Advances in synthesis of monocyclic β-lactams

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Abstract

Recent years have witnessed significant advancement in cycloaddition and cyclization strategies for the synthesis of monocyclic β-lactams. Cycloadditions include the Staudinger's ketene – imine cycloaddtions and related reaction. Cyclization reactions are reported to furnish β-lactams through N_1-C_2, N_1-C_4 and C_3-C_4 bond formations employing substrates like β-amino esters, β-amino alcohols, β-hydroxamate esters, and α-amino diazocarbonyls, etc. Some other strategies are silyl carbonylation reactions, ring-enlargement of aziridines, cleavage of one ring of a bicyclic β-lactam, and functional group transformations on the β-lactam rings. Recently, some multi-component reactions have also been designed. This article reviews the advances made in synthetic approaches to monocyclic β-lactams during last five years.

Keywords: β-Lactams, cycloadditions, ketenes, nitrones, β-amino esters, aziridines

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1. Introduction

β-Lactams, the name still in vogue for four-membered cyclic amides 2-azetidinones, need no introduction to synthetic and medicinal organic chemists due to their widespread popularity as potential antibiotics and valuable building blocks in organic synthesis. β-Lactams constitute the most important class of antibiotics in both human and veterinary medicine and share more than 65% of the world antibiotics market. They are also in other clinical uses, like clavulanic acids as β-lactamase inhibitors and ezetimibe as cholesterol absorption inhibitor. Several other biological activities such as anticancer activity, hypoglycemic activity, antitubercular activity and antileishmanial activity have also been observed in compounds containing β-lactam ring. Over the years, monocyclic β-lactams have also emerged as powerful synthons and their reactivity has been exploited in synthesis of diverse type of acyclic and cyclic compounds including complex heterocyclic compounds of natural origin and of potential biological interest. Accordingly, the researches on synthesis,[1] biological activity,[2-5] and applications of β-lactams in organic synthesis,[6-13,] have been reviewed from time to time.[1,14-19] This article aims to update the reports on synthesis of monocyclic β-lactams during last five years.

2. Synthetic Approaches to Construct β-Lactam Ring

The main synthetic approaches to construct the β-lactam ring involve either cycloaddition reactions or cyclization reactions. Cycloaddition reactions include the Staudinger's ketene-imine cycloaddtions, ester enolate-imine cycloadditions, alkyne-nitrone cycloadditions, alkene-isocyanate cycloadditions, and Torii's cyclocarbonylation of allyl halides with imines.

Cyclizations to monocyclic 2-azetidinones are reported recently through formation of N_1-C_2, N_1-C_4, and C_3-C_4 bonds. Methods involving N_1-C_2 bond formation employ *N*-protected or unprotected β-amino esters as substrate. Some other strategies involve cyclization of β-amino esters, β-amino alcohols suitably substituted amino diazocarbonyls. Different approaches have

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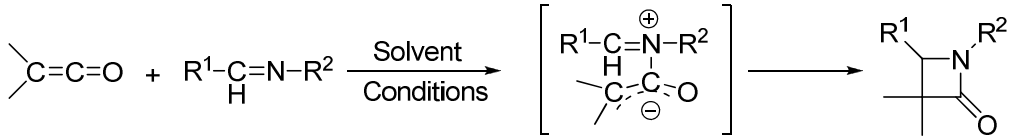
been applied to synthesize the β-amino esters. Hydroxamate esters cyclize by N_1-C_4 bond formation. *N*,*N*-Disubstituted α-halo amides cyclize by C_3-C_4 bond formation.

Some other strategies for architecture of β-lactam ring employ ring-enlargement of aziridines or ring-contraction of isoxazolidines. Recently, some multi-component reactions have also been employed to achieve the goal.

2.1 Staudinger's Ketene-Imine Reactions

The Staudinger's ketene-imine cycloaddition is the most fundamental and versatile method for the synthesis of 2-azetidinones (Scheme 1).[20] Although it is classified [2+2]-cycloaddition it involves a two-step process. The first step is the nucleophilic attack of the imine nitrogen to the electrophilic central carbon of a ketene, generated *in situ* from an acid chloride and a base, to form a *zwitterionic* intermediate followed by a conrotatory ring closure to give the four-membered cycloadduct. Stereoselectivity is yet a challenging endeavor in this reaction.[21] Tuba has recently reviewed transition metal-promoted Staudinger reactions.[22] In recent years several new ketene precursors, new azomethine precursors, and acid activators have been developed. Both carboxylic acid chlorides or carboxylic acids themselves have been used as ketene precursors. An alternative method for generation of ketenes involves the Wolff-rearrangement of α-carbonyl carbenes, generated from thermal or photochemical decomposition of α-diazocarbonyls.[23] The generation of ketenes using microwave irradiation and polymer-support are also reported.[24,25] A detailed review of the literature on such reactions is described in the succeeding paragraphs.



Scheme 1

2.1.1. Applications of new ketene precursors. The reaction of a chiral ketene, generated from the alkoxyacetic acid **1** bearing an α-glycoside group as a chiral auxiliary, with *N*-chresenyl aldimine **2** in the presence of Mukaiyama's reagent **3** yielded a 45:55 mixture of the β-lactams **4** and **5** containing carbohydrate moiety in 70% combined yields.[26] The separation of products by column chromatography and an acid-induced removal of the sugar moiety afforded the corresponding enantiopure products **6** and **7** (Scheme 2).

The [2+2] cycloaddition of hydrazones **8**, prepared from aliphatic aldehydes and (2*R*,5*R*)-1-amino-2,5-dimethylpyrrolidine, to *N*-benzyl-*N*-(benzyloxycarbonyl)aminoketene, generated *in situ* from the carboxylic acid **9**, occurs in the presence of *i*-Pr_2EtN base affording the corresponding 2-azetidinones **10** in good yields with *dr's* ranging from 54:46 upto 99:1 (Scheme 3).[27] The reactions proceed with excellent stereocontrol to afford products having *R* configuration at C-3 position. A strong influence of temperature was observed on the

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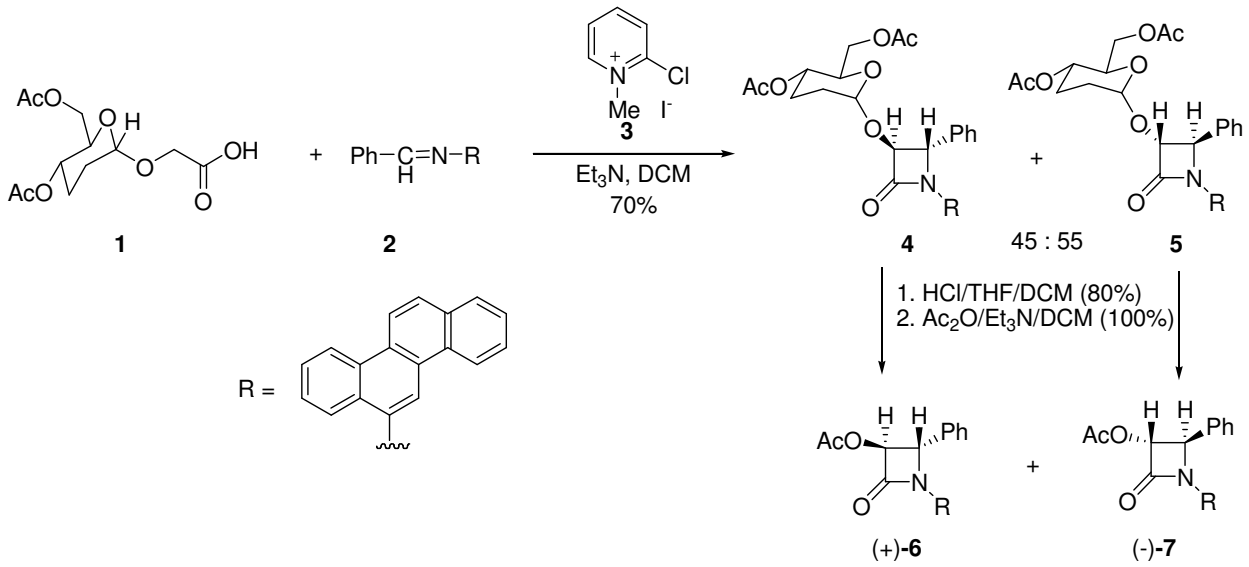
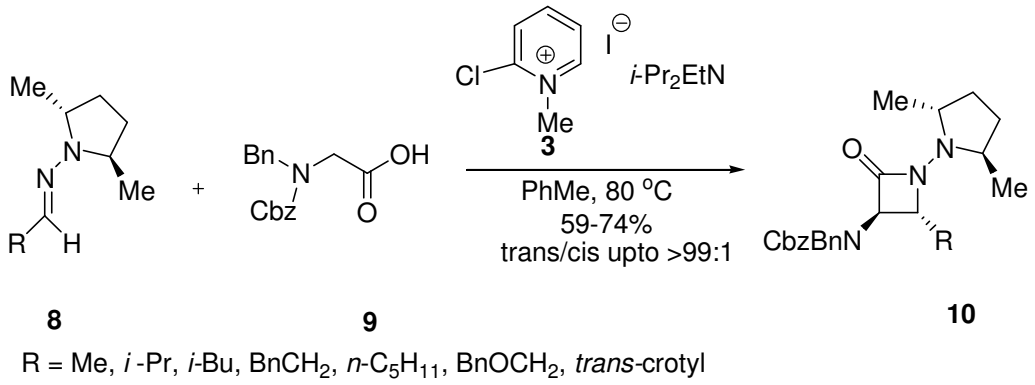
diastereoselectivity allowing in most cases the isolation of a single *trans* or *cis* cycloadducts simply by performing the reactions at 80 °C or room temperature, respectively.



Scheme 2



Scheme 3

Another example of a nitrogen-substituted ketene precursor is 2-(1*H*-pyrrol-1-yl)acetic acid **12**. 2-(1*H*-Pyrrol-1-yl)ketene, generated from 2-(1*H*-pyrrol-1-yl)acetic acid **12** using Mukaiyama's reagent **3**, reacts with some well-known aldimines **11** to afford the 3-pyrrol-1-yl-2-azetidinones **13** (Scheme 4).[28]

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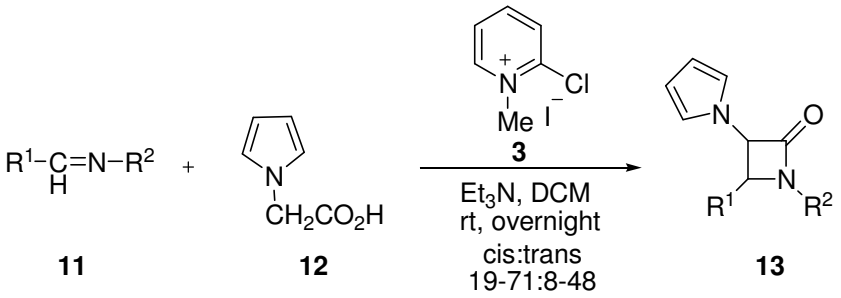
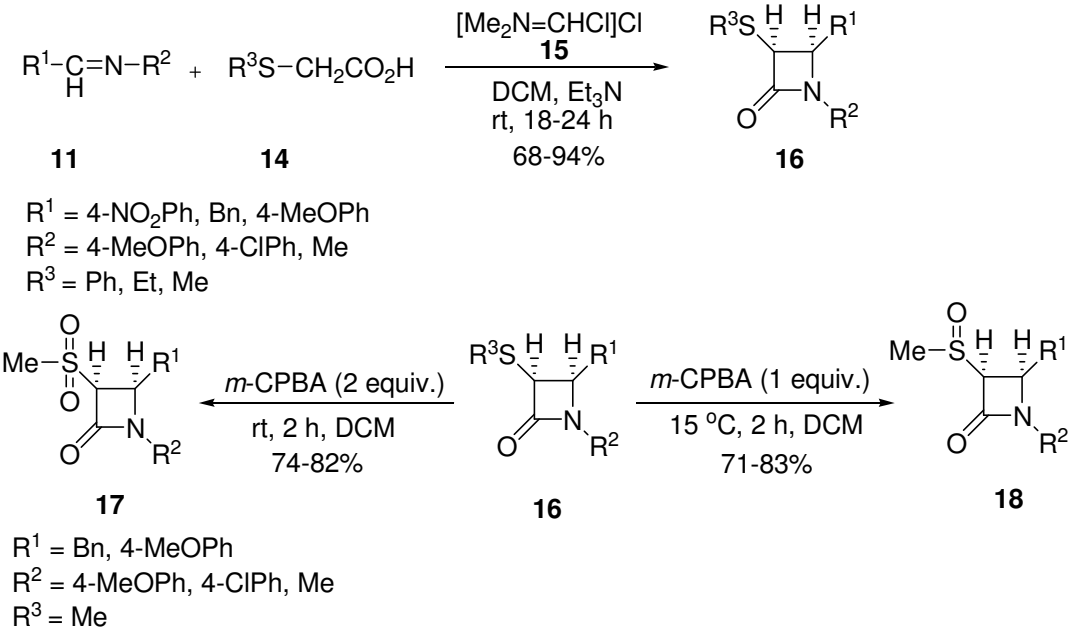


Scheme 4

The Staudinger reaction of mercaptoacetic acids **14** with Schiff bases **11** in the presence of the Vilsmeier reagent **15** at room temperature leading to the formation 3-thiolated 2-azetidinones **16** in good to excellent yields constitutes an excellent example of application of a sulfur-substituted ketene precursor in the Staudinger reaction (Scheme 5).[29] The reactivity of sulfur group on C-3 position has been further explored and selected 3-methylthio-2-azetidinones **16** have been transformed to the corresponding 3-(methylsulfonyl)- **17** and 3-(methylsulfinyl) **18** 2-azetidinones by treating with *m*-CPBA under different reaction conditions.



Scheme 5

Bari and coworkers have reported diastereoselective synthesis of novel selenium-substituted 2-azetidinones **20** by reaction of suitably substituted imines **11** and ketenes, generated

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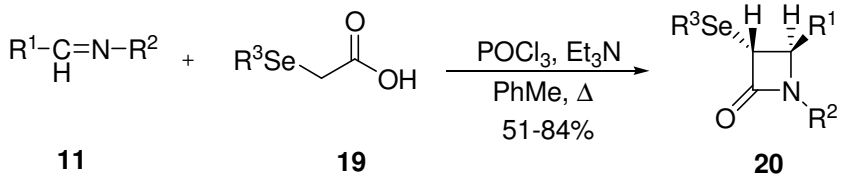
from appropriate aryl- and alkylselenium-substituted acids **19** using $POCl_3$ and triethylamine in refluxing toluene (Scheme 6) or benzene.[30,31] The products obtained in good to excellent yields were having *cis* configuration of hydrogen atoms at C-3/C-4.

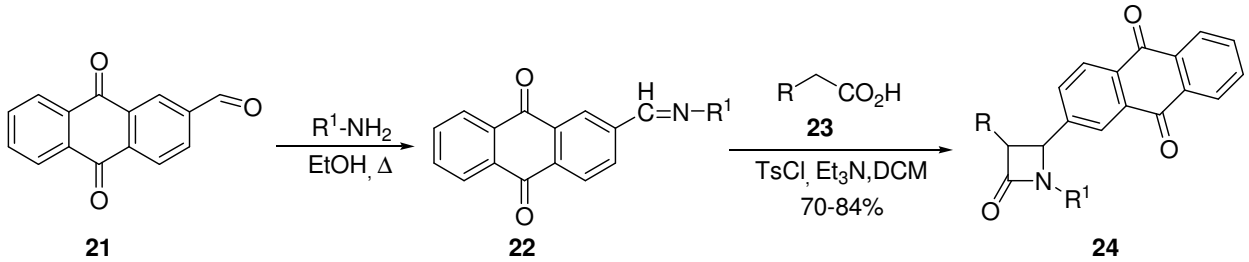


11 **19** **20**

R^1 = Ph, 4-MeOPh, 4-ClPh, HC=CHPh
R^2 = Ph, 4-MeOPh, 4-MePh, 4-ClPh, Bn
R^3 = Bn, $CHPh_2$, 1-naphthyl, Ph

Scheme 6

2.1.2 Applications of new azomethines. More recently, the synthesis of a novel series of 2-azetidinones **24** bearing an anthraquinone moiety at C-4 position has been reported using the imines **22** of 9,10-anthraquinone-2-carboxaldehyde **21** and ketenes, generated from aryloxy- and phthalimido-substituted acetic acids **23** in the presence of *p*-toluenesulfonyl chloride and triethylamine (Scheme 7).[32]



21 **22** **24**

R^1 = 1-naphthyl, 4-MeOPh, $4\text{-Me}_2\text{NPh}$
R = PhO, 4-ClPhO, 1-naphthoxy, PhthN, $2,4\text{-Cl}_2\text{PhO}$

Scheme 7

The reaction of vicinal diimines **25** and acyl chlorides in the presence of triethylamine furnishes 3-imino-β-lactams **26** and/or bis-β-lactams chemo-, regio-, and stereoselectively.[33] The selectivities in the reaction have been investigated using different substrates such as symmetric diimines derived from vicinal diketones, and unsymmetrical diimines from vicinal ketoaldehydes. The study revealed that all diimines reacted with various ketenes providing mono-*cis*- 2-azetidinones **26** diastereoselectively due to the electron-withdrawing property of another imino group in the vicinal diimines (Scheme 8). Bis-2-azetidinones were obtained from diimines via mono-2-azetidinones. Usually the formation of first β-lactam ring inhibited the formation of the second ring. But the ketene with strong electron-donating substituent such as

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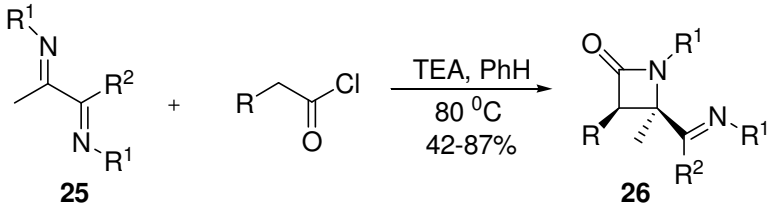
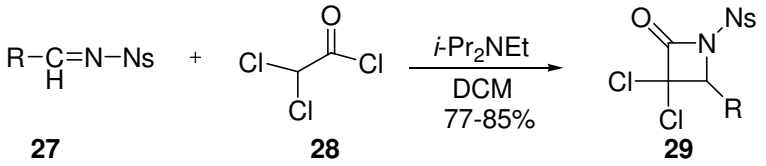
ethoxyketene reacted with the mono-cis-2-azetidinones containing azomethine linkage to provide the bis-2-azetidinones.



