Tetrahedron 67 (2011) 8959–9061

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 954

Applications of allylamines for the syntheses of aza-heterocycles☆

Somnath Nag †, Sanjay Batra *

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, PO Box 173, Lucknow 226001, UP, India

ARTICLE INFO

Article history:
Received 25 July 2011
Available online 3 August 2011

This article is dedicated to one of our beloved colleagues, Dr. Vinod Bhakuni who left for his heavenly abode on 15th July, 2011

Keywords:
Allylamine
Cycloaddition
Nucleophilic reaction
Free radical reaction
Aza-heterocycles

Contents

Abbreviations: ACCN, 1,1′-azo-bis-cyclohexane-1-carbonitrile; AIBN, 2,2′-azobisisobutyronitrile; 9-BBN, 9-borabicyclo [3.3.1]nonane; BHT, 2,6-di-*tertiary*-butyl-4-methyl phenol; BINAP, 2,20-ais(diphenylphosphanyl)-1,10-binaphthyl; BOP, benzotriazole-1-yl-oxy-tris-(dimethylamino) phosphonium hexafluorophosphate; BTH, *tert*-butyl-4-methyl phenol; CBI, cycloprabenzindol-4-one; CFL, compact fluorescent light; Cp, cyclopentadienyl; Cp*, 1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl; cod, 1,5-cyclooctadiene; Cy_3P, tricyclohexyl phosphine; dba, *trans*,*trans*-dibenzylideneacetone; DAB1, 1,4-dideoxy-1,4-imino-D-arabinitol; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; DEAD, diethyl azodicarboxylate; DIA, diisopropylamine; DIPEA, diisopropylethylamine; Dipp, 2,6-diisopropylphenyl; DLP, dilauroyl peroxide; DMAD, dimethyl acetylenedicarboxylate; 1,3-DMBA, 1,3-dimethylbarbituric acid; DMDO, dimethyldioxirane; DME, 1,2-dimethoxyethane; 2,2-DMP, 2,2-dimethoxy propane; 1,4-DMP, 1,4-dimethyl piperazine; DMS, dimethyl sulfate; DPPA, diphenylphosphoryl azide; dppp, 1,3-bis(diphenylphosphino)propane; EDCI, *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide; EDDA, ethylenediamine diacetate; Fe(Pc), iron phthalocycnine; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl, uronium, hexafluorophosphate methanaminium; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol; HFIPA, 1,1,1,3,3,3-hexafluoroisopropyl acrylate; HOBt, 1-hydroxybenzotriazole; HQD, 3-hydroxy quinuclidine; H8-Binap, 2,2′-bis(diphenylphosphanyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl; IBX, *ortho*-iodoxybenzoic acid; IBCF, *iso*-butyl chloroformate; Ipr, 2,6-diisopropylbenzene; KHMDS, potassium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; MBH, Morita–Baylis–Hillman; Mbs, *p*-methoxybenzenesulfonyl; Menth, *para*-menthyl; MOM, methoxymethyl; NHC, *N*-heterocyclic carbene; Ns, nosyl, *o*-nitrobenzenesulfonyl; *o*-DCB, *ortho*-dichlorobenzene; on, overnight; Pfp, pentafluorophenyl; PhTMG, 2-phenyl-1,1,3,3-tetramethylguanidine; PIFA, phenyliodine-(III) bis(trifluoroacetate); PMB, *para*-methoxybenzoyl; PMP, *para*-methoxyphenyl; PPTS, pyridinium *p*-toluenesulfonate; PTC, phase transfer catalyst; *p*-TSA, *para*-toluene sulfonic acid; SES, 2-trimethylsilylethylsulfonyl; *t*-AmOH, *tertiary*-amyl alcohol; TBAF, tetrabutyl ammonium fluoride; TBATB, tetrabutyl ammonium tribromide; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TBTH, tributyltinhydride; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical; TFA, trifluoroacetic acid; TFEA, trifluoroethanol; TFP, tri-2-furylphosphane; TFE, 2,2,2-trifluoroethanol; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TPA, tripyridyl amine; TPAP, tetrapropylammonium perruthenate; TTMSS, tris(trimethylsilyl)silane; UHP, urea-hydrogen peroxide.

☆ CDRI Communication No. 8045.

* Corresponding author. Tel.: +91 522 2612411 18x4234, 4368; fax: + 91 522 2623405, 2623938; e-mail addresses: batra_san@yahoo.co.uk, s_batra@cdri.res.in (S. Batra).
† Present Address: Aurigene Discovery Technologies Limited, No-39/40, KIADB Industrial Area, Electronic City-Phase II, Hosur Road, Bangalore 560 100, Karnataka, India.

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.07.087

1. Introduction

Allylamine represents one of the elementary units in organic chemistry. Its ubiquitous presence in several natural products including gabaculine,[1] ocyzosymicine[2] and cytosinine[3] and its utility as a synthetic precursor to important structural motifs, such as α- and β-amino acids,[4] alkaloids,[5] carbohydrate derivatives[6] and other compounds[7] make it a scaffold of great synthetic value. In unsubstituted allylamine, the two functionalities, the nucleophilic amino group and the free alkene can ideally participate in addition reactions, condensation reactions, nucleophilic substitution reactions, radical reactions, cycloaddition reactions, cross-coupling reactions, cycloisomerizations and metathesis reactions to achieve a plethora of synthetic targets. Although strategies concerning the synthesis of allylamines were reviewed initially in 1983 and then in 1998,[8] there exists no concise assimilation of literature pertaining to the synthetic utility of allylamines.

Owing to our interest in studies related to the synthetic applications of the derivatives afforded via MBH chemistry, we have been involved in generating cyclic compounds especially aza-heterocycles from allylamines obtained from MBH adducts. During the course of our studies, we discovered that a wide variety of substituted or unsubstituted allylamines serve as precursors to a diverse range of aza-heterocycles. The lack of a review on this topic has motivated us to overview the literature showcasing this aspect of allylamines. A Scifinder search since 2005 using the keyword 'allylamine' produces more than 30,000 hits. In order to limit the size of the overview we decided to include articles appearing between January, 2006 and May, 2010 during the Scifinder search. During the course of the literature survey, we observed that the generation of aza-systems of various ring sizes from several allylamines employing ring-closing metathesis, cycloisomerisation, Pauson–Khand reactions[9] and metal-based oxidative cyclizations has been extensively employed using similar catalysts or identical reaction conditions (Fig. 1). Hence, these topics have been excluded from scope of the present review. Reactions where allyamines were used as the protecting group or were utilized for the synthesis of carbocycles have also been exempted. Moreover, allylamines where the nitrogen or the double bond is a part of a cyclic framework have been excluded. Further, this overview may not be considered to be exhaustive and includes only representative examples. The contents of the review are classified on the basis of type of chemical reaction or wherever necessary on the basis of the type of scaffold generated.

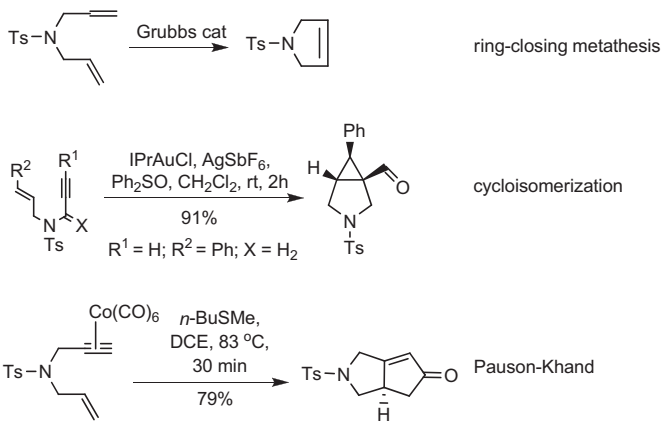


Fig. 1. Representations of ring-closing metathesis, cycloisomerisation and Pauson–Khand reactions, which have been excluded from this review.

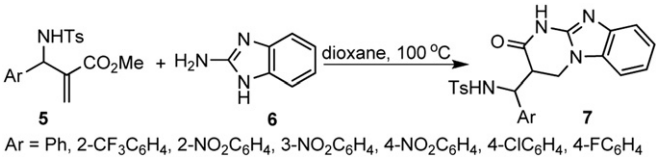
2. Nucleophilic addition onto alkenes or alkynes

The original double bond of the allylamine or one of the unsaturated chain attached with the allylamine acts as acceptor to an internal or external nucleophile for the formation of a cyclic framework. Such nucleophilic addition is facilitated either by the presence of an electron-withdrawing group on the unsaturated system or by a catalyst. Syntheses of different heterocycles employing this strategy are exemplified below.

2.1. Reactions involving *N*-nucleophiles

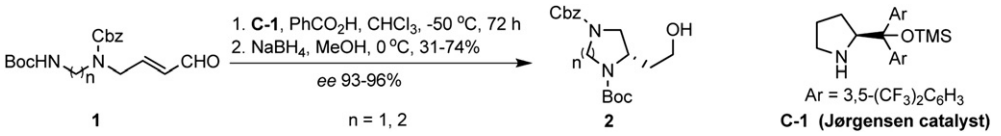
2.1.1. Intramolecular addition of N-nucleophiles onto activated alkenes. Fustero et al. reported organocatalyst-promoted intramolecular asymmetric aza-Michael reaction of allyl carbamate onto the double bond of the allylamine (**1**) activated by an aldehyde unit as an efficient tool to generate enantiopure imidazolidine and piperazine (**2**) (Scheme 1).[10] The strategy was extended for the synthesis of several piperidine-based alkaloids including (+)-sedamine, (+)-allosedamine and (+)-conine.

(**6**) via sequential Michael addition followed by intramolecular cyclization, as shown in Scheme 3.[12]



Scheme 3.

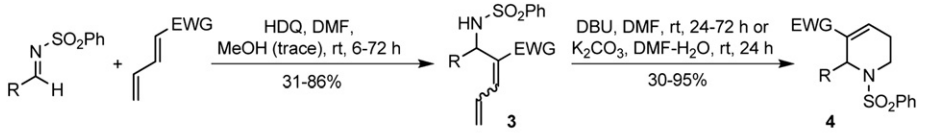
In another example related to this strategy Bandini et al. developed a new synthetic approach to 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones (**10**) via base-catalyzed intramolecular 1,4-addition of the indole nitrogen to α,β-unsaturated esters originating from the 2-position of the ring in the indole derivatives **9** (Scheme 4). The indole **9** in turn was generated from the substituted allylamine **8**. This protocol was extended to prepare a dibromopyrrole alkaloid, *N*-Bn-longamide **b**.[13] The reaction of **8** with 1*H*-pyrrole-2-carbonyl chloride afforded the amide **11**,



Scheme 1.

Sorbetti et al. employed aza-MBH reactions of substituted *N*-(phenylsulfonyl)aldimines with conjugated dienes activated by sulfone or ester moieties to achieve the synthesis of highly functionalized allylamines (**3**), the *E*-isomer of which underwent a base-promoted intramolecular conjugate addition of NH onto the double bond to afford functionalized piperidines (**4**) (Scheme 2).[11]

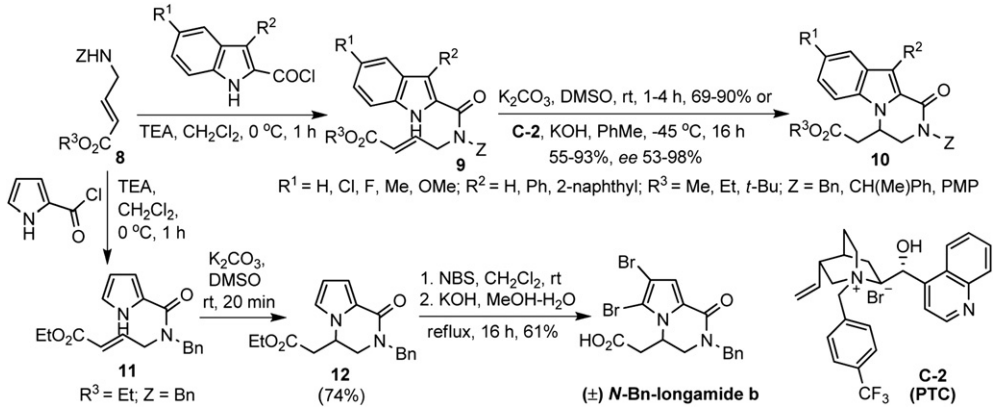
which undergo a base-mediated intramolecular cyclization to produce a bicyclic product **12**. Bromination of **12** with NBS followed by a base-promoted hydrolysis gave the alkaloid. Later, this reaction was conducted in the presence of cinchonidine-based chiral PTC to achieve enantioselective synthesis of the same moiety (Scheme 4).[14]



Scheme 2.

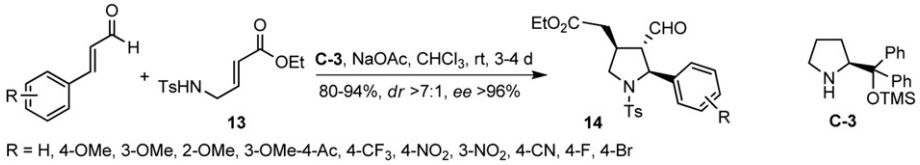
Chen et al. demonstrated the synthesis of benzimidazo[1,2-*a*]pyrimidine derivatives (**7**) in good yield by reacting the allylamines (**5**), derived via an aza-MBH reaction, with 2-aminobenzimidazole

2.1.2. Intermolecular addition of N-nucleophiles onto activated alkenes. Wang et al. described highly enantio- and diastereoselective organocatalyst-mediated aza-Michael-Michael of α,β-unsaturated



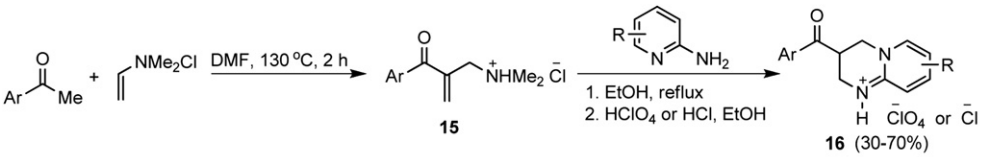
Scheme 4.

aldehydes with *trans*-γ-Ts protected amino α,β-unsaturated ester (**13**) to access highly functionalized chiral pyrrolidines (**14**) as depicted in Scheme 5.[15]



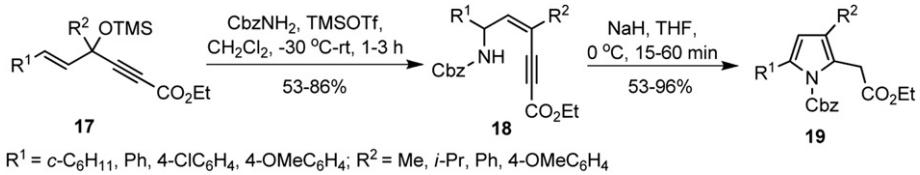
Scheme 5.

Bluhm et al. reported a sequential addition–elimination reaction of 2-aminopyridines with allylamine-based Mannich bases (**15**) to obtain 3-aroylpyrido[1,2-*a*]pyrimidines (**16**) (Scheme 6). Biological assessment of these compounds showed that some of the pyrido[1,2-*a*]pyrimidines inhibited nitric oxide synthase (NOS) enzyme efficiently, sometimes even better than the well-known inhibitors 7-NI or L-NNA.[16]



Scheme 6.

2.1.3. Intramolecular addition of N-nucleophiles onto activated alkynes. The allyl carbamates (**18**), generated from **17**, undergo metal-free Lewis acid-catalyzed intramolecular amino-Michael reactions onto the activated alkyne attached at the rear end of the carbamate to produce 1,3,5-trisubstituted (pyrrol-2-yl)-acetic acid esters (**19**) as demonstrated by Saito et al. (Scheme 7).[17] They observed that the geometry in **18** across the olefin bond should be *Z* to initiate the conjugated addition. The cyclization was reported to be unsuccessful if R^1 and R^2 were both aliphatic groups.



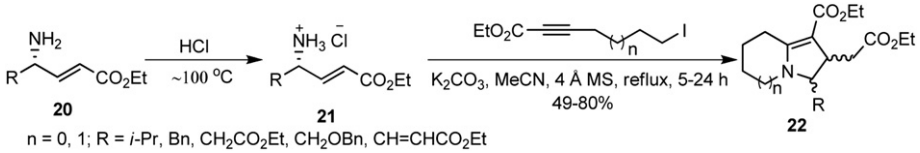
Scheme 7.

Ma and Zhu reported a cascade process for the synthesis of polysubstituted pyrrolizidines and indolizidines (**22**) involving a sequential S_N2 reaction, intramolecular aza-Michael addition followed by Michael addition of the HCl salts (**21**) of the γ-amino-α,β-unsaturated esters (**20**) with ω-iodo-α,β-alkynoates under basic conditions (Scheme 8).[18]

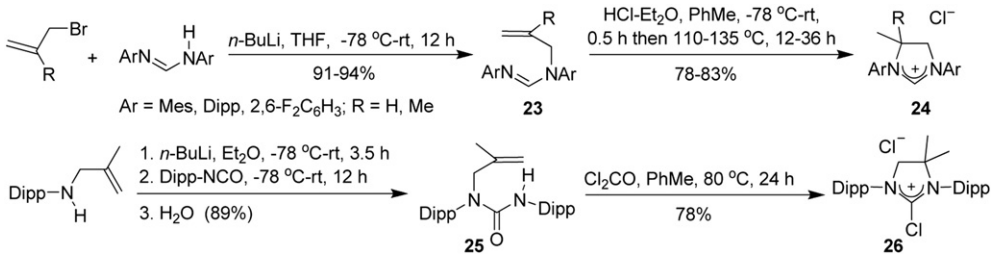
2.1.4. Addition of N-nucleophiles on unactivated alkenes. Bertrand et al. developed HCl-mediated intramolecular hydroiminiumation and 3-amidiniumation of alkenyl-aldimines, -formamidines and -amidines (**23**) to generate the alkenyl-aldiminium, -formamidinium and -amidinium salts, which undergo regioselective ring-closure reactions to afford the corresponding cyclic aldiminium, dihydroisoquinolinium and imidazolinium salts (**24**) (Scheme 9). On the other hand addition of phosgene to the alkenyl urea **25** followed by gentle heating, yielded the *C*-chloro-imidazolinium salt (**26**).[19] A probable mechanism for the cyclization proceeding via an intramolecular proton transfer to the double bond was proposed on the basis of deuterium labelling experiments.

DMDO- or I_2–K_2CO_3-promoted intramolecular cyclization of *N*-allyl guanidines (**27**) was described by Albrecht et al. as a synthetic tool for the synthesis of five- and six-membered cyclic guanidines (**28** and **29**), as depicted in Scheme 10.[20] They discovered that, in the DMDO-promoted reaction, during purification on silica gel, migration of Boc group from N to the OH group takes place.

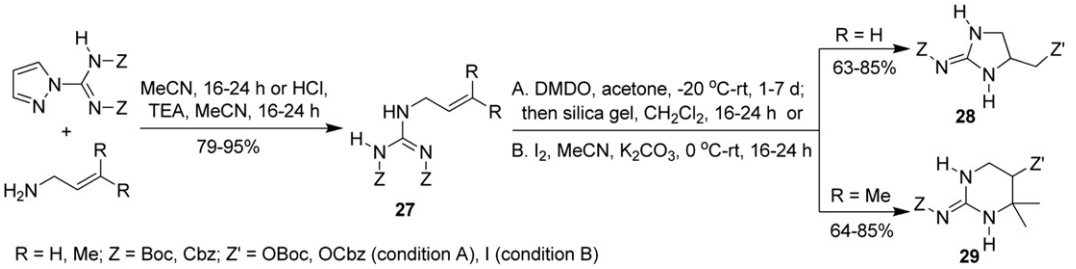
O'Neil et al. achieved the synthesis of chiral bicyclic lactam (**31**) and lactam *N*-oxides (**32** and **34**) via Cope elimination followed by reverse-Cope elimination of the allylamides (**30** and **33**) afforded from the reaction between allylamine and *N*-substituted (*S*)-proline or (*R*)-pipecolic acid (Scheme 11).[21]



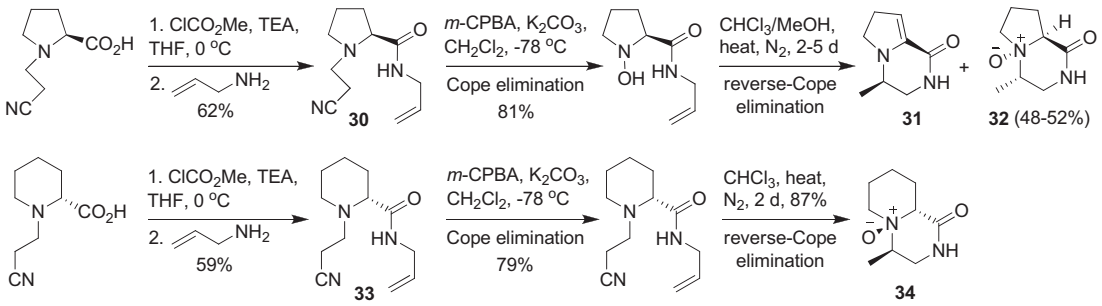
Scheme 8.



Scheme 9.

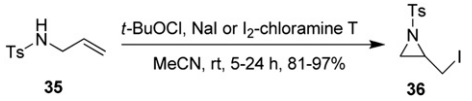


Scheme 10.



Scheme 11.

Minakata et al. reported *t*-BuOI-mediated novel ionic iodine-atom-transfer cyclization of *N*-allyl tosylamide **35** leading to iodomethylated aziridine (**36**) in excellent yield with complete stereoselectivity (Scheme 12).[22] Later, they demonstrated that such cyclization also proceed efficiently in the presence of I_2–chloramine-T and compared to the *t*-BuOI-mediated procedure, this method was observed to be more efficient.[23]



Scheme 12.

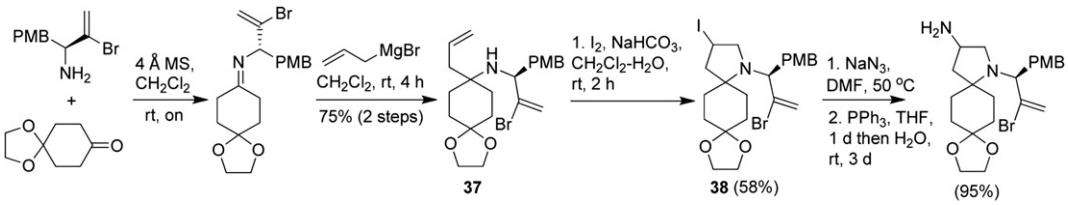
Similarly, I_2-promoted 5-*endo* iodoaminocyclization reaction of 4-allyl-4-(alkylamino)-cyclohexanone derivative (**37**) in turn prepared from a substituted allylamine enabled Bonjoch et al. to achieve the synthesis of the corresponding iodo derivative of 1-azaspiro[4.5]decane (**38**) as described in Scheme 13.[24]

A novel approach for the transformation of *N*-allyl anilines (**39**) to indoline derivatives (**41**) was demonstrated by Tellitu et al. via aza-Claisen rearrangement of **39** to aniline **40** followed by PIFA-mediated formation of an *N*-acylnitrenium ion and its subsequent intramolecular trapping by the olefin fragment (Scheme 14).[25]

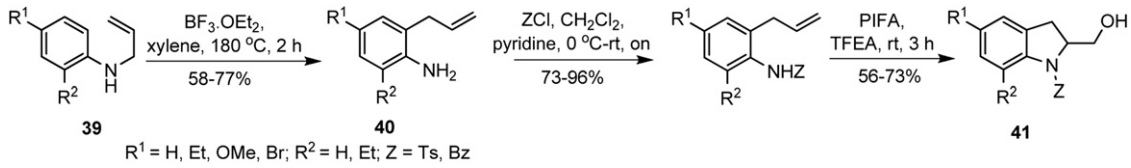
2.2. Reactions involving *C*-nucleophiles

2.2.1. Base-promoted cyclizations. Kim's group successfully synthesized the pyrrole derivatives **43** and **45** from the allylamines **42** and **44**, respectively via sequential N-alkylation, Michael addition and DBU-mediated oxidative aromatization as delineated in Scheme 15.[26]

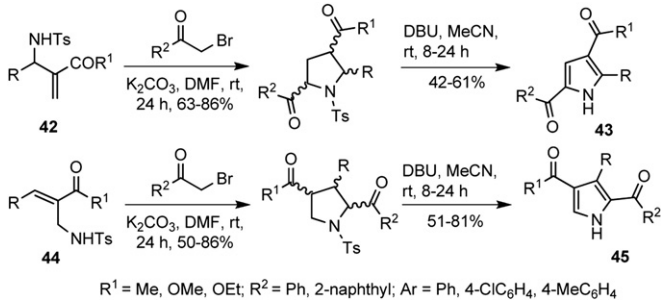
2.2.2. Carbometalation reactions. Chemla et al. described the transformation of substituted allylamines (**46**) into enantioenriched



Scheme 13.



Scheme 14.

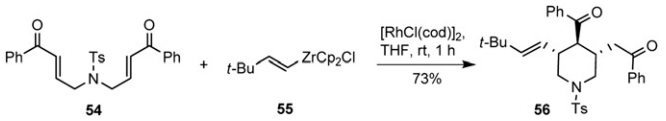


Scheme 15.

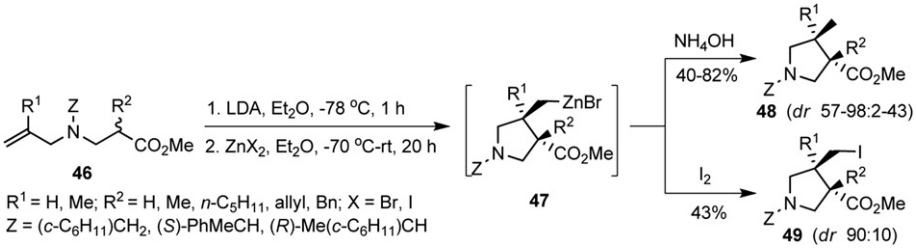
3,4-disubstituted β-prolines (**48** and **49**) in a highly diastereocontrolled carbometalation reaction involving a *C*-centred Zn-enolate **47**, as shown in Scheme 16.[27]

Lam et al. demonstrated the synthesis of piperidine derivative (**53**) in moderate yield, but with high diastereoselectivity and enantioselectivity via a chiral copper-bisphosphine-catalyzed reductive Michael cyclization of the bisallylamine **52**, using siloxanes as stoichiometric reductants (Scheme 18).[29]

[RhCl(cod)]$_2$-catalyzed 1,4-conjugate addition of alkenylzirconocene chloride **55** to a bis-enone derivative (**54**) enabled Hanzawa et al. to furnish the piperidine ring system (**56**) with three contiguous stereocenters (Scheme 19).[30]

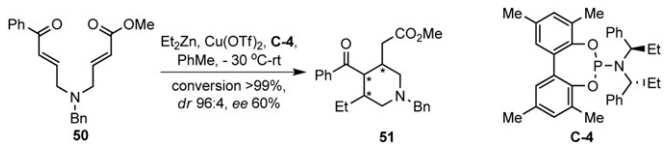


Scheme 19.



Scheme 16.

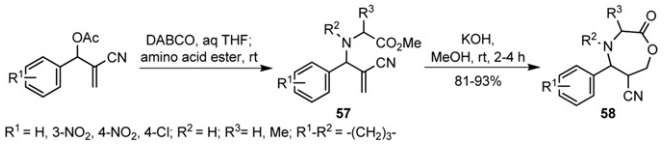
Li and Alexakis during their studies on copper-catalyzed enantioselective conjugate addition of a dialkylzinc to bis-α,β-unsaturated carbonyl compounds followed by the intramolecular trapping of the Zn-enolate in the presence of chiral phosphoramidite ligands evaluated the cyclization of allylamine **50** and found that it resulted in the cyclic derivative **51** with good diastereoselectivity, but poor enantioselectivity (Scheme 17).[28]



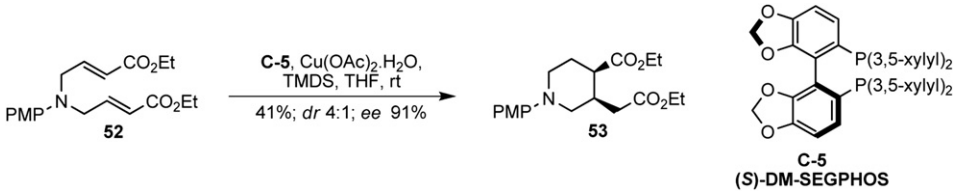
Scheme 17.

2.3. Reactions involving *O*-nucleophiles

Yadav et al. disclosed a base-catalyzed intramolecular Michael addition reaction of the allylamines (**57**), obtained from the reaction between the MBH acetates and amino acid esters, to afford 1,4-oxazepan-2-ones (**58**) in excellent yields (Scheme 20).[31]

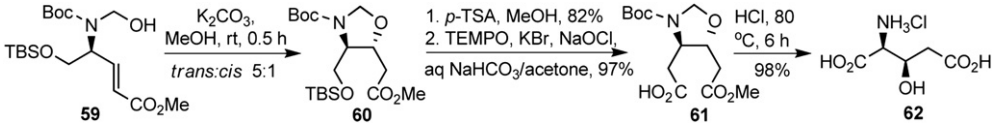


Scheme 20.



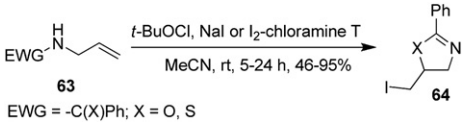
Scheme 18.

According to Kim et al. the conjugated (*E*)-ester **59** with an *N*-hydroxymethyl group as an internal nucleophile underwent a smooth intramolecular conjugate addition in the presence of a weak base to give the *trans*-oxazolidine **60** as the major product with good selectivity (Scheme 21). This *trans*-oxazolidine **60** was transformed into **61**, which was converted into *threo*-β-hydroxy-L-glutamic acid **62**, an attractive target as a biologically active compound and as a chiral synthon.[32]



Scheme 21.

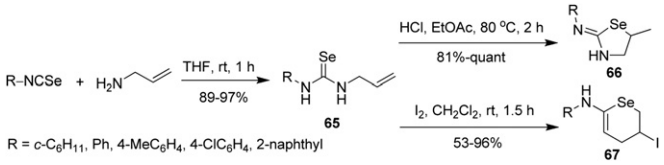
In addition to the use of the *t*-BuOI and I_2–chloramine-T for the synthesis of cyclopropane derivatives, Minakata et al. also demonstrated[22] the use of these reagents for stereoselective ionic iodine-atom-transfer cyclization of allylbenzamide or allylbenzthioamide **63** to oxazoline (**64**; X=O) and thiazoline (**64**; X=S) derivatives, respectively as shown in Scheme 22.



Scheme 22.

2.4. Reactions involving Se-nucleophiles

Koketsu et al. studied the regioselective intramolecular cyclization of *N*-allylselenoureas (**65**) afforded from unsubstituted primary allylamine under different conditions. They observed that the treatment of *N*-allylselenoureas **65** with HCl afforded 2-imino-1,3-selenazolidines (**66**) preferentially through 5-*endo* closure, whereas the treatment with I_2 afforded 2-amino-5-iodo-1,3-selenazines (**67**) through 6-*exo* ring closure (Scheme 23).[33]



Scheme 23.

3. Carbolithiation reactions

The intramolecular sequential process involving halogen–Li exchange and addition of the carbanion onto an alkene of the attached allylamine provides access to different heterocycles. The lithium amide obtained via aminolithiation can also undergo intramolecular addition, resulting in cyclic compounds.

Sanz et al. reported that the organolithium intermediate, which originated from *N*-allyl-*N*-(2-bromoallyl)anilines (**68**) via sequential halogen–Li exchange and intramolecular 5-*exo* cyclization in the presence of *t*-BuLi furnished 3-substituted-4-alkyledene-1-arylpyrrolidines (**69**) upon quenching with water or isocyanates (Scheme 24). It was observed that the presence of TMEDA accelerated the ring closure of the aryllithium intermediate generated during the reaction.[34]

A (−)-sparteine-mediated synthesis of 3,3-disubstituted indolines **71** from *N*-benzyl-*N*-allyl-2-bromoanilines (**70**) via an intramolecular asymmetric carbolithiation reaction in the presence of *t*-BuLi was disclosed by Groth et al. (Scheme 25). They studied the effect of the nature of the side chain (R^1) on the yields and enantioselectivity of the product formed in detail.[35]

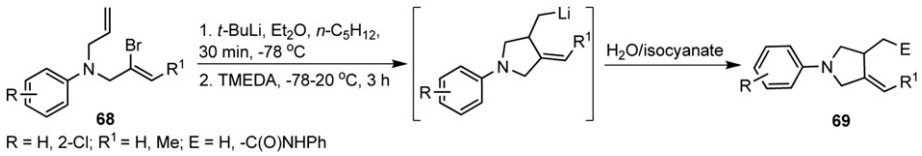
Later, adopting an identical approach, Bailey et al. disclosed the synthesis of 3-substituted 4-, 5-, 6- and 7-azaindolines (2,3-dihydro-1*H*-pyrrolopyridines) (**74**, **77** and **78**) via intramolecular carbolithiation of the aryllithium (**73** or **76**) derived from an appropriate (*N*,*N*-diallylamino)bromopyridine (**72** or **75**) (Scheme 26). It was reported that, although cyclization proceeded as expected to give 1-allyl-3-methyl-4-azaindoline (**74**; X=N; W=CH) and 1-allyl-3-methyl-6-azaindoline (**74**; X=CH; W=N) following protonation of the 3-CH_2Li group of the azaindoline **73**, the isomeric 3-methyl-5-azaindoline (**77**; Z=N; Y=CH) and 3-methyl-7-azaindoline (**78**; Z=CH; Y=N) were generated as 3-methyl-*N*-allyl anions prior to quenching with MeOH.[36]

Alternatively, Tomioka's group successfully achieved double cyclization of the allylaminoalkenes (**79**) via tandem aminolithiation–carbolithiation by employing the lithium amide as a lithiating agent as well as a protonating agent to prepare bicyclic octahydro-indolizines (**80** and **81**) and hexahydro-1*H*-pyrrolizine (**82**) in high yield and good diastereoselectivity (Scheme 27). They demonstrated that the use of a catalytic amount of the lithium amide stopped the reaction after the aminolithiation step to offer the monocyclic product, whereas an increase in the lithium amide resulted in an increase in the bicyclic to monocyclic ratio. The use of a bulkier amine (*tert*-butyltritylamine) improved the yield of the bicyclic product with increased diastereoselectivity.[37]

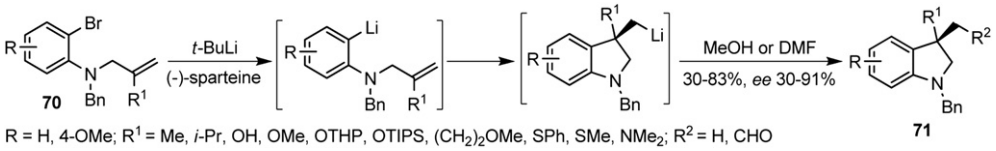
4. Condensation reactions

4.1. Intramolecular condensation of amine with carbonyl moiety

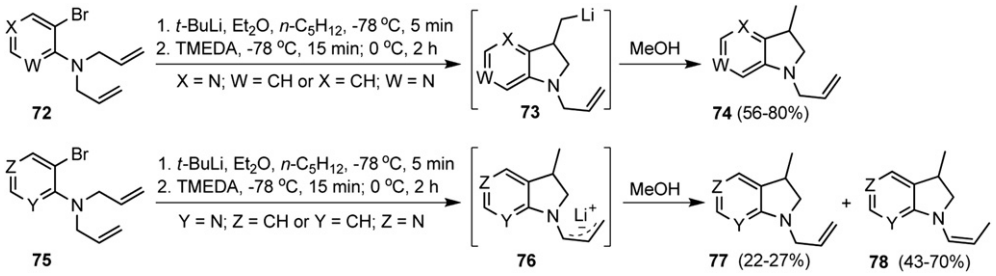
Intramolecular and intermolecular reductive amination of the carbonyl moiety with the amino group of the allylamine provides



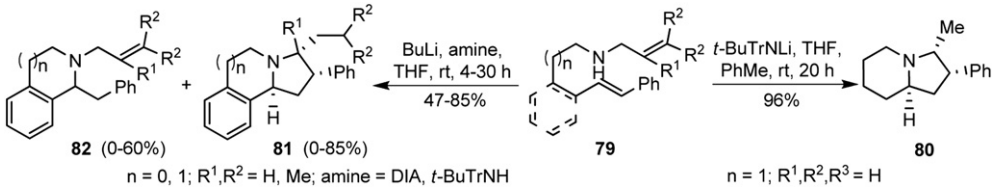
Scheme 24.



Scheme 25.



Scheme 26.



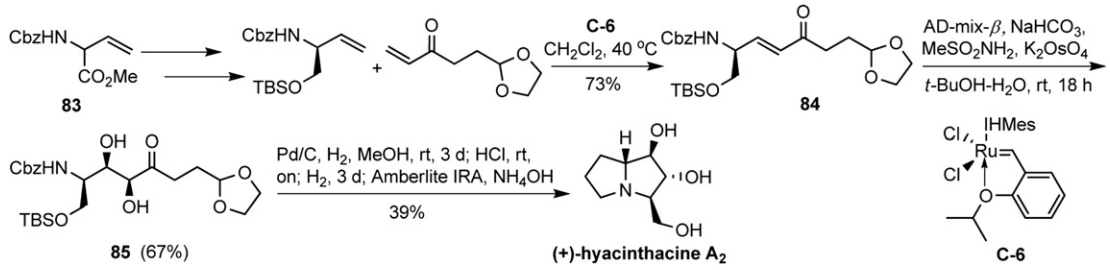
Scheme 27.

an easy access to aza-systems. Additionally the presence of another nucleophilic group in the substituted allylamine capable of participating in the condensation reaction leads to cyclic frameworks with more than one heteroatom.

Dewi-Wuelfing and Blechert achieved the synthesis of an alkaloid, (+)-hyacinthacine A_2, from (*S*)-*N*-Cbz-vinylglycine (**83**) via a sequential double intramolecular reductive cyclization of the masked dicarbonyl **85**, originating from Sharpless asymmetric dihydroxylation of the olefin cross-metathesis product **84** (Scheme 28).[38]

benzoquinone (Scheme 30).[40] They also developed an alternative route for the synthesis of the protected nucleoside (**97**), as shown in Scheme 31. Initially reaction of allylamine with 3,5-di-*tert*-butyl-1,2-benzoquinone (**94**) to produce 2-vinyl-4,6-di-tert-butylbenzoxazole (**95**), which was coupled with 5-iodo-3′,5′-di-*O*-benzoyl-2′-deoxyuridine (**96**) under Heck conditions to afford the desired nucleoside (**97**).

In a modification, Eriksson et al. prepared the hydroxylamine derivative **100** from the carbamate **99**, which in turn was obtained from the allyl carbamate **98**. An acid-catalyzed intramolecular



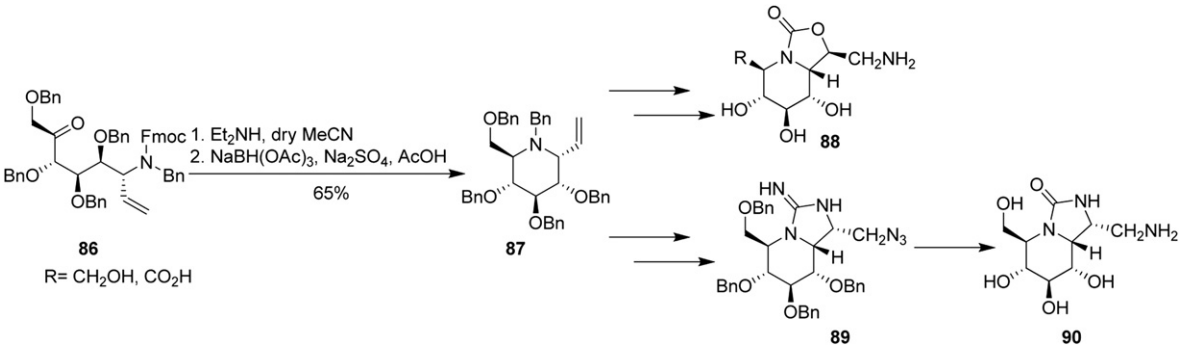
Scheme 28.

Cipolla et al. also adopted an intramolecular reductive amination approach to induce the transformation of allyl carbamate **86** into α-*C*-vinyl nojirimycin **87**, which was further converted into bicyclic structures, containing a cyclic carbamate (**88**), urea (**90**) or guanidine (**89**) functionality (Scheme 29).[39] The biological activity of these compounds against different glucosidases and bacteria was also examined.

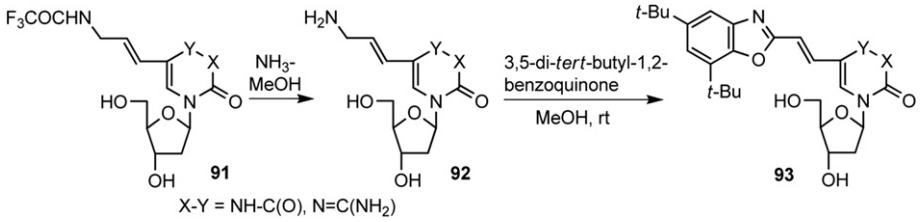
Timoshchuk and Hogrefe disclosed the synthesis of fluorescent nucleosides (**93**) by simple interaction of the allylamine moiety of 5-modified pyrimidine nucleosides (**92**) with 3,5-di-*tert*-butyl-1,2-

condensation of **100** with the masked aldehyde led to 2-methyl tetrahydropyridine-*N*-oxide (**101**), which was subsequently transformed into the naturally occurring alkaloids (+)- and (−)-dihydropinidine (**102**), potential antifeedants against the pine weevil, *Hylobius abietis* (Scheme 32).[41]

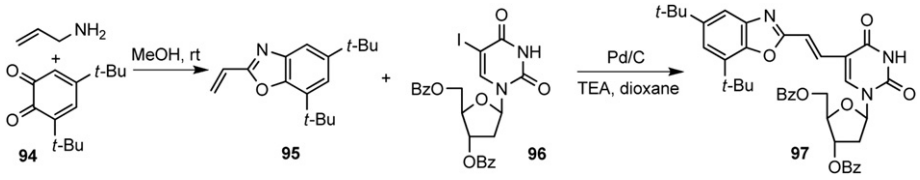
Balazs et al. accomplished an efficient synthesis of cycloalkane-fused and phenyl-substituted 1,4-diazepin-5-ones (**105**) via acid-catalyzed, MW-assisted intramolecular condensation in formyl methyl carboxamides **104**. Substrates **104** were readily generated by oxidative cleavage of the C–C double bond in **103**, which in turn



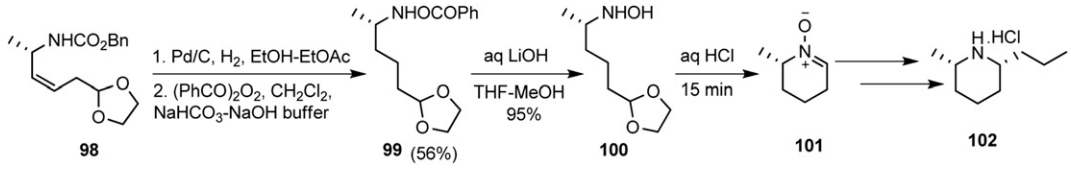
Scheme 29.



Scheme 30.



Scheme 31.

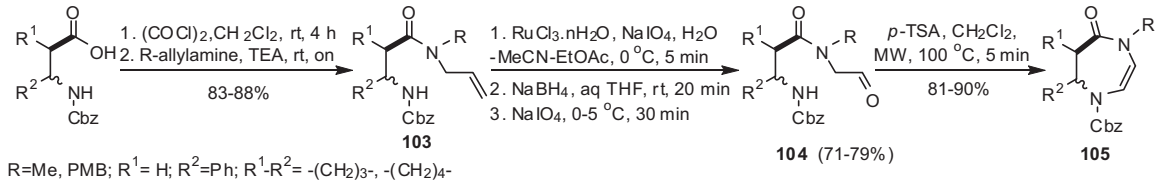


Scheme 32.

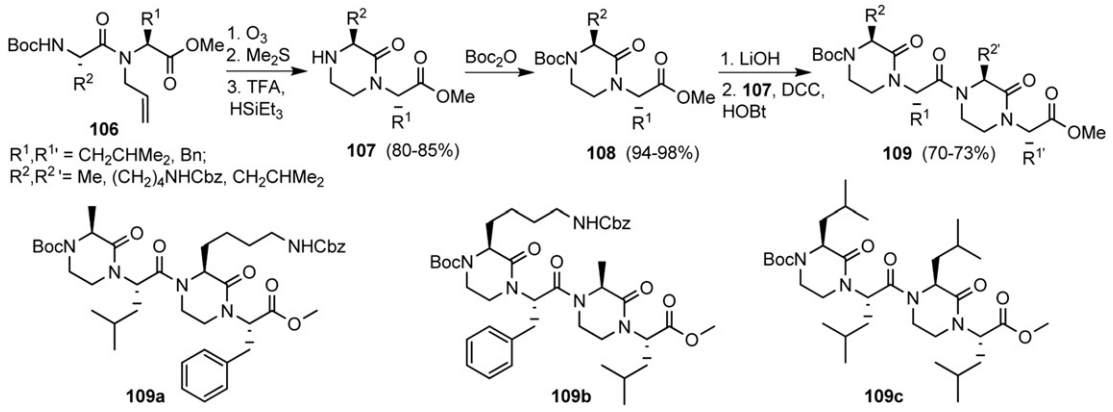
was afforded from the reaction between β-amino acids and allylamine as outlined in Scheme 33.[42]

Tosovska and Arora achieved the synthesis of a new class of nonpeptidic α-helix mimetics (**109**) with chiral backbones from the allylamine derivatives **106**. An initial O_3-mediated oxidative cleavage of the alkene functionality of **106** followed by condensation of the generated formyl group with the terminal amino group afforded **107**, which were coupled with their *N*-Boc-protected anlogues **108** to furnish the products, as shown in Scheme 34.[43] NMR and circular dichroism spectroscopies, in combination with molecular modelling studies, provided compelling evidence that oligooxopiperazine dimers (**109a**–**c**) adopted stable conformations that reproduced the arrangement of *i*, *i*+4 and *i*+7 residues on an α-helix.

Our group has engineered a facile synthesis of [1,4]diazepino [5,6-*b*]quinolines via reductive cyclization of the allylamine derivatives obtained from the MBH adducts of 2-nitrobenzaldehyde (Scheme 35).[44] Treatment of the tosyl-protected allylamine (**110**, Z=Ts) with Fe–AcOH followed by the addition of water produced **111** through sequential reductive cyclization of the nitro group onto

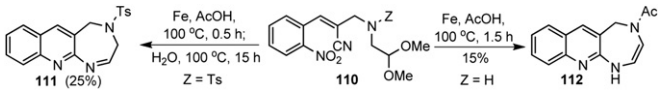


Scheme 33.



Scheme 34.

the nitrile, followed by imine formation. For the unprotected allylamine **110** (Z=H), however, treatment with Fe–AcOH produced **112** through double bond-isomerization of the in situ-generated imine.

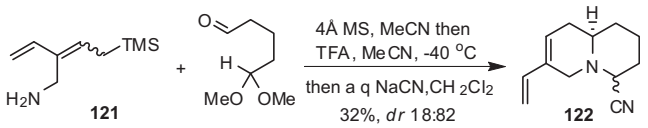


Scheme 35.

Arbour et al. utilized the allylamine derivative **113** to produce a mixture of cyclic enamine **114** via a sequential hydroxyl deprotection–oxidation followed by imine formation and double bond isomerization along with keto aldehyde **115** in a variable ratio. Compound **115** was converted into imino alcohol **116** by piperidine-mediated aldol condensation of the enamine formed after deprotection of the nitrogen onto the ketone (Scheme 36).[45]

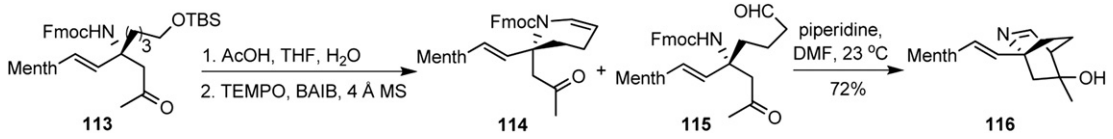
4.2. Intermolecular condensation of amine with carbonyl moiety

A TFA-mediated condensation between the substituted allylamine **121** and monoprotected dialdehyde via an iminium ion cascade reaction and subsequent trapping with cyanide produced a bicyclic aminonitrile **122**, as disclosed by Martin et al. (Scheme 38).[47]



Scheme 38.

Pedrosa et al. achieved condensation of amino alcohols (**123**) with different aldehydes to form the chiral perhydro-1,3-benzoxazine-attached cinnamylamines (**124**) (Scheme 39). The cinnamylamines were regio- and diastereoselectively methoxy-

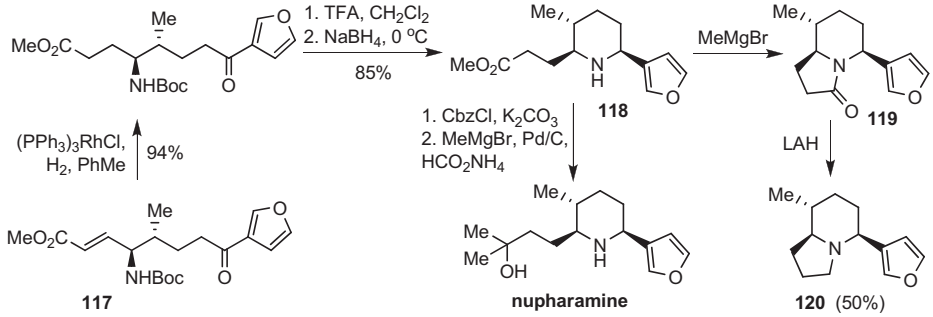


Scheme 36.

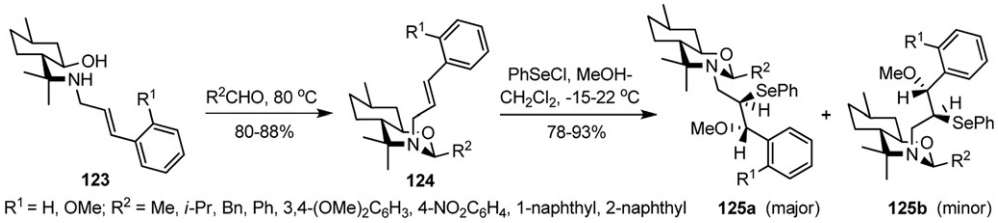
Recently, a highly diastereoselective synthesis of the piperidine derivative **118** via Wilkinson's catalyst-mediated double-bond reduction of the allylamine **117** followed by intramolecular reductive amination was disclosed by Bates and Lim (Scheme 37).[46] The piperidine derivative was used as a precursor to afford the nuphar alkaloid, nupharamine, and the bicyclic heterocycle **119**. Reduction of **119** with LAH afforded the saturated analogue **120**.

selenenylated across the double bond by treatment with benzeneselenenyl chloride in a mixture of MeOH–CH_2Cl_2 to afford the seleno-compounds (**125a**,**b**).[48]

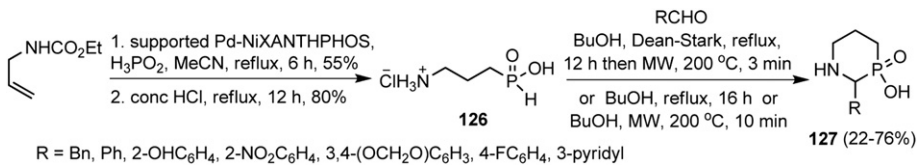
Montchamp's group accomplished the synthesis of *P*,*N*-heterocycles (**127**) via intramolecular Kabachnik–Fields reaction of aldehydes and 3-amino-*H*-phosphinic acid (**126**).[49] The 3-amino-*H*-phosphinic acid (**126**) was in turn prepared from the primary allylamine, as depicted in Scheme 40.



Scheme 37.

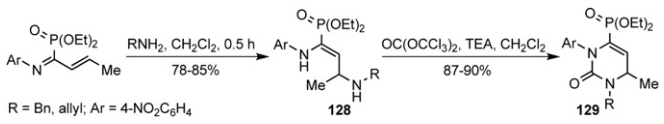


Scheme 39.



Scheme 40.

In a different strategy reported recently, Vicario et al. employed triphosgene to effect the condensation reaction with diamines **128**, in turn generated from aza-Michael reactions of various amines with an α,β-unsaturated imine, leading to phosphorylated pyrimidone derivatives (**129**) in good yields, as depicted in Scheme 41.[50]



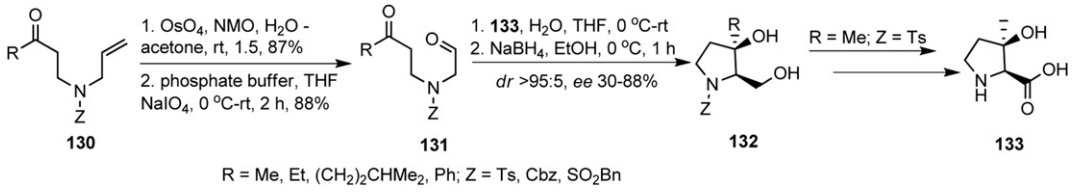
Scheme 41.

4.3. Aldol condensation

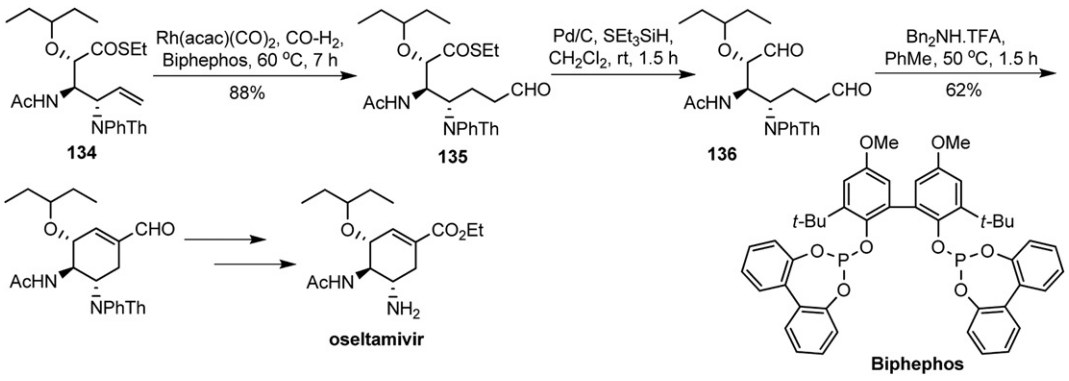
A highly efficient synthesis of large quantities of (2*S*,3*R*)-3-hydroxy-3-methylproline (**133**), which is a component of polyoxypeptins, was disclosed by Hamada's group as shown in Scheme 42.[51] They found that (2*S*,3*R*)-3-hydroxy-3-methylproline **133** also serves as an efficient organocatalyst for intramolecular aldol reaction of the aminoacetaldehyde derivative **131** to afford the intermediate **132** with two continuous asymmetric carbons containing a quaternary stereogenic centre. Compound **131** in turn was afforded via dihydroxylation followed by oxidation of the double bond of the substituted allylamine **130**. This strategy was observed to be general, as it provided several analogues of the proline compound.

Oshitari and Mandai developed a highly enantioselective azide-free synthesis of oseltamivir (tamiflu) through an intramolecular aldol condensation of the dialdehyde (**136**), which in turn was accessed from phthaloyl-protected analogue (**135**) of functionalized allylamine **134**, as depicted in Scheme 43.[52]

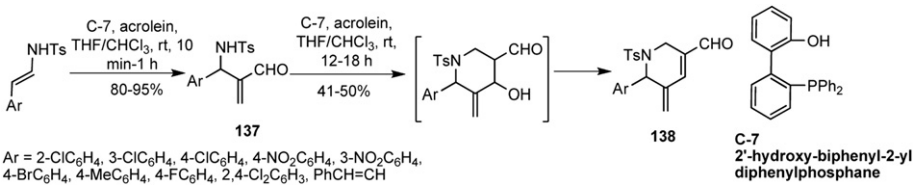
Meng et al. transformed the allylamines **137**, obtained via aza-MBH reaction of *N*-(aryl)-4-methylbenzenesulfonamides and acrolein, into dihydropyridines (**138**) through a sequential intermolecular Michael reaction, intramolecular aldol reaction and a dehydration process in the presence of 2′-hydroxy-biphenyl-2-yl diphenylphosphane and an excess of acrolein (Scheme 44).[53] They



Scheme 42.



Scheme 43.



Scheme 44.

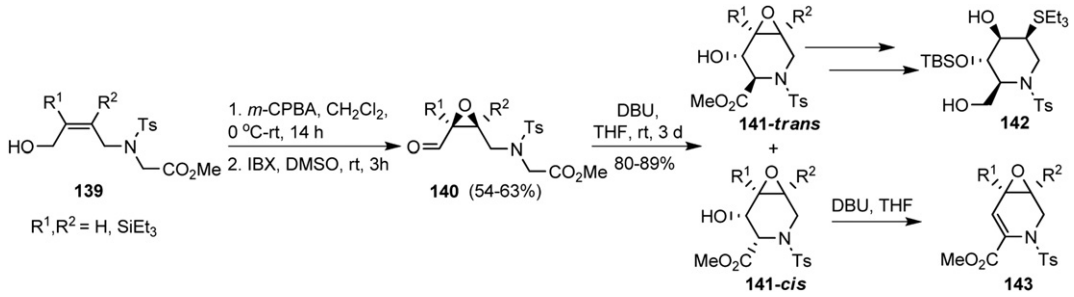
discovered that the use of non-polar solvent improved the yield of **138** and reduced the reaction time.

Malacria et al. also reported the intramolecular aldolization of 2- or 3-silyl-epoxy aldehydes (**140**) bearing a glycinyl side chain, afforded from the corresponding alcohol **139**, to construct the *N*-heterocyclic frameworks of the type **141**, which were used for the synthesis of polyhydroxylated piperidine **142** and dehydroamino esters **143** (Scheme 45).[54] They observed that the presence or absence of a triethylsilyl group in a neighbouring position relative to the aldehyde strongly influences the overall selectivity of the cyclization.

4.4. Intramolecular hemiketalisation

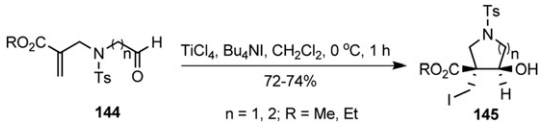
Benfatti et al. demonstrated that the silyl enol ether-functionalized allylamines (**149**), generated by Michael addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to alkylideneacetoacetates (**148**), spontaneously undergo intramolecular hemiketalisation to afford ethyl 5-hydroxyisoxazolidine-4-carboxylates (**150**) in high yield (Scheme 48).[57] The mechanism was studied at the DFT level, which was in complete agreement with the experimental evidence.

Hoffman et al. reported that the β-hydroxy amide (**153**), generated from acetoin protected allylamine (**151**) by sequential



Scheme 45.

Douelle et al. successfully transformed allylamines (**144**) bearing an α,β-unsaturated enoate and an aldehyde into pyrrolidine or piperidine derivatives (**145**), containing vicinal quaternary and tertiary stereocenters, via an intramolecular iodo-aldol heterocyclization reaction (Scheme 46).[55]



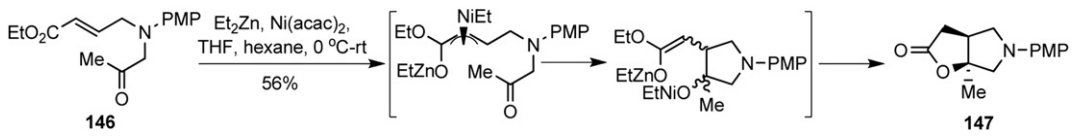
Scheme 46.

Lam's group developed the synthesis of a bicyclic lactone **147** from an α,β-unsaturated carbonyl compound (**146**) tethered to a ketone electrophile through an amide via Et_2Zn–$Ni(acac)_2$-catalyzed reductive aldol cyclization, as delineated in Scheme 47.[56]

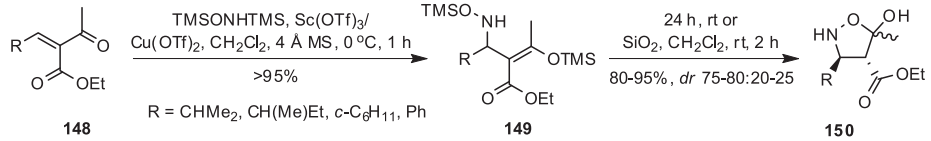
deprotection and EDCI-mediated coupling with amino acid (**152**), produced the corresponding oxazole **154** via a cyclodehydration–aromatization process (Scheme 49). This oxazole derivative was the C7–C14 fragment of ulapualide A, a natural product with promising antitumour activity.[58]

4.5. Schweizer reaction

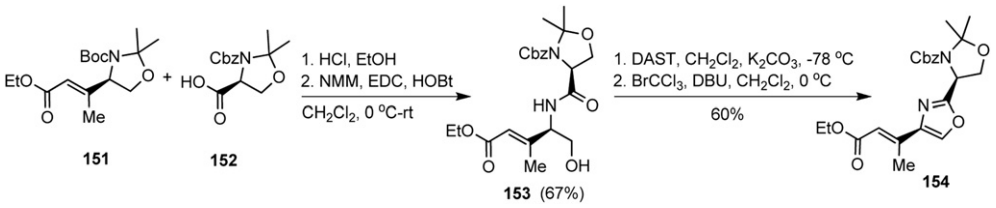
Kim's group engineered the synthesis of 3,4-disubstituted pyridines (**158**) from the allylamines (**155**). A Schweizer reaction between **155** and vinyltriphenylphosphonium bromide afforded the intermediate **156**, which cyclized to **157**. Base-promoted elimination of tosyl group in **157** followed by a 1,3-proton shift yielded the required pyridines **158** (Scheme 50).[59]



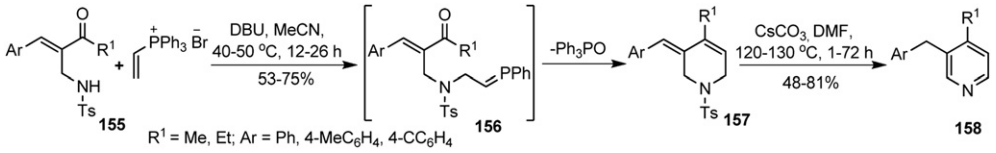
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.

5. Nucleophilic substitution reactions

The nucleophilic nature of the amine has been widely used for displacing the leaving group at an appropriate position in the substituted allylamine or that has been introduced by functionalization of the double bond for preparing aza-systems. Besides nitrogen, C- and *O*-nucleophiles present in the functionalized allylamine also offer an opportunity for cyclization via an intramolecular substitution reaction.

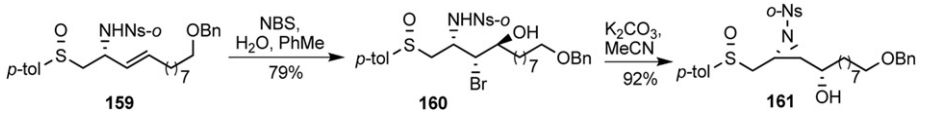
5.1. Reactions involving *N*-nucleophiles

5.1.1. Intramolecular reactions. Raghavan and Krishnaiah reported the conversion of the bromohydrin **160**, obtained from *N*-allyl sulfonamide (**159**), into the aziridine **161** via base-mediated substitution of the β-bromo group with nitrogen, as shown in Scheme 51.[60] Indeed, the aziridine was formed instead of the intended epoxide, which was being synthesized as part of a synthetic plan to furnish the natural product pinaresid in A.

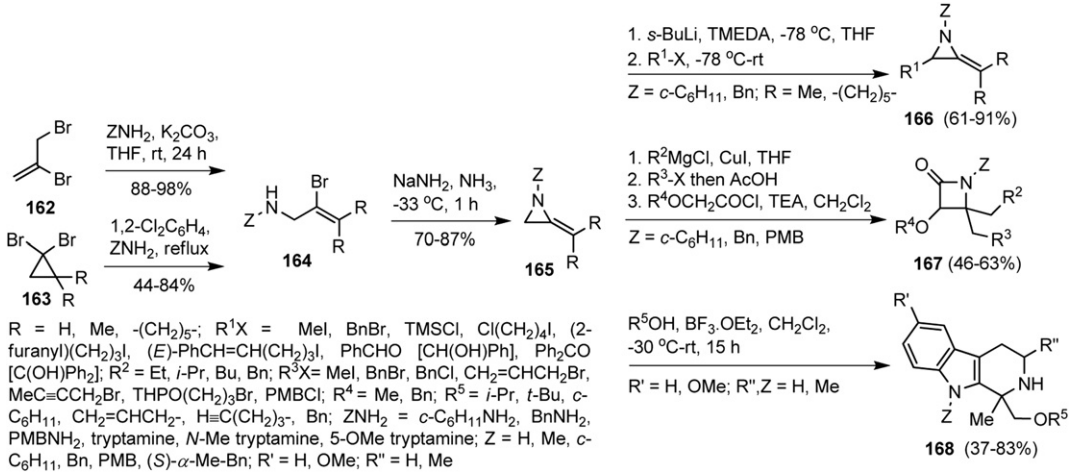
Shipman's group developed a strategy for the synthesis of 2-methyleneaziridines (**165**) from 2-bromopropenylamines (**164**) via a base-promoted nucleophilic displacement of the halide (Scheme 52). The 2-methyleneaziridines (**165**) were subsequently utilized for the synthesis of several aza-systems (**166**–**168**).[61]

De Kimpe et al. employed substituted allylamines for the efficient synthesis of 3-fluoroazetidines (**171**). This transformation was achieved in three steps involving sequential imine formation and bromofluorination of alkene followed by reductive cyclization, as delineated in Scheme 53. When the allylamine (**169**) was treated with diphenyl ketone during the imine (**170**) formation step, the substituted aziridine **172** was formed along with the azetidine (**171**) (Scheme 53).[62] Subsequently, these workers extended the strategy to the synthesis of 3-fluoroazetidine-3-carboxylic acid from 2-(4-methoxyphenoxymethyl)-2-propylamine (**171**, R^3=CO_2H) where in the final step, the *p*-OMe group was removed with CAN to provide the alcohol, which was oxidized with Ru in the presence of $NaIO_4$ to afford the corresponding acid.

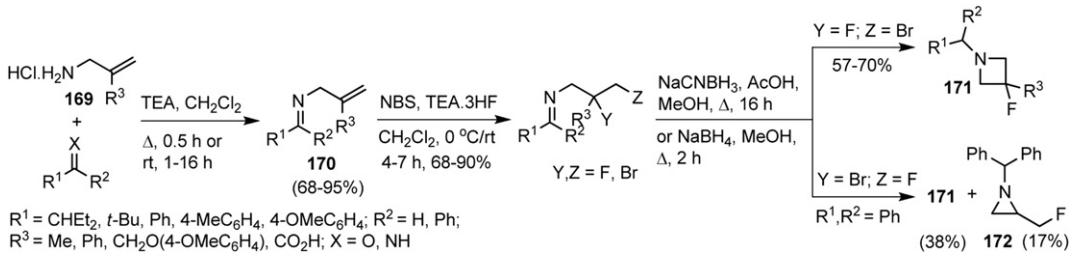
Simultaneously, this group also reported the synthesis of new small-ring aza-heterocyclic α- and β-amino acids (aziridines **176** and azetidines **177**) via dibromination of the double bond of the allylamine **173** followed by base-mediated nucleophilic sub-



Scheme 51.

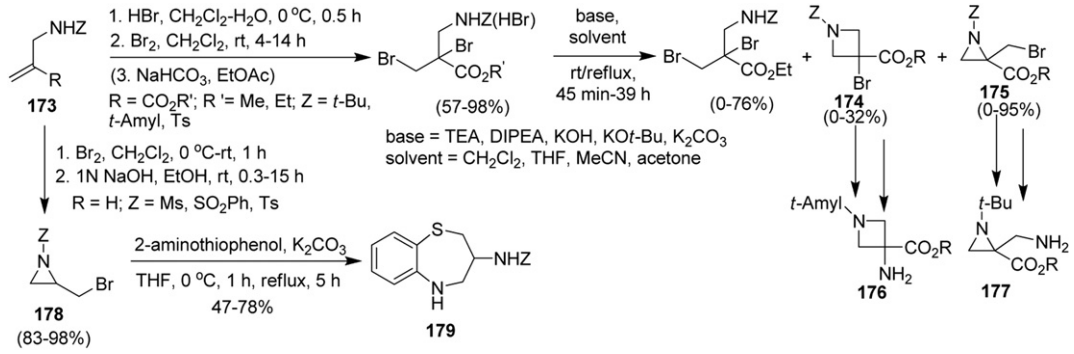


Scheme 52.



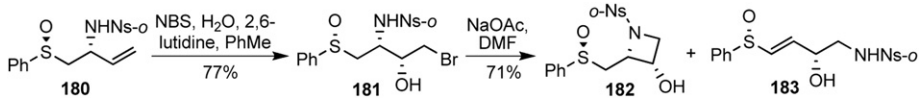
Scheme 53.

stitution of a bromide. These substrates were envisaged to be useful synthons and transformation of aziridines **178** into benzothiazepines **179** was exemplified (Scheme 54).[63]



Scheme 54.

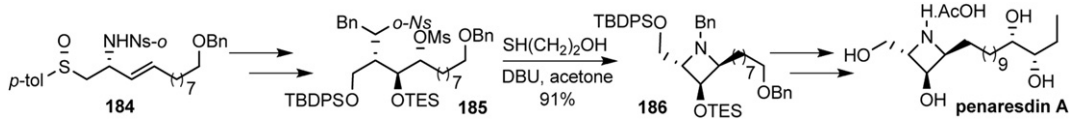
Raghavan et al. demonstrated the synthesis of azetidine (**182**) along with unsaturated sulfoxide (**183**) in variable amounts by treating the bromohydrin (**181**), obtained via reaction between *N*-allyl sulfonamide (**180**) and NBS, with NaOAc in anhydrous DMF, as shown in Scheme 55.[64]



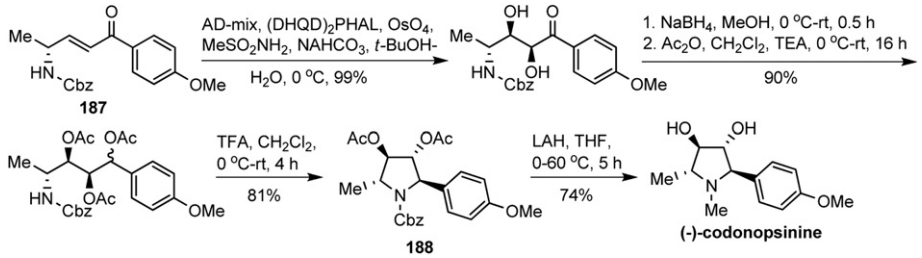
Scheme 55.

The same workers achieved the asymmetric synthesis of penaresidin A, containing an azetidine diol subunit. Initially, the regio- and stereoselective functionalization of the key intermediate

Reddy and Rao successfully performed the synthesis of the antibiotic (−)-codonopsinine, through the intermediate afforded from a chiral allylamine **187**. The key steps of the strategy were the asymmetric dihydroxylation of the allylic double bond in **187** via a modified Sharpless reaction and a highly stereoselective intramolecular acid-catalyzed amidocyclization by nucleophilic displacement of the acetate with carbamate to afford **188** (Scheme 57).[65]

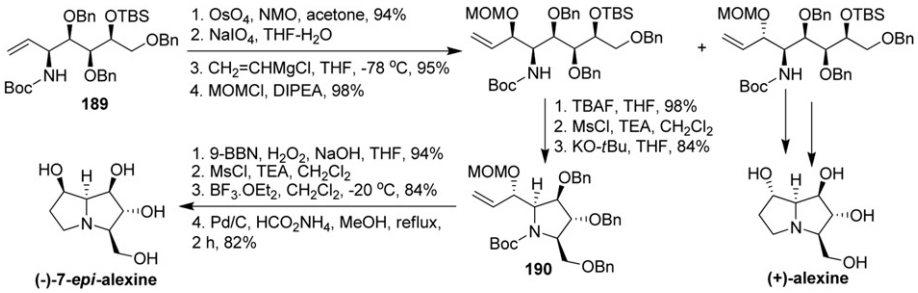


Scheme 56.



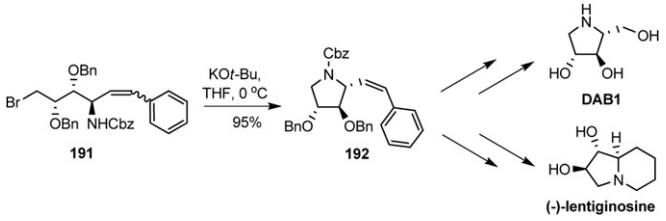
Scheme 57.

