannulated medium ring heterocycles are of great importance in medicinal chemistry. The impressive number of publications that appeared during the last few years bears ample testimony to the enormous interest in this field. Although much fascinating chemistry in this area is already known, further exploration will be made for developing more enantioselective methodologies using chiral ligands or catalyst, or even chiral auxiliary. It is hoped that the use of such heterocyclic scaffolds for the development of drugs and in total synthesis of biologically active complex natural products will continue. In this context, this review will help researchers interested in the field of the chemistry of medium ring heterocycles.

ACKNOWLEDGEMENTS

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