R^1 = 4-MeOPh, Ph_2CH, Ph, Bn
R^2 = Me, H
R = EtO, PhthN, Cl, Me

Scheme 8

Tato and coworkers have reported the Staudinger reaction of *N*-nosyl imines **27** and dichloroketene, generated *in situ* from dichloroacetyl chloride **28**, to furnish the 1-nosyl-3,3-dichloro-2-azetidinones **29** in good yields (Scheme 9).[34] These 2-azetidinones undergo ring-opening to afford highly functionalized building block. The reaction of chloroacetyl chloride with some bis-imines in the presence of zeolite is reported by microwave irradiation forming bis-2-azetidinones.[35]



R = Ph, 2-naphthyl, 4-*i*-PrPh, 3-CNPh, 2-FPh
Ns = SO_2-4-$NO_2C_6H_4$

Scheme 9

Azomethines **32** are generated *in situ* by copper-catalyzed reaction of the Grignard reagents with *N*-substituted methyleneaziridines **30** inducing aziridine ring opening and alkylation of the resulting metalloenamine **31** (Scheme 10).[36] These azomethines reacted with alkoxyketenes, generated from acyl chlorides **33** and Et_3N, to yield C-3 alkoxy-substituted 2-azetidinones **34**.

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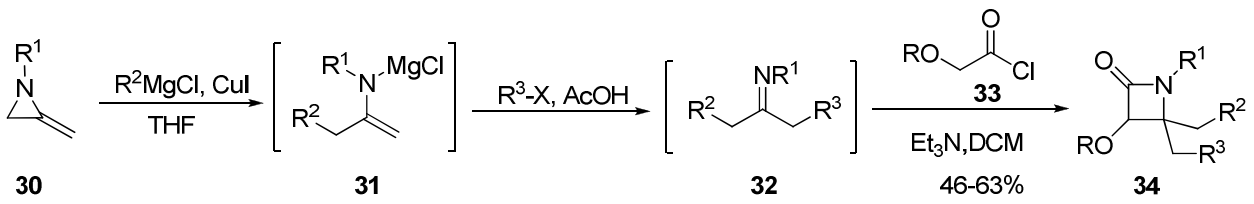
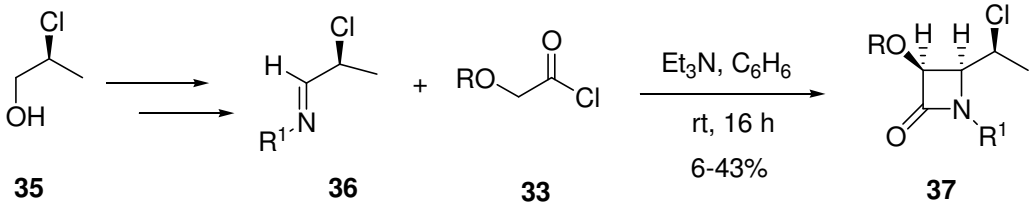


R^1 = 4-MeOBn, Bn, *C*-Hex
R^2 = Bn, Et, *i*-Pr
R^3-X = BnBr, BnCl, CH_2=$CHCH_2Br$, PMBCl, MeI, $THPO(CH_2)_3Br$, $H_3CC{\equiv}CCH_2Br$
R = Bn, Me

Scheme 10

(*S*)-2-Chloropropan-1-ol **35** has been used as azomethine precursor in an efficient one-pot approach towards chiral 2-azetidinones **37** in reasonable yields (32-61%, 19-43% after purification) and high diastereomeric (80-89%) and enantiomeric excess (90%).[37] An oxidation of alcohol **35** with pyridinium cholorochromate (PCC) afforded the corresponding aldehyde which on treatment with 1 equivalent of amines yielded the (*S*)-*N*-(2-chloropropylidene)amines **36**. The reaction of azomethines **36** with benzyloxy- or methoxyacetyl chloride **33** under Staudinger conditions gave the corresponding 2-azetidinones (Scheme 11). The reaction of methoxyketene with imine containing *N*-butyl group, however, afforded an extremely low yield of 6% due to unexplained reasons.



R^1 = Bn, allyl, Bu, *i*-Bu, *i*-Pr
R = Bn, Me

Scheme 11

The use of *N*-phenylsulfenylimines **38** in the Staudinger reaction with methoxy- or benzyloxyacetyl chlorides **33** afforded 3,4-disubstituted *N*-phenylsulfenyl-2-azetidinones **39** in good to excellent yields and with moderate *cis*/*trans* diastereoselectivity (Scheme 12).[38] The choice of diisopropylethylamine as a non-nucleophilic Lewis base was essential for the success of reaction. The *cis*-diastereomers were the major products with benzyloxy and methoxyketene and this diastereoselectivity increased with the electron-withdrawing ability of the substituent on imine. However, the *trans*-diastereomer was the major product with imines derived from electron-rich aldehydes.

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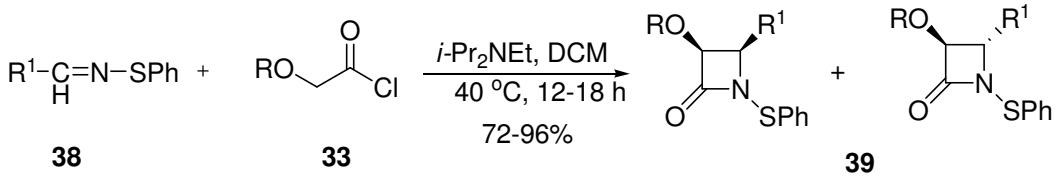
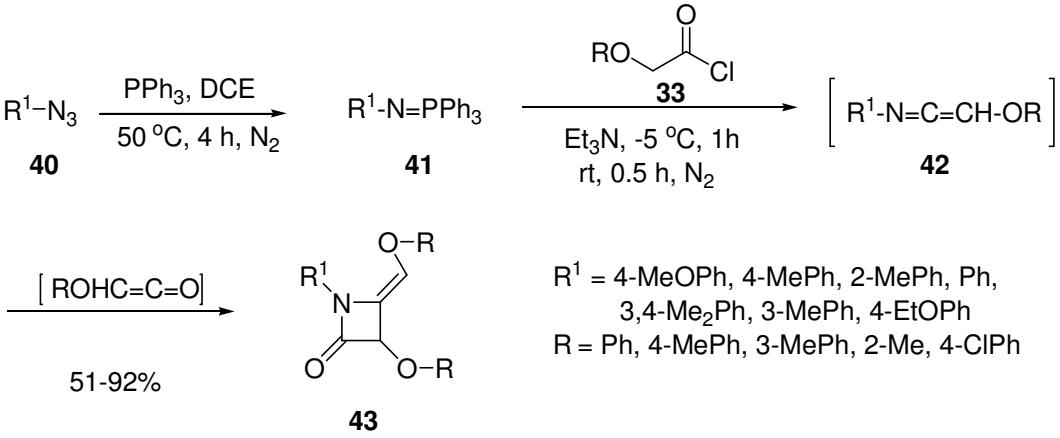


R^1 = *i*-Pr, *t*-Bu, Ph, 4-Me_2NPh, 4-MeOPh, 4-MeSPh, 4-FPh, 2-FPh, 3-FPh, 4-CF_3Ph, 4-$MeCO_2$Ph, 4-CNPh, 4-NO_2Ph, 2-pyridyl, 2-furyl, 2-thienyl
R = Me, Bn

Scheme 12

A one-pot cascade approach to 4-alkylidine-2-azetidinones **43** from aryl azides **40** and aryloxyacetyl chlorides **33** has been reported.[39] The cascade process involves an aza-Wittig reaction of ketenes, generated *in situ* from acid chlorides **33**, with triphenylphosphazenes **41** forming ketenimines **42**, which in turn, react with ketenes by a [2+2]-cycloaddition. The electron-rich aryl azides offered better yields than the electron-deficient aryl azides (Scheme 13).



R^1 = 4-MeOPh, 4-MePh, 2-MePh, Ph, 3,4-Me_2Ph, 3-MePh, 4-EtOPh
R = Ph, 4-MePh, 3-MePh, 2-Me, 4-ClPh

Scheme 13

A highly diastereoselective one-pot synthesis of trifluoromethylated *trans*- 2-azetidinones **45** using *N*-tosyl-1-chloro-2,2,2-trifluoroethylamine **44** and various nonactivated aliphatic acid chlorides in the presence of DMEA is reported (Scheme 14).[40] The reaction provided the 2-azetidinones in good yields with excellent diastereoselectivity upto 99:1. An improved yield was, however, obtained from 3-phenylpropanoyl chloride. Although the diastereomeric ratio was high with R = Me and Et the diastereoselectivity was total with bulkier R groups (Pr, *i*-Pr, Bu, *t*-Bu, CH_2Ph).

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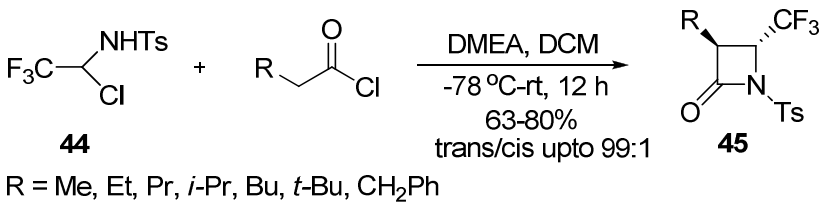
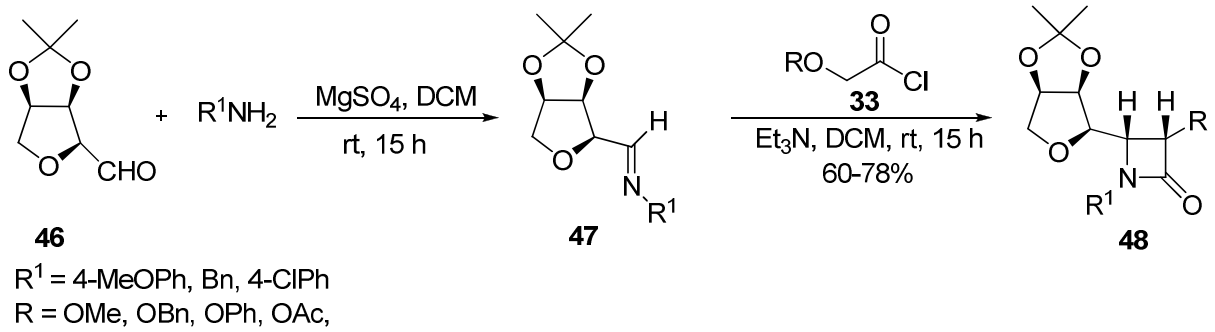


Scheme 14

Deshmukh and coworkers have employed isosorbide, a by-product from starch industry, to synthesize chiral bicyclic aldehydes **46**. Imines **47** of this aldehyde react with alkoxy-, acetoxy-, phenoxy-, and benzyloxyketenes, obtained from the respective acyl chlorides **33**, to afford the *cis*-2-azetidinones **48**, as a single diastereoisomer (Scheme 15).[41] The application of isosorbide-derived chiral acetic acid derivatives as ketene precursors, however, resulted in moderate to low diastereoselectivity.



Scheme 15

2.1.3 Development of new acid activators. Several reports in recent years especially from Zarei and coworkers focused on the efficient use of new acid activators, such as diethyl chlorophosphate **49**,[42] cyanuric chloride-DMF complex **50**,[43] thiocarbonyldiimidazole **51**,[44] and DMF-dimethyl/diethylsulfate **52**,[45] in Staudinger reactions. The reactions of various imines **11** and substituted acetic acids **23** in the presence of these reagents at room temperature afford 2-azetidinones **53** in excellent yields (Scheme 16). More recently Zarei group has reported cyanuric fluoride,[46] and phosphonitrilic chloride,[47] as efficient acid activators.

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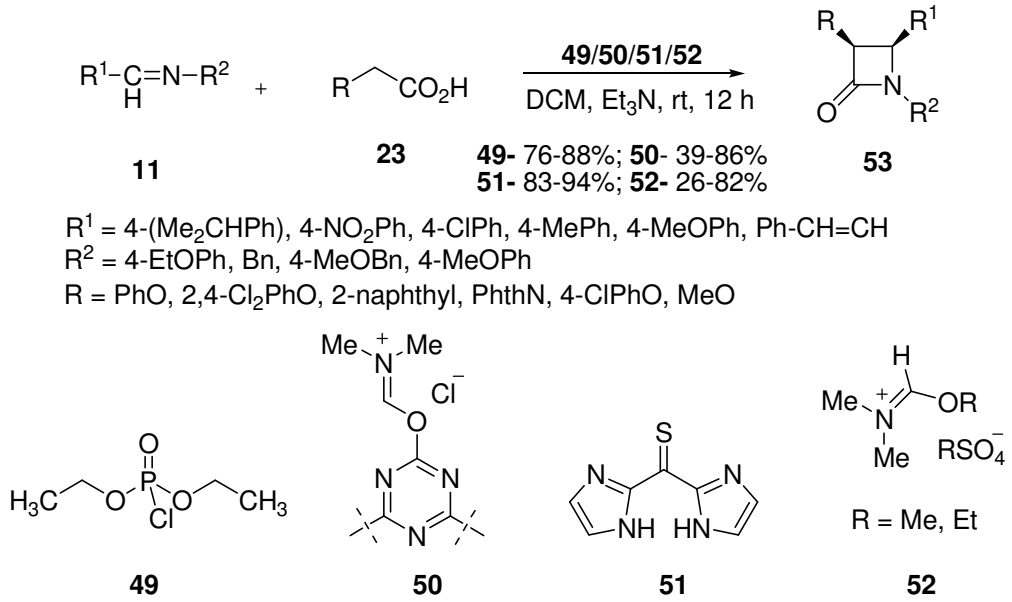

Scheme 16

2.1.4 Some other stereoselective Staudinger reactions. A highly stereoselective synthesis of 3-(1*H*-pyrrol-2-yl)-substituted 2-azetidinones **58** and **59** is reported through the Staudinger reaction of imines **11** with phthalimido acetic acid **53** affording the 2-azetidinones **54** and **55** (Scheme 17).[48] Treatment of the latter compounds with ethylenediamine afforded 3-amino-2-azetidinones **56** and **57** which reacted with 2,5-dimethoxytetrahydrofuran in the presence of bismuth nitrate to afford the 3-pyrrole-substituted 2-azetidinones **58** and **59**, respectively. The reaction was relatively much faster under microwave irradiation. The polyaromatic imines derived from 6-chrysenyl amine produced (+)-*trans* isomer exclusively. The electron-withdrawing aromatic groups at the C- and N- terminus of the imine led to the formation of the *trans* isomer. The formation of *trans* isomer in the case of *N*-chrysenyl imines and diarylimines was rationalized through isomerization of the enolate as described by Banik and coworkers.[49] A polyaromatic group at the nitrogen stabilizes the iminium ion, but in the case of a monocyclic aromatic group, the electron-withdrawal properties are not sufficient to have complete isomerization of the enolate resulting into formation of a mixture of *trans* and *cis* isomers.

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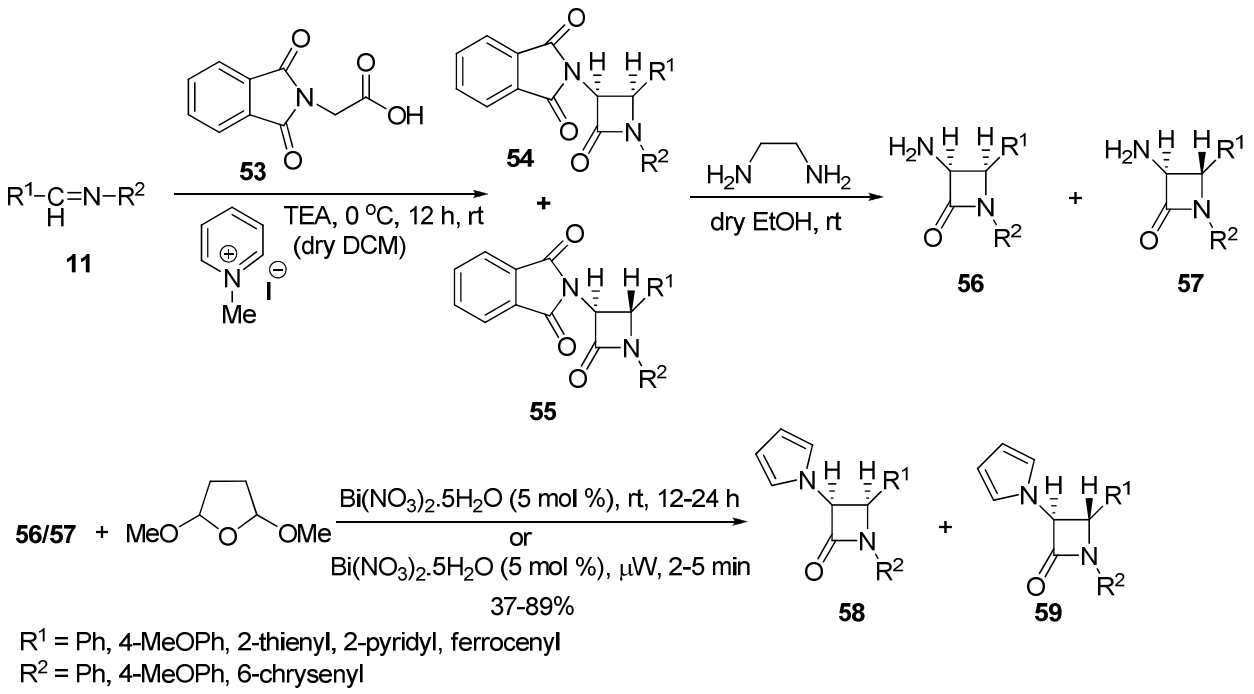
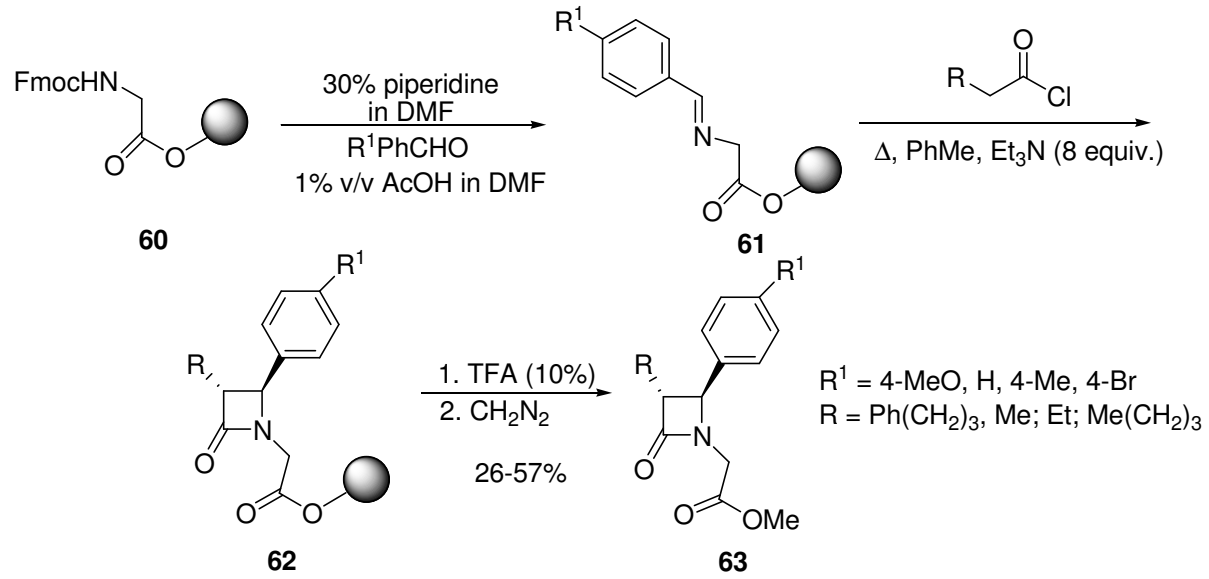