Homochiral allylamine (**189**), derived from L-xylose, was used by Yoda et al. as a precursor for the asymmetric synthesis of the naturally occurring polyhydroxylated pyrrolizidine alkaloids, (+)-alexine and (−)-7-*epi*-alexine, potent glycosidase inhibitor as delineated in Scheme 58. In the first stage allylamines **189** afforded the functionalized pyrrolidines **190**, which were then synthetically manipulated to the desired alkaloids.[66]



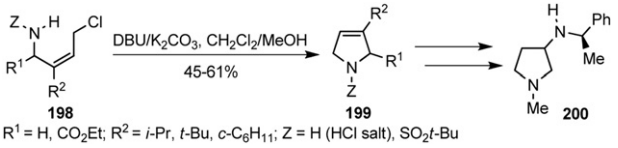
Scheme 58.

In an analogous protocol, Jung et al. employed the substituted allylamine **191** to produce a pyrrolidine derivative **192**, which served as precursor to DAB1 and (−)-lentiginosine, as shown in Scheme 59.[67]



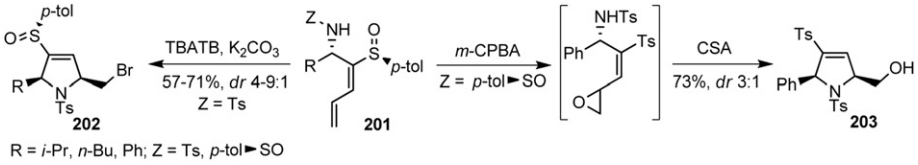
Scheme 59.

In a modified approach, Gais et al. and, later Madhusudhan et al. synthesized 3-pyrroline (**199**) from δ-chloro allylamine (**198**) via base-induced intramolecular substitution of the chloride with amine (Scheme 61). Maddaluno et al. utilized the synthesized 3-pyrroline as a precursor to generate 3-aminopyrrolidines (e.g., **200**) and the corresponding lithium amides were evaluated as chiral ligands for enantioselective hydroxyalkylation with *n*-BuLi (Scheme 61).[69]



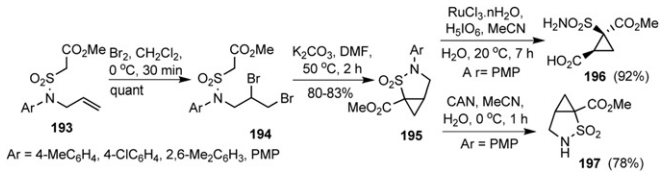
Scheme 61.

Viso et al. also utilized substituted allylamines **201** to obtain highly functionalized 3-sulfinyl (**202**) and 3-sulfonyl 2,5-*cis*-dihydropyrroles (**203**), respectively. In the developed strategy a leaving group was introduced at the terminal alkene and then a nucleophilic displacement reaction was performed with amide (Scheme 62).[70]



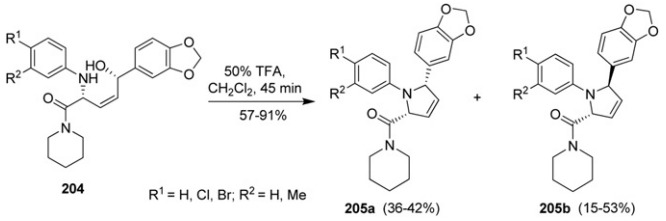
Scheme 62.

de Meijere et al. demonstrated that *N*-(2,3-dibromopropyl)-(methoxycarbonyl) methanesulfanilides (**194**), generated via dibromination of **193**, upon treatment with K_2CO_3 in DMF underwent intramolecular cyclodialkylation of their C,H-acidic positions to furnish cyclopropane-annulated five-membered sultams (**195**) (Scheme 60).[68] Treatment of sultam (**195**; Ar=PMP) with $RuCl_3$ and periodic acid, as the co-oxidant, furnished sulfamoyl-substituted monomethyl cyclopropane-1,2-dicarboxylate (**196**) in high yield, whereas $NaIO_4$ as co-oxidant yielded the same product in only 30% yield. CAN-mediated deprotection of the PMP group afforded the sultam (**197**) with free nitrogen.



Scheme 60.

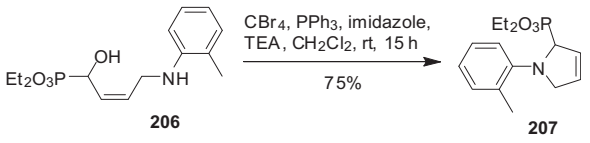
In another approach Krchnak et al. converted the hydroxyl functionality of the amino alcohols (**204**) into a better leaving group, which underwent a facile displacement reaction with amine to produce diastereomeric 2,5-dihydropyrroles (**205a**,**b**) (Scheme 63).[71]



Scheme 63.

In an identical strategy, Monbaliu and Marchand-Brynaert converted the amino alcohol **206** into an activated species with CBr_4–PPh_3-mediated activation. This reactive intermediate underwent an intramolecular nucleophilic substitution by the aniline

in the presence of imidazole to afford the 2,5-dihydropyrrole derivative **207** (Scheme 64).[72]



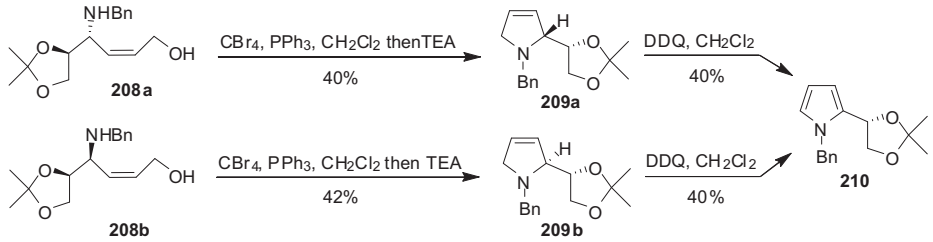
Scheme 64.

In previously reported work by Diez et al., such as CBr_4—PPh_3-mediated activation of a hydroxyl group was also applied to chiral allylamines **208a**,**b** to achieve the synthesis of 2,3-dihydropyrroles **209a**,**b** (Scheme 65). The dihydropyrroles were readily oxidized to 2-substituted pyrrole **210** in the presence of DDQ.[73]

This strategy of intramolecular cyclization was extended to the synthesis of 6-, 7- or higher membered analogues of azaheterocycles. Krishna and Dayaker reported the synthesis of (−)-andrachcinidine, a 2,6-disubstituted piperidine derivative, from the intermediate **218**, which in turn was obtained from the allylamine **216**, through intramolecular cyclization of the intermediate **217** (Scheme 68).[76]

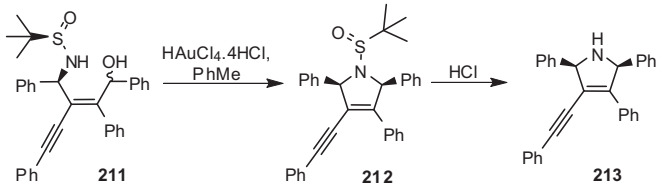
Gupta and Vankar achieved the synthesis of 2-*C*-methylene-*N*-glycosyl amines **220a** and **220b** from the sugar-based allylamines **219a** and **219b**, respectively. These products (**220a**,**b**) were employed as starting materials for the synthesis of L-*allo*-, L-*altro*- and L-*ido*-deoxynojirimycin (DNJ), which are moderate inhibitors of human lysosomal α-mannosidase (Scheme 69).[77]

Winkler et al. achieved the synthesis of tricyclic ketones **224a** and **224b** starting from the allyl carbamate **221** via an NaH-



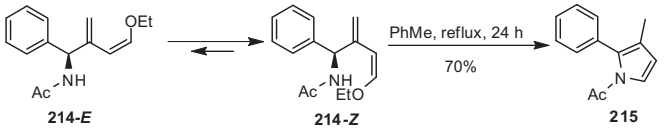
Scheme 65.

Recently, Yin accomplished the synthesis of highly substituted chiral dihydropyrroles (e.g., **212**) from protected allylamine (**211**) via the use of Au-catalyzed activation and cyclization. Acid-promoted deprotection of **212** yielded the deprotected pyrrole **213** (Scheme 66).[74]



Scheme 66.

Botta's group also reported the formation of a 1,2,3-trisubstituted pyrrole derivative **215** via intramolecular cyclization of the allylamine **214** with elimination of ethanol in refluxing toluene (Scheme 67).[75]



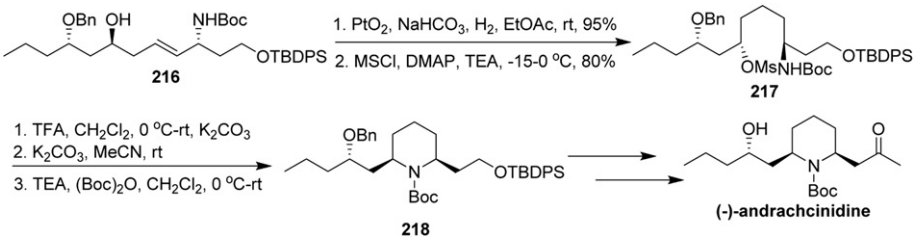
Scheme 67.

mediated intramolecular nucleophilic displacement of the tosyl-protected hydroxyl group with amide (Scheme 70). Initially **221** was transformed to the *N*-alloc-protected eight-membered intermediate **222**. Deprotection of the alloc group followed by reaction with 3-butyne-2-one produced **223**, which underwent intrmolecular cyclization in the presence of UV light to afford **224a** and **224b**. These tricyclic ketones were used in the preparation of simplified analogues of manazamine A, a marine natural product.[78]

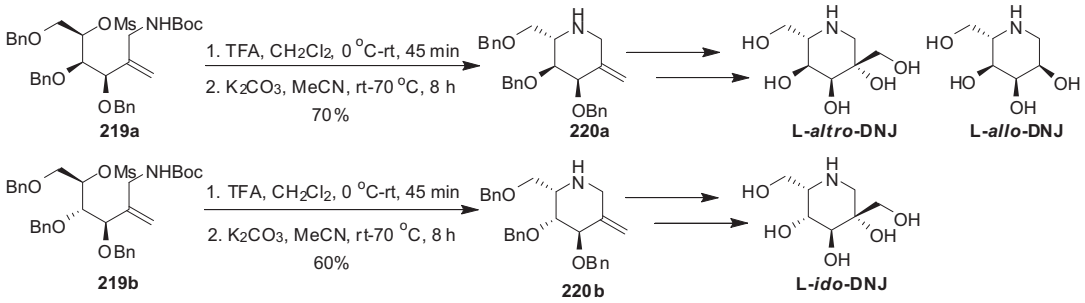
The protecting group present on the amino group of the allylamine has also been demonstrated to be a leaving group, leading to an intramolecular nucleophilic substitution reaction to afford cyclic frameworks. The synthesis of a 5′-protected bicyclic cytosine analogue **226** was accomplished by Williams et al. via the treatment of trifluoroacetyl-protected allylamine-tethered nucleoside **225** with aqueous ammonia (Scheme 71).[79] Phosphitylation of **226** with 2-cyanoethyl-*N*,*N*′-diisopropyl chlorophosphoramidite afforded the phosphoramidite derivative **227**.

The enantioselective synthesis of both enantiomers of 4,5,6- and 3,4,5,6-substituted azepanes (**230** and **231**) was achieved by Lee and Beak from highly diastereo- and enantioenriched enecarbamates **229**, which in turn were generated by (−)-sparteine-mediated asymmetric deprotonative lithiations of *N*-Boc-*N*-PMP-2,3-substituted allylamines (**228**) with *n*-BuLi, followed by conjugate addition to ethyl *p*-bromocinnamate (Scheme 72).[80]

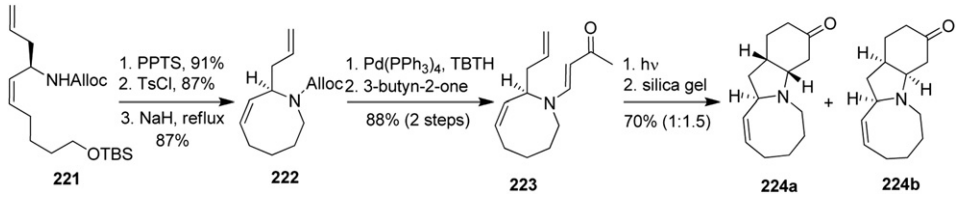
Tanaka et al. achieved the synthesis of a series of 6-substituted 4-sulfonyl-1,4-diazepane-2,5-diones **233** from the



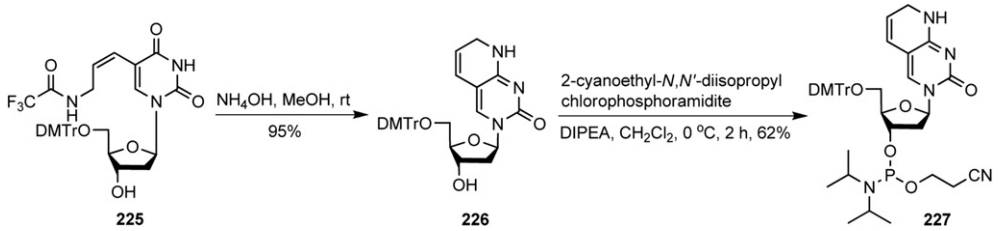
Scheme 68.



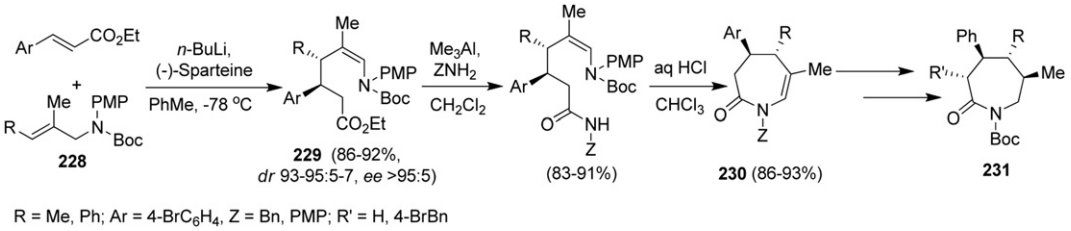
Scheme 69.



Scheme 70.



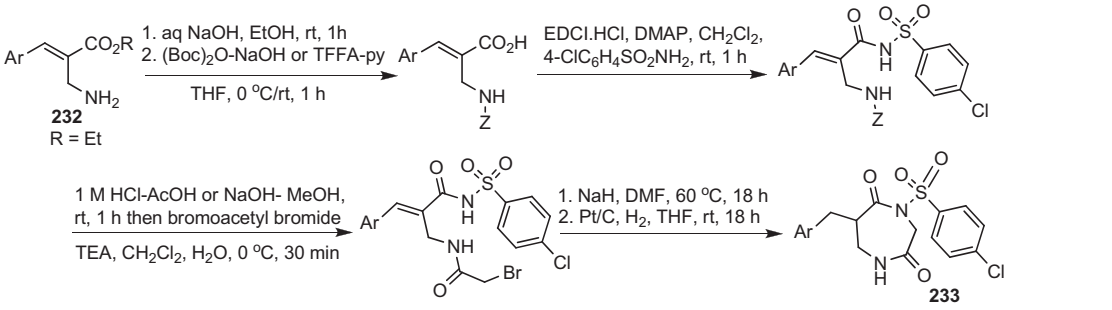
Scheme 71.



Scheme 72.

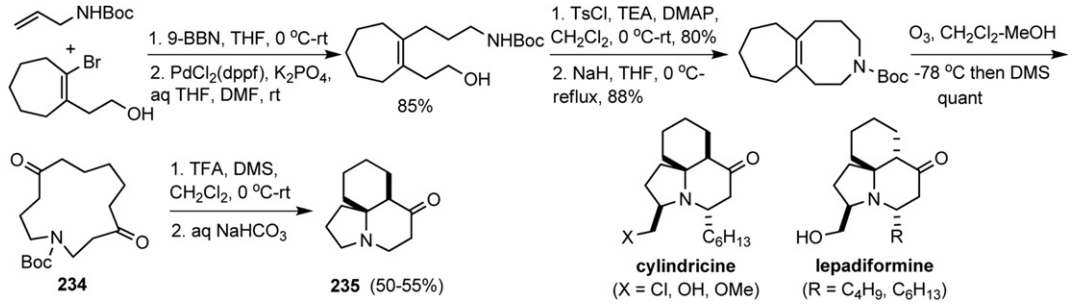
primary allylamines **232** generated via MBH chemistry as delineated in Scheme 73. These compounds were reported to exhibit good inhibitory activity against recombinant human chymase.[81]

5.1.2. Intermolecular reactions. The preparation of a tricyclic pyrroloquinoline derivative **235**, representing the framework of the cylindricine and lepadiformine alkaloids, was accomplished by Tanner et al. in a single operation via a transannular Mannich



Scheme 73.

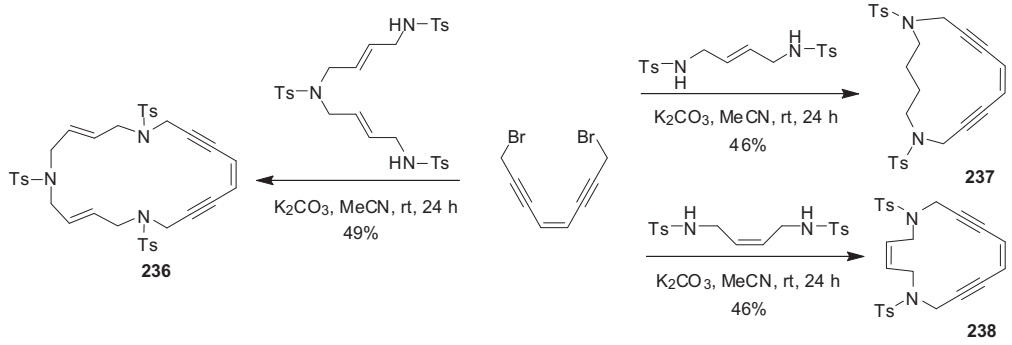
reaction involving a macrocyclic diketoamine **234**, which was in turn obtained from the *N*-Boc-allylamine as shown in Scheme 74.[82]



Scheme 74.

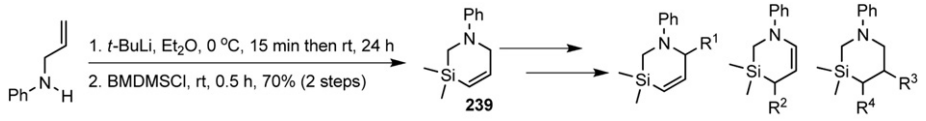
Gonzalez et al. reported the synthesis of unsaturated aza-macrocycles (**236**–**238**) via the reaction of a bispropargyl bromide enediyne with several bis-NH–allylsulfonamide nucleophiles under basic conditions (Scheme 75).[83]

An identical strategy was adopted by Fang and Assoud to achieve the synthesis of tri- and tetrasubstituted 1,2-azaborolyls (Ab) (**243** and **244**). The dilithiation-directed cyclization of substituted allylamines **240** gave **241**, which via transmetalation afforded the

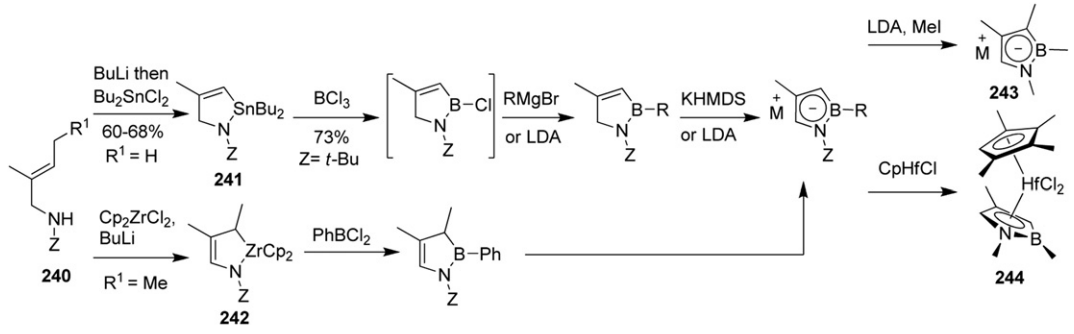


Scheme 75.

Malacria's group disclosed a novel synthesis of 3-silapiperidines (e.g., **239**). The key step involved a formal double nucleophilic substitution reaction between (bromomethyl)dimethylsilyl chloride (BMDMSCl) and an *N*,*C*-sp^2-1,4-dianionic species generated from *N*-phenyl allylamine (Scheme 76).[84] Functionalization of the target compounds in good yields. For methylallylamine, the dilithiation protocol was successful, but, for terminally methylated allylamine, 1- ,2-azazircona-4-cyclopentane **242** were prepared (Scheme 77).[85] In particular, the generated anionic 1,2,4-trimethyl-1,2-azaborolyl **243** and 1,2,3,4-tetramethyl-1,2-azaborolyl **244** were



Scheme 76.

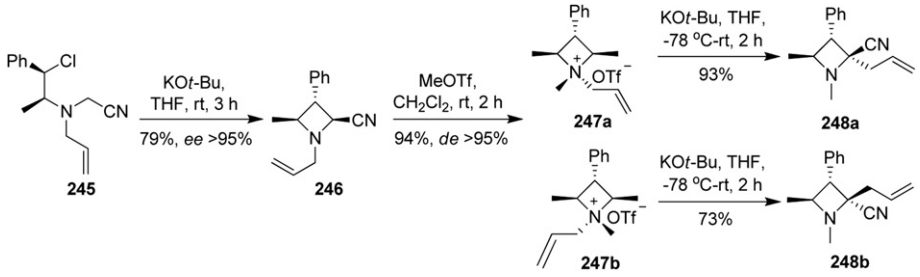


Scheme 77.

shown to be good supporting ancillary ligands in group IV metal complexes.

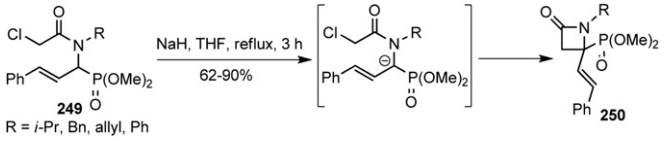
5.2. Reactions involving *C*-nucleophiles

An intramolecular nucleophilic attack involving the carbon nucleophiles in substituted allylamines also results in the formation of aza-systems. Couty's group managed the synthesis of an enantiomerically pure *N*-allyl azetidine (**246**) from the allylamine derivative **245** via a base-promoted intramolecular nucleophilic displacement of the chloride. The triflate salts (**247a**,**b**) of the azetidine underwent a base-mediated stereoelective [1,3]-sigmatropic shift to produce the azetidines (**248a**,**b**), respectively, with an α-quaternary centre (Scheme 78).[86]



Scheme 78.

In an earlier reported strategy quite similar to that reported above, Van Speybroeck et al. isolated phosphono-β-lactams **250** by treating the aminophosphonates **249** with base, as delineated in Scheme 79.[87]



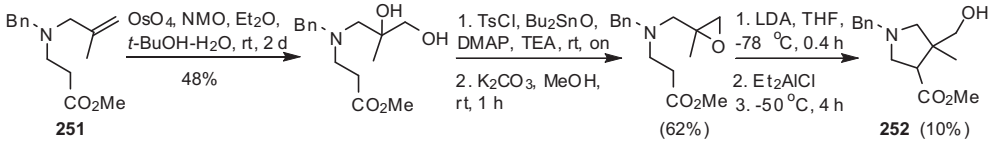
Scheme 79.

Compernolle et al. disclosed the preparation of pyrrolidine **252** from allylamine **251** via OsO_4-mediated bishydroxylation of the double bond, and epoxide formation followed by base-mediated epoxide ring opening and concomitant ring closure (Scheme 80).[88]

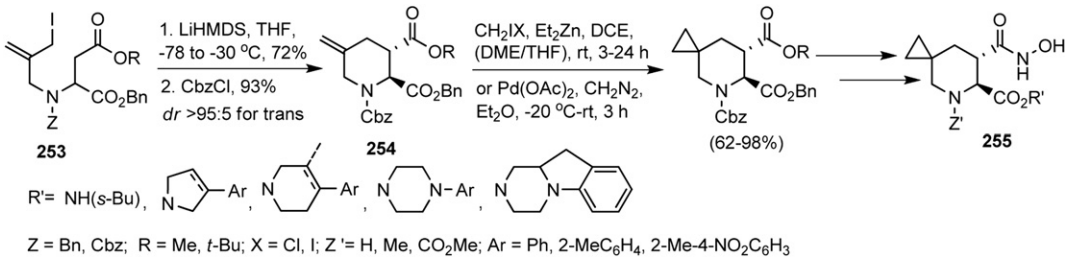
Yao et al. synthesized a novel class of conformationally restricted (6*S*,7*S*)-*N*-hydroxy-6-carboxamide-5-azaspiro[2.5]octane-7-carboxamides (**255**), which inhibit the protease that is responsible for human epidermal growth factor receptor-2 (HER-2) shedding and has been implicated in the pathogenesis of various cancers.[89] The cyclic precursor to **255**, which is **254**, was prepared from the substituted allylamine **253** via a base-promoted nucleophilic reaction, as delineated in Scheme 81.[90]

Hayes' group initially disclosed a strategy for the enantioselective synthesis of (−)-omuralide and 7-*epi*-(−)-omuralide, which utilized a base-mediated ring closure of a substituted allylamine **256** to obtain 3-pyrroline **257**, which was the starting substrate (Scheme 82).[91] Later, they discovered a second general route to these natural products and also disclosed the synthesis of (+)-lactacystin.[92]

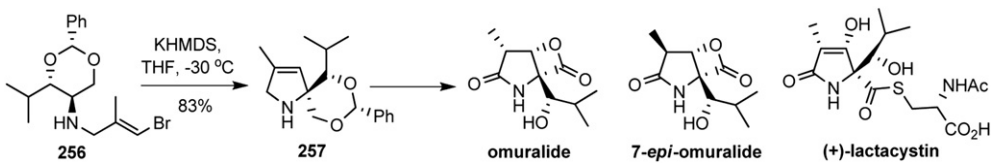
The allylamides (**258**) were utilized by Prati et al. for the generation of 2-substituted and 2,3-disubstituted pyrroles (**259**). The protocol involved chlorination of the amide **258** followed by base-induced displacement of the chloro functionality with a *C*-nucleophile, as depicted in Scheme 83.[93]



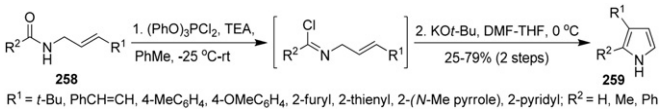
Scheme 80.



Scheme 81.

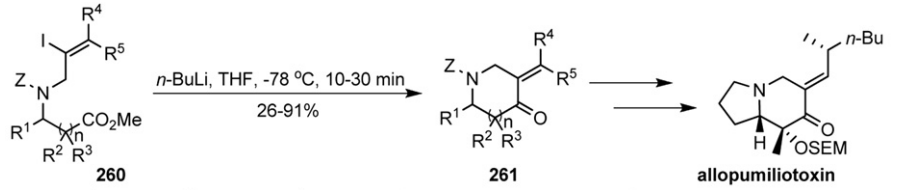


Scheme 82.



Scheme 83.

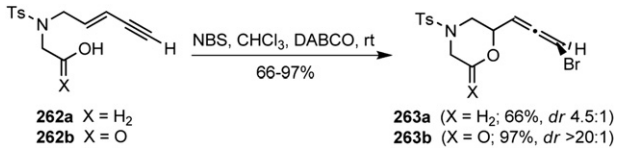
Wang et al. synthesized α-alkylidene aza-cycloketones (**261**) with defined olefin geometry through sequential I–Li exchange in vinyl iodide (**260**) followed by intramolecular nucleophilic acyl substitution of the β-amino-alkenyllithium ester (Scheme 84). This key transformation was used to perform a concise total synthesis of allopumiliotoxin.[94]



Scheme 84.

5.3. Reactions involving *O*-nucleophiles

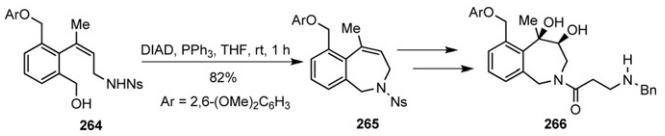
Braddock et al. reported stereoselective intramolecular *syn*-bromoetherification of enyne **262a** to generate the morpholine-attached disubstituted-allene (**263a**).[95] More recently the strategy was emulated by Tang's group to achieve the synthesis of lactone **263b** with allenes **262b** (Scheme 85).[96]



Scheme 85.

6. Intramolecular Mitsunobu reactions

Functionalized allylamines bearing an alcohol moiety have been widely employed for the Mitsunobu reaction to access aza-frameworks of variable ring size. Evans et al. achieved the synthesis of the bicyclic core, 2,3-dihydro-2-benzazepine **265**, of a bioactive compound **266**, exhibiting potent muscarinic (M3) activity, from the allylamine derivative **264** under Mitsunobu conditions, as depicted in Scheme 86.[97]



Scheme 86.

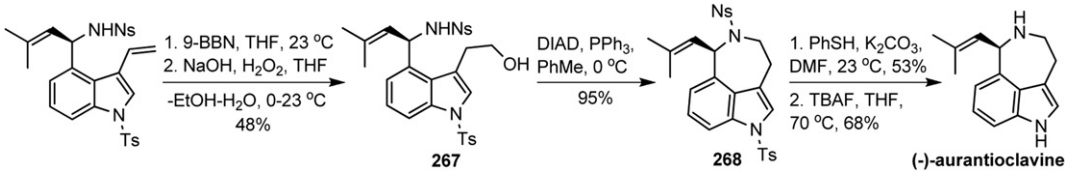
The seven-membered ring structure **268** of (−)-aurantioclavine, an ergot alkaloid of the isopavine family originally isolated from Papaveraceae plants, was generated from the indole derivative (**267**) under Mitsunobu conditions in excellent yield by Stoltz et al. (Scheme 87).[98]

Fukuyama's group described an enantioselective synthesis of the ABCE rings of manzamine A. In particular the synthesis of the eight-membered E-ring **270** of manzamine A was achieved by an intramolecular Mitsunobu reaction of the substituted allylamine **269** (Scheme 88).[99]

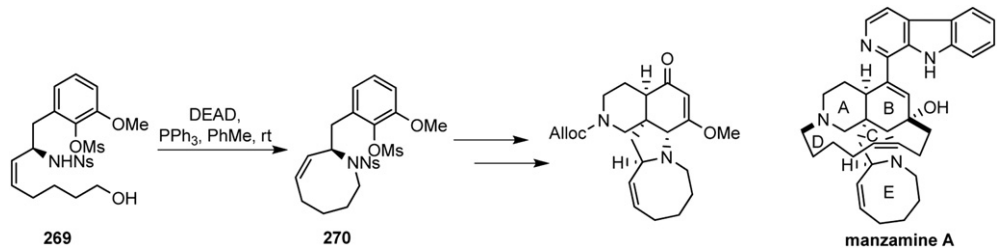
Tomooka et al. reported the synthesis of a chiral nine-membered diallylic cyclic amide (**272**) without any stereogenic carbon, through an intramolecular Mitsunobu reaction of the (*E*)-allyl amide on the (*Z*)-allyl alcohol in **271** under high dilution (0.01 M) (Scheme 89). These nine-membered diallylic cyclic aza-heterocycles were shown to display a remarkably stable planar chirality.[100]

7. Lactamization reactions

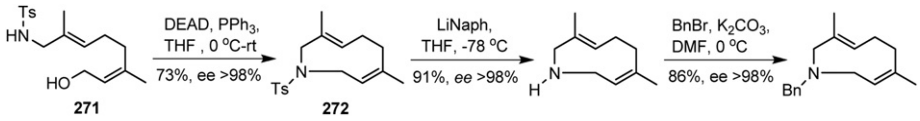
Amide coupling of the carboxylic acid or substitution of the alkoxy group of the ester by an internal amino group of an appro-



Scheme 87.



Scheme 88.

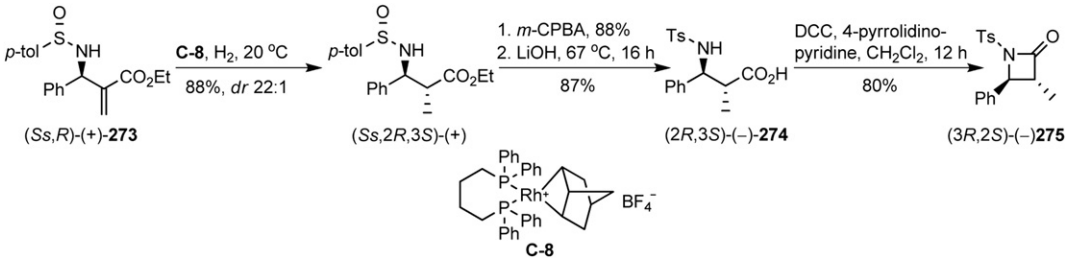


Scheme 89.

priately substituted allylamine induces cyclization leading to a lactam. Essentially the size of the lactam ring is dependent on the relative position of the amine and the acid or the alkoxy group.

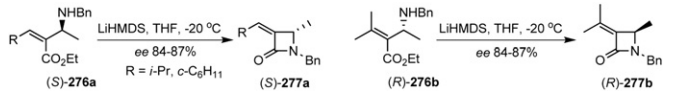
7.1. Synthesis of β-lactams

An enantiopure substituted azetidine (**275**) was generated by Davis et al. from a β-amino acid (**274**) via DCC-mediated intramolecular amide coupling, as depicted in Scheme 90. The amino acid **274** was in turn obtained from the aza-MBH adduct **273** via cationic Rh-catalyzed hydrogenation, *m*-CPBA-mediated oxidation of the sulfinyl group and saponification of the ester.[101]



Scheme 90.

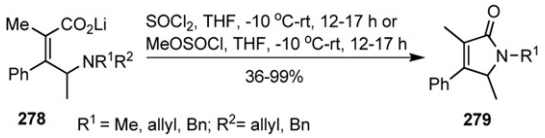
LiHMDS-mediated intramolecular cyclization in the dehydro-β-amino esters **276a**,**b** enabled Benfatti et al. to achieve a highly enantioselective synthesis of the β-lactams **277a**,**b** with retention of the stereochemistry (Scheme 91).[102]



Scheme 91.

7.2. Synthesis of γ-lactams

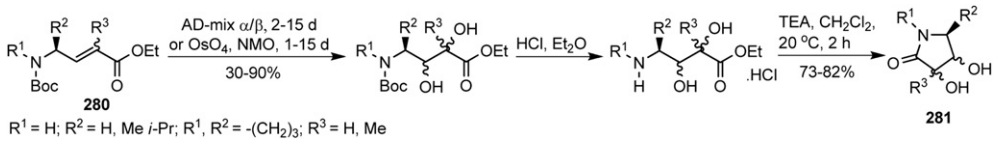
The amino enolates **278** underwent intramolecular N-acylation in the presence of $SOCl_2$ or MeOSOCl to produce the corresponding multisubstituted γ-butyrolactams **279** in good yields as disclosed by Shindo et al. (Scheme 92).[103] They further observed that the reaction was successful if only one of the leaving groups, such as benzyl is activated.



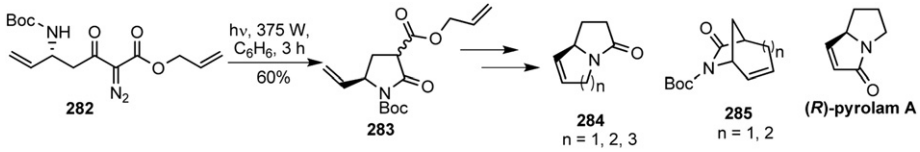
Scheme 92.

Grison's group synthesized the 3,4-dihydroxy-pyrrolidin-2-ones **281** via a simple strategy based on the asymmetric dihydroxylation of the γ-amino-α,β-unsaturated esters (**280**) followed by TEA-induced intramolecular lactamization (Scheme 93). These compounds exhibited a partial inhibition for α-glucosidase, but were inactive towards other glycosidases.[104]

Very recently Mo et al. disclosed the synthesis of a chiral pyrrolidine derivative **283** from the *N*-Boc-protected diazo compound **282** via a Wolff rearrangement under photochemical irradiation conditions (Scheme 94).[105] The pyrrolidine derivative **283** was utilized for the synthesis of a variety of condensed (**284**) and transannular ring structures **285** incorporating pyrrolidine via RCM as a key step. Using the strategy these workers were also able to achieve the synthesis of (*R*)-pyrolam A.

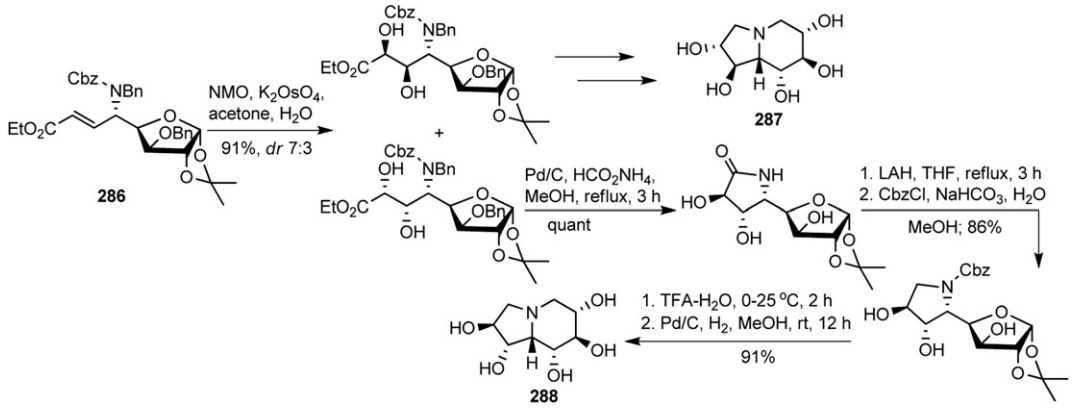


Scheme 93.



Scheme 94.

Dhavale et al. demonstrated the synthesis of new pentahydroxyindolizidine alkaloids **287** and **288** from the pyrrolidines, which in turn were generated from a sugar-derived γ-amino α,β-unsaturated ester (**286**). Their synthetic strategy to generate the pyrrolidines involved asymmetric dihydroxylation, and hydrogenation followed by Pd/C-mediated catalytic hydrogenation and *N*-Cbz deprotection (Scheme 95). Removal of the 1,2-acetonide functionality followed by reductive amination gave the final products. Glycosidase inhibitory activity studies indicated that **287** and **288** inhibit β-xylanase and β-glucosidase in the millimolar range.[106]



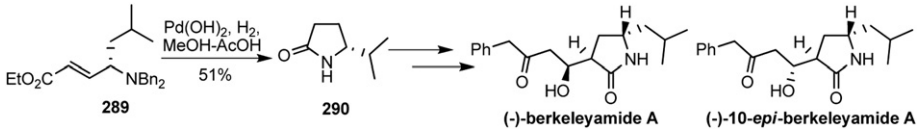
Scheme 95.

Very recently, Sperry et al. reported $Pd(OH)_2$-mediated hydrogenation of the allylamine derivative **289** under acidic conditions to effect lactamization to afford the 2-pyrrolidinone **290** (Scheme 96). The pyrrolidinone **290** was further utilized to achieve the synthesis of the natural product, (−)-berkeleyamide A, along with (−)-10-*epi*-berkeleyamide A.[107]

In a similar strategy, Sudalai's group achieved the synthesis of chiral pyrrolidones **297** and **298** (Scheme 98).[109] After dihydroxylation of the double bond in **295**, the product **296**, upon hydrogenation in the presence of Raney-Ni, yielded **297**. On the other hand, a direct hydrogenation of **295** yielded a lactam **298**.

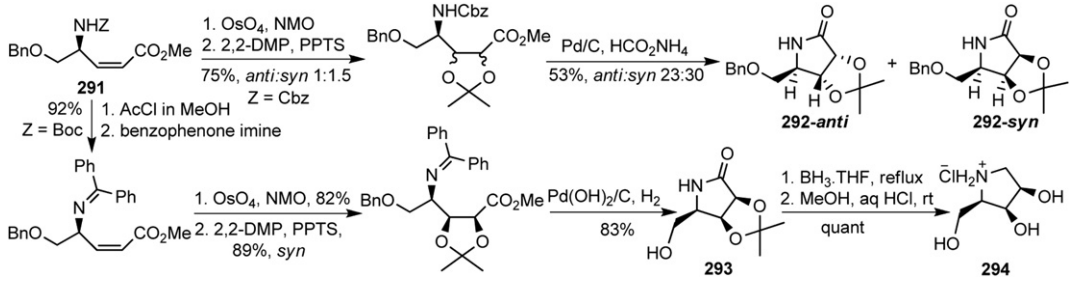
Davies et al. demonstrated that chemoselective *N*-allyl deprotection of the conjugate addition products **299** and **301** of lithium amide and *N*,*N*-bisallylamine by treating with $Pd(PPh_3)_4$ and 1,3-DMBA followed by intramolecular cyclization yielded aminopyrrolidinones **300** and **302**, respectively, in excellent yields and high ees (Scheme 99).[110]

De Kimpe et al. reported that the conversion of 2-alkoxy-4-amino-2-pentanoate (**303**) into 1-isopropyl-3-methoxy-5,5-

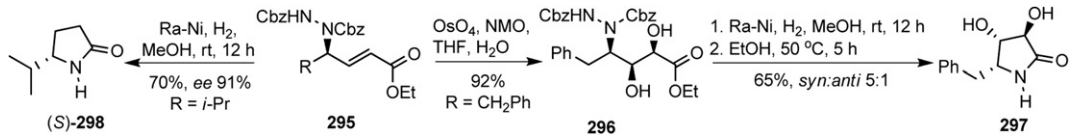


Scheme 96.

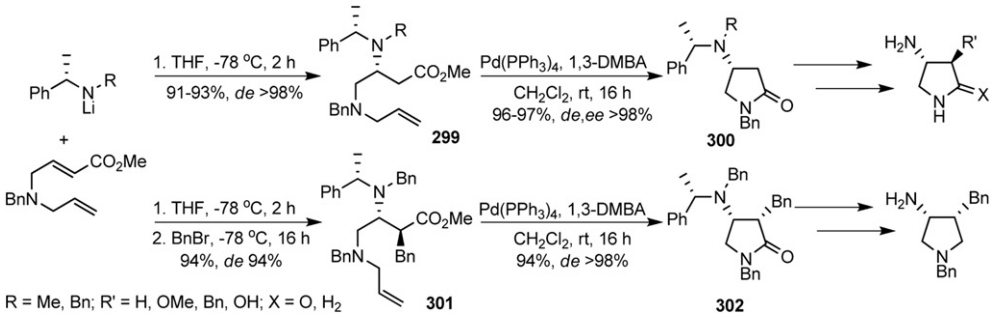
Kim et al. synthesized the γ-lactams **292** and **293** including D-iminolyxitol (**294**), a potent α-galactosidase inhibitor as shown in Scheme 97. The process involved dihydroxylation of the double bond in **291** followed by transformation into an isopropylidene dimethylpyrrolidin-2-one (**305**), through spontaneous cyclization of the intermediate 2-methoxypentanoate, originated by alkaline work up of the hydrogenated product of the hydrochloride salt of **304** on silica gel (Scheme 100).[111]



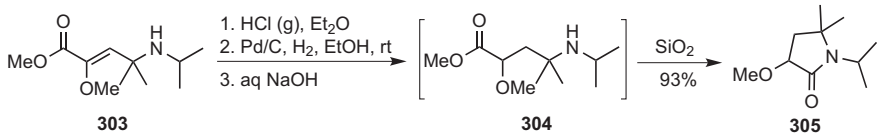
Scheme 97.



Scheme 98.

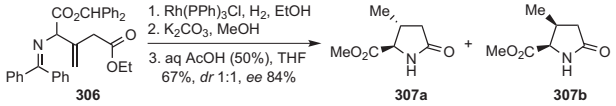


Scheme 99.



Scheme 100.

Elsner et al. described the transformation of the α-vinylated imino ester **306** into the corresponding 2,3-disubstituted γ-lactams (**307a**,**b**) by a three-step process involving homogeneous hydrogenation of the double bond with Wilkinson's catalyst followed by transesterification of the two ester groups and subsequent hydrolysis/cyclization with aq AcOH, as shown in Scheme 101.[112]



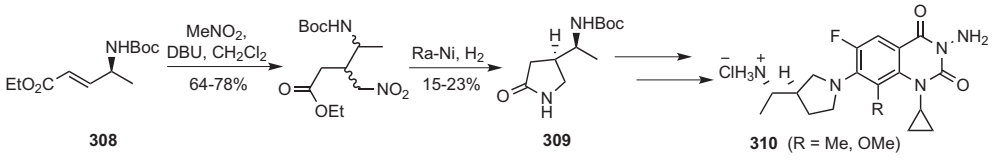
Scheme 101.

Beylin et al. described the synthesis of the chiral γ-lactam (**309**), side chain of the potent gyrase/topoisomerase inhibitors and antibacterial agents, amino-quinazolinediones (**310**), by intramolecular reductive cyclization of the Michael addition product of $MeNO_2$ to enantiomerically enriched δ-aminoenoate (**308**) (Scheme 102).[113]

Mukaiyama et al. developed a new method for the synthesis of dihydropyridin-2-one (**316**) under weakly basic conditions from the substituted allylamine **315**, accessed by an addition reaction of Brassard's diene to nosyl imine **314** (Scheme 104).[115]

With the objective of developing an easy and scalable approach for the antitubercular compound R207910, our group developed a strategy to obtain 3-arylidene-2-quinolones (**318**) from the allylamines **317** via TFA-mediated tandem Claisen rearrangement, intramolecular cyclization and subsequent isomerization. A similar synthetic protocol with the MBH derivatives of acrylonitrile provided the 3-aryl-2-aminoquinolines (**319**) (Scheme 105).[116]

Lamaty et al. developed a new approach for the synthesis of 4-aryl-1-methyl-4-1*H*-pyrrolo [3,2-*c*]quinoline (**324**) and 4-amino-1-methyl-4-1*H*-pyrrolo-[3,2-*c*]quinoline (**325**) derivatives from the allylamine **320** using MW-assisted chemistry. The key steps involved RCM of the *N*,*N*-bisallylamine (**320**), and base-catalyzed aromatization and intramolecular lactamization to obtain **322**. Lactam (**322**) by $POCl_3$-mediated chlorination produce the imidoyl chloride (**323**). Pyrrolo[3,2-*c*]quinolines (**324** and **325**) were generated in good yields through amination or Pd-catalyzed cross coupling of the imidoyl chloride under MW conditions (Scheme 106).[117]

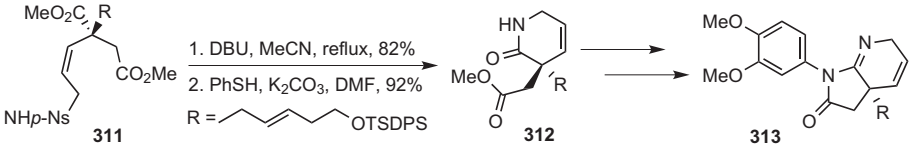


Scheme 102.

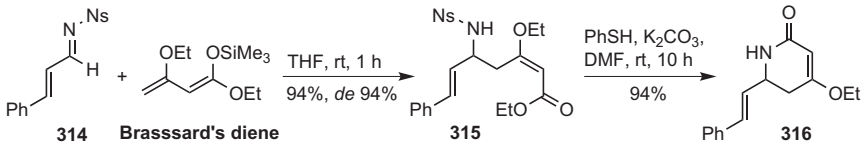
7.3. Synthesis of δ-lactams

The six-membered δ-lactam (**312**) was synthesized by Zhou and Magomedov from the appropriately substituted *N*-nosyl allylamine **311** via DBU-mediated intramolecular coupling of amine with ester in refluxing MeCN. The δ-lactam (**312**) was used as a precursor for preparing pyrrolo[2,3-*b*]pyridin-2-one (**313**) (Scheme 103).[114]

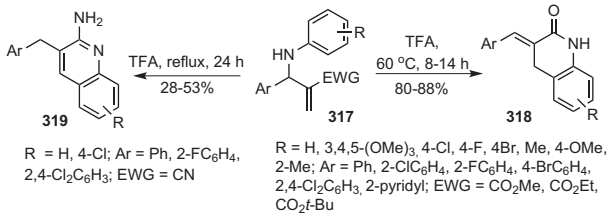
Breuning and Hein reported the first enantioselective synthesis of a C_2-symmetric 2-*endo*,6-*endo*-disubstituted bispidine (3,7-diazabicyclo[3.3.1]nonane) (**329**). The key step in the process was a Michael addition of the protected β-amino ester, methyl (*R*)-3-{*N*-



Scheme 103.



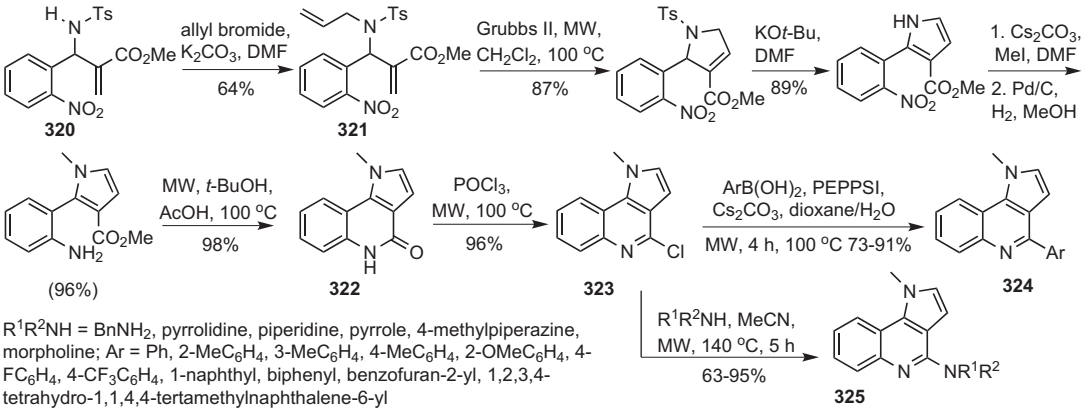
Scheme 104.



Scheme 105.

inhibitors, some of which were found to be effective via oral administration in a mouse model of chronic dermatitis (Scheme 108).[119] The strategy involved condensation of **330** with glycine ethyl ester followed by deprotection of the Boc group. Subsequent introduction of a TMB group followed by ester hydrolysis gave the amino acid, which upon lactamization furnished **331**, which was transformed to **332**.

Sakai et al. demonstrated that, on treatment with *t*-BuLi, linear 3-aminoalkanoates (**333**) were converted stereoselectively into five- and seven-membered lactams (*trans*-**334** and *cis*-**335a**, R^2=H



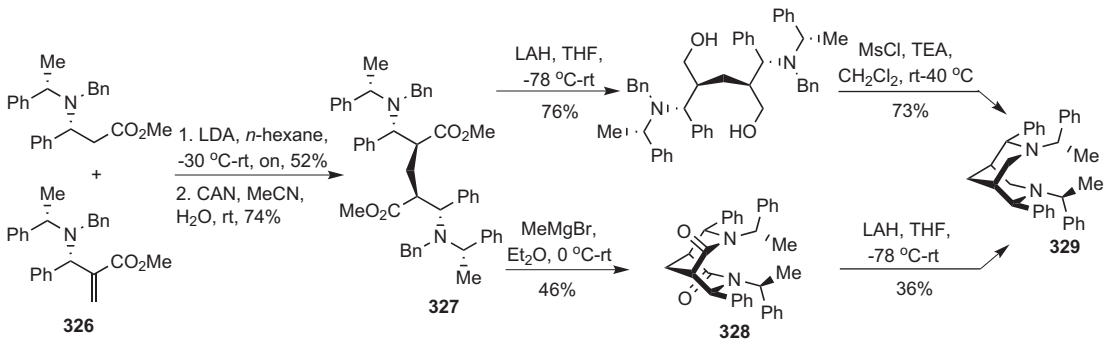
Scheme 106.

benzyl-*N*-[(*S*)-1-phenylethyl]amino}-3-phenylpropionate, to its α-methylene derivative (**326**), delivering an *anti*,*anti*-configured α,α′-methylene-bridged bis(β-amino ester) (**327**) as the major diastereomer. Oxidative debenzylation, and reduction of the ester group afforded the bis-alcohol, which upon mesylation undergo spontaneous cyclization to yield bispiperidine (**329**) in 73% yield (Scheme 107).[118] Alternative cyclization-reduction via dilactam (**328**) was less successful and gave **329** in low yields.

or **335b** R^2=Me) via an initial cyclization of **333** to the azetidin-2-one and a subsequent aza-[1,2] or -[2,3] rearrangement reaction (Scheme 109).[120]

7.5. Synthesis of macrocyclic lactams

Dory et al. achieved the synthesis of four C_n-symmetric macrocyclic lactams, *cyclo*-[$NHCH_2$–CH=CH–CH_2–CO]$_n$ (**340**,

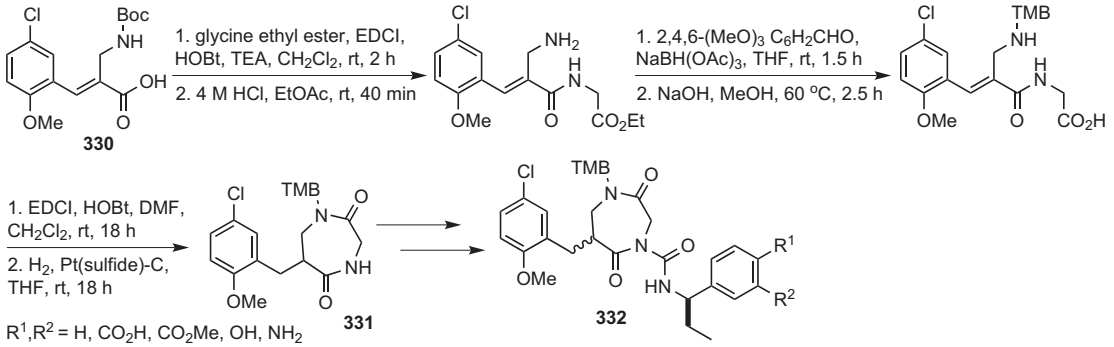


Scheme 107.

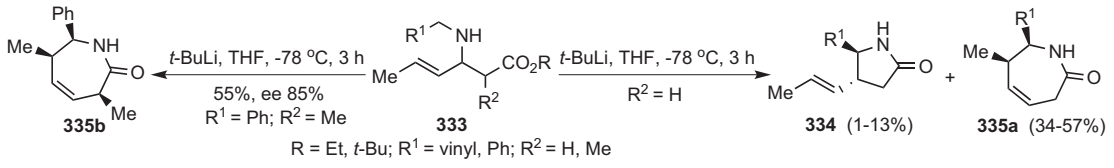
7.4. Synthesis of seven-membered lactams

Maruoka et al. synthesized a series of 6-benzyl-substituted 4-aminocarbonyl-1,4-diazepane-2,5-diones (**332**) from the β-amino acid (**330**). These compounds were evaluated as human chymase

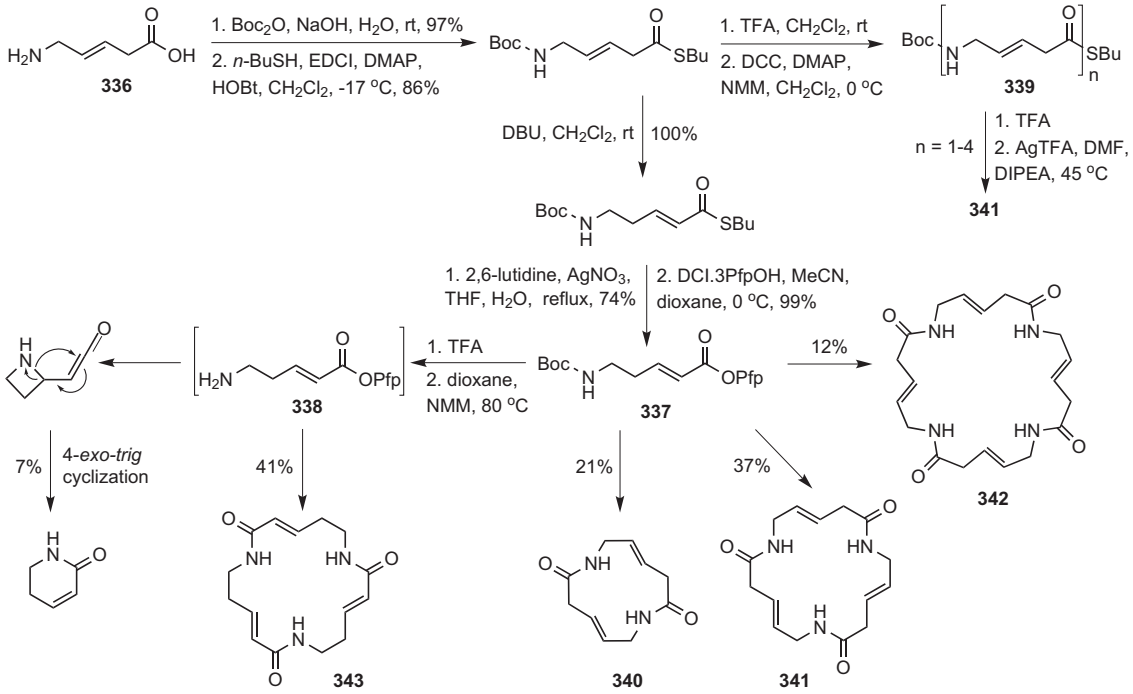
n=2; **341**, *n*=3; **342**, *n*=4) and *cyclo*-[NH–CH_2–CH_2–CH=CH–CO]$_3$ (**343**), through macrocyclization or cyclo-oligomerization of the aminoesters (**337**, **338**) or aminothioester (**339**), which were generated from *trans*-β-hydromuconic acid (**336**) (Scheme 110).[121]



Scheme 108.



Scheme 109.



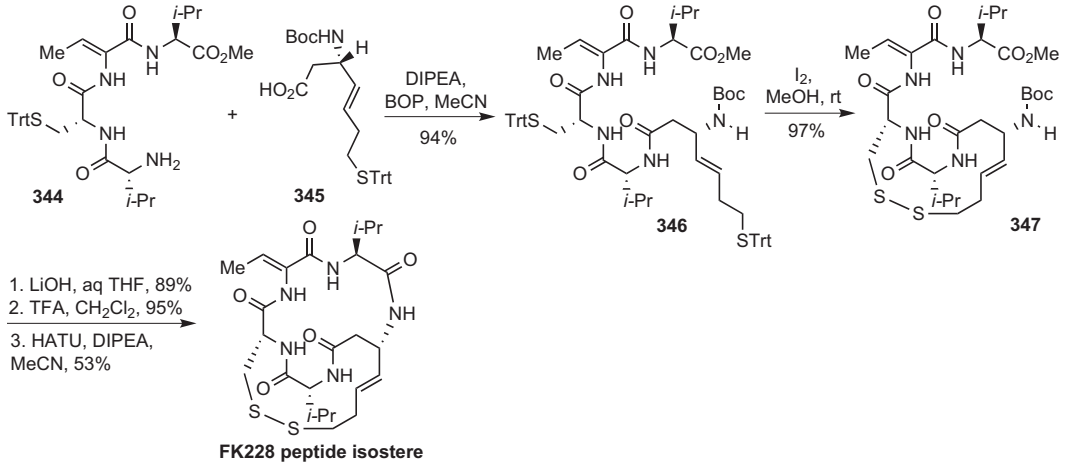
Scheme 110.

Bowers et al. engineered the synthesis of the naturally occurring and potent histone deacetylase (HDAC) inhibitor peptide isostere of FK228, via sequential I_2-mediated S–S bond formation and amide coupling (Scheme 111).[122] A coupling reaction of the allylamine **344** with **345** produced the amine **346**, which on treatment with I_2 underwent oxidative deprotection of the bis(thiotrityl) groups and concomitant cyclization to yield **347** in excellent yields. Saponification of the ester followed by removal of the Boc group gave the TFA salt, which underwent a macrolactamization reaction in the presence of HATU to the desired product.

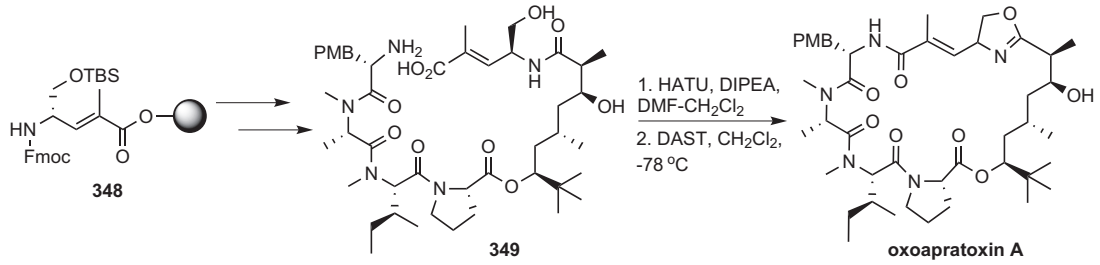
Cavelier's group accomplished a solid-support synthesis of oxoapratoxin A, an oxazoline analogue of apratoxin A, from the allylamine derivative **348** using Fmoc chemistry (Scheme 112).[123] The macrocyclization of the intermediate **349** was performed without epimerization, using HATU as the reagent, although BOP or DPPA also gave a similar product. Finally, DAST was employed for the conversion of the serine moiety into the corresponding oxazoline derivative to yield oxoapratoxin A in quantitative yield.

8. Synthesis of oxazolidinones

Oxazolidine is an important heterocyclic motif and serves as a useful synthetic intermediate, which can be manipulated to a range of significant structural subunits. Compounds belonging to this class could be readily generated from the allylamine derivatives through several routes such as (a) cyclization through intramolecular nucleophilic displacement of an alkoxy group with a neighbouring hydroxyl functionality, (b) opening of the epoxide ring generated on the alkene of an allyl carbamate by the neighbouring carbamate moiety, (c) CO_2 insertion and (d) CO insertion.



Scheme 111.



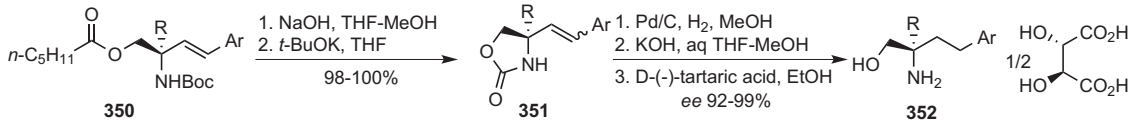
Scheme 112.

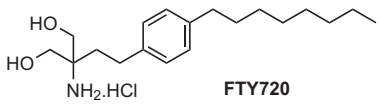
8.1. Synthesis via participation of neighbouring hydroxyl functionality

Nishi's group reported the synthesis of oxazolidinones (**351**) by deprotection of the ester group of substituted allyl carbamates **350** followed by KO*t*-Bu-mediated intramolecular cyclization as shown in Scheme 113. These oxazolidinones were transformed into enantiomerically enriched α,α-disubstituted α-amino alcohols **351**, which were precursors to intermediates of a novel immunomodulator FTY720.[124]

Similarly, Martinkova et al. employed NaH-mediated intramolecular cyclization to transform the allyl carbamate **354** into oxazolidinone **355**, which was utilized for the stereoselective synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid (*ent*-HMG) and (+)-myriocin (Scheme 115).[126]

Oxazolidinone **357**, generated from the acetonide-protected allylamine **356** and subsequent NaH-mediated intramolecular cyclization, was used by Ichikawa et al. for the synthesis of a cytotoxic anhydrosphingosine marine natural product, pachastrissamine, as depicted in Scheme 116.[127]

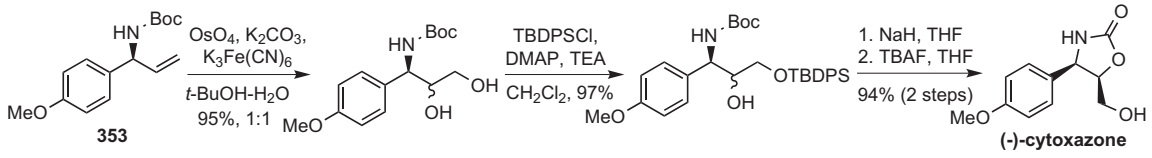




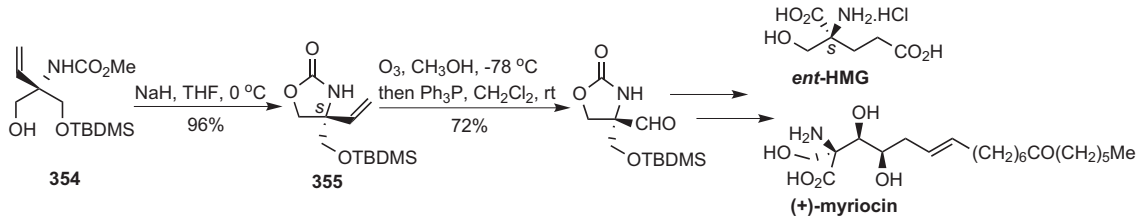
Scheme 113.

Singh and Han transformed the achiral *N*-Boc protected allylamine **353** into (−)-cytoxazone, a cytokinin modulator isolated from *Streptomyces* species, via base-promoted displacement of the alkoxy group of the carbamate with a secondary hydroxyl functionality (Scheme 114).[125]

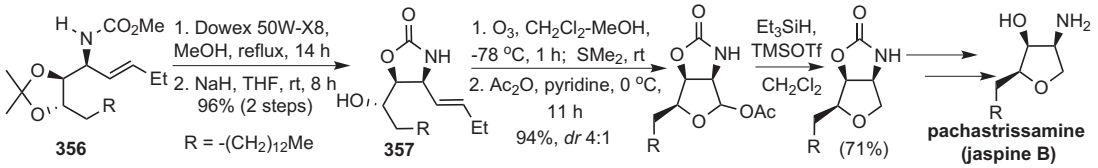
Mann's group prepared the oxazolidone derivative **359** by treating the *anti*-allylamine **358** with NaH, as shown in Scheme 117. The *anti* stereochemistry of **358** was assigned on the basis of an NOE experiment of the synthesized oxazolidone derivative (**359**).[128] The amine was also employed for the synthesis of



Scheme 114.

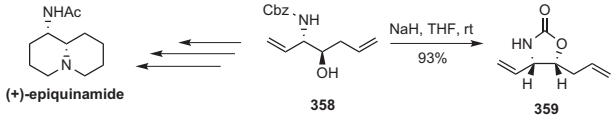


Scheme 115.



Scheme 116.

(+)-epiquinamide. The allylamine derivative was reacted with isopropenyl acetate to yield the *N*-acylated product. Hydroformylation of the double bond followed by hydrogenation in the presence of Pearlman's catalyst led to the production of (+)-epiquinamide via four reductive reactions in one pot.



Scheme 117.

Kim et al. described the stereoselective synthesis of bioactive (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid hydrochloride salt (**362**) by functional transformation of the substituted allylamine **360** via an oxazolidinone intermediate **361** (Scheme 118).[129]

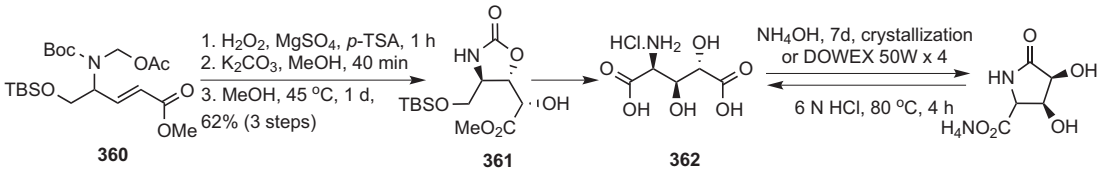
Similarly, Evans et al. also demonstrated the synthesis of oxazolidinone (**367**) from 3-amino-substituted 1-arylthio-1-nitroalkene (**366**). In the presence of SiO_2, the intramolecular epoxide ring opening initiated by the carbamate led to subsequent elimination of the nitro group followed by migration of the thioester group (Scheme 121).[132]

Seo et al. developed a strategy to convert allyl carbamates **368** into the corresponding α-hydroxy-β-amino acids (**370**) using oxazolidinones **369a**,**b** as the intermediates (Scheme 122).[133]

Lindsley's group prepared oxazolidinone **372** by treating the allylamine **371** with $SOCl_2$, which was transformed into **373**, an intermediate that was used in the synthesis of lucentamycin A (Scheme 123).[134]

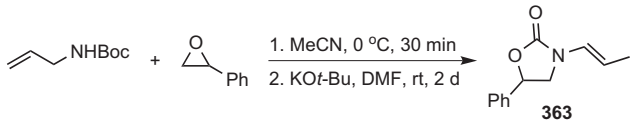
8.3. Synthesis via CO_2 insertion reactions

Munoz et al. developed a one-pot procedure for the convenient synthesis of oxazolidinones (**375**) from substituted allylamines **374**



Scheme 118.

In a different approach, Wrobel et al. synthesized oxazolidinone **363** using base-mediated intermolecular attack of the hydroxyl functionality, originated by epoxide ring opening of 2-phenyloxirane with allyl carbamate (Scheme 119).[130]



Scheme 119.

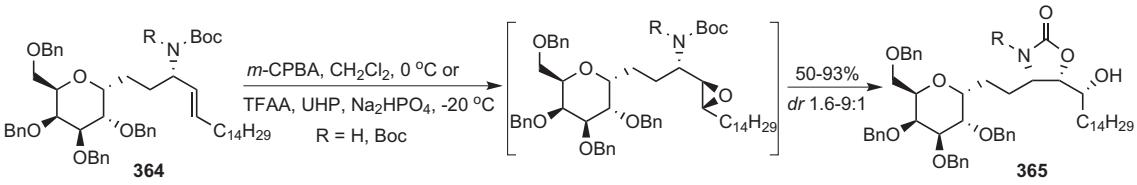
8.2. Synthesis via participation of neighbouring carbamate functionality

Wipf and Pierce reported the synthesis of oxazolidinones (**365**) from the allyl carbamates **364** via epoxidation of the alkene with *m*-CPBA followed by in situ ring opening by the carbamate group (Scheme 120).[131]

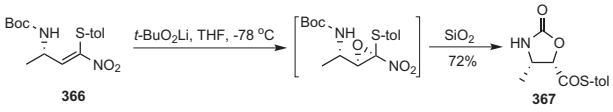
using PhTMG as a base and a solution of CO_2 in MeCN followed by the addition of I_2 (Scheme 124).[135] Later, they extended this methodology for the asymmetric synthesis of *N*-protected oxazolidinones **377**. Here, the iodocyclization was applied to enantiomerically pure allylphenethyl amine **376** in the presence of CO_2 (Scheme 125).

The synthesis of 5-vinyloxazolidinones (**379**) from (*E*)-4-(benzylamino)-2-butenyl methyl carbonates (**378**) by Yoshida's group involved a CO_2 fixation–elimination process in the presence of a Pd catalyst. They observed that the presence of DBU is necessary for the efficient fixation of CO_2 (Scheme 126). Carrying out the reaction in argon atmosphere decreased the yield significantly, due to the formation of aziridines **380** (Scheme 126).[136]

Vargas et al. disclosed a one-pot procedure for the preparation of enantiomerically pure oxazolidinone, e.g., **383** from the *N*,*N*-dibenzylallylamine derivative **381** via sequential epoxide formation to generate **382**, and monodeprotection of the amino group followed by $NaHCO_3$ treatment (Scheme 127).[137]



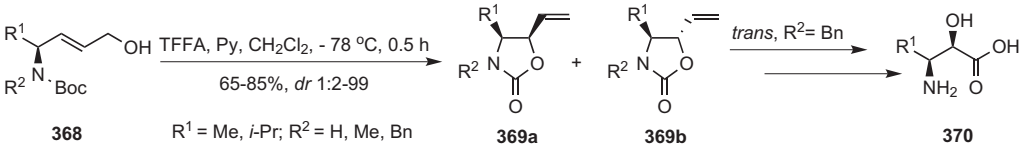
Scheme 120.



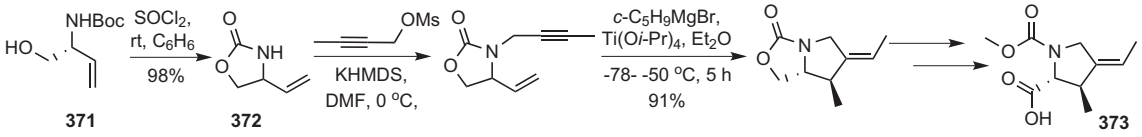
Scheme 121.

8.4. Synthesis via CO insertion reactions

Chandrasekhar and Tiwari achieved the stereoselective synthesis of the C10–C24 fragment (**386**) of a macrocyclic spermidine alkaloid, (+)-cannabisativine, via a ring-closing metathesis reaction of the oxazolidinone (**385**), generated from the highly substituted



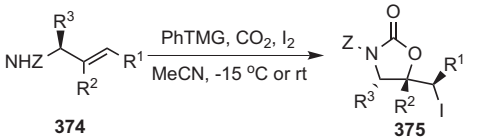
Scheme 122.