Scheme 17



Scheme 18

A solid-phase strategy has been employed for the rapid generation of two small libraries of *trans* 3-alkyl-substituted 2-azetidinones.[50] The synthetic sequence of the glycine-derived library originates from the Wang resin-tethered Fmoc-glycine **60**. Addition of a controlled excess of alkanoyl chlorides (4 equiv.) and triethylamine (8 equiv.) to the resin bound imines **61** in

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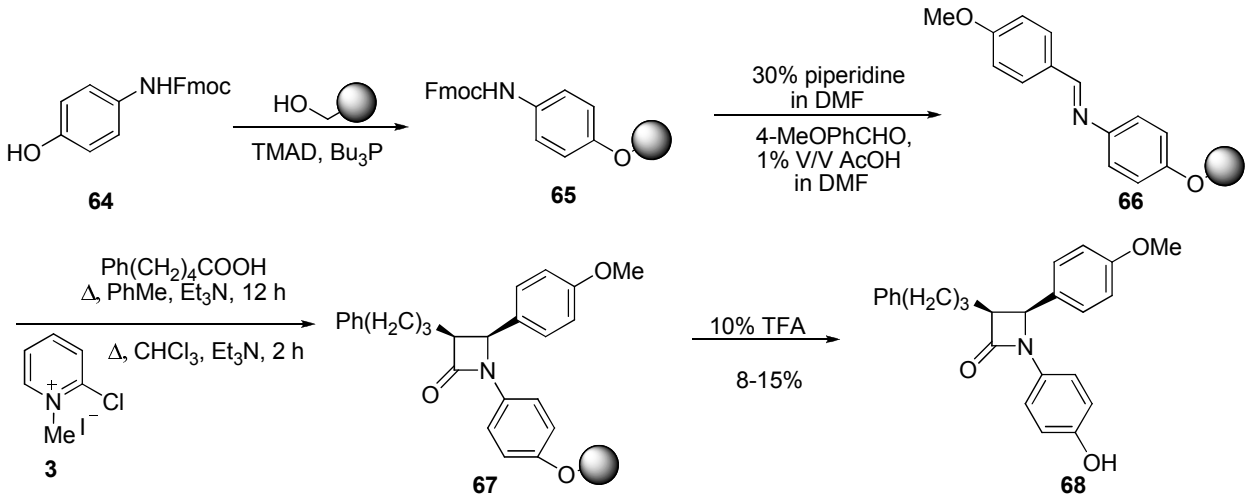
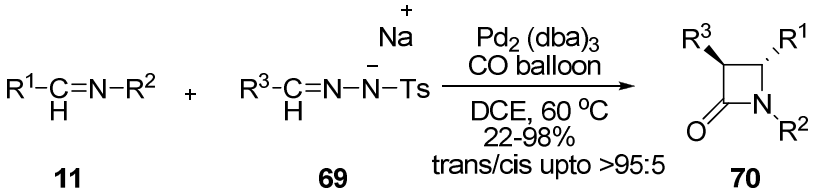
refluxing toluene led to the formation of 2-azetidinones **62**. Cleavage from the resin surface using trifluoroacetic acid and treatment with diazomethane afforded the 3-alkyl 2-azetidinones **63** as a single product with excellent *trans* selectivity (Scheme 18). In the second library, Fmoc-protected *p*-aminophenol **64** was attached to the Wang resin. The resin bound imine **66**, obtained from the reaction of resin-bound aminophenol **65** and *p*-anisaldehyde, was then reacted with 5-phenylpentanoic acid in the presence of triethylamine using the Mukaiyama's reagent **3**. The detachment of resin from the 2-azetidinone **67** by trifluoroacetic acid afforded the 2-azetidinone **68** (Scheme 19).



Scheme 19

The Pd-catalyzed tandem carbonylation-Staudinger cycloaddition gives 2-azetidinones **70** in good yields with excellent *trans* diastereoselectivity except in cases where an *N*-benzyl-substituted imine or the *N*-tosylhydrazone salt containing a strong electron-donating substituent was used.[51] When *N*-tosylhydrazone salts **69** are heated in the presence of a palladium catalyst under pressure of CO, ketene intermediates are generated *in situ* that undergo reaction with imines **11** to afford the 2-azetidinones **70** (Scheme 20).



R^1 = Ph, 4-MeOPh, 4-NO_2Ph
R^2 = Me, Bn, 4-MeOPh
R^3 = Ph, 4-MePh, 4-ClPh, 4-MeOPh, 4-$MeCO_2$Ph, 2,4-Cl_2Ph, 2-naphthyl, 2-furyl

Scheme 20

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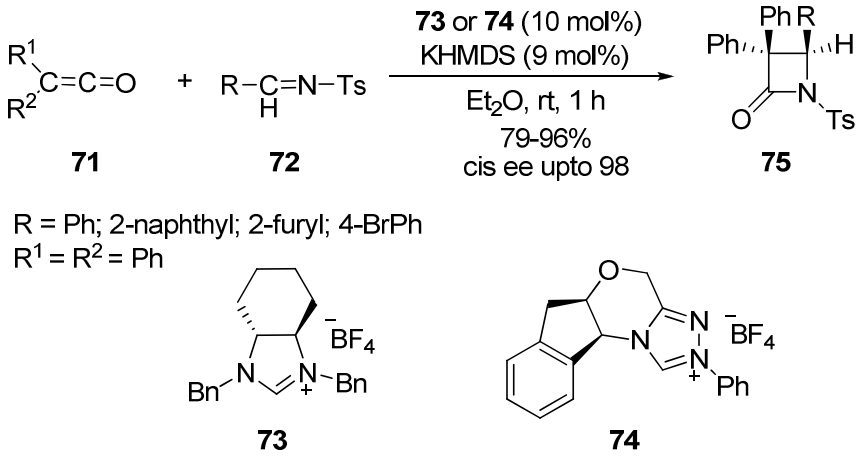
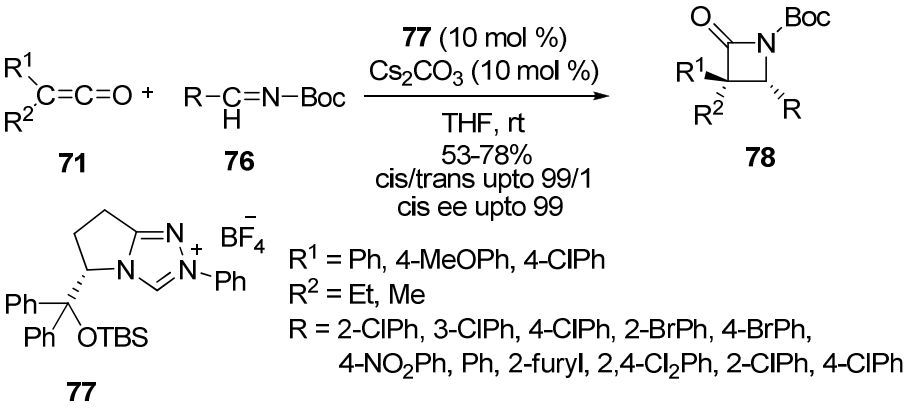
An asymmetric synthesis of 2-azetidinones through the ketene-imine [2+2]-cycloaddition has been achieved employing *N*-heterocyclic carbenes (NHCs) as efficient catalysts.[52,53] The imidazolinium catalyst **73** or triazolium catalyst **74** has been used in the reaction of diphenylketene **71** with *N*-tosylaldimines **72** to give the corresponding 2-azetidinones **75** in excellent yields (Scheme 21).[54] Another chiral NHC **77**, derived from L-pyroglutamic acid, catalyzed the reactions of arylalkylketenes **71** with a variety of *N-tert*-butoxycarbonyl arylimines **76** to give the corresponding *cis*-2-azetidinones **78** in good yields with good diastereoselectivities and excellent enantioselectivity (upto 99% ee) (Scheme 22).[55]



Scheme 21



Scheme 22

A highly diastereoselective synthesis of *trans*-2-azetidinones **82** by a [2+2] cycloaddition between silyl ketene acetals **79** and imines **80** using a phosphonium fluoride multifunctional catalyst **81** (Scheme 23) has been reported.[56] The phosphonium fluoride precatalyst activates the nucleophile and also directs the reaction process for high yield and diastereoselectivity. The precatalyst acts to initiate the reaction because of the high affinity of the fluoride ion for the

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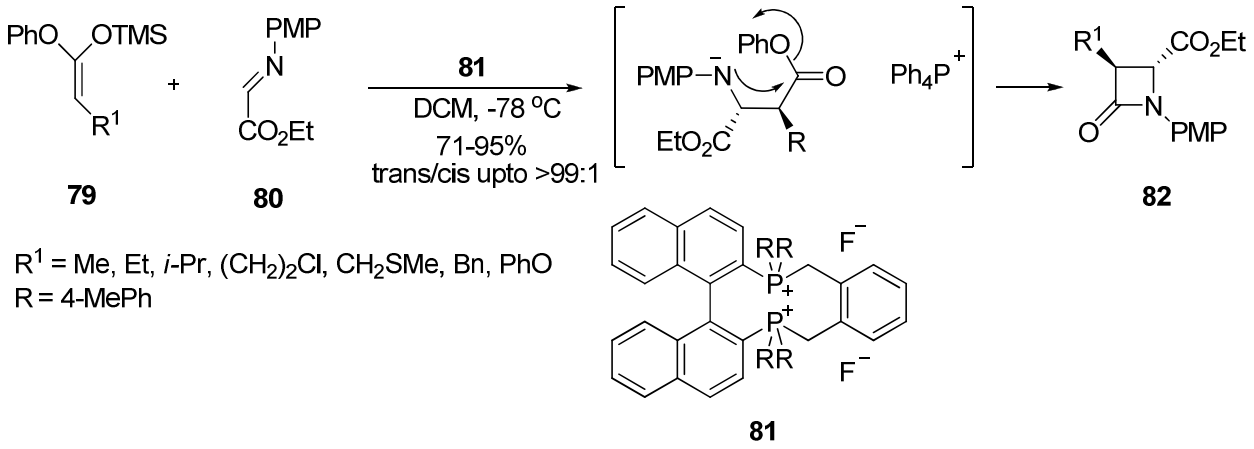
TMS group of the silyl ketene acetal **79.** The bulk of the phosphonium cation was also essential to organize a transition state in such a way that the *trans*-diastereomer is kinetically favored.



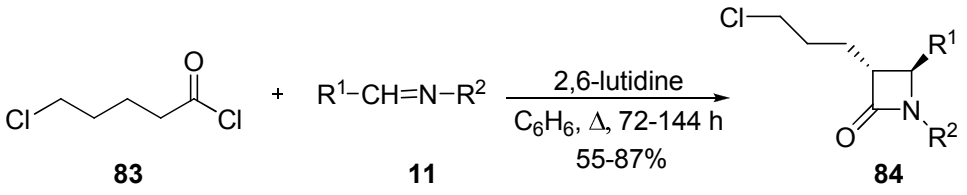
79 **80** **82**

R^1 = Me, Et, *i*-Pr, $(CH_2)_2Cl$, CH_2SMe, Bn, PhO
R = 4-MePh

81

Scheme 23

De Kimpe and coworkers have reported the synthesis of *trans*-4-aryl-3-(3-chloropropyl)azetidin-2-ones **84** in good yields by the Staudinger reaction between imines **11** and 5-chloropentanoyl chloride **83** in the presence of 2,6-lutidine (Scheme 24).[57] The product azetidin-2-ones serve as precursor for 2-arylpiperidine-3-carboxylates.



83 **11** **84**

R^1 = *i* -Pr, Et, Bn, 4-MeOBn, *C*-Hex
R^2 = Ph, 4-MePh, 4-MeOPh

Scheme 24

Singh and coworkers have reported the reaction of *trans*-cinnamaldehyde imines **85** with azido-ketene, generated *in situ* from 2-azidoethanoic acid **86** in the presence of *p*-toluenesulfonyl chloride and triethylamine in dry dichloromethane, to afford the *cis*-3-azido-2-azetidinones **87** (Scheme 25).[58] The reductive cleavage of azide group in the latter compounds afforded 3-amino-2-azetidinones **88**. A [2+3]-cycloaddition of the azide group with various alkynes led to the synthesis of triazole-tethered 2-azetidinones. Both azide and amino functionalities are of immense significance in organic synthesis and can be further transformed to diverse types of compounds containing β-lactam ring.

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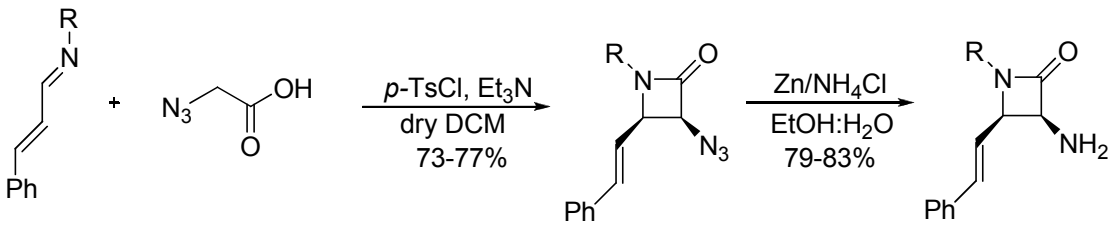
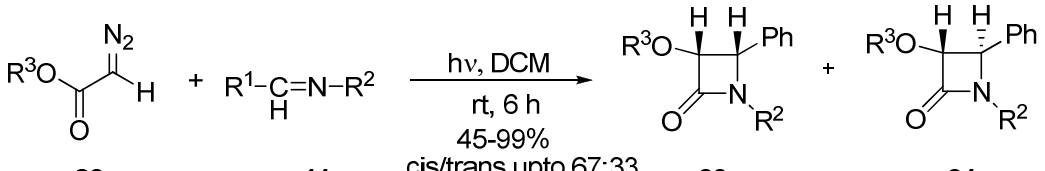


85 **86** **87** **88**

R = Ph, 4-MePh, 4-ClPh, *C*-hex, Bn

Scheme 25

2.1.5 Application of α-diazocarbonyls as ketene precursors. α-Diazocarbonyls are well-known to furnish ketenes under thermal and photochemical conditions.[23] The photochemical reaction of 2-diazo-1,2-diphenylethanone with some imines to yield 2-azetidinones was reported by our group in 1980s.[59] Recently, 3-alkoxy/aryloxy- 2-azetidinones **90** and **91** have been synthesized in satisfactory to good yields by a photo-induced Staudinger reaction of imines **11** and alkyl/aryl diazoacetates **89**.[60] The alkoxy/aryloxyketenes, generated, *in situ* from photochemical decomposition of diazoacetates **89** and the Wolff rearrangement of the resulting carbenes,[61] underwent the Staudinger reaction with various imines **11** to give the 2-azetidinones **90** and **91** (Scheme 26). The *trans*-2-azetidinones were the major products from linear imines that is attributed to the isomerization of the imines from their *trans* isomers into *cis*-isomers under UV irradiation.



89 **11** **90** **91**

R^1 = Ph; R^2 = Ph, Bn; R^3 = *i*-Pr, Bn, Ph

Scheme 26

Our group has reported recently the thermal decomposition of 2-diazo-1,2-diarylethanones **92** in the presence of *N*-substituted imines of 1-methylindole-3-carboxaldehydes **93** affording 3,3-diaryl-4-(1-methylindol-3-yl)-2-azetidinones **94** in good yields (Scheme 27).[62] These 2-azetidinones exhibited excellent antileishmanial activity besides some antibacterial, antifungal, and crown gall-tumor activity.[63] Previously, similar reactions of *N*-salicylideneamines were reported to afford the 2-azetidinones with significant antibacterial and antifungal activity.[64]

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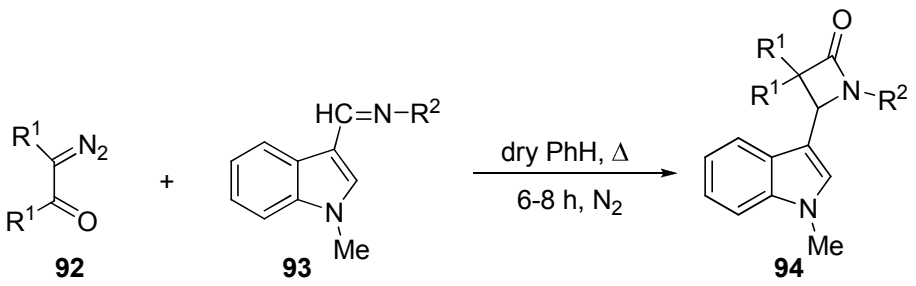
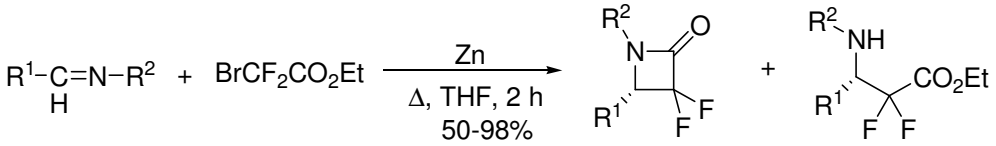


R^1 = Ph, 4-MePh
R^2 = Ph, 4-MePh, 4-MeOPh, 4-EtOPh, 4-ClPh

Scheme 27

2.2 Ester-Enolate Cycloadditions

The ester enolate – imine cyclocondensation provides 2-azetidinones in good yields with higher stereoselectivity. Some recent reactions have been mediated by zinc,[65] rhodium,[66] indium,[67] and diethylzinc.[68] Boyer and coworkers have studied the parameters influencing the selective synthesis of 2-azetidinones **96** or β-amino esters **97** during the Reformatsky reaction of ethyl bromodifluoroacetate **95** with imines **11**.[65] The ratio between β-amino ester and β-lactam depends on the nature of the imine and the reactions conditions. The diastereoselectivity of the reaction was highly dependent on the nature of the chiral auxiliary. Moreover *gem*-difluoro-2-azetidinones **96** and *gem*-difluoro-β-amino esters **97** were obtained with high stereoselectivity by using either (*R*)-phenylglycinol or (*R*)-methoxyphenylglycinol (Scheme 28). The diethylzinc-mediated Reformatsky-type reaction of ethyl dibromofluoroacetate **98** with imines **11** led to the diastereoselective synthesis of *cis*-α-bromo-α-fluoro-2-azetidinones **99** in good yields (Scheme 29).[68] In this reaction, the imine from the reaction of cyclohexane carboxaldehyde and *p*-anisidine gave a mixture of products that were unstable on silica gel.



11 **95** **96** **97**

R^1 = Ph, 4-pyridyl, 3-pyridyl
R^2 = (*R*)-phenylglycinol, (*R*)-methoxyphenylglycinol,
(α)-(*R*)methylbenzylamine, *p*-methoxybenzylamine

Scheme 28

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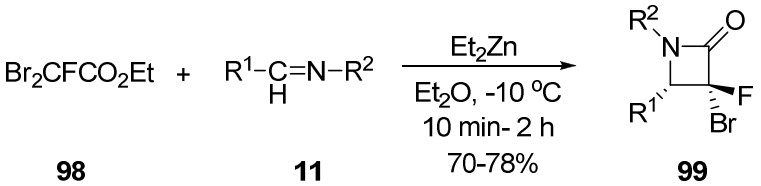
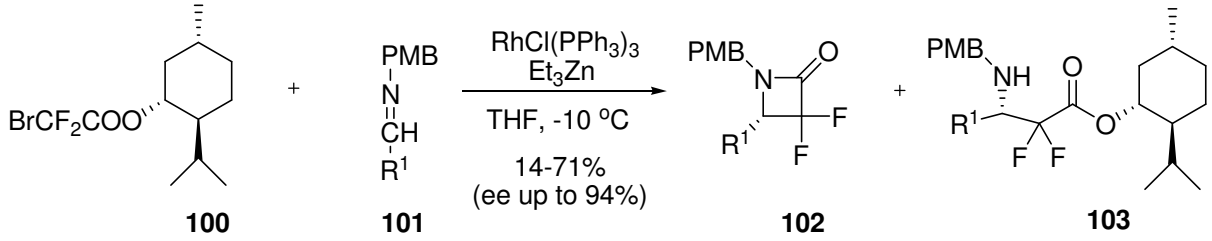


Scheme 29

Tarui and coworkers have reported an asymmetric synthesis of (*S*)-3,3-difluoro-2-azetidinones **102** in moderate to good yields with high diastereoselectivity together with a β-amino ester **103** by the Reformatsky type reaction of (-)-menthyl bromodifluoroacetate **100** with imines **101** in the presence of $RhCl(PPh_3)_3$, followed by spontaneous elimination of the chiral auxiliary (Scheme 30).[66] Among the imines of aromatic aldehydes, those bearing electron-donating groups offered higher enantioselectivity (ee 92-94%) than those bearing electron-withdrawing groups (ee 80-87%). Isobutyraldehyde imine in this reaction, however, afforded a racemate. Another enantioselective synthesis of 3-monosubstituted-, and 3,3-disubstituted 2-azetidinones containing carbohydrate moiety has been reported via an indium-mediated reaction of imines and bromoesters.[67] For example, the reaction of carbohydrate-derived imine **104** with 2-alkyl/phenyl-2-bromoesters **105** in the presence of indium led to the synthesis of 2-azetidinones **106** (Scheme 31). The 2-azetidinone formation is stereoselective at the new nitrogenated stereocenter (C-4). An additional stereocenter is formed at C-3, hence a mixture of epimeric 2-azetidinones at C-3, in which presumably the kinetically controlled product is the major isomer, is obtained.



Scheme 30

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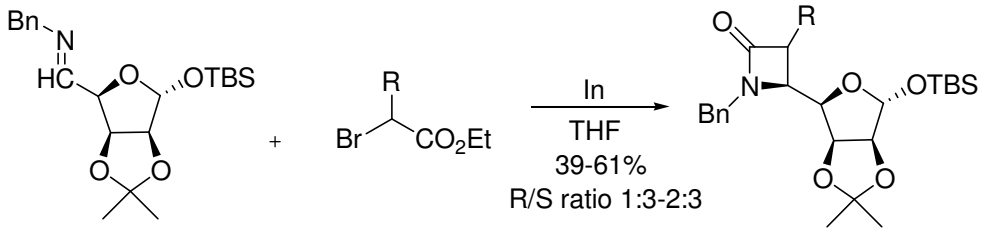


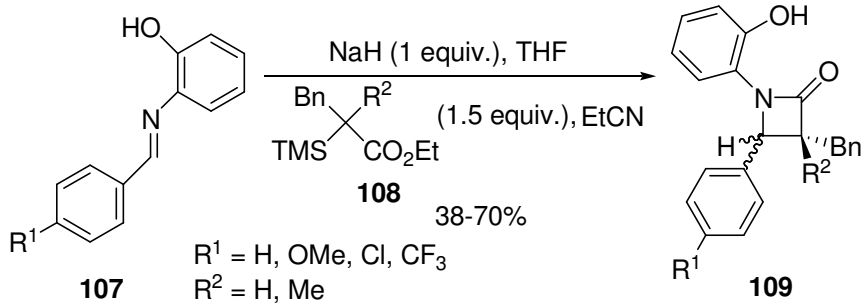
104
R = Ph, Me, *n*-Pr

105

106

Scheme 31

A straightforward approach for the synthesis of β-lactams **109** in moderate to good yields and diastereomeric ratio ranging from 22:78 to 54:46 (*cis:trans*) by employing ETSA derivatives **108** was also reported.[69] The latter compounds react with sodium salts of *N*-(2-hydroxyphenyl)aldimines **107** in a THF-EtCN mixture (Scheme 32). This method has advantage over use of other ketene precursors like acyl chlorides or α-diazocarbonyls because the hydroxyl group in imines needs not be protected.



107

108

38-70%

R^1 = H, OMe, Cl, CF_3
R^2 = H, Me

109

Scheme 32

The reaction of *N*-substituted imines **110** of oxirane carboxaldehydes with *in situ* generated lithium ester enolates from symmetrically α-disubstituted esters **111** and LDA has led to the diastereoselective synthesis of functionalized β-lactams **113** (de up to 99%) through cyclization in intermediate **112** (Scheme 33).[70] When the mono- α-substituted esters were used as enolate precursors, unexpected side reactions occurred with loss of diastereoselectivity. This was attributed to the presence of the additional acidic proton next to the carbonyl group. An enantiomerically-enriched imine (2*S*,3*S*) gave the corresponding 2-azetidinone (2*S*,3*S*,4'*R*).

A three-step protocol for the synthesis of various functionalized *gem*-difluorinated β-lactams **118** in moderate to good yields has been developed by reactions between the Reformatsky reagent derived from ethyl bromodifluoroacetate **115** and the appropriate aldimines **114**.[71] The 3,3-difluoro-2-azetidinones **116** were the major or the only isolated products except in the case of imine with a benzyloxy carbamate group. In the latter case, the β-lactam and β-amino ester

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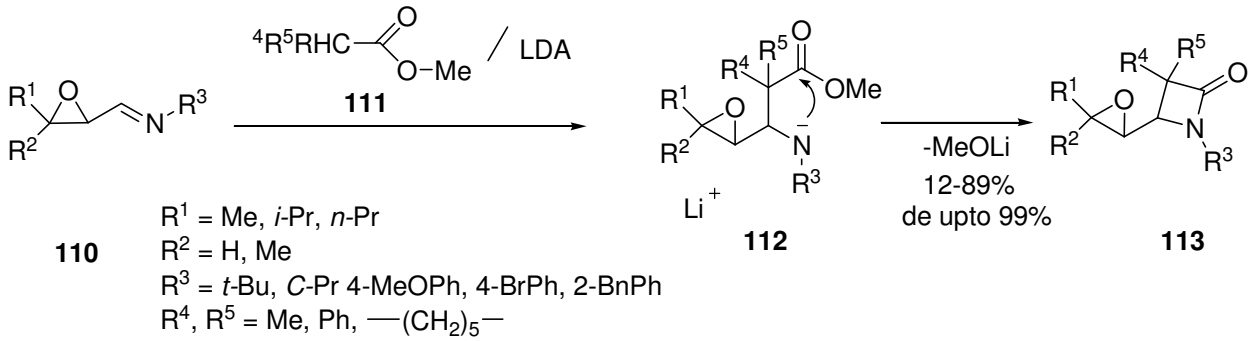
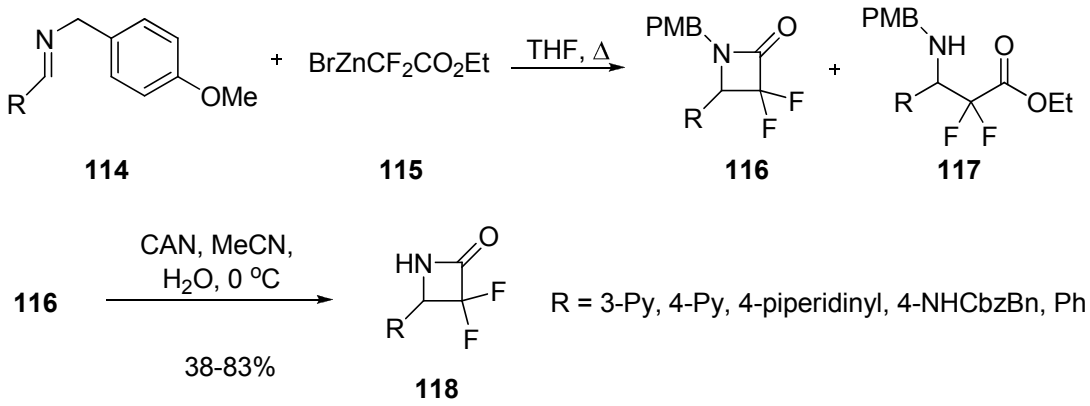
118 were obtained in 1:1 ratio in good overall yield because the presence of a primary carbamate disfavored the cyclization step. Deprotection of the nitrogen atom in 2-azetidinones **116** using ceric ammonium nitrate (CAN) leads to the formation of 2-azetidinones **117** with free NH (Scheme 34).



Scheme 33



Scheme 34

2.3 Alkyne-Nitrone Cycloadditions

The alkyne-nitrone cycloadditions, commonly known as the Kinugasa reaction, has emerged as a powerful tool for the synthesis of diverse types of β-lactams. A formal synthesis of the powerful cholesterol inhibitor ezetimibe **124**, based on a Cu(I)-mediated Kinugasa cycloaddition/rearrangement is reported.[72] The reaction of terminal alkyne **120,** derived from acetonide of L-glyceraldehyde, with suitable *C,N*-diarylnitrone **119** is reported to form the 2-azetidinone **121** (Scheme 35). The adduct (3*R*,4*S*)-2-azetidinone, obtained with high stereoselectivity, was subsequently subjected to opening of the acetonide ring to afford another 2-azetidinone **122**. The glycolic cleavage in 2-azetidinone **122** led to formation of the

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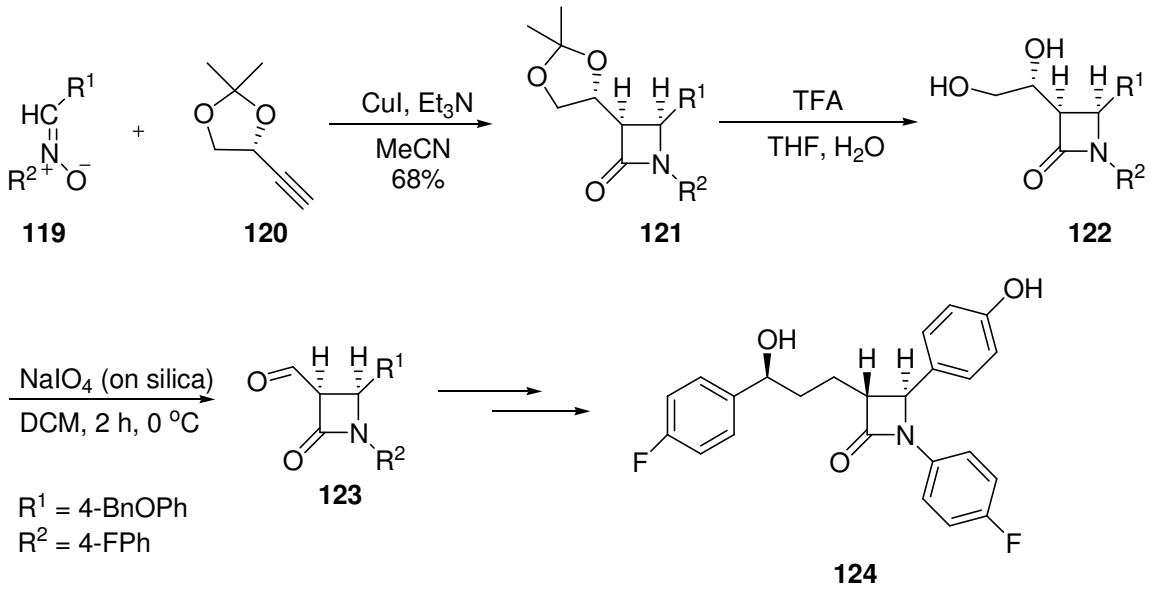
azetidinone carboxaldehyde **123** which was transformed into ezetimibe by the Schering-Plough group.[73]



Scheme 35

The Kinugasa reaction has been efficiently carried out employing ynamides.[74] The reaction of nitrones **119** with 3-ethynyloxazolidin-2-ones **125** led to highly stereoselective (dr 82:18 to ≥ 95:5) synthesis of chiral 3-amino-2-azetidinones **126** (Scheme 36). The application of this methodology has been demonstrated by reductive cleavage and subsequent Boc-protection in **126** resulting into formation of the 3-amino-2-azetidinone **127**. Deprotection of N-1 of the 2-azetidinone **127** with CAN afforded NH 2-azetidinone **128**.

Pezacki and coworkers have reported an "On water" application of Kinugasa reaction in 2-azetidinones' synthesis by a micelle-promoted Cu(I)-catalyzed multicomponent Kinugasa reaction.[75] Reactions were performed for a series of *in situ* generated *C,N*-diarylnitrones with phenylacetylene **131** in the presence of copper sulfate in aqueous media yielding 2-azetidinones **132** in the range of 45-85% together with an amide **133** as a side product (Scheme 37). According to proposed mechanism, Na-ascorbate reduces the Cu(II) to Cu(I) and allows for *in situ* generation of Cu(I) phenylacetylide. This intermediate reacts with *in situ* generated nitrones from substituted benzaldehydes **129** and *N*-phenylhydroxyl amine **130** by a formal [3+2]-cycloaddition forming an isoxazoline intermediate. Protonation of isoxazoline and subsequent rearrangement of the resulting oxaziridine produce a mixture of *cis*- and *trans*-2-azetidinones. The reaction is tolerant to substituents at the α-aryl position of the nitrone, and higher yields of β-lactams were obtained when electron-withdrawing substituents were employed.

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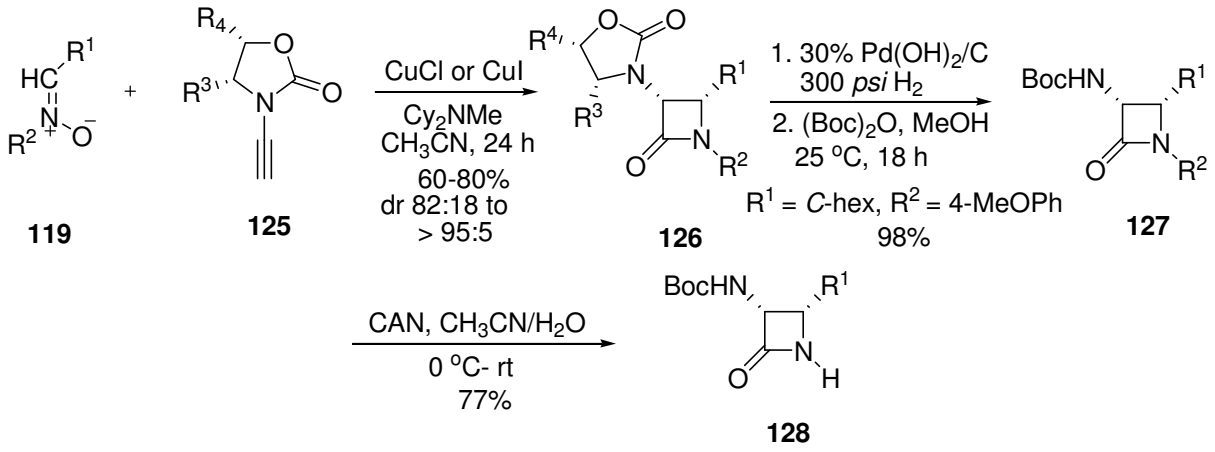
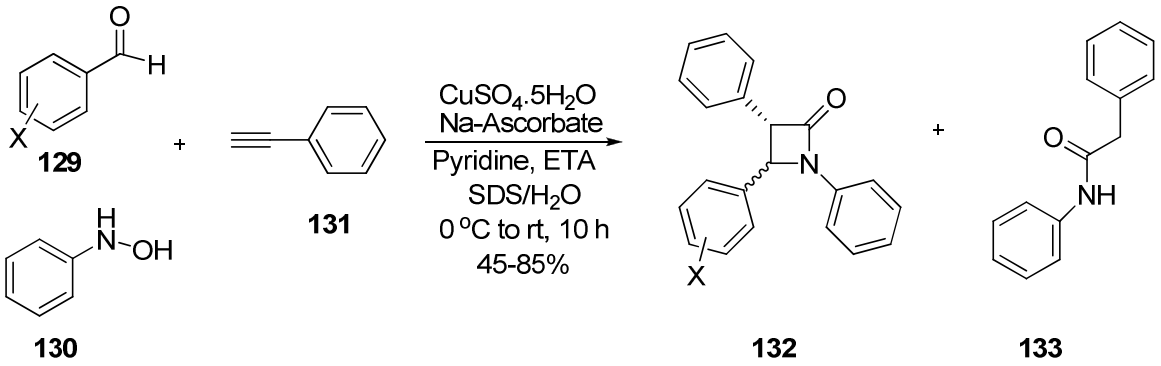


R^1 = 4-BrPh, 1-naphthyl, styryl, 2-furyl, 2-thienyl, Ph, *C*-hex
R^2 = Ph, 4-MeOPh, 4-ClPh, 4-COEt
R^3 =Ph, *i*-Pr, $CHPh_2$, Bn
R^4 = Ph, H, Me

Scheme 36



X = H, 4-Me, 4-OMe, 2-OMe, 4-Br, 4-CO_2Me, 4-CN, 2-NO_2, 4-NO_2

Scheme 37

Treatment of the chiral propargylic alcohols and ethers **134** with diaryl nitrones **119** furnished mainly the *cis* β-lactams **135** (Scheme 38).[76] The subsequent oxidation/epimerization of the *cis*-adduct by treatment with PCC afforded the *trans* isomer. For the first time, the unprotected chiral propargylic alcohols have also been utilized in the Kinugasa reaction.