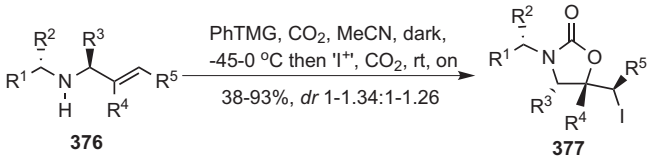
Scheme 123.

allylamine derivative (**384**) containing a β-hydroxyl group by reacting with $(Im)_2CO$ (Scheme 128).[138]

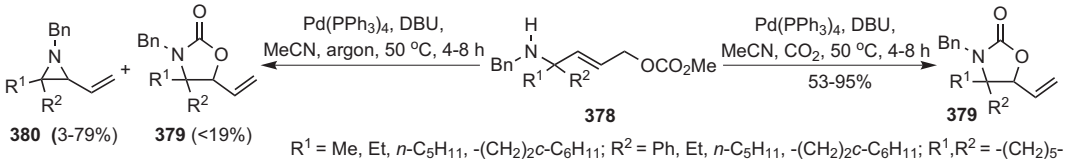
In a more recent report, Pyne's group adopted similar strategy for the conversion of allylamine derivative **387** to hyacinthacine alkaloids, hyacinthacines B3 and B7, which are known to exhibit relatively weak glycosidase inhibitory activities and their absolute configuration was also established (Scheme 129).[139] Triphosgene



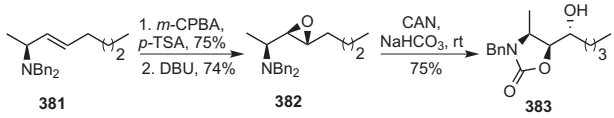
Scheme 124.



Scheme 125.



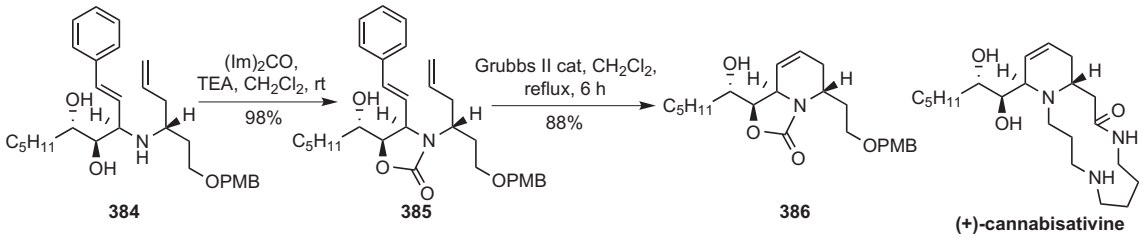
Scheme 126.



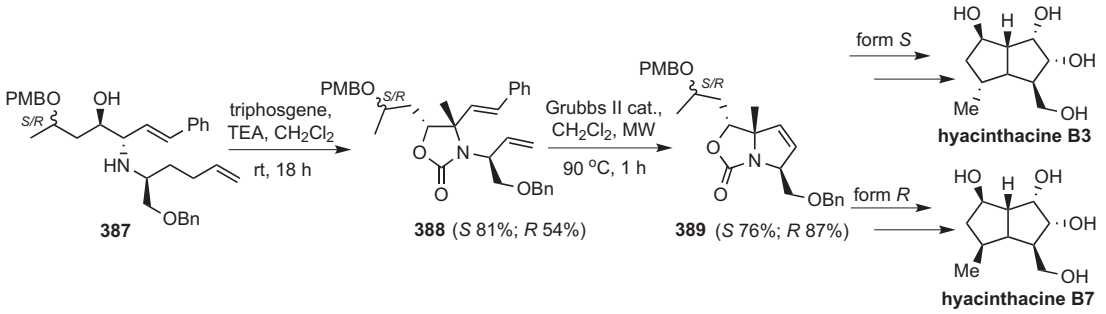
Scheme 127.

was used as the CO source by these workers to prepare the oxazolidine **388**, which undergoes the metathesis reaction to yield the bicyclic compound **389**.

In order to determine the stereochemistry of the diamines **391**, Cui et al. transformed **390** into their corresponding imdazolidine-2-thiones (**392**) as illustrated in Scheme 130.[140] The diamine,

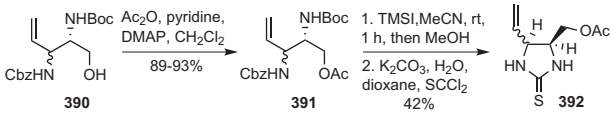


Scheme 128.



Scheme 129.

obtained by sequential hydroxyl protection followed by amino deprotection, was treated with thiophosgene in the presence of a base to give their corresponding imdazolidine-2-thiones (**392**).



Scheme 130.

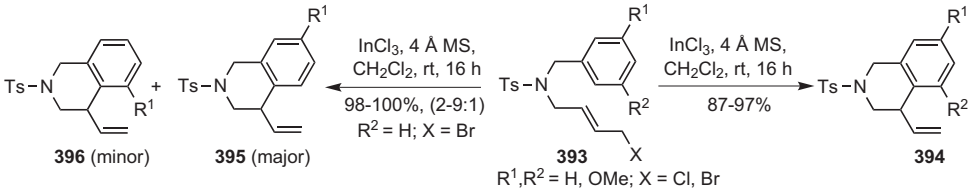
9. Friedel–Crafts reactions

Intramolecular Friedel–Crafts alkylation of *N*-benzylated or -arylated allylamines has been successfully employed to achieve the synthesis of a variety of *N*-heterocycles. Hayashi and Cook synthesized the *N*-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline derivatives (**394**–**396**) from the *N*-benzylated allylamines (**393**) by an $InCl_3$-mediated intramolecular Friedel–Crafts reaction (Scheme 131).[141]

Bandini et al. transformed the allylamines **400** tethered to an indole moiety into 4-substituted 1,2,3,4-tetrahydro-β-carbolines (**401a**,**b**) by $InBr_3$-catalyzed intramolecular Friedel–Crafts cyclization (Scheme 133). The amines **400** in turn were prepared from another amine **399** via ring-closing metathesis. An asymmetric version of this reaction was attempted with aluminium-based chiral Lewis acids to yield products with low ees.[143]

Subsequently, these workers described an alternative procedure for the conventional Friedel–Crafts strategy to generate 4-vinyl-1,2,3,4-tetrahydro-β-carbolines (**403**) and 1-vinyl-1,2,3,4-tetrahydro-γ-carbolines (**404** and **406**). The approach involved Pd-catalyzed regioselective intramolecular allylic alkylation of the allylamines (**402** and **405**) present at the 2-position of the indole subunit (Scheme 134).[144]

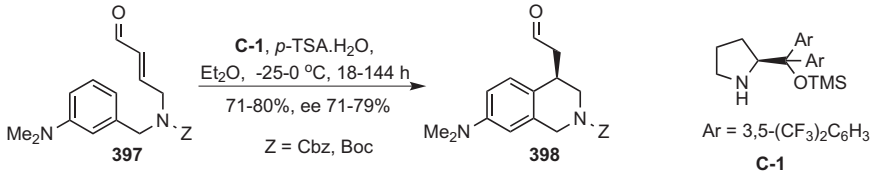
Liu and Widenhoefer used stoichiometric $CuCl_2$ as a terminal oxidant to construct a tetrahydro-β-carbolinone derivative (**408**) from the substituted allylamide **407** through Pd-catalyzed carboalkoxylation of the unactivated olefin (Scheme 135).[145]



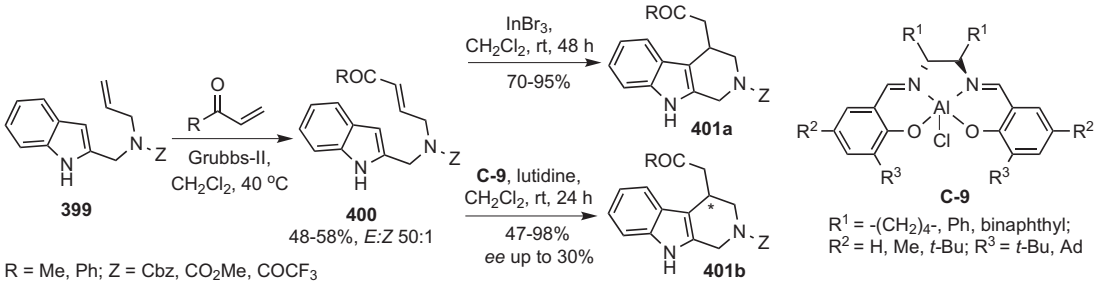
Scheme 131.

Xiao's group used an organocatalyst (**C-1**) for the enantioselective transformation of *N*-protected 4-[3-(dimethylamino)benzylamino] but-2-enals (**397**) into the corresponding tetrahydroisoquinolines (**398**) in good yields through intramolecular hydroarylations (Scheme 132).[142]

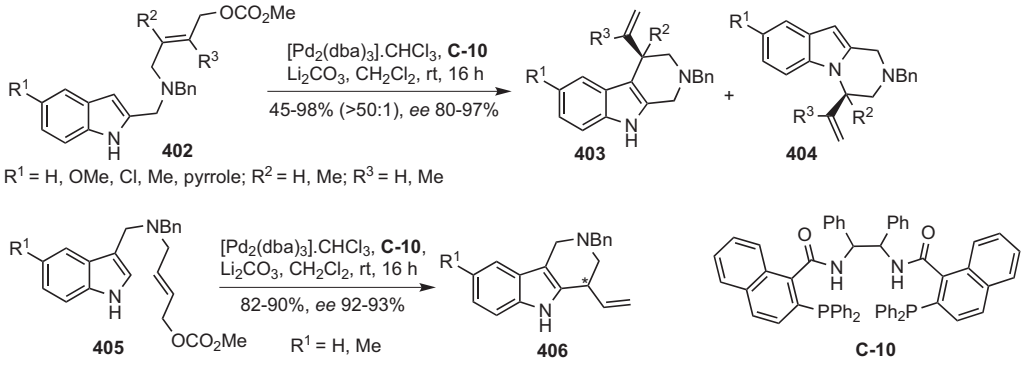
$AlCl_3$-mediated Friedel–Crafts cyclization followed by acetyl deprotection allowed Sakami et al. to transform the *N*-allyl acetanilide (**409**) into 4,4-dimethyl-1,2,3,4-tetrahydroquinoline (**410**)



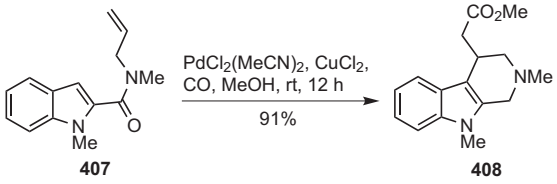
Scheme 132.



Scheme 133.



Scheme 134.



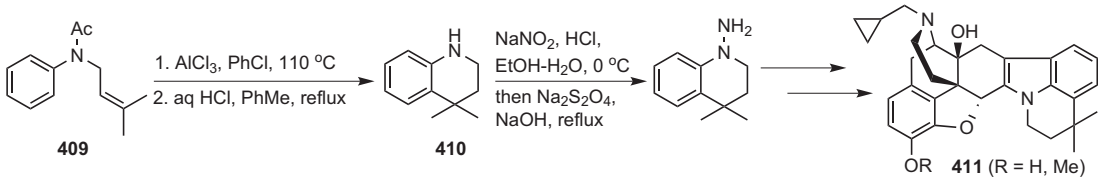
Scheme 135.

(Scheme 136), precursor of naltrindole (NTI) (**411**, R=H), a typical δ opioid antagonist, which exerted a marked and long-lasting antitussive effect in mice and rats.[146]

tetramethyl-8-methoxyjulolidine (**413**) via two sequential Friedel–Crafts type electrophilic aromatic substitution reactions. Compound **413** in turn was prepared from 3-methoxy-*N*,*N*-bis(3-methylbut-2-enyl)aniline **412** (Scheme 137).[147]

Lim and RajanBabu demonstrated that seleniranium ions at low temperatures (−90 to −78 °C) efficiently initiate Friedel–Crafts cyclization if a suitably placed arene is allowed to react, even when the arene is unactivated. This was exemplified by the synthesis of 1,2,3,4-tetrahydroquinolines (**417**) from *N*-allyl anilines (**416**) (Scheme 138).[148]

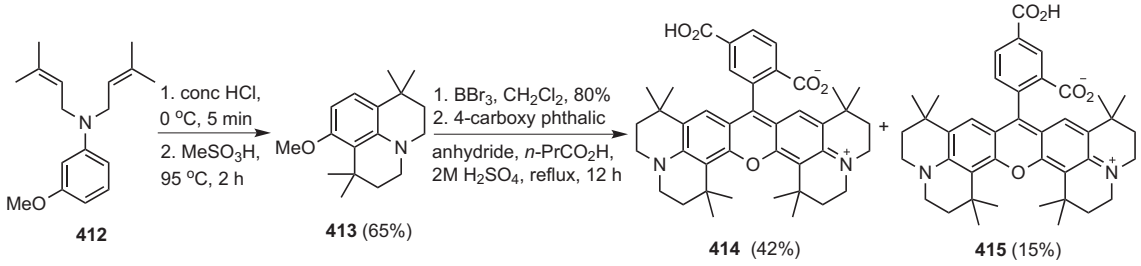
The superelectrophilic activation of *N*-allylic sulfonamides (**418**) in superacid (HF–SbF_5) was demonstrated by Thibaudeau et al. to



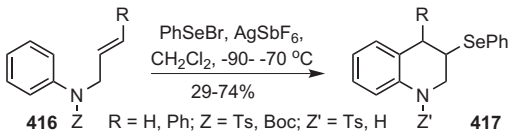
Scheme 136.

Uddin and Marnett achieved the synthesis of fluorescent dyes, 5- and 6-carboxy-X-rhodamines (**414** and **415**), having multiple *n*-propylene or γ,γ-dimethylpropylene groups bridging terminal nitrogen atoms and the central xanthene core, from 1,1,7,7-

be an efficient method to access either benzofused sultams (**419**–**423**) of different ring size through intramolecular Friedel–Crafts reaction or acyclic fluorinated products via hydrofluorination reactions (Scheme 139).[149] In the HF–SbF_5-promoted reactions, the



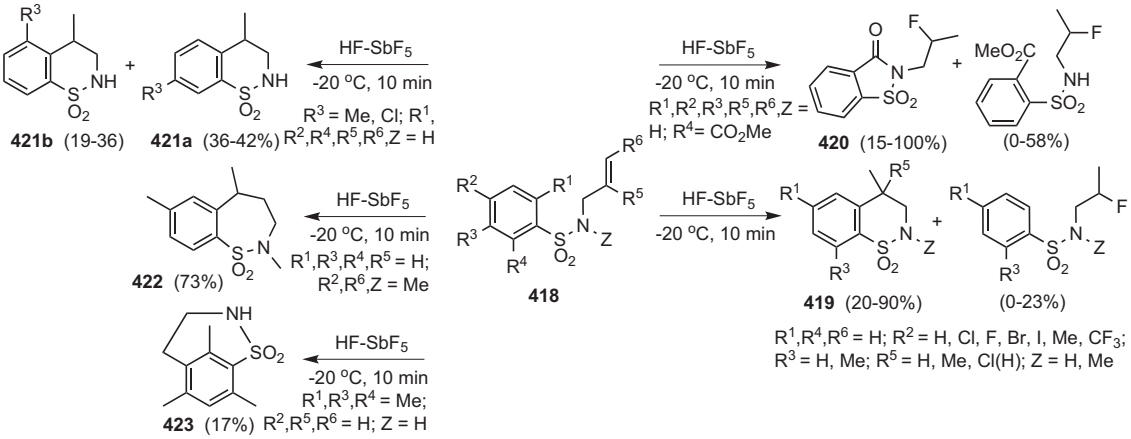
Scheme 137.



Scheme 138.

saponification and PPA-mediated intramolecular cyclization, as depicted in Scheme 142.[152]

N-Allyl-*N*-benzyl-substituted α-naphthylamines (**434**) were demonstrated by Palma et al. to undergo sequential aromatic amino-Claisen rearrangement and intramolecular Friedel–Crafts alkylation to provide access to a series of 13-acetyl-7,12-dihydro-7-ethylbenz[*e*]naphtho[1,2-*b*]azepines (**435**), as described in Scheme 143.[153] In continuation of this work, the same research group

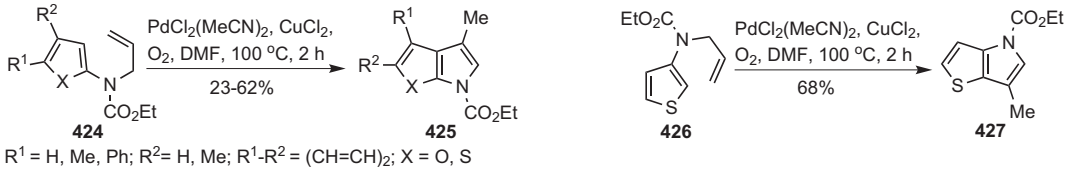


Scheme 139.

conditions were observed to be crucial for the selective formation of the sultam.

N-Allyl-*N*-carbethoxy-substituted aminothiophenes and furans (**424** and **426**) were subjected to Pd(II)-catalyzed intramolecular oxidative coupling reactions by Beccalli et al. to afford thieno- and furopyrroles (**425** and **427**), as shown in Scheme 140. The process involved nucleophilic attack of a heteroaromatic carbon or the internal carbon of the π-olefin complex through a 5-*exo*-*trig* ring formation.[150] The catalytic cycle was promoted by the use of $CuCl_2$ as the cocatalyst and O_2 as the re-oxidant.

synthesized a novel set of functionalized dibenzo[*c*,*f*]thiazolo[3,2-*a*]azepines (**436**) in a four-step protocol, starting from the substituted *N*-allyl-*N*-benzyl anilines (**434**).[154] Initially, dihydromorphanthridines (**437**) were prepared via a similar aromatic amino-Claisen-intramolecular Friedel–Crafts alkylation sequence. Dihydromorphanthridines (**437**) on selective oxidation with PCC followed by cyclocondensation of the oxidized products, morphanthridines (**438**), with mercaptoacetic acid produced dibenzo[*c*,*f*]thiazolo[3.2-*a*]azepines (**439**).

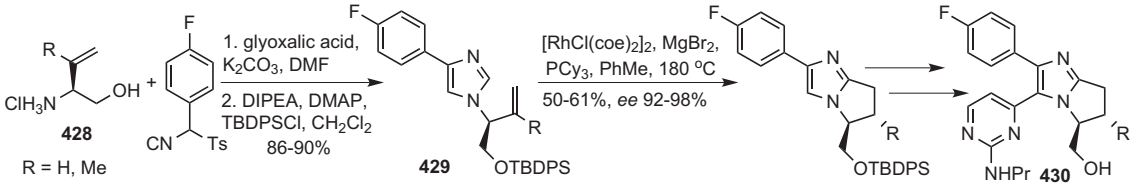


Scheme 140.

Ellman's group successfully transformed the substituted allylamines (**428**) into potent kinase inhibitors **430** by condensation with 4-fluorophenyl tosylmethyl isonitrile in the presence of glyoxylic acid followed by Rh-catalyzed intramolecular alkylation by C–H bond activation of the enantiopure *N*-allyl imidazoles (**429**) (Scheme 141).[151]

10. Cycloaddition reactions

The presence of a double bond in the allylamine makes it a suitable substrate for cycloaddition reactions. In the last few years, applications of allylamine derivatives for cycloaddition reactions to produce aza-systems have grown tremendously.

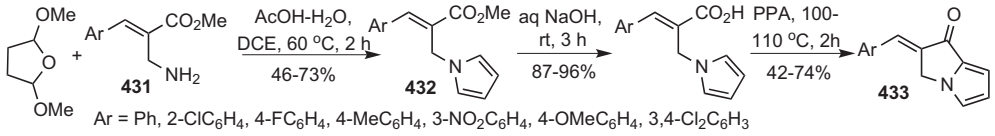


Scheme 141.

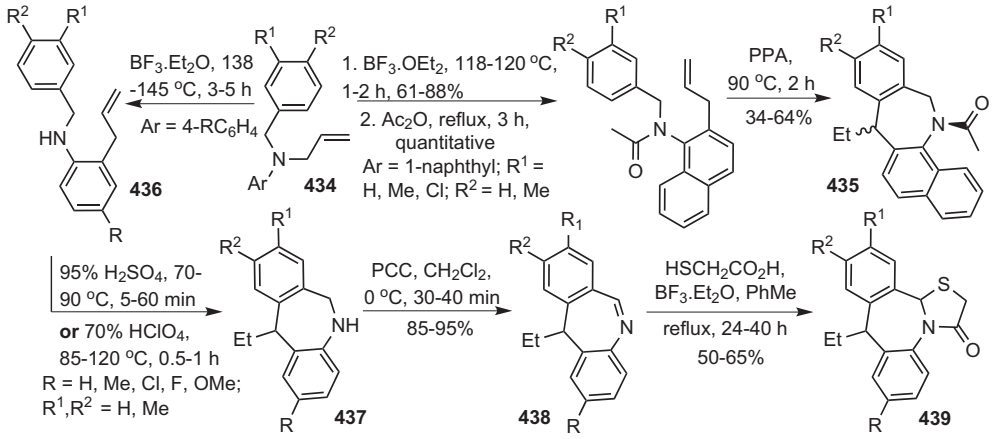
Our group has developed a general strategy to access 2-arylidene-2,3-dihydro-pyrrolizin-1-ones (**433**) via treatment of primary allylamines (**431**), afforded from the MBH adducts, with dimethoxytetrahydrofuran to produce **432** followed by

10.1. [1,3]-Dipolar cycloaddition reactions

Allylamine acts as an efficient dipolarophile to undergo cycloaddition reactions with different 1,3-dipoles including azomethine



Scheme 142.



Scheme 143.

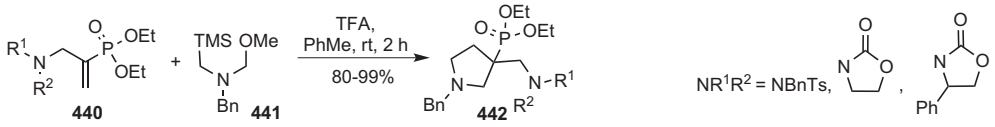
ylide, nitrile oxide, nitrone, nitrileimine and azide present within the allylamine or generated by functional manipulation, leading to the formation of fused heterocyclic systems. This reaction could be achieved intermolecularly by the use of an external 1,3-dipole to offer novel heterocycles.

Rabasso and Fadel synthesized β-aminopyrrolidinephosphonates (**442**) via 1,3-dipolar cycloaddition of amine **441** with vinylphosphonates **440** in the presence of trifluoroacetic acid (TFA) under mild conditions (Scheme 144). On the other hand similar reactions of **441** with the *Z*-isomer of β-(aminomethyl)vinylphosphonate afforded the *cis*-γ-aminopyrrolidinephosphonate (*cis*-**444**), whereas the *E*-isomer led to the *trans*-product (*trans*-**444**) (Scheme 145).[155]

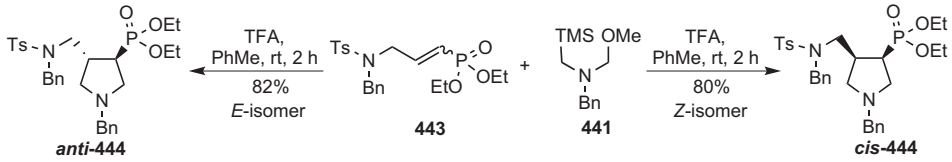
Neuschl et al. demonstrated the reaction of 2-allylamino benzaldehyde (**450**) with *N*-substituted glycine esters under MW irradiation and solvent-free conditions to generate ethyl hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylates (**451**), as shown in Scheme 147.[158]

This group also generated **453** from the allylamide **452**. The allylamine **453** yielded imidazolidin-4-one (**454**) via an intermolecular [1,3]-dipolar cycloaddition of the in situ formed azomethine ylide precursor **453** with the allylic double bond, under MW conditions (Scheme 148).[159]

Park et al. disclosed the synthesis of 1,2-dihydropyrrolo[3,4-*b*]indolizin-3-ones (**456**) having a fully colour-tunable fluorescent



Scheme 144.

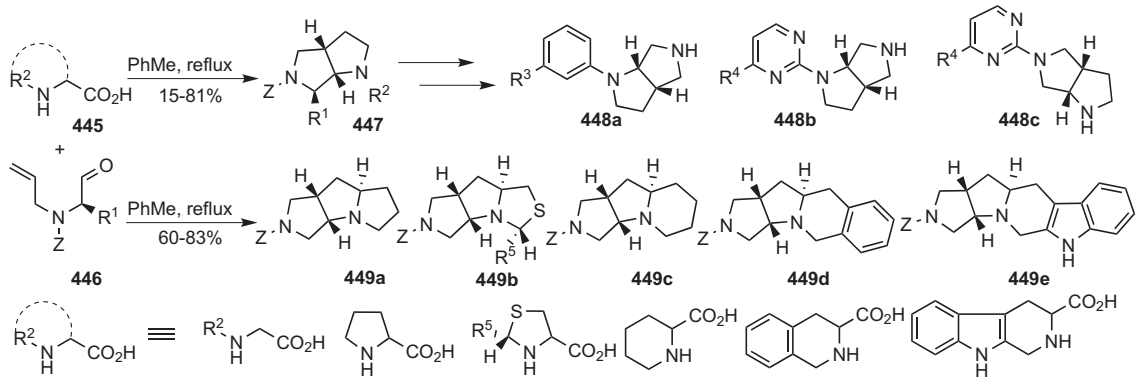


Scheme 145.

Huck et al. reported [1,3]-dipolar cycloadditions of azomethine ylides, obtained by reacting *N*-allyl-tethered alkenyl aldehydes (**446**) and *N*-benzylglycines **445**, to the double bond of the allylamine to form a series of orthogonally protected 2,7-diazabicyclo [3.3.0]octane (DABO) derivatives (**447** and **449**), as shown in Scheme 146.[156] These compounds displayed good potency at the 5-HT_{2C} receptor. Later, Poornachandran's group reported a similar strategy to access structurally important pyrrolo[3,4-*b*]pyrroles (**448**) and N-1–C-2 fused derivatives of pyrrolo[3,4-*b*]pyrroles (**449**). In their approach, they treated the *N*-allyl aldehyde (**446**) with glycine derivatives (**445**) and various cyclic secondary amino acids, respectively (Scheme 146).[157]

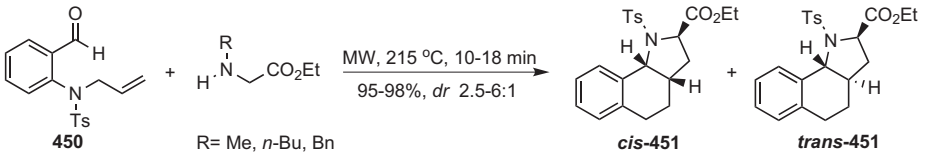
core skeleton via a base-induced [1,3]-dipolar cycloaddition in azomethine ylide **455** followed by DDQ-induced oxidation (Scheme 149).[160] The photophysical properties were studied with the deprotected analogues (**457**).

Ji et al. obtained a series of pyridine-substituted 3,6-diazabicyclo [3.2.0]heptanes **462** and **463**, which were observed to be selective agonists for α4β2 nicotinic acetylcholine receptor (Scheme 150).[161] The bicyclic core **461** of these compounds was generated from an allylamine **458**, which upon [1,3]-dipolar cycloaddition reaction yielded **459** isoxazolidine ring. Cleavage of this isoxazolidine yielded **460**, which after chiral resolution and cyclization gave the required subunit.

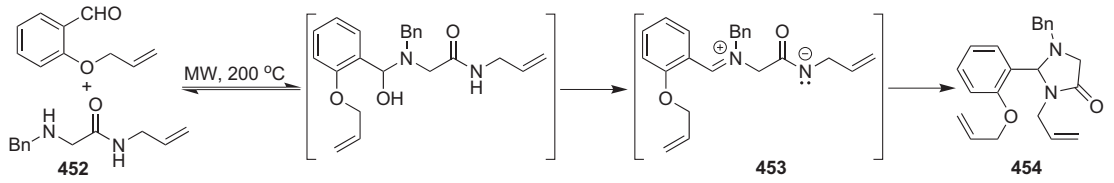


R^1 = H, Et, Bn; R^2 = H, Me, Bn, Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$NO_2C_6H_4$; R^3 = Cl, F, CF_3;
R^4 = CF_3, 2,3-$Cl_2C_6H_3$, 2,5-$F_2C_6H_3$; R^5 = H, Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4; Z = H, CO_2Et, Ts, SO_2Ph

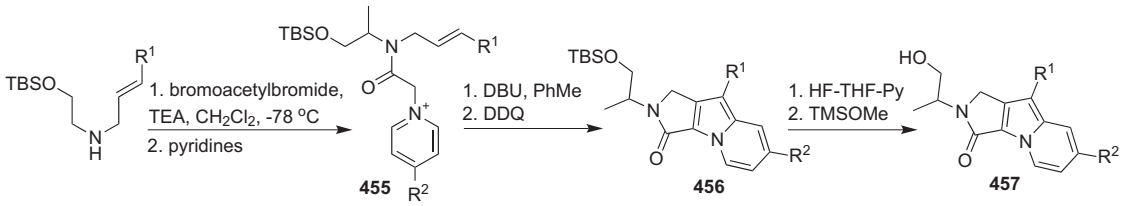
Scheme 146.



Scheme 147.

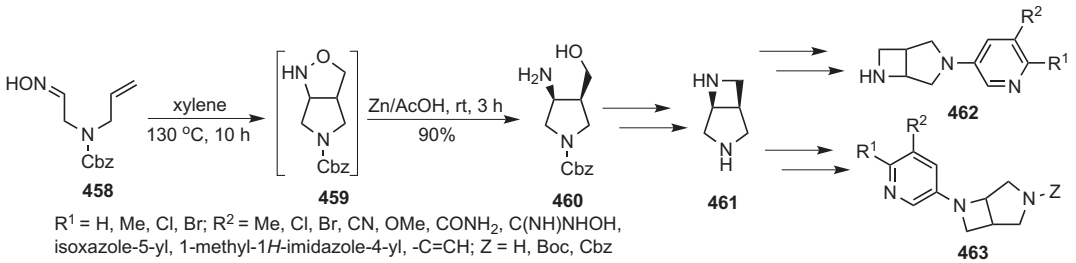


Scheme 148.



R^1 = Me, Ph, 2-$OMeC_6H_4$, thiophenyl; R^2 = H, OMe, CN, Ac, Ph

Scheme 149.

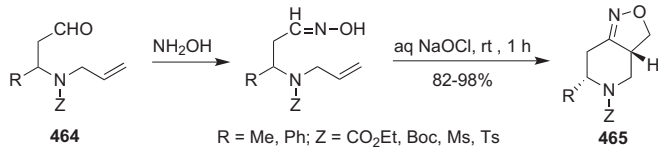


R^1 = H, Me, Cl, Br; R^2 = Me, Cl, Br, CN, OMe, $CONH_2$, C(NH)NHOH,
isoxazole-5-yl, 1-methyl-1*H*-imidazole-4-yl, -C=CH; Z = H, Boc, Cbz

Scheme 150.

Noguchi et al. described the synthesis of hexahydroisoxazolo [4,3-*c*]pyridines (**465**) via intramolecular [1,3]-dipolar cycloaddition reactions of nitrile oxides, derived from hydroxylamine derivatives of 3-(*N*-allylamino)propionaldehydes (**464**) (Scheme 151). They proposed that the *gauche–gauche* interaction between the substituents at the carbon atom adjacent to the tethered nitrogen caused the high levels of stereoselectivity.[162]

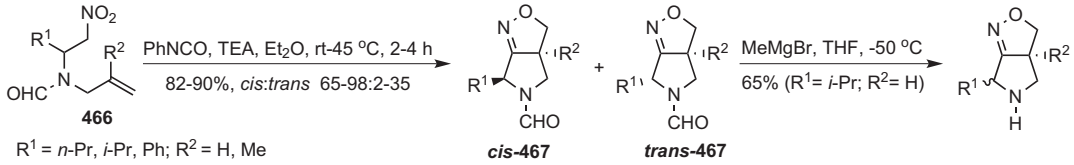
Similar intramolecular nitrile oxide cycloaddition (INOC) reactions of *N*-allyl-β-nitro amides (**466**) enabled Kamimura et al. to achieve the stereoselective synthesis of pyrroloisoxazoles (**467**) (Scheme 152).[163]



Scheme 151.

depicted in Scheme 156.[167] The compounds synthesized in this fashion were evaluated against free and intracellular live forms of *Trypanosoma cruzi* and *Leishmania chagasi* parasites using in vitro assays and their cytotoxicity determined.

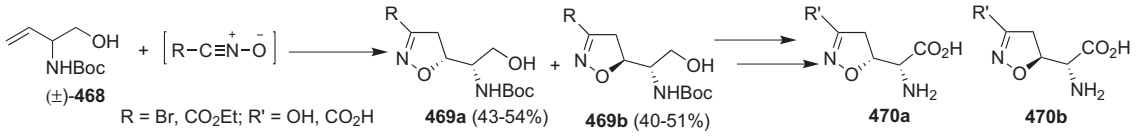
In the intermolecular version of this reaction, Crimmins et al. obtained the spirocyclic isoxazolidine **480** from the allyl carbamate and spironitrone **479**, as shown in Scheme 157.[168]



Scheme 152.

The intermolecular version of this reaction between the allyl carbamate (**468**) and nitrile oxide performed by De Micheli's group, yielded *erythro*- and *threo*-tricholomic acids (**470a**,**b**) via the alcohols **469a**,**b** and their activities at iGluRs and mGluRs were evaluated (Scheme 153).[164]

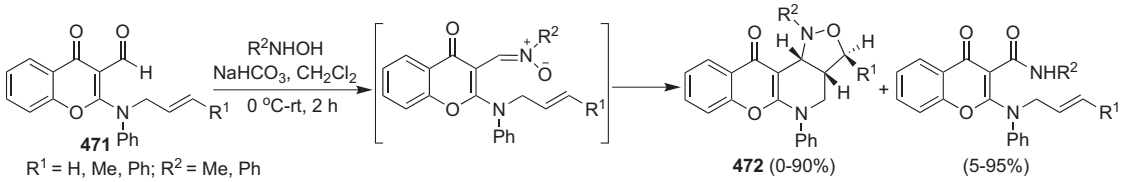
Unsaturated amino silyl nitronates, which are the intermediates in the reaction of the allylamines **481** with DBU–TMSCl, were shown by Dumez et al. to be efficient precursors to the highly selective intramolecular silylnitronate olefin cycloaddition (ISOC reaction) to afford trimethylsilyl isoxazolidines (**482**) (Scheme 158).[169]



Scheme 153.

Ishar et al. obtained fused isoxazolidines (**472**) in low-to-moderate yields via intramolecular [1,3]-cycloaddition of the nitrones generated in situ by reacting 2-(*N*-allyl-anilino)-3-formylchromones (**471**) and hydroxylamine derivatives, as displayed in Scheme 154.[165]

De Benassuti et al. developed a synthetic route to the enantiopure 2,3,3a,4,5,6-hexahydro-pyrrolo[3,4-*c*]pyrazoles (**485**) by means of a stereoselective intramolecular [1,3]-dipolar cycloaddition of homochiral nitrilimines (**484**) generated from the *N*,*N*-bisallylamino acetates (**483**) (Scheme 159).[170]

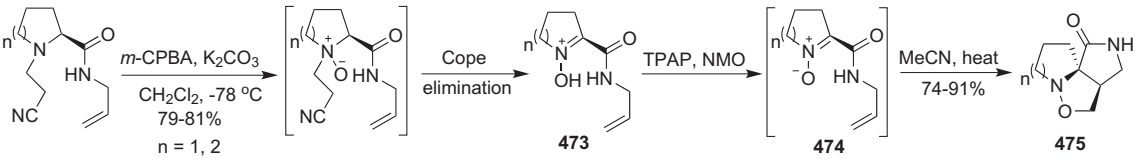


Scheme 154.

The tricyclic lactams (**475**) were synthesized by O'Neil's group from the nitrones (**474**), generated from the functionalized hydroxylamine derivatives **473** of (*S*)-proline or pipecolic acid by Cope elimination, and subsequent TPAP-promoted oxidation followed by an intramolecular [1,3]-dipolar cycloaddition reaction (Scheme 155).[166]

Quiclet-Sire and Zard discovered that the diazo intermediates formed in the reaction of hydrazones (**486a**,**b**) with I_2 could be trapped by an internal alkene, leading to pyrrolo[3,4-*c*]pyrazoles (**487a**,**b**) (Scheme 160).[171]

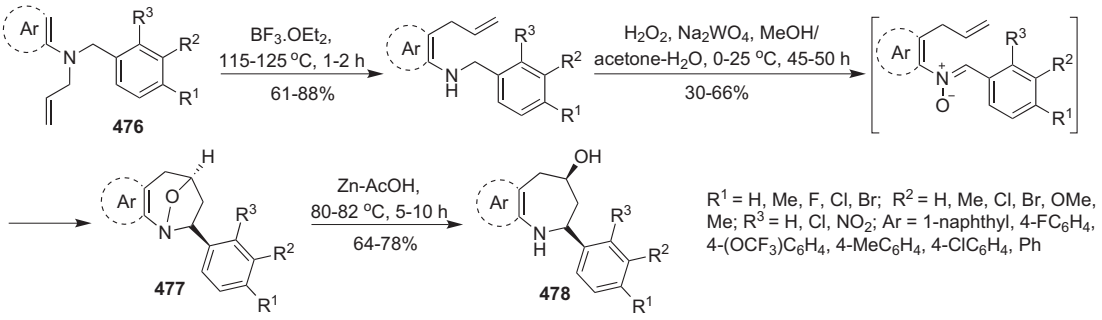
The intramolecular [1,3]-dipolar cycloaddition of linear azido alkynes **489** derived from aza-MBH adducts **488** enabled Lamaty's



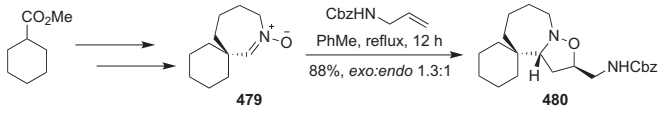
Scheme 155.

Palma et al. described the conversion of the *N*-allyl anilines (**476**) into isoxazolidines (**477**) in a sequential aromatic amino-Claisen rearrangement, and N-oxidation followed by an in situ [1,3]-dipolar cycloaddition reaction. These isoxazolidines (**477**) yielded *cis*-2-aryl-4-hydroxy-2,3,4,5-tetrahydro-1-benzazepines (**478**) via reductive cleavage of the isoxazolidinic N–O bond, as group to produce the *trans*-disubstituted triazolodiazepines **490** in good yields (Scheme 161).[172]

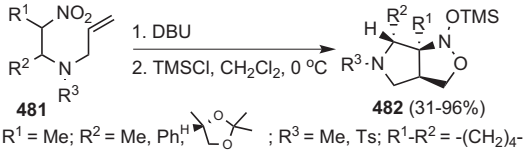
In a very recent report, our group has disclosed the synthesis of analogous annulated triazoles (**492**) from the appropriately substituted allylamines (**48**).[173] Our strategy was based on the modification of the ester moiety to produce the azide **491**, which



Scheme 156.



Scheme 157.



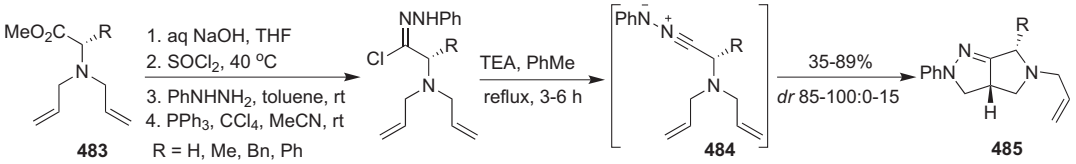
Scheme 158.

underwent 1,3-dipolar cycloaddition with the acetylene group present on the amino group (Scheme 162).

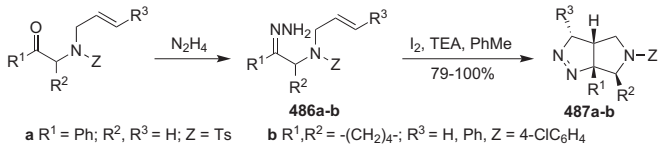
10.2. [2+2]-Cycloaddition reactions

Tkachenko et al. synthesized 4-fluoro-2,4-methanoproline (**495**), the first fluorinated analogue of a naturally occurring non-proteinogenic amino acid 2,4-methanoproline (**495a**), via photochemical intramolecular [2+2]-cyclization of diene **493** to obtain the 2-azabicyclo[2.1.1]hexane skeleton **494** followed by deprotection of the amine under acidic conditions (Scheme 163).[174]

N,*N*-Bisallylamine or *N*-vinyl allylamine derivatives undergo intramolecular [2+2]-cycloddition reactions leading to cyclobutane-fused bicyclic frameworks. Chirik et al. synthesized 3-azabicyclo [0.2.3]heptane derivatives (**497**) via Fe-catalyzed intramolecular [2+2]-cycloaddition reactions of bis-allylamines **496**, as shown in Scheme 164.[175]



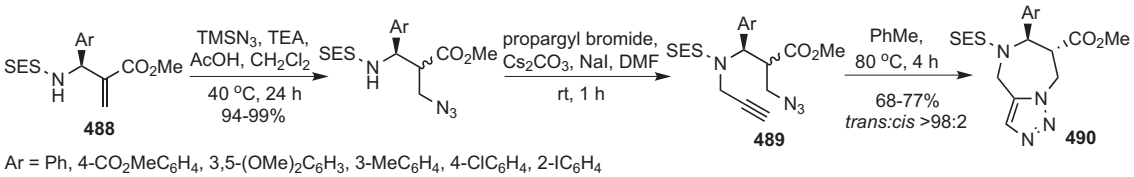
Scheme 159.



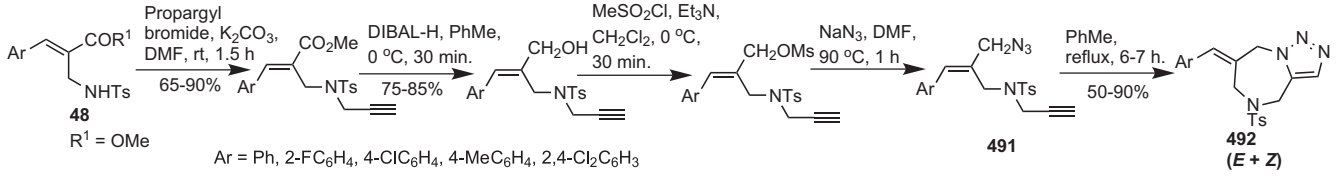
Scheme 160.

Alternatively, Malik et al. reported the synthesis of analogous compounds **498** from the bis-allylamines **496** under photochemical conditions in the presence of a Cu(I) catalyst in an ionic liquid at room temperature (Scheme 165).[176]

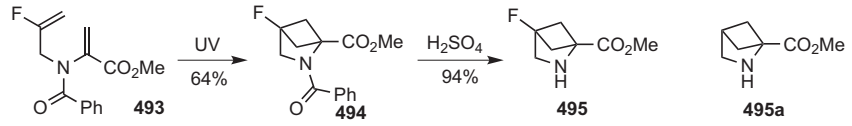
Sakamoto et al. reported the synthesis of tetracycles (**500**) from *N*,*N*-diallylcoumarin carboxamides **499** via photochemical reactions in the solid or solution phase (Scheme 166).[177]



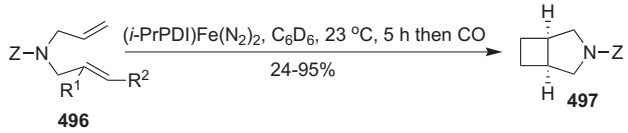
Scheme 161.



Scheme 162.

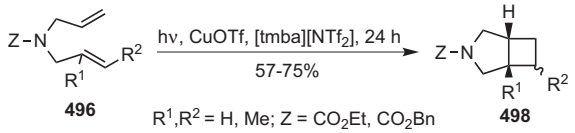


Scheme 163.



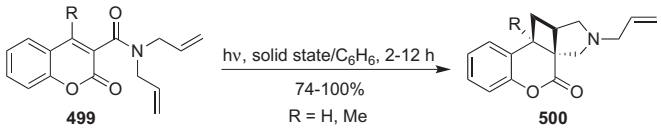
$R^1 = R^2 = H$, Z = H, *t*-Bu, Bn, Boc; *i*-PrPDI = 2,6-(2,6-*i*-$Pr_2C_6H_3NCMe)_2C_5H_3N$

Scheme 164.



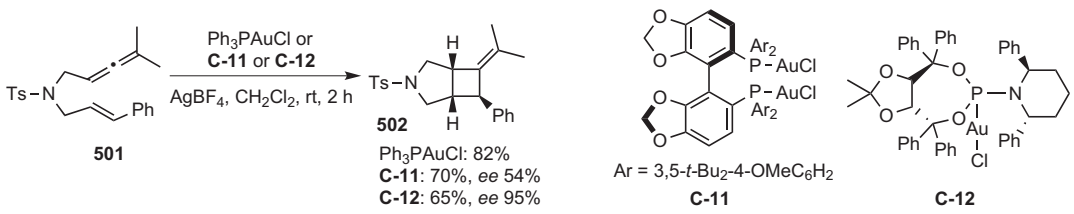
R^1,R^2 = H, Me; Z = CO_2Et, CO_2Bn

Scheme 165.



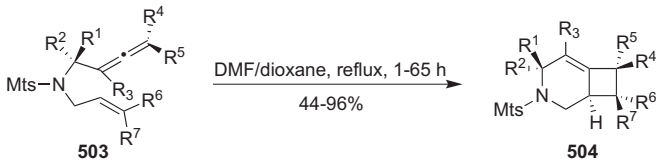
Scheme 166.

In another variation Luzung et al. disclosed the synthesis of 3-azabicyclo[3.2.0]heptane **502** containing an exocyclic double bond via a chiral biarylphosphinegold(I) (**C-11**)-catalyzed [2+2]-cycloaddition in **501** (Scheme 167).[178] Later, Fuerstner et al. demonstrated that the use of a gold–phosphoramidite complex **C-12**, bearing a TADDOL subunit with an acyclic backbone, produced the bicyclic aza-heterocycle **502** in excellent enantiomeric excess.[179]



Scheme 167.

Tanaka et al. disclosed a highly regio- and stereoselective formation of 3-azabicyclo[4.2.0]oct-5-ene derivatives (**504**) through intramolecular [2+2] cycloaddition of allenes **503** under thermal conditions, as shown in Scheme 168.[180]



R^1 = Me, *i*-Pr; R^2 = H, Me; R^3 = H, Me; R^4,R^5 = H, Me, Bu; R^6 = H, Me, CO_2Me, CN, Ph, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 4-CNC_6H_4; R^7 = H, Me, CN

Scheme 168.

Akritopoulou-Zanze et al. reported a new strategy for the construction of novel and uniquely shaped 3-azabicyclo[4.2.0]octan-4-one derivatives (**505**) containing up to five stereocenters by combining the Ugi multicomponent reaction with [2+2] enone-olefin photochemical transformations (Scheme 169).[181]

Ragains and Winkler developed a general approach for the synthesis of a bridged amino ketone **507** from the allyl carbamate **506** by a photocycloaddition reaction.[182] The cascade reaction involved the formation of a crossed aldol product and a retro Michael reaction (Scheme 170). The strategy was applied to the synthesis of peduncularine a core alkaloid of *Aristotelia*. Winkler and Fitzgerald extended the strategy for the stereoselective transformation of substituted *N*-vinyl allylamines **508** to 8-substituted azabicyclooctanones **509**.[183] The process involved sequential photocycloaddition, and retro-Mannich and Mannich reactions, as delineated in Scheme 171.

10.3. [3+2]-Cycloaddition reactions

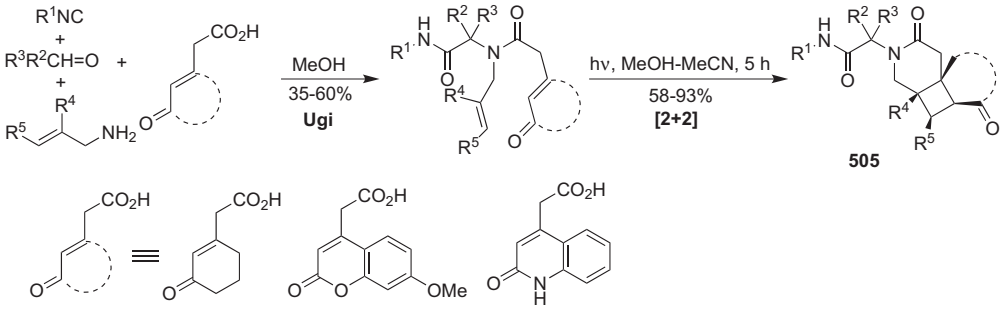
Intramolecular [3+2]-cycloaddition reactions involving the alkene moiety of the appropriately substituted allylamine provide an easy access to a wide range of fused-heterocyclic systems. Mascarenas et al. disclosed Pd-catalyzed intramolecular [3+2]-cycloaddition reactions of *N*-tethered alk-5-enylidenecyclopropanes **510** leading to cyclopenta[*c*]pyrrol-4(5*H*)-ones (**511**) with three stereocenters (Scheme 172).[184] Based on DFT study a probable mechanism for the transformation was postulated.

In an analogous reaction catalyzed by Rh(I), Yu's group demonstrated that vinylcyclopropanes without electron-withdrawing activating groups act as three-carbon synthons. They transformed the *trans*-vinylcyclopropane-enes (**512**) into five-membered ring systems (**513**) (Scheme 173).[185]

Very recently, these workers reported Rh(I)-catalyzed intramolecular [3+2]-cycloaddition reactions of 1-ene-, 1-yne and 1-allene-vinylcyclopropanes as an efficient tool to achieve the synthesis of octahydrocyclopenta[*c*]pyrroles (**515**) from substituted allylamines **514**, as shown in Scheme 174.[186]

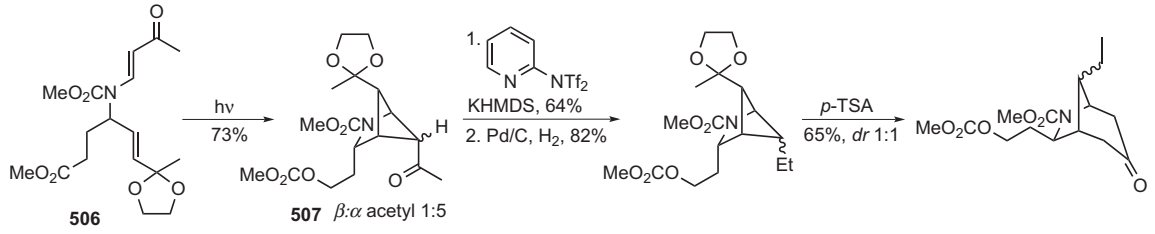
Ye et al. developed a metal-free catalytic intramolecular ylide annulations for the construction of a bicyclo[3.3.0] ring system **517** with three continuous stereogenic centrescentres in a single manipulation from the bisallylamine **516**, as shown in Scheme 175.[187]

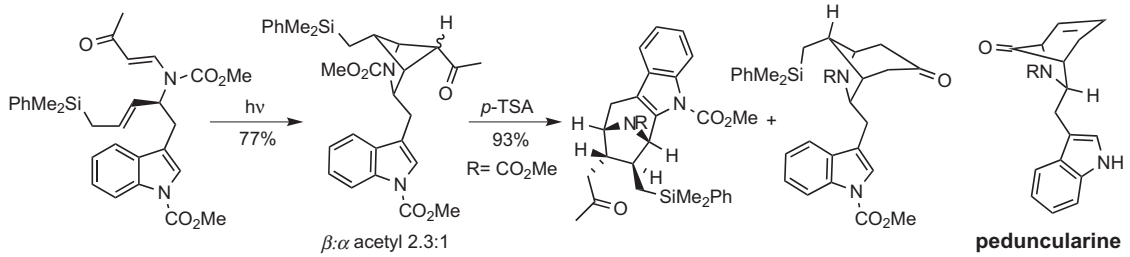
Later, Lee et al. reported the formation of linearly fused triquinanes **519a**,**b** from the bisallylamine derivative **518**, via intramolecular [3+2]-cycloaddition reactions of trimethylenemethane diyls, which were generated from the reaction of malonate anions with propynyl iodonium salts via alkylidene carbene intermediates (Scheme 176).[188]



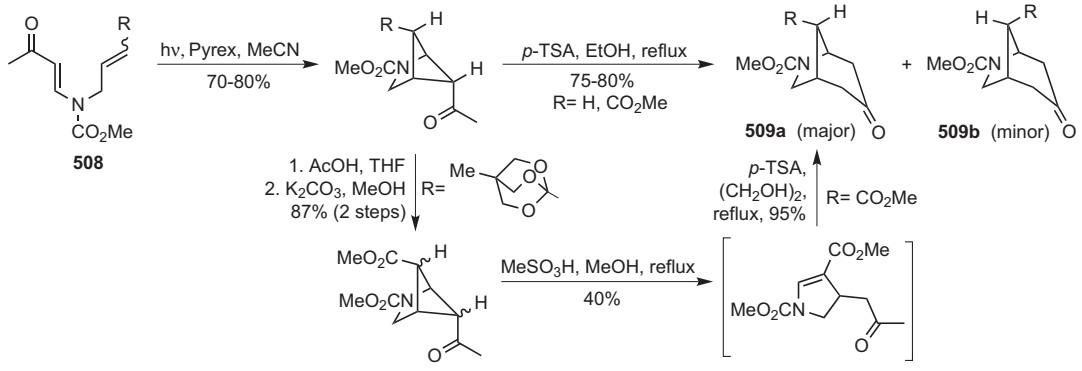
R^1 = *i*-Pr, Bn; R^2 = Me, 4-ClC$_6$H$_4$; R^3 = H, Me; R^2,R^3 = -(CH$_2$)$_5$-; R^4 = H, Me; R^5 = H; R^4-R^5 = -(CH$_2$)$_4$-

Scheme 169.

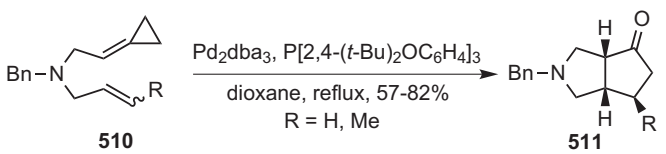




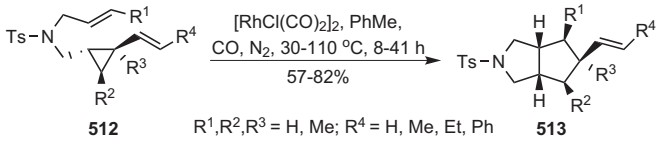
Scheme 170.



Scheme 171.



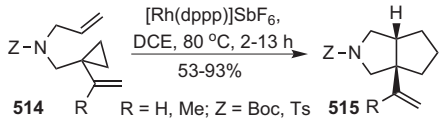
Scheme 172.



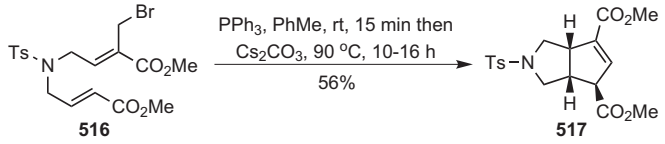
Scheme 173.

An Au-catalyzed conversion of the allylamine derivative **520** into the polyheterocyclic system **522** via a diastereoselective [3+2]-cycloaddition reaction of the azomethine ylide intermediate **521** was described by Shin's group (Scheme 177).[189]

In a slight variation of this strategy, Liang et al. reported the synthesis of an oxabicyclo [3.2.1]octane ring skeleton **524** from *ortho*-alkynyl-substituted benzaldehydes **523** via an iodine-catalyzed tandem cyclization–cycloaddition reaction (Scheme 178).[190]

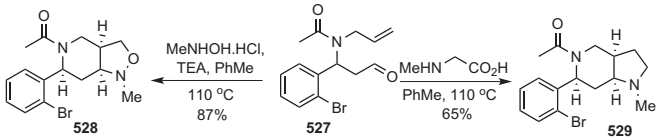


Scheme 174.

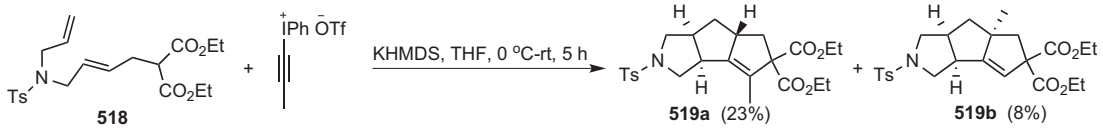


Scheme 175.

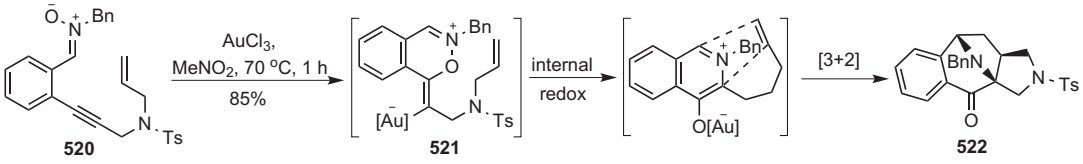
Sunderhaus et al. demonstrated the synthesis of aza-bicycles **528** and **529** via [3+2]-cycloaddition reactions of the condensation product of sarcosine or *N*-methyl hydroxylamine, respectively, with the allylamine derivative **527** (Scheme 181).[193] Significantly, the heterocyclic scaffolds present in **528** and **529** are found in compounds that are chemokine CCR5 receptor antagonists and inhibitors of dipeptidyl peptidase IV (DPP-IV).



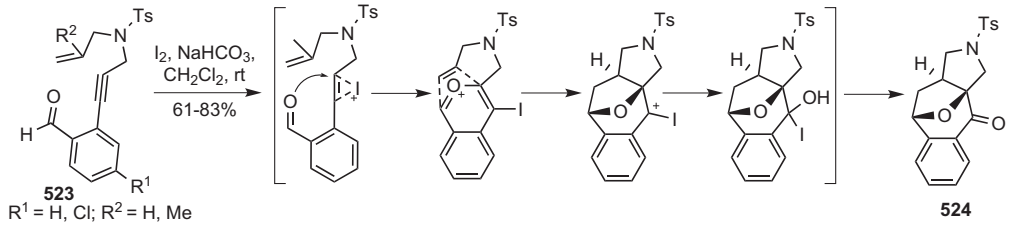
Scheme 181.



Scheme 176.

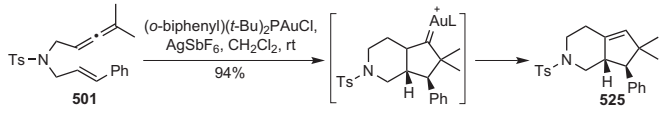


Scheme 177.



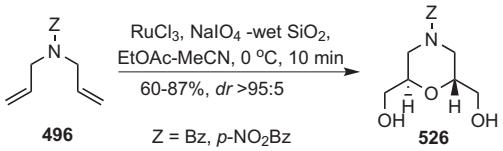
Scheme 178.

Toste et al., having earlier utilized the *N*-tethered allenene **501** for the [2+2]-cycloaddition reaction, now employed it for an Au(I)-catalyzed [3+2]-cycloaddition to access the aza-bicycle **525** (Scheme 179).[191]



Scheme 179.

Ruth and Stark reported that the intermediate Ru complex, formed in the reaction of in situ-generated RuO_4 and bis-allylamines **496**, transformed into the morpholine derivatives (**526**) via [3+2]-cycloaddition (Scheme 180).[192]



Scheme 180.

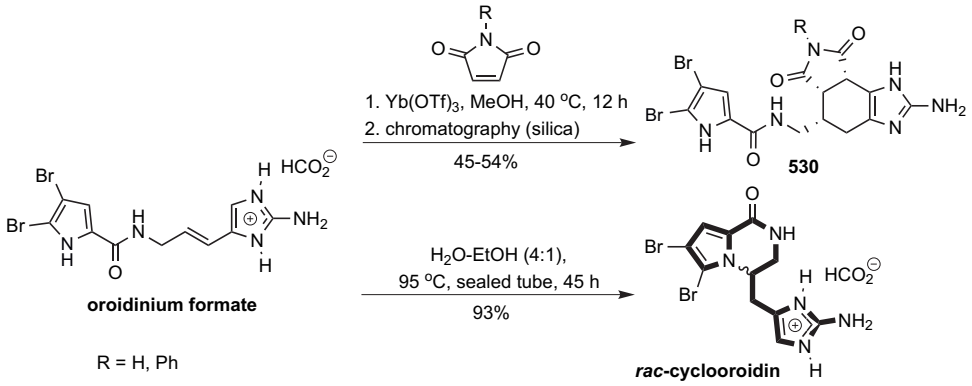
10.4. [4+2]-Cycloaddition (Diels–Alder) reactions

Appropriately substituted allylamines bearing a conjugated double bond or synthetically transformed into a diene react with an internal or external dienophile, resulting in a cyclic scaffold. On the other hand, the double bond of the allylamine may also act as a dienophile to react with a diene for similar objectives.

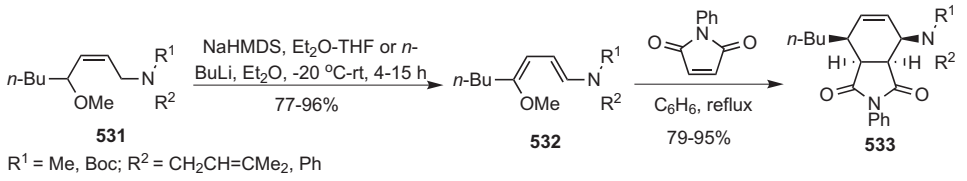
10.4.1. Intermolecular Diels–Alder reactions. Lindel et al. demonstrated that the marine key metabolite, oroidin, underwent Diels–Alder reactions with electron-poor dienophiles, leading to a tricyclic scaffold **530**. On heating in the absence of any reaction partner, however, oroidin cyclized to the pyrrole-imidazole alkaloid, cyclooroidin, as shown in Scheme 182.[194]

Later, Tayama and Sugai reported the synthesis of bicyclic framework **533**, via the Diels–Alder reaction of 4-substituted-1-amino-1,3-dienes (**532**), originated through a base-induced highly (1*E*,3*E*)-stereoselective 1,4-elimination reaction of 1-amino-4-methoxy-(2*Z*)-alkenes (**531**), with maleimide under thermal conditions (Scheme 183).[195]

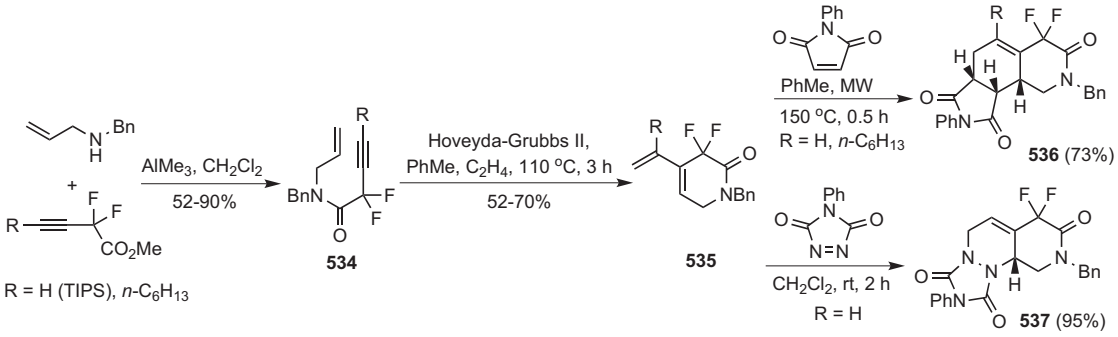
Hammond's group adopted a similar strategy for the conversion of dienes **535**, generated by ring-closing metathesis of difluorinated 1,7-enyne carbonyl compounds **534**, into 4,4-difluoroisoquinolin-3-ones (**536** and **537**) by reaction with maleimide, as shown in Scheme 184.[196]



Scheme 182.



Scheme 183.



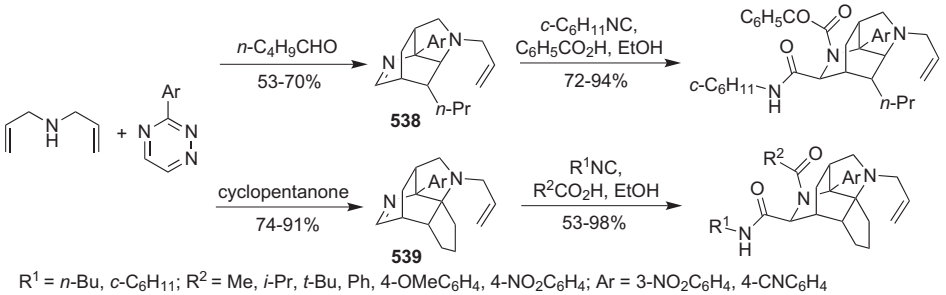
Scheme 184.

In a different approach, Bromley et al. and, later, Murrison et al. demonstrated a straightforward methodology for the construction of complex nitrogen-containing polycycles (**538** and **539**) by a diastereoselective one-pot procedure from substituted 1,2,4-triazines and enamines, produced in situ from carbonyl components and bisallylamine (Scheme 185). The transformation proceeded via a pericyclic reaction cascade, which involved inverse electron-demand Diels–Alder followed by retro-Diels–Alder and intramolecular Diels–Alder reactions.[197]

cycloaddition reaction.[198] Reduction of the double bond in the mixture of **541** and **542**, however yielded the reduced product **543**.

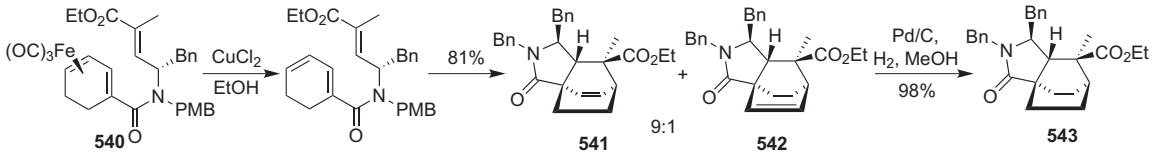
Noguchi's group described the transformation of the allylamine derivatives **544** into azepine (**545**) and/or pyran derivatives (**546**) via a thermal ene reaction and a [4+2]-cycloaddition reaction, respectively, as shown in Scheme 187.[199] Compound **547** was formed as a result of a homo Diels–Alder reaction within the system.

An efficient stereoselective synthesis of aza-triquinane (**550**) and aza-sterpurane (**551**) frameworks was achieved by Singh et al.

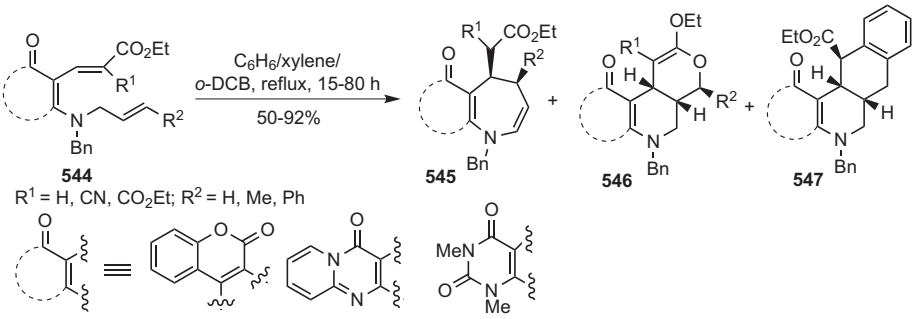


Scheme 185.

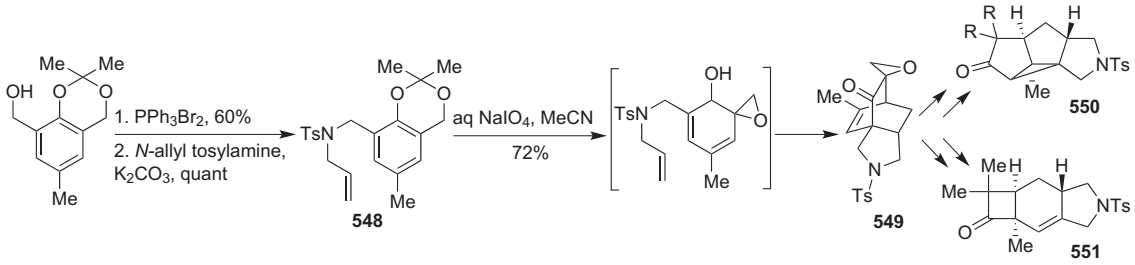
10.4.2. Intramolecular Diels–Alder reactions. Pearson et al. reported that the allylamide **540** led to a mixture of tricyclic compounds **541** and **542** in a 9:1 ratio (Scheme 186) via an intramolecular [4+2]- from the allylamide **548** (Scheme 188). The methodology involved in situ generation of cyclohexa-2,4-dienones containing an allylamine chain followed by an intramolecular [4+2]-cycloaddition



Scheme 186.



Scheme 187.



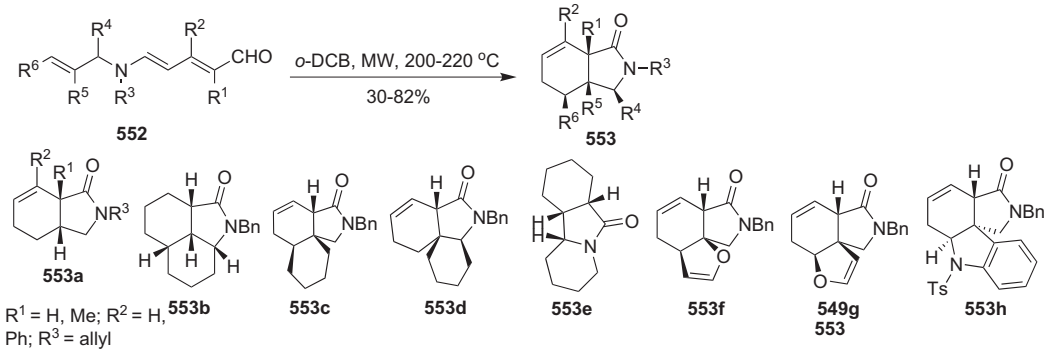
Scheme 188.

that resulted in a bicyclo[2.2.2]octenone-annulated pyrrolidine (**549**). Further manipulation of the afforded adduct followed by photochemical sigmatropic shifts readily furnished the aza-triquinane and aza-sterpurane frameworks.[200]

A novel pericyclic reaction cascade reaction was reported by Steinhardt and Vanderwal that resulted on heating Zincke aldehydes (**552**) derived from unsaturated amines to deliver rigid polycyclic lactam scaffolds (**553**) of diverse structure with potential utility for natural product synthesis and medicinal chemistry (Scheme 189).[201]

proceed through exocyclization and a 1,2-alkyl or 1,2-hydrogen shift, which occurred from the carbene complex intermediate containing a bicyclo[3.3.0]octane skeleton.[202]

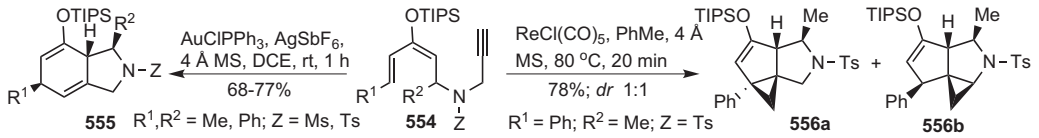
Chukhajian et al. reported the cyclization of dimethylcrotyl(3-vinyl- or -3-isopropenylpropyn-2-yl)ammonium bromides (**557**) in the presence of base to afford a mixture of isomeric 2,2-dialkyl-4-methyl- and 2,2-dialkyl-4,6-dimethyl-2,6,7,7a-tetrahydro-1*H*-isoindolium bromides (**558**) (Scheme 191). Basic fission of the salts obtained at increased temperature produced a mixture of the isomeric *N*,*N*-disubstituted di- and trimethylbenzylamines (**559a**,**b**).[203]



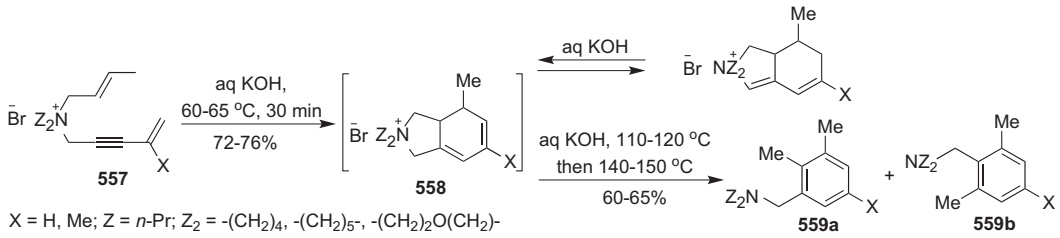
Scheme 189.

Iwasawa et al. reported that the aza-dienyne (**554**) cyclized stereoselectively in the presence of an Au(I) catalyst to afford bicyclic enol silyl ethers **555** (Scheme 190), but in the presence of a Re catalyst aza-dienyne underwent a cascade cyclization to produce the tricyclic compounds (**556a**,**b**). The reaction was proposed to

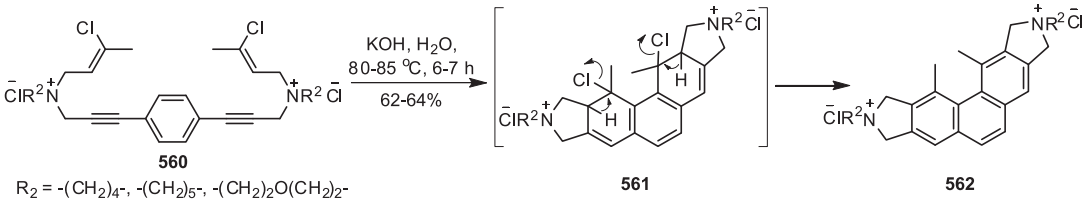
As an extension of this work, reported recently, they prepared a novel series of nitrogen heterocycles with a phenanthrene fragment (**562**) from *p*-bis{3-[*N*-(3-chlorobuten-2-yl)pyrrolidinio(piperidinio or morpholinio)]propyn-1-yl}benzene dichlorides (**560**) (Scheme 192). The products were formed via **561** through



Scheme 190.



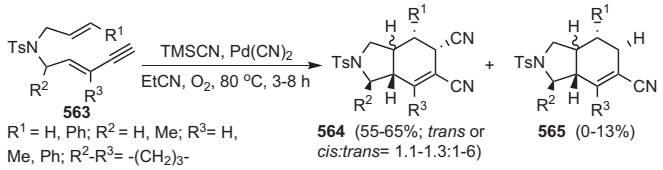
Scheme 191.



Scheme 192.

cyclization followed by a dehydrochlorination process under basic conditions in an aqueous medium.[204]

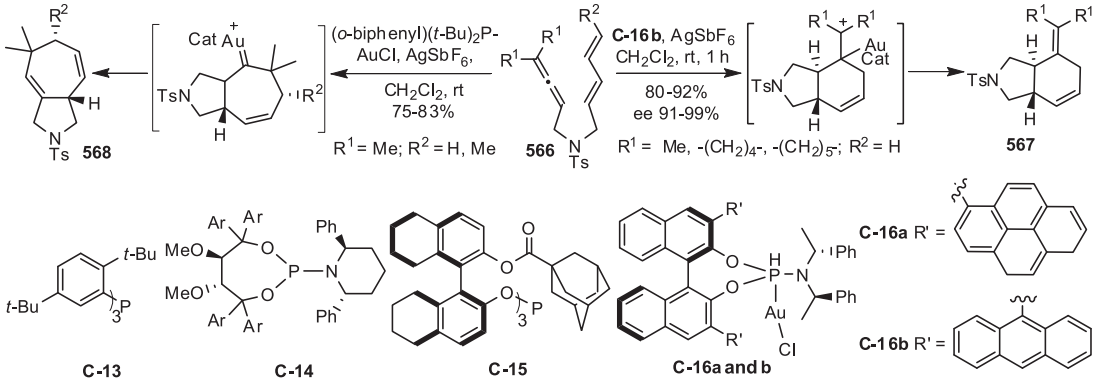
Employing an identical methodology, a synthesis of pyrrolidine-fused cyclohexenes (**564** and **565**) was recently disclosed by Arai et al. The reaction proceeded through the formation of four C–C bonds in only one operation via dicyanative [4+2]-cycloaddition of the dienynes (**563**) triggered by cyanopalladation (Scheme 193).[205] The stereochemistry of the enyne played a significant role in this reaction. The *trans*-enyne produced the *trans*-fused cycloadduct as the major or exclusive product, but the *cis*-enyne failed to react.



Scheme 193.

Toste et al. and Lopez et al. reported that the product selectivity in Au(I)-catalyzed cycloaddition reactions of *N*-tethered allene-dienes (**566**) could be influenced by modulating the relative stability of the cationic transition states generated during the course of the cycloadditions, the use of electron-rich σ-donor ligands favouring the pathway leading to the *trans*-fused [4+3]-cycloadducts **567**. On the other hand π-acceptor ligands divert the reaction to the [4+2]-cycloadduct, affording the isoindoles **568** (Scheme 194).[206] Later, Fuerstner et al. adopted the same strategy for the synthesis of hexahydro-isoindole derivatives **567** via a [4+2]-cycloaddition reaction of the *N*-tethered allene-dienes (**566**) under the catalytic influence of an asymmetric gold–phosphoramidite complex.[179]

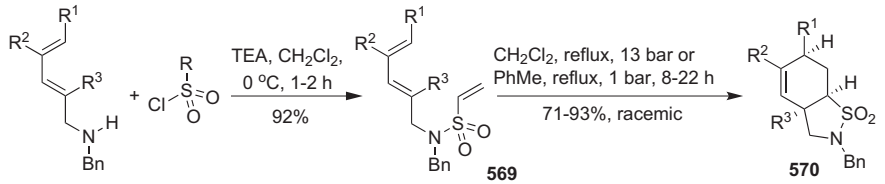
10.4.3. Synthesis of γ-sultams. Allylamines bearing a conjugated double bond attached to a vinylsulfone functionality undergo intramolecular [4+2]-cycloaddition reactions to yield the bicyclic γ-sultams. The vinyl sulfonamide having an *EE*-diene (**569**) yield γ-sultams



Scheme 194.

fused with cyclohexene **570** in a purely thermal reaction performed under high pressure, as reported by Rogachev and Metz (Scheme 195).[207]

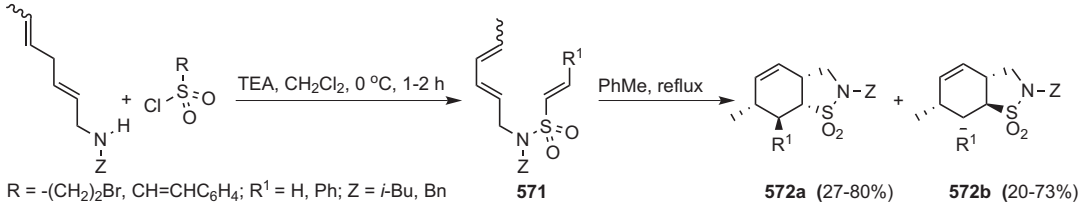
Brodney et al. demonstrated that the intermediate allyl carbamate **577**, attached to a furan ring, undergoes intramolecular [4+2]-cycloaddition and alkene rearrangement cascade reactions to produce



Scheme 195.

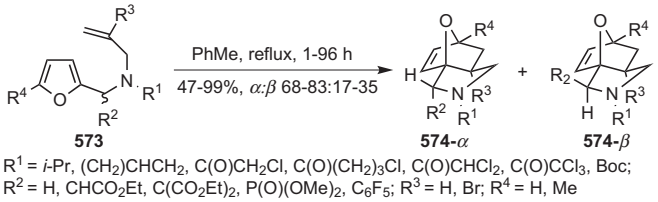
Application of a similar protocol to a mixture of sulfonamides **571** bearing *EE* or *ZE* dienes resulted in the generation of bicyclic sultams **572a**,**b**, as demonstrated by Evans et al. (Scheme 196).[208]

N-Boc-hexahydro-1*H*-indoline-5-(6*H*)-one **578**. This product upon $NaCNBH_3$-mediated carbonyl reduction yielded *N*-Boc-5-hydroxy octahydro-1*H*-indoline is **579a**,**b** as outlined in Scheme 199.[211]

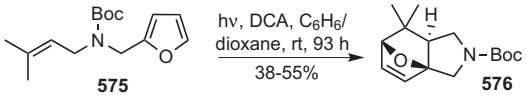


Scheme 196.

10.4.4. Reactions involving furan as diene. Allylamines attached to a furan moiety make it a viable precursor for the intramolecular [4+2]-cycloaddition reaction. Several research groups have utilized this strategy to produce pyrrolidine-fused oxabicyclo[2.2.1]heptanes **574**-α,-β from the allylamines **573** by making subtle variations in the substitutions (Scheme 197).[209] Arai et al. achieved the stereoselective synthesis of the bridged compound **576** by exposing **575** to UV light in the presence of 9,10-dicyanoanthracene (DCA) (Scheme 198).[210]

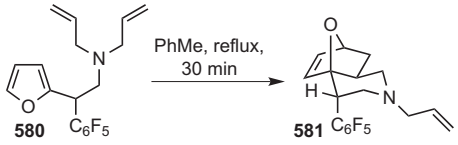


Scheme 197.



Scheme 198.

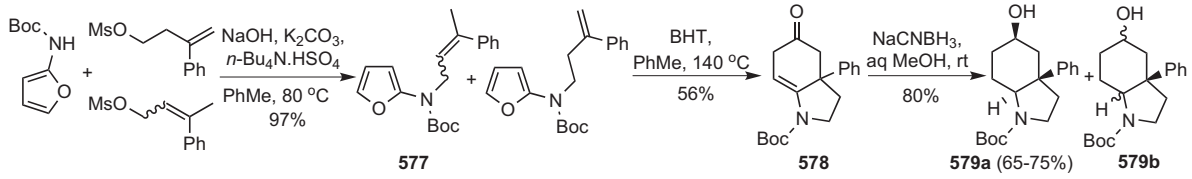
Dilman et al. prepared a furan ring-tethered diallylamine (**580**), which upon heating in toluene underwent [4+2]-cycloaddition to afford a tricyclic ring **581** (Scheme 200).[212]



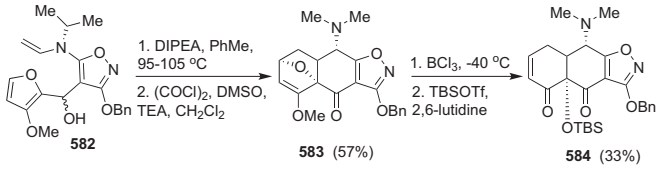
Scheme 200.

An enantioselective synthetic route to a key precursor **584** of the tetracycline antibiotics, developed by Brubakers and Myers, involved an *endo*-selective intramolecular furan Diels–Alder reaction of the intermediate isoxazole-tethered allylamine **582** to afford **583** as the key intermediate (Scheme 201).[213]

10.4.5. Reactions involving alkynes as dienophiles. An alkyne attached to an amine may react as a dienophile with an internal diene in the presence of a transition metal catalyst, leading to a heterocyclic unit. Chung's group observed that the $Co_2(CO)_8$-mediated cycloaddition of dienynes **585** could occur through three main competing reaction routes, depending upon the substrate and the reaction conditions, two carbonylative cycloaddition reactions and a Diels–Alder reaction leading to the formation of pyrrolidine-

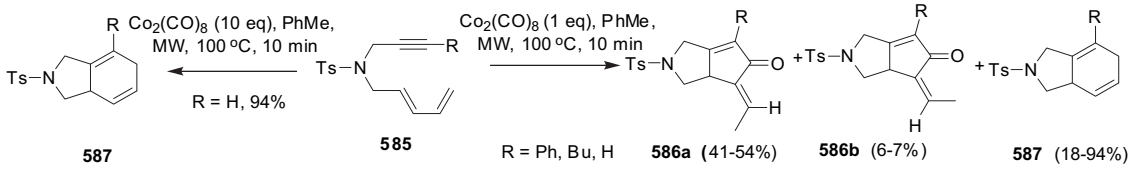


Scheme 199.



Scheme 201.

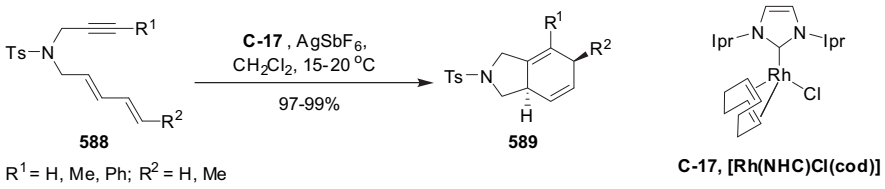
fused cyclopentenones (**586a**,**b**) and cyclohexadienes (**587**), respectively, as shown in Scheme 202.[214]



Scheme 202.

Further, these workers generated the cyclohexene derivatives **589** as the sole product from the dienynes (**588**) containing a diene with an *EE* configuration, via Rh-*N*-heterocyclic carbene-catalyzed [4+2]-cycloaddition reactions (Scheme 203).[215]

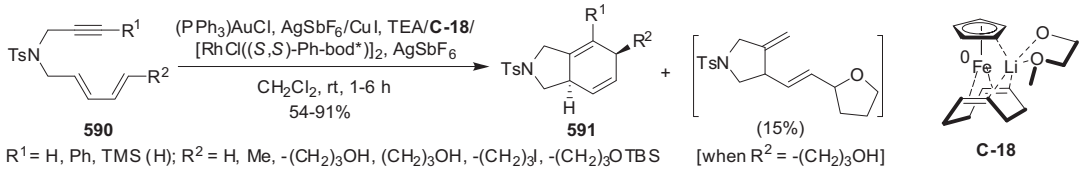
Fuerstner and Stimson used a Cu(I) catalyst for the preparation of aza-bicycles **596** from **595** via the cyclization of α,β-unsaturated carbonyl with alkyne under hetero-Diels–Alder reaction conditions (Scheme 206).[216a]



Scheme 203.

Later, Fuerstner et al. demonstrated the synthesis of similar cyclohexenes **591** from *N*-tethered dienynes **590** via Au(I)-, Cu(I)- or Fe(0)-catalyzed reactions (Scheme 204).[216] On the other hand, Shintani et al. used chiral cationic Rh complex to catalyze the asymmetric intramolecular [4+2]-cycloaddition to generate cyclohexenes (**591**) with high enantiomeric excess (Scheme 204).[217]

Raghunathan et al. demonstrated that the intermediate α,β-unsaturated carbonyl moiety **598**, generated by Knoevenagel condensation of *N*-prenylated aliphatic aldehydes (**597**) and 1-methylquinoline-2,4-dione, reacted with the internal prenyl group under thermal conditions to produce the tetracyclic skeleton **599** via an intramolecular hetero-Diels–Alder reaction, as depicted in Scheme 207.[219]



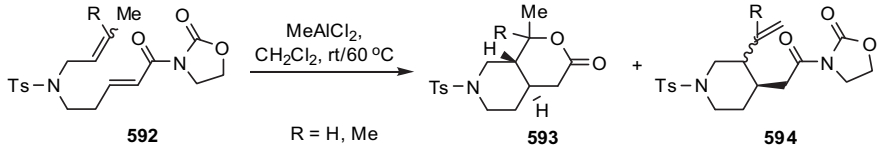
Scheme 204.

10.4.6. Hetero-Diels–Alder reactions. Appropriately substituted allylamines have been demonstrated to be suitable substrates for the hetero-Diels–Alder reaction. The substitution on the amino group has been represented either by an α,β-unsaturated carbonyl group or an imine.

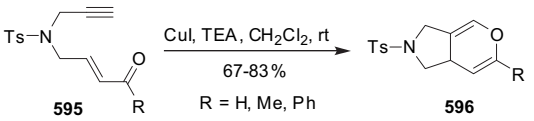
10.4.6.1. Intramolecular reactions. Snaith et al. reported that the α,β-unsaturated carbonyl functionality, activated by oxazolidinone, attached to an allylamine **592** undergoes Lewis acid-catalyzed cyclization to afford a mixture of the hetero-Diels–Alder product, i.e., pyrano[3,4-*c*]pyridin-3-ones (**593**), and the ene product, i.e., substituted piperidines (**594**) (Scheme 205).[218]

Later, the same research group synthesized cis- and trans-isomers of pyranopyrrole derivatives (**601** and **602**) from **600** under MW irradiation as well as by a conventional thermal reaction employing an identical sequence of Knoevenagel and intramolecular hetero-Diels–Alder reactions (Scheme 208).[220] They found that although under both conditions the trans-isomers were formed as the major product, the use of MW irradiation improves the overall yield of the products as well as the stereoselectivity.

A similar approach was adopted by Lee and Hung to realize the synthesis of polycycles fused to tetrahydroquinolines **605** from **604**,

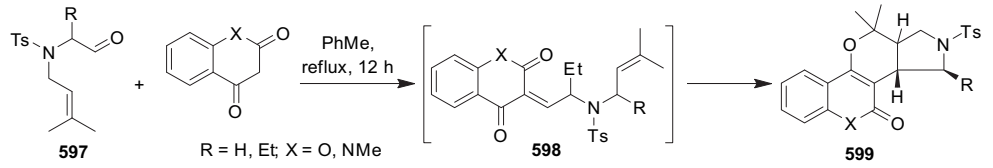


Scheme 205.

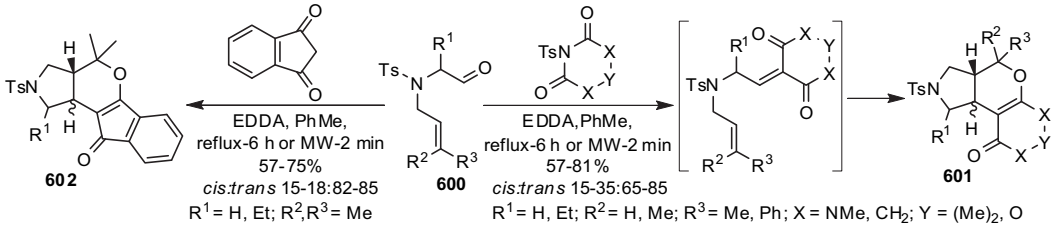


Scheme 206.

Baruah and Bhuyan demonstrated the synthesis of pyrano[2,3-*b*]- and pyrido[2,3-*b*]quinolines (**609** and **610a**,**b**) from the allylamine derivatives **606** in an aqueous medium via a similar domino sequence of Knoevenagel reaction followed by intramolecular hetero-Diels–Alder reaction of the in situ-generated 1-oxa-1,3-butadienes (**607** or **608**) (Scheme 210).[222]



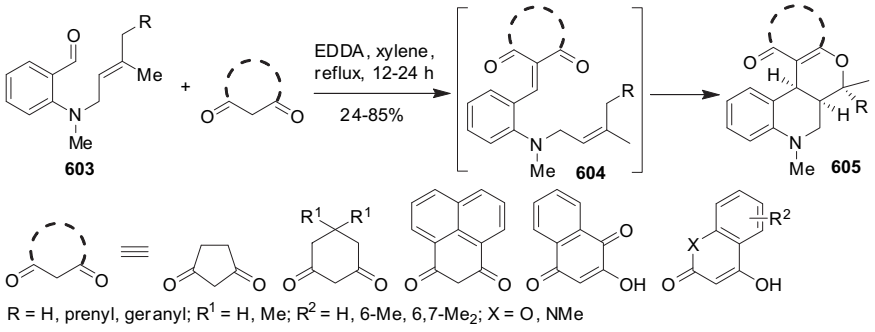
Scheme 207.



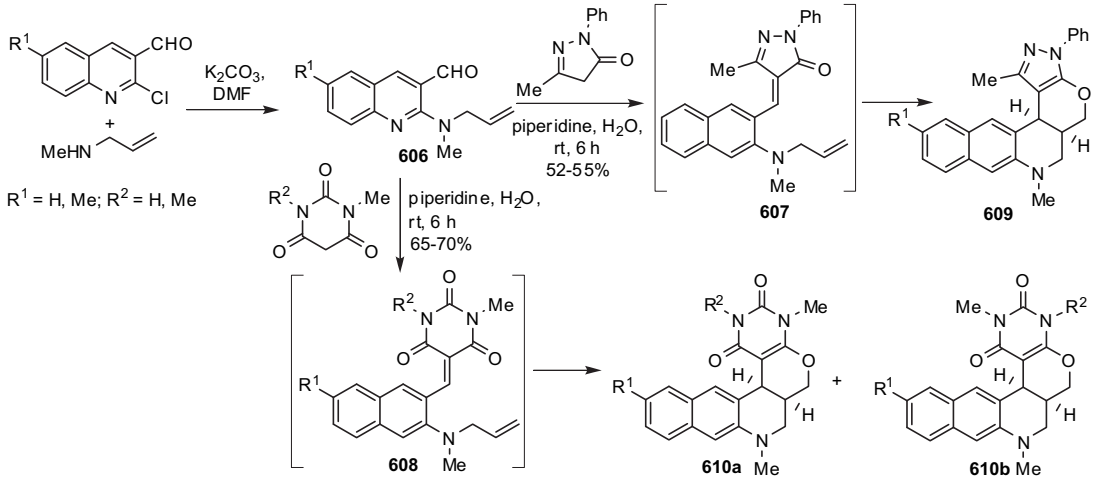
Scheme 208.

which in turn were generated from the reaction between **603** and dicarbonyl derivatives, as delineated in Scheme 209.[221]

Yadav et al. achieved the stereoselective synthesis of functionalized *trans*-fused benzo-annulated decahydrofuro[3,2-*h*][1,6]



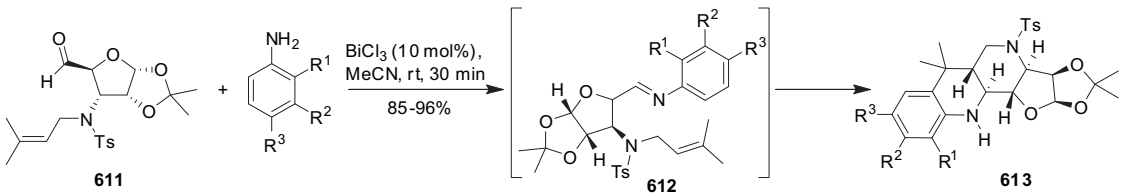
Scheme 209.



Scheme 210.

naphthyridine derivatives (**613**) through the Lewis acid-catalyzed intramolecular hetero-Diels–Alder reaction between imines (**612**), generated from an *N*-prenylated sugar aldehyde (**611**) and different aromatic amines (Scheme 211).[223]

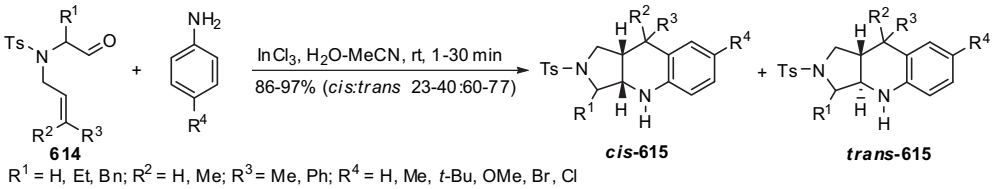
Botta et al. used DEAD as dienophile in the intermolecular hetero-Diels–Alder reaction of diene **622**, leading to the formation of diastereomeric dihydropyridazine **623** (Scheme 215).[75]



Scheme 211.

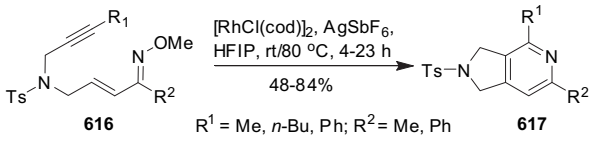
Raghunathan et al. extended this methodology to *N*-prenylated aliphatic aldehydes (**614**) to access the hexahydropyrrolo[3,4-*b*] quinolines (**615**) in the presence of $InCl_3$ (Scheme 212).[224]

Presset et al. reported a direct synthesis of pentacyclic oxazinones (**624**) from primary allylamine, aldehydes and cyclic 2-diazo-1,3-diketone via an MW-assisted multicomponent domino sequence involving four elemental reactions imine formation, Wolff rearrangement, intermolecular hetero-Diels–Alder and intramolecular Diels–Alder allowing the stereocontrolled creation of six chemical bonds and four rings in a single catalyst-free reaction (Scheme 216).[227]



Scheme 212.

Saito et al. described that an in situ-generated cationic Rh(I) catalyst, derived from $[RhCl(cod)]_2$ and $AgSbF_6$ in HFIP, efficiently catalyzed the formation of annulated pyridines **617** from ω-alkynyl-vinyl oximes **616** (Scheme 213).[225]



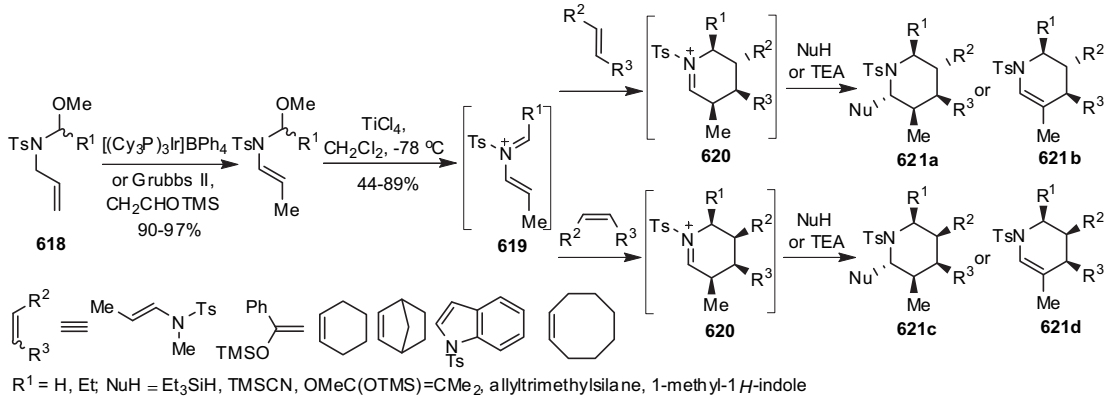
Scheme 213.

10.4.6.2. Intermolecular reactions. Sarkar et al. reported sequential multicomponent cycloaddition and iminium ion functionalization reactions of *N*-alkenyl iminium ions (**619**), afforded from the substituted allylamines **618**, with various dienophiles leading to **620**, which afford structurally diverse and stereochemically rich piperidine derivatives (**621a**–**d**), as depicted in Scheme 214.[226]

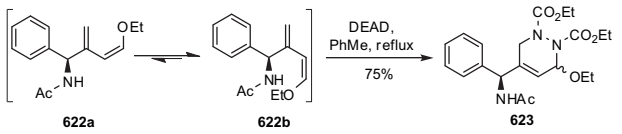
10.5. [4+3]-Cycloaddition reactions

Pd-catalyzed intramolecular [4+3]-cycloaddition of *N*-tethered alkylidenecyclopropane and dienes (**625**) was elaborated by Mascarenas et al. to generate the bicyclic aza-heterocycles **626** and **627** (Scheme 217).[228] The reaction was best achieved via the use of a phosphorous ligand C-20.

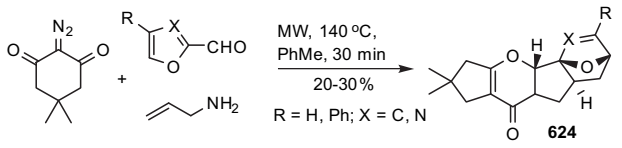
Later, the same workers achieved the synthesis of a tricyclic compound **629** in a completely diastereo- and regioselective fashion via $PtCl_2$-catalyzed [4+3]-cycloaddition of the allenediene **628** (Scheme 218).[229]



Scheme 214.



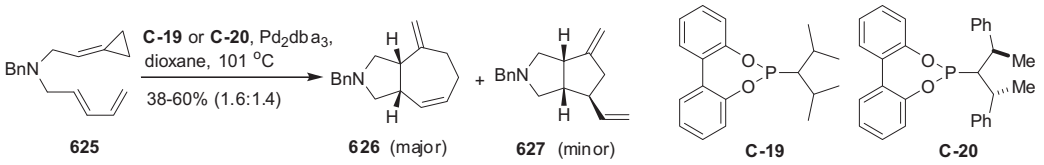
Scheme 215.



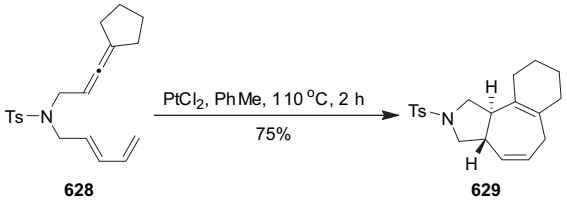
Scheme 216.

10.7. [2+2+1]-Cycloaddition reactions

Inagaki and Mukai described $[RhCl(CO)_2]_2$-catalyzed intramolecular [2+2+1]-cycloaddition reactions of substituted allylamines **634**, leading to the formation of azabicyclo[4.3.0]non-1(9)-en-8-ones and azabicyclo[5.3.0]dec-1(10)-en-9-ones (**635**) (Scheme 221). This method provided a new procedure for the construction of the bicyclo[4.3.0]-non-1(9)-en-8-one skeleton having an alkyl appendage at the ring junction, which was hardly obtained in satisfactory yield by the Pauson–Khand reaction of the corresponding enynes.[231] Wender et al. adopted a similar strategy to convert **636** into bicyclic aza-heterocycles (**637**–**639**) in the presence of CO, as shown in the Scheme 222.[232]



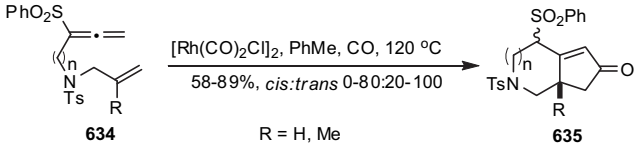
Scheme 217.



Scheme 218.

10.6. [5+2]-Cycloaddition reactions

Wender et al. reported the intramolecular asymmetric [5+2]-cycloaddition between the alkene/alkyne and vinylcyclopropane of an allylamine derivative **630** under the catalytic influence of a chiral Rh complex (C-21), leading to cyclohepta[*c*]pyrrole derivatives (**631**) (Scheme 219).[230] Likewise, Chung et al. used a Rh-based *N*-heterocyclic carbene catalyst (**C-17**) to effect an analogous transformation (Scheme 221).[215] Fuerstner's group has demonstrated that Fe(0) complexes, such as **C-18** and **C-22** also efficiently catalyze similar transformation in substituted allylamines **632** to generate **633a** and **633b** (Scheme 220).[216b]

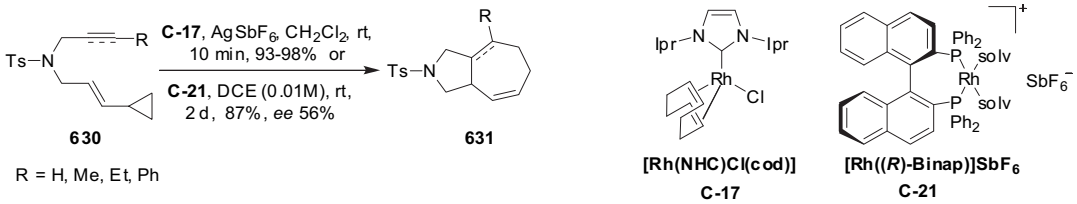


Scheme 221.

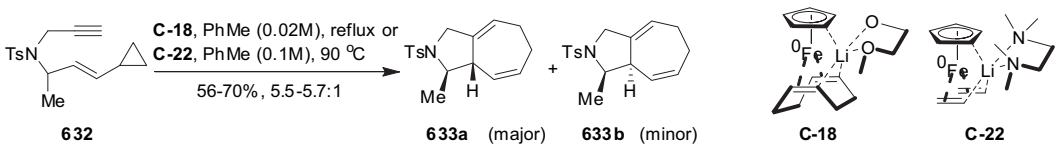
10.8. [2+2+2]-Cycloaddition reactions

Shibata and Tahara developed an enantioselective intramolecular [2+2+2]-cycloaddition which enabled them to convert 1,4-dieneynes **640** into strained polycyclic aza-heterocycles (**641** and **642**) with quaternary carbon stereocenters, as depicted in Scheme 223.[233]

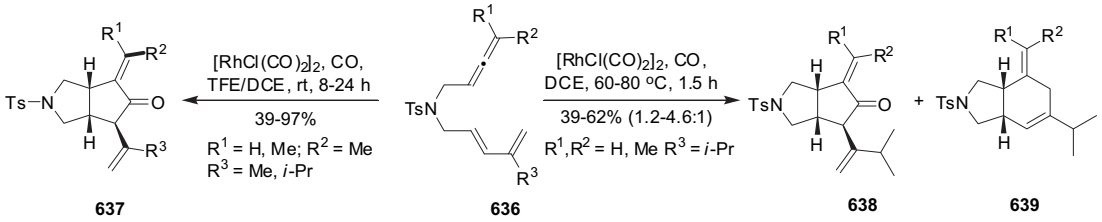
Recently, Evans et al. described highly regio- and diastereoselective intermolecular Rh-catalyzed [(2+2)+2]-carbocyclization of *N*-tethered terminal 1,6-enyne derivatives (**643**) with a range of alkyl substituted methyl propiolates as an efficient route to afford aza-bicyclohexa-1,3-dienes (**644** and **645**) (Scheme 224).[234] This strategy offered the option to control the formation of either regioisomer through judicious choice of the ancillary ligand.



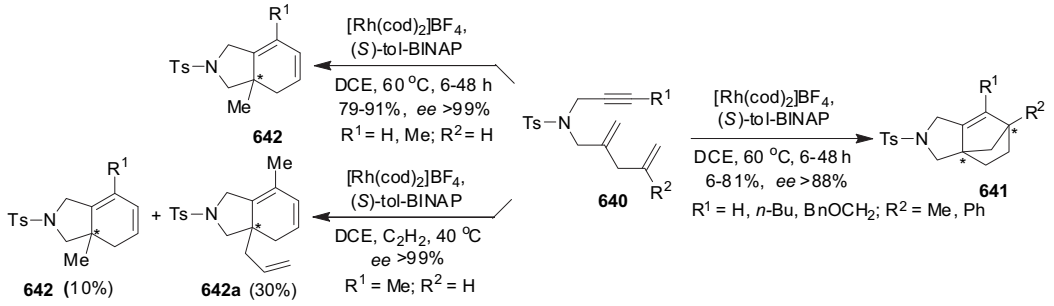
Scheme 219.



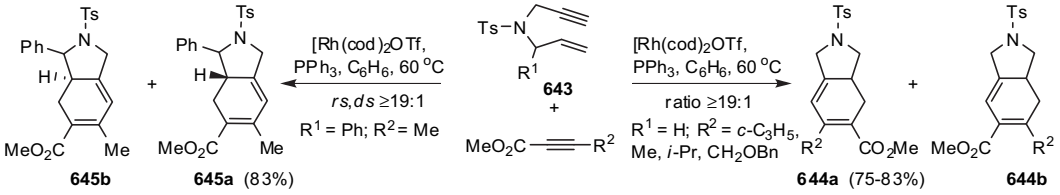
Scheme 220.



Scheme 222.



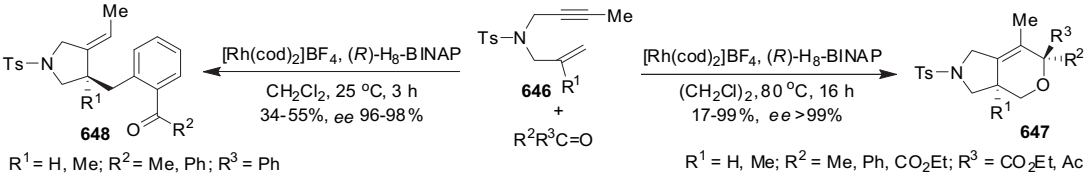
Scheme 223.



Scheme 224.

Later, Tanaka et al. reported that the cationic Rh(I)–(*R*)-H_8-BINAP complex catalyzes the intermolecular [2+2+2]-cycloaddition of *N*-tethered 1,6-enynes (**646**) with electron-deficient ketones to afford fused dihydropyrans containing two quaternary carbon centres (**647**) with excellent regio-, diastereo- and enantioselectivity (Scheme 225). Electron-rich aryl ketones reacted with 1,6-enynes in the presence of the same catalyst to give *ortho*-functionalized aryl ketones **648** with excellent regio- and enantioselectivity.[235]

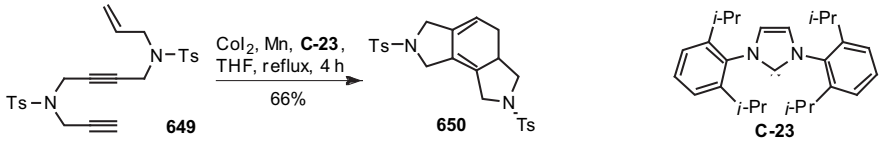
Adriaenssens et al. synthesized a 3-tosyl-1-vinyl-3-azabicyclo [3.1.0]hexane scaffold (**652a**,**b**) from 3-aza-1,6-enyne (**651**) via an Ru-catalyzed selected [2+2+2]-cycloaddition, alkene–alkyne coupling and fusion of enyne with a diazo compound (Scheme 227).[237] They described it to be the first example of a bio-tolerant and air-tolerant C–C bond formation reaction catalyzed by a synthetic organometallic compound. The reaction proceeded under ambient aerobic aqueous conditions in the



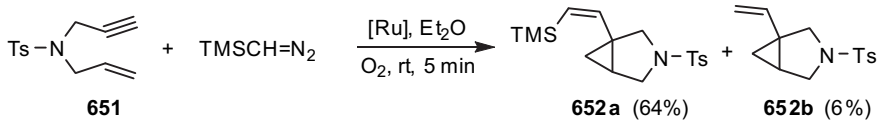
Scheme 225.

Geny et al. disclosed the transformation of *N*-tethered enediyne **649** into cyclohexadiene **650** via an intramolecular [2+2+2]-cycloaddition in the presence of CoI_2, Mn and an *N*-heterocyclic carbene (**C-23**) (Scheme 226).[236]

presence of bodily fluids or cell lysates. Biological fluids used as reaction media included *Rattus norvegicus* urine (male lab. rat urine), *Escherichia coli* cell lysate, foetal bovine serum or human serum.



Scheme 226.



651 652a (64%) 652b (6%)

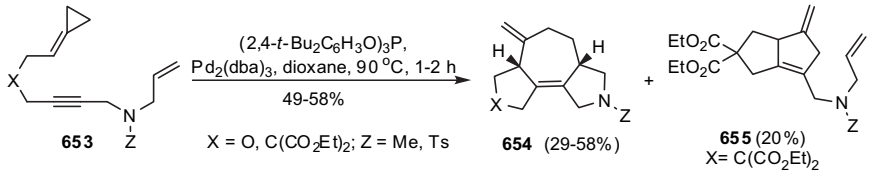
Scheme 227.

10.9. [3+2+2]-Cycloaddition reactions

Mascarenas et al. developed a Pd-catalyzed multicomponent intramolecular [3+2+2]-cycloaddition reaction between alkylidenecyclopropanes (3C), alkynes (2C) and alkenes (2C), which enabled access to *N*-containing 5–7–5 tricyclic systems (**654**) with moderate-to-excellent chemoselectivities and complete diastereoselectivities. The allylamine subunit shown in structure **653** represented the alkene part (Scheme 228).[238] In addition, another bicyclic product **655** was isolated in minor yields.

Ashida and Murakami demonstrated that in the presence of a Ni(0) catalyst, a cyclobutanone reacted with enyne **664** to produce a bicyclic eight-membered ring ketone **665** via a formal [4+2+2]-type annulation reaction (Scheme 232).[242]

Tan's group demonstrated that the *tert*-butylsulfonamides obtained by oxidation of the corresponding sulfinamides **666** underwent Evans' Rh-catalyzed butadiene [4+2+2]-cycloaddition with enynes to afford [5,8]-bicyclic cyclooctapyrrolidine scaffolds

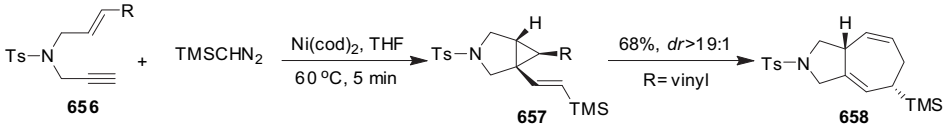


653 654 (29-58%) 655 (20%) X= $C(CO_2Et)_2$

Scheme 228.

10.10. [4+2+1]-Cycloaddition reactions

Ni and Montgomery developed a new Ni-catalyzed [4+2+1]-cycloaddition of (trimethylsilyl)diazomethane with alkynes tethered to allylamines (**656**) to produce 1-vinyl-3-azabicyclo[3.1.0]hexanes (**657**) (Scheme 229). The aza-bicycle having a divinylcyclopropane functionality underwent a [3,3]-sigmatropic rearrangement to generate the cyclohepta[*c*]pyrrole moiety **658** (Scheme 229).[239]



656 R = H, vinyl 657 (R = H; 60%, *E*/*Z* = 10:1) 658

Scheme 229.

10.11. [4+2+2]-Cycloaddition reactions

Wender and Christy synthesized cyclooctadienes **660a**,**b**, via Rh(I)-catalyzed [4+2+2]-cycloaddition of alkyne and *N*-tethered triene **659**, having a conjugated *syn*-configured diene system (Scheme 230).[240]

Gilbertson et al. also used a Rh complex to catalyze the [4+2+2]-annulation reaction of dienynes **661** with a second alkyne **662** to produce cyclooctatrienes **663**, as depicted in Scheme 231.[241]

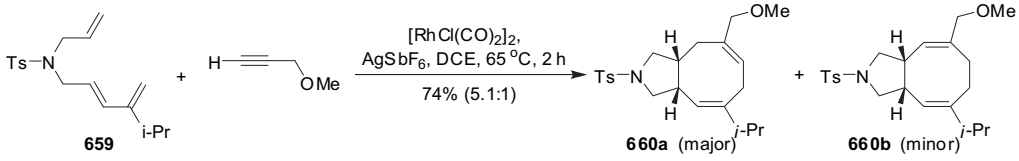
synthesis of nine-membered carbocycles fused with a pyrrolidine (**669a**,**b**) (Scheme 234) or quinoline (**671a**,**b**) moiety (Scheme 235).[244a]

10.12. [4+3+2]-Cycloaddition reactions

Satio et al. investigated a Ni(0)-catalyzed [4+3+2]-cycloaddition reaction of ethyl cyclopropylideneacetate with *N*-tethered dienynes (**668** and **670**) as an efficient route for the

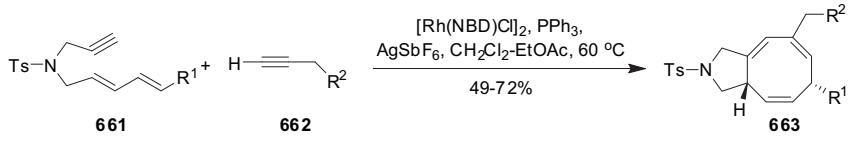
10.13. [5+2+1]-Cycloaddition reactions

Yu et al. reported the synthesis of pyrrolidine- or piperidine-fused cyclooctenones (**673a**,**b**) via a Rh(I)-catalyzed two-compo-



659 660a (major) 660b (minor)

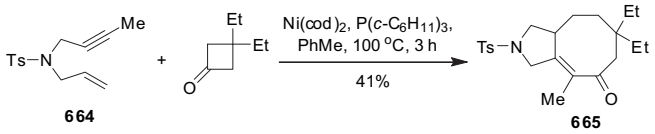
Scheme 230.



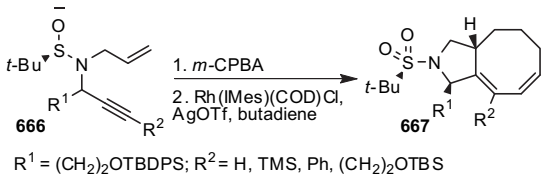
661 662 663

R^1 = H, Me; R^2 = OBn, NHTs, (*E*)-$NTsCH_2CH{=}CHCH{=}CHMe$

Scheme 231.



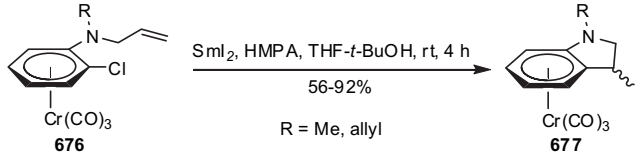
Scheme 232.



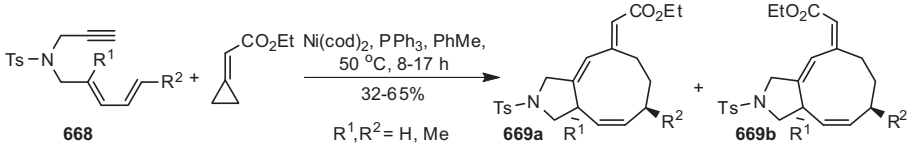
Scheme 233.

Allylamines bearing rear *o*-haloaryl substituents, i.e., on the terminal C of the alkene, also undergo radical cyclization reactions to form heterocycles of variable ring size.

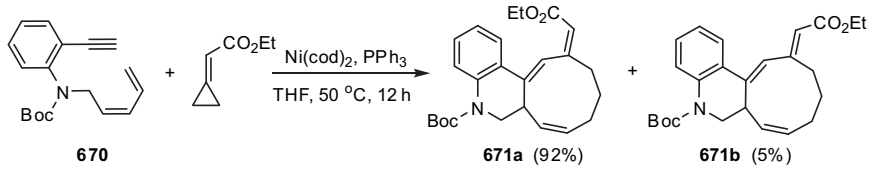
Li et al. studied the SmI_2-mediated radical cyclization of *o*-allylaminochlorobenzene–$Cr(CO)_3$ complexes (**676**) to generate indoline derivatives **677** and observed that the coordination of $Cr(CO)_3$ to chlorobenzenes significantly reduced the C–Cl bond-dissociation energy resulting in the substrate being suitable for facile radical reactions under mild conditions in good-to-excellent yields (Scheme 238).[246]



Scheme 238.



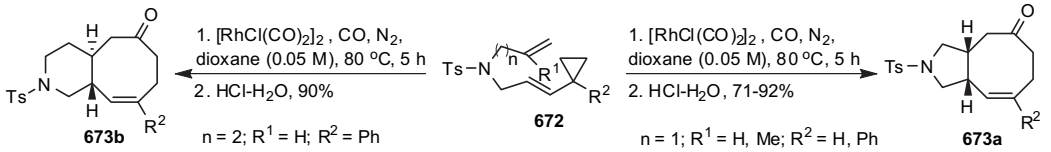
Scheme 234.



Scheme 235.

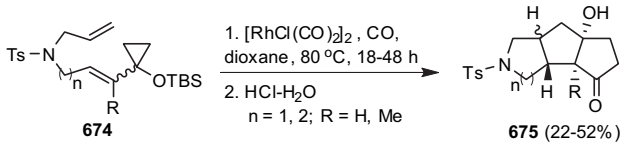
nent [5+2+1]-cycloaddition reaction of ene-vinylcyclopropanes **672** (Scheme 236).[244b]

Guthrie and Curran described radical and anionic cyclization reactions of axially chiral atropisomers of substituted allylamine



Scheme 236.

Later, they developed a tandem reaction involving the Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition and an aldol condensation to construct the *N*-containing tricyclo[6.3.0.0]undecane skeleton (**675**) from the allylamines **674** (Scheme 237).[245]



Scheme 237.

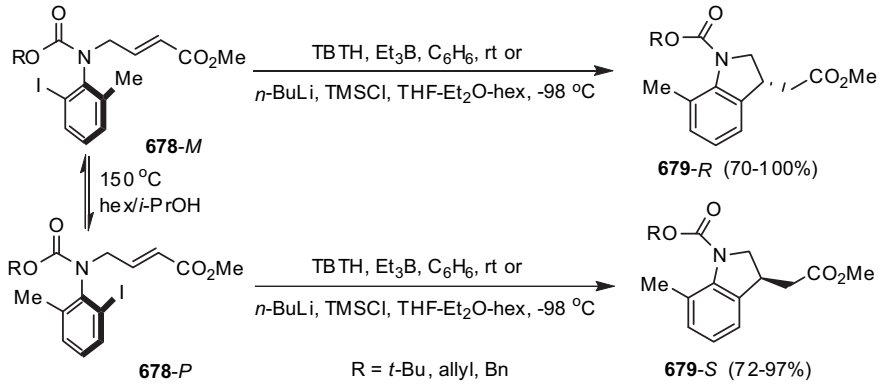
11. Radical cyclizations

11.1. Radical cyclization involving aryl halide as precursor

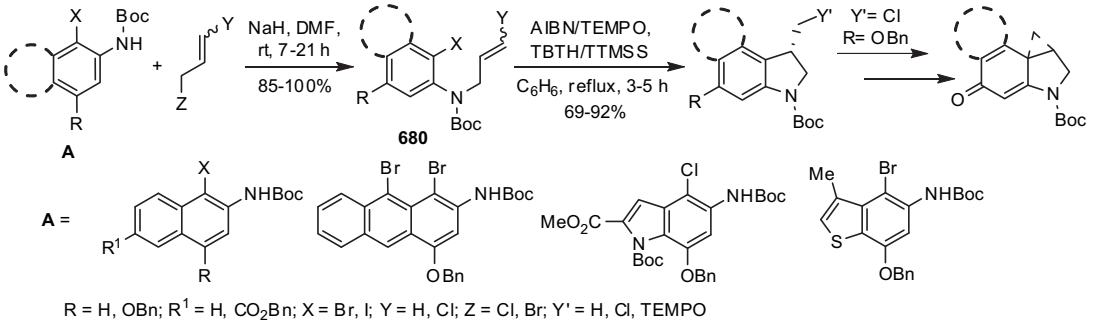
An allylamine bearing an *o*-haloaryl substituted amine provides entry to indole derivatives via radical cyclization onto the double bond of the allylamine. This strategy has been explored extensively to generate several important indole-based bioactive motifs. derivatives **678**-*M* and **678**-*P* and observed high levels of chirality transfer from the *N*-Ar axis to the new stereocenter in the substituted dihydroindoles **679**-*R* and **679**-*S*, respectively (Scheme 239).[247]

Boger's and Tietze's groups independently achieved the synthesis of various indole-based antitumour agents including *ent*-(−)-yatakemycin, (+)-duocarmycins, analogues of CC-1065 and pentagastrin seco-CBI derivatives, etc. via asymmetric radical cyclization of allyl carbamates **680** in the presence of AIBN or TEMPO (Scheme 240).[248] Allyl carbamates **680** in turn were prepared from different prototypes of A.

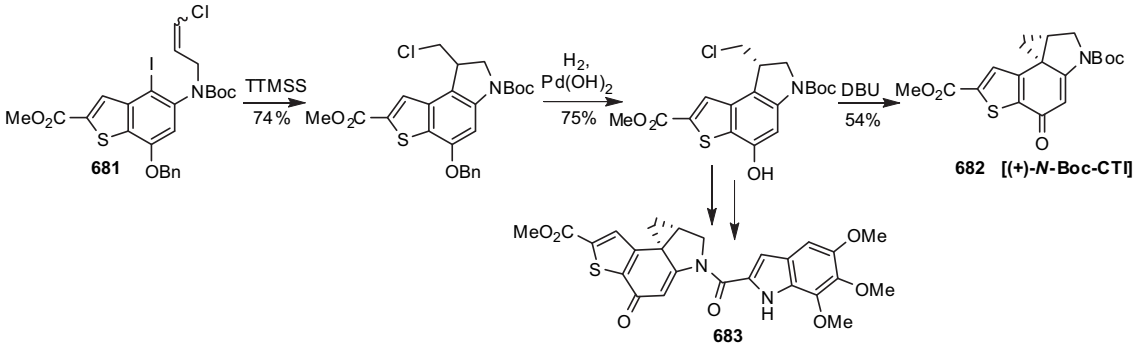
Recently, Boger et al. also synthesized methyl 1,2,8,8a-tetrahydrocyclopropa[*c*]thieno[3,2-*e*]indol-4-one-6-carboxylate (CTI) derivatives (**682** and **683**), having a single atom change (N to S) in the duocarmycin SA alkylation subunit, via 5-*exo*-*trig* aryl radical-alkene cyclization of the allylamine derivative **681**, and examined their biological activity (Scheme 241).[249] Replacement of a pyrrole NH of the alkylation subunit of duocarmycin SA with a sulfur atom maintains or slightly enhances the biological potency of the natural product, but not to the extent observed with MeCTI.



Scheme 239.

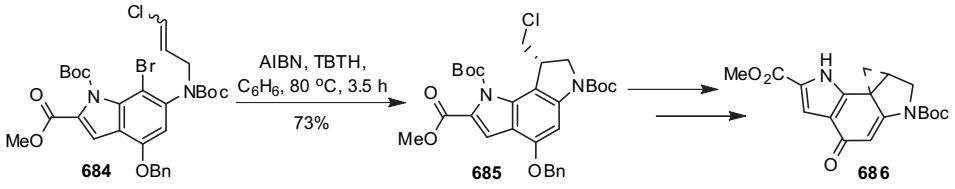


Scheme 240.



Scheme 241.

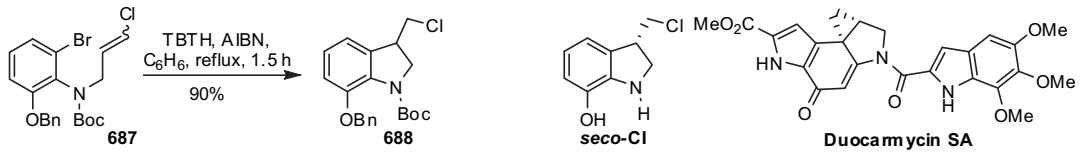
More recently, Boger et al. also synthesized *iso*-duocarmycin SA **685** and *iso*-yatakemycin **686** from the allyl carbamate **684** using a similar strategy (Scheme 242).[250a]



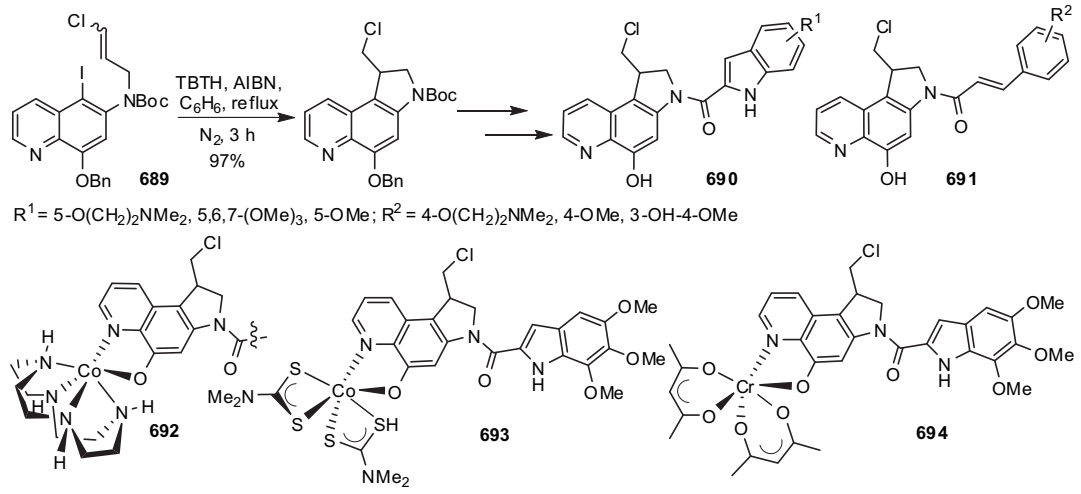
Scheme 242.

Choi and Ma reported the synthesis of the simple achiral *seco*-CI subunit **688** of the duocarmycin pharmacophore from 2-bromo *N*-allyl aniline **687** via TBTH–AIBN mediated 5-*exo*-*trig* aryl radical-alkene cyclization, as depicted in Scheme 243.[250b]

Denny et al. synthesized 1*H*-pyrrolo[3,2-*f*]quinoline analogues (**690** and **691**) from **689** employing a similar strategy and observed that they retain the characteristic high and enantiomerically selective cellular potencies of the broad class of CBI-toxins (Scheme 244).[251] 1*H*-Pyrrolo[3,2-*f*]quinolines form stable cobalt and chromium complexes (**692**–**694**) with a variety of ancillary ligands. The corresponding cobalt–cyclen complexes **692** and **693** were markedly less cytotoxic than the corresponding free effectors and also showed significant hypoxic cell-selective toxicity (7.7- to 40-fold), demonstrating their utility as hypoxia-activated cytotoxins. Complexes **692** and **693** also showed efficient and close-to-quantitative release of their effectors on exposure to ionizing radiation, supporting the suitability of the cobalt-cyclen 1*H*-pyrrolo[3,2-*f*]quinoline complexes for the radiolytic release of cytotoxins.



Scheme 243.

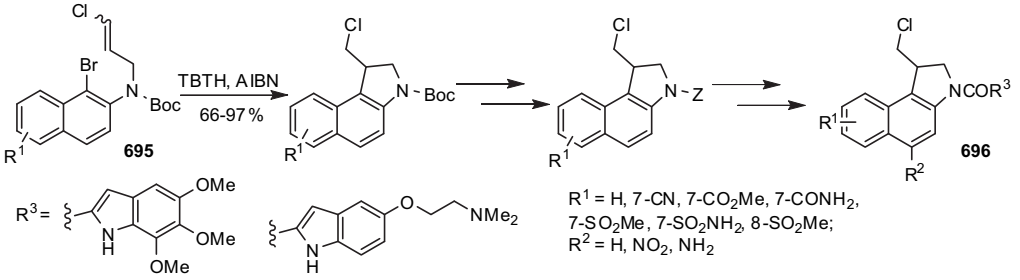


Scheme 244.

These workers extended the strategy for the synthesis of analogues of nitrochloromethylbenzindolines (nitroCBIs) (**696**), a new class of hypoxia-activated prodrugs for antitumour therapy, bearing an extra electron-withdrawing substituent, which caused a rise in one-electron reduction potential of the nitroCBI from the *N*-allyl naphthylamine derivatives (**695**) (Scheme 245).[252] It was observed that the compounds with a basic side chain and a sulfonamide or carboxamide substituent displayed high hypoxic selectivity.

In an alternative strategy Hirashita et al. transformed the allylamine **700** into the corresponding indoline derivative (**702**), via a Br–Li exchange, generation of an allylic indium compound (**701**) and subsequent intramolecular radical cyclization to afford the 5-*exo-trig* product (Scheme 247).[254]

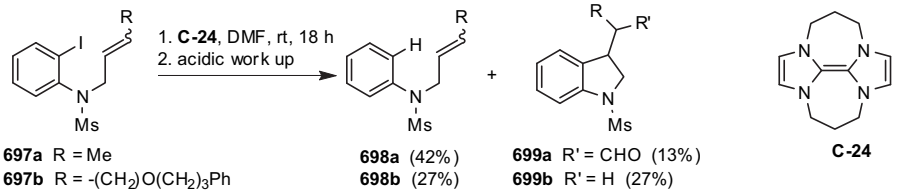
Kim et al. demonstrated a radical cyclization of the enamide derivatives **704**, afforded from the allylamines **703** containing *o*-haloaryl substituents at the rear position, to yield dihydropyrido [2,1-*a*]isoindolone derivatives **705** (Scheme 248).[255]



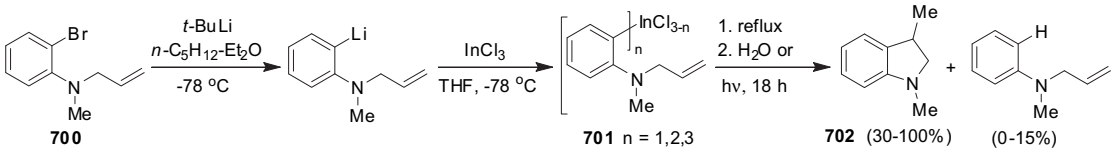
Scheme 245.

Murphy et al. employed the imidazolylidene-derived enetetramine (**C-24**) as a radical initator for the cyclization of **697a**,**b** to generate the indolines **699a**,**b** along with **698** (Scheme 246).[253]

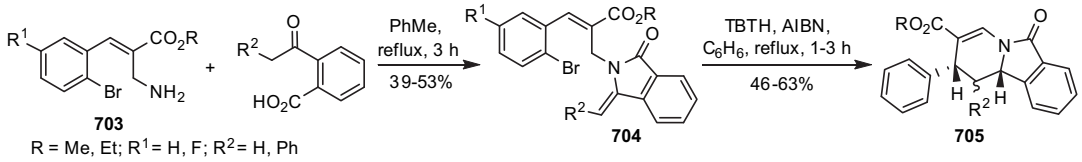
In continuation of this work, the same group developed an expedient method for the synthesis of 1,4,5,6-tetrahydropyridines (**707**) by a radical cyclization protocol involving consecutive 1,5-



Scheme 246.



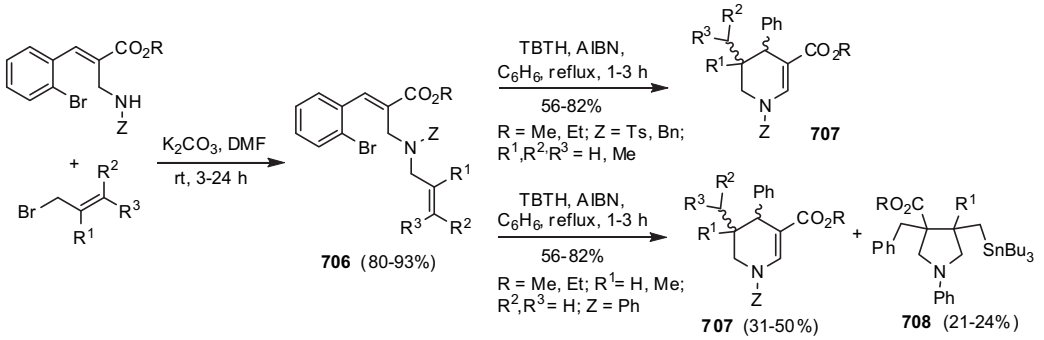
Scheme 247.



Scheme 248.

hydrogen transfer and double bond isomerization process from the substituted allylamines **706** (Z=Ts, Bn) (Scheme 249).[256] In contrast the allylamine **706** (R^1=Ph) under similar conditions afforded **708** in minor yields along with tetrahydropyridines **707**.

exo-trig radical cyclization, and a hydrogen- or bromine-atom transfer process using alkyl bromides **709** as radical precursors and transformed them into the corresponding biologically active GABA derivatives, pregabalin and CAMP (Scheme 250).[257]



Scheme 249.

11.2. Radical cyclization involving alkyl halide as a precursor

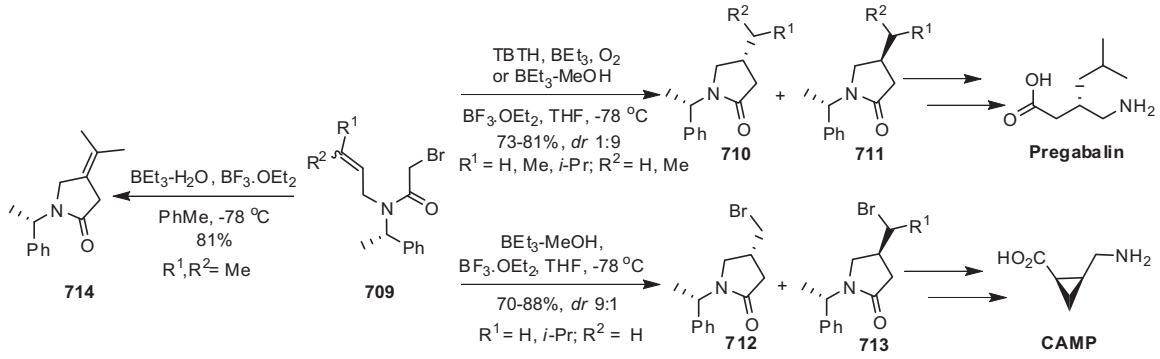
Besides the building up of aromatic systems via radical cyclization, this strategy has been successfully exploited for the generation of non-benzenoid systems. In this regard, allylamines carrying a suitable halide chain have been utilized as the starting materials. Not only halides, but even thio and nitro groups present in the side chain, have been demonstrated to serve as radical precursors for such reactions.

Rodriguez-Soria et al. synthesized optically pure 4-alkyl-pyrrolin-2-ones (**710**–**714**) from chiral *N*-allyl-α-bromoacetamides in a highly selective and stereocontrolled fashion, via a sequential 5-

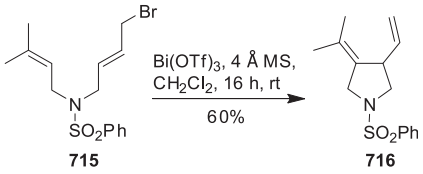
Hayashi and Cook accomplished the synthesis of the pyrrolidine derivative **716** from bisallylamine **715** bearing an allyl bromide functionality via a halophilic $Bi(OTf)_3$-catalyzed 5-*exo-trig* cyclization involving allyl bromide activation (Scheme 251).[258]

Activation of the allylamines **717** and **5** by transforming them into vinyl or allyl bromide derivatives **718** and **720**, respectively, followed by TBTH–AIBN-mediated intramolecular cyclization was described by Kim et al. as a synthetic tool for generating *N*-tosyl-3,3-disubstituted-4-vinylpyrrolidines (**719**) and piperidines (**721**) (Scheme 252).[259]

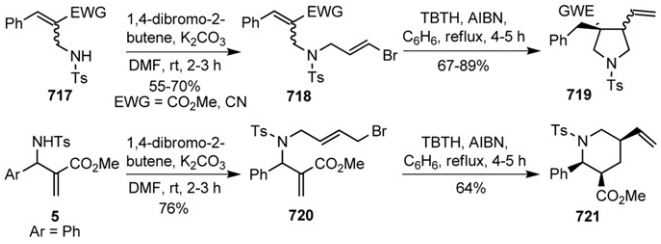
Larraufie et al. reported a novel radical cascade reaction of *N*-acyl cyanamide **722**. The domino process involving the formation of



Scheme 250.

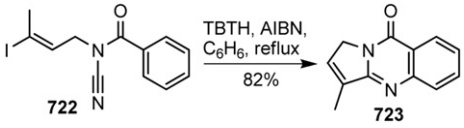


Scheme 251.



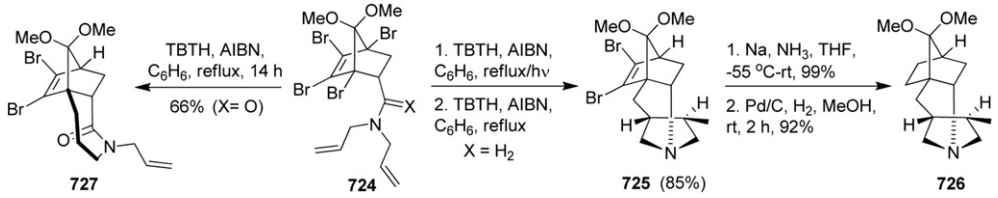
Scheme 252.

a C–C and a C–N bond enabled these workers to achieve the synthesis of the annulated quinazolinone derivative (**723**) (Scheme 253).[260] The key step involved the radical migration of hydrogen atoms or carbon substituents triggered by re-aromatization of a cyclohexadienyl radical generated by radical addition to the aromatic ring.



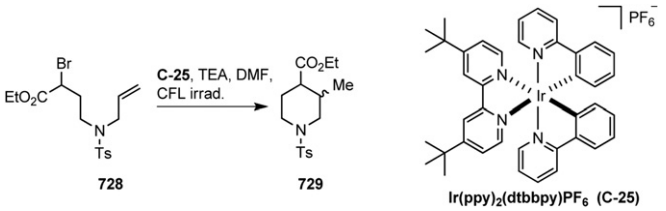
Scheme 253.

Khan and Upadhaya reported a practical and expedient synthesis of racemic as well as optically pure antipodes of tetracyclic amines (**725** and **726**) involving a stereoselective $C^{7n}C^{5x}$ free radical cascade protocol and screened them as catalysts for asymmetric MBH reactions. Bisallylamide (**724**, X=O) when subjected to radical cascade conditions resulted in the C^{7n} monocyclized product **727** (Scheme 254).[261]



Scheme 254.

Stephenson et al. disclosed an Ir complex [$Ir(ppy)_2(dtbbpy)PF_6$] as an efficient visible light photoredox catalyst in a classic free radical-mediated reaction, namely cyclization onto unactivated π-systems. It was postulated that a reactive radical intermediate is generated by the single-electron reduction of an activated C–Br bond by an electron-rich redox catalyst, which converted the allylamine derivative **728** into the 3,4-disubstituted piperidine **729** via a 6-*exo*-*trig* cyclization (Scheme 255).[262]



Scheme 255.

De Kimpe et al. reported the transformation of 1-allyl- and 1-(3-phenylallyl)-substituted 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones (**732**; R^1=H) into 3-substituted 7-alkoxy-5,5-dimethyl-1-azabicyclo[4.2.0]octane-8-ones (**733**) and 4-(2-bromo-1,1-dimethylethyl)-1-(2-methylallyl)azetidin-2-ones (**732**; R^1=Me, R^2=H) into 8-alkoxy-3,6,6-trimethyl-1-azabicyclo[5.2.0]nonan-9-ones (**734**) in good diastereomeric excess through TBTH and AIBN-mediated radical cyclization using bromoalkane **731** as radical precursor (Scheme 256).[263] Compound **731** was in turn generated from the reaction between the allylamine **730** and 3,3-dimethyl-1-bromopropanal.

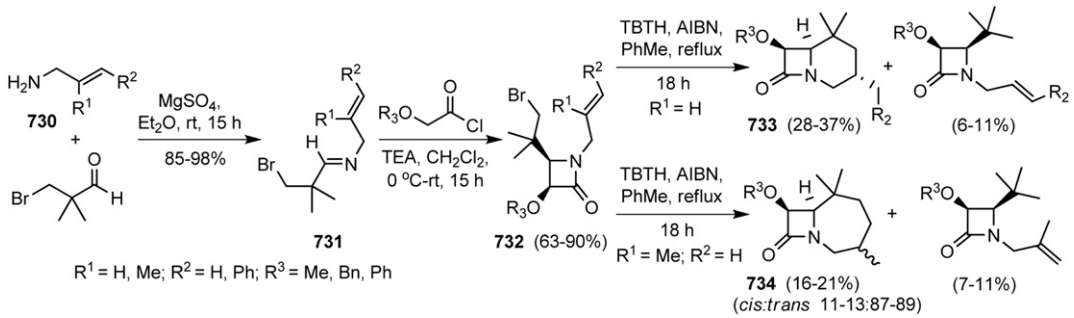
11.3. Other radical precursors

Nair et al. reported the stereoselective intramolecular cyclization of epoxypropyl cinnamylamines **735** in the presence of CAN, leading to the synthesis of functionalized piperidines (**736a**,**b**) (Scheme 257).[264] They postulated that the epoxide ring undergoes a single-electron transfer oxidation by CAN to afford a radical cation, which oxidized the Ce(III) to Ce(IV).

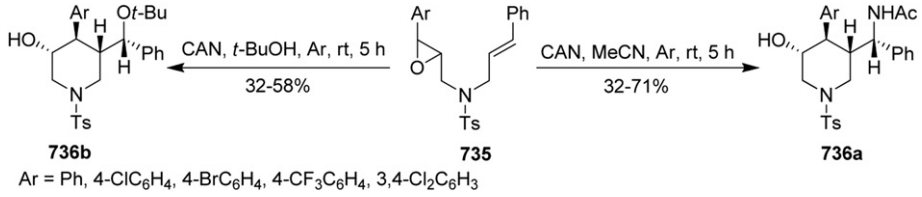
Majumdar and Mondal demonstrated an efficient route for the synthesis of substituted 9-deazaxanthines (**739**) from the *N*-allylated uracil derivatives **737** via a sequential aza-Claisen rearrangement followed by intramolecular radical cyclization of the rearranged product **738** (Scheme 258).[265]

Asahi and Nishino reported $Mn(OAc)_3$ and $Cu(OAc)_2$ as radical initiators to effect the intramolecular oxidative cyclization of *N*-propenyl-3-oxobutanamides (**740**) to produce 3-azabicyclo[3.1.0]hexan-2-ones (**741**) in good yields. Other cyclized products (**742**–**744**) were also isolated (Scheme 259).[266]

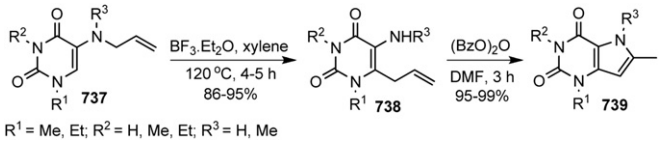
In a recent report, the iodine-atom-transfer 8-*endo* and 5-*exo* cyclization of α-carbamoyl radicals in the presence of a bidentate chelating ligand (**C**-**26**) was investigated by Li's group.[267] They observed that the bidentate chelation dramatically increased the efficiency of cyclization as well as the regio- and stereoselectivity. The 5-*exo* cyclization of *N*-ethoxycarbonyl-substituted iodoamides **745** with the aid of $Mg(ClO_4)_2$ and a bis(oxazoline) ligand (**C**-**26**) led to the formation of pyrrolidinones **746** exclusively as single stereoisomers (Scheme 260). The cyclization–reduction sequence carried out for **747** produced both azocanones (**748**) and pyrrolidinones (**749**) (Scheme 261). The 8-*endo* cyclization products **748** were isolated as single stereoisomers, whereas the 5-*exo* cyclization product pyrrolidinones consisted of at least three isomers with **749** as the major isomers. The 8-*endo* cyclization was even slightly preferred over the corresponding 5-*exo* cyclization. With an increase in bulkiness of the R group in **747**, the yield of 8-*endo* cyclization product decreased. Furthermore in comparison the BEt_3–O_2-initiated radical cyclization of allylamine **750** devoid of *N*-



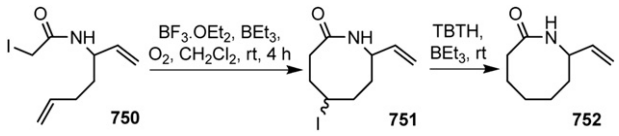
Scheme 256.