The asymmetric version of this reaction has been carried out by using nitrones **136** and terminal alkynes **137** in the presence of copper complex of (*S*)-4-*tert*-butyl-2-[3-(diphenylphosphino)thiohen-2-yl]-4,5-dihydrooxazole **138** as a catalyst to afford the 2-azetidinones **139** and **140** in good diatereoselectivity but moderate enantioselectivity (Scheme 39).[77] Diastereoselectivity of the products depends on the nature of the alkynes. Most alkynes

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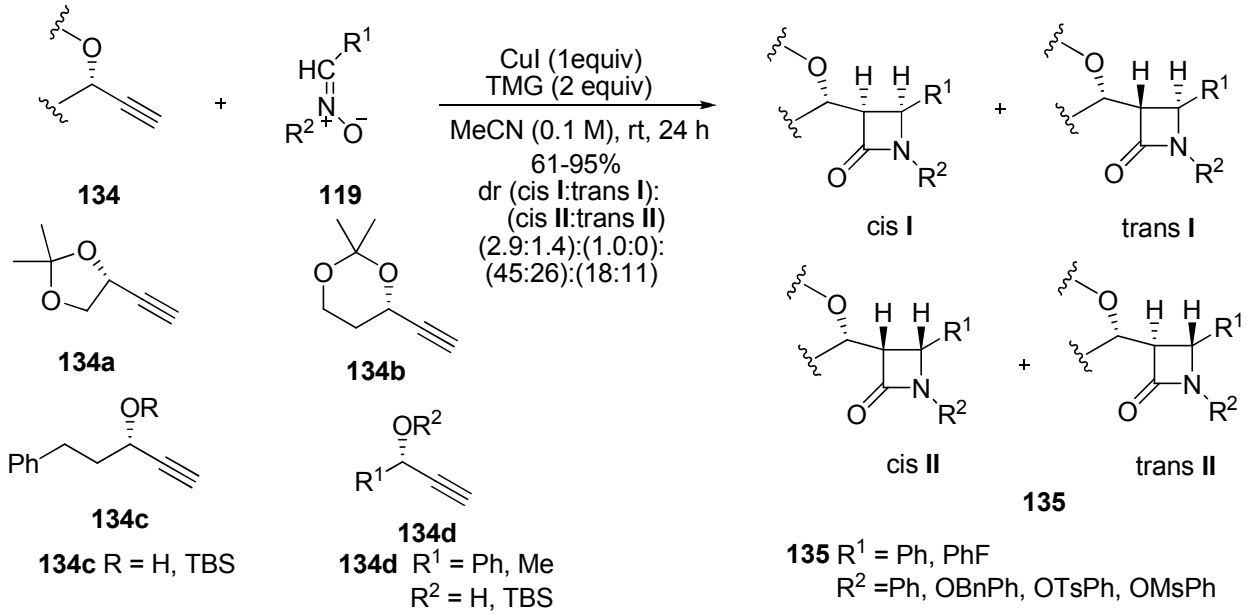
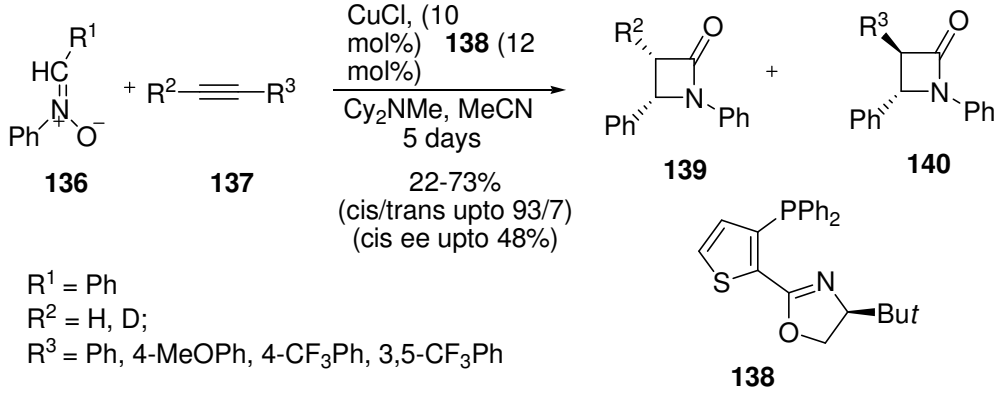
afforded the *cis*-adducts except 3,5-trifluoromethylacetylene which furnished trans-adducts. Very recently, Chen and coworkers have reported chiral tris(oxazoline)] **142**/Cu(I) complex as a novel efficient catalyst for an asymmetric Kinugasa reaction of terminal alkynes **141** with *C*-aryl nitrones **119** to afford the 2-azetidinones **143** and **144** in highly diastereo- and enantioselective manner (Scheme 40).[78] Another highly enantioselective Kinugasa reaction of nitrones **136** with terminal alkynes **145** in the presence of bis-oxazoline **146**/$Cu(OTf)_2$ and dibutylamine has been reported to yield 2-azetidinones **147** and **148** (Scheme 41).[79] The scope of alkyne-nitrone cycloadditions has been further expanded by Sierra and coworkers who used ferrocene- and ruthecene-containing alkynes to synthesize metal-containing 2-azetidinones.[80]



Scheme 38



Scheme 39

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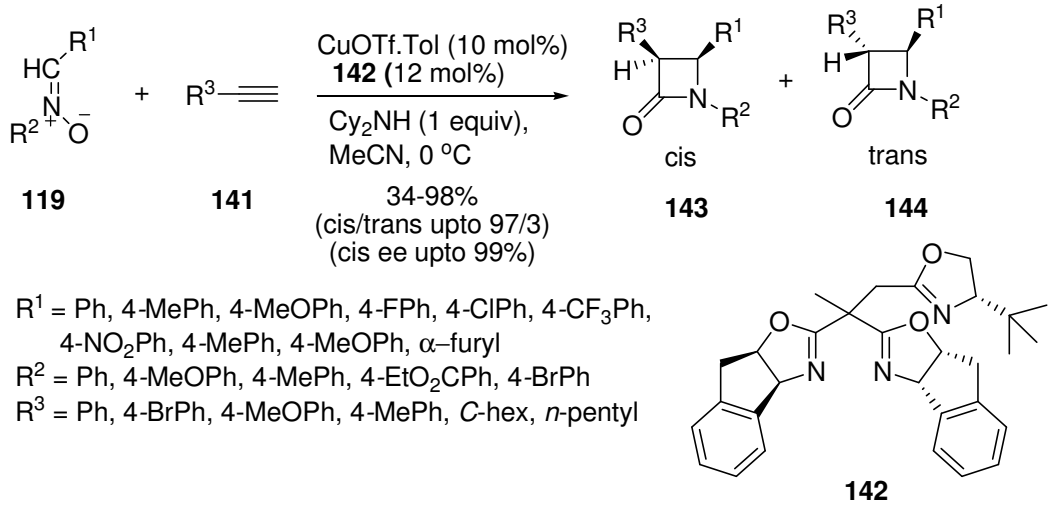
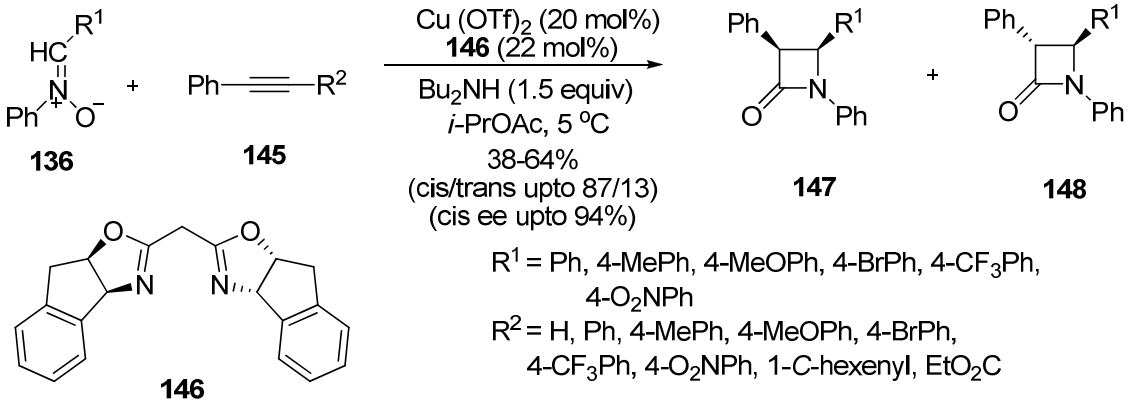


Scheme 40



Scheme 41

2.4 Alkene-Isocyanate Cycloadditions

The cycloaddition of vinyl acetate **149** and chlorosulfonyl isocyanate **150** has been employed recently by Lee in the synthesis of 3-isopropylthio-2-azetidione **154** (Scheme 42).[81] After *in situ* reductive removal of the chlorosulfonyl group from the 2-azetidinone **151**, the resulting 2-azetidinone **152** was thioalkylated using sodium isopropylthiolate **153** to yield the 2-azetidinone **154**.

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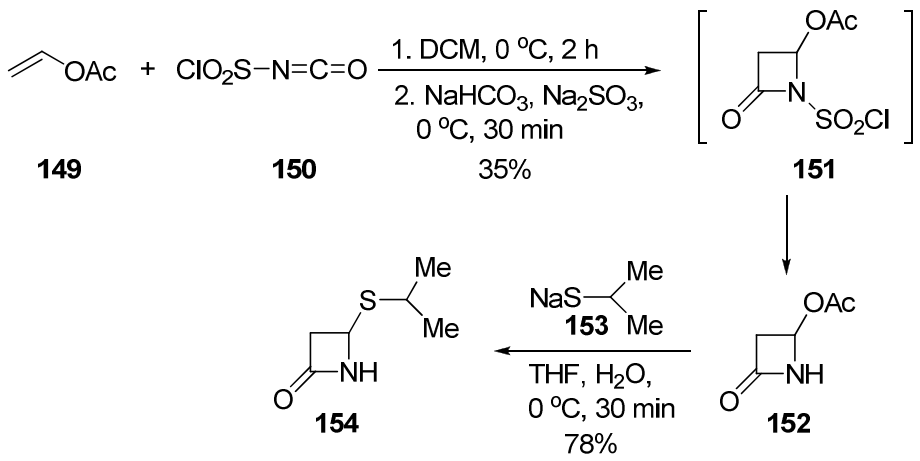
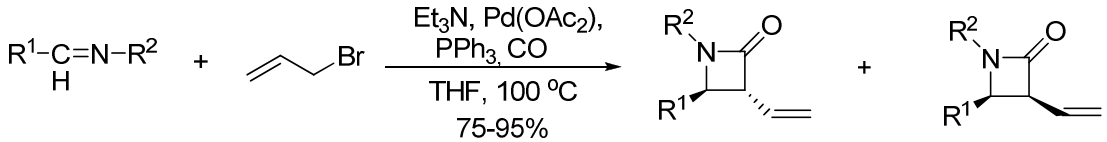


Scheme 42

2.5 Torii's Cyclocarbonylation of Allyl halides with Imines

The imines react with allyl bromide by [2+2]-cycloaddition under CO pressure in the presence of Et_3N, $Pd(OAc)_2$ and Ph_3P.[82] Imines conjugated with a carbonyl group furnish *cis*-2-azetidinones whereas the nonconjugated imines afford *trans*-2-azetidinones.[83,84] The synthesis of 2-azetidinones **155** and **156** with high diastereoselectivity is reported by a palladium-catalyzed [2+2]-carbonylative cycloaddition of allyl bromide with *N*-alkyl imines **11** of benzaldehyde and many other heteroaromatic aldehydes (Scheme 43).[85] An efficient carbonylative [2+2]-cycloaddition of benzyl halides and phosphates with imines **11** in the presence of $[(Bmim)PdI_2]_2$ catalyst leading to the formation of 2-azetidinones **157** in a highly stereoselective manner (trans/*cis* ratio up to >95/5) with up to 96% yield is reported (Scheme 44).[86] 3,4-Diaryl 2-azetidinones **158** have been prepared with high stereoselectivity via palladium-catalyzed [2+2]-carbonylative cycloaddition of benzyl halides with *N*-benzylideneamines and many other *N*-heteroarylideneamines **11** (Scheme 45).[87] It appeared that the substituent on nitrogen atom of the imines influenced the stereoselectivity. The phenyl and the *n*-butyl groups led to cyclization toward the formation of the *trans* isomer. Conversely, the bulky *tert*-butyl group favored the cyclization toward the *cis* isomer.



R^1 = Ph, 2,4-dimethylthiazole, 2-methylbenzothiazole, 4-MePy, 2-MePy, 3-MePy
R^2 = *t*-Bu, *n*-Bu, *i*-Pr, Et

Scheme 43

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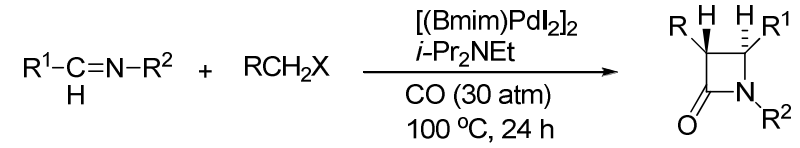
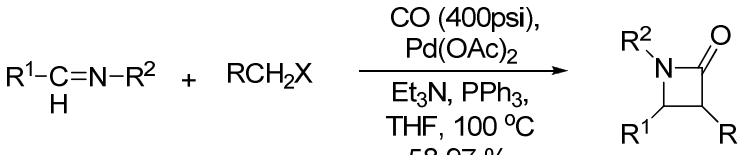


11 **157**

X= Cl, Br, $OP(O)(OEt)_2$
R = Ph, 4-ClPh, 4-BrPh, 4-MePh, 2-MeOPh, 4-MeOPh, 1-Naphthyl
R^1 = Ph, 4-ClPh 4-BrPh, 4-MePh, 2-MeOPh, 2,3-MeO_2Ph, 4-Me_2NPh, 1-Naphthyl, (*E*)-PhCH=CH
R^2 = Bn, Ph, *n*-Pr, CH_2CO_2Me

Scheme 44



11 **158**

R = Ph, 2,4-Me_2Ph, 2-Me,4-MeOPh
R^1 = 2,4-dimethylthiazole, 2-methylbenzothiazole, 2-MePy, 4-MePy, Ph
R^2 = Ph, *n*-Bu, *t*-Bu
X = Br, Cl

Scheme 45

2.6 Expansion of Aziridine Rings

The palladium-catalyzed carbonylative ring expansion of vinyl aziridines **159** is reported to yield the 2-azetidinones **160** (Scheme 46).[88] The 2-azetidinones **160c** was the predominant diastereomer (dr 76-100%) with cinamyl aziridines as substrate. The reversal of diastereoselectivity to *cis* isomer **160b** was possible at high pressure of CO, low Pd concentration and low temperature. A methyl-substituted vinyl aziridine decomposed under standard reaction conditions but yielded the *trans* 2-azetidinone **160a** at 50 bar pressure of CO. The reaction involved a Pd(0)-mediated isomerization of vinyl aziridines followed by carbonylation and ring closure.

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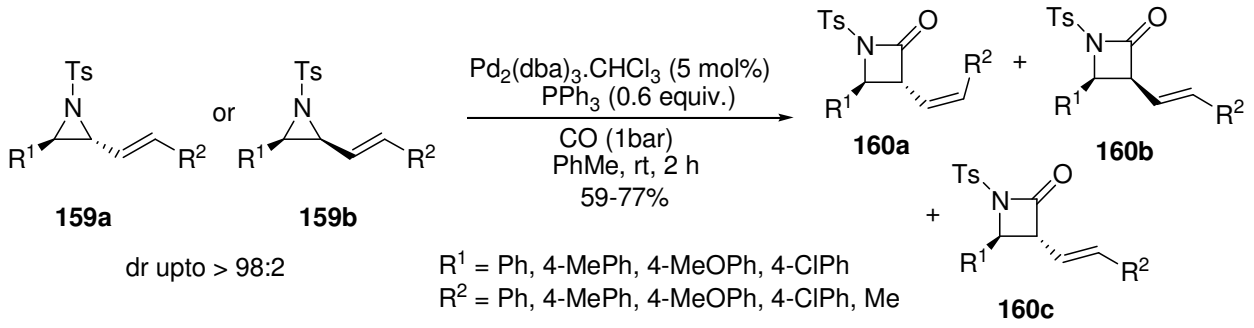
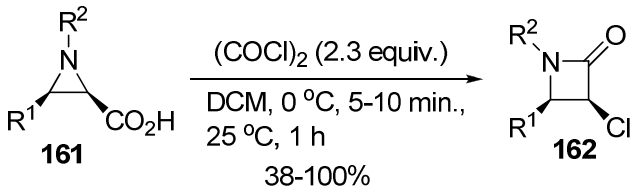


Scheme 46

Wulff and coworkers have published their study on reactions of aziridine-2-carboxylic acids **161** with oxalyl chloride under different conditions.[89] This group observed exclusive formation of 2-azetidinones **162** in case of aziridines containing an alkyl group on C-3 position (Scheme 47). The reactions of *cis*-aziridines led to the formation of *cis*-2-azetidinones and *tran*s-aziridines led to the formation of *trans*-2-azetidinones; thus the reaction is stereospecific.



Scheme 47

2.7 Cyclization by Formation of N_1-C_2 Bond

1'-Aminoalkyldioxolan-4-ones **164**, obtained by an acid-induced removal of sulfinyl protecting group from the 1'-*N*-sulfinylaminoalkyl-dioxolan-4-ones **163**, are reported to undergo cyclization affording chiral 3-hydroxy-2-azetidinones **165** in good yields and excellent diastereoselectivity (Scheme 48).[90] The base-induced cyclization in the unprotected dioxolan-4-ones **164** by nucleophilic attack of the amino group on carbonyl carbon followed by dioxolane ring opening and hydrolysis of the resulting ester has been reported to afford the final products.