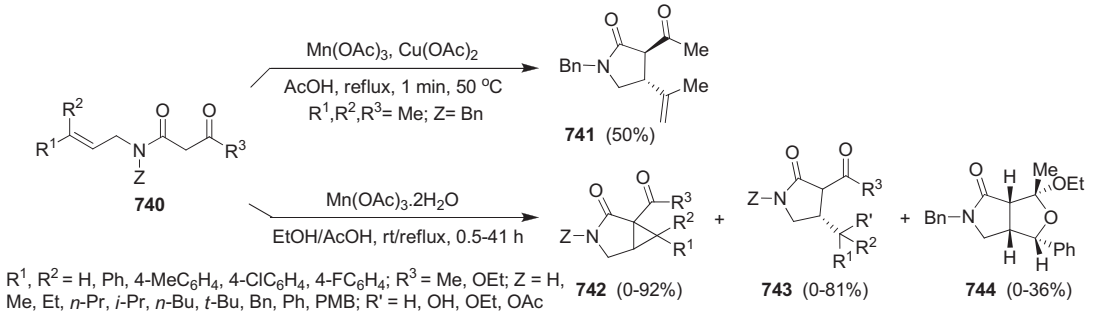
Scheme 257.



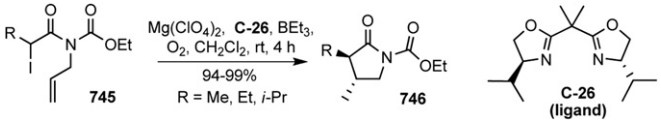
Scheme 258.



Scheme 262.

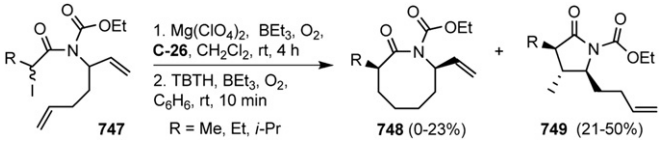


Scheme 259.



Scheme 260.

ethoxycarbonyl substitution proceeded smoothly at room temperature to afford only the 8-*endo* product **752** via the intermediate **751** (Scheme 262).

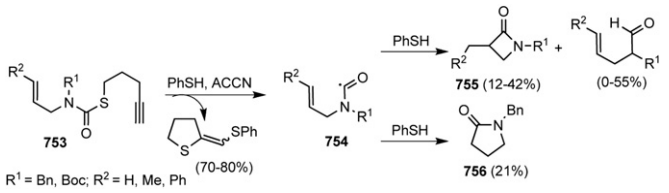


Scheme 261.

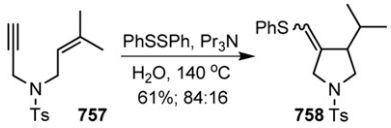
11.4. Radical cyclization involving *S*-based radical precursors

The low bond-dissociation energy of C–S bonds makes the sulfur-based compounds, such as thiols, xanthates etc., good precursors for the *C*-centred radical reaction. The carbamoyl radicals **754** could be generated from a tin-free radical reaction of thiophenol with *S*-4-pentynyl carbamothioates **753** via an intramolecular substitution at sulfur by the initial sulfanylvinyl radicals. This approach was efficiently used by Benati et al. to access *N*-benzylcarbamoyl radical 5-*exo* and 4-*exo* cyclizations, leading to azetidinones (**755**) and pyrrolidinones (**756**), respectively, as shown in Scheme 263.[268]

Ishibashi's group reported that the benzenethiyl radical formed from diphenyl disulfide and tripropylamine via a single-electron-transfer (SET) reaction reacts with 1,6-enynes **757** to generate the 5-*exo* product, 3-methylenepyrrolidine (**758**) (Scheme 264).[269]



Scheme 263.



Scheme 264.

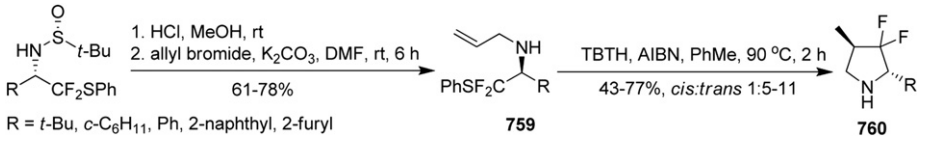
Li and Hu achieved the transformation of $PhSCF_2$-containing sulfinamides (**759**) into chiral 2,4-*trans*-disubstituted 3,3-difluoropyrrolidines (**760**) through an intramolecular radical cyclization methodology (Scheme 265).[270] This was considered to be a new synthetic approach for $TMSCF_2SPh$, a difluoromethylene radical-anion synthon based on the selective cleavage of the F_2C–Si bond.

Likewise the pyrrolo[2,3-*b*]pyridines (**767**) were generated from *N*-allyl-N-(6-chloropyridin-2-yl)acetamide (**766**, Z=Ac). The pyridine-2-allyl carbamates containing a Boc or OAc group (**766**, Z=Boc, –OCOMe), however yielded imidazopyridin-5-one derivatives (**768**) via an unprecedented regioselective radical ring closure onto the pyridine nitrogen (Scheme 269).[274]

11.5. Use of seleno-compounds in radical cyclization

In a recent report, Srivastava and Engman utilized the imines (**770**), prepared by condensing allylamine and readily available α-phenylselenenyl ketones **762**, as precursors to produce the cyclic imines **771** via 5-*exo* radical cyclization, as depicted in Scheme 270.[275]

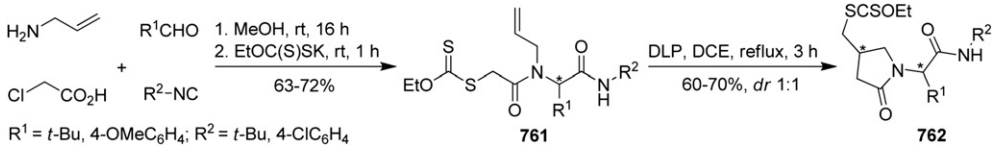
Yang et al. described an efficient route for the stereoselective synthesis of *trans*-α,β-disubstituted γ-butyrolactams (**773** and **774**) in moderate-to-good yields through a photoinduced PhSe group transfer radical cyclization reaction in **772** (Scheme 271). The size of the substituent on the nitrogen atom (*Z* group) of the tertiary amides was found to positively correlate with the yield of the product in this reaction. The key intermediate (**775**), which was used for the total synthesis of the natural product (±)-isocynometrine, by these workers was obtained in 40% overall yield from the *N*-methylated derivative.[276]



Scheme 265.

Xanthates are widely used as convenient radical precursors. El Kaiem et al. reported the synthesis of pyrrolidinones **762**, via an Ugi reaction involving allylamine followed by xanthate-induced radical cyclization onto alkenes in the Ugi product **761**, as shown in Scheme 266.[271]

Bennasar et al. reported the regioselective 7- and 8-*endo* cyclizations of selenoester (**776**) derived 2-indolylacyl radicals upon an amino tethered alkene to synthesize azepino[3,2-*b*]- and azocino-[4,3-*b*]indoles (**777** and **778a**,**b**), the tricyclic subunit present in the indole alkaloids, mersicarpine and apparicine, respectively

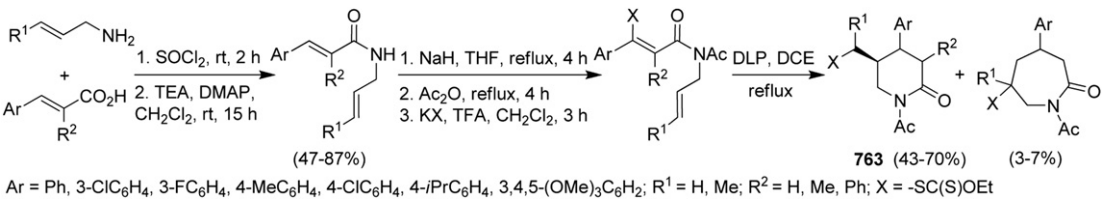


Scheme 266.

Vila and Zard synthesized a series of 5-substituted-4-arylpiperidin-2-ones (**763**) from allylamines in a four-step sequence involving a radical 6-*exo*-*trig* cyclization as the key step (Scheme 267).[272]

(Scheme 272).[277] The selenoester **776** (*n*=0) furnished δ-carbolines (**779**) as the side products in minor yields.

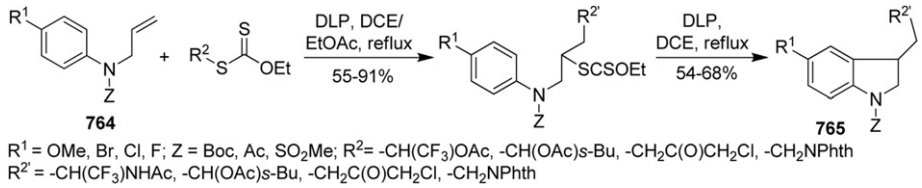
Later, this group accomplished the first total synthesis of (±)-apparicine via a vinyl halide Heck cyclization in **783** to close the



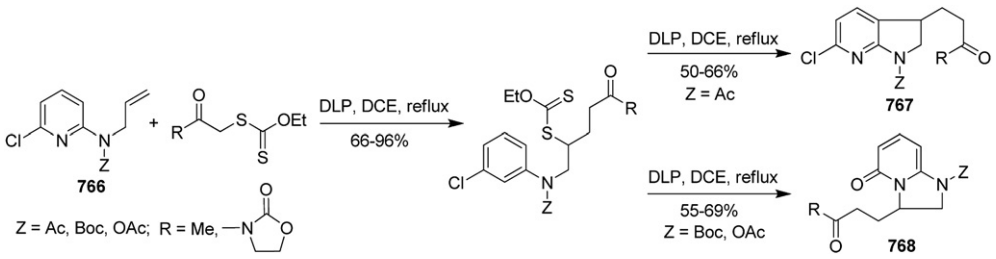
Scheme 267.

Subequently, Zard's group, using a modified approach, reported a facile xanthate addition to the double bond of *N*-aryl allylamines (**764**) followed by intramolecular radical ring closure onto the phenyl ring to generate the indole derivatives (**765**) (Scheme 268).[273]

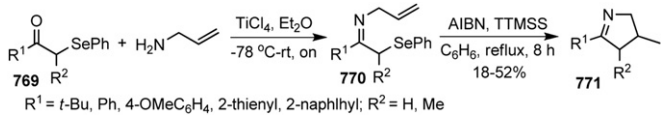
bridged piperidine ring in the last synthetic step. The key azocinoindole intermediate **782** was successfully assembled by an acyl radical cyclization of the allylamine derivative **781** generated from **780** followed by ketone–alkene functional group interconversion (Scheme 273).[278]



Scheme 268.



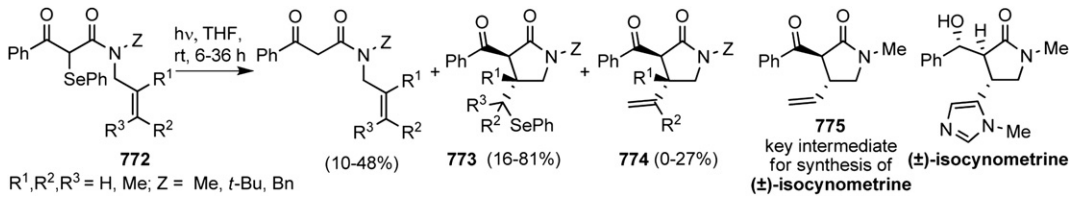
Scheme 269.



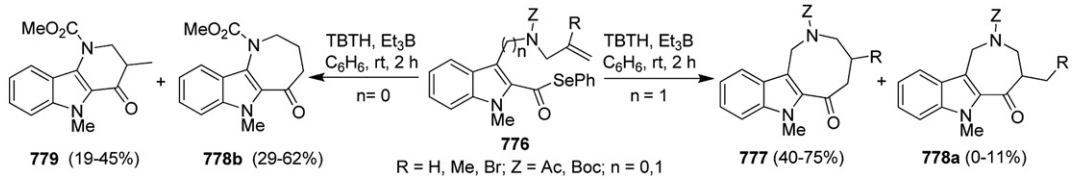
Scheme 270.

11.6. Radical cyclization involving nitro-alkanes as radical precursors

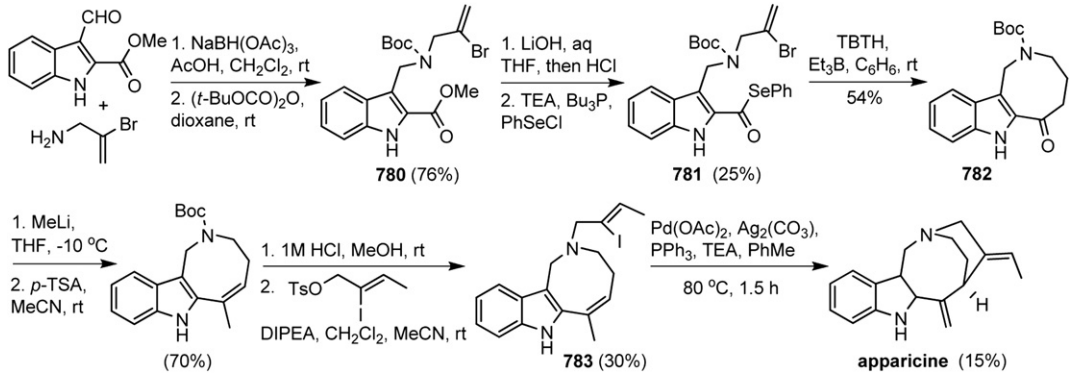
Kamimura et al. reported the synthesis of pyrrolidine **785** in good yield via the radical cyclization of the allyl formamide **784** under standard conditions using the nitro-alkane as radical precursor (Scheme 274).[279]



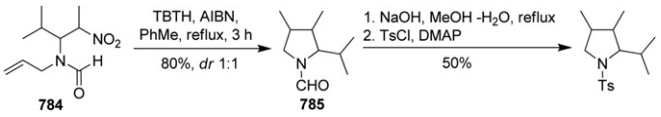
Scheme 271.



Scheme 272.

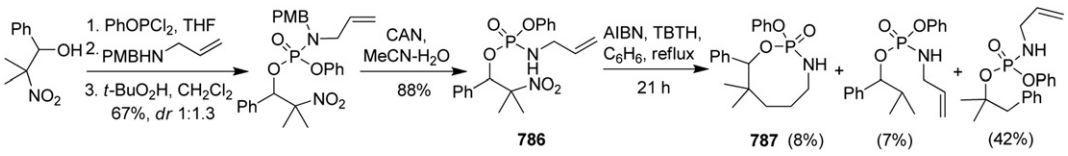


Scheme 273.



Scheme 274.

Crich et al. reported that treatment of the phosphoramide **786** with TBTH–AIBN produced 1,3,2-azoxaphosphocane **787** as the minor product, via a relatively uncommon 8-*endo-trig* cyclization (Scheme 275).[280]

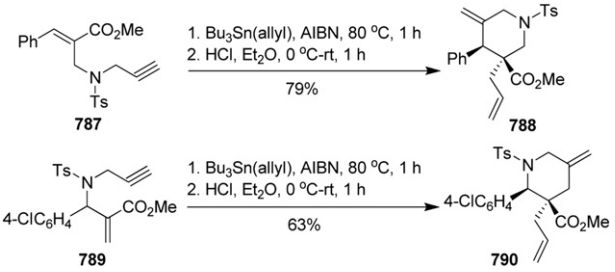


Scheme 275.

11.7. Radical cyclization via functional-group migration

The migration of a functional group in a radical intermediate resulting in a more stable radical followed by cyclization lead to several novel cyclic systems.

11.7.1. Radical 1,2-aryl migration. Gowrisankar et al. disclosed stereoselective syntheses of two types of regioisomeric methyl 5-methylenepiperidine-3-carboxylates (**788** and **790**) from the allylamines **787** and **789** via an allyltributylstannane-mediated vinyl radical cyclization as the key step (Scheme 276). The process involved sequential 5-*exo-trig* cyclization followed by 1,2-aryl migration.[281]



Scheme 276.

11.7.2. Radical 1,4-aryl migration. Tchabanenko et al. reported the radical reactions of a series of *N*-(2-bromoallyl)arylcarboxamides (**791** and **794**) to afford 4-arylpyrrolidin-2-ones (**792** and **795**) along with reduced materials (**793** and **796**) in comparable yields (Scheme 277). The cascade process involved sequential 5-*exo-trig* spirocyclization, radical 1,4-aryl migration (β-scission) and formal 5-*endo-trig* cyclization of the resulting acyl radical to the pyrrolidinone products.[282]

In an extension of their work they later demonstrated that the 5-*exo* cyclization of vinyl, aryl and alkyl radicals onto the aryl group of arylcarboxamides is followed by β-scission of the resulting spirocyclohexadienyl radicals with ejection of a carbamoyl radical (Scheme 278). Although the fate of this radical depends on the substrate, in their study they observed that either 5-*endo* cyclization or direct reduction led to phthalimides, biaryls or β-arylethylamines. Further, they also addressed the limitations caused by rotameric preferences about the amide.[283]

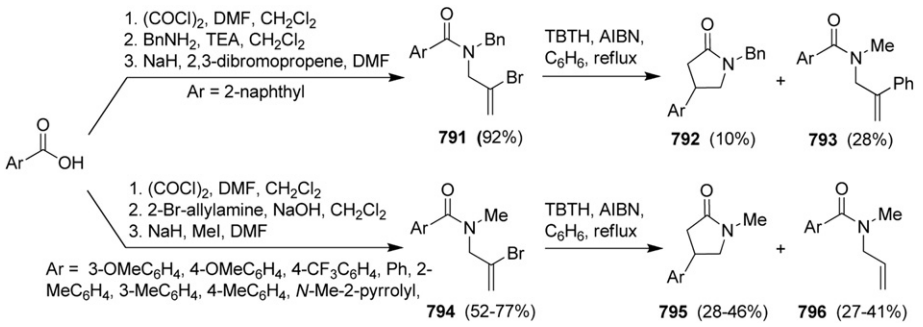
Zard et al. explored a route to 3-arylpiperidines (**800**–**802**) and 3-arylpyridines (**803**) involving radical 1,4-aryl migrations. This strategy involved a xanthate (**797**) addition to an *N*-allylarylsulfonamide (**798**), followed by acetylation and treatment with DLP to give the corresponding 1,4-aryl transfer product **799**, which was converted into the desired piperidine derivative following acidic hydrolysis (Scheme 279).[284]

11.7.3. Radical 1,3-alkyl migration. Dieltiens and Stevens demonstrated that the *o*-ethynylbenzyl α-aminophosphonates **804** when heated under MW conditions undergo a rearrangement involving a 5-*exo-dig* cyclization followed by a 1,3-alkyl shift and, finally aromatization to result in the formation of the phosphonylated isoindoles **805** (Scheme 280).[285]

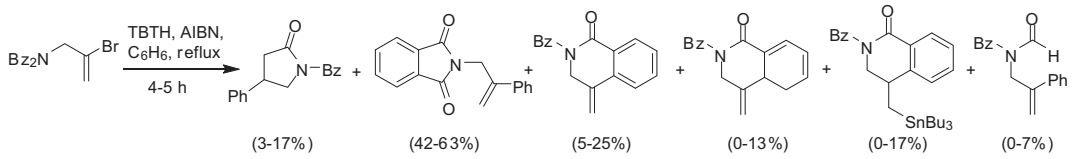
11.8. Atom transfer radical cyclization reactions

Transition-metal-catalyzed atom transfer radical cyclization (ATRC)[286] or Kharasch reactions have been extensively studied over the past few years. The driving force for this research has been the desire to find nonreductive catalytic alternatives to organotin hydrides in mediating radical cyclization reactions in organic synthesis. Active catalysts for cyclization processes are derived mainly from Rh, Fe, or Cu complexes, with those based upon the coordination chemistry of Cu being the most popular.

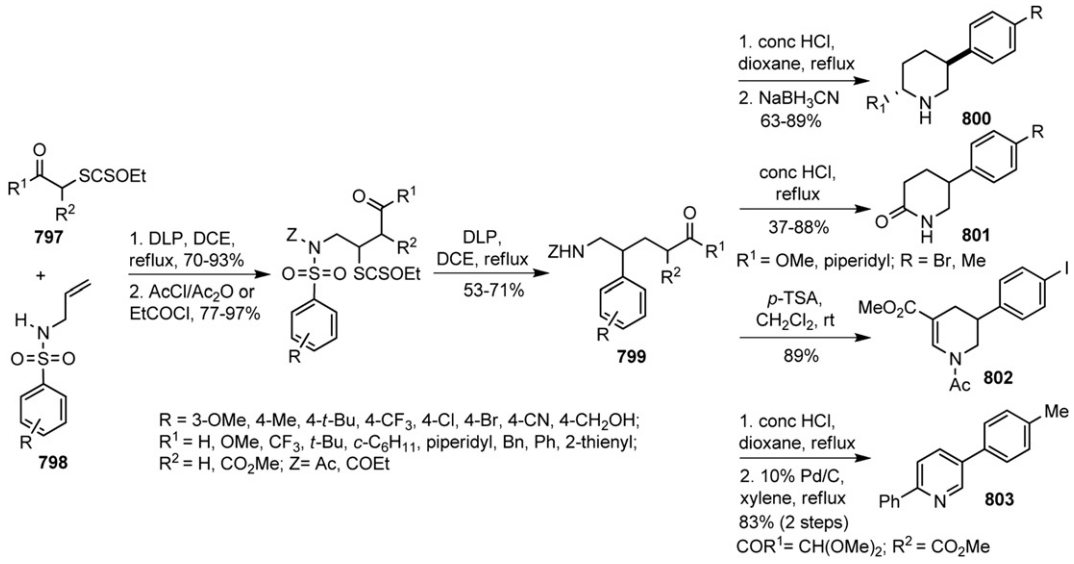
Different groups have extensively studied the Rh[287] and Cu-catalyzed[288] ATRC reactions of *N*-allyl haloacetamides (**807**), generated from the allylamines **806** and an appropriate α-halo acid or acyl halide, and synthesized highly substituted halo pyrrolidinones (**808**) through 5-*exo-trig* cyclization (Scheme 281).



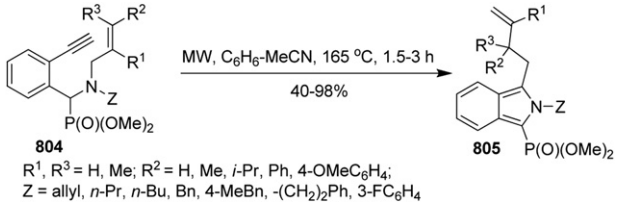
Scheme 277.



Scheme 278.

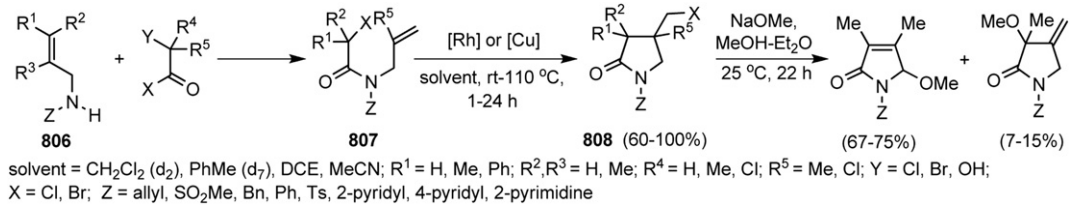


Scheme 279.



Scheme 280.

Clark et al. reported that the reaction of 2-substituted dienamides **811a**,**b** and **814** with catalytic amounts of Cu(I) halide–TPA furnished either 5-*exo* or 6-*endo* products (**813a**,**b** and **815**) (Scheme 283), depending upon the radical initiating unit. β-Lactams (**813a**) were isolated in minor yields from the reaction of 3-substituted dienamides **811a**. This formation proceeded via a 4-*exo* cyclization with termination of the reaction by either halogen atom transfer, trapping with oxygen, elimination, or radical–radical coupling, depending upon the diene.[290]



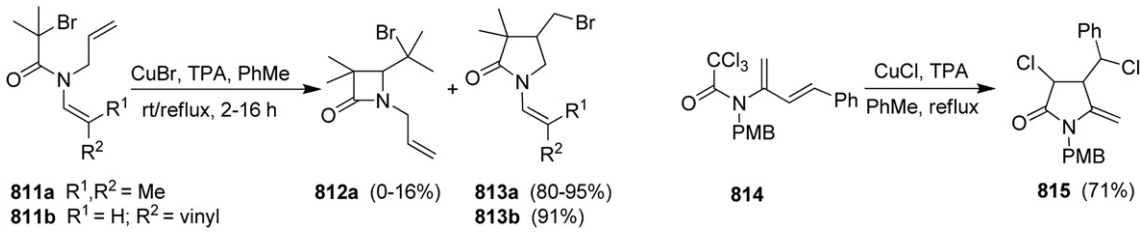
Scheme 281.

Quayle et al. discovered that *N*-allylic α,α,α-trichloroacetamide (**809**) provides a rapid access to 4-benzylated γ-lactams (**810**) through sequential cross metathesis–Kharasch cyclizations promoted by a Grubbs catalyst (**C-27**) (Scheme 282).[289]

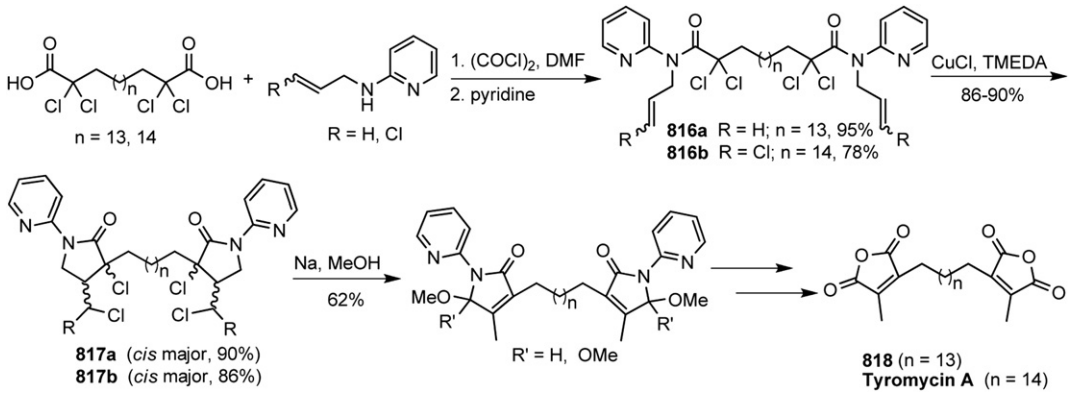
Scheme 282.

Roncaglia et al. reported the synthesis of tyromycin A and that of the non-natural lower homologue **818**, via a CuCl–TMEDA-catalyzed ATRC of **816a**,**b** and a functional rearrangement of the resulting polyhalogenated 2-pyrrolidinones **817a**,**b** (Scheme 284).[291]

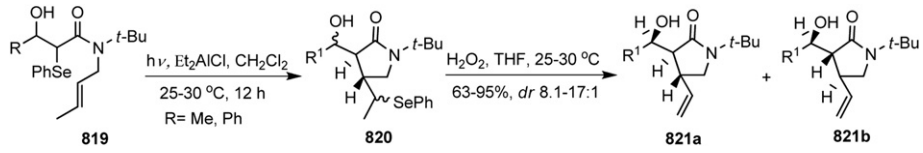
3-(1-Hydroxyalkyl)pyrrolidinones **821a**,**b** with three contiguous stereocenters were constructed by Lian's group in one step in high yields and diastereoselectivity.An Et_2AlCl-catalyzed group transfer radical cyclization reaction of *N*-alkenyl-β-hydroxyalkanamides (**819**) under 125-W UV-lamp irradiation afforded the pyrrolidine **820**, which was immediately subjected to H_2O_2-mediated oxidation to furnish the **821a**,**b** (Scheme 285).[292]



Scheme 283.

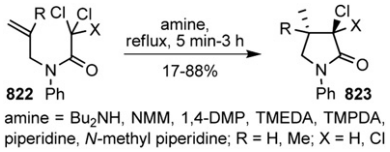


Scheme 284.

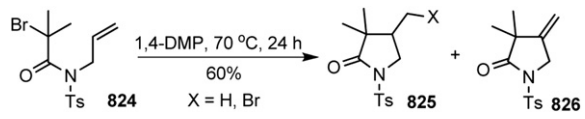


Scheme 285.

Ishibashi et al. demonstrated that the radical cyclization of *N*-allyl α-halogenated acetamides (**822**) to afford γ-lactams (**823**) could be effected by different secondary and tertiary amines under reflux but the best result was obtained with 1,4-DMP (Scheme 286).[293] Neither heavy metals (Sn, Ni, Mn, etc.) nor photochemical conditions were required for these radical reactions. Furthermore, easy purification of the cyclized products was realized by the use of volatile 1,4-DMP. In one recent work Clark et al. also proved the utility of 1,4-DMP in the ATRC reaction (Scheme 287).[294] They observed that heating the allylamine **824** in 1,4-DMP in a sealed tube yielded **825** and **826** in a combined yield of 60%. They discovered that only the dry 1,4-DMP works in their reaction. In contrast, Shibashi et al. observed that the presence of water with 1,4-DMP increased the efficiency to induce the ATRC reaction in **828**, which was prepared from the allylamine **827** (Scheme 288).[295] It was observed that the addition of 5 equiv of water increased the yield of the pyrrolidone derivative **829** to 57%, but distilled 1,4-DMP gave **829** in only 7% yield.



Scheme 286.



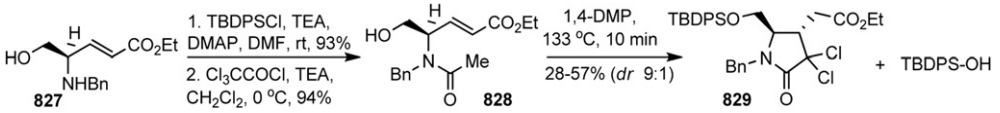
Scheme 287.

11.9. Atom transfer radical addition-atom transfer radical cyclization

The formation of C–C bonds using atom transfer radical addition (ATRA) of a suitable substrate (R-X) to protected or unprotected bisallylamine derivatives of the type **830** followed by a second ATRC is a popular synthetic tool for the generation of diverse substituted pyrrolidines Table 1.[296] Legros et al. reported the synthesis of analogues of DMAP labelled with fluorous chains (F-DMAPs) (**831**) employing this methodology. A similar approach had been pursued by several research groups. Essentially, the variations were made in the R-X, as illustrated in Table 1.

Chemla et al.[297] developed a domino process involving Michael addition and carbocyclization, starting from β-*N*-allylamino enoates (**832**) and various organometallic reagents (organozinc halides, diorganozinc reagents and Cu–Zn mixed species) to generate 3,4-disubstituted pyrrolidines **833** and **834** (Scheme 289). The domino reaction was evidenced to involve a radical-polar crossover mechanism.

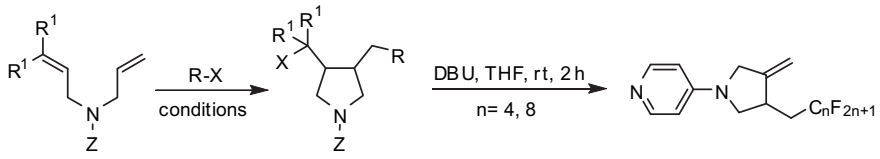
Miyabe et al. successfully performed the enantioselective radical addition–cyclization-trapping reaction of the allylamides **835**, which



827 828 829

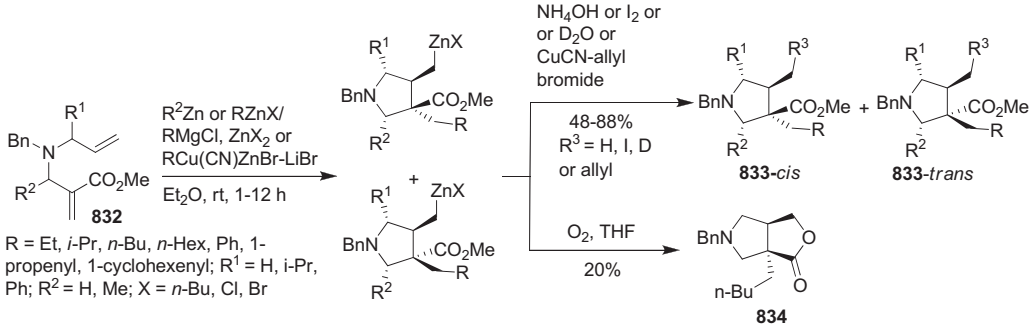
Scheme 288.

Table 1
Examples of formation of pyrrolidines via ATRA followed by ATRC



830 831

Ref.	Conditions	R^1, Z	R-X	Yield (*dr*) (%)
296a	$Na_2S_2O_4$, $NaHCO_3$, MeCN-H_2O, rt, 2 h	H, 4-pyridyl	C_4F_9I	40
			$C_8F_{17}I$	34
296b	[Cu(II)(TPMA)Cl][Cl], AIBN/V-70, MeOH	H, $COCF_3$	Cl_3C-Cl	73-90 (73-84:16-27)
296c	*t*-BuN=N*t*-Bu, C_6H_6, sun lamp 300 W, 4 h	Me, Ts	$PhSO_2$-N_3	89 (1:1)
296d	MW, PhMe, 150 °C, 1 h	H, Boc	$Ph_2P(S)$-H	60
			PhP(OctO)(S)-H	70 (1.9:1)
296e	TBTH, AIBN, PhMe, reflux	H, Ts	$(OEt)_2P(O)CF_2$-SePh (H)	16 (7:3)
			$(OEt)_2P(S)CF_2$-SePh (H)	51 (7:3)
296f	DLP, DCE, reflux	Me, SO_2Ph	BzOCH(CN)-SC(S)OEt	9
			BzOCHSC(S)OEt-CN	45 (3:3:1:1)

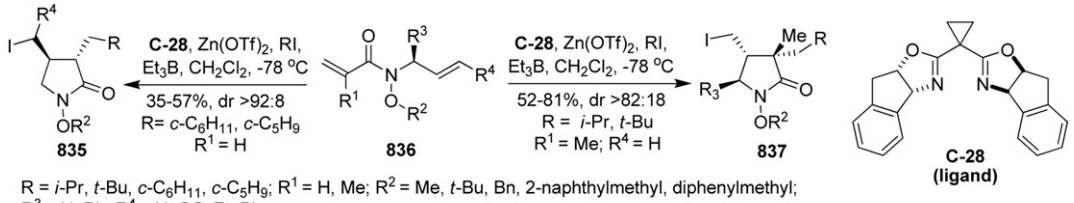


832 833-*cis* 833-*trans* 834

Scheme 289.

offered a powerful synthetic approach to chiral γ-lactams (**836** and **837**) (Scheme 290).[298] The Lewis acid and the presence of ligand **C-28** was demonstrated to provide the observed enantioselectivity.

Fujiwara et al. reported the synthesis of a β-alkylidene pyrrolidine ring (**843**) via the radical coupling of carbamotelluroate with 1,6-enyne (**842**) under irradiation by visible light (Scheme 293).[301]

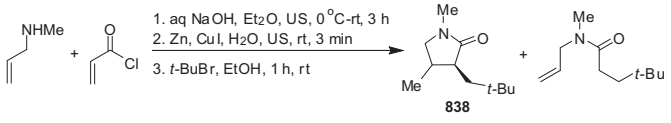


835 836 837

Scheme 290.

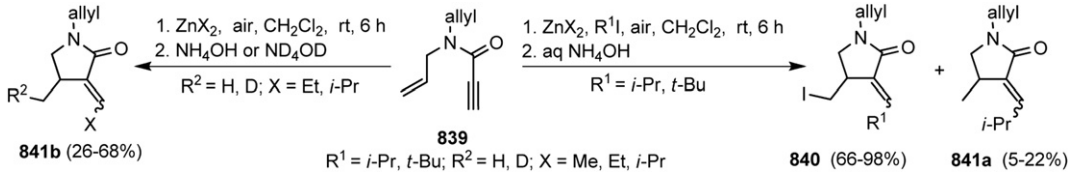
Garrigues et al. reported the synthesis of a substituted *N*-methyl pyrrolidone **838**, under sonochemical (US) conditions (Scheme 291).[299]

Feray and Bertrand achieved a dialkylzinc-mediated alkylative cycloisomerization of *N*,*N*-diallylpropiolamide (**839**) into α-alkylidene-γ-lactams (**840**, **841a**,**b**) in an aerobic medium (Scheme 292).[300]

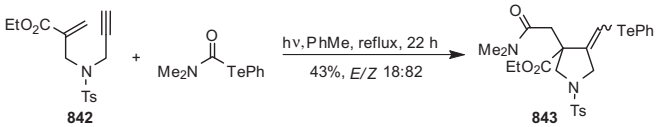


838

Scheme 291.

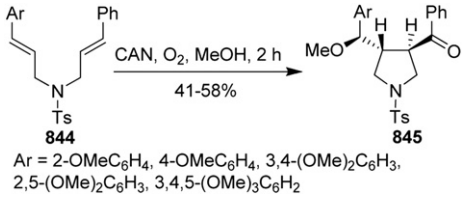


Scheme 292.



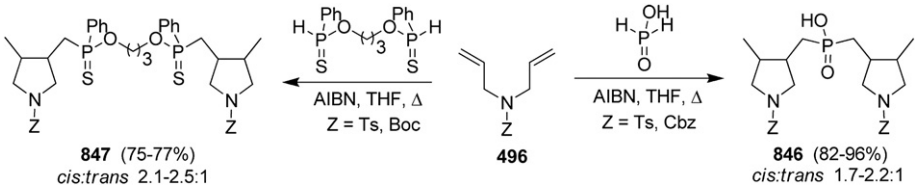
Scheme 293.

Nair et al. successfully employed CAN for intramolecular cyclization reactions of bis-(cinnamyl)tosylamides (**844**), leading to the synthesis of pyrrolidines **845** in moderate yields (Scheme 294).[302]



Scheme 294.

Parsons and Wright disclosed the sequential radical addition–cyclization reactions of bis-allylamines (**496**) using either hypophosphorous acid or a bisphosphinothioate to afford bis-pyrrolidines (**846** and **847**) in good-to-excellent yields (Scheme 295).[303]



Scheme 295.

11.10. Organomercury compounds in radical cyclizations

Dhavale et al. disclosed the synthesis of sugar-substituted pyrrolidines **850** through an intramolecular aminomercuration reaction of sugar-derived β-hydroxy-γ-alkenylamines (**849**) afforded from the allylamines **848** (Scheme 296). The pyrrolidines **850** were elaborated for the synthesis of polyhydroxylated indolizidine alkaloids, namely castanospermine, 1-*epi*-castanospermine and 8a-*epi*-castanospermine.[304]

Han's group reported the first asymmetric synthesis of (+)-*iso*-6-cassine from the piperidine derivative **852** generated by intramolecular amidomercuration of the allylamide **851** (Scheme 297).[305]

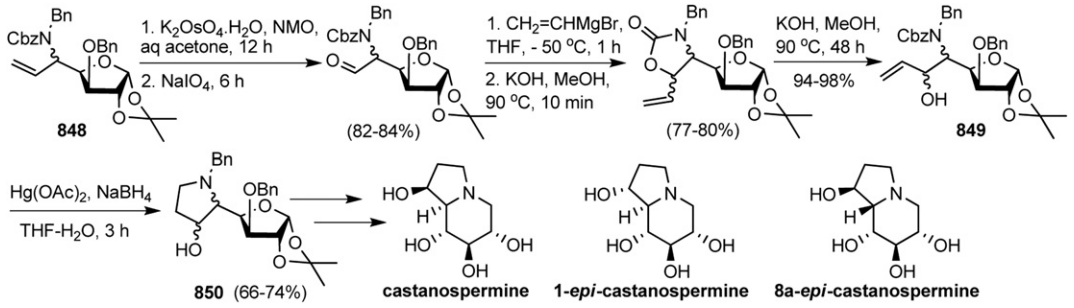
11.11. Fe-promoted radical reactions

Recently, Ishibashi et al. reported that the treatment of 1,6-dienes (**853**) with $FeCl_3$ or Fe(Pc) in the presence of $NaBH_4$ and air or O_2 caused radical cyclization to afford five-membered functionalized pyrrolidines (**854** and **855**) (Scheme 298). Under similar reaction conditions the 1,6-enynes (**856**) were transformed into 3-methylenepyrrolidines (**857**) (Scheme 299).[306] They further reported the sequential steps that involved radical addition of a nitro group to 1,6-dienes **858** promoted by the thermal decomposition of $Fe(NO_3)_3$ nonahydrate, cyclization and trapping of the resulting terminal radicals by a halogen atom in the presence of a halide salt, leading to pyrrolidines (**859**; X=CH_2) and pyrrolidine-2-ones (**859**; X=CO) (Scheme 300).[307]

Jahn et al. reported that the enolates generated by deprotonation of *N*-allylic β-alanine esters (**860**) underwent ferrocenium hexafluorophosphate (**C-29**)-mediated 5-*exo* cyclization to produce the pyrrolidine derivatives (**861a**–**c**) (Scheme 301).[308]

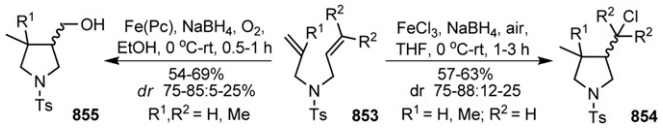
11.12. Ti-promoted radical reactions

Echavarren et al. achieved the synthesis of polyalkylated pyrrolidines (**863**), with excellent stereoselectivity, by a Ni–Ti-promoted Oppolzer-type radical cyclization of the substituted allylamines **862** (Scheme 302).[309]

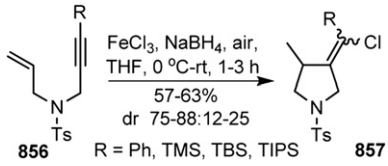


Scheme 296.

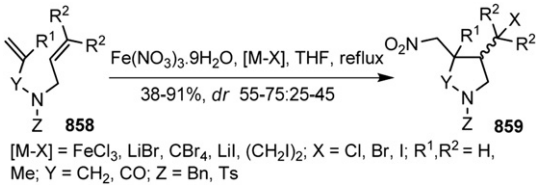
Scheme 297.



Scheme 298.



Scheme 299.



Scheme 300.

Likewise Xu and Huang achieved a Ti(III)-promoted synthesis of 3-vinyl-4-hydroxymethylpyrrolidine (**868**) via intramolecular free radical cyclization of epoxyallene ether **867** in an *exo*-mode. The epoxyallene ether **867** in turn was prepared from allylamine, as depicted in Scheme 304.[311]

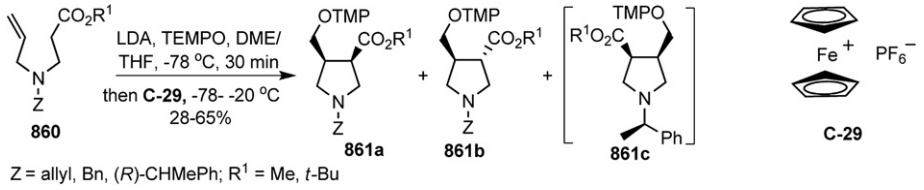
Oltra et al. synthesized the piperidine derivatives (**870a**,**b**) from the allylamine **869** via a Barbier-type cyclization of the ketone using a Ti(III)catalyst, generated in situ from a commercial Ti(IV) precursor (Scheme 305).[312]

11.13. Reactions involving nitrogen-centred radicals

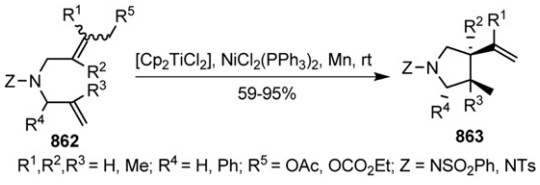
Interestingly, several substituted allylamines have been utilized for creating nitrogen-centred radicals, which, when captured by internal olefins, give rise to different nitrogen heterocycles.

Banwell and Lupton utilized allylamine **871** to synthesize the nitrogen-radical precursor **872**, which underwent tandem radical cyclization reactions leading to the tricyclic core (**873**) associated with certain post-secodine alkaloids, such as ibophyllidine (Scheme 306).[313]

Sharp and Zard reported the construction of the indole alkaloid (±)-aspidospermidine from **875**, generated via a cascade radical cyclization, of an amidyl radical obtained by treating **874** with TBTH–AIBN (Scheme 307).[314]



Scheme 301.

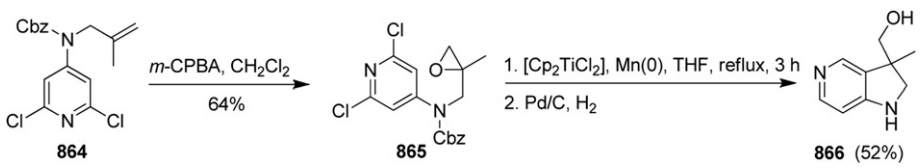


Scheme 302.

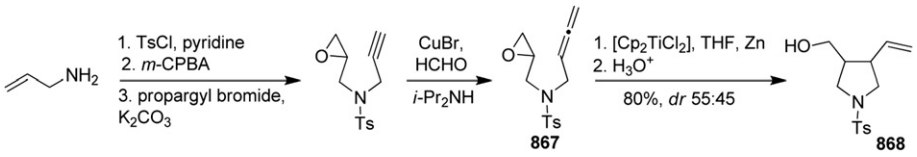
Wipf and Maciejewski demonstrated that the titanocene dichloride- and Mn metal-promoted radical annulation of epoxide tethered to substituted aminopyridine (**865**) generated from the allyl carbamate (**864**), formed the 3,3-disubstituted azaindoline **866** (Scheme 303).[310]

Later, the same group employed this strategy for the construction of the key indolizidine cores (**877** and **878**) from the substituted allylamine **876** in one step, leading to the synthesis of (±)-3-deoxyserratine (Scheme 308).[315] Compound **878** was employed for the synthesis of 1,3-deoxyseratine.

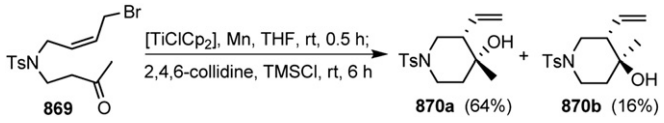
Naito's group demonstrated that an oxime ether, hydrazone and imine carrying an unsaturated ester or amide (**879**) produced the *N*-norpyrroloquinoline (**880**) as a major product via radical addition–cyclization–elimination (RACE) reaction when treated with TBTH and AIBN (Scheme 309). The radical reaction of aldehyde and ketone (**881**) carrying an α, β-unsaturated ester proceeded stereoselectively to yield *cis*-furoquinolines (**882**) and *cis*-hydroxyesters (**883**) (Scheme 310).[316]



Scheme 303.



Scheme 304.

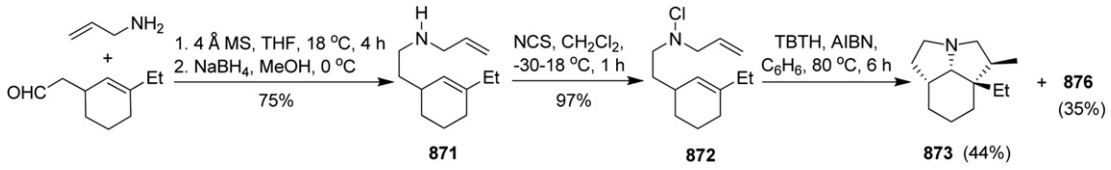


Scheme 305.

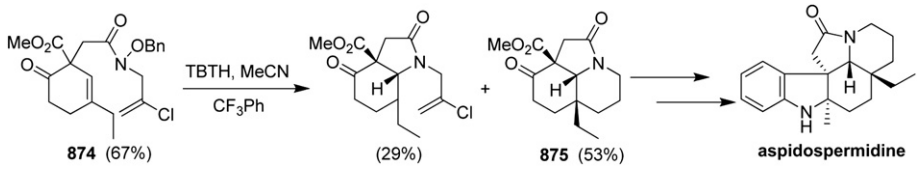
formyl alkane-substituted allylamine (carbonyl-ene reaction) or bisallylamine has been used as an efficient synthetic tool to access aza-heterocycles of variable ring size.

12.1. Carbonyl-ene cyclizations

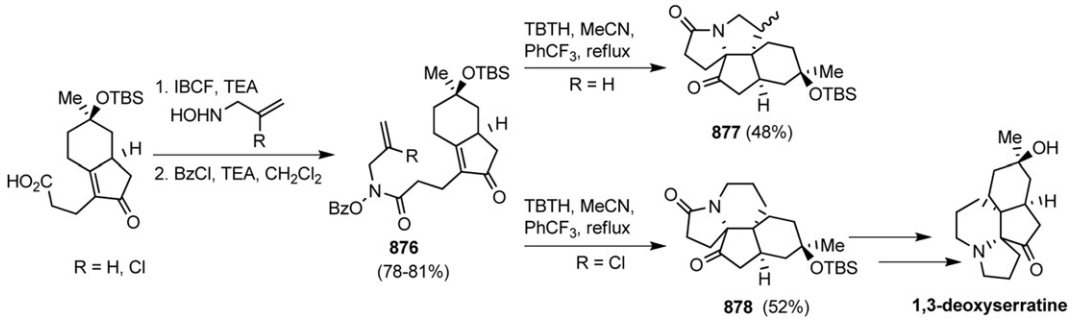
Snaith's group studied the Bronsted and Lewis acid-catalyzed carbonyl-ene cyclization of the amino aldehydes **884** to furnish



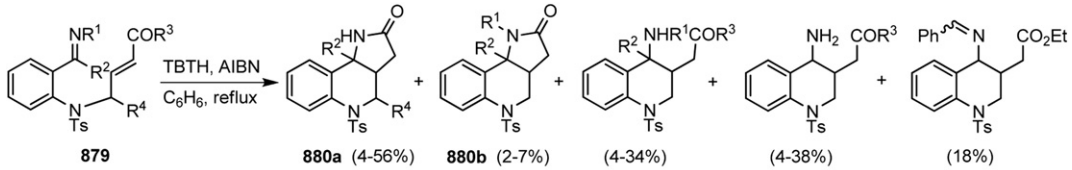
Scheme 306.



Scheme 307.



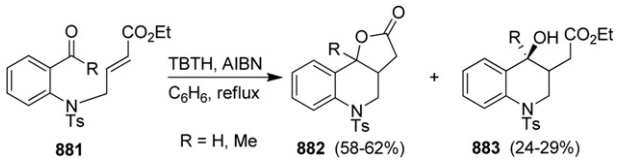
Scheme 308.



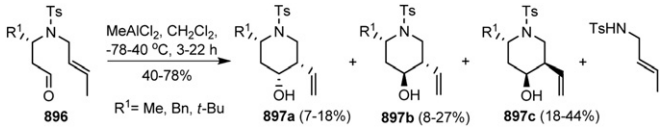
Scheme 309.

12. Ene reactions

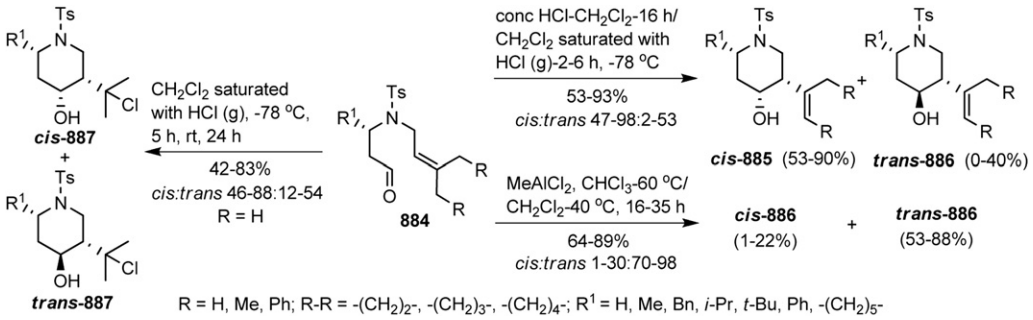
The Lewis acid- or transition-metal-catalyzed intramolecular ene reaction offers an attractive route to ring closure, forming a carbon–carbon bond with concomitant generation of two contiguous stereocenters.[317] The intramolecular ene reaction of α- or β-*cis*- and *trans*-3,4-di- or 2,4,5-trisubstituted vinylpiperidines **886** and **897**, as demonstrated in Scheme 311.[318] In the case of the $MeAlCl_2$-catalyzed reaction, the kinetically stable cis-isomer (*cis*-**886**) was formed as the major product at low temperature, whereas the reaction performed at higher temperature with **884** bearing a small substituent (R^1) on the carbon adjacent to nitrogen afforded



Scheme 310.

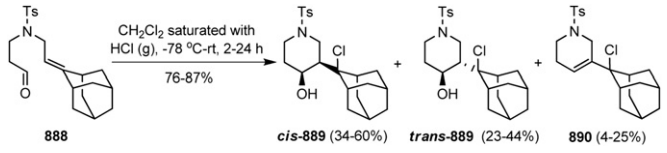


Scheme 314.



Scheme 311.

the thermodynamically stable *trans*-piperidines (*trans*-**886**) with diastereomeric ratios of up to 93:7. The use of CH_2Cl_2 saturated with HCl (g) worked best to afford *cis*-vinylpiperidines with diastereomeric excesses of up to 96% at −78 °C, but prolongation of the reaction time resulted in the HCl addition products **887** with a similar stereochemical outcome (Scheme 311).[319] The less reactive adamantyl system **888** also underwent a facile cyclization in CH_2Cl_2 saturated with HCl (g) to generate *cis*- and *trans*-chloro derivatives (**889**), along with chloroalkene **890** (Scheme 312).[318a] Treatment of the aza-diene (**891**) having an ester functionality at the α-position to the nitrogen in CH_2Cl_2 saturated with HCl (g) afforded a mixture of four products, which included the expected carbonyl-ene product (**892**), lactone (**894**) and their HCl addition products **893** and **895**, all having *cis*,*cis*-stereochemistry (Scheme 313). Stirring the mixture of esters in CH_2Cl_2 saturated with HCl (g) resulted in the complete HCl addition products in roughly equal amounts. In contrast, treating **891** with 1 equiv of $MeAlCl_2$ at room temperature produced the lactone **894** exclusively (Scheme 313).



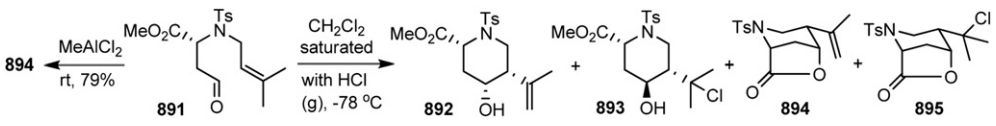
Scheme 312.

The thermal or Lewis acid-catalyzed ene cyclization of a variety of 4-aza-1,7-dienes containing activated enophile (**898**) produced substituted piperidines (**899** and **901**), the ene cyclization product, along with bicyclic lactones (**900** and **902**), formed via a competing hetero-Diels–Alder reaction (Scheme 315). Activation of the enophile with a single ester facilitated a thermal ene cyclization, but the reaction was not amenable to Lewis acid catalysis. With other activating groups on the enophile, it was found that the Lewis acid-catalyzed reaction was facile, although there was a fine balance between the desired ene cyclization and the competing hetero-Diels–Alder reaction, with the product distribution being influenced by the activating group on the enophile, the nature of the ene component, and the Lewis acid used.[218]

Andres et al. described an efficient route to enantiopure *cis*-3,4-disubstituted 3-hydroxypyrrolidines (**905a**,**b**) via Lewis acid-induced intramolecular carbonyl-ene cyclization reaction of 2-acyl-3-allyl-perhydro-1,3-benzoxazine derivatives (**904a**,**b**) obtained from the allylamine **903** (Scheme 316).[320] The diastereoselectivity of the cyclization was influenced by the nature of the Lewis acid.

Chalker et al. reported Pd(0)-catalyzed Zn-ene cyclization of the substituted bis-allylamines **906** and **908** to generate the pyrrolidine core **907a**,**b** of the marine alkaloid, (−)-kainic acid and its analogues **909a** and **909b** with the required stereochemistry, as depicted in Scheme 317.[321]

Hara et al. reported that the $Pd_2(dba)_3$–(*S*)-9-NapBN-mediated asymmetric metallo-ene reaction of the bisallylamine **910** to afford

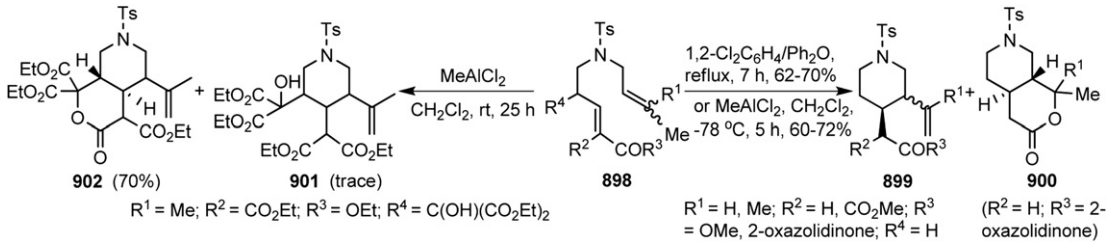


Scheme 313.

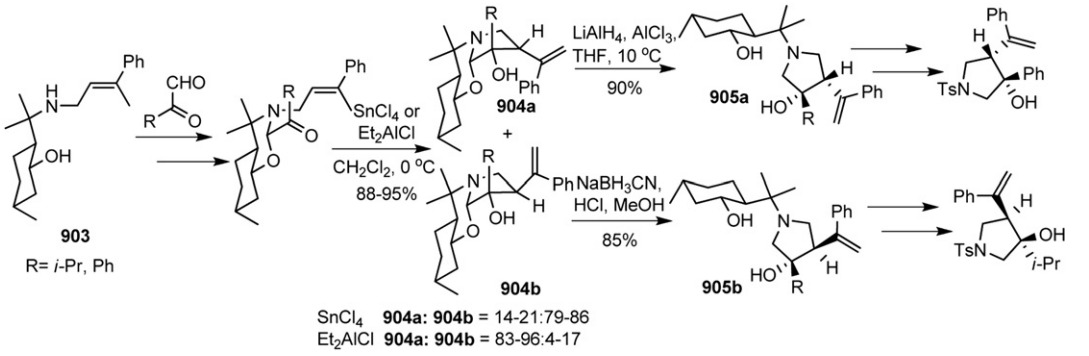
After successful cyclization of the substrates containing a prenyl ene moiety, the same workers investigated the fate of the analogous substrates **896** containing a crotyl moiety under similar reaction conditions. This reaction, however, resulted in a mixture of products (**897a**–**c**), each in low yields, indicating **896** not to be a good substrate for this reaction (Scheme 314).[319]

the pyrrolidine **911** proceeds poorly. The final products were isolated in poor yield and low enantioselectivity (Scheme 318).[322]

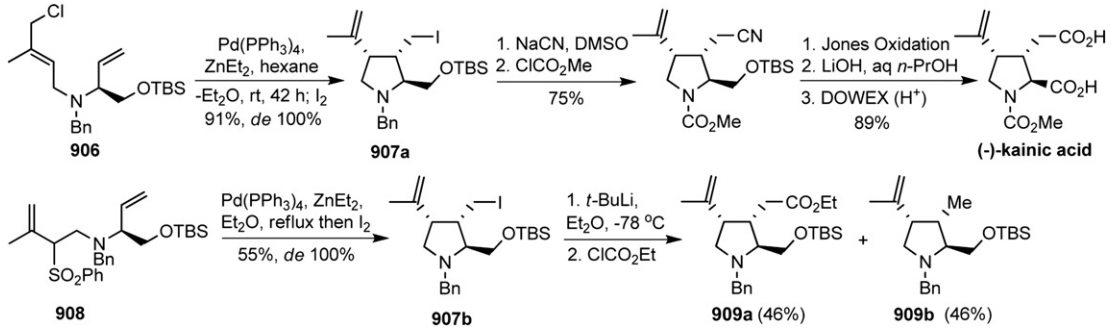
Jacobsen et al. described the formation of 3-vinylpyrrolidine (**913**) with two contiguous stereocenters via a Cr(III)–Schiff base complex-catalyzed highly diastereo- and enantioselective carbonyl-ene cyclization of *N*-prenyl aldehyde (**912**) (Scheme 319).[323]



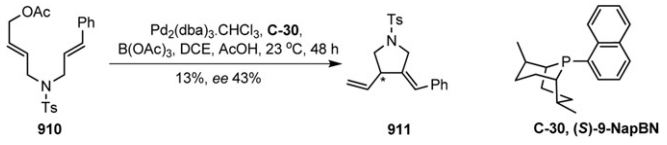
Scheme 315.



Scheme 316.

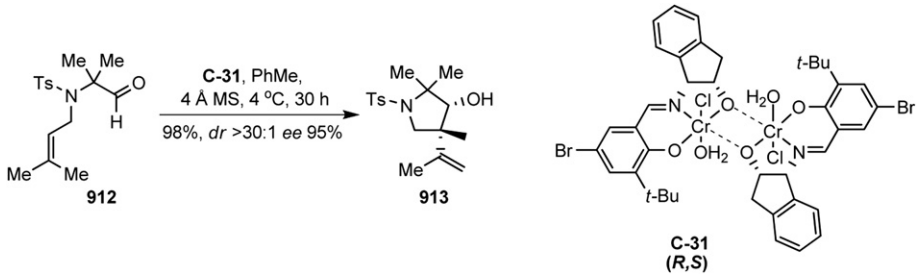


Scheme 317.

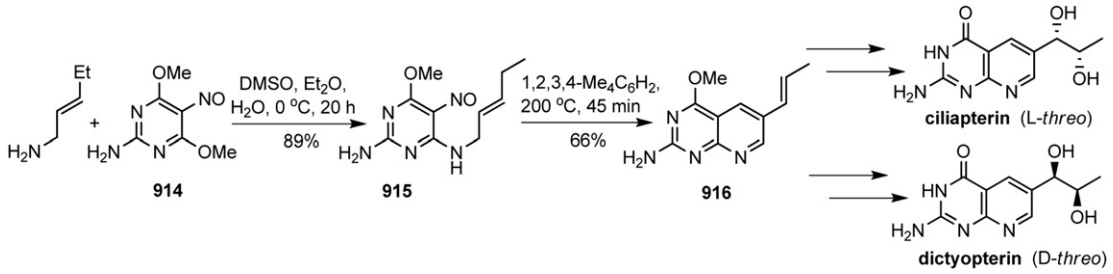


Scheme 318.

Zhang and Vasella prepared an (alkenylamino)-nitroso-pyrimidine (**915**) by substitution of the dimethoxy-nitroso-pyrimidine (**914**) with the allylamine, and **915** was cyclized through an intramolecular thermal ene process to produce the pteridine (**916**) (Scheme 320). The pteridine (**916**) was transformed into ciliapterin and dictyopterin through asymmetric dihydroxylation under Sharpless conditions followed by deprotection of the imino ether. During their study, they observed that the (alkenylamino)-nitroso-pyrimidine (**915**) was less reactive than the corresponding (acylamino)-nitroso-pyrimidine towards the intramolecular ene reaction.[324]



Scheme 319.



Scheme 320.

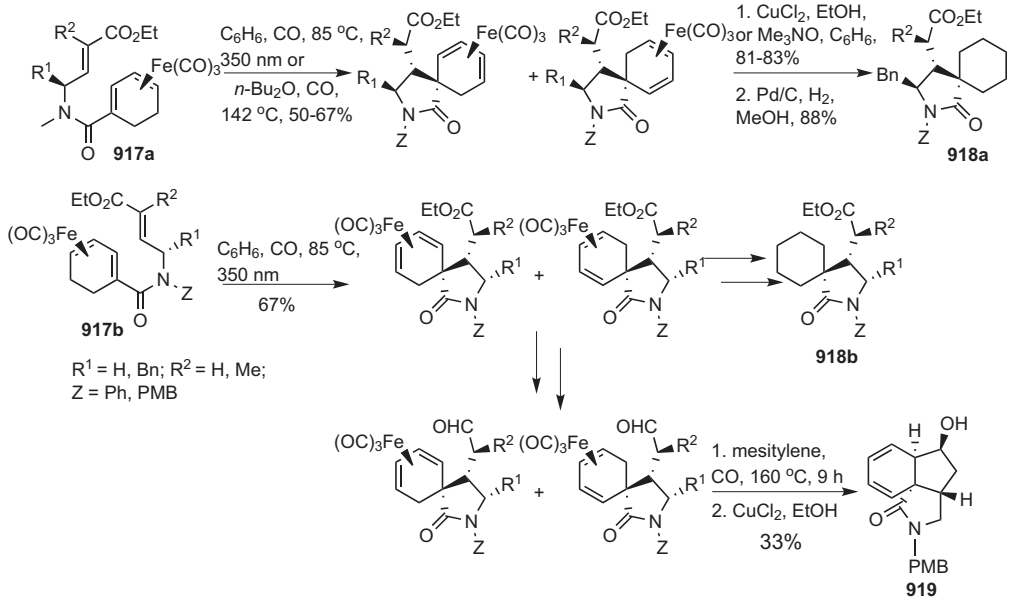
12.2. [6+2]-Ene cyclizations

Pearson et al. reported $Fe(CO)_3$-promoted [6+2]-ene spirocyclization reactions of the allylamides **917a**,**b** to produce densely substituted spirolactams (**918a**,**b**) with high optical purity, using a single stereogenic centre as a control element. A second ene-type cyclization allowed the construction of a tricyclic structure **919**, again with complete stereocontrol (Scheme 321).[198,325]

transform aliphatic (**922**) and aromatic (**924**) aldehydes tethered to different Michael acceptors into 4-substituted pyrrolidine-3-one (**923**) and 3-substituted 2,3-dihydroquinolin-4-one (**925**) derivatives, respectively (Scheme 323).[327]

12.4. Alder-ene reactions

The Alder-ene cyclization reaction is another important tool that transforms allylamine attached to a 4π-system into novel aza-



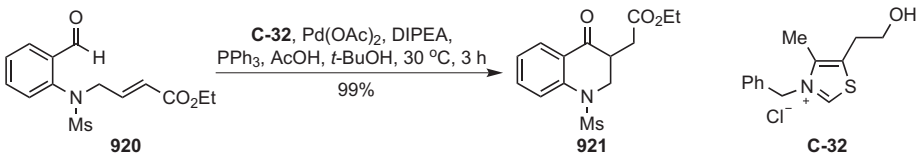
Scheme 321.

12.3. Stetter reactions

Hamada et al. disclosed a novel route to 3-substituted 2,3-dihydroquinolin-4-ones, such as **921** via a thiazolium salt-catalyzed Stetter reaction of *N*-allyl aniline (**920**), which in turn

heterocycles. Fuerstner et al. described the synthesis of 3-methylenepyrrolidines (**927a**,**b**) via a Fe-catalyzed Alder-ene cyclization of the enynes **926** (Scheme 324).[216b]

Wipf's group has reported the transformation of *N*-allyl diphenylphosphinic amides (**928**) into novel spirocyclic and tri-

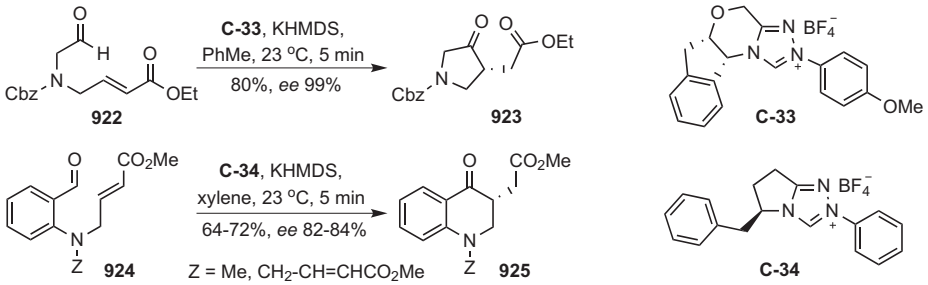


Scheme 322.

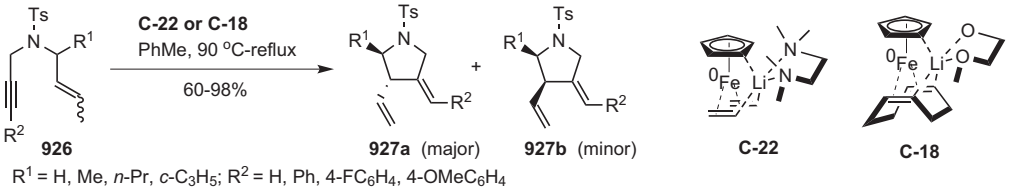
was produced from Pd(0)-catalyzed allylic amination of γ-acetoxy α,β-unsaturated carbonyl compounds with 2-amino benzaldehyde derivatives (Scheme 322).[326]

Later, Rovis et al. also disclosed triazolium salt-catalyzed highly enantioselective intramolecular Stetter reactions to

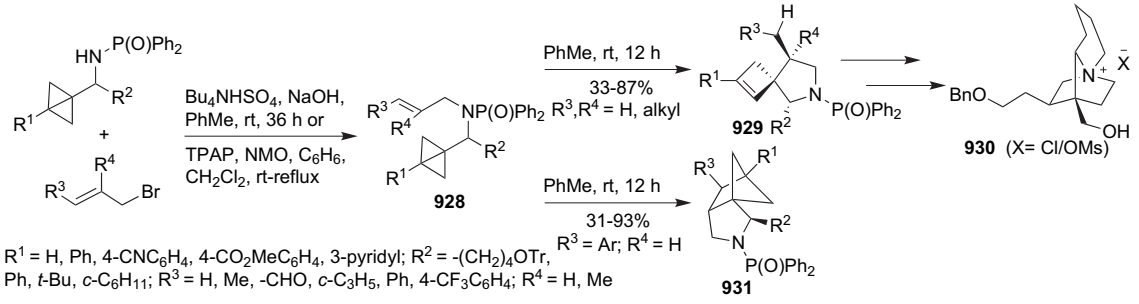
cyclic pyrrolidine heterocycles (**929** and **931**) through highly diastereoselective cascade rearrangements by formal Alder-ene or [2+2] pathways. The tetracyclic nitrogen core **930** of the daphniglaucins was generated from the spirocyclic pyrrolidine (Scheme 325).[328]



Scheme 323.



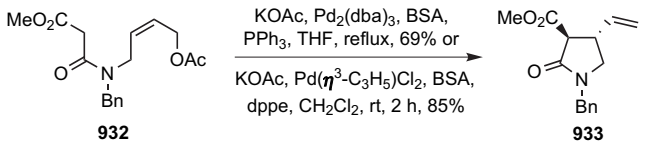
Scheme 324.



Scheme 325.

13. Metal-catalyzed C–C bond formation reactions involving active methylene and alkene

Poli et al. reported a Pd-catalyzed intramolecular asymmetric allylic alkylation of *N*-acyl allylamine (**932**), allowing access to disubstituted γ-lactam (**933**). The use of (*R*)-*t*-Bu-OMeBiphep as ligand in a biphasic medium produced the desired product with up to 84% ee (Scheme 326).[329] In order to seek rationalization for the direction and extent of the stereochemistry, DFT studies were performed by the authors.

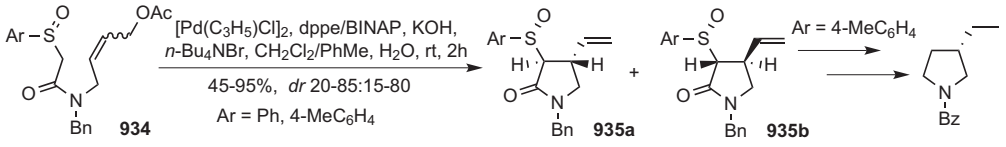


Scheme 326.

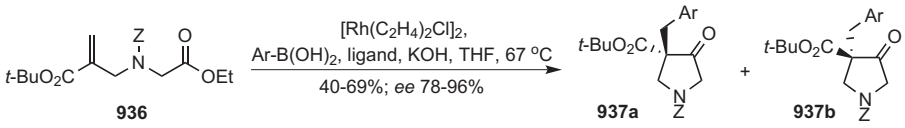
Very recently the same group extended the strategy to generate disubstituted sulfinyl γ-lactams (**935a**,**b**) from substituted allylamines **934** via a similar methodology, as shown in Scheme 327.[330] The concomitant use of an enantiopure sulfinyl-derived substrate of defined absolute configuration together with BINAP as ligand under biphasic conditions (CH_2Cl_2/H_2O or $PhMe/H_2O$) allowed products of opposite diastereoselectivities to be obtained.

Frost et al. developed Rh-catalyzed enantioselective Dieckmann-type annulations of the allylamine derivatives (**936**) to form pyrrolidines (**937a**,**b**) with quaternary stereogenic centres (Scheme 328). They observed that the use of the *R*-ligand produced **937a** as the major products, whereas **937b** were formed as the major products when ligands with an S-configuration were used.[331]

Li and Yu demonstrated the first example of conjugated diene-assisted Rh(I)-catalyzed activation of an allylic C–H bond and its addition to the alkene of the conjugated diene moiety in ene-2-diene substrates.[332] This reaction enabled the generation of multisubstituted tetrahydropyrroles (**939** and **940**) from *N*-tethered



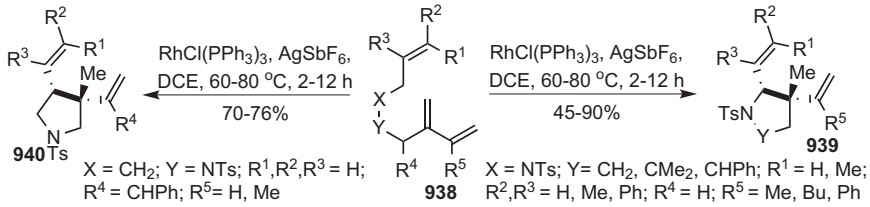
Scheme 327.