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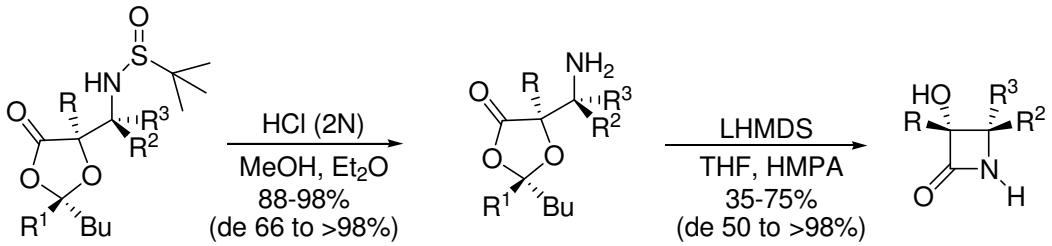
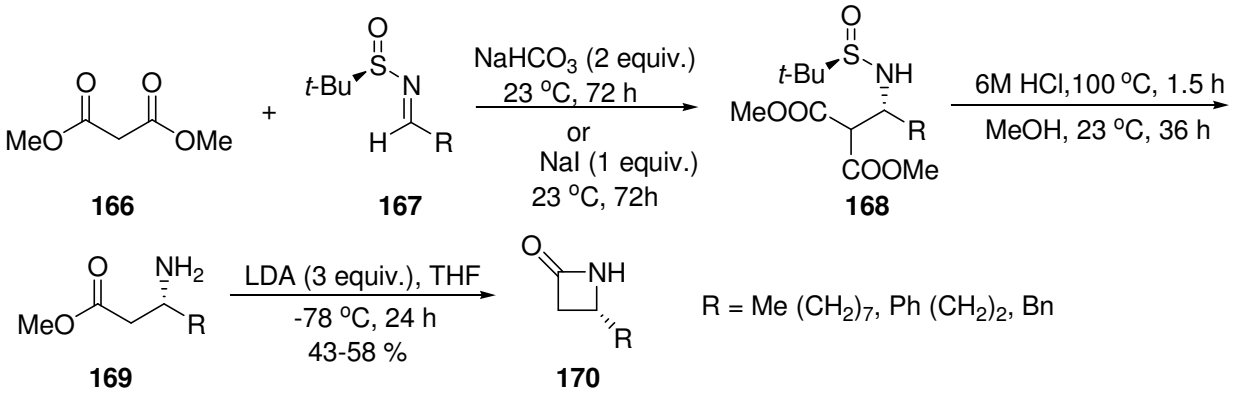


163 **164** **165**

R = Me, Ph; R^1 = Me, H; R^2 = Me, Et, *n*-Pr, *n*-Oct; R^3 = Me, Et, *n*-Pr, *n*-Oct

Scheme 48

In the next example, the β-amino esters **169** have been cyclized in the presence of LDA to furnish the corresponding 2-azetidinones **170** with high optical purity (Scheme 49).[91] The β-amino esters were accessed by the highly diastereoselective direct Mannich-type reaction of dimethyl malonate **166** with *N*-(*tert*-butyl)sulfinyl imines **167** under solvent-free conditions using $NaHCO_3$ or NaI as base promoters and deprotection of the *N*-*tert*-butylsulfinyl group from the resulting adducts **168**.



166 **167** **168** **169** **170**

Scheme 49

Kashikura and coworkers have developed a catalytic enantioselective Mannich-type reaction of aldimines **76** with difluoroenol silyl ether **171** by employing biphenol-derived chiral phosphoric acid **172** (Scheme 50).[92] The resulting Mannich adduct, an α-gem-difluoro-β-amino ketone **173** furnished the corresponding β-amino ester **174** without loss of enantioselectivity on treatment with *m*-CPBA in DCM/HFIP (hexafluoroisopropanol) in the presence of aqueous phosphate buffer. Deprotection of amino group in this ester and the subsequent base-promoted cyclization afforded the 3,3-difluoro-4-phenylazetidin-2-one **175** (Scheme 50). Melchiorre and coworkers have reported cyclization of aspartic acid derivative **176** leading to enantioselective synthesis of 2-azetidinones (Scheme 51).[93] The protection of NH group in 2-azetidinone **177** with Boc group afforded (3*R*,4*S*)-*N*-Boc-2-azetidinone **178**.

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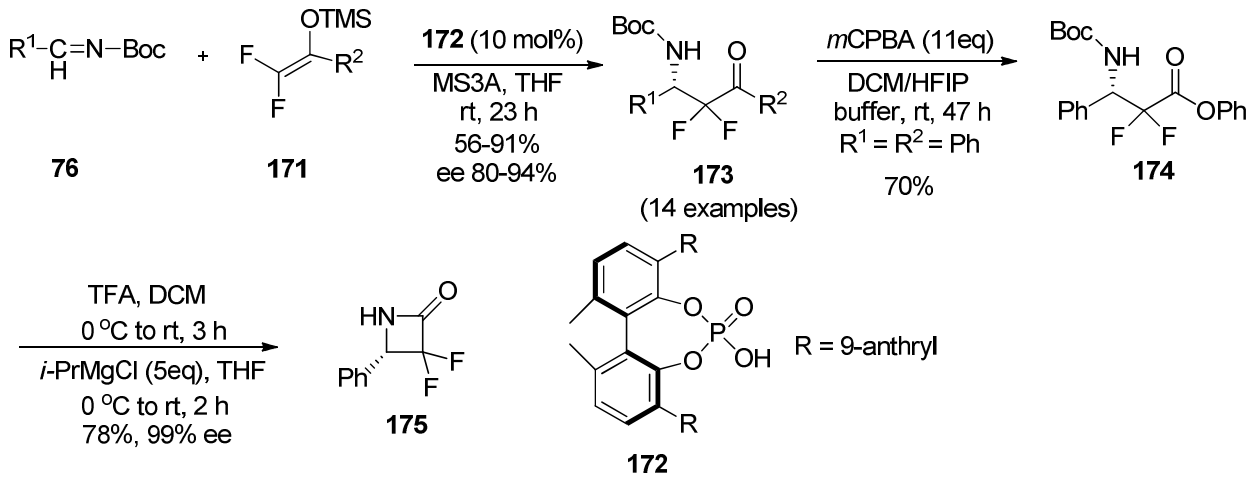
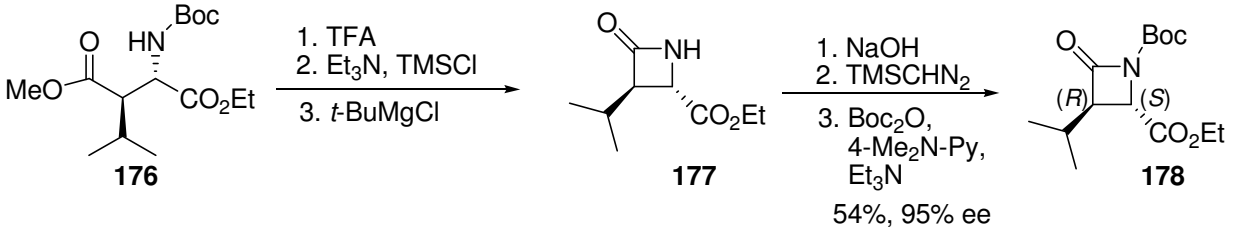
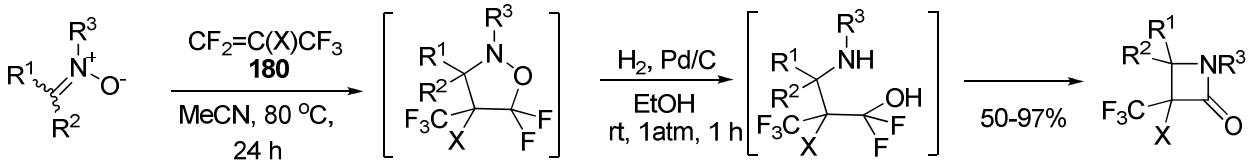


Scheme 50



Scheme 51

The cyclization of β-amino alcohols **182**, formed *in situ* by catalytic hydrogenolysis of the fluorinated isoxazolidines **181**, has led to the formation of α-trifluoromethyl-2-azetidinones **183** in good to excellent yields (Scheme 52).[94] The isoxazolidines were, in turn, synthesized by 1,3-dipolar cycloaddition of nitrones **179** with fluorinated alkenes **180**.



R^1 = aryl, heteroaryl; R^2 = H, Ph; R^3 = Me, -$(CH_2)_3$OH
X = H, F

Scheme 52

An excellent methodology for stereodivergent synthesis of both *cis* and *trans*-β-lactams has been developed by cyclization of α-aminoketenes **189**.[95] The synthesis originates from an

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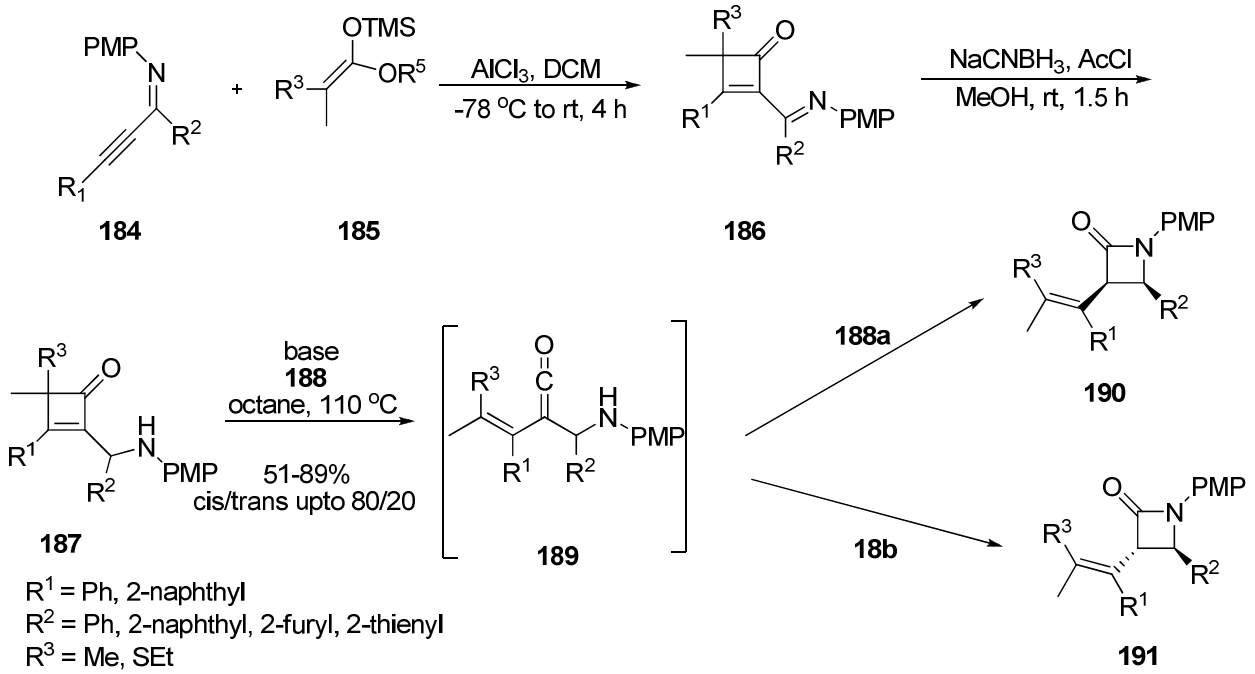
addition of alkynyl imines **184** to ketene silyl acetals **185** forming iminocyclobutenones **186** (Scheme 53). A chemoselective reduction of azomethine linkage in iminocyclobutenones **186** by sodium cyanoborohydride affords aminocyclobutenones **187** that rearrange to α-aminoketenes **189** in the presence of amine bases **188**. The ketenes that cyclize by intramolecular nucleophilic addition of the amino group to the carbonyl carbon furnish either *cis* or *trans*-β-lactams **190** and **191**, respectively, depending on the nature of the base used. Application of 1,4-dimethyl- and 1,4-diethylpiperazines **188a** led to the formation of *cis*-β-lactams **190** while in the presence of stronger bases such as DBN and DBU **188b**, the *cis*-β-lactams isomerized into thermodynamically more stable *trans*-β-lactams **191** (Scheme 53).



Scheme 53

Another methodology based on cyclization of α-aminoketenes is reported by employing an α-diazo-*N*-methoxy-*N*-methyl (Weinreb)-β-keto amide, containing an amino group at an appropriate position, as ketene precursor.[96] The formation of enantiometrically pure 2-azetidinones **195** and **196** was observed on photolysis of α-diazo-*N*-methoxy-*N*-methyl (Weinreb) β-ketoamide **192** (Scheme 54). Both MVL (Medium pressure mercury vapor lamp) and CFL (continuous flow lamp) were utilized to promote the photolysis; the latter afforded a safe and environment-friendly alternative to standard photolysis conditions. The mechanism involved the cyclization of *in situ* generated ketene **193** through the 2-hydroxyazetine **194**. The diastereoselectivity was observed to vary from the modest to nearly complete.

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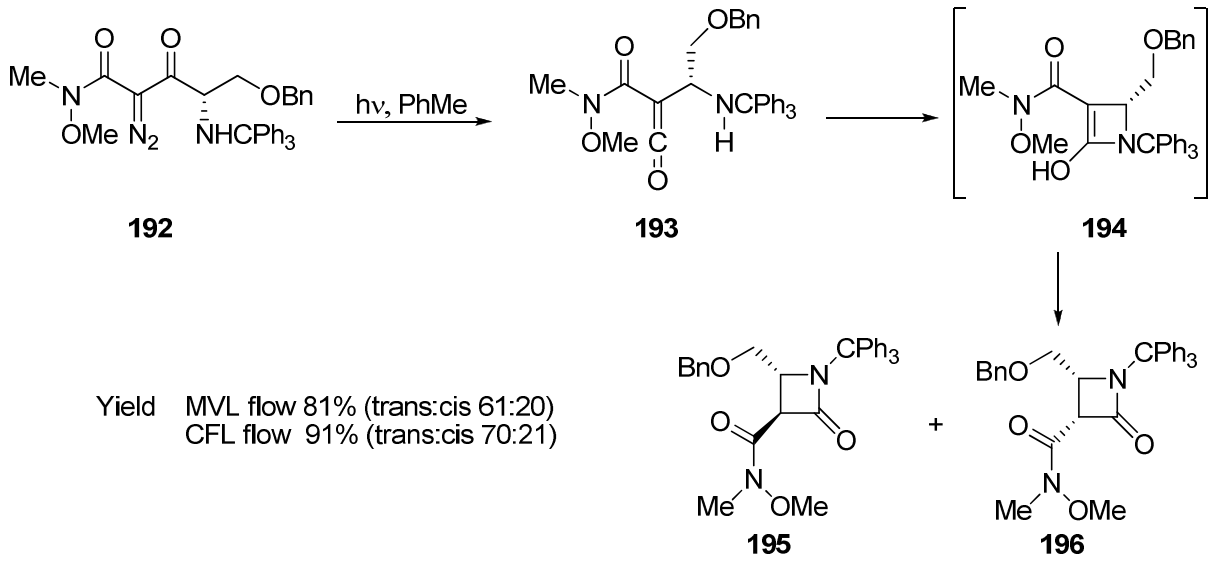
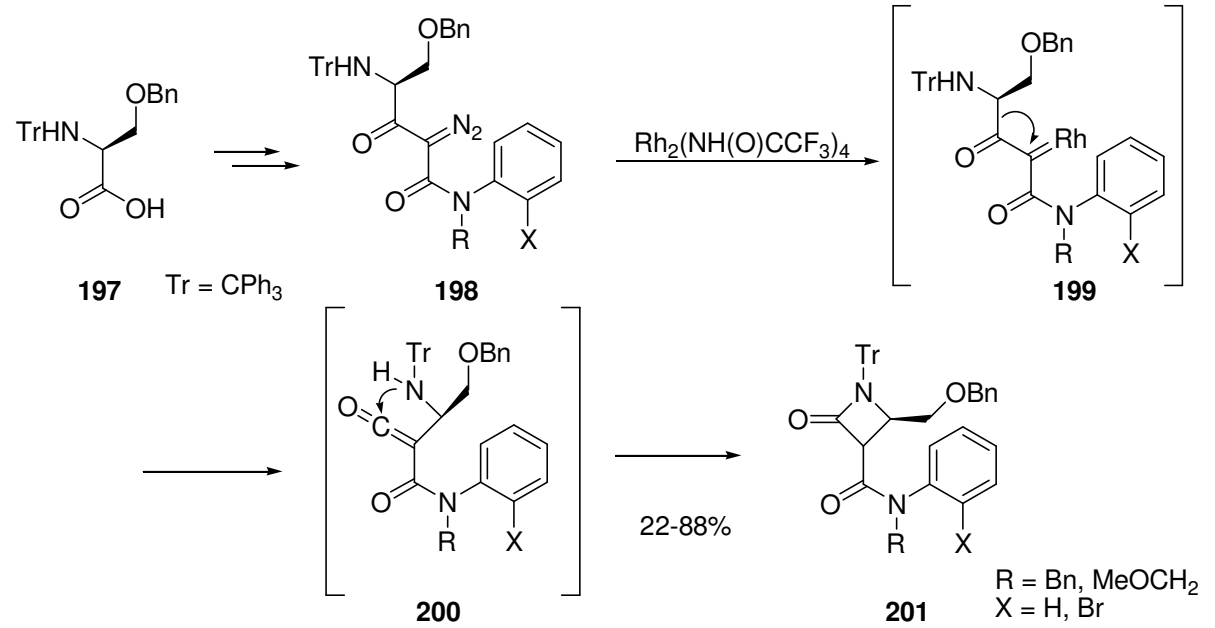


Scheme 54

Decomposition of the α-diazo β-ketoamides **198,** derived from Tr-Ser(OBn)-OH **197,** under photochemical or rhodium catalysis afforded the ketene intermediate **200** by the Wolff rearrangement of rhodium carbenoid **199** (in case of rhodium catalysis) (Scheme 55).[97] The ketene undergoes intramolecular attack by the trityl-protected amine to provide the *trans*-trityl-protected β-lactams **201.** The amino acid stereocenter was incorporated, the second chiral center was induced, and trityl protection of the β-lactam ring has been realized for the first time. This is the direct formation of the β-lactam nucleus from α-amino acids.



Scheme 55

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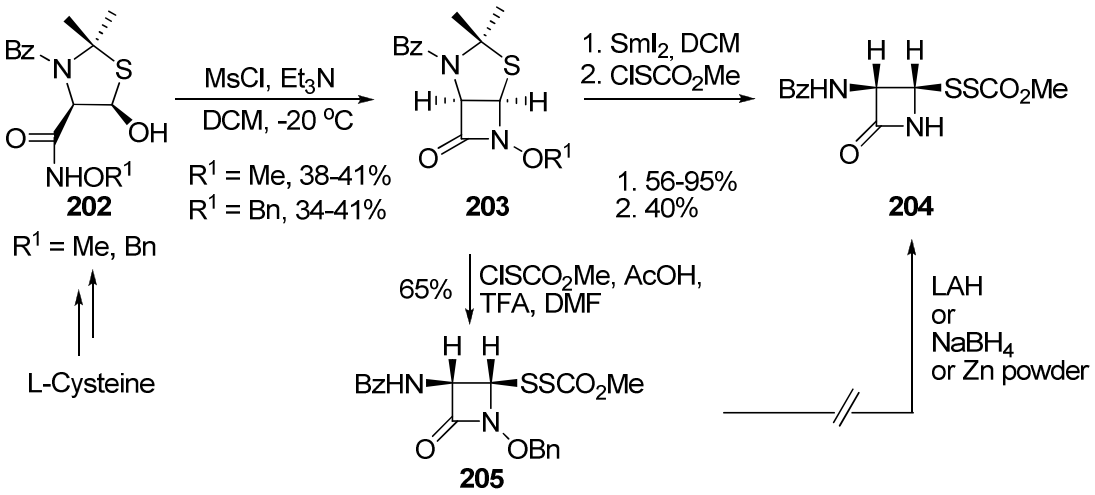
2.8 Cyclization by Formation of N_1-C_4 Bond

L-Cysteine-derived thiazolidine hydroxamate esters **202** are cyclized to the thiazolidine-fused 2-azetidinones **203** using methyl sulfonyl chloride.[98] The cleavage of the thiazolidine ring with methoxycarbonylsulfenyl chloride afforded the monocyclic β-lactam **205** in 65% yield (Scheme 56). Attempts to deprotect the nitrogen in β-lactam **205** using LAH, $NaBH_4$, Zn powder, etc. and obtain the β-lactam **204** proved futile due to cleavage of N1-C4 bond of the β-lactam ring. Ultimately the β-lactam **204** could be accessed by first deprotection of the nitrogen in thiazolidine-fused β-lactam **203**, and then cleavage of the thiazolidine ring in it.



Scheme 56

A NaOH-promoted intramolecular aza-Michael addition of α-carbamoyl,α-(1-chlorovinyl)ketene-*S,S*-acetals **206** followed by the nucleophilic vinylic substitution reaction yielded 1,4,4-trisubstituted 3-alkylidene-2-azetidinones **209**.[99] An intramolecular aza-Michael addition of the nitrogen atom to the unsaturated β-carbon of ketene-*S,S*-acetals **206** under basic conditions, generates carbanionic intermediates **207**, which subsequently undergo protonation reaction in alcoholic aqueous media to afford the intermediate products **208** (Scheme 57)**.** Finally, the displacement of chloride in compounds **208** by alkoxide ion via nucleophilic vinylic substitution reaction gives rise to 2-azetidinones **209** in 41-94% yields**.** In most of the cases only (*E*)-isomer was obtained. The cyclization was successful in ethanol and methanol but not in *tert*-butanol presumably due to steric effect and low nucleophilicity of *tert*-butoxide.

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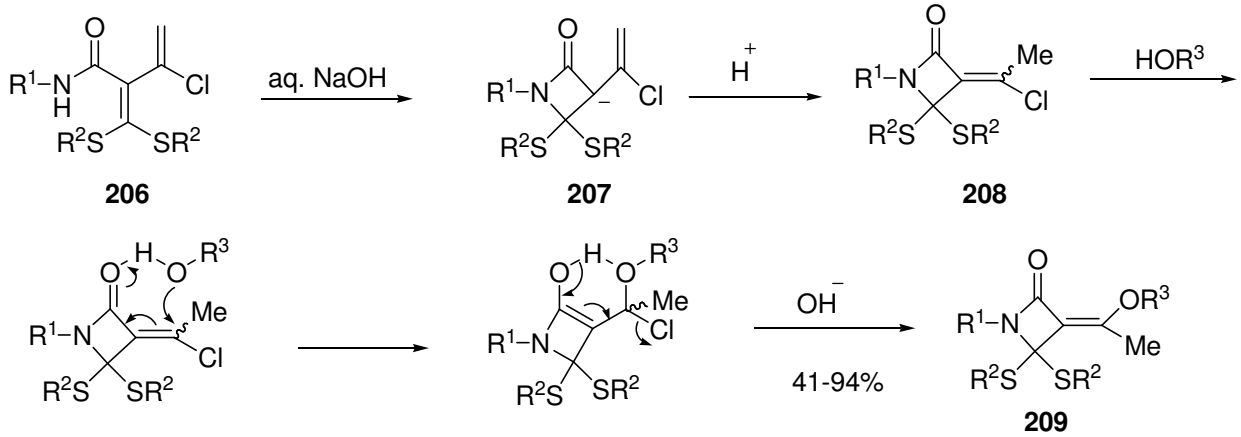
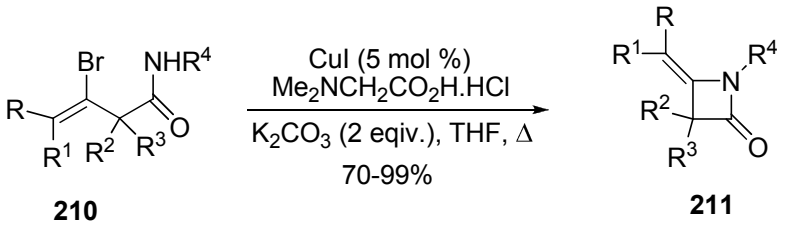


R^1 = Ph, 4-MePh, 4-MeOPh, 4-ClPh, 2,4-Me_2Ph, Me
R^2 = Me, Et
R^3 = Et, Me, *i*-Pr, *t*-Bu

Scheme 57

Zhao and Li have reported a highly efficient method for the synthesis of 4-alkylidene-2-azetidinones **211** *via* a copper-catalyzed intramolecular C-N coupling in 3-bromo-but-3-enamides **210** (Scheme 58).[100] Under Cu(I) catalysis, the 4-*exo* ring closure was preferred over other modes of cyclization.



R = H, Me
R^1 = R^3 = H, C_6H_{13}, Me
R^2 = H, Me, Bn
R^4 = Ph, 4-CO_2MePh, 4-MePh, 4-MeOPh, $C_{12}H_{25}$, *C*-hex, Bn

Scheme 58

2.9 Cyclization by Formation of C_3-C_4 Bond

Acylation of α-amino esters **213**, obtained from Tyr(Bz)-OMe and H-Tyr(2,6-ClBz)-OMe **212** via imine formation and reduction of the imine, with (*S*)-2-chloropropanoic acid **214** is reported to afford *N,N*-disubstituted 2-chloropropanamides **215** (Scheme 59).[101] The products **215** cyclized in the presence of *tert*-(butylimino)tris(pyrrolidino)phosphorane (BTPP) to afford the 2-azetidinones **216**.

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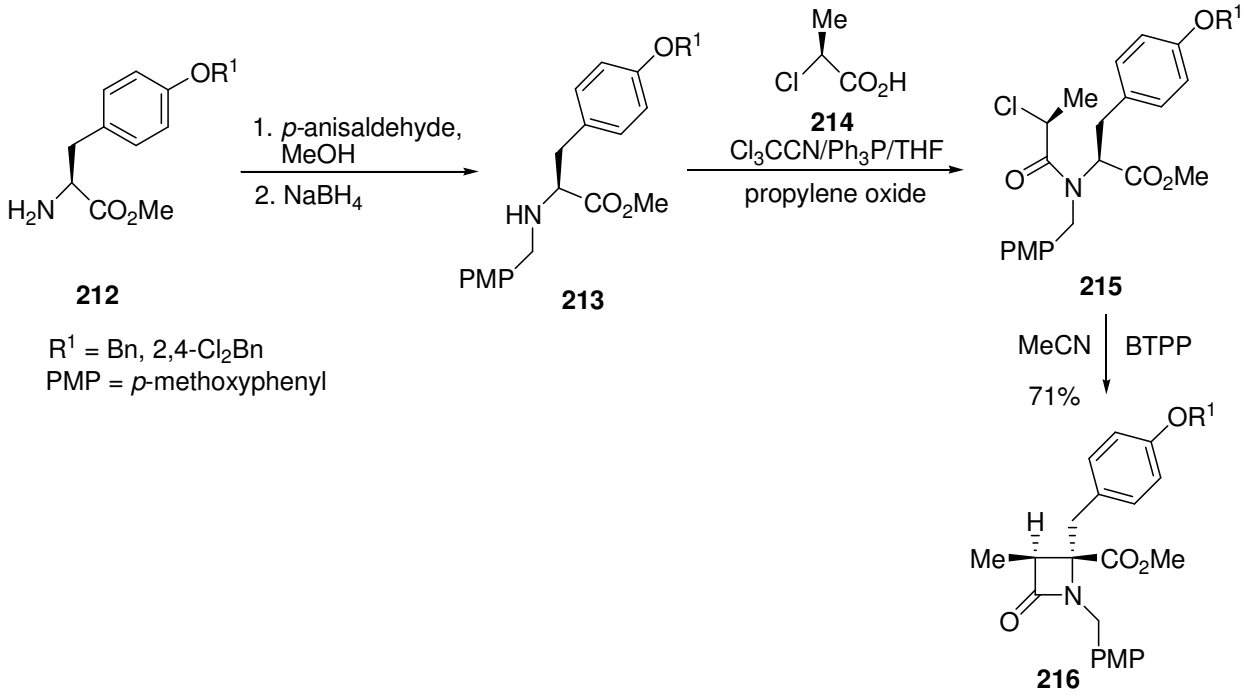
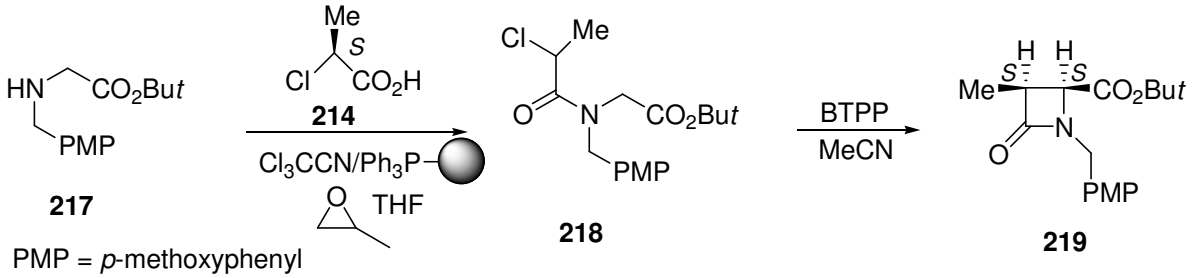


Scheme 59

The BTPP-induced cyclization of 2-(*S*)-chloropropionyl amino ester **218**, obtained from (*S*)-2-chloropropanoic acid **214** and amino ester **217**, led to the synthesis of 1,3,4-trisubstituted 2-azetidinones **219** in enantiopure form (Scheme 60).[102] A significant amount of a morpholine-dione-derivative, the product of *O*-alkylation, was also formed in the reaction. The enantioselectivity has been explained by theoretical calculation of the energies of the transition states leading to either *R,S* or *S,S* enantiomer.



Scheme 60

An excellent electrochemical process is reported for the synthesis of 2-azetidinones employing intramolecular nucleophilic substitution as the key reaction.[103] Electrochemically generated imidazolium carbene **221** is used to generate the carbanions **222** from the *N,N*-disubstituted α-bromoamides **220.** Displacement of the bromide by carbanioinc carbon in intermediate **222** affords 2-azetidinones **223** (Scheme 61).

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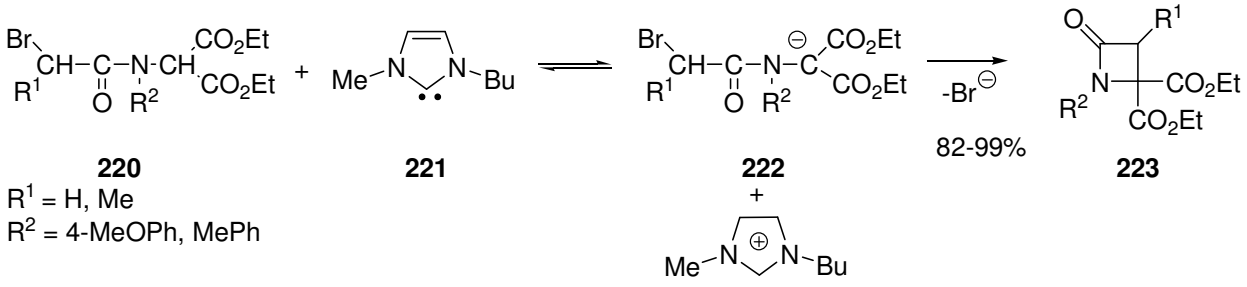
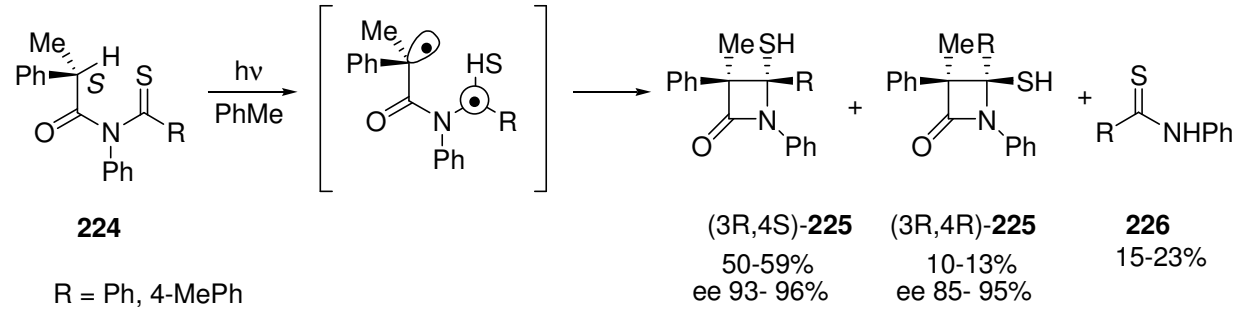


Scheme 61

As a first example of a chiral memory effect for a photochemical γ-hydrogen abstraction, Sakamoto and coworkers have reported the formation of optically active 4-mercapto-2-azetidinones **225** by C_3 – C_4 bond formation *via* photochemical intramolecular γ-hydrogen abstraction of thioimides **224**.[104] When optically active monothioimides in toluene solution were irradiated with Pyrex-filtered light from a 500-W high-pressure mercury lamp under argon atmosphere, two diastereomeric 4-mercapto-2-azetidinones were formed together with benzthioanilide **226** in small amounts (Scheme 62).



Scheme 62

A photo-induced reaction of α-diazomalonic amide esters is reported in hexane and in nonconventional media such as water or a film with UV light from a mercury vapor high-pressure lamp.[105] The photolytic decomposition of α-diazomalonic amide esters **227** in hexane and in water or a film afforded the corresponding β-lactam-3-carboxylates or 3-phosphonate **228** (Scheme 63) in reasonable yields and in some cases with good diastereoselectivity with no need to use a metallic catalyst. The reaction in water was relatively slow and took 48-72 h where as it occurred in around 24 h in hexane. Experimental studies on chiral substrates demonstrated retention of configuration and thus suggesting C-H insertion via singlet carbene.

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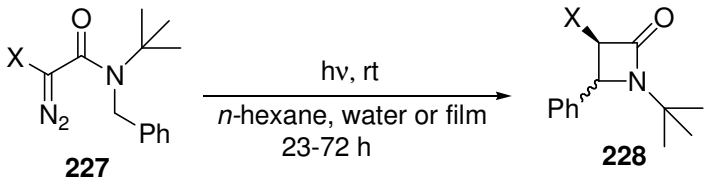


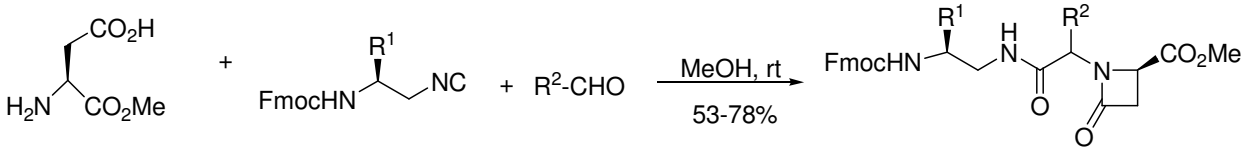
X = CO_2Et, $PO(OEt)_2$, CO_2Me

Yield 48-71% cis:trans 0:1-0.7:1 in water
62-75% 0.1:1-0.5:1 in hexane
54-56% 0.2:1-0.5:1 in film

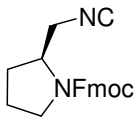
Scheme 63

2.10 Multi-Component Reactions

The design of methodologies involving more than two substrates, usually referred as multi-component reactions (MCRs), for complex molecular architecture has become an important area of research in organic, medicinal, and combinatorial chemistry.[106-108] Such strategies reduce the number of reaction steps, thus avoiding too many complicated purification procedures and allowing saving of both solvents and reagents. The Ugi multi-component reactions (MCRs) have been used to construct a variety of 2-azetidinones starting from β-amino acids, aldehydes, and isonitriles by Vishwanatha and coworkers.[109] This group has employed, L-aspartic acid α-methyl/peptide ester **229**, chiral N^{β}-Fmoc amino alkyl isonitriles **230** and aldehydes **231** in the Ugi multi-component reactions to obtain functionalized β-lactam peptidomimetics **232** (Scheme 64). The reaction is believed to occur through nucleophilic addition of isonitriles on protonated imines **233**, followed by cyclization of the resulting intermediates **234** to generate oxazepinones **235** (Scheme 65). An intramolecular *N*,*O*-acyl migration in oxazepinones **235** leads to the formation of β-lactam products.[109]



R^1 = H, Me, Bn, *i*-Pr, CH_2OBn, CH_2CO_2BzI, $(CH_2)_4$ NHZ,
R^2-CHO = H, Ph, *iso*-Bu



Scheme 64

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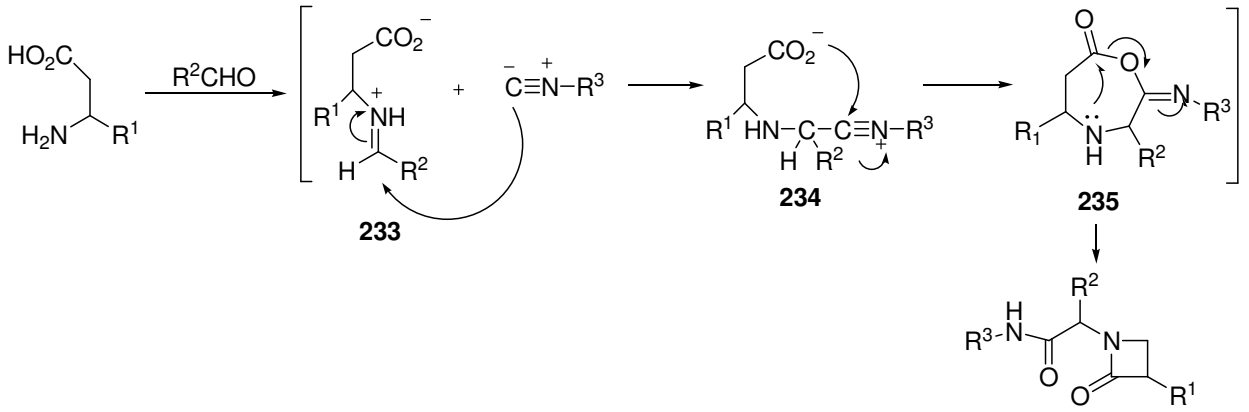
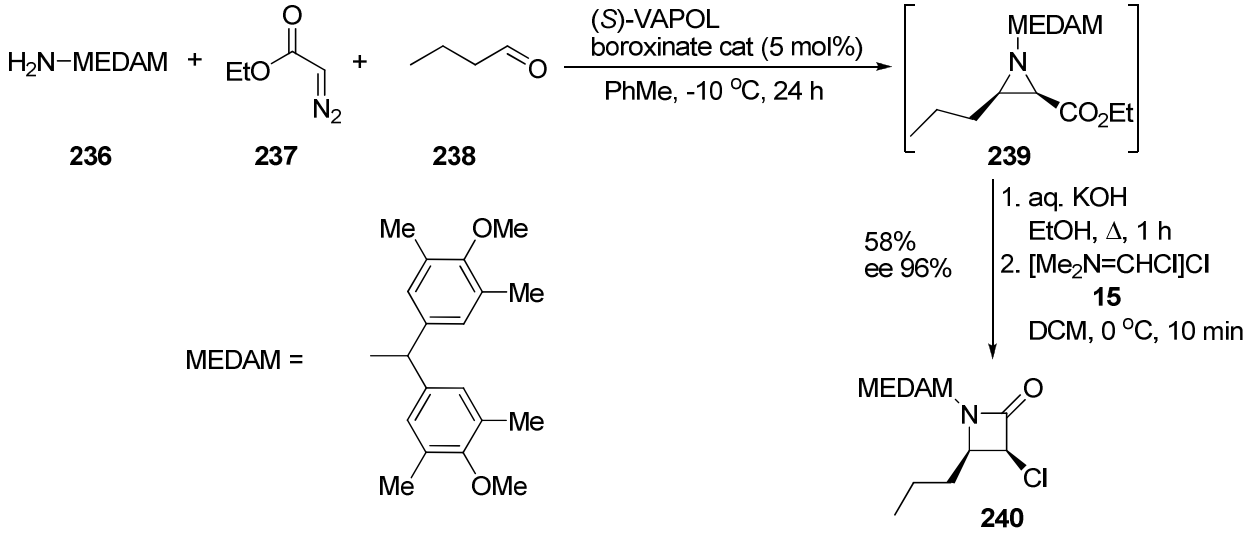


Scheme 65

Wulff and coworkers have extended their methodology for a multi-component asymmetric synthesis of aziridines from aldehydes, amines, and ethyl diazoacetate to the asymmetric synthesis of 2-azetidinone.[89,110] The reaction of ethyl diazoacetate **237**, butyraldehyde **238** and amine **236** followed by treatment of the resulting aziridine **239** with a base and theVilsmeier reagent led to the formation of 2-azetidinone **240** (Scheme 66).