Scheme 328.

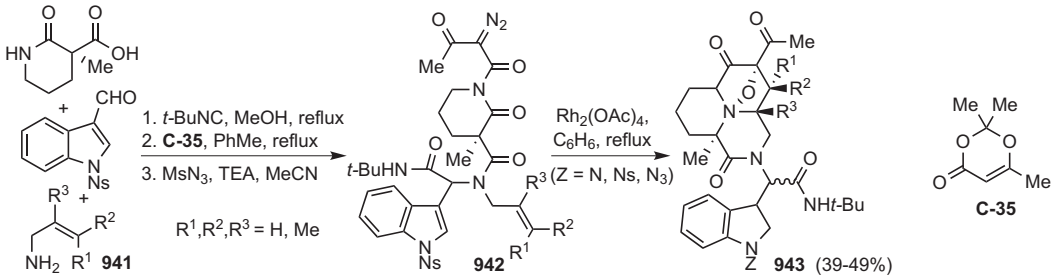
ene-2-dienes (**938**) bearing quaternary carbon centres with high chemo- and diastereoselectivity (Scheme 329).

Ho synthesized the quinoline derivative **949** from the *N*-allyl aniline **948** via cyanative alkene–aldehyde coupling



Scheme 329.

Mizoguchi et al. disclosed the development of a divergent synthetic process involving four steps to access the fused skeletons (**943**), which appear in aspidoplytine and transtangolide. The branched precursor **942** was obtained via three-step processing of the allylamine **941**. This involved Ugi condensation of the amine with 3-indolecarbaldehyde, *tert*-butyl isonitrile and a terminal olefin and installation of diazoimide followed by Rh-catalyzed reaction of **942** involving a 1,3-dipolar cycloaddition of the ylide intermediate with the terminal olefin to afford a separable 1:1 diastereomeric mixture of **943** (Scheme 330).[333]



Scheme 330.

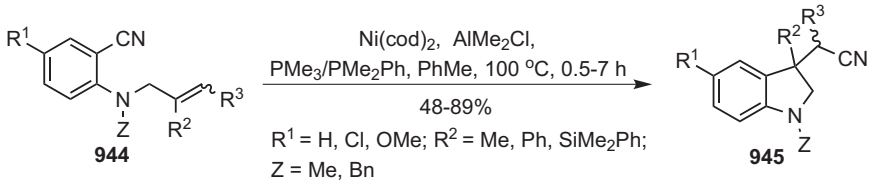
14. Intramolecular arylcyanation reactions

Nakao et al. successfully achieved the intramolecular arylcyanation of alkenes **944** to prepare a range of cyclic compounds containing nitriles with a benzylic quaternary carbon (**945**) (Scheme 331).[334]

15. Cross-coupling reactions

15.1. Intramolecular Heck reactions

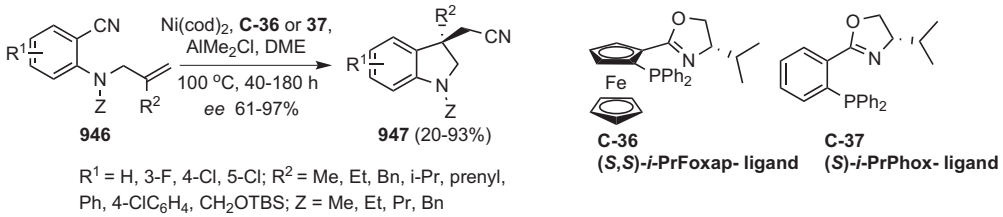
Pd-catalyzed intramolecular C–C cross-coupling reactions between the olefin and aryl halide in *o*-halophenyl- or *o*-halobenzyl-



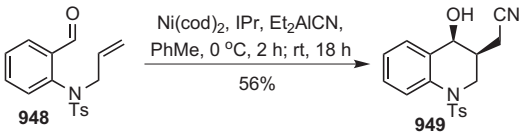
Scheme 331.

Recently, these workers also demonstrated that an enantioselective intramolecular arylcyanation reaction of the 2-cyano *N*-allyl anilines **946** afforded a variety of 3,3-disubstituted indolines (**947**) bearing a benzylic quaternary carbon using a chiral Ni-Lewis acid as co-operative catalyst with phosphinoxazoline ligands (Scheme 332).[335]

substituted allylamines give the organic chemist a valuable tool to access substituted indoles or isoquinolines, respectively. The intramolecular Heck-type cyclization reactions of allylamine bearing haloalkane substituents on nitrogen have also been studied by different research groups for the generation of five-, six- or seven-membered aza-heterocycles. In addition, vinyl halides also undergo



Scheme 332.



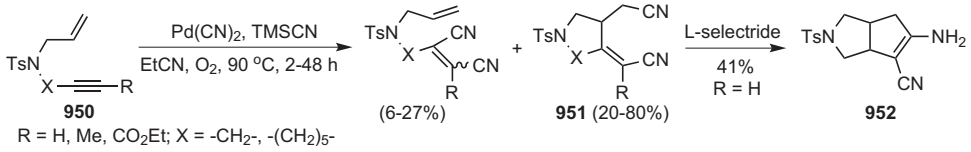
Scheme 333.

such cyclization reactions. Further subclassification in this section has been made on the basis of the scaffold generated.

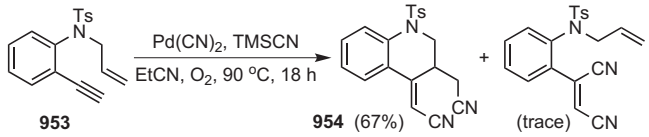
15.1.1. Synthesis of indole derivatives. Demont et al. reported synthesis the of 3,5,7-trisubstituted indoles (**956** and **957**) via a Pd-catalyzed Heck cyclization of allylamines with *o*-halophenyl substituent (**955**) (Scheme 336).[338]

In an alternative strategy, Mejia-Oneto and Padwa used Pd-salt-promoted intramolecular cyclization in allylamine derivative **960** to afford the indole core (**961**) of (±)-aspidophytine, as depicted in Scheme 338.[340]

Hall et al. synthesized the indole derivative **963** from the *N*-allyl *o*-halobenzene derivative **962**. Compound **963** was utilized to generate a new indole derivative **964**, which was discovered to be an EP1 receptor antagonist (Scheme 339).[341]



Scheme 334.



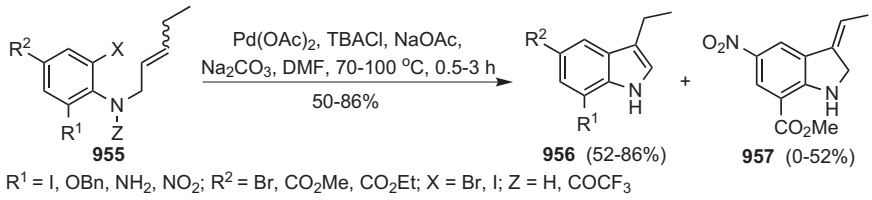
Scheme 335.

A ligand-free intramolecular Heck reaction of allylamine derivatives **965** enabled Majumdar et al. to access the indole-fused tricycles **966**, as shown in Scheme 340.[342]

Yao et al. subjected the bisaryl compound **967** to an intramolecular Heck reaction to afford the dimeric indole derivative **968**, which served as precursor to the dimeric L-6-chloropyrroloindoline derivative (**969**) (Scheme 341).[343]

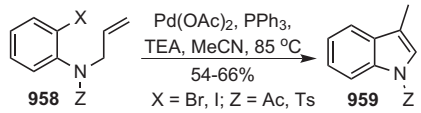
Kim's group disclosed a Pd-mediated reductive Heck-type cyclization of 2-bromo *N*-allyl anilines (**970**) as an efficient synthetic approach for achieving the synthesis of 3-substituted indoles (**972a**,**b**) via the indoline derivatives **971**. Adopting different reaction conditions, compound **970** resulted in 3,3-disubstituted indolines (**973**) from the same starting materials (Scheme 342).[344]

On the other hand Grimaud's group used the Ugi–Smiles reaction coupled with Heck cyclization to engineer an easy access to



Scheme 336.

Zhang et al. generated 3-methyl-*N*-substituted-1*H*-indoles **959** from 2-halo *N*-allyl anilines (**958**), which were obtained from the reaction between aniline and allyl bromide (Scheme 337).[339] The effects of temperature, solvent, time, proportion and the amount of catalyst on the reaction were investigated.



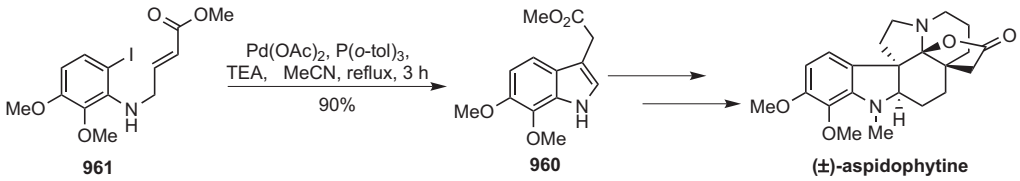
Scheme 337.

indoles or aza-indoles **974** by employing allylamine as the amine component in the Ugi reaction (Scheme 343).[345]

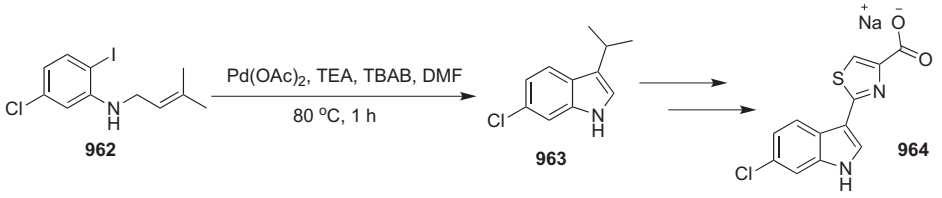
The highly substituted indole core (**976**) of DG-041, used for treatment of peripheral artery disease, was synthesized by Zembower et al. from *N*-allyl haloaniline (**975**), via two sequential intramolecular and intermolecular Heck reaction (Scheme 344).[346]

3,3-Disubstituted indolines (**978**) were synthesized from *N*-allyl anilines **977** by Liu et al. in a ligand-free Pd-catalyzed reductive Heck cyclization under mild conditions (Scheme 345).[347]

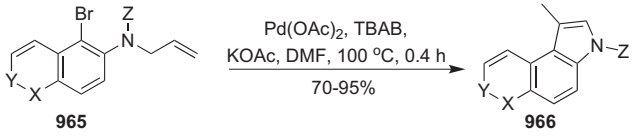
Jorgensen's group developed a novel one-flask approach for the conversion of primary allylamines into indoles and aza-indoles



Scheme 338.



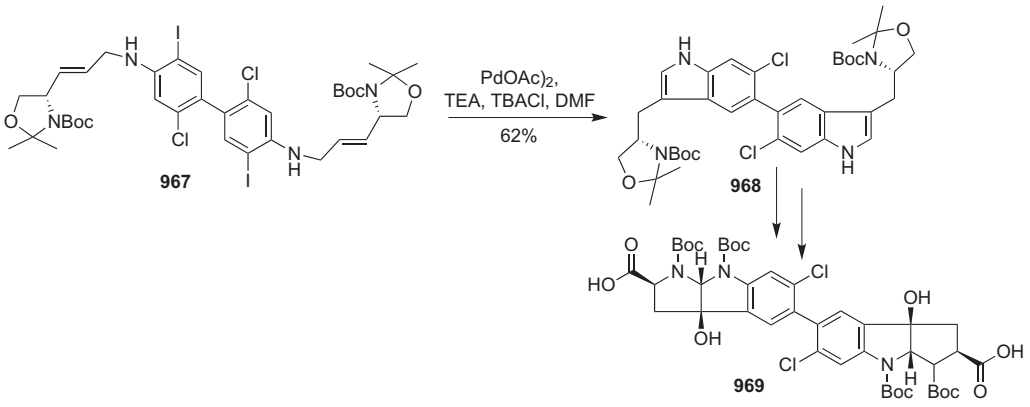
Scheme 339.



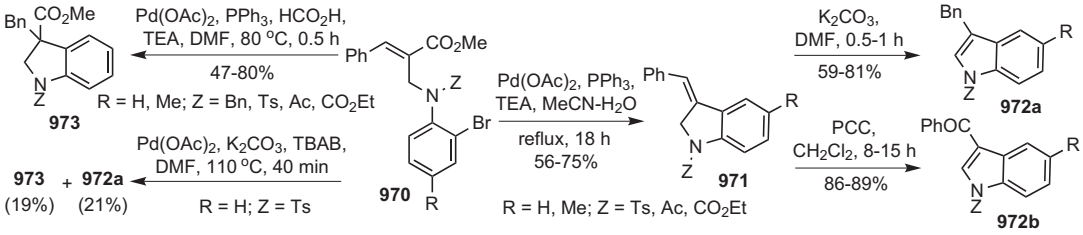
Scheme 340.

(**979** and **980**), via sequential aryl amination and Heck cyclization reactions employing a single catalyst (Scheme 346).[348]

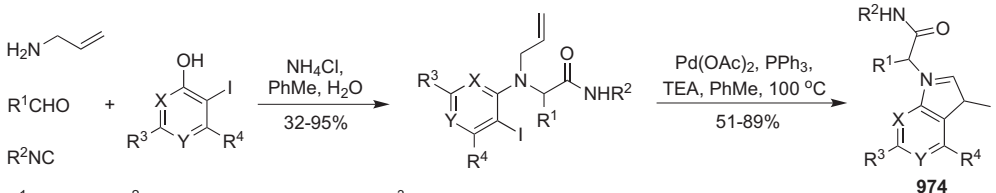
Recently, Baxter et al. demonstrated a regiocontrolled synthesis of 3-methylindoles **983** from the protected allylamines. In this three-step reaction sequence, the 2-aryl-*N*-Boc allylamines (**981**), produced by intermolecular Heck reactions of chlorotriflates and protected allylamines, underwent carbamate/aryl chloride



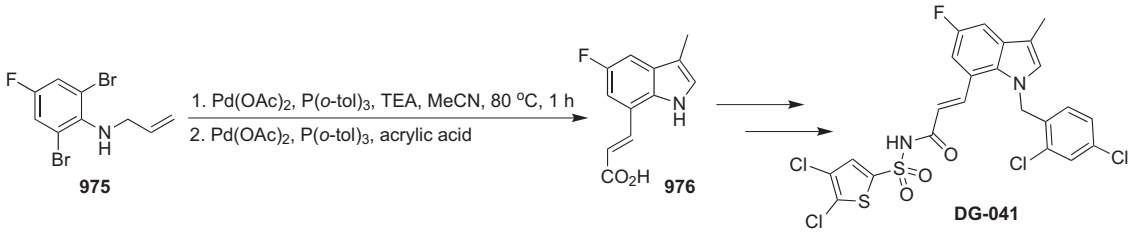
Scheme 341.



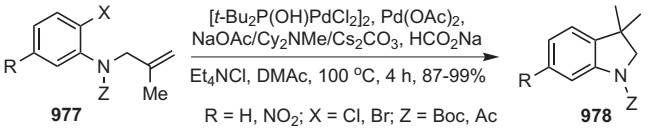
Scheme 342.



Scheme 343.

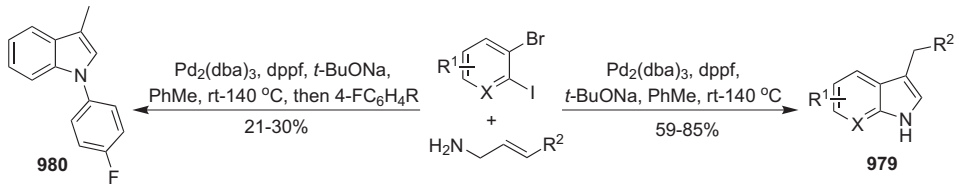


Scheme 344.



Scheme 345.

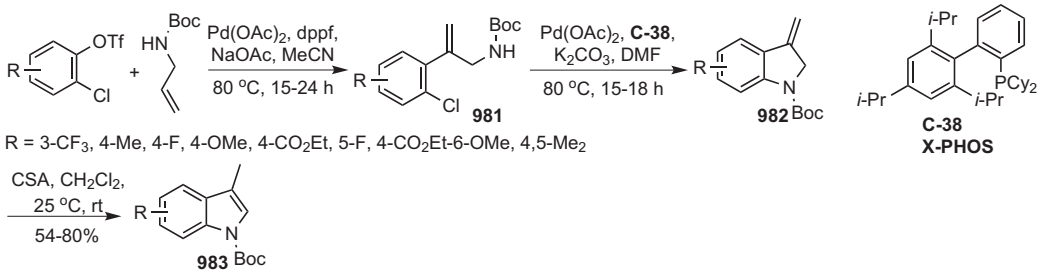
terminate a catalytic cycle by undergoing a regioselective C–H activation in **988**, leading to the spiro cyclopropane derivative (**989**) along with a minor amount of **990a** (Scheme 350).[346b] They observed that if the neopentyl–Pd intermediate contains a heteroatom at a suitable position, C–H activation did not occur and stable palladacycles (**991**) were formed.



Scheme 346.

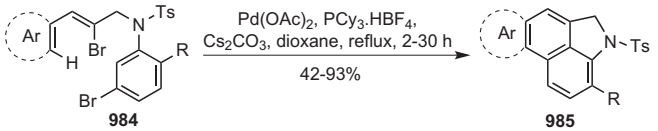
coupling leading to methylene-substituted indolines (**982**), which isomerized to 3-methylindoles (**983**) (Scheme 347).[349]

Ishibashi's group accomplished an intramolecular cascade Mizoroki–Heck reaction of the allyl carbamate **992** to construct



Scheme 347.

Ohno et al. developed a novel strategy for the construction of fused heterocyclic systems (**985**) from the allylamine derivatives **984** by two sequential Pd-catalyzed Heck cyclizations, which progressed through 'zipper-mode' double C–H bond activation (Scheme 348).[350]



Scheme 348.

Zhao and Larock transformed *N*-allyl-3-iodoaniline **986** into 4-vinylindoles (**987a**,**b**) via a Pd-catalyzed Mizoroki–Heck ring-closure reaction (Scheme 349).[351]

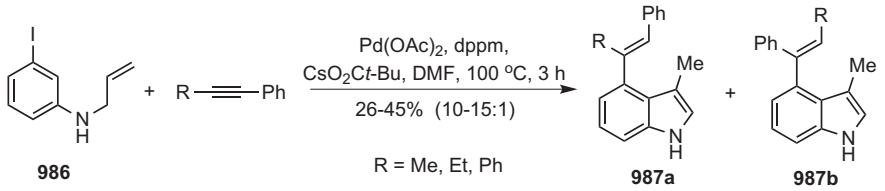
Liron and Knochel demonstrated that, in the absence of any trapping agent, stable neopentyl–Pd intermediates could

a diaryl quaternary centre and tricyclic framework **993** of the indenotetrahydropyridine unit of a cytotoxic alkaloid, haouamine A (Scheme 351).[352]

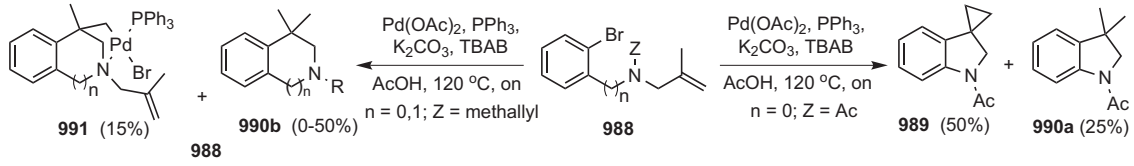
Seomoon et al. could demonstrated the success of Pd-catalyzed allyl cross-coupling reactions using allylindium species generated in situ by treatment of allyl acetates (**994**) with In and $InCl_3$ in the presence of a Pd(0) catalyst for the preparation of 3-vinyl indoline (**997**) (Scheme 352).[353]

Grigg et al. reported a sequential one-pot process involving the in situ Pd-catalyzed formation of a tributylstannyl-1,2-carbodialkylidene from the corresponding 1,6-diynes and TBTH followed by coupling with iodobenzene containing a proximate alkene group (**996**) and anion capture, leading to the indoline derivatives (**997**) in good yields (Scheme 353).[354]

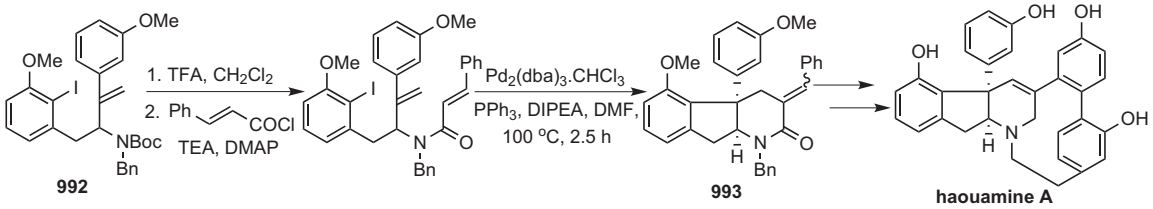
Rene et al. demonstrated a domino palladium-catalyzed Heck-intermolecular direct arylation reaction of the *o*-bromo-*N*-allyl aniline with a variety of sulfur-containing heterocycles including thiazoles, thiophenes and benzothiophene, leading to indolines (**998**) in almost quantitative yields (Scheme 354).[355]



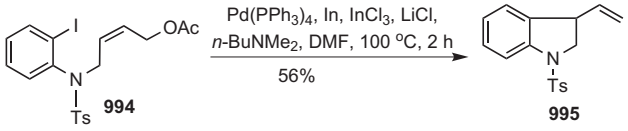
Scheme 349.



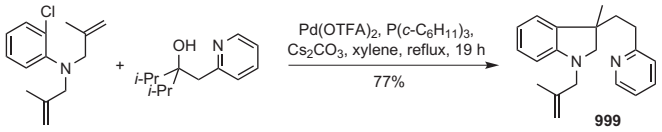
Scheme 350.



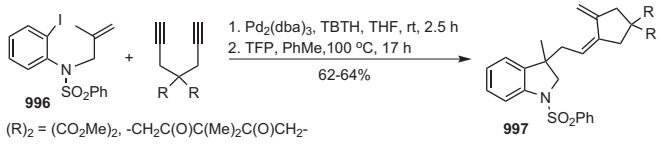
Scheme 351.



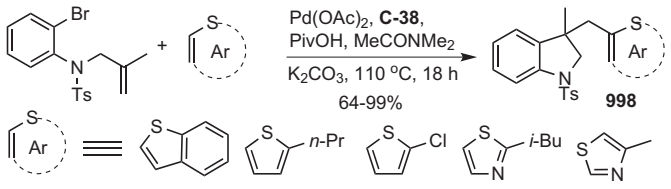
Scheme 352.



Scheme 355.



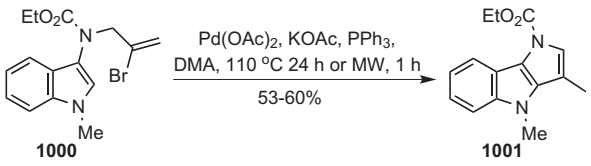
Scheme 353.



Scheme 354.

Niwa et al. reported the formation of a pyridylethyl-substituted dihydroindole (**999**) via Pd-catalyzed 2-pyridylmethyl transfer from a 2-(2-pyridyl)ethanol derivative to *N*-allyl-2-chloroaniline by chelation-assisted cleavage of unstrained sp^3–sp^3 bonds (Scheme 355).[356]

In another approach Beccalli et al., besides generating several heteropolycyclic systems also synthesized ethyl 3,4-dimethylpyrrolo[3,2-*b*]indole-1(4*H*)-carboxylate (**1001**) via an intramolecular Pd-catalyzed coupling reaction of vinyl bromide **1000** onto the 2-position of the indole under MW irradiation or heating (Scheme 356).[357]

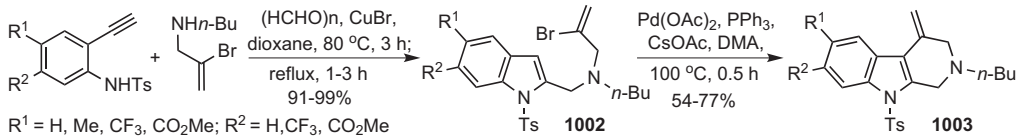


Scheme 356.

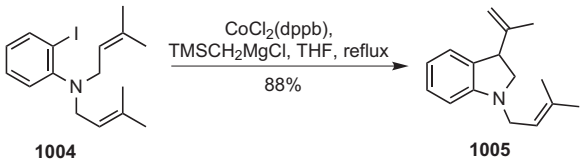
Ohta et al. adopted an analogous approach to achieve the synthesis of polycyclic indole skeletons (**1003**). A Pd-catalyzed C–H functionalization of the C-3 position of 2-(aminomethyl)indoles (**1002**), afforded via Cu-catalyzed domino three-component coupling–cyclization of 2-ethynylanilines with *N*-butyl allylamine and paraformaldehyde resulted in the required products **1003** (Scheme 357).[358]

Co- and Ni-based catalysts are known to catalyze the intramolecular Heck reactions. Oshima et al. extensively studied the Co-catalyzed intramolecular cross-coupling reaction of allylamine *N*-allyl *o*-haloanilines (**1004**) and also synthesized a 3-vinyl indole derivative (**1005**) during the process, beside oxygen containing heterocycles (Scheme 358).[359]

Park et al. prepared a novel tetrahedral Co(II)–crown carbene complex (**C-39**). This complex was reduced in a one-electron process to a Co(I)-complex that acted as a powerful single-electron donor, reducing aryl halides. This complex was observed to be an



Scheme 357.



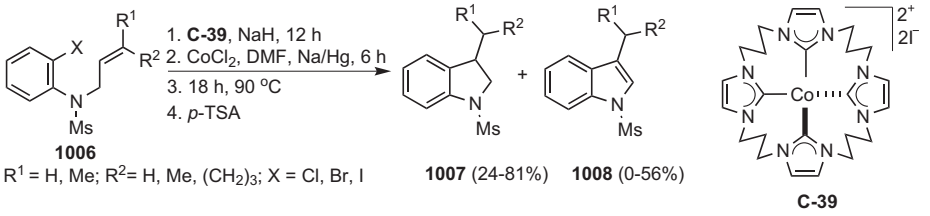
Scheme 358.

effective catalyst in electrochemical reductions of aryl halides and was utilized for the synthesis of 2,3-disubstituted indoline (**1007**) and indole (**1008**) derivatives via reductive activation of **1006** (Scheme 359).[360]

Heck reaction under the same reaction conditions, however, cyclopropa[*d*]-fused isoquinoline derivatives **1017** were afforded via a domino sequence (Scheme 362).[362]

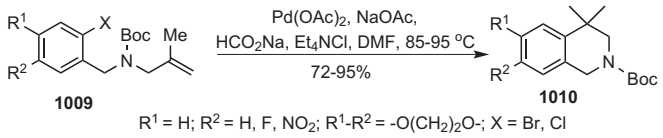
In another recent disclosure, Jia et al. reported an efficient Pd-catalyzed domino reaction involving a C–H activation process in substrates belonging to the prototype **1018**. They formulated the synthesis of tetrahydroisoquinoline (**1019**) or tetracycle (**1020**) by trapping the palladacycle intermediate with an alkene or aryl moiety, respectively, through a Heck reaction (Scheme 363).[363]

Broggini et al. developed a new protocol for the direct synthesis of 4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-ones (**1022**) from *N*-allylamides of 2-iodobenzoic acids (**1021**) by means of a Pd-catalyzed carbonylative Heck cyclization (Scheme 364).[364]



Scheme 359.

15.1.2. Synthesis of isoquinoline derivatives. Allylamines bearing an *o*-halobenzyl substituent on the nitrogen serve as precursors to isoquinoline derivatives. Liu et al. reported the formation of 1,2,3,4-tetrahydroisoquinolines (**1010**) from *N*-allyl benzylamines **1009** by Pd-catalyzed reductive Heck cyclization in ligand-free conditions (Scheme 360).[347]



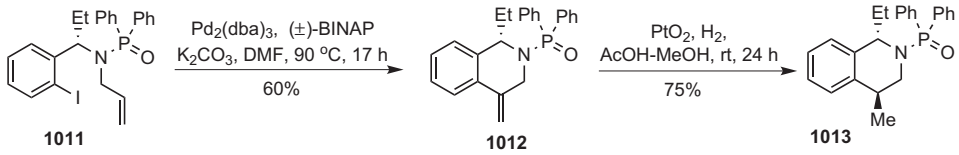
Scheme 360.

Tetrahydroisoquinoline (**1012**) with an exocyclic double bond was obtained in the intramolecular Heck cyclization of iodobenzene with the olefin of the allylamine (**1011**), as performed by Bonnaventure and Charette (Scheme 361).[361] Reduction of **1012** with PtO_2 resulted in a hexahydroisoquinoline **1013**.

Majumdar et al. also prepared *N*-substituted 4-methyl- and 4-ethylisoquinolone derivatives (**1024**) from different *N*-allylbenzamide derivatives (**1023**) in a single step through a ligand-free Heck cyclization (Scheme 365).[365]

Threadgill et al. reported the Pd-catalyzed Heck cyclizations of tertiary and secondary *N*-allyl and *N*-cinnamyl 2-iodo-3-nitrobenzamides (analogous to **1025**) to afford two isomeric isoquinolinones, 4-alkyl-5-nitroisoquinolin-1-ones (**1026a**) and 4-alkyl-5-nitro-3,4-dihydroisoquinolin-1-ones (**1026b**) (Scheme 366).[366] Optimum yields of the 4-alkyl-5-nitroisoquinolin-1-ones (**1026a**) were obtained in the presence of TBAC and with rapid heating of the reaction at 150 °C. Hydrogenation of the nitro groups gave 4-methyl- and 4-benzyl-5-aminoisoquinolin-1-ones (**1027**), which were found to be potent inhibitors of PARP-1 activity. A few of the 4-substituted 5-aminoisoquinolin-1-ones (5-AIQ) exhibited significantly increased potency for inhibition of human PARP-1.

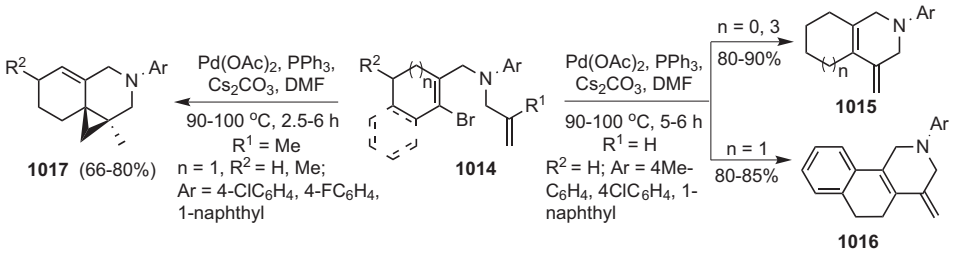
N-Protected 1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**1030**) was generated from **1029**, which was constructed by De Kimpe's group via an intramolecular Heck reaction of *N*-protected 2-(allylamino)methyl-3-bromo-1,4-dimethoxynaphthalene (**1028**).



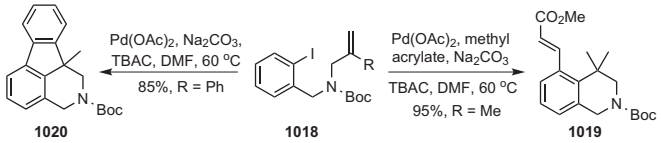
Scheme 361.

More recently, Nandi and Ray reported the formation of fused tetrahydropyridine derivatives (**1015** and **1016**) via Pd(0)-mediated 6-*exo*-*trig* cyclization of *N*-aryl allylamines (**1014**; R^1=H). When the *N*-methallylated derivatives (**1014**; R^1=Me) were subjected to the

They extended this strategy to the synthesis of the corresponding 4-methyl derivatives (**1032a**,**b**) from *N*-protected 2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**1031**) (Scheme 367).[367]

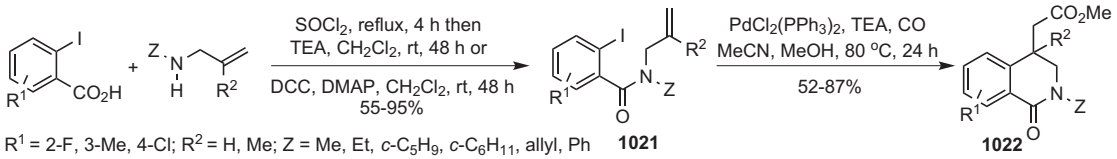


Scheme 362.

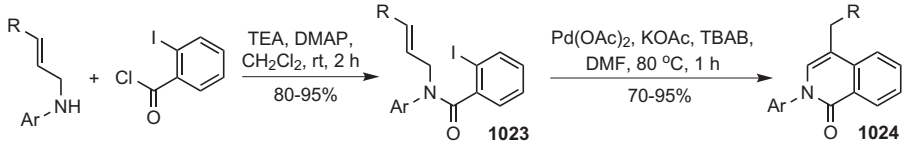


Scheme 363.

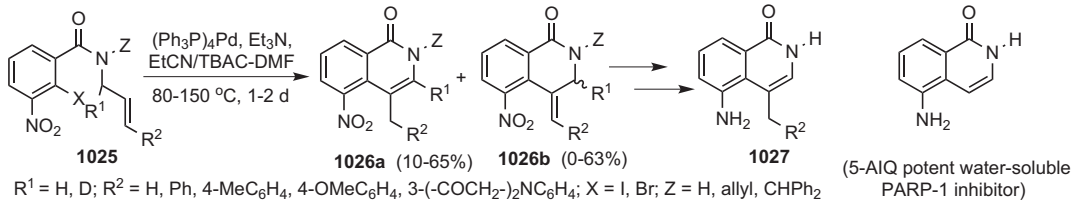
Broggini et al. reported a simple entry into new 4-spiroannulated tetrahydroisoquinolines (**1033**) (Scheme 368) although the products were isolated in somewhat unsatisfactory yields. They observed that prolonged heating of the reaction in the absence of isocyanate resulted in isoquinolin-1-ones (**1034** and **1035**), which were presumed to be the reason for the low yields of the spiroannulated products.[368]



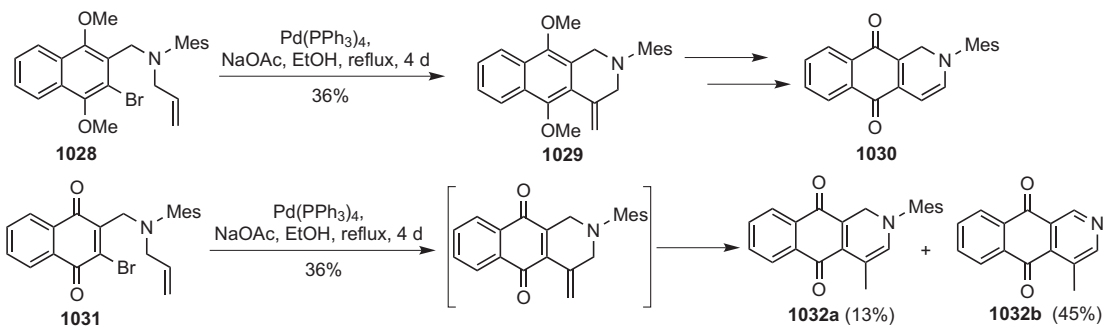
Scheme 364.



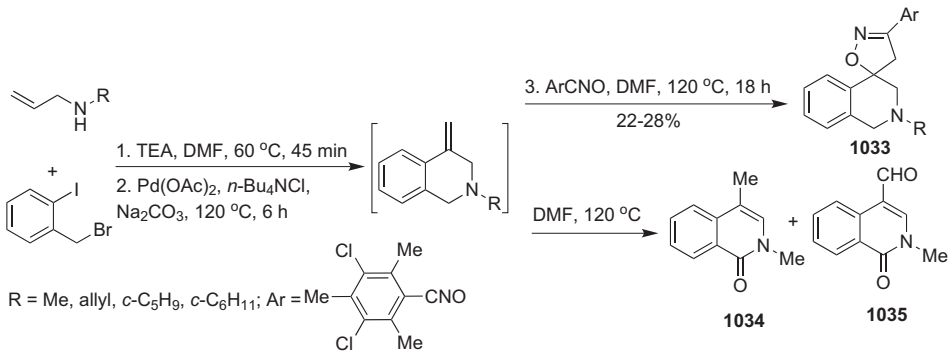
Scheme 365.



Scheme 366.

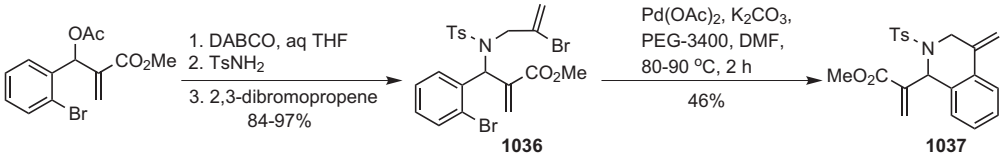


Scheme 367.



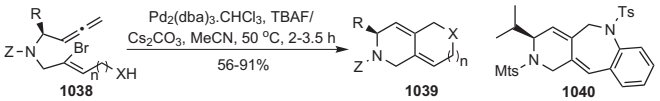
Scheme 368.

Gowrisankar et al. reported the synthesis of the isoquinoline derivative (**1037**) via a Pd-catalyzed Heck-type cyclization of the allylamide **1036** (Scheme 369).[369]



Scheme 369.

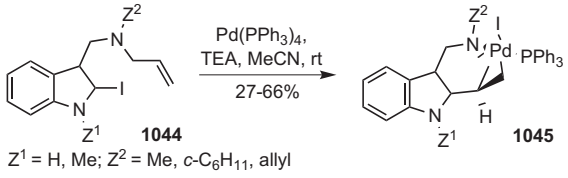
Okano et al. described a novel strategy for generating bicyclic and tricyclic heterocycles (**1039** and **1040**). This involved a 'zipper-mode' cascade cyclization of allenic bromoalkenes (**1038**) bearing a nucleophilic moiety initiated by a catalytic amount of Pd(0) in the presence of TBAF or Cs_2CO_3 in MeCN (Scheme 370).[370]



n = 1, 2, 3; R = H, Me, *i*-Pr; Z = Ts, Ns, Mts; X = O, NTs, $C(CO_2Me)_2$, 2-$NHTsC_6H_4$
Mts = 2,4,6-trimethylphenylsulfonyl

Scheme 370.

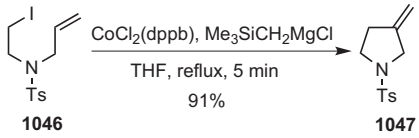
Similar to the work of Liron and Knochel (Scheme 358), who isolated palladacycles during their synthesis of indolines, Broggini et al. also reported the isolation of palladacycles.[371] They observed that during Pd-catalyzed intramolecular Heck reactions of *N*-allyl-2-halobenzylamines (**1041**, Y=CH_2) the β-hydride elimination from the σ-alkylpalladium Heck intermediates was inhibited, resulting in the isolation of a series of stable bridged five-membered palladacycles (**1043**) with the metal centre bearing a PPh_3 ligand and a Br atom (Scheme 371). Further, under similar conditions, stable palladacycles (**1045**) of indolyl substrates (**1044**) were also isolated and crystallized (Scheme 372). They discovered that an sp^3-hybridized carbon atom at the benzylic carbon is essentially required for the stability of the palladacycle. On changing from sp^3 to sp^2 as in diallylamide (**1041**, Y=CO), only intramolecular Heck reaction followed by isomerization to afford **1042** occurred (Scheme 371). A change in the nature of the benzylic carbon, however, by considering an aryl iodide with an sp^2-hybridized carbon atom, as in the diallylamide the formation of 2-allyl-4-methylisoquinolin-1(2*H*)-one (**1042**) occurred by an intramolecular Heck reaction followed by isomerization of the normal Heck product.



Z1 = H, Me; Z2 = Me, *c*-C_6H_{11}, allyl

Scheme 372.

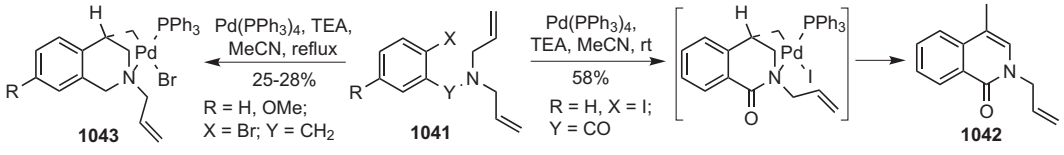
15.1.3. Synthesis of pyrrolidines. Oshima et al. reported the synthesis of indolines utilizing the Co-catalyzed trimethylsilylmethylmagnesium-promoted radical alkylation of alkyl halides to generate 3-methylenepyrrolidine (**1047**) from iodoalkanes (**1046**), as shown in Scheme 373.[356]



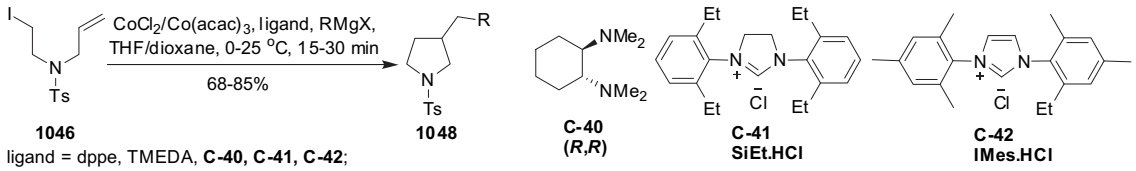
Scheme 373.

This research group has also reported the synthesis of 3-substituted pyrrolidines **1048** via a Co-catalyzed Heck type cyclization reaction of the allylamine derivatives (**1046**) performed in the presence of Grignard reagents (Scheme 374).[372]

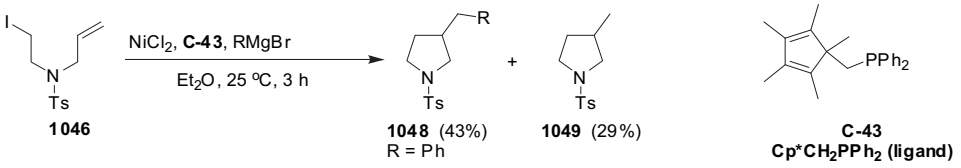
Further, these workers investigated the feasibility of using a Ni catalyst in this type of Heck reaction and generated 3-substituted pyrrolidines (**1048**, R=Ph and **1049**) from the allylamine derivative **1046** (Scheme 375). Here, too, the reaction was performed



Scheme 371.



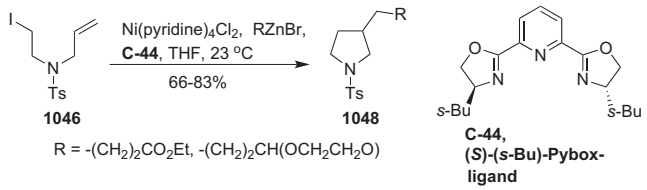
Scheme 374.



Scheme 375.

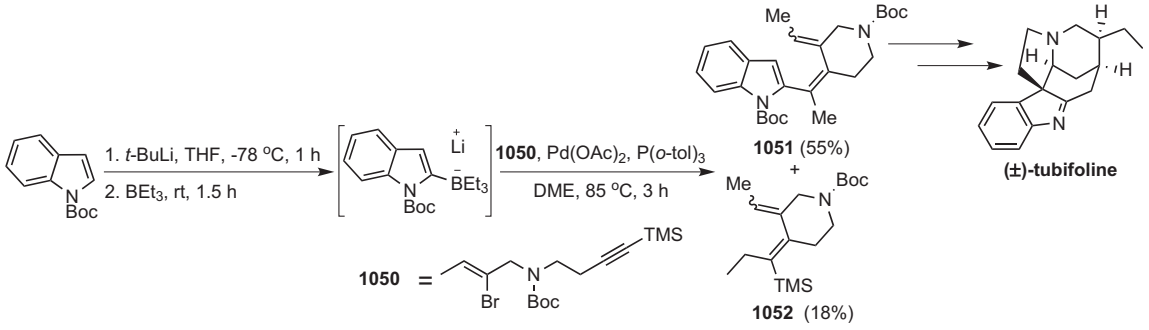
in the presence of an aryl Grignard reagent along with the use of the newly synthesized $Cp^*CH_2PPh_2$ as ligand.[373]

Cardenas et al. also synthesized the 3-substituted pyrrolidines (**1048**) by reacting the substituted iodoalkane **1046** in the presence of a Ni catalyst (Scheme 376).[374] Interestingly, they used zinc halides in place of Grignard reagents.



Scheme 376.

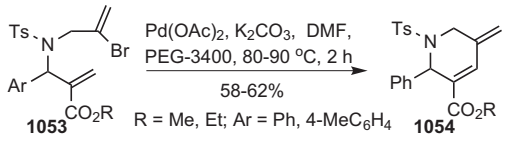
15.1.4. Synthesis of piperidines. Ishikura et al. reported a Pd-catalyzed tandem cyclization-cross-coupling protocol for 1*H*-indol-2-yltrialkylborane and the allylamine derivative (**1050**) for the generation of 2-(4-piperidylmethyl)indole (**1051**), which was used as precursor for the preparation of (±)-tubifoline (Scheme 377).[375] This reaction afforded **1052** as the side product in minor yields.



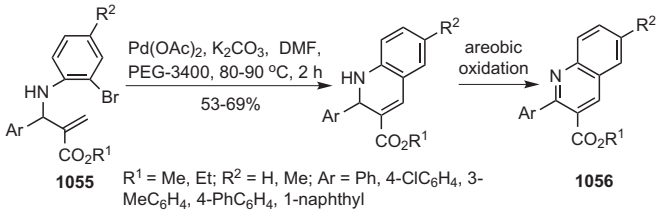
Scheme 377.

In addition to the synthesis of isoquinolines, Kim's group demonstrated that the amides (**1053**) upon Pd-catalyzed cyclization yielded tetrahydropyridines (**1054**) in moderate yields (Scheme 378).[369]

In an alternative strategy, the allylamines **1055** underwent sequential Heck-type cyclization and concomitant aerobic oxidation to furnish 2-arylquinolines (**1056**), as shown in Scheme 379.[369]



Scheme 378.

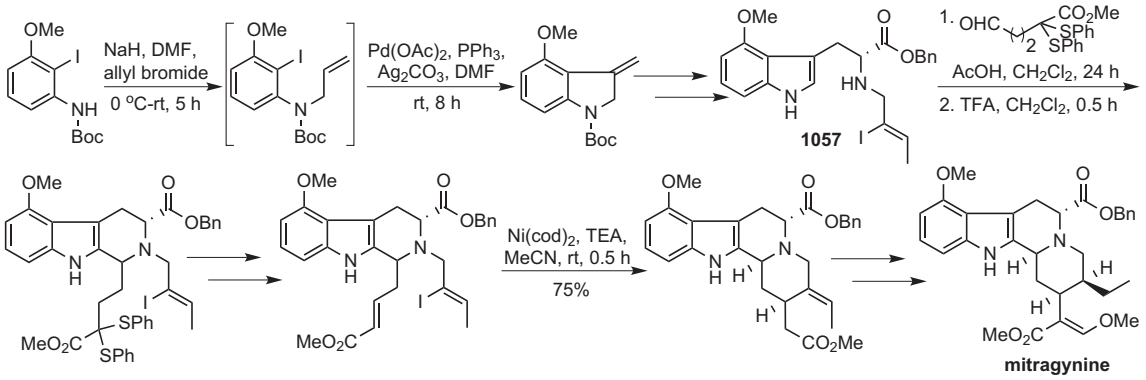


Scheme 379.

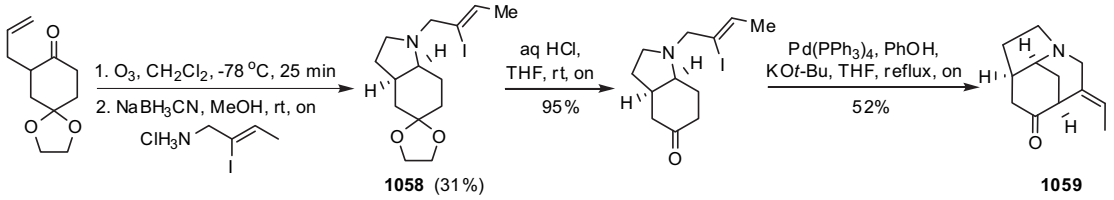
Cook et al. reported the synthesis of the opioid agonistic alkaloid mitragynine, through the allylamine (**1057**) intermediate, which in turn was generated via an asymmetric Pictet–Spengler reaction and a $Ni(cod)_2$-mediated cyclization as the key steps (Scheme 380).[376]

Sole et al. obtained the CDE ring system (**1059**) of the indole alkaloid, strychnopivotine via a Pd(0)-promoted coupling of a ketone enolate and an amino-tethered vinyl iodide (**1058**) generated by reductive amination of an allylamine with a carbonyl moiety (Scheme 381).[377]

In an analogous approach, Martin and Vanderwal reported an intramolecular Heck cyclization of vinyl iodide onto the



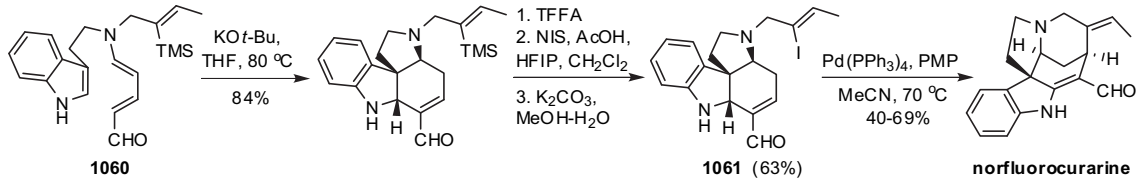
Scheme 380.



Scheme 381.

unsaturated aldehyde (**1061**) generated via a base-mediated anionic bicyclization reaction of tryptamine-derived Zincke aldehyde (**1060**) to afford the *Strychnos* alkaloid, norfluorocurarine (Scheme 382).[378]

15.1.5. Synthesis of azapanes. Lamaty et al. achieved the intramolecular Pd-catalyzed Heck reaction of substituted allylamines (**1066**) to afford a series of benzazepines (**1067**) (Scheme 385). They used PEG-3400 as a soluble polymeric support as an alternative to

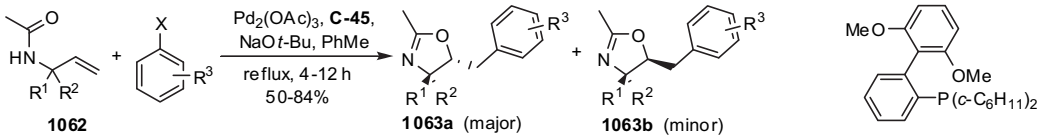


Scheme 382.

Oshima's group prepared benzyl-substituted oxazolines (**1063a**,**b**) via a Pd-catalyzed carboetherification reaction of *N*-allylacetamides **1062** with aryl halides, performed in the presence of SPHOS (**C-45**), which served as ligand, and of NaO*t*-Bu (Scheme 383).[379]

a phosphine ligand for the success of the reaction. In a slight variation, they also successfully accomplished the reaction under MW conditions.[381]

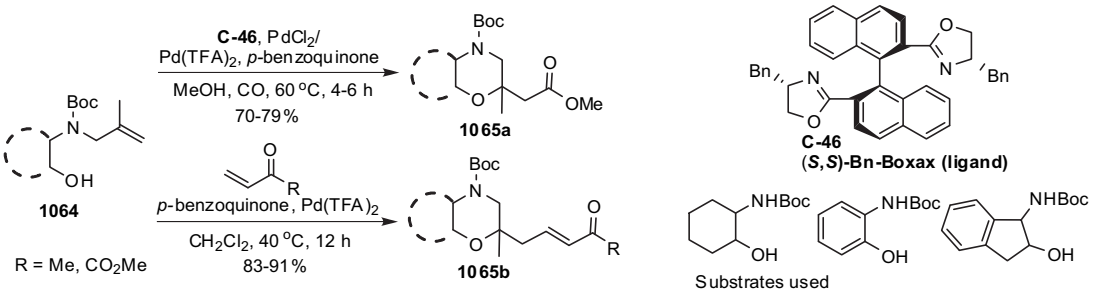
Stewart et al. reported the conversion of the allylamine derivative (**1068**) into the seven-membered ring aza-heterocycle,



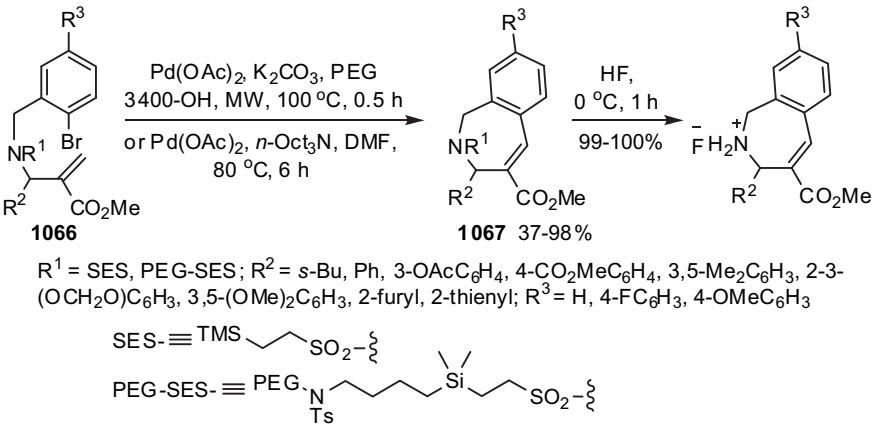
Scheme 383.

Tietze et al. described a strategy for the conversion of the substituted allylamine derivatives **1064** into the perhydro-1,4-oxazines (**1065a**,**b**) via domino-Wacker-carbonylation and Wacker–Mizoroki–Heck reactions (Scheme 384).[380] The methodology was based on an efficient Pd-catalyzed domino reaction, initiated by a Wacker oxidation and subsequent insertion of the Pd-species formed into the π-bonds of the CO of esters or α,β-unsaturated ketone.

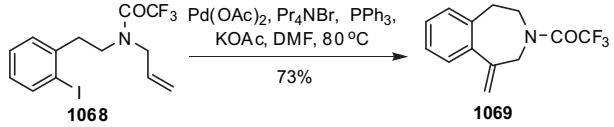
3-benzazepine with an exocyclic double bond (**1069**), via a Pd-catalyzed 8-*endo-trig* cyclizations (Scheme 386). Under similar reaction conditions the indole-based allylamines **1070** produced azepino[4,5-*b*]indole ring systems (**1071a**–**c**) via 7-*exo-trig* cyclization through double Heck cyclization. In the case of **1070** (Z=allyl) an azepinobenzindolizine derivative (**1072**) was also isolated (Scheme 387).[382]



Scheme 384.



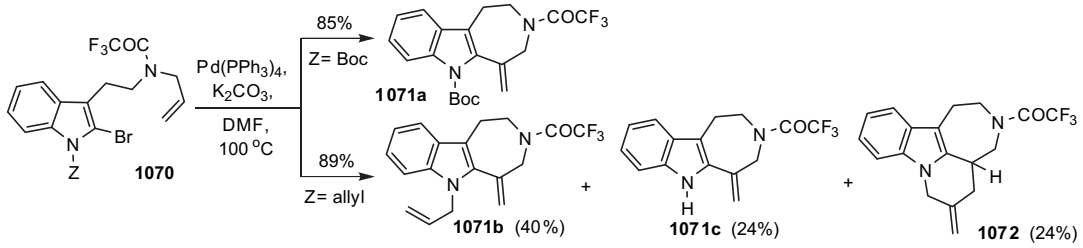
Scheme 385.



Scheme 386.

achieve the synthesis of benzofused seven-membered aza-heterocycles (**1076**) from the substituted allyl carbamates (**1075**), as depicted in Scheme 389.[353]

15.1.6. Synthesis of azocines. Martin et al. synthesized the aza-tricycles **1078a**,**b** via Pd-catalyzed MW-assisted Heck reaction of allylamine derivative **1077** (Scheme 390).[193]

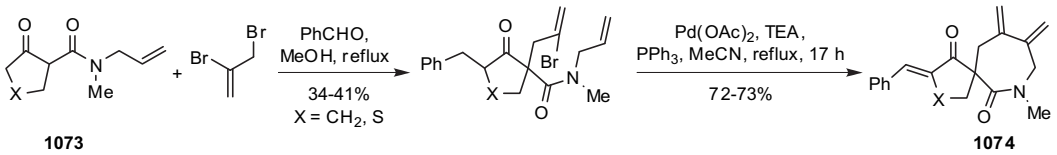


Scheme 387.

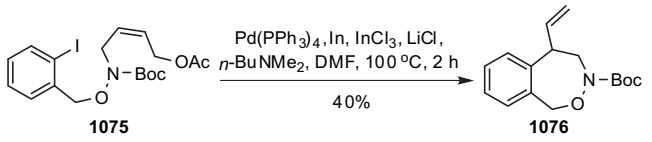
Habib-Zhamani et al. developed a new strategy for the synthesis of spiroheterocycles (**1073**) from simple cyclic β-ketoamides (**1074**) via a sequential selective three-component reaction and a Pd-catalyzed carbocyclization (Scheme 388).[383]

Seomoon et al. used a Pd-catalyzed intramolecular allyl cross-coupling reaction performed in the presence of In–$InCl_3$ to

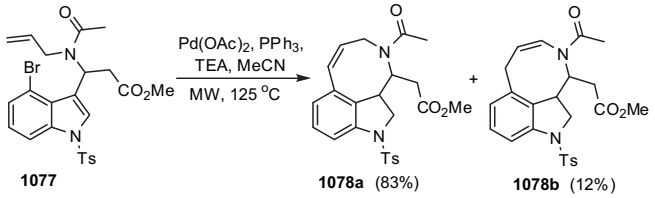
Majumdar et al. synthesized several coumarin and quinoline-annulated benzazocine derivatives (**1080**) from substituted allyl-amines (**1079**) via sequential aza-Claisen rearrangement and intramolecular Heck reactions as the key steps (Scheme 391).[384] Later they extended their strategy to accomplish the synthesis of



Scheme 388.



Scheme 389.



Scheme 390.

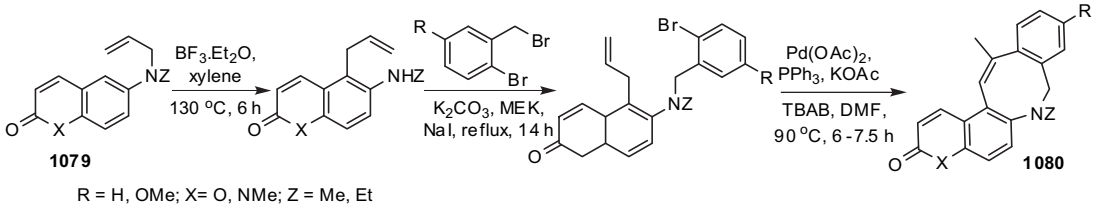
by Akiyama and Mikami to afford the sulfonamide rings **1089** containing chiral quaternary carbon centres along with the unexpected olefin reduction products (**1090**) (Scheme 395).[388]

The successful transformation of aza-MBH adducts **1091** of 2-halosulfonamides into highly constrained bicyclic 6,7-dihydro-5-thia-6-aza-benzocycloheptene 5,5-dioxides (**1092**) via the intramolecular Heck reaction was achieved by Vasudevan et al. (Scheme 396).[389]

15.2. Stille couplings

Lin and Kazmaier converted the substituted vinylstannanes (**1093**) into indoles (**1094** and **1095**) and isoquinoline (**1096**) derivatives through intramolecular Stille couplings (Scheme 397).[390]

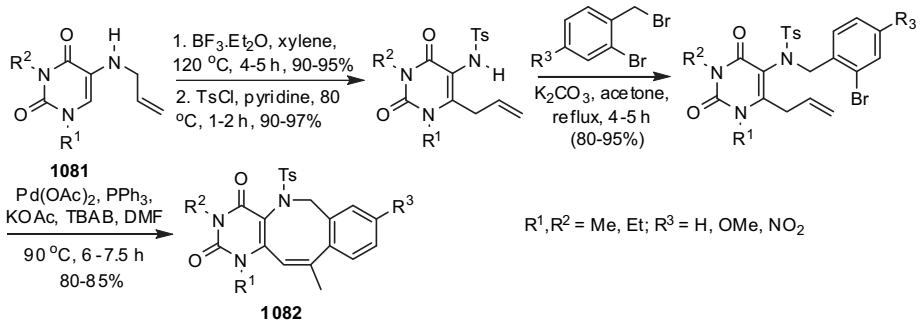
Later, Bukovec and Kazmaier synthesized a six-membered lactam **1098** via $[Pd(allyl)Cl]_2$–PPh_3 catalyzed Stille coupling of the stannylated allylamine **1097** with iodoacrylate, as shown in Scheme 398.[391]



Scheme 391.

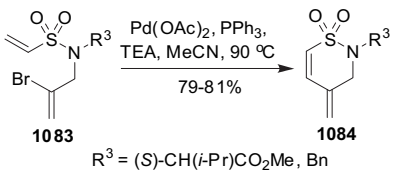
pyrimidine-fused azocine derivatives (**1082**) from substituted allylamines **1081** (Scheme 392).[385]

Echavarren et al. reported that an Au(I) complex (**C-48**) acts as an efficient catalyst for intramolecular allyl–allyl coupling of allyl



Scheme 392.

15.1.7. Synthesis of sultams. Zhou et al. demonstrated Pd(0)-catalyzed regioselective intramolecular Heck cyclization of vinyl sulfonamides **1083** to produce δ-sultams (**1084**) (Scheme 393).[386] The synthesis was a part of a 'click, click, cyclize' approach developed by these authors to generate diverse sultams utilizing vinyl sulfonamide linchpins.



Scheme 393.

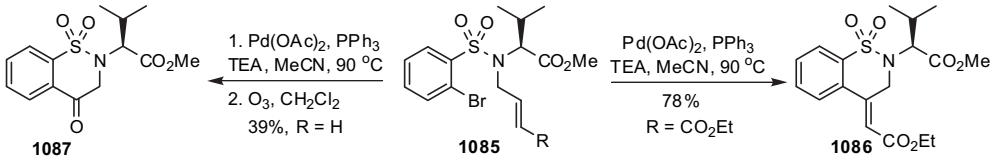
The same group later accomplished the synthesis of benzofused δ-sultams **1086** and **1087** via Pd(0)-catalyzed Heck reactions of α-haloarylsulfonamides (**1085**) (Scheme 394).[387]

An intramolecular Heck-type reaction of arylboronic acids onto the double bond of the allylamine subunit in **1088** was performed acetate with allylstannane (**1099**) to yield substituted piperidine with an exocyclic double bond (**1100**). They found that this process was mechanistically very different from that catalyzed by either Pd(0) or Rh(I) (Scheme 399).[392]

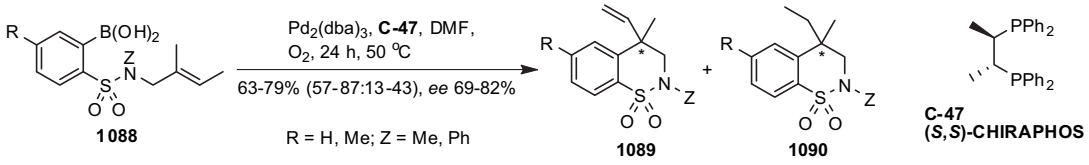
15.3. C–N cross-coupling reactions

Allylamines have also served as substrates for transition-metal-catalyzed C–N cross-coupling reactions, resulting in new aza-systems.

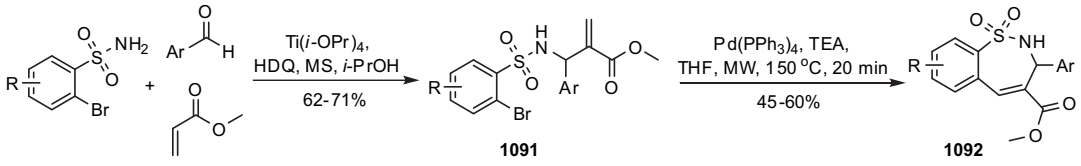
15.3.1. Generation of five-membered aza-heterocycles. 15.3.1.1. Intermolecular cross-coupling reactions. Scarborough and Stahl demonstrated that the Pd(II)-catalyzed oxidative coupling of *N*-allyl tosylamides with butyl vinyl ether or various styrene derivatives resulted in 2,4-disubstituted pyrrolidines (**1101** or **1102**) (Scheme 400). Molecular oxygen together with a Cu(II)-cocatalyst was used to re-oxidize the Pd-catalyst. During this work, the beneficial effects of several non-traditional cocatalysts including catechol, methyl acrylate and 1,5-cyclooctadiene (cod) on the reactions were also investigated.[393]



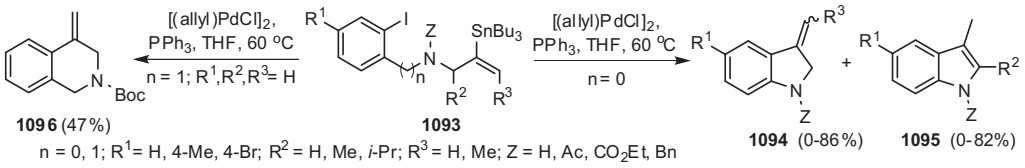
Scheme 394.



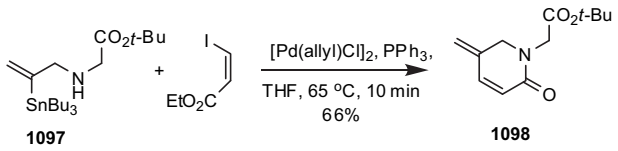
Scheme 395.



Scheme 396.



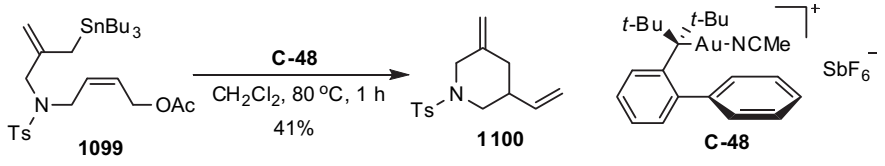
Scheme 397.



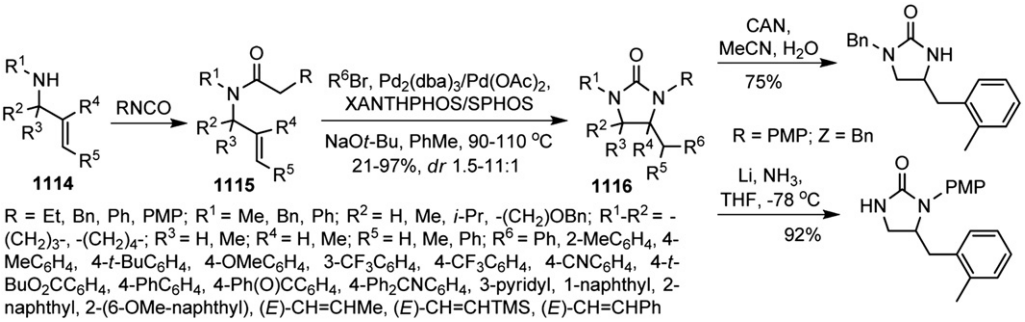
Scheme 398.

O'Neil and Fuerstner converted Boc-protected allylamine into a 2-substituted pyrrolidine (**1103**) via a Pd-catalyzed boronate-alkyl Suzuki coupling and subsequent Michael reaction (Scheme 401).[394] Interestingly, the boronate, which participated in the Suzuki coupling was generated in situ under this strategy.

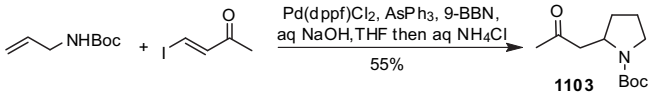
In a different approach, Shi et al. reported the synthesis of imidazolidin-2-one **1105** in good yield with high regio-, diastereo- and enantioselectivity from a conjugated diene **1104** via $Pd_2(dba)_3$-



Scheme 399.

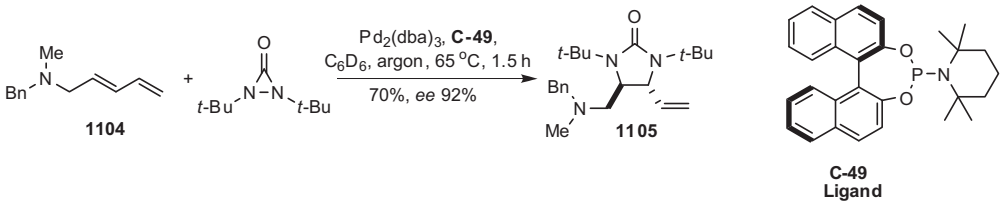


Scheme 400.



Scheme 401.

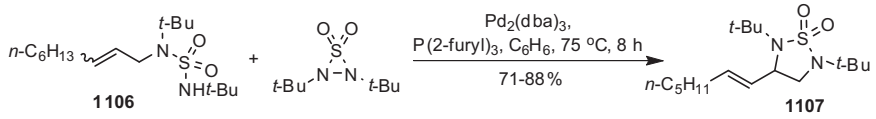
catalyzed asymmetric diamination of the terminal olefin in the presence of phosphorus amidite (**C-49**) as ligand and di-*tert*-butyldiaziridinone as the nitrogen source (Scheme 402).[395]



Scheme 402.

Later, they extended this methodology to generate a diaza sultam **1107** from the allyl sulfamides (**1106**) using *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide as the nitrogen source via a dehydrogenative allylic diamination–cyclization process (Scheme 403).[396]

Schultz and Wolfe have extensively studied the Pd-catalyzed carboamination reactions and developed a new cascade reaction for the synthesis of tricyclic aza-heterocycles (**1118**) via sequential alkene aminopalladation–carbopalladation reactions of *N*,2-

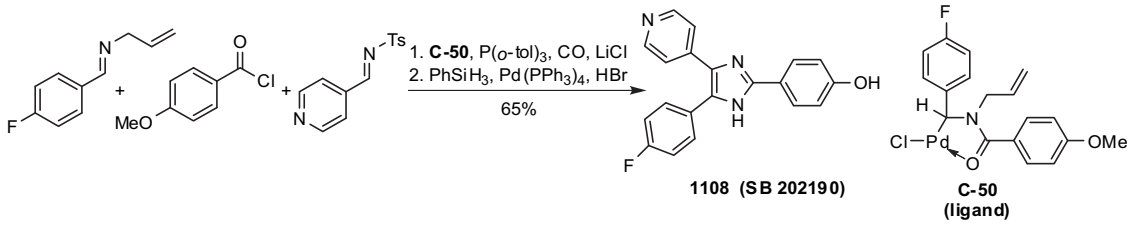


Scheme 403.

Siamaki and Arndtsen disclosed a one-step regioselective synthesis of imidazole derivative **1108** (SB 202190), a potent p38 MAP kinase inhibitor, via Pd-catalyzed coupling of imines and acid chloride (Scheme 404). This compound was projected as a lead for the design of new anti-inflammatory agents.[397]

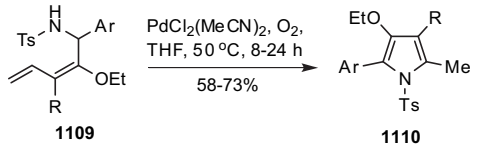
diallylaniline derivatives (**1117**) (Scheme 408). In these reactions the bicyclic indolines **1119** were also formed as minor products.[401]

Thomas et al. subjected the substituted allylamine (**1120**) to a Pd(0)-catalyzed amino-Heck reaction to obtain the imidazole derivative (*R*)-**1121** in high enantiomeric excess (Scheme 409).[402]



Scheme 404.

15.3.1.2. Intramolecular cross-coupling reactions. *N*-Tosylalkoxydienylamines **1109** were used by Prandi et al. as the starting materials for the synthesis of tri- and tetrasubstituted *N*-tosylpyrroles (**1110**) through an aminopalladation process under a dioxygen atmosphere (Scheme 405).[398]



Scheme 405.

Gabriele et al. reported PdI_2–KI-catalyzed oxidative carbonylation of (*Z*)-(2-ene-4-ynyl)amines (**1111**) to afford carbonyl derivatives, such as pyrrole-2-acetic ester (**1112**) and (pyridine-2-one)-3-acetic amides (**1113**), depending on the substitution pattern of the substrate and the reaction conditions (Scheme 406). The presence of an excess of CO_2 proved to be beneficial to the reaction rate as well as the product selectivity in most of the cases.[399]

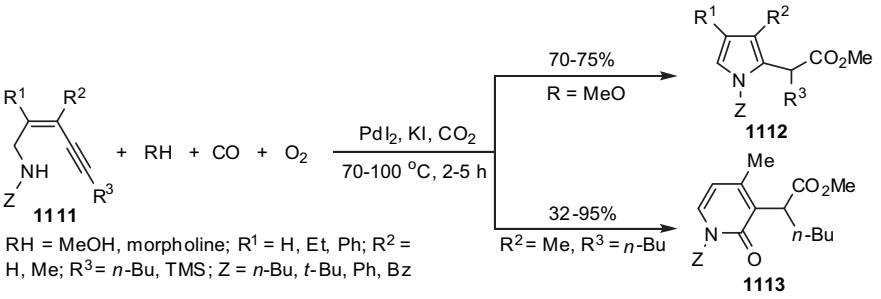
Wolfe et al. also described a new and robust strategy to obtain substituted imidazolidin-2-ones (**1116**) in two steps from allylamines (**1114**) via $Pd_2(dba)_3$–Xanthphos induced carboamination of *N*-allylureas (**1115**), as depicted in Scheme 407.[400] They observed that the use of *S*-Phos minimizes N-arylation of the substrate and prevents the formation of mixtures of regioisomeric product.

Fukumoto et al. used $RhCl(PPh_3)_3$–NH_4BF_4 as the catalyst system to effect the cyclization of terminal alkynes with allylamines to give (*E*)-3-alkylidene-3,4-dihydro-2*H*-pyrroles (**1122**), as depicted in Scheme 410.[403] They observed that the addition of various ammonium salts suppressed the oligomerization of the terminal alkynes, resulting in increased yield.

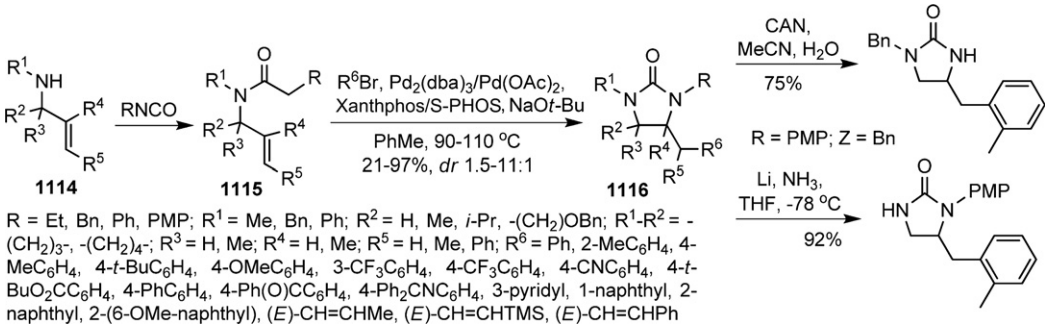
15.3.2. Generation of six-membered aza-heterocycles. Park et al. demonstrated that allylamine act as a precursor for the synthesis of dihydroquinoline (**1123**) via a Pd-catalyzed intramolecular C–N coupling process (Scheme 411).[404]

Chen et al. achieved the synthesis of 2-*Z*-alkenyl tetrahydroquinoline (**1125**) via a Pd-catalyzed intramolecular amination of the allylamine derivative (**1124**) (Scheme 412).[405]

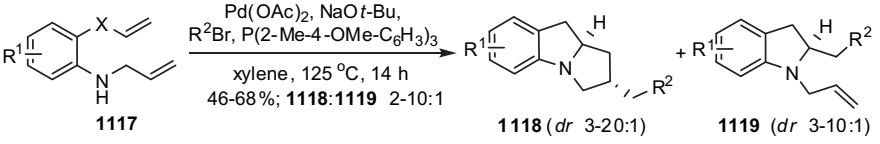
3,5-Disubstituted piperazinones (**1127**) were synthesized in quantitative yields by Ferber et al. via a Pd(II)-catalyzed intramolecular allylic amination in **1126** in the presence of LiCl (Scheme 413) and without a re-oxidizing system. The



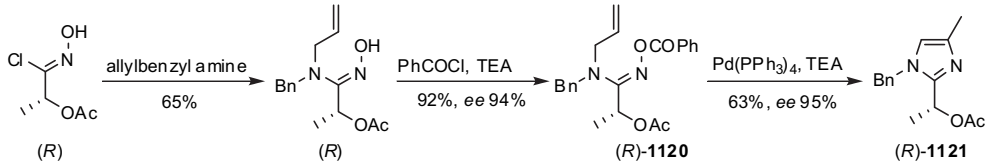
Scheme 406.



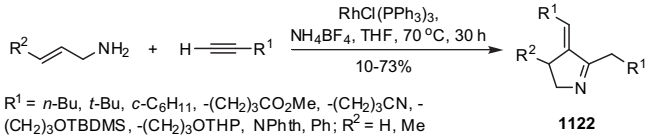
Scheme 407.



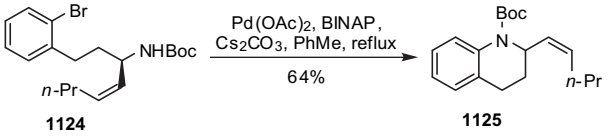
Scheme 408.



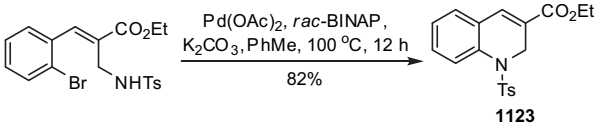
Scheme 409.



Scheme 410.



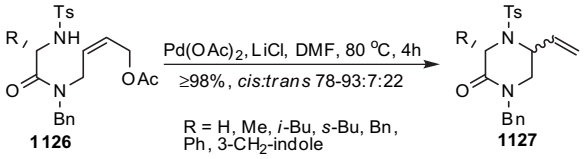
Scheme 412.



Scheme 411.

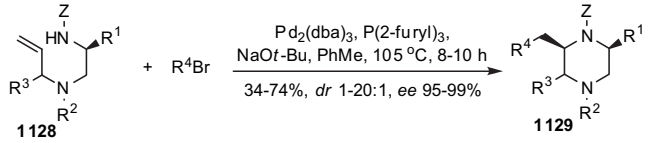
stereoselectivity was reversed when the reaction was performed in the absence of LiCl.[406]

Later, Wolfe et al. disclosed another approach to access highly diastereo- and enantiomerically enriched *cis*-2,6-disubstituted piperazines (**1129**). Their strategy proceeded via Pd-catalyzed carboamination reactions between aryl or alkenyl halides and substituted *N*-allyl ethylenediamine derivatives (**1128**), as depicted



Scheme 413.

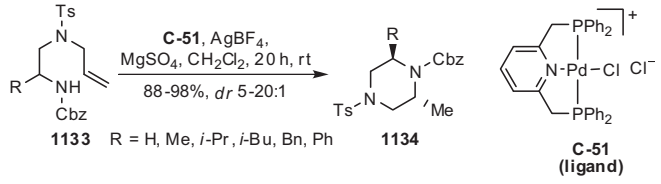
in Scheme 414.[407] Alternatively *o*-phenylenediamines **1130** afforded the tetrahydroquinoxalines (**1132**) under identical conditions (Scheme 415).[408] The use of appropriately substituted *N*-allyl ethylenediamine or *N*-allyl-1,2-phenylenediamine derivatives (**1128** or **1131**) allowed the installation of different groups at N-1, N-4, C-2 and C-6 and the construction of 2,3-disubstituted piperazines (**1129**) as well as tetrahydroquinoxalines (**1132**).



R^1 = H, Me, *i*-Pr, *i*-Bu, Bn, 4-ClBn, CH_2OBn; R^2 = allyl, PMP, Bn; R^3 = H, Me; R^4 = 4-PhC_6H_4, TMSCH=CH, 4-$NMe_2C_6H_4$, 4-CNC_6H_4, 4-$OMeC_6H_4$, 4-*t*-BuC_6H_4, 4-*t*-$BuCO_2C_6H_4$, 4-$CF_3C_6H_4$, PhCH=CH, CH_2=C(Ph), 3-pyridyl; Z = Boc, Ph, PMP, 4-CNC_6H_4, 4-ClC_6H_4

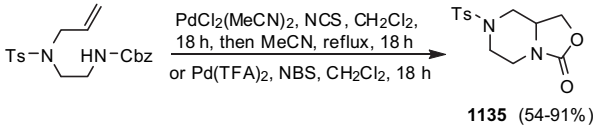
Scheme 414.

Later, Cochran and Michael also reported a stereoselective route for the transformation of unactivated alkenes (**1133**) into enantiopure *trans*-2,6-disubstituted piperazines (**1134**) with differently protected nitrogen atoms by Pd-catalyzed intramolecular hydroamination, which takes place via inhibition of β-hydride elimination (Scheme 416).[409]



Scheme 416.

In a continuation of their studies, they synthesized 7-tosyl-tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (**1135**) from a substituted allylamine by performing the Pd-catalyzed reaction in the presence of a halogenating agent, such as NCS or NBS (Scheme 417). The process involved intramolecular haloamination followed by halide displacement by the neighbouring carbamate group.[410]



Scheme 417.

Fueloep et al. demonstrated Pd(II)-catalyzed intramolecular oxidative cyclization for the conversion of *cis*- and *trans*-*N*-allyl-2-aminocyclohexanecarboxamides (**1136**) into cyclohexane-fused pyrimidin-4-ones (**1137**–**1139**) and 1,5-diazocin-6-ones (**1140**) via *cis*-amino palladation (Scheme 418). During the course of this study they observed a marked solvent effect on both the regio- and diastereoselectivity of the reaction.[411]

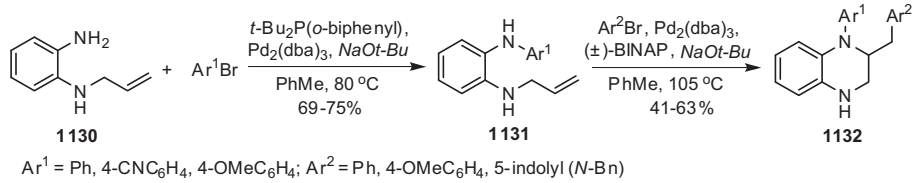
Olson and Du Bois reported Rh-catalyzed C–H activation in the unsaturated sulfamate derivatives (**1141**), which resulted in the formation of oxathiadiazinanes (**1142**) (Scheme 419).[412] They proposed that such C–H amination provides a new general route to C–N bond formation. These oxathiadiazinanes were shown to be precursors of differentially protected vicinal diamines.

Later, in collaboration with Trost they reported the synthesis of aziridine **1144** from an unsaturated sulfamate ester **1143**. The tricyclic aziridine **1144** underwent an asymmetric transformation into a polyamine structure **1146** via a seven-membered precursor (**1145**), as depicted in Scheme 420.[413]

15.4. Hydroformylation reactions

Very recently, Zhang et al. reported that the linear aldehyde (**1148**), generated along with **1147** from Rh-catalyzed asymmetric hydroformylation of *N*-Boc allylamine, was transformed into 2-hydroxypyrrolidine (**1149**) in quantitative yield by intramolecular attack of the primary amide on the carbonyl group (Scheme 421).[414]

Helmchen's group reported a short route to chiral 2-substituted pyrrolidines (**1150** and **1151**), based on Rh-catalyzed hydroformylation of allylamines and their *N*-alkyl and *N*-acyl derivatives (Scheme 422).[415] The outcome of the hydroformylation reaction was controlled by the substituent on the nitrogen and not by the substituent on the carbon. In the case of *N*-alkyl allylamines, in situ reduction to the pyrrolidine occurs, whereas with *N*-acyl derivatives hemiaminals and with primary amines cyclic imines were formed. This strategy allowed the authors to achieve a very short synthesis of (*S*)-nicotine and the alkaloid 225C using **1152** as the starting substrate.



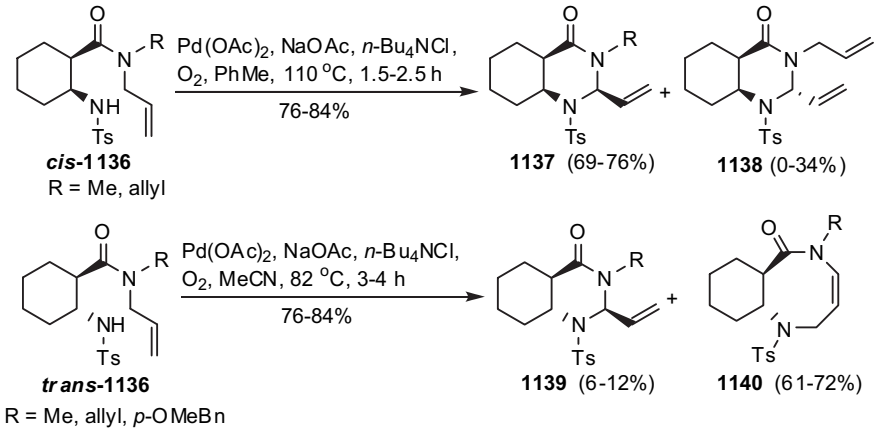
Ar^1 = Ph, 4-CNC_6H_4, 4-$OMeC_6H_4$; Ar^2 = Ph, 4-$OMeC_6H_4$, 5-indolyl (*N*-Bn)

Scheme 415.

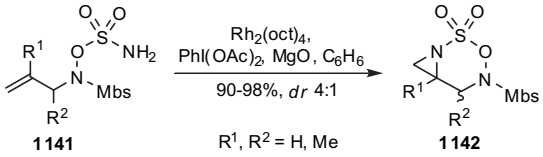
Oshitari and Mandai accomplished the synthesis of a neurokinin substance P receptor antagonists (+)-CP-99,994, which involved piperidine ring (**1154**) formation from the allylamine (**1153**) via a Rh-catalyzed hydroformylation (Scheme 423).[416]

Eilbracht's group developed an approach for the synthesis of tryptamines (**1156** and **1159**) and 2,3-disubstituted indoles (**1157** and **1158**) from the protected allylamines (**1155**) and phenylhydrazine via Rh-catalyzed tandem hydroformylation and Fischer indole synthesis (Scheme 424). Rh-catalyzed hydroformylation in the presence of phenylhydrazine allowed the in situ-formed aldehyde to be trapped as the hydrazone, and subsequent acid-catalyzed indolization furnished the desired indoles in moderate-to-good yields.[417]

1-Azabicyclo[4.3.0]alkane amino acid derivatives (**1161**) and their congeners were synthesized by Chiou et al. by means of Rh–BIPHEPHOS-catalyzed extremely regioselective cyclohydrocarbonylation (CHC) of the allylamides (**1160**) under mild conditions. The reaction involved two consecutive cyclization steps, the first of which produced the cyclic *N*-acyliminium key



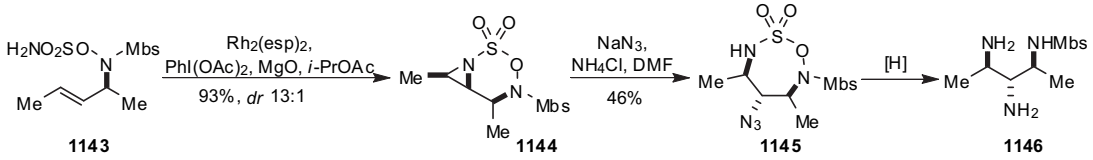
Scheme 418.



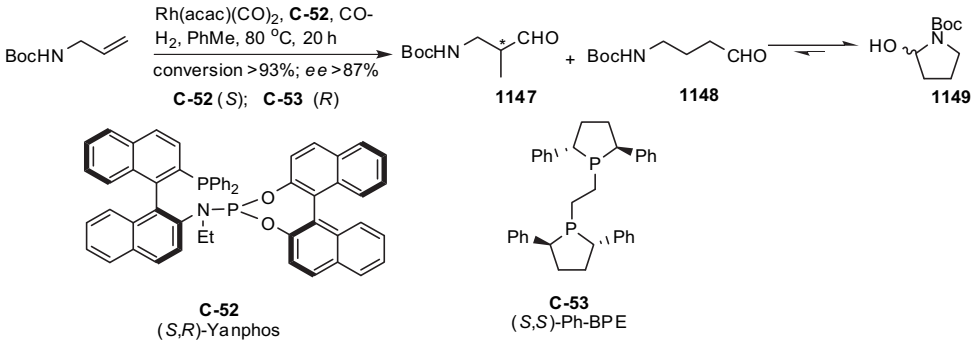
Scheme 419.

intermediate via CHC, whereas the second yielded the corresponding 1-azabicyclo[4.3.0] system (**1161**) with high diastereoselectivity, as shown in Scheme 425.[418]

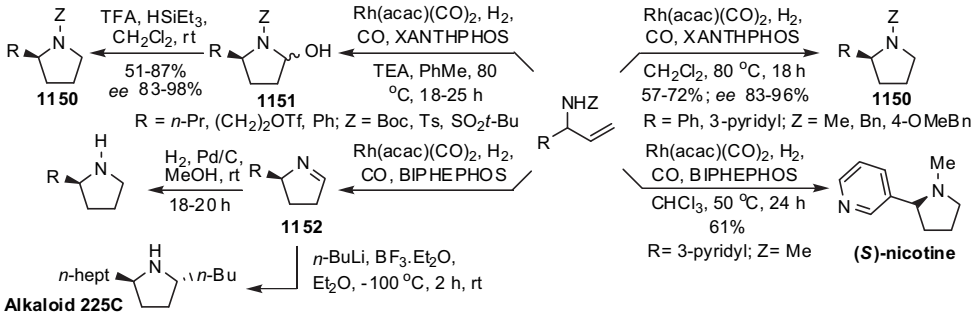
Later these workers reported Rh-catalyzed CHC-bicyclization of *N*-allylic amides of arylacetic acids (**1162** and **1165**) to construct tricyclic aza-heterocyclic structures (**1163** and **1166**) including the



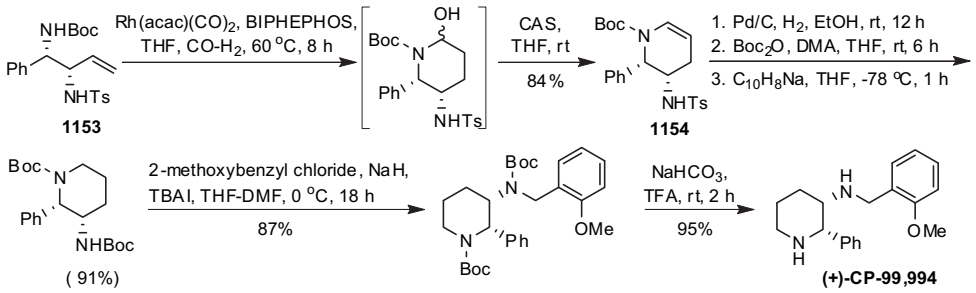
Scheme 420.



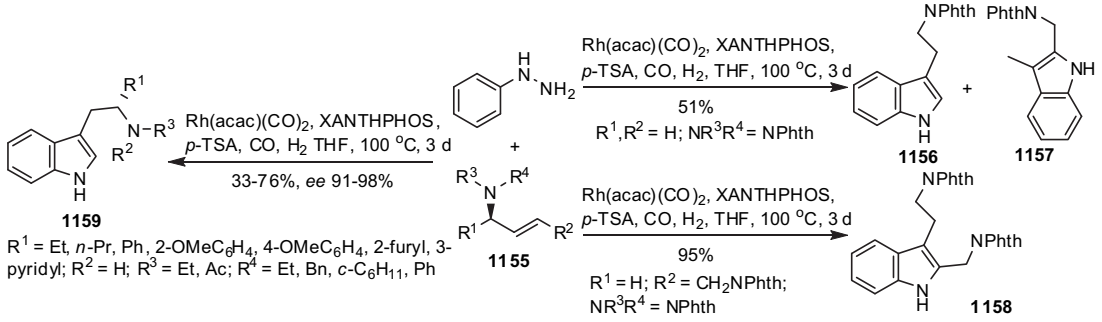
Scheme 421.



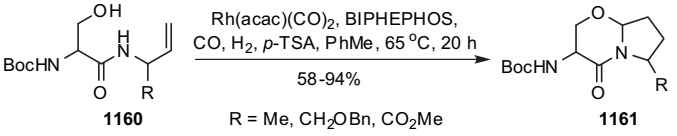
Scheme 422.



Scheme 423.



Scheme 424.



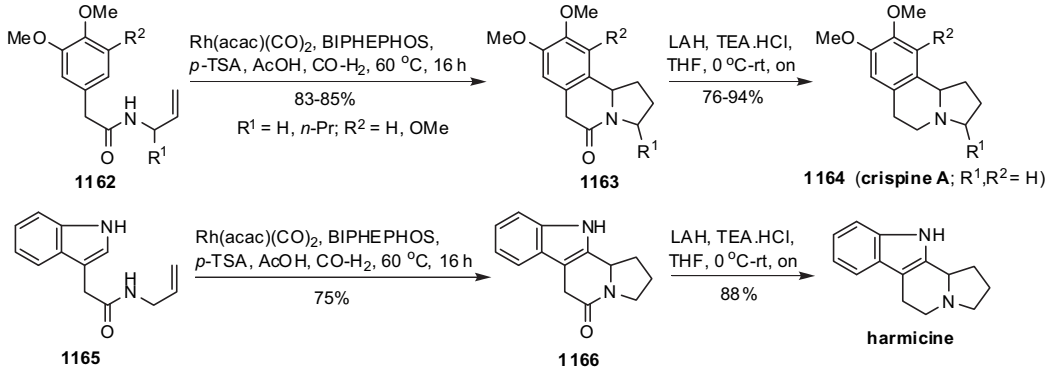
Scheme 425.

tricyclic indolizidine alkaloids, crispine A and its analogues (**1164**) as well as the tetracyclic β-carboline alkaloid, harmicine, as depicted in Scheme 426.[419]

Li and Jones reported the cyclization of diallylanilines (**1174**) in the presence of catalytic $Co_2(CO)_8$ under a CO atmosphere to afford the 2,3-substituted quinolines (**1175**) in good yields. The steric and electronic influence of the substituents and the solvent and temperature effects were studied and it was observed that electron-withdrawing groups inhibit the reaction (Scheme 428).[421]

16. Reductive cyclization

The domino process involving reduction of the nitro group of *N*-allyl *o*-nitroaniline coupled with Michael addition of the generated

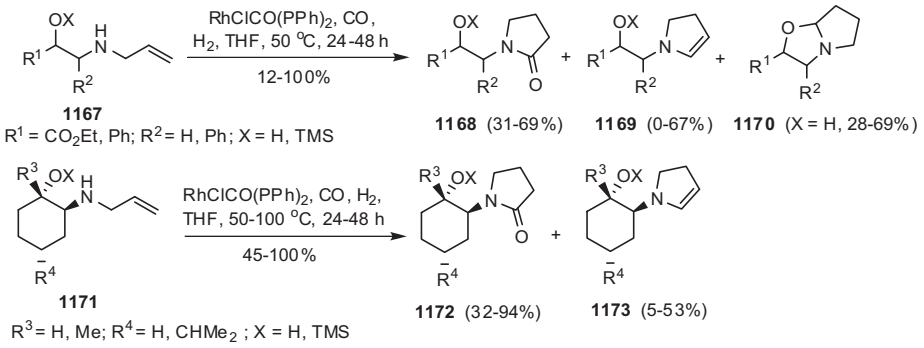


Scheme 426.

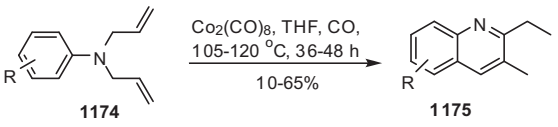
da Rosa et al. reported Rh-catalyzed carbonylation of allylamine derivatives **1167** and **1171** in an atmosphere of CO/H_2 mixed in various ratios to produce γ-lactams (**1168** and **1172**), pyrrolines (**1169** and **1173**) and bicyclic oxazolidines (**1170**) in moderate-to-excellent yields, depending on the substrate used and the reaction conditions. The results indicated that an increase in the chelating ability of the substrate (−OH and −NHR moieties) decreased the conversion and selectivity of the ensuing reaction (Scheme 427).[420]

amine onto the allylic double bond give rise to heterocyclic scaffolds. The Beifuss group constructed 1,2,3,4-tetrahydroquinoxalines (**1177a,b**) in one step under MW conditions by $P(OEt)_3$-mediated reductive domino cyclization of the *N*-allyl-2-nitroanilines **1176** (Scheme 429).[422]

Later, they observed that the reductive cyclization of ω-nitroalkene (**1178**) can also be effected with excess $NaBH_4$–NaOEt or with $Pd(OAc)_2$–CO-mediated reductive heteroannulation, but the formation of a mixture of products was attributed to the poor yield



Scheme 427.

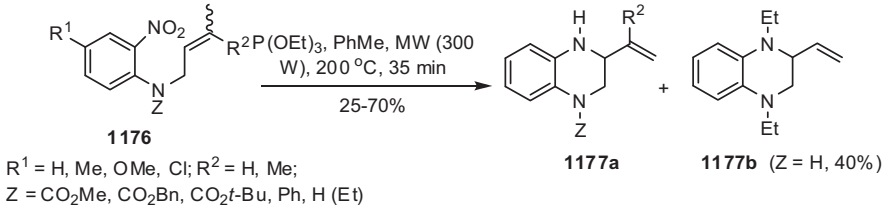


Scheme 428.

entry into polysubstituted thiomorpholine derivatives (**1182**) (Scheme 432).[425]

17. Tsuji–Trost reactions

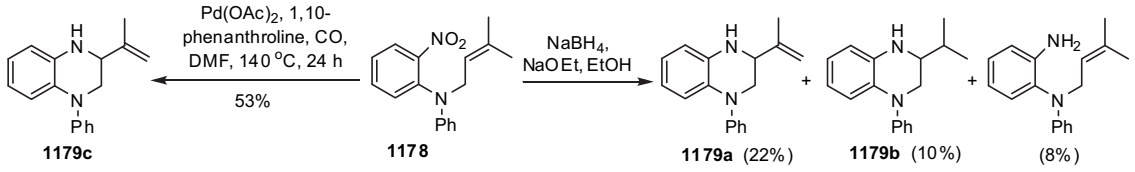
Saicic et al. synthesized *N*-tosyl-4-vinylpyrrolidine-3-carbaldehyde (**1184**) through stereoselective Tsuji–Trost 5-*exo*-cyclization of allylamine tethered aldehyde (**1183**), by a synergistic



Scheme 429.

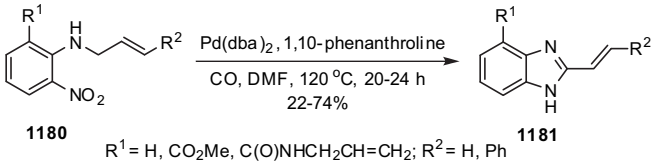
of the 1,2,3,4-tetrahydroquinoxaline (**1179a–c**) obtained during the reaction (Scheme 430). Nevertheless, an increase in the catalytic load of $Pd(OAc)_2$ improved the yield of the product.[423]

combination of organotransition metal catalysis and organocatalysis (Scheme 433).[426] When the reaction was performed at 0 °C in the presence of the chiral organocatalyst (*R*)-(BINAP)Pd, the



Scheme 430.

Hubbard et al. disclosed the synthesis of 2-alkenyl substituted benzimidazoles (**1181**) via a Pd-catalyzed reductive N-heteroannulation of *N*-allyl-2-nitroanilines (**1180**), using CO as an ultimate reducing agent (Scheme 431).[424]



Scheme 431.

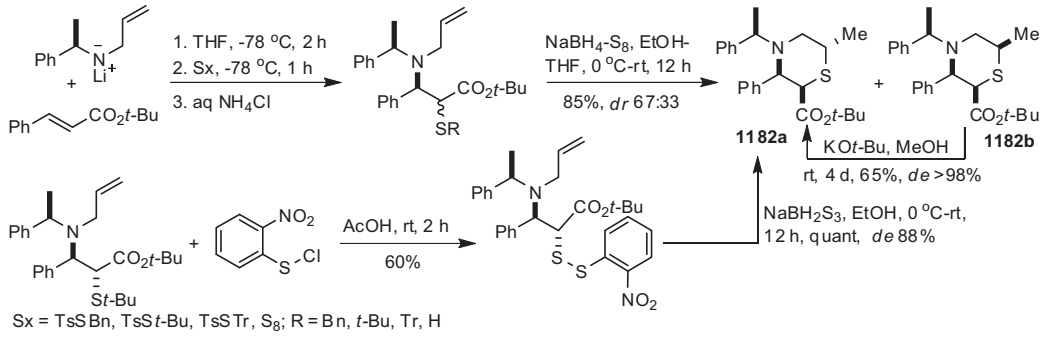
Davies et al. demonstrated that the conjugate addition of homochiral lithium *N*-allyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate followed by enolate trapping by various electrophilic sulfur sources, conversion of the *S*-alkyl functionality into a disulphide, and reduction with Lalancette's reagent offered an efficient optically enriched pyrrolidine derivative **1184** was obtained with 59% ee, albeit in lower yield.

In an analogous approach the substituted allylamine (**1185**) was manipulated to the pyrrolidone derivative (**1187**) via intramolecular Pd-catalyzed allylic alkylation of the allylic sulfone (**1186**) by Thuong et al. (Scheme 434). The pyrrolidone derivative (**1187**) was used as a precursor for the synthesis of (−)-α-kainic acid.[427]

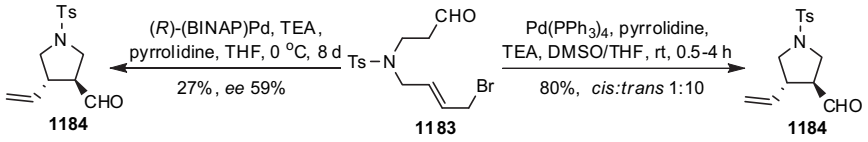
Later Webber and Krische modified this methodology to attain an easy access to *N*-protected piperidines (**1189**) from the enone-allyl carbonates (**1188**) (Scheme 435). In principle this Pd(0)-catalyzed enone cycloallylation reaction combined the nucleophilic features of the MBH reaction and the electrophilic features of the Tsuji–Trost reaction.[428]

18. Zirconocene-promoted reactions

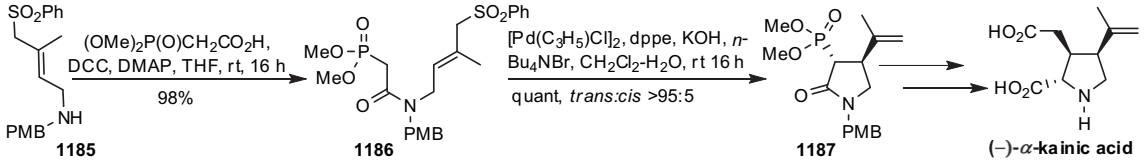
Hunter et al. converted the bis-allylamines (**1190** and **1192**) into the corresponding 3-benzyl-4-methylpyrrolidines (**1191** and **1193**)



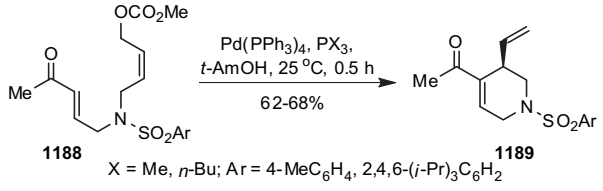
Scheme 432.



Scheme 433.

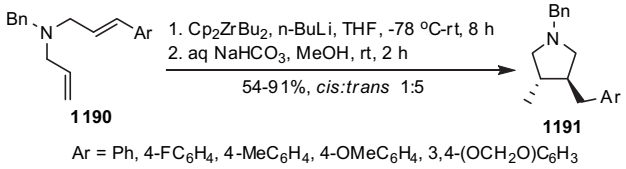


Scheme 434.



Scheme 435.

via Zr-mediated (Negishi's reagent) cyclization both in solution (Scheme 436) and on solid phase (Scheme 437), the latter method giving higher overall yields. Under similar conditions, the allylamines **1194** produced 3-arylpyrrolidines (**1195**) or 4-arylpiperidines (**1196**) (Scheme 438), whereas **1197** yielded 3-benzylidenepyrrolidines (**1198**) (Scheme 439).[429]



Scheme 436.

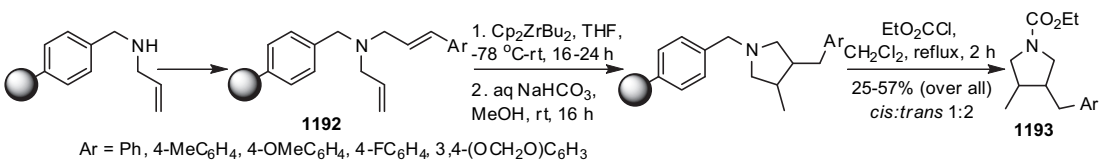
These workers also synthesized 3,4-disubstituted azepanes (e.g., **1200**) and 4-alkylideneazepanes or benzazepanes (**1202**) from 4-azanona-1,8-dienes (e.g., **1199**) and 4-azanona-1,8-enynes (**1201**) (Scheme 440), respectively, under similar reaction conditions.[430]

An optically active azetidine (**1205**) was synthesized from the *O*-protected analogue (**1204**) of the secondary allylamine (**1203**) by Ahari et al. in a one-pot process, which involved a hydrozirconation and an iodination sequence as the key steps (Scheme 441). (*R*)-2-Phenylglycinol played the role of chiral inducer during the reaction.[431]

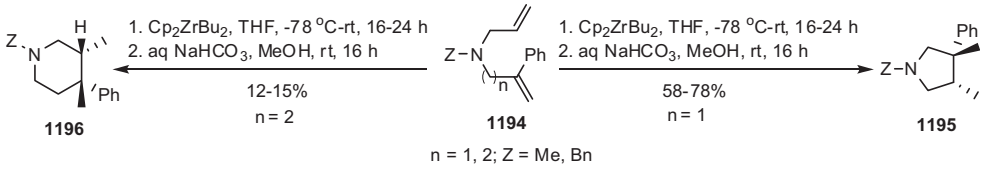
The same group described an efficient approach to enantiomerically pure *trans*-2,3-disubstituted piperidines (**1208**) from the substituted allylamines (**1207**); generated from (**1206**) by sequential hydrozirconation, iodination and base-mediated ring-closure reactions (Scheme 442). This methodology provided an opportunity to construct a broad range of biologically active piperidine derivatives, such as (+)-epilupinine and 2-*epi*-CP-99,994.[432]

19. Kulinkovich reaction

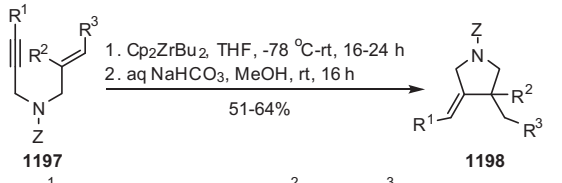
Ollivier's group reported a diastereoselective synthesis of functionalized pyrrolidinone (**1211a**) from the isopropyl ester of *N*-allyl-*N*-benzylaspartic acid (**1209**) via unconventional ring opening of cyclopropanol through a cyclopropanol–methylketone rearrang-



Scheme 437.



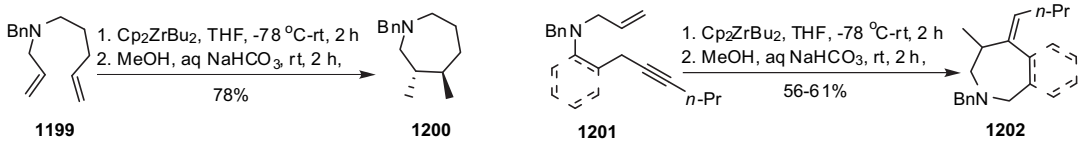
Scheme 438.



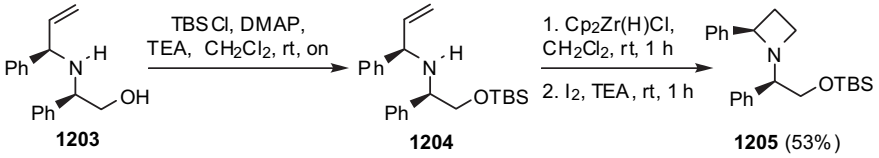
Scheme 439.

reagent, since an increase in the concentration of *i*-PrMgBr produced **1211b** in higher yields (Scheme 443).[434] Performing a similar reaction with allylamine **1212** produced an inseparable mixture of *cis*- and *trans*-aza-bicyclo[3.1.0]hexanols **1213** and **1214a**,**b** depending on the concentration of *i*-PrMgCl used (Scheme 444).

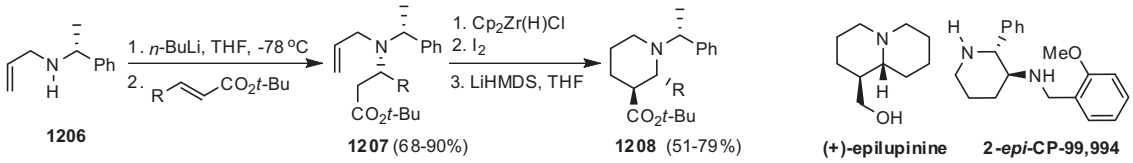
They also subjected various natural and unnatural β-amino acid derivatives (**1215**) to a Kulinkovich cyclopropanation reaction to generate the azabicyclo[3.1.0]hexan-1-ols (**1216**) and converted these into diverse intermediates such as pyrrolidinones (**1217**), piperidinones (**1218a**,**b**), pyridines (**1219**), dihy-



Scheme 440.



Scheme 441.

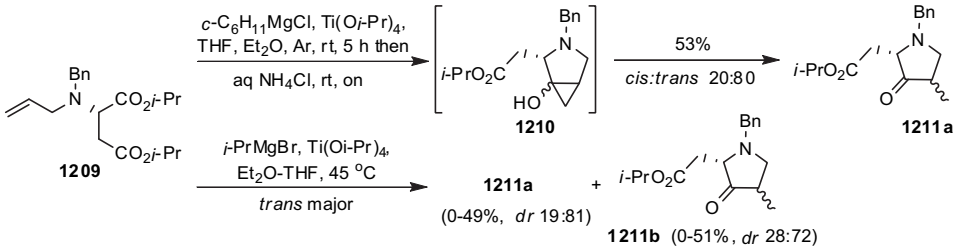


Scheme 442.

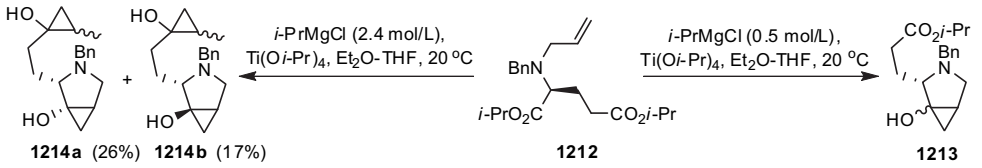
ement of the intermediate azabicyclo[3.1.0]hexan-1-ols (**1210**), generated by a Ti-mediated intramolecular cyclopropanation (Kulinkovich) reaction performed in the presence of *c*-$C_6H_{11}MgCl$, as shown in Scheme 443.[433] When *i*-PrMgBr was used, however, the formation of pyrrolidinone **1211a** was observed along with **1211b**. These workers discovered that the yield of the pyrrolidinone was highly dependent on the concentration of the organometallic

dropiperidinones (**1220**) and tricyclic piperidinones (**1221**) through ring cleavage and subsequent rearrangement (Scheme 445).[435] Such diverse intermediates were envisaged to find use in pharmaceuticals.

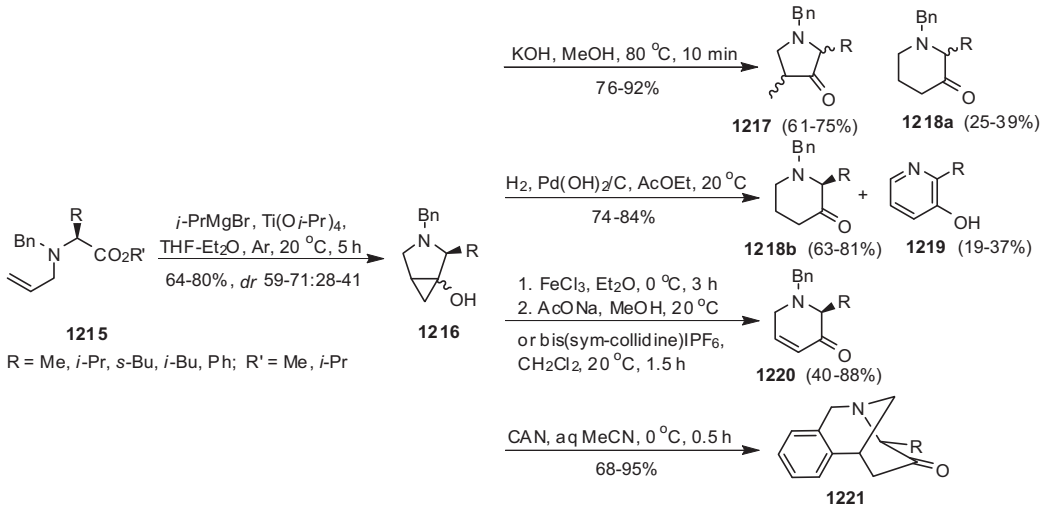
The conversion of (*S*)-phenylglycinate derivative **1222** into (*S*)-2-phenylpiperidine-3-one (**1223**), a chiral intermediate used for the preparation of potent NK-1 antagonists, was also achieved by



Scheme 443.



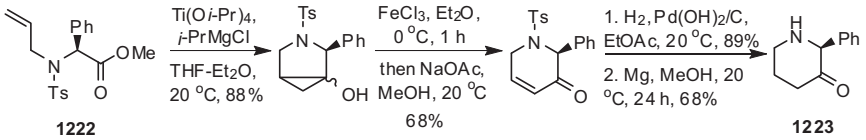
Scheme 444.



Scheme 445.

Olliver et al. via sequential Kulinkovich cyclopropanation, Saegusa oxidation, hydrogenative reduction and, finally, detosylation, as depicted in Scheme 446.[436]

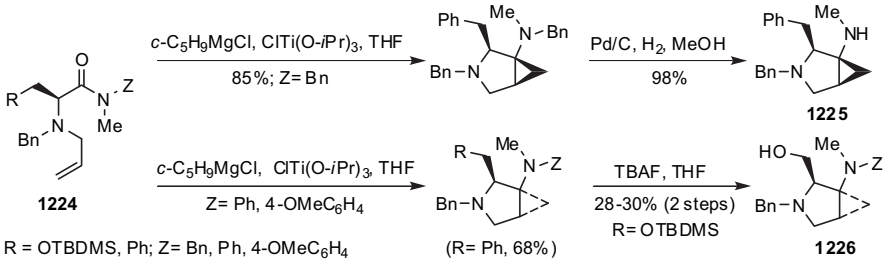
Later, in an extension of their studies related to this reaction, they observed that, although the azabicyclo[3.1.0] systems (**1229**) were formed preferentially over other cyclic systems, a slight



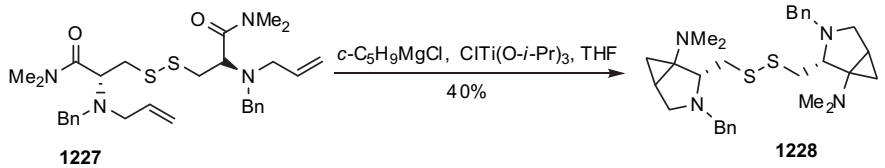
Scheme 446.

Joullie's group has reported Ti(II)-mediated coupling of a terminal olefin and *N*,*N*′-disubstituted carboxamide derivatives (**1224** and **1227**) of amino acids to produce a series of novel [3.1.0] bicyclic cyclopropylamines (**1225, 1226** and **1228**) (Schemes 447 and 448).[437]

change in cyclization conditions led to poor yields of the cyclopropylated bicycles, due to the formation of monocyclic side products (**1230a**,**b** and **1231**). They transformed the azabicyclo [3.1.0]hexanols derived from amino acid derivatives containing two

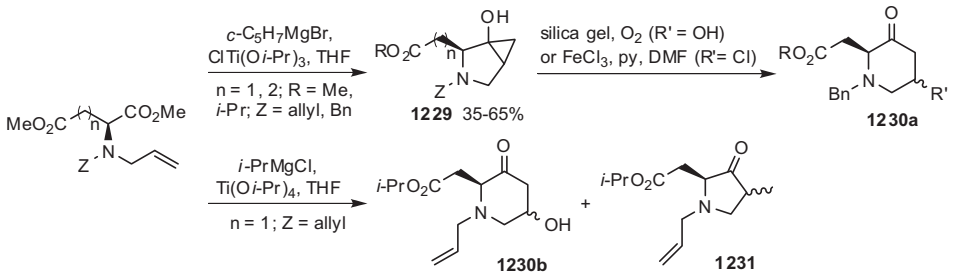


Scheme 447.



Scheme 448.

ester moieties into piperidin-3-ones (**1230a**) under different conditions (Scheme 449).[438]



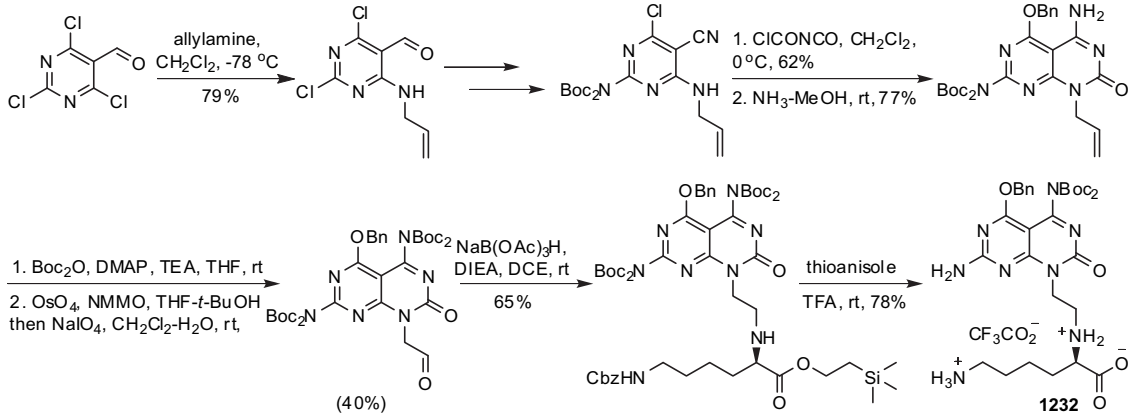
Scheme 449.

20. Miscellaneous reactions

The synthetic strategy for obtaining the chiral molecule **1232** was developed by Johnson et al. in a total of 13 steps involving the primary allylamine as one of the essential ingredients. This single chiral molecule was reported to express mirror image chiroptical outputs upon self assembly into pseudomirror image supramolecular conformational isomers (chiromers) (Scheme 450).[439]

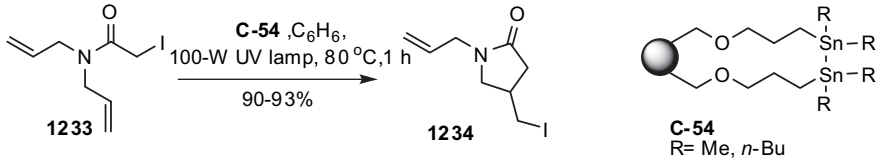
Kamimura et al. demonstrated a DBU–I_2–Ag_2O-mediated diastereoselective cyclopropanation reaction of β-nitro amides (**1235**) to afford azabicyclo [3.1.0]hexane (**1236**) (Scheme 452).[441] Cyclopropanation also occurred in the absence of Ag_2O, but the diastereoselectivity was completely lost. On the other hand, if the reaction was performed with DBU–Ag_2O, in the absence of I_2, the substituted pyrrolidine **1237** was afforded as a mixture of diastereomers.

Kwak et al. reported the formation of 1-(arylsulfonyl)-4-vinylimidazolidin-2-ones (**1239**) and *N*-(4-vinyloxazolidin-2-yl) arylsulfonamides (**1240**) in approximately equal ratios in a base-



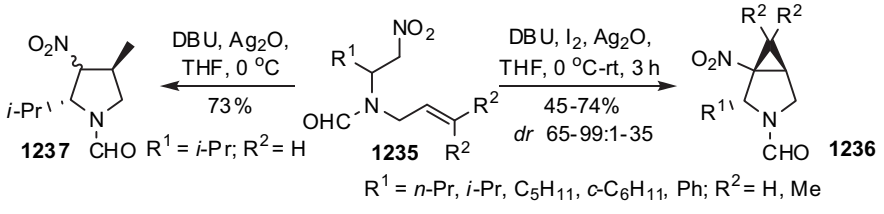
Scheme 450.

Kilburn et al. carried out the cyclization of diallylamide **1233** with 10 mol % of resin-bound organotin reagents to furnish 1-allyl-4-(iodomethyl)pyrrolidin-2-one (**1234**) under photochemical conditions (Scheme 451).[440]

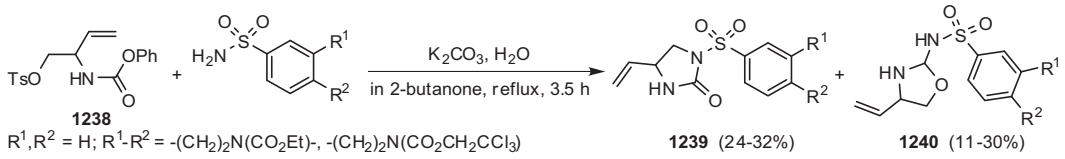


Scheme 451.

mediated reaction of allyl carbamate (**1238**) with arylsulfonamides (Scheme 453). The vinylimidazolidin-2-ones (**1239**) were evaluated as anticancer agents, but did not exhibit promising activity.[442]



Scheme 452.

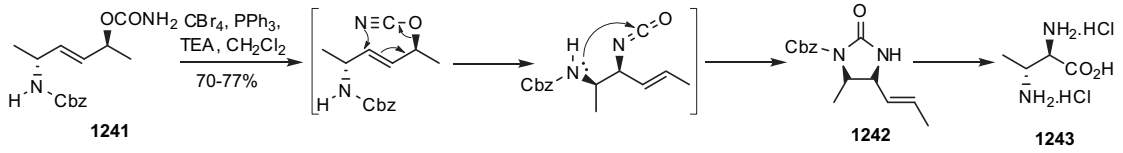


Scheme 453.

Ichikawa et al. developed the synthesis of imidazolidin-2-one (**1242**) from the allyl carbamate (**1241**) via in situ trapping of allyl isocyanate, formed by tandem dehydration of the allyl carbamate under modified Appel conditions followed by a [3.3]-sigmatropic rearrangement (Scheme 454). Imidazolidin-2-one **1242** was converted into *syn*-(2*R*,3*S*)-2,3-diaminobutanoic acids **1243** through a completely stereocontrolled process.[443]

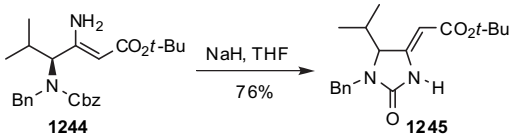
Qing et al. synthesized *gem*-4,4-difluoromethylenated iminosugars (**1249** and **1250**) from the allylamine **1248** (Scheme 457) and their biological activity as glycosidase inhibitors was evaluated at different pH values. Simultaneously, the effect of the fluorine substituent on the bioactivity was also studied.[446]

Thibaudeau et al. disclosed the rapid conversion of various *N*,*N*-diallylic amines and amides (**1251**) to fluorinated piperidines



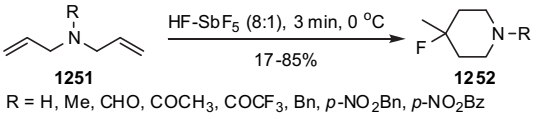
Scheme 454.

Later Hoang et al. in an alternative strategy reported that treating enamino ester (**1244**) with base resulted in attack of the amino group onto the nitrogen of the carbamate, leading to the imidazolidin-2-one (**1245**) (Scheme 455).[444]



Scheme 455.

Allylamines **1246** were transformed into simplified analogues (**1247**) of bengazole A by Sellanes et al. via a sequential amide coupling followed by tandem cyclodehydration process (Scheme 456). Some of these products were tested in vitro as cytotoxics and anthelmintics and showed the same level of activities as bengazole A.[445]

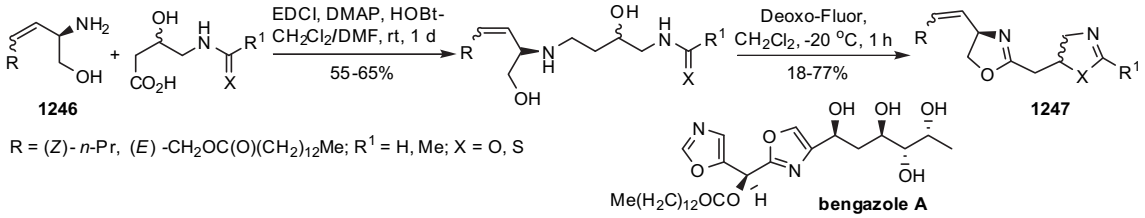


Scheme 458.

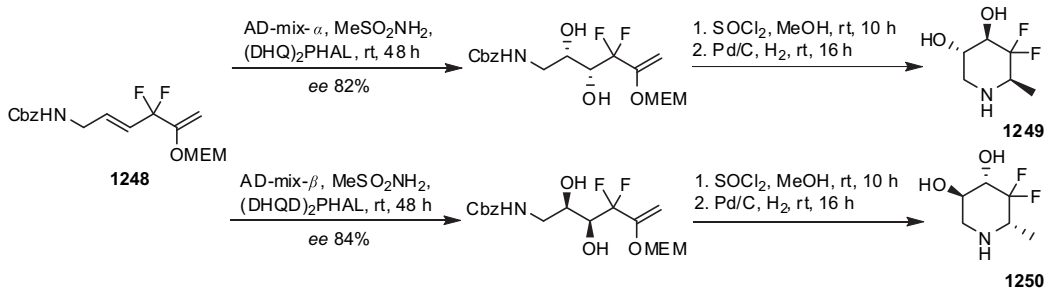
(**1252**) by a novel cyclization–fluorination reaction in superacid, HF–SbF_5 (Scheme 458).[447]

Bates and Lu converted the 1,3-amino alcohol **1254**, obtained from the allylamine **1253** by sequential cross metathesis and hydrogenation, into the bicyclic *N*,*O*-acetal **1255**, which was used as precursor for the synthesis of C6-*epi* porantheridine.[448] A formal synthesis of porantheridine was also achieved from **1256**, which too was prepared from **1254** (Scheme 459).

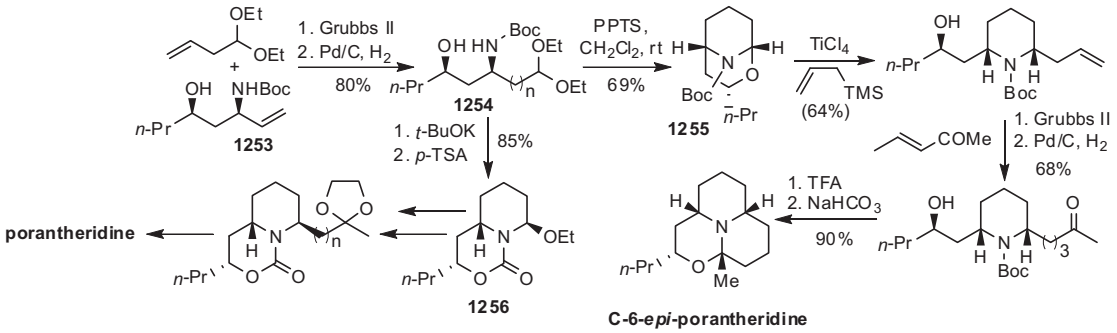
Banwell et al. reported the synthesis of the 1-azaspiro[5.5] undecane framework **1258** associated with the potent neurotoxin, perhydrohistrionicotoxin, from the allyl carbamate **1257** via



Scheme 456.

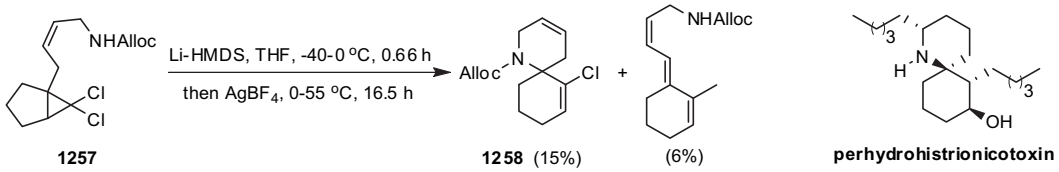


Scheme 457.



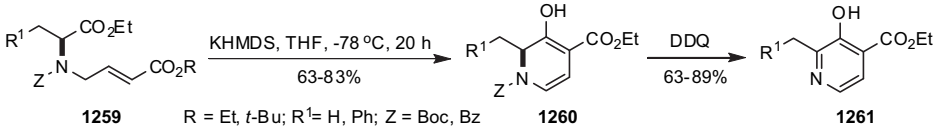
Scheme 459.

LiHMDS–$AgBF_4$-induced intramolecular decyclopropanation–chloride elimination sequence (Scheme 460).[449]



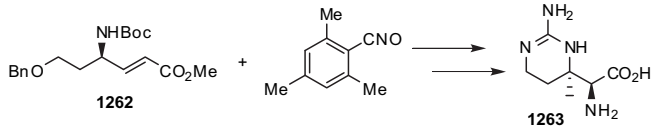
Scheme 460.

Monguchi et al. generated the chiral 1,2-dihydropyridines (**1260**) by Dieckmann condensation of the *N*-allyl α-amino acid derivatives (**1259**). These dihydropyridines (**1260**) underwent DDQ-mediated aromatization to yield 2,3,4-trisubstituted pyridines (**1261**) (Scheme 461).[450]



Scheme 461.

Martinkova et al. developed a domino approach to the stereocontrolled synthesis of advanced intermediates in the synthesis of a nonproteinogenic amino acid, (2*S*,3*R*)-capreomycidine (**1263**), from the allylamine **1262** (Scheme 462).[451]

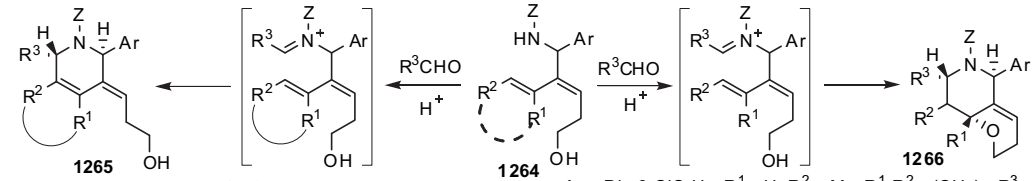


Scheme 462.

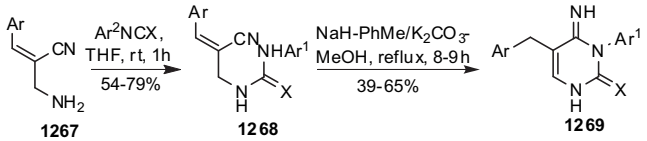
Chen and Micalizio demonstrated the synthesis of fused bicyclic heterocycles (**1265**) via cationic annulation of the allylamines **1264** with aldehydes under Pictet–Spengler reaction conditions (Scheme 463).[452] The 1,3-diene-containing allylic amines **1264** also provided bi-, tri- and tetracyclic piperidines (**1266**) with up to four stereogenic centres in very high levels of stereoselection through the cationic annulations terminated by C–O bond formation via aza-Prins-initiated cyclization.

Primary and secondary allylamines afforded from the MBH adducts were successfully transformed into different aza-heterocycles by our group. Several 1-(2-cyano-3-aryl-allyl)-3-aryl-ureas and thioureas (**1268**) were constructed via the reaction between substituted isocyanates or isothiocyanates and primary allylamines (**1267**), afforded from the MBH adducts of acrylonitrile. Further, these urea and thiourea derivatives were cyclized in the presence of base, leading to the formation of 5-arylmethyl-4-imino-3-aryl-3,4-dihydro-1*H*-pyrimidin-2-ones (**1269**) (Scheme 464).[453] During an antibacterial bioevaluation, a few compounds showed superior activity or were equipotent to standard antibacterial agents.

Primary allylamines (**1270**) obtained from the MBH adducts of methyl acrylate were utilized to access 5-benzyl-4(3*H*)-pyrimidinones (**1272**) in a one-pot protocol via initial N-formylation of the primary allylamines to afford **1271** in neat formamide followed by cyclization in the presence of ammonium formate. These pyrimidinones were converted into 5-benzylpyrimidin-4-amine (**1274**) via the reaction of 4-chloropyrimidine (**1273**), originated via $POCl_3$-mediated chlorination of **1272**, with primary amine. 4-



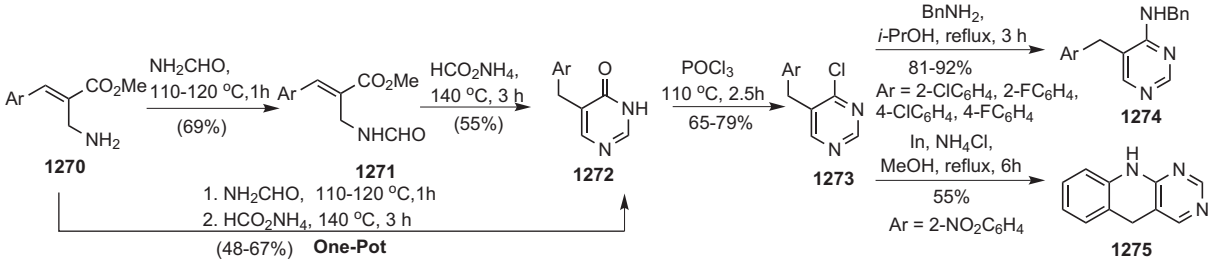
Scheme 463.



X = O, S; Ar = Ph, 2-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 2-thienyl; Ar^1 = 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 3,4-Cl$_2$C$_6$H$_4$, 3-Cl-4-MeC$_6$H$_3$

Scheme 464.

Chloropyrimidine (**1273**) having a 2-nitrobenzyl substituent at the C-5 position underwent an intarmolecular cyclization to produce 3,4-dihydropyrimido[4,3-*b*]quinoline (**1275**) via an In–NH$_4$Cl-mediated reductive cyclization (Scheme 465).[152]



Ar = Ph, 2-ClC$_6$H$_4$, 2-FC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 3,4-(OMe)$_2$C$_6$H$_3$, 2-thienyl

Ar = 2-ClC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$

Ar = 2-NO$_2$C$_6$H$_4$

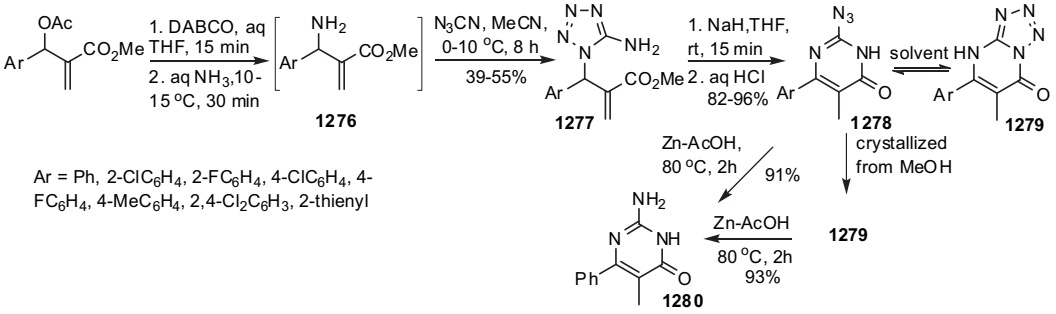
Scheme 465.

The primary allylamines **1276**, which were generated from MBH acetates using aqueous NH$_3$, were immediately reacted with freshly prepared azidonitrile to afford 5-aminotetrazoles **1277**, which were further cyclized intramolecularly to 2-azido-5-methyl-6-arylpyrimidin-4(3*H*)-ones (**1278**) (Scheme 466).[454] It was observed that **1278** exist as equilibrium mixtures with 6-methyl-5-phenyltetrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **1279** in solution. Reduction of the **1278** resulted in 2-amino-pyrimidin-6-ones **1280**. During this study, primary allylamines **1270** were also successfully subjected to a similar set of reaction sequences, as depicted in Scheme 467. The allylamines **1270** initially afforded the tetrazoles **1281**, which rearranged in the presence of base to yield the azides **1282**. The azides **1282** crystallized under methanolic solution to the annulated tetrazoles **1283** whereas upon reduction produced the amines **1284**.

In another study, the synthesis of tetrazole-fused diazepinones (**1288**) from the allylamines (**232**) was accomplished by our group.[455] Initially, **232** were transformed into the corresponding isonitriles (**1285**), followed by an MCR Ugi reaction of these isonitriles with TMSN$_3$, aliphatic amines and aldehydes or ketones to afford 1-substituted tetrazoles **1286**, which were first converted to acids **1287** and then to tetrazolo-fused diazepinones **1288** via sequential ester hydrolysis and amide coupling (Scheme 468).

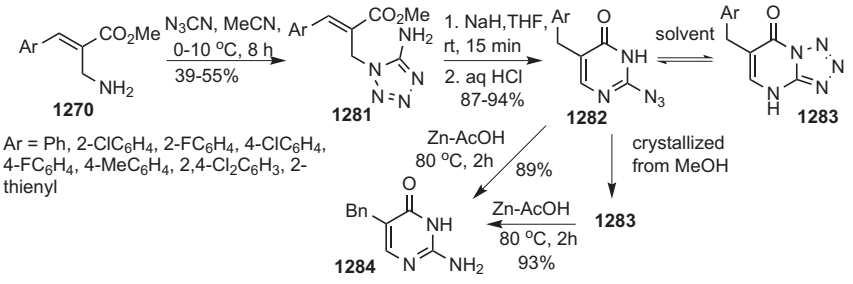
Alternatively, the primary allylamines **1267**, which were generated from the derivatives of acrylonitrile were used as precursors for generating isonitriles (**1289**), which participated in IMCR to yield substituted imidazo[1,2-*a*]pyridines (**1290**) (Scheme 469). Reduction of the 2-nitro-group in an analogue of **1290** (R=2-NO$_2$C$_6$H$_4$) followed by CNBr-mediated cyclization produced **1291** in good yield.[456]

A highly simplified approach for the generation of a substituted pyrimido[2,1-*b*]quinazoline core from **1267** and **1270** was formulated via sequential reductive alkylation with 2-nitrobenzaldehyde or substituted 2-nitrobenzaldehyde, reduction of the aromatic nitro group with In and CNBr-promoted intramolecular cyclization



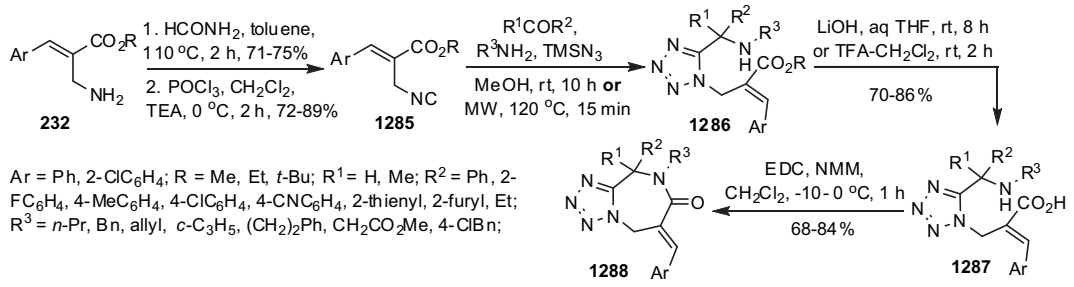
Ar = Ph, 2-ClC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2-thienyl

Scheme 466.

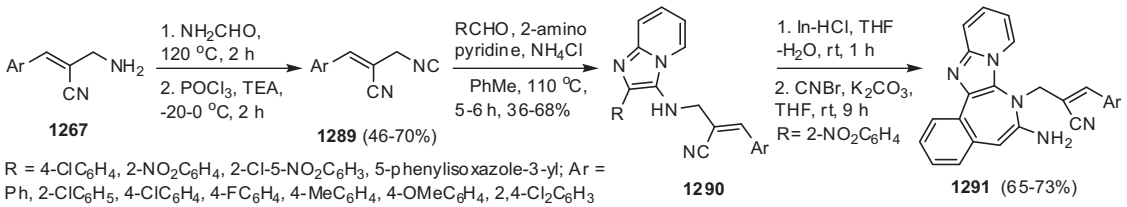


Ar = Ph, 2-ClC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2-thienyl

Scheme 467.



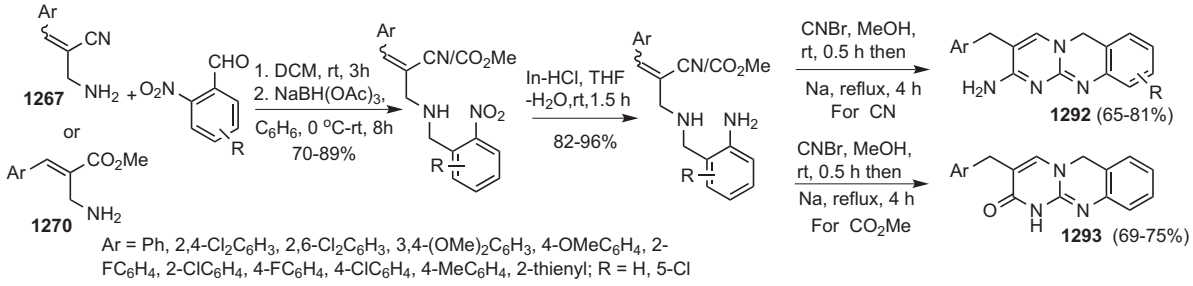
Scheme 468.



Scheme 469.

followed by NaOMe-mediated further intramolecular cyclization (Scheme 470).[457] The allylamines **1267** afforded from the MBH adducts of acrylonitrile gave 2-amino-3-arylmethyl-6*H*-pyrimido[2,1-*b*]quinazolines (**1292**) and those (**1270**) of methyl acrylate produced 3-arylmethyl-1,6-dihydro-2*H*-pyrimido[2,1-*b*]quinazoline-2-ones (**1293**).

In a similar strategy [1,4]diazepino[5,6-*b*]quinolin-2-ones (**1300** and **1301**) were generated from the differently protected allylamines **1298**. In the case of the tosyl-protected amine, reduction of the nitro functionality with Fe–AcOH produced 2-aminoquinoline (**1299**), which was transformed into **1300** via an NaH-mediated intramolecular cyclization. The cy-

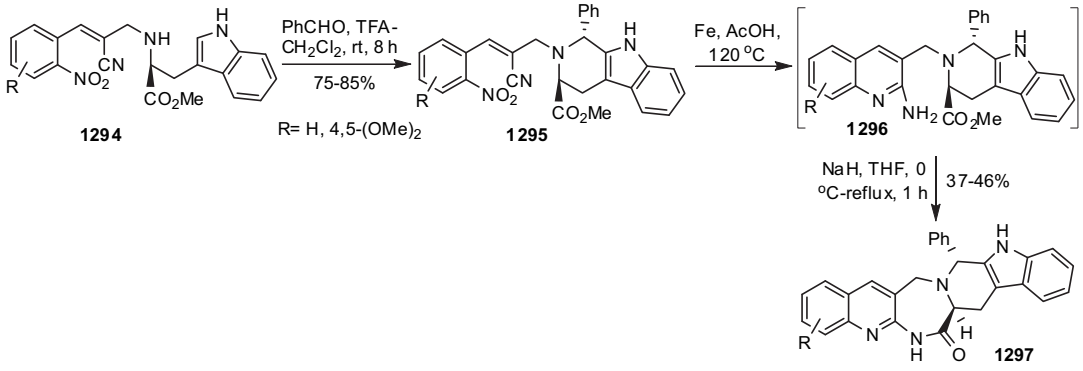


Scheme 470.

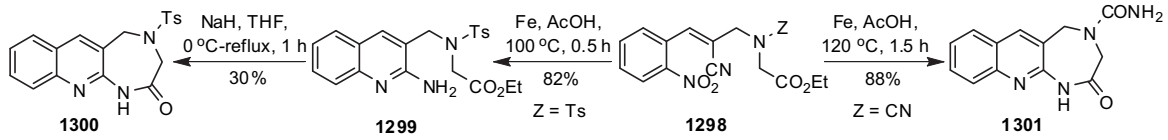
Later, different routes for the synthesis of 1,4-diazepin-2-one-fused polycyclic systems from the allylamines (**1294**) were also developed.[44] The β-carbolines **1295** generated via the Pictet–Spengler reaction of **1294** with benzaldehyde, underwent intramolecular reductive cyclization on heating with Fe–AcOH at 120 °C to afford 2-aminoquinoline **1296**, which upon treatment with NaH in THF furnished **1297** (Scheme 471).

anamide of **1298**, however, upon treating with Fe–AcOH, produced [1,4]diazepino[5,6-*b*]quinolin-2-one (**1301**) in one-pot (Scheme 472).[44]

Our group has also demonstrated the synthetic utility of derivatized allylamines (**1302** and **1303**) for the generation of substituted 3-methylenebenzo[*b*][1,4]diazepin-2-ones (**1304** and **1305**) and benzo[*b*][1,4]diazepin-2-ylamines (**1306**) in moderate-

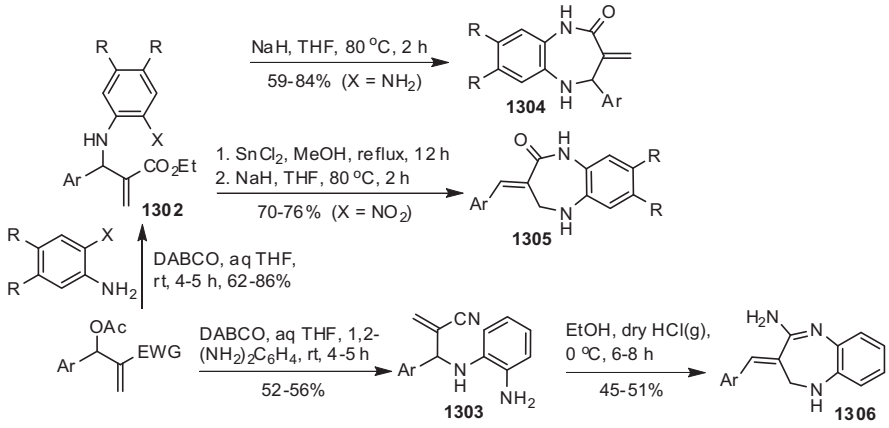


Scheme 471.



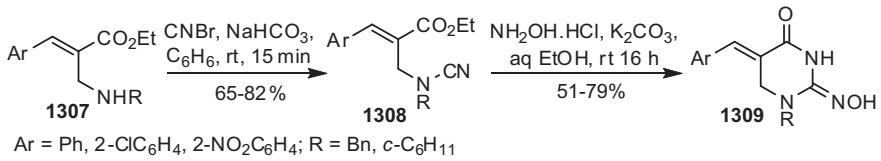
Scheme 472.

to-good yields through a base-mediated intramolecular cyclization or Pinner reaction, respectively (Scheme 473).[458]



Scheme 473.

The substituted cyanamides (**1308**), generated from the secondary allylamines (**1307**), were utilized by our group to generate 2-(hydroxyimino)pyrimidin-4-ones (**1309**) by reacting with $NH_2OH{\cdot}HCl$ in a basic medium, as depicted in Scheme 474.[459]



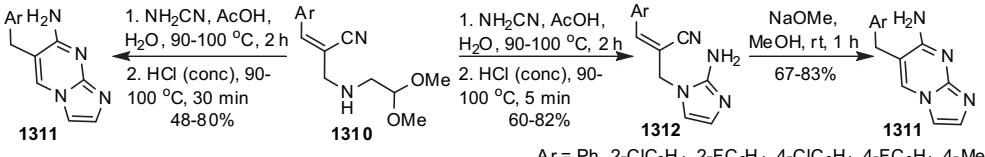
Scheme 474.

The secondary allylamines (**1310**), obtained from MBH adducts of heterocyclic aldehydes, which undergo fast MBH reactions, were converted into 6-arylmethylimidazo[1,2-*a*]pyrimidin-7-ylamines (**1311**) in a one-pot procedure by reacting with cyanamide under acidic conditions (Scheme 475).[460] All other aldehydes, however, yielded similar products in a two-pot procedure. Initially, the reaction of allylamines with cyanamide under acidic conditions produced the 2-amino imidazoles (**1312**), which under basic conditions undergo intramolecular cyclization to afford analogues of **1311**.

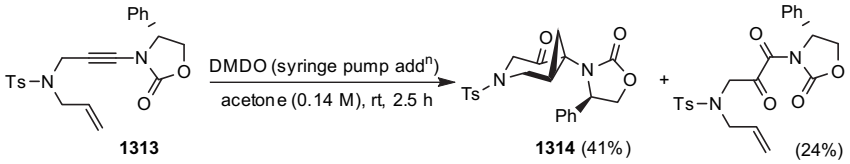
Al-Rashid and Hsung reported the synthesis of the amidocyclopropane (**1314**) via intramolecular cyclopropanations of a chiral push–pull carbene derived from DMDO-mediated alkyne oxidation of nitrogen-tethered ynamide (**1313**) (Scheme 476).[461]

Beauchemin et al. utilized the benzoic hydrazides (**1315**) as the precursors for the synthesis of piperazines (**1316**) via intramolecular hydroamination reaction under MW irradiation, as shown in Scheme 477.[462]

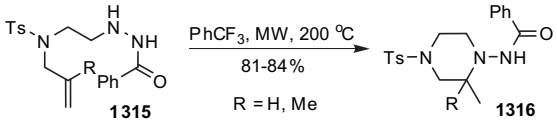
Our group has successfully utilized the allylamines (**1317**) to afford the substituted imidazo[1,2-a]pyrimidin-2-ones (**1319**) in a sequential Raney-Ni-mediated reduction of the nitrile group to



Scheme 475.

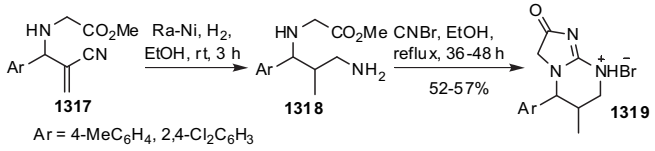


Scheme 476.



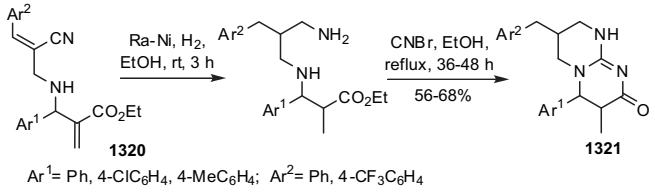
Scheme 477.

obtain diamines (**1318**) followed by intramolecular cyclization via reaction with CNBr, as depicted in Scheme 478.[463]



Scheme 478.

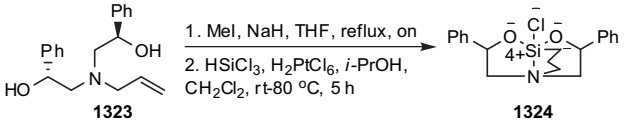
This strategy was extended to achieve the synthesis of hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones (**1321**) from the bis-allylamines (**1320**) (Scheme 479). These compounds exhibited significant antileishmanial activity.[464]



Scheme 479.

Sener et al. reported the synthesis of the macrocyclic system (**1322**) using primary allylamine (Scheme 480).[465]

In a multistep protocol, Wu et al. synthesized the heterocyclic silino compound (**1324**) from *N*,*N*-bis(2-hydroxy-2-phenylethyl) allylamine (**1323**) (Scheme 481).[466]



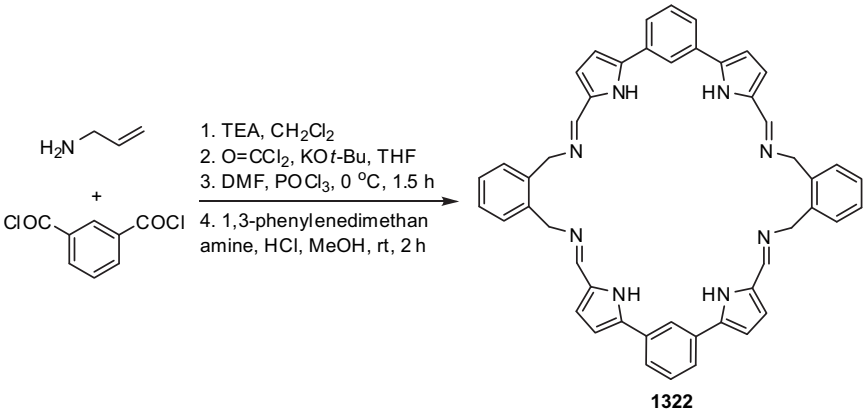
Scheme 481.

21. Conclusions

This review, which updates the recent applications of allylamines or their substituted analogues for the construction of aza-heterocycles, clearly demonstrates the synthetic utility of allylamines. An impressive number of very different aza-cycles have recently been prepared through diverse reactions such as intramolecular condensation, cycloaddition, cycloisomerization, Pauson–Khand reactions, ring-closing metathesis and transition-metal-catalyzed reactions. The diverse substitutions, which could be installed in the basic unit further expand the repertoire of reactions, which may be applied to design the synthesis of required nitrogen heterocycles. With the continuous discovery of new allylamines, new reaction protocols and new catalysts the versatility of the allylamines in synthetic organic chemistry will continue to evolve.

Acknowledgements

One of the authors (S.N.) gratefully acknowledges the financial support from UGC, New Delhi in the form of fellowship. The work on allylamines performed in this lab is funded by DST, New Delhi.



Scheme 480.

References and notes

1. (a) Kobayashi, K.; Miyazama, A.; Terrahara, H.; Mishime, H.; Kurihare, H. *Tetrahedron Lett.* **1976**, *17*, 537–540; (b) Rsndo, R. R.; Bangerter, F. *J. Am. Chem. Soc.* **1976**, *98*, 6762–6764; (c) Rando, R. R.; Bangaeter, F. *J. Am. Chem. Soc.* **1977**, *99*, 5141–5145; (d) Allan, R. D.; Johnstone, G. A. R.; Twitchin, B. *Neurosci. Lett.* **1977**, *4*, 51–54 CA **1977**, *86*, p 15039o.
2. (a) Hashimoto, T.; Kondo, S.; Naganawa, H.; Takita, T.; Maede, K.; Umezawa, H. *J. Antibiot.* **1974**, *27*, 86–87; (b) Hashimoto, T.; Takahashi, S.; Naganawa, H.; Kakita, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 350–355; (c) Teng, C. Y. P.; Garmen, B. *Tetrahedron Lett.* **1982**, *23*, 313–316.
3. Kondo, T.; Nakai, H. *Tetrahedron* **1973**, *29*, 1801–1806.
4. (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301–6311; (b) Jumnah, R.; Williams, J. M. J.; Williams, A. C. *Tetrahedron Lett.* **1993**, *34*, 6619–6622; (c) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411–1420; (d) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758–4763.
5. (a) Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087–11110; (b) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173–1192.
6. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444–458.
7. (a) Aminoallylsilanes: Franciotti, M.; Mordini, A.; Taddei, M. *Synlett* **1992**, 137–138; (b) Aminoepoxides: Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492; (c) Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 7187–7190; (d) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653–657; (e) Branat, J.; Kvarnstrm, I.; Classon, B.; Samuelson, B.; Nilroth, U.; Danielson, H.; Karlen, A.; Halberg, A. *Tetrahedron Lett.* **1997**, *38*, 3483–3486; (f) Iodocyclocarbamates: Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079–5082; (g) Isoxazolines: Nishi, T.; Moreisawa, Y. *Heterocycles* **1989**, *29*, 1835–1842.
8. (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708; (b) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685–700.
9. (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283; (b) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, pp 2328–2336.
10. Fustero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286.
11. Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3326–3331.
12. Wang, Y.; Shafiq, Z.; Liu, L.; Wang, D.; Chen, Y.-J. *J. Heterocycl. Chem.* **2010**, *47*, 373–378.
13. Bandini, M.; Eichholzer, A.; Monari, M.; Piccinelli, F.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2007**, 2917–2920.
14. Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241.
15. Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636–5638.
16. Bluhm, U.; Boucher, J.-L.; Buss, U.; Clement, B.; Friedrich, F.; Girreser, U.; Heber, D.; Lam, T.; Lepoivre, M.; Rostaie-Gerylow, M.; Wolschendorf, U. *Eur. J. Med. Chem.* **2009**, *44*, 2877–2887.
17. Ishikawa, T.; Aikawa, T.; Watanabe, S.; Saito, S. *Org. Lett.* **2006**, *8*, 3881–3884.
18. Ma, D.; Zhu, W. *Synlett* **2006**, 1181–1184.
19. Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492–3499.
20. Albrecht, C.; Barnes, S.; Boeckemeier, H.; Davies, D.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Jones, I.; Leitmann, V.; Murphy, P. J.; Rowles, R.; Nash, R.; Stephenson, R. A.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron Lett.* **2008**, *49*, 185–188.
21. Ellis, G. L.; O'Neil, I. A.; Ramos, V. E.; Cleator, E.; Kalindjian, S. B.; Chorlton, A. P.; Tapolczay, D. J. *Tetrahedron Lett.* **2007**, *48*, 1683–1686.
22. Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 3335–3337.
23. Morino, Y.; Hidaka, I.; Oderaotoshi, Y.; Komatsu, M.; Minakata, S. *Tetrahedron* **2006**, *62*, 12247–12251.
24. Diaba, F.; Puigbo, G.; Bonjoch, J. *Eur. J. Org. Chem.* **2007**, 3038–3044.
25. Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316–8319.
26. Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4119–4122.
27. Denes, F.; Perez-Luna, A.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 398–406.
28. Li, K.; Alexakis, A. *Chem.—Eur. J.* **2007**, *13*, 3765–3771.
29. Oswald, C. L.; Peterson, J. A.; Lam, H. W. *Org. Lett.* **2009**, *11*, 4504–4507.
30. Hanzawa, Y.; Takebe, Y.; Saito, A.; Kakuuchi, A.; Fukaya, H. *Tetrahedron Lett.* **2007**, *48*, 6471–6474.
31. Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2009**, *50*, 1423–1426.
32. Kim, H.; Yoo, D.; Kwon, S.; Kim, Y. G. *Tetrahedron: Asymmetry* **2009**, *20*, 2715–2719.
33. Koketsu, M.; Kiyokuni, T.; Sakai, T.; Ando, H.; Ishihara, H. *Chem. Lett.* **2006**, *35*, 626–627.
34. Sanz, R.; Castroviejo, M. P.; Miguel, D.; Fananas, F. J. *Lett. Org. Chem.* **2006**, *3*, 470–476.
35. Groth, U.; Koettgen, P.; Langenbach, P.; Lindenmaier, A.; Schuetz, T.; Wiegand, M. *Synlett* **2008**, 1301–1304.
36. Bailey, W. F.; Salgaonkar, P. D.; Brubaker, J. D.; Sharma, V. *Org. Lett.* **2008**, *10*, 1071–1074.
37. Tsuchida, S.; Kaneshige, A.; Ogata, T.; Baba, H.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3635–3638.
38. Dewi-Wuelfing, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852–1856.
39. Cipolla, L.; Fernandes, M. R.; Gregori, M.; Airoldi, C.; Nicotra, F. *Carbohydr. Res.* **2007**, *342*, 1813–1830.
40. Timoshchuk, V. A.; Hogrefe, R. I. *Nucleosides, Nucleotides Nucleic Acids* **2009**, *28*, 464–472.
41. Eriksson, C.; Sjoedin, K.; Schlyter, F.; Hoegberg, H.-E. *Tetrahedron: Asymmetry* **2006**, *17*, 1074–1080.
42. Balazs, A.; Van der Eycken, E.; Fulop, F. *Tetrahedron Lett.* **2008**, *49*, 4333–4335.
43. Tosovska, P.; Arora, P. S. *Org. Lett.* **2010**, *12*, 1588–1591.
44. Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2009**, 3454–3466.
45. Arbour, M.; Roy, S.; Godbout, C.; Spino, C. *J. Org. Chem.* **2009**, *74*, 3806–3814.
46. Bates, R. W.; Lim, C. J. *Synlett* **2010**, 866–868.
47. Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222–3231.
48. Pedrosa, R.; Andres, C.; Mendiguchia, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 5388–5391.
49. Queffelec, C.; Ribiere, P.; Montchamp, J.-L. *J. Org. Chem.* **2008**, *73*, 8987–8991.
50. Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452–455.
51. Yoshitomi, Y.; Makino, K.; Hamada, Y. *Org. Lett.* **2007**, *13*, 2457–2460.
52. Oshitari, T.; Mandai, T. *Synlett* **2009**, 787–789.
53. Meng, X.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2008**, *14*, 6852–6856.
54. Boglio, C.; Lamas, M.-C.; Thorimbert, S.; Malacria, M. *ARKIVOC* **2008**, *vii*, 57–72.
55. Douelle, F.; Capes, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 1931–1934.
56. Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Luebbers, T.; Lam, H. W. *J. Am. Chem. Soc.* **2008**, *130*, 7328–7338.
57. Benfatti, F.; Bottoni, A.; Cardillo, G.; Gentilucci, L.; Monari, M.; Mosconi, E.; Stenta, M.; Tolomelli, A. *Eur. J. Org. Chem.* **2008**, 6119–6127.
58. Hoffman, T. J.; Dash, J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 2756–2759.
59. Lee, M. J.; Kim, C. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 439–442.
60. Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748–761.
61. (a) Montagne, C.; Prevost, N.; Shiers, J. J.; Prie, G.; Rahman, S.; Hayes, J. F.; Shipman, M. *Tetrahedron* **2006**, *62*, 8447–8457; (b) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762–9764; (c) Mumford, P. M.; Shiers, J. J.; Tarver, G. J.; Hayes, J. F.; Shipman, M. *Tetrahedron Lett.* **2008**, *49*, 3489–3491.
62. (a) Van Brabandt, W. G.; De Smaele, D.; Duvey, G.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7100–7102; (b) Van Hende, E.; Verniest, G.; Deroose, F.; Thuring, J.-W.; Macdonald, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 2250–2253.
63. Mangelinckx, S.; Zukauskaite, A.; Buinauskaite, V.; Sackus, A.; De Kimpe, N. *Tetrahedron Lett.* **2008**, *49*, 6896–6900.
64. Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498–501.
65. Reddy, J. S.; Rao, B. V. *J. Org. Chem.* **2007**, *72*, 2224–2227.
66. Takahashi, M.; Maehara, T.; Sengoku, T.; Fujita, N.; Takabe, K.; Yoda, H. *Tetrahedron* **2008**, *64*, 5254–5261.
67. Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*, 4101–4104.
68. Rassadin, V. A.; Tomashevskiy, A. A.; Sokolov, V. V.; Ringe, A.; Magull, J.; de Meijere, A. *Eur. J. Org. Chem.* **2009**, 2635–2641.
69. (a) Tiwari, S. K.; Gais, H.-J.; Schneider, A. L.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Koehler, F.; Guenter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, *128*, 7360–7373; (b) Duguet, N.; Petit, S. M.; Marchand, P.; Harrison-Marchand, A.; Maddaluno, J. *J. Org. Chem.* **2008**, *73*, 5397–5409; (c) Rajesh, T.; Azeez, S. A.; Naresh, E.; Madhusudhan, G.; Mukkanti, K. *Org. Process Res. Dev.* **2009**, *13*, 638–640.
70. Viso, A.; Fernandez de la Pradilla, R.; Urena, M.; Colomer, I. *Org. Lett.* **2008**, *10*, 4775–4778.
71. Krchnak, V.; Waring, K. R.; Noll, B. C.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 4559–4567.
72. Monbaliu, J.-C.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2008**, *49*, 1839–1842.
73. Diez, D.; Anton, A. B.; Garcia, P.; Nunez, M. G.; Garrido, N. M.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2006**, *17*, 2260–2264.
74. Yin, C.; Hui, X.-P.; Xu, P.-F.; Niu, L.-F.; Chen, Y.-F.; Wang, B. *Adv. Synth. Catal.* **2009**, *351*, 357–362.
75. Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M. *Eur. J. Org. Chem.* **2007**, 3676–3686.
76. Krishna, P. R.; Dayaker, G. *Tetrahedron Lett.* **2007**, *48*, 7279–7282.
77. Gupta, P.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 1925–1933.
78. Winkler, J. D.; Londregan, A. T.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 2591–2594.
79. Shibata, T.; Buurma, N. J.; Brazier, J. A.; Thompson, P.; Haq, I.; Williams, D. M. *Chem. Commun.* **2006**, 3516–3518.
80. Lee, S. J.; Beak, P. *J. Am. Chem. Soc.* **2006**, *128*, 2178–2179.
81. Tanaka, T.; Muto, T.; Maruoka, H.; Imajo, S.; Fukami, H.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3431–3434.
82. Vital, P.; Hosseini, M.; Shanmugham, M. S.; Gotfredsen, C. H.; Harris, P.; Tanner, D. *Chem. Commun.* **2009**, 1888–1890.
83. Gonzalez, I.; Roglans, A.; Benet-Buchholz, J.; Roura, P. *Synlett* **2006**, 3041–3044.
84. Blaszykowski, C.; Brancour, C.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2009**, 1674–1678.
85. Fang, X.; Assoud, J. *Organometallics* **2008**, *27*, 2408–2410.
86. Drouillat, B.; Couty, F.; Marrot, J. *Synlett* **2009**, 767–770.
87. Van Speybroeck, V.; Moonen, K.; Hemelsoet, K.; Stevens, C. V.; Waroquier, M. *J. Am. Chem. Soc.* **2006**, *128*, 8468–8478.
88. Vanlaer, S.; Voet, A.; Gielens, C.; De Maeyer, M.; Compernolle, F. *Eur. J. Org. Chem.* **2009**, 643–654.

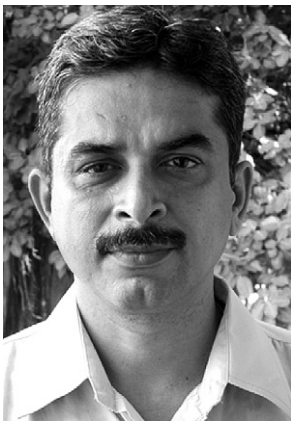
89. Yao, W.; Zhuo, J.; Burns, D. M.; Xu, M.; Zhang, C.; Li, Y.-L.; Qian, D.-Q.; He, C.; Weng, L.; Shi, E.; Lin, Q.; Agrios, C.; Burn, T. C.; Caulder, E.; Covington, M. B.; Fridman, J. S.; Friedman, S.; Katiyar, K.; Hollis, G.; Li, Y.; Liu, C.; Liu, X.; Marando, C. A.; Newton, R.; Pan, M.; Scherle, P.; Taylor, N.; Vaddi, K.; Wasserman, Z. R.; Wynn, R.; Yeleswaram, S.; Jalluri, R.; Bower, M.; Zhou, B.-B.; Metcalf, B. *J. Med. Chem.* **2007**, *50*, 603–606.
90. Zhuo, J.; Burns, D. M.; Zhang, C.; Xu, M.; Weng, L.; Qian, D.-Q.; He, C.; Lin, Q.; Li, Y.-L.; Shi, E.; Agrios, C.; Metcalf, B.; Yao, W. *Synlett* **2007**, 460–464.
91. Hayes, C. J.; Sherlock, A. E.; Selby, M. D. *Org. Biomol. Chem.* **2006**, *4*, 193–195.
92. Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008**, *73*, 2041–2051.
93. Spaggiari, A.; Vaccari, D.; Davoli, P.; Prati, F. *Synthesis* **2006**, 995–998.
94. Wang, B.; Zhong, Z.; Lin, G.-Q. *Org. Lett.* **2009**, *11*, 2011–2014.
95. Braddock, D. C.; Bhuva, R.; Perez-Fuertes, Y.; Pouwer, R.; Roberts, C. A.; Ruggiero, A.; Stokes, E. S. E.; White, A. J. P. *Chem. Commun.* **2008**, 1419–1421.
96. Zhang, W.; Xu, H.; Xu, H.; Tang, W. *J. Am. Chem. Soc.* **2009**, *131*, 3832–3833.
97. Evans, P.; Lee, A. T. L.; Thomas, E. J. *Org. Biomol. Chem.* **2008**, *6*, 2158–2167.
98. Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754.
99. Kita, Y.; Toma, T.; Kan, T.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 3251–3253.
100. Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963–965.
101. Davis, F. A.; Qiu, H.; Song, M.; Gaddiraju, N. V. *J. Org. Chem.* **2009**, *74*, 2798–2803.
102. Benfatti, F.; Cardillo, G.; Gentilucci, L.; Mosconi, E.; Tolomelli, A. *Org. Lett.* **2008**, *10*, 2425–2428.
103. Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.—Eur. J.* **2006**, *12*, 524–536.
104. Coutrot, P.; Claudel, S.; Didierjean, C.; Grison, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 417–420.
105. Mo, F.; Li, F.; Qiu, D.; Wang, J. *Tetrahedron* **2010**, *66*, 1274–1279.
106. Kumar, K. S. A.; Chaudhari, V. D.; Puranik, V. G.; Dhavale, D. D. *Eur. J. Org. Chem.* **2007**, 4895–4901.
107. Sperry, J.; Harris, E. B. J.; Brimble, M. A. *Org. Lett.* **2010**, *12*, 420–423.
108. Jeon, J.; Lee, J. H.; Kim, J.-W.; Kim, Y. G. *Tetrahedron: Asymmetry* **2007**, *18*, 2448–2453.
109. Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001–1004.
110. Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Rodriguez-Solla, H.; Smith, A. D. *Chem. Commun.* **2006**, 2664–2666.
111. Dejaegher, Y.; D'Hooghe, M.; De Kimpe, N. *Synlett* **2008**, 1961–1964.
112. Elsner, P.; Bernardi, L.; Dela Salla, G.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897–4905.
113. Beylin, V.; Boyles, D. C.; Curran, T. T.; Macikenas, D.; Parlett, R. V., IV; Vrieze, D. *Org. Process Res. Dev.* **2007**, *11*, 441–449.
114. Zhou, J.; Magomedov, N. A. *J. Org. Chem.* **2007**, *72*, 3808–3815.
115. Mukaiyama, T.; Maruyama, Y.; Kitazawa, T. *Heterocycles* **2008**, *76*, 221–225.
116. Pathak, R.; Madapa, S.; Batra, S. *Tetrahedron* **2007**, *63*, 451–460.
117. Benakki, H.; Colacino, E.; Andre, C.; Guenoun, F.; Martinez, J.; Lamaty, F. *Tetrahedron* **2008**, *64*, 5949–5955.
118. Breuning, M.; Hein, D. *Tetrahedron: Asymmetry* **2007**, *18*, 1410–1418.
119. Maruoka, H.; Muto, T.; Tanaka, T.; Imajo, S.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3435–3439.
120. Sakai, T.; Yamada, K.-i.; Tomioka, K. *Chem.—Asian J.* **2008**, *3*, 1486–1493.
121. Baillargeon, P.; Bernard, S.; Gauthier, D.; Skouta, R.; Dory, Y. L. *Chem.—Eur. J.* **2007**, *13*, 9223–9235.
122. Bowers, A. A.; Greshock, T. J.; West, N.; Estiu, G.; Schreiber, S. L.; Wiest, O.; Williams, R. M.; Bradner, J. E. *J. Am. Chem. Soc.* **2009**, *131*, 2900–2905.
123. Gilles, A.; Martinez, J.; Cavelier, F. *J. Org. Chem.* **2009**, *74*, 4298–4304.
124. Nakamura, T.; Tsuji, T.; Iio, Y.; Miyazaki, S.; Takemoto, T.; Nishi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 2781–2792.
125. Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 7094–7098.
126. (a) Raschmanova, J.; Martinkova, M.; Gonda, J. *Proc. Int. Electronic Conf. Synthetic Org. Chem.* **2007**, 1–30; (b) Martinkova, M.; Gonda, J.; Raschmanova, J.; Uhrikova, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1879–1885.
127. Ichikawa, Y.; Matsunaga, K.; Masuda, T.; Kotsuki, H.; Nakano, K. *Tetrahedron* **2008**, *64*, 11313–11318.
128. Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528–531.
129. Kim, H.; Yoo, D.; Choi, S. Y.; Chung, Y. K.; Kim, Y. G. *Tetrahedron: Asymmetry* **2008**, *19*, 1965–1969.
130. Wrobel, Z.; Bobin, M.; Karczewski, R. *Pol. J. Chem.* **2006**, *80*, 907–912.
131. Wipf, P.; Pierce, J. G. *Org. Lett.* **2006**, *8*, 3375–3378.
132. Evans, L. A.; Adams, H.; Barber, C. G.; Caggiano, L.; Jackson, R. F. W. *Org. Biomol. Chem.* **2007**, *5*, 3156–3163.
133. Seo, W. D.; Curtis-Long, M. J.; Jeong, S. H.; Jun, T. H.; Yang, M. S.; Park, K. H. *Synthesis* **2007**, 209–214.
134. Daniels, R. N.; Melancon, B. J.; Wang, E. A.; Crews, B. C.; Marnett, L. J.; Sulikowski, G. A.; Lindsley, C. W. *J. Org. Chem.* **2009**, *74*, 8852–8855.
135. (a) Fernandez, I.; Munoz, L. *Tetrahedron: Asymmetry* **2006**, *17*, 2548–2557; (b) Garcia-Egido, E.; Fernandez, I.; Munoz, L. *Synth. Commun.* **2006**, *36*, 3029–3042.
136. Yoshida, M.; Ohsawa, Y.; Sugimoto, K.; Tokuyama, H.; Ihara, M. *Tetrahedron Lett.* **2007**, *48*, 8678–8682.
137. Vargas, G. E.; Afonso, M. M.; Palenzuela, J. A. *Synlett* **2009**, 1471–1473.
138. Chandrasekhar, S.; Tiwari, B. *Tetrahedron: Asymmetry* **2009**, *20*, 1924–1929.
139. Au, C. W. G.; Nash, R. J.; Pyne, S. G. *Chem. Commun.* **2010**, 713–715.
140. Cui, Y.; Jiao, Z.; Gong, J.; Yu, Q.; Zheng, X.; Quan, J.; Luo, M.; Yang, Z. *Org. Lett.* **2010**, *12*, 4–7.
141. Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311–1314.
142. Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2009**, *15*, 2742–2746.
143. Angeli, M.; Bandini, M.; Garelli, A.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Org. Biomol. Chem.* **2006**, *4*, 3291–3296.
144. Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425.
145. Liu, C.; Widenhoefer, R. A. *Chem.—Eur. J.* **2006**, *12*, 2371–2382.
146. Sakami, S.; Kawai, K.; Maeda, M.; Aoki, T.; Fujii, H.; Ohno, H.; Ito, T.; Saitoh, A.; Nakao, K.; Izumimoto, N.; Matsuura, H.; Endo, T.; Ueno, S.; Natsume, K.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 7956–7967.
147. Uddin, Md. J.; Marnett, L. J. *Org. Lett.* **2008**, *10*, 4799–4801.
148. Lim, H. J.; RajanBabu, T. V. *Org. Lett.* **2009**, *11*, 2924–2927.
149. Liu, F.; Martin-Mingot, A.; Jouannetaud, M.-P.; Zunino, F.; Thibaudeau, S. *Org. Lett.* **2010**, *12*, 868–871.
150. Beccalli, E. M.; Borsini, E.; Broggini, G.; Rigamonti, M.; Sottocornola, S. *Synlett* **2008**, 1053–1057.
151. Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490–491.
152. Nag, S.; Madapa, S.; Batra, S. *Synthesis* **2008**, 101–109.
153. Yepez, A. F.; Palma, A.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. M. *Tetrahedron Lett.* **2006**, *47*, 5825–5828.
154. Palma, A.; Galeano, N.; Bahsas, A. *Synthesis* **2010**, 1291–1302.
155. Rabasso, N.; Fadel, A. *Tetrahedron Lett.* **2010**, *51*, 60–63.
156. Huck, B. R.; Llamas, L.; Robarge, M. J.; Dent, T. C.; Song, J.; Hodnick, W. F.; Crumrine, C.; Stricker-Krongrad, A.; Harrington, J.; Brunden, K. R.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2891–2894.
157. (a) Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2008**, *64*, 6461–6474; (b) Poornachandran, M.; Raghunathan, R. *Tetrahedron: Asymmetry* **2008**, *19*, 2177–2183; (c) Poornachandran, M.; Raghunathan, R. *Synth. Commun.* **2009**, *39*, 917–926; (d) Narayanan, N. V.; Gayathri, D.; Velmurugan, D.; Ravikumar, K.; Poornachandran, M. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o2213–o2215; (e) Nirmala, S.; Palani, K.; Sudha, L.; Poornachandran, M.; Raghunathan, R. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o2254–o2255; (f) Kamala, E. T. S.; Palani, K.; Sudha, L.; Poornachandran, M.; Raghunathan, R. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o2256–o2257; (g) Sundaramoorthy, S.; Gayathri, D.; Velmurugan, D.; Ravikumar, K.; Poornachandran, M. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o2057–o2059; (h) Vennila, K. N.; Gayathri, D.; Velmurugan, D.; Ravikumar, K.; Poornachandran, M. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o2228–o2229.
158. Neuschl, M.; Bogdal, D.; Potacek, M. *Molecules* **2007**, *12*, 49–59.
159. Pospisil, J.; Potacek, M. *Tetrahedron* **2007**, *63*, 337–346.
160. Kim, E.; Koh, M.; Ryu, J.; Park, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 12206–12207.
161. Ji, J.; Schrimpf, M. R.; Sippy, K. B.; Bunnelle, W. H.; Li, T.; Anderson, D. J.; Faltynek, C.; Surowy, C. S.; Dyhring, T.; Ahring, P. K.; Meyer, M. D. *J. Med. Chem.* **2007**, *50*, 5493–5508.
162. Noguchi, M.; Tsukimoto, A.; Kadowaki, A.; Hikata, J.; Kakehi, A. *Tetrahedron Lett.* **2007**, *48*, 3539–3542.
163. Kadowaki, A.; Nagata, Y.; Uno, H.; Kamimura, A. *Tetrahedron Lett.* **2007**, *48*, 1823–1825.
164. Conti, P.; De Amici, M.; Roda, G.; Pinto, A.; Tamborini, L.; Madsen, U.; Nielsen, B.; Braeuner-Osborne, H.; De Micheli, C. *Tetrahedron* **2007**, *63*, 2249–2256.
165. Singh, G.; Ishar, M. P. S.; Gupta, V.; Singh, G.; Kalyan, M.; Bhella, S. S. *Tetrahedron* **2007**, *63*, 4773–4778.
166. Ellis, G. L.; O'Neil, I. A.; Ramos, V. E.; Kalindjian, S. B.; Chorlton, A. P.; Tapolczay, D. J. *Tetrahedron Lett.* **2007**, *48*, 1687–1690.
167. (a) Gomez Ayala, S. L.; Stashenko, E.; Palma, A.; Bahsas, A.; Amaro-Luis, J. M. *Synlett* **2006**, 2275–2277; (b) Palma, A.; Yepes, A. F.; Leal, S. M.; Coronado, C. A.; Escobar, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2360–2363.
168. Crimmins, D.; Dimitrov, I.; O'Connor, P. D.; Caprio, V.; Brimble, M. A. *Synthesis* **2008**, 3319–3325.
169. Dumez, E.; Durand, A.-C.; Guillaume, M.; Roger, P.-Y.; Faure, R.; Pons, J.-M.; Herbette, G.; Dulcere, J.-P.; Bonne, D.; Rodriguez, J. *Chem.—Eur. J.* **2009**, *15*, 12470–12488.
170. De Benassuti, L.; Del Buttero, P.; Molteni, G. *Tetrahedron: Asymmetry* **2006**, *17*, 842–845.
171. Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2006**, 1831–1832.
172. Declerck, V.; Toupet, L.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2009**, *74*, 2004–2007.
173. Mishra, A.; Hutait, S.; Bhowmik, S.; Rastogi, N.; Roy, R.; Batra, S. *Synthesis* **2010**, 2731–2748.
174. Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. K.; Grygorenko, O. O.; Komarov, I. V. *Org. Lett.* **2009**, *11*, 5674–5676.
175. Bouwkamp, M. W.; Bowman, A. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13340–13341.
176. Malik, C. K.; Vaultier, M.; Ghosh, S. *Synthesis* **2007**, 1247–1250.
177. Sakamoto, M.; Kato, M.; Oda, E.; Kobaru, S.; Mino, T.; Fujita, T. *Tetrahedron* **2006**, *62*, 3028–3032.
178. Luzung, M. R.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403.
179. Teller, H.; Fluegge, S.; Goddard, R.; Fuerstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1949–1953.
180. Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378–4389.

181. Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299–1302.
182. Ragains, J. R.; Winkler, J. D. *Org. Lett.* **2006**, *8*, 4437–4440.
183. Winkler, J. D.; Fitzgerald, M. E. *Synlett* **2009**, 562–564.
184. Gulias, M.; Garcia, R.; Delgado, A.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 384–385.
185. Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178–7179.
186. Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, 1059–1061.
187. Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951–5954.
188. Lee, H.-Y.; Yoon, Y.; Lim, Y.-H.; Lee, Y. *Tetrahedron Lett.* **2008**, *49*, 5693–5696.
189. Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043.
190. Xie, Y.-X.; Yan, Z.-Y.; Qian, B.; Deng, W.-Y.; Wang, D.-Z.; Wu, L.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2009**, 5451–5453.
191. Mauleon, P.; Zeldin, R. M.; Gonzalez, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349.
192. Roth, S.; Stark, C. B. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6218–6221.
193. Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469.
194. Poeverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819–821.
195. Tayama, E.; Sugai, S. *Tetrahedron Lett.* **2007**, *48*, 6163–6166.
196. Arimitsu, S.; Fernandez, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656–2661.
197. (a) Bromley, W. J.; Gibson, M.; Lang, S.; Raw, S. A.; Whitwood, A. C.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 6004–6014; (b) Murrison, S.; Glowacki, D.; Einzinger, C.; Titchmarsh, J.; Bartlett, S.; McKeever-Abbas, B.; Warriner, S.; Nelson, A. *Chem.—Eur. J.* **2009**, *15*, 2185–2189.
198. Pearson, A. J.; Sun, H.; Wang, X. *J. Org. Chem.* **2007**, *72*, 2547–2557.
199. Noguchi, M.; Sunagawa, T.; Akao, R.; Yamada, H.; Yamamoto, H.; Kakehi, A. *Tetrahedron* **2007**, *63*, 4548–4557.
200. Singh, V.; Sahu, B. C.; Mobin, S. M. *Synlett* **2008**, 1222–1224.
201. Steinhardt, S. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7546–7547.
202. Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4269–4272.
203. Chukhajian, E. O.; Nalbandyan, M. K.; Gevorkyan, A. R.; Shakhatuni, K. G.; Panosyan, G. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 671–676.
204. Chukhajian, E. O.; Khachatryan, A. A.; Gevorkyan, A. R.; Panosyan, H. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 426–429.
205. Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Am. Chem. Soc.* **2010**, *132*, 4522–4523.
206. (a) Gonzalez, A. Z.; Toste, F. D. *Org. Lett.* **2010**, *12*, 200–203; (b) Alonso, I.; Trillo, B.; Lopez, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledos, A.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030.
207. (a) Rogachev, V. O.; Metz, P. *ARKIVOC* **2007**, *v*, 167–190; (b) Rogachev, V. O.; Filimonov, V. D.; Froehlich, R.; Kataeva, O.; Metz, P. *Heterocycles* **2006**, *67*, 589–595; (c) Rogachev, V. O.; Metz, P. *Nat. Protoc.* **2006**, *1*, 3076–3087.
208. Kelleher, S.; Muldoon, J.; Mueller-Bunz, H.; Evans, P. *Tetrahedron Lett.* **2007**, *48*, 4733–4736.
209. (a) Dadwal, M.; Kesharwani, M. K.; Danayak, V.; Ganguly, B.; Mobin, S. M.; Muruganantham, R.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2008**, 6106–6118; (b) Claeys, D. D.; Moonen, K.; Roman, B. I.; Nemykin, V. N.; Zhdankin, V. V.; Waroquier, M.; Van Speybroeck, V.; Stevens, C. V. *J. Org. Chem.* **2008**, *73*, 7921–7927; (c) Demircan, A.; Karaarslan, M.; Turac, E. *Heterocycl. Commun.* **2006**, *12*, 233–240.
210. Arai, N.; Tanaka, K.; Ohkuma, T. *Tetrahedron Lett.* **2010**, *51*, 1273–1275.
211. Brodney, M. A.; Cole, M. L.; Freemont, J. A.; Kyi, S.; Junk, P. C.; Padwa, A.; Riches, A. G.; Ryan, J. H. *Tetrahedron Lett.* **2007**, *48*, 1939–1943.
212. Dilman, A. D.; Gorokhov, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2006**, *47*, 6217–6219.
213. Brubaker, J. D.; Myers, A. G. *Org. Lett.* **2007**, *9*, 3523–3525.
214. Park, K. H.; Choi, S. Y.; Kim, S. Y.; Chung, Y. K. *Synlett* **2006**, 527–532.
215. Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71*, 91–96.
216. (a) Fuerstner, A.; Stimson, C. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8845–8849; (b) Fuerstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.
217. Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277–7280.
218. Walker, S. M.; Williams, J. T.; Russell, A. G.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem.* **2007**, *5*, 2925–2931.
219. (a) Chinnakali, K.; Sudha, D.; Jayagopi, M.; Raghunathan, R.; Fun, H. K. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2007**, *E63*, o4650–o4651; (b) Chinnakali, K.; Sudha, D.; Jayagobi, M.; Raghunathan, R.; Fun, H. K. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2009**, *E65*, o2943–o2944.
220. Jayagobi, M.; Raghunathan, R. *Tetrahedron Lett.* **2009**, *50*, 6886–6890.
221. Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338–7346.
222. Baruah, B.; Bhuyan, P. J. *Tetrahedron* **2009**, *65*, 7099–7104.
223. Sabitha, G.; Maruthi, C.; Reddy, E. V.; Srinivas, C.; Yadav, J. S.; Dutta, S. K.; Kunwar, A. C. *Helv. Chim. Acta* **2006**, *89*, 2728–2731.
224. (a) Jayagobi, M.; Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2009**, *50*, 648–650; (b) Chinnakali, K.; Sudha, D.; Jayagobi, M.; Raghunathan, R.; Fun, H. K. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2009**, *E65*, o2924–o2925; (c) Chinnakali, K.; Sudha, D.; Jayagobi, M.; Raghunathan, R.; Fun, H. K. *Acta Crystallogr. Sect. E Struct. Rep. Online* **2009**, *E65*, o2956–o2957.
225. Saito, A.; Hironaga, M.; Oda, S.; Hanzawa, Y. *Tetrahedron Lett.* **2007**, *48*, 6852–6855.
226. Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222–9223.
227. Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2009**, *11*, 5706–5709.
228. Gulias, M.; Duran, J.; Lopez, F.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 11026–11027.
229. Trillo, B.; Lopez, F.; Gulias, M.; Castedo, L.; Mascarenas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951–954.
230. Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302–6303.
231. Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217–1220.
232. Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2459–2462.
233. Shibata, T.; Tahara, Y.-k. *J. Am. Chem. Soc.* **2006**, *128*, 11766–11767.
234. Evans, P. A.; Sawyer, J. R.; Inglesby, P. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 5746–5749.
235. Tanaka, K.; Otake, Y.; Sagae, H.; Noguchi, K.; Hirano, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1312–1316.
236. Geny, A.; Gaudrel, S.; Slowinski, F.; Amatore, M.; Chouraqui, G.; Malacria, M.; Aubert, C.; Gandon, V. *Adv. Synth. Catal.* **2009**, *351*, 271–275.
237. Adriaenssens, L.; Severa, L.; Vavra, J.; Salova, T.; Hyvl, J.; Cizkova, M.; Pohl, R.; Saman, D.; Teply, F. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1023–1034.
238. Bhargava, G.; Trillo, B.; Araya, M.; Lopez, F.; Castedo, L.; Mascarenas, J. L. *Chem. Commun.* **2010**, 270–272.
239. Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609–2614.
240. Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354–5355.
241. DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799–804.
242. Ashida, S.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 885–893.
243. Bauer, R. A.; DiBlasi, C. M.; Tan, D. S. *Org. Lett.* **2010**, *12*, 2084–2087.
244. (a) Satio, S.; Maeda, K.; Yamasaki, R.; Kitamura, T.; Nakagawa, M.; Kato, K.; Azumaya, I.; Masu, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 1830–1833; (b) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060–10061.
245. Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421–4430.
246. Lin, H.; Chen, Q.; Cao, L.; Yang, L.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2006**, *71*, 3328–3331.
247. Guthrie, D. B.; Curran, D. P. *Org. Lett.* **2009**, *11*, 249–251.
248. (a) Tichenor, M. S.; Trzupek, J. D.; Kastrinsky, D. B.; Shiga, F.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 15683–15696; (b) Tichenor, M. S.; MacMillan, K. S.; Stover, J. S.; Wolkenberg, S. E.; Pavani, M. G.; Zanella, L.; Zaid, A. N.; Spalluto, G.; Rayl, T. J.; Hwang, I.; Baraldi, P. G.; Boger, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 14092–14099; (c) Jin, W.; Trzupek, J. D.; Rayl, T. J.; Broward, M. A.; Vielhauer, G. A.; Weir, S. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 15391–15397; (d) Tietze, L. F.; Panknin, O.; Major, F.; Krewer, B. *Chem.—Eur. J.* **2008**, *14*, 2811–2818; (e) Tietze, L. F.; von Hof, J. M.; Krewer, B.; Mueller, M.; Major, F.; Schuster, H. J.; Schuberth, I.; Alves, F. *ChemMedChem* **2008**, *3*, 1946–1955; (f) Gauss, C. M.; Hamasaki, A.; Parrish, J. P.; MacMillan, K. S.; Rayl, T. J.; Hwang, I.; Boger, D. L. *Tetrahedron* **2009**, *65*, 6591–6599.
249. MacMillan, K. S.; Lajiness, J. P.; Cara, C. L.; Romagnoli, R.; Robertson, W. M.; Hwang, I.; Baraldi, P. G.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6962–6965.
250. (a) MacMillan, K. S.; Nguyen, T.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 1187–1194; (b) Choi, T.; Ma, E. *Bull. Kim. Chem. Soc.* **2009**, *30*, 2815–2818.
251. Milbank, J. B. J.; Stevenson, R. J.; Ware, D. C.; Chang, J. Y. C.; Tercel, M.; Ahn, G.-O.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **2009**, *52*, 6822–6834.
252. Tercel, M.; Atwell, G. J.; Yang, S.; Stevenson, R. J.; Botting, K. J.; Boyd, M.; Smith, E.; Anderson, R. F.; Denny, W. A.; Wilson, W. R.; Pruijn, F. B. *J. Med. Chem.* **2009**, *52*, 7258–7272.
253. Murphy, J. A.; Schoenebeck, F.; Findlay, N. J.; Thomson, D. W.; Zhou, S.-z.; Garnier, J. *J. Am. Chem. Soc.* **2009**, *131*, 6475–6479.
254. Hirashita, T.; Hayashi, A.; Tsuji, M.; Tanaka, J.; Araki, S. *Tetrahedron* **2008**, *64*, 2642–2650.
255. Gowrisankar, S.; Kim, S. J.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4419–4422.
256. Lee, H. S.; Kim, E. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2274–2277.
257. (a) Rodriguez-Soria, V.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron* **2008**, *64*, 2750–2754; (b) Rodriguez, V.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2007**, *48*, 4305–4308.
258. Hayashi, R.; Cook, G. R. *Tetrahedron Lett.* **2008**, *49*, 3888–3890.
259. Lee, H. S.; Kim, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2008**, *64*, 2397–2404.
260. Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacote, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381–4387.
261. Khan, F. A.; Upadhyay, S. K. *Tetrahedron Lett.* **2008**, *49*, 6111–6114.
262. Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, 4985–4987.
263. Leemans, E.; D'hooghe, M.; Dejaegher, Y.; Toernroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 1422–1428.
264. Nair, V.; Mohanan, K.; Suja, T. D.; Suresh, E. *Tetrahedron Lett.* **2006**, *47*, 705–709.
265. Majumdar, K. C.; Mondal, S. *Tetrahedron* **2009**, *65*, 9604–9608.
266. Asahi, K.; Nishino, H. *Synthesis* **2009**, 409–423.
267. Fang, X.; Liu, K.; Li, C. *J. Am. Chem. Soc.* **2010**, *132*, 2274–2283.
268. Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 3192–3197.
269. Taniguchi, T.; Fujii, T.; Idota, A.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3298–3301.
270. Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489–2492.
271. El Kaiem, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259–8261.
272. Vila, X.; Zard, S. Z. *Heterocycles* **2006**, *70*, 45–50.

273. (a) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278–290; (b) Bagal, S. K.; Tournier, L.; Zard, S. Z. *Synlett* **2006**, 1485–1490; (c) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279–3282; (d) Gagosz, F.; Zard, S. Z. *Org. Synth.* **2007**, *84*, 32–42.
274. El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, 4422–4424.
275. Srivastava, P.; Engman, L. *Tetrahedron Lett.* **2010**, *51*, 1149–1151.
276. Yang, D.; Lian, G.-Y.; Yang, H.-F.; Yu, J.-D.; Zhang, D.-W.; Gao, X. *J. Org. Chem.* **2009**, *74*, 8610–8615.
277. Bennasar, M.-L.; Roca, T.; Garcia-Diaz, D. *J. Org. Chem.* **2007**, *72*, 4562–4565.
278. Bennasar, M.-L.; Zulaica, E.; Sole, D.; Roca, T.; Garcia-Diaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359–8368.
279. Kamimura, A.; Kadowaki, A.; Nagata, Y.; Uno, H. *Tetrahedron Lett.* **2006**, *47*, 2471–2473.
280. Crich, D.; Shirai, M.; Brebion, F.; Rumthao, S. *Tetrahedron* **2006**, *62*, 6501–6518.
281. Gowrisankar, S.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 5785–5788.
282. Palframan, M. J.; Tchabanenko, K.; Robertson, J. *Tetrahedron Lett.* **2006**, *47*, 8423–8425.
283. Robertson, J.; Palframan, M. J.; Shea, S. A.; Tchabanenko, K.; Unsworth, W. P.; Winters, C. *Tetrahedron* **2008**, *64*, 11896–11907.
284. Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007**, *63*, 7187–7212.
285. Dieltiens, N.; Stevens, C. V. *Org. Lett.* **2007**, *9*, 465–468.
286. (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11; (b) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519–564; (c) Martin, P.; Steiner, E.; Bellus, D. *Helv. Chim. Acta* **1980**, *63*, 1947–1957; (d) Nagashima, H.; Gondo, M.; Masuda, S.; Kondo, H.; Yamaguchi, Y.; Matsubara, K. *J. Chem. Soc., Chem. Commun.* **2003**, 442–443.
287. (a) Motoyama, Y.; Hanada, S.; Shimamoto, K.; Nagashima, H. *Tetrahedron* **2006**, *62*, 2779–2788; (b) Dutta, B.; Scopelliti, R.; Severin, K. *Organometallics* **2008**, *27*, 423–429; (c) Wolf, J.; Thommes, K.; Briel, O.; Scopelliti, R.; Severin, K. *Organometallics* **2008**, *27*, 4464–4474; (d) Thommes, K.; Icli, B.; Scopeliti, R.; Severin, R. *Chem.—Eur. J.* **2007**, *13*, 6899–6907; (e) Lee, G. M.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1988**, *44*, 4671–4678.
288. (a) Clark, A. J.; Geden, J. V.; Thom, S. *J. Org. Chem.* **2006**, *71*, 1471–1479; (b) Bellesia, F.; Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parsons, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746–757; (c) Bull, J. A.; Hutchings, M. G.; Lujan, C.; Quayle, P. *Tetrahedron Lett.* **2008**, *49*, 1352–1356; (d) Ghelfi, F.; Pattarozzi, M.; Roncaglia, F.; Parsons, A. F.; Felluga, F.; Pagnoni, U. M.; Valentin, E.; Mucci, A.; Bellesia, F. *Synthesis* **2008**, 3131–3141; (e) Clark, A. J.; Wilson, P. *Tetrahedron Lett.* **2008**, *49*, 4848–4850; (f) Motoyama, Y.; Kamo, K.; Yuasa, A.; Nagashima, H. *Chem. Commun.* **2010**, 2256–2258; (g) Pattarozzi, M.; Roncaglia, F.; Giangiordano, V.; Davoli, P.; Prati, F.; Ghelfi, F. *Synthesis* **2010**, 694–700.
289. Edlin, C. D.; Faulkner, J.; Quayle, P. *Tetrahedron Lett.* **2006**, *47*, 1145–1151.
290. Clark, A. J.; Geden, J. V.; Thom, S.; Wilson, P. *J. Org. Chem.* **2007**, *72*, 5923–5926.
291. Roncaglia, F.; Stevens, C. V.; Ghelfi, F.; Van der Steen, M.; Pattarozzi, M.; De Buyck, L. *Tetrahedron* **2009**, *65*, 1481–1487.
292. Lian, G.-Y.; Yu, J.-D.; Yang, H.-F.; Lin, F.; Gao, Q.; Zhang, D.-W. *Chem. Lett.* **2007**, *36*, 408–409.
293. Ishibashi, H.; Haruki, S.; Uchiyama, M.; Tamura, O.; Matsuo, J.-i. *Tetrahedron Lett.* **2006**, *47*, 6263–6266.
294. Clark, A. J.; Coles, S. R.; Collis, A.; Fullaway, D. R.; Murphy, N. P.; Wilson, P. *Tetrahedron Lett.* **2009**, *50*, 6311–6314.
295. Taniguchi, T.; Sasaki, M.; Ishibashi, H. *Heterocycles* **2010**, *80*, 657–662.
296. (a) Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2008**, *129*, 974–977; (b) Ricardo, C.; Pintauer, T. *Chem. Commun.* **2009**, 3029–3031; (c) Mantrand, N.; Renaud, P. *Tetrahedron* **2008**, *64*, 11860–11864; (d) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Eur. J. Org. Chem.* **2006**, 1547–1554; (e) Pignard, S.; Lopin, C.; Gouhier, G.; Piettre, S. R. *J. Org. Chem.* **2006**, *71*, 31–37; (f) Bagal, S. K.; de Greef, M.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 147–150.
297. Denes, F.; Cutri, S.; Perez-Luna, A.; Chemla, F. *Chem.—Eur. J.* **2006**, *12*, 6506–6513.
298. Miyabe, H.; Asada, R.; Toyoda, A.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 5863–5866.
299. Garrigues, B.; Oussaid, A.; Mazieres, S. *J. Nature* **2006**, *18*, 3–11.
300. Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164–3170.
301. Fujiwara, S.-i.; Shimizu, Y.; Makita, Y.; Shin-ike, T.; Kambe, N. *Heterocycles* **2008**, *76*, 1577–1584.
302. Nair, V.; Mohanan, K.; Suja, T. D.; Suresh, E. *Tetrahedron Lett.* **2006**, *47*, 2803–2806.
303. Parsons, A. F.; Wright, A. *Synlett* **2008**, 2142–2146.
304. Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667–4670.
305. Singh, S.; Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 8270–8273.
306. Taniguchi, T.; Goto, N.; Nishibata, A.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 112–115.
307. Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 124–126.
308. Jahn, U.; Kafka, F.; Pohl, R.; Jones, P. G. *Tetrahedron* **2009**, *65*, 10917–10929.
309. Campana, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Oltra, J. E.; Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7515–7519.
310. Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383–4386.
311. Xu, L.; Huang, X. *Tetrahedron Lett.* **2008**, *49*, 500–503.
312. Estevez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; Garcia-Ruiz, J. M.; Robles, R.; Gansauer, A.; Cuerva, J. M.; Oltra, J. E. *Chem.—Eur. J.* **2009**, *15*, 2774–2791.
313. Banwell, M. G.; Lupton, D. W. *Heterocycles* **2006**, *68*, 71–92.
314. Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831–834.
315. Callier-Dublanchet, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803–4816.
316. (a) Miyata, O.; Shirai, A.; Yoshino, S.; Nakabayashi, T.; Takeda, Y.; Kiguchi, T.; Fukumoto, D.; Ueda, M.; Naito, T. *Tetrahedron* **2007**, *63*, 10092–10117; (b) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464–4475.
317. Snider, B. B. In *Comp. Org. Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 527–561.
318. (a) Williams, J. T.; Bahia, P. S.; Kariuki, B. M.; Spencer, N.; Philp, D.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 2460–2471; (b) Cariou, C. A. M.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 51–53.
319. Cariou, C. A. M.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem.* **2008**, *6*, 3337–3348.
320. Andres, C.; Gonzalez, I.; Nieto, J.; Roson, C. D. *Tetrahedron* **2009**, *65*, 9728–9736.
321. Chalker, J. M.; Yang, A.; Deng, K.; Cohen, T. *Org. Lett.* **2007**, *9*, 3825–3828.
322. Hara, O.; Fujino, H.; Makino, K.; Hamada, Y. *Heterocycles* **2008**, *76*, 197–202.
323. Grachan, M. L.; Tuidge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469–1472.
324. Zhang, F.-L.; Vasella, A. *Helv. Chim. Acta* **2008**, *91*, 2351–2360.
325. Pearson, A. J.; Sun, H. *J. Org. Chem.* **2007**, *72*, 7693–7700.
326. Nemoto, T.; Fukuda, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 4365–4368.
327. Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033–2040.
328. (a) Wipf, P.; Walczak, M. A. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4172–4175; (b) Ueda, M.; Walczak, M. A. A.; Wipf, P. *Tetrahedron Lett.* **2008**, *49*, 5986–5989.
329. Bantreil, X.; Prestat, G.; Madec, D.; Fristrup, P.; Poli, G. *Synlett* **2009**, 1441–1444.
330. Vogel, S.; Bantreil, X.; Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *Tetrahedron Lett.* **2010**, *51*, 1459–1461.
331. Hargrave, J. D.; Allen, J. C.; Kociok-Kohn, G.; Bish, G.; Frost, C. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 1825–1829.
332. Li, Q.; Yu, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4542–4543.
333. Mizoguchi, H.; Oguri, H.; Tsuge, K.; Oikawa, H. *Org. Lett.* **2009**, *11*, 3016–3019.
334. Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874–12875.
335. Hsieh, J.-C.; Ebata, S.; Nakao, Y.; Hiyama, T. *Synlett* **2010**, 1709–1711.
336. Ho, C.-Y. *Chem. Commun.* **2010**, 466–468.
337. Arai, S.; Sato, T.; Koike, Y.; Hayashi, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4528–4531.
338. Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synthesis* **2006**, 3467–3477.
339. Zhang, X.-L.; Zhang, W.-H.; Yang, H.-X. O. *Asia-Pac. J. Chem. Eng.* **2009**, *4*, 821–825.
340. (a) Mejia-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275–3278; (b) Mejia-Oneto, J. M.; Padwa, A. *Helv. Chim. Acta* **2008**, *91*, 285–302.
341. Hall, A.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hurst, D. N.; Naylor, A.; Patel, S.; Scoccitti, T.; Theobald, P. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2684–2690.
342. Majumdar, K. C.; Chakravorty, S.; Shyam, P. K.; Taher, A. *Synthesis* **2009**, 403–408.
343. Hong, W.-X.; Chen, L.-J.; Zhong, C.-L.; Yao, Z.-J. *Org. Lett.* **2006**, *8*, 4919–4922.
344. (a) Kim, H. S.; Gowrisankar, S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 3858–3861; (b) Kim, H. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 3154–3157.
345. El Kaim, L.; Gizzi, M.; Grimaud, L. *Org. Lett.* **2008**, *10*, 3417–3419.
346. (a) Zegar, S.; Tokar, C.; Enache, L. A.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F. W.; Zembower, D. E. *Org. Process Res. Dev.* **2007**, *11*, 747–753; (b) Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943–4946.
347. Liu, P.; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 2307–2310.
348. Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jorgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888–890.
349. Baxter, C. A.; Cleator, E.; Alam, M.; Davies, A. J.; Goodyear, A.; O'Hagan, M. *Org. Lett.* **2010**, *12*, 668–671.
350. Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. *Org. Lett.* **2007**, *9*, 4813–4815.
351. Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340–5348.
352. Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *J. Org. Chem.* **2009**, *74*, 2624–2626.
353. Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem.—Eur J.* **2007**, *13*, 5197–5206.
354. Anwar, U.; Fielding, M. R.; Grigg, R.; Sridharan, V.; Urch, C. J. *J.Organomet. Chem.* **2006**, *691*, 1476–1487.
355. Rene, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560–4563.
356. Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643–2645.
357. Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Synthesis* **2008**, 136–140.
358. Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J.Org. Chem.* **2009**, *74*, 7052–7058.
359. Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068–8077.
360. Park, S. R.; Findlay, N. J.; Garnier, J.; Zhou, S.; Spicer, M. D.; Murphy, J. A. *Tetrahedron* **2009**, *65*, 10756–10761.
361. Bonnaventure, I.; Charette, A. B. *Tetrahedron* **2009**, *65*, 4968–4976.
362. Nandi, S.; Ray, J. K. *Tetrahedron Lett.* **2009**, *50*, 6993–6997.
363. Lu, Z.; Hu, C.; Guo, J.; Li, J.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 480–483.
364. Ardizzoia, G. A.; Beccalli, E. M.; Borsini, E.; Brenna, S.; Broggini, G.; Rigamonti, M. *Eur. J. Org. Chem.* **2008**, 5590–5596.
365. Majumdar, K. C.; Chakravorty, S.; Ray, K. *Synthesis* **2008**, 2991–2995.

366. Dhami, A.; Mahon, M. F.; Lloyd, M. D.; Threadgill, M. D. *Tetrahedron* **2009**, *65*, 4751–4765.
367. Jacobs, J.; Mbala, B. M.; Kesteleyn, B.; Diels, G.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 6364–6371.
368. Beccalli, E. M.; Broggini, G.; Martinelli, M.; Masciocchi, N.; Sottocornola, S. *Org. Lett.* **2006**, *8*, 4521–4524.
369. Gowrisankar, S.; Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1670–1673.
370. Okano, A.; Mizutani, T.; Oishi, S.; Tanaka, T.; Ohno, H.; Fujii, N. *Chem. Commun.* **2008**, 3534–3536.
371. Beccalli, E. M.; Borsini, E.; Brenna, S.; Galli, S.; Rigamonti, M.; Broggini, G. *Chem.—Eur. J.* **2010**, *16*, 1670–1678.
372. (a) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889; (b) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207–2213; (c) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093–3096; (d) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565–1567; (e) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 8609–8618.
373. Uemura, M.; Yorimitsu, H.; Oshima, K. *Chem. Commun.* **2006**, 4726–4728.
374. Phapale, V. B.; Bunuel, E.; Garcia-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795.
375. Ishikura, M.; Takahashi, N.; Yamada, K.; Abe, T. *Heterocycles* **2008**, *75*, 107–118.
376. (a) Ma, J.; Yin, W.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491–3494; (b) Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2009**, *74*, 264–273.
377. Sole, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177–10184.
378. Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.
379. Fujino, D.; Hayashi, S.; Yorimitsu, H.; Oshima, K. *Chem. Commun.* **2009**, 5754–5756.
380. (a) Tietze, L. F.; Wilckens, K. F.; Yilmaz, S.; Stecker, F.; Zinngrebe, J. *Heterocycles* **2006**, *70*, 309–319; (b) Tietze, L. F.; Heins, A.; Soleiman-Beigi, M.; Raith, C. *Heterocycles* **2009**, *77*, 1123–1146.
381. (a) Ribiere, P.; Declerck, V.; Nedellec, Y.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *Tetrahedron* **2006**, *62*, 10456–10466; (b) Declerck, V.; Ribiere, P.; Nedellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2007**, 201–208.
382. Stewart, S. G.; Heath, C. H.; Ghisalberti, E. L. *Eur. J. Org. Chem.* **2009**, 1934–1943.
383. Habib-Zahmani, H.; Viala, J.; Hacini, S.; Rodriguez, J. *Synlett* **2007**, 1037–1042.
384. Majumdar, K. C.; Nandi, R. K.; Samanta, S.; Chattopadhyay, B. *Synthesis* **2010**, 985–990.
385. Majumdar, K. C.; Mondal, S.; Ghosh, D.; Chattopadhyay, B. *Synthesis* **2010**, 1315–1320.
386. Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett.* **2009**, *11*, 531–534.
387. Rayabarapu, D. K.; Zhou, A.; Jeon, K. O.; Samarakoon, T.; Rolfe, A.; Siddiqui, H.; Hanson, P. R. *Tetrahedron* **2009**, *65*, 3180–3188.
388. Akiyama, K.; Mikami, K. *Heterocycles* **2007**, *74*, 827–834.
389. Vasudevan, A.; Tseng, P.-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591–8593.
390. Lin, H.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 1221–1227.
391. Bukovec, C.; Kazmaier, U. *Org. Lett.* **2009**, *11*, 3518–3521.
392. Porcel, S.; Lopez-Carrillo, V.; Garcia-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1883–1886.
393. Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251–3254.
394. O'Neil, G. W.; Fuerstner, A. *Chem. Commun.* **2008**, 4294–4296.
395. Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.
396. Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224–8227.
397. Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051.
398. Blangetti, M.; Deagostino, A.; Prandi, C.; Tabasso, S.; Venturello, P. *Org. Lett.* **2009**, *11*, 3914–3917.
399. Gabriele, B.; Salerno, G.; Fazio, A.; Veltri, L. *Adv. Synth. Catal.* **2006**, *348*, 2212–2222.
400. (a) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531–2534; (b) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838–6852; (c) Rosen, B. R.; Ney, J. E.; Wolfe, J. P. *J. Org. Chem.* **2010**, *75*, 2756–2759.
401. Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028–1031.
402. Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665–2668.
403. Fukumoto, Y.; Kinashi, F.; Kawahara, T.; Chatani, N. *Org. Lett.* **2006**, *8*, 4641–4643.
404. Park, Y. S.; Cho, M. Y.; Kwon, Y. B.; Yoo, B. W.; Yoon, C. M. *Synth. Commun.* **2007**, *37*, 2677–2685.
405. Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941–944.
406. Ferber, B.; Prestat, G.; Vogel, S.; Madec, D.; Poli, G. *Synlett* **2006**, 2133–2135.
407. (a) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279–3282; (b) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. *Tetrahedron* **2009**, *65*, 6549–6570.
408. Kim, D. E.; Choi, C.; Kim, I. S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Jeong, N. *Adv. Synth. Catal.* **2007**, *349*, 1999–2006.
409. Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329–332.
410. Michael, F. E.; Sibbald, P. A.; Cochran, B. M. *Org. Lett.* **2008**, *10*, 793–796.
411. Balazs, A.; Hetenyi, A.; Szakonyi, Z.; Sillanpaeae, R.; Fueloep, F. *Chem.—Eur. J.* **2009**, *15*, 7376–7381.
412. Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249.
413. Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190–4191.
414. Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4047–4050.
415. Dubon, P.; Farwick, A.; Helmchen, G. *Synlett* **2009**, 1413–1416.
416. Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395–3398.
417. (a) Linnepe, P.; Schmidt, A. M.; Eilbracht, P. *Org. Biomol. Chem.* **2006**, *4*, 302–313; (b) Bondzic, B. P.; Farwick, A.; Liebich, J.; Eilbracht, P. *Org. Biomol. Chem.* **2008**, *6*, 3723–3731.
418. Chiou, W.-H.; Mizutani, N.; Ojima, I. *J. Org. Chem.* **2007**, *72*, 1871–1882.
419. Chiou, W.-H.; Lin, G.-H.; Hsu, C.-C.; Chaterpaul, S. J.; Ojima, I. *Org. Lett.* **2009**, *11*, 2659–2662.
420. Limberger, J.; Mottin, M.; Nachtigall, F. F.; Castellano, E. E.; da Rosa, R. G. *J. Mol. Catal. A: Chem.* **2008**, *294*, 82–92.
421. Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707–10713.
422. (a) Merisor, E.; Conrad, J.; Klaiber, I.; Mika, S.; Beifuss, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 3353–3355; (b) Merisor, E.; Conrad, J.; Mika, S.; Beifuss, U. *Synlett* **2007**, 2033–2036.
423. Merisor, E.; Beifuss, U. *Tetrahedron Lett.* **2007**, *48*, 8383–8387.
424. Hubbard, J. W.; Piegols, A. M.; Soederberg, B. C. G. *Tetrahedron* **2007**, *63*, 7077–7085.
425. Candela-Lena, J. I.; Davies, S. G.; Roberts, P. M.; Roux, B.; Russell, A. J.; Sanchez-Fernandez, E. M.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1135–1145.
426. (a) Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063–5066; (b) Vulovic, B.; Bihelovic, F.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2009**, *65*, 10485–10494.
427. Thuong, M. B. T.; Sottocornola, S.; Prestat, G.; Broggini, G.; Madec, D.; Poli, G. *Synlett* **2007**, 1521–1524.
428. Webber, P.; Krische, M. J. *J. Org. Chem.* **2008**, *73*, 9379–9387.
429. Hunter, R. A.; Macfarlane, D. P. S.; Whitby, R. J. *Synlett* **2006**, 3314–3318.
430. Macfarlane, D. P. S.; Norton, D.; Whitby, R. J.; Tupper, D. *Synlett* **2006**, 3439–3442.
431. Ahari, M.; Joosten, A.; Vasse, J.-L.; Szymoniak, J. *Synthesis* **2008**, 61–68.
432. Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473–2476.
433. (a) Garnier, J.-M.; Jida, M.; Ollivier, J. *Synlett* **2006**, 2739–2742; (b) Jida, M.; Ollivier, J. *Eur. J. Org. Chem.* **2008**, 4041–4049.
434. Jida, M.; Gaucher, X.; Ollivier, J. *Synlett* **2010**, 1627–1630.
435. Jida, M.; Guillot, R.; Ollivier, J. *Tetrahedron Lett.* **2007**, *48*, 8765–8767.
436. Gaucher, X.; Jida, M.; Ollivier, J. *Synlett* **2009**, 3320–3322.
437. Faler, C. A.; Cao, B.; Joullie, M. M. *Heterocycles* **2006**, *67*, 519–522.
438. Faler, C. A.; Joullie, M. M. *Tetrahedron Lett.* **2008**, *49*, 6512–6513.
439. Johnson, R. S.; Yamazaki, T.; Kovalenko, A.; Fenniri, H. *J. Am. Chem. Soc.* **2007**, *129*, 5735–5743.
440. Hernan, A. G.; Horton, P. N.; Hursthouse, M. B.; Kilburn, J. D. *J. Organomet. Chem.* **2006**, *691*, 1466–1475.
441. Kamimura, A.; Kadowaki, A.; Yoshida, T.; Takeuchi, R.; Uno, H. *Chem.—Eur. J.* **2009**, *15*, 10330–10334.
442. Kwak, S.-H.; Bang, S.-C.; Seo, H.-H.; Shin, H.-R.; Lee, K.-C.; Hoang, L. T. A.; Jung, S.-H. *Arch. Pharmacal Res.* **2006**, *29*, 721–727.
443. Ichikawa, Y.; Egawa, H.; Ito, T.; Isobe, M.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2006**, *8*, 5737–5740.
444. Hoang, C. T.; Bouillere, F.; Johannesen, S.; Zulauf, A.; Panel, C.; Pouilhes, A.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Org. Chem.* **2009**, *74*, 4177–4187.
445. Sellanes, D.; Scarone, L.; Mahler, G.; Manta, E.; Baz, A.; Dematteis, S.; Saldana, J.; Dominguez, L.; Wipf, P.; Serra, G. *Lett. Drug Des. Discovery* **2006**, *3*, 35–43.
446. Wang, R.-W.; Qiu, X.-L.; Bols, M.; Ortega-Caballero, F.; Qing, F.-L. *J. Med. Chem.* **2006**, *49*, 2989–2997.
447. Vardelle, E.; Gamba-Sanchez, D.; Martin-Mingot, A.; Jouannetaud, M.-P.; Thibaudeau, S.; Marrot, J. *Chem. Commun.* **2008**, 1473–1475.
448. Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9465.
449. Banwell, M. G.; Vogt, F.; Wu, A. W. *Aust. J. Chem.* **2006**, *59*, 415–425.
450. Monguchi, D.; Majumdar, S.; Kawabata, T. *Heterocycles* **2006**, *68*, 2571–2578.
451. Martinkova, M.; Gonda, J.; Dzoganova, M. *Collect. Czech. Chem. Commun.* **2006**, *71*, 1199–1210.
452. Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4982–4985.
453. Nag, S.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3824–3828.
454. Nag, S.; Bhowmik, S.; Gauniyal, H. M.; Batra, S. *Eur. J. Org. Chem.* **2010**, 4705–4712.
455. Nayak, M.; Batra, S. *Tetrahedron Lett.* **2010**, *51*, 510–516.
456. Nayak, M.; Kanojiya, S.; Batra, S. *Synthesis* **2009**, 431–437.
457. Nag, S.; Mishra, A.; Batra, S. *Tetrahedron* **2008**, *64*, 10162–10171.
458. Pathak, R.; Nag, S.; Batra, S. *Synthesis* **2006**, 4205–4211.
459. Nag, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2007**, 911–917.
460. Nag, S.; Mishra, A.; Batra, S. *Eur. J. Org. Chem.* **2008**, 4334–4343.
461. Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661–663.
462. Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740–8741.
463. Pathak, R.; Batra, S. *Tetrahedron* **2007**, *63*, 9448–9455.
464. Kaur, J.; Kumar, P.; Tyagi, S.; Pathak, R.; Batra, S.; Singh, P.; Singh, N. *Antimicrob. Agents Chemother.* **2011**, *55*, 659–666.
465. Sener, M. K.; Sanchez-Garcia, D.; Akkurt, M.; Yildirim, S. O.; Fun, H.-K.; Sessler, J. L. *Turkish J. Chem.* **2006**, *30*, 243–251.
466. Wu, P.; Santoni, G.; Froeba, M.; Rehder, D. *Chem. Biodiv.* **2008**, *5*, 1913–1926.

Biographical sketch



Sanjay Batra was born in 1965 in Lucknow, India. He completed his Ph.D. in 1993 from the Medicinal and Process Chemistry Division at the CSIR-Central Drug Research Institute, Lucknow. He has been working as a scientist in the same department since 1995. His area of interest includes the development of new antimalarials and development of chemistry associated with the Morita–Baylis–Hillman reaction and heterocyclic chemistry. He has been the recipient of Bronze-medal from the Chemical Research Society of India for the year 2010–2011. A Tetrahedron report co-authored by him in 2008 received the Tetrahedron most cited publication award for 2009 and stands out as one of the most cited publications of Tetrahedron in last the five years. He is also Co-Chief-Editor of *Anti-Infective agents* published by Bentham Publications.

Somnath Nag received his M.Sc. degree in chemistry in 2004 from Jadavpur University, Kolkata, India. Thereafter he joined the Medicinal and Process Chemistry Division of the CSIR-Central Drug Research Institutes, Lucknow, India to pursue his Ph.D. under the supervision of Dr. Sanjay Batra. He completed his dissertation on 'Synthetic application of allylamine and 1,3-amino alcohol derived from Morita–Baylis–Hillman chemistry' from Jawaharlal Nehru University, New Delhi in 2010. Presently he is working as Associate Scientist in Aurigene Discovery Technologies Ltd, Bangalore, India.