Scheme 66

2.11 Other Approaches

A silylcarbocyclization process by the reaction of *p*-tosylamides **241** with hydrosilane **242** in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) leads to the formation of α-silylmethylene-2-azetidinones **243** together with a β-amido aldehyde **244** (Scheme 67).[111] The structure of the propargyl precursors played a crucial role in the selectivity

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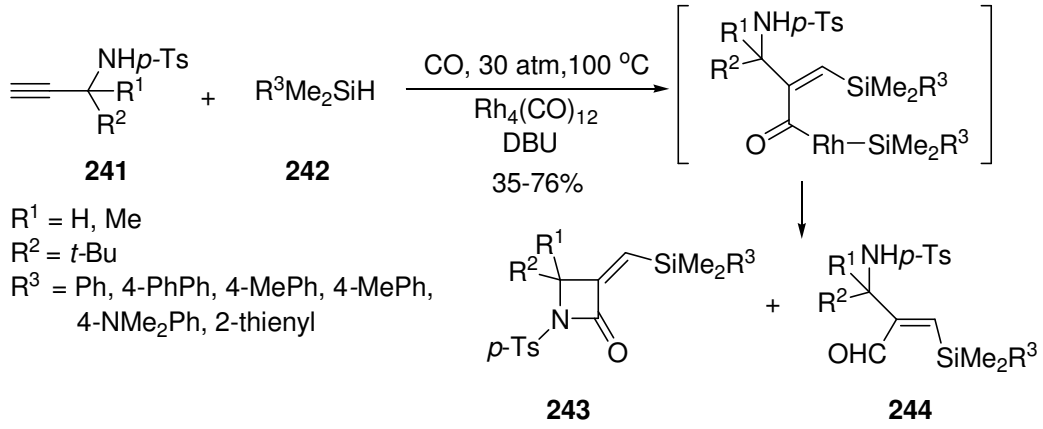
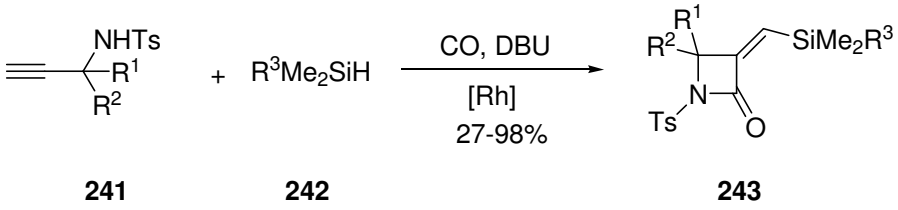
of the reaction, the presence of a bulky propargyl carbon being essential to force the closure of the ring. Moreover the high acidity of the NH-tosyl proton seemed to be fundamental for the β-lactam formation since the cyclisation process requires the removal of the nitrogen proton by the base DBU. Another report makes use of rhodium nanoparticles derived from mesitylene-solvated Rh atoms and deposited on inorganic (C, γ-Al_2O_3, Fe_2O_3) and organic matrices (PBI) (Scheme 68).[112] The MVS (Metal vapor Synthesis) supported nanoclusters, especially Rh/C, showed a specific activity much better than the corresponding commercial catalysts Rh/C and Rh/ γ-Al_2O_3 as well as homogenous $Rh_4(CO)_{12}$. The high catalytic activity encountered with Rh/C could be ascribed to the easy leaching of metal nanoparticles from carbon into solution. The minor specific activity observed in the cases of metal particles deposited on polar matrices such as PBI and Fe_2O_3 could be due to stronger interactions between the rhodium nanoclusters and the support. Therefore MVS Rh/C species represents a source, stable with ageing at room temperature, of highly active metal nanoparticles.



Scheme 67



Scheme 68

An approach involving thiazolidine ring opening of penam nucleus is reported for synthesis of *N*-isothiazolidinone substituted 2-azetidinone from penam amides **246,** which in turn was derived by amidation of 6-phthalimido-penicillanic acid **245**. The reaction involved treatment of

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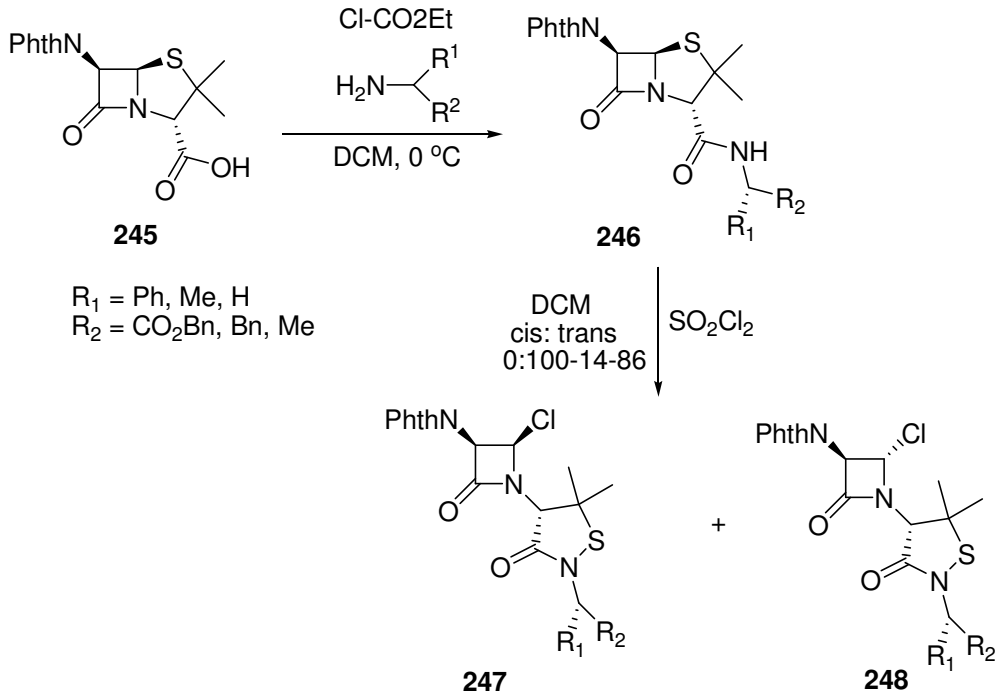
phthalimido-penam amides with sulfuryl chloride to afford a mixture of *cis* **247** and *trans* **248** diastereoisomers of monocyclic 2-azetidinones (Scheme 69).[113]



Scheme 69

3. Concluding Remarks

The research on methodologies to synthesize monocyclic 2-azetidinone ring has advanced remarkably during the last five years. Several new heteroatom-substituted ketenes have been employed efficiently in the Staudinger reaction furnishing 2-azetidinones containing heteroatoms such as nitrogen, sulfur, fluorine, and selenium at C-3 position. Several novel azomethines have been employed too. These include *N*-nosyl imines, *N*-sulfenyl imines, anthraquinone imines, *N*-tosyl-1-chloro-2,2,2-trifluoroethylamine, and also the Wittig reagent. Several new efficient acid activators such as diethyl chlorophosphate, cyanuric chloride-DMF complex, thiocarbonyldiimidazole, cyanuric fluoride, and phosphonitrilic chloride have been invented. Application of heterocyclic carbenes in the Staudinger reactions has led to a highly enantioselective synthesis of 2-azetidinones. Besides the ester-enolate cycloadditions, alkyne-nitrone cycloadditions have emerged as a powerful method for enantioselective synthesis of monocyclic 2-azetidinones. Diverse types of new β-amino esters have been synthesized and cyclized to 2-azetidinones. Photochemical and catalytic decompositions of appropriate diazocarbonyls followed by cyclization also constitute appealing methodology for synthesizing monocyclic 2-azetidinones. The Ugi multi-component reactions (MCRs) have been used to

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construct a variety of 2-azetidinones starting from β-amino acids, aldehydes, and isonitriles. Another multicomponent reaction of ethyl diazoacetate, amine and aldehyde has led to a highly enantioselective synthesis of 2-azetidinones through aziridine ring-expansion. This significant development would definitely continue to encourage further research in this area.

Abbreviations

BTPP .....*tert*-(Butylimino)tris(pyrrolidino)phosphorane
CAN .....Cerium(IV) ammonium nitrate
Cbz .....Benzyloxycarbonyl
$ClSCO_2Me$ .....(Methoxycarbonyl)sulfenyl chloride
Cy_2NMe .....*N,N*-Dicyclohexylmethylamine
DBN .....1,5-Diazabicyclo[4.3.0]non-5-ene
DBU .....1,8-Diazabicyclo [5.4. 0]undec-7-ene
DCE.....Dichloroethane
DCM .....Dichloromethane
DMAP 4-Dimethylaminopyridine
DMEA.....Dimethylethanolamine
ETSA.....Ethyl (trimethylsilyl)acetate
ETA.....Ethanolamine
HFIP.....Hexafluoroisopropanol
HMPA .....Hexamethylphosphoramide
KHMDS .....Potassium bis(trimethylsilyl)amide
LDA .....Lithium diisopropylamide
LHMDS.....Lithium hexamethyldisilazide
m-CPBA.....*m*-Chloroperoxybenzoic acid
MsCl.....Methanesulfonyl chloride
Ns .....Nosyl
PhthN .....Phthalimido
PMB .....*p*-Methoxybenzyl
PMP.....*p*-Methoxyphenyl
SDS .....Sodium dodecyl sulfate
TBDPSCl .....*tert*-Butyldiphenyl chlorosilane
TCT .....2,4,6-Trichloro-[1,3,5]-triazine
TCT-DMF .....2,4,6-Trichloro-1,3,5-triazine-dimethyl formamide
TEA.....Triethylamine
TFA .....Trifluoroacetic acid
TMAD.....Tetramethylazodicarboxamide

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TMG.....Trimethylglycine
TMS .....Trimethylsilyl
$TMSCHN_2$.....Trimethylsilyldiazomethane
TMSCl.....Chlorotrimethylsilane
Ts.....Tosyl
VAPOL----------2,2'-Diphenyl-4-(biphenanthrol)

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References

1. Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. *Curr. Org. Synth.* **2009**, *6*, 325. http://dx.doi.org/10.2174/157017909788921899
2. Hwu, J. R.; Ethiraj, K. S.; Hakimelahi, G. H. *Min-Rev. Med. Chem.* **2003**, *3*, 205.
3. Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69. http://dx.doi.org/10.2174/1389557043487501
4. Singh, G. S. *Min-Rev. Med. Chem.* **2004**, *4*, 93.
5. Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 5541. http://dx.doi.org/10.1016/j.ejmech.2010.09.035
6. Mukerjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547. http://dx.doi.org/10.1055/s-1975-23842
7. Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. http://dx.doi.org/10.2174/0929867043364856
8. Deshmukh, A. R. A. S; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889. http://dx.doi.org/10.2174/0929867043364874
9. Van Brabandt, W.; Dejaegher, Y.; De Kimpe, N. *Pure Appl. Chem.* **2005**, *77,* 2061. http://dx.doi.org/10.1351/pac200577122061
10. Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. http://dx.doi.org/10.1021/cr0307300
11. D'hooghe, M.; Dekeukeleire, S.; Leemans, E.; De Kimpe, N. *Pure Appl. Chem.* **2010**, *82*, 1749.
12. Singh, G. S. *Mod. Chem. Appl.* **2013**, *1*, e108.

 ©ARKAT-USA, Inc.

http://dx.doi.org/10.4172/mca.1000.e108
13. Alcaide, B.; Almendros, P. *Chem. Record* **2011**, *11*, 311. http://dx.doi.org/10.1002/tcr.201100011
14. Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. http://dx.doi.org/10.1016/0040-4020(78)80209-9
15. Singh, G. S. *Tetrahedron* **2003**, 59, 7631. http://dx.doi.org/10.1016/S0040-4020(03)01099-8
16. Singh, G. S.; D'hooghe, M.; De Kimpe, N. In *Azetidines, Azetines, and Azetes* in *Comprehensive Heterocyclic Chemistry-III*; eds. Katritzky, A. R.; Ramsden, C. A.; Scriven, E.; Taylor, R.; Elsevier: UK, 2008; vol. 2, p 1. http://dx.doi.org/10.1016/B978-008044992-0.00201-7
17. Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, *67*, 1989. http://dx.doi.org/10.1016/j.tet.2011.01.013
18. Kamath, A.; Ojima, I. *Tetrahedron* **2012**, *68*, 10640. http://dx.doi.org/10.1016/j.tet.2012.07.090
19. Alcaide, B.; Almendros, P.; Aragoncillo, C. *Curr. Opin. Drug Disc. Dev.* **2010**, *13*, 685.
20. Staudinger, H. *Liebigs Annal. chem.* **1907**, *356*, 51.
21. Xu, J. *Arkivoc* **2009**, *ix*, 21.
22. Tuba, R. *Org. Biomol. Chem.* **2013**, *11*, 5976. http://dx.doi.org/10.1039/c3ob41048j
23. Singh, G. S. *Curr. Org. Synth.* **2005**, *2*, 377. http://dx.doi.org/10.2174/1570179054368536
24. Bose, A. K.; Banik, B. K.; Manhas, M. S. *Tetrahedron Lett.***1995**, *36*, 213. http://dx.doi.org/10.1016/0040-4039(94)02225-Z
25. Laborde, M. A.; Mata, E. G. *Mini-Rev. Med. Chem.* **2006**, *6*, 109. http://dx.doi.org/10.2174/138955706775197794
26. Banik, B. K.; Banik, I.; Becker, F. F. *Eur. J.Med. Chem.* **2010**, *45*, 846. http://dx.doi.org/10.1016/j.ejmech.2009.11.024
27. Marques-Lopez, E.; Martin-Zamora, E.; Diez, E.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2008**, *17*, 2960. http://dx.doi.org/10.1002/ejoc.200800194
28. Islami, M. R.; Allen, A. D.; Vukovic, S.; Tidwell, T. T. *Org. Lett.* **2011**, *13*, 494. http://dx.doi.org/10.1021/ol102837n
29. Zarei, M.; Mohamadzadeh, M. *Tetrahedron* **2011**, *67*, 5832. http://dx.doi.org/10.1016/j.tet.2011.05.043
30. Bari, S. S.; Bhalla, A.; Nagpal, Y.; Mehta, S. K.; Bhasin, K. K. *J. Organometall. Chem.* **2010**, *695*, 1979. http://dx.doi.org/10.1016/j.jorganchem.2010.05.005
31. Bhalla, A.;Venugopalan, P.; Bhasin, K. K.; Bari, S. S. *Tetrahedron* **2007**, *63*, 3195. http://dx.doi.org/10.1016/j.tet.2007.02.001

 ©ARKAT-USA, Inc.

32. Jarrahpour, A.; Ebrahimi, E.; Khalifeh, R.; Sharghi, H.; Sahraei, M.; Sinou, V.; Latour, C.; Brunel, J. M. *Tetrahedron* **2012**, *68*, 4740. http://dx.doi.org/10.1016/j.tet.2012.04.011
33. Wang, Z.; Chen, N.; Xu, J. *Tetrahedron* **2011**, *67*, 9690. http://dx.doi.org/10.1016/j.tet.2011.10.044
34. Tato, F.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2008**, *73*, 7837. http://dx.doi.org/10.1021/jo8014193
35. Venkateshwarlu, J.; Ramakanth, P.; Meshram, J. S.; Chopde, H. N.; Malladi, L. *J. Heterocycl. Chem.* **2013**, 50, E160. http://dx.doi.org/10.1002/jhet.1108
36. Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *3*, 9762. http://dx.doi.org/10.1021/jo801664g
37. D'hooghe, M.; Brabandt, W. V.; Dekeukeleire, S.; Dejaegher,Y.; De Kimpe, N. *Chem. Eur. J.* **2008**, 6336. http://dx.doi.org/10.1002/chem.200800845
38. Coantic, S.; Mouysset, D.; Mignani, S.; Tabart, M.; Stella, L. *Tetrahedron* **2007**, *63*, 3205. http://dx.doi.org/10.1016/j.tet.2007.01.051
39. Yang, Y-Y.; Shou, W-G.; Hong, D.; Wang, Y-G. *J. Org. Chem.* **2008**, *73*, 3574. http://dx.doi.org/10.1021/jo702733h
40. Petrik, V.; Roschenthaler, G. V.; Cahard, D. *Tetrahedron* **2011**, *67*, 3254. http://dx.doi.org/10.1016/j.tet.2011.03.001
41. Shaikh, A. L.; Kale, A.S.; Shaikh, M. A.; Puranik, V. G.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 3380. http://dx.doi.org/10.1016/j.tet.2007.02.022
42. Zarei, M. *J. Chem. Res.* **2012**, 118.
43. Zarei, M.; Jarrahpour, A. *Synlett* **2011**, 2572.
44. Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. *Synth. Commun.* **2013**, *43*, 728. http://dx.doi.org/10.1080/00397911.2011.607935
45. Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, *50*, 1568. http://dx.doi.org/10.1016/j.tetlet.2009.01.092
46. Zarei, M. *J. Chem. Res.* **2013**, 25.
47. Zarei, M. *Tetrahedron* **2013**, *69*, 6620. http://dx.doi.org/10.1016/j.tet.2013.05.121
48. Bandopadhyay, D.; Cruz, J.; Banik, B. K. *Tetrahedron* **2012**, *68*, 10686. http://dx.doi.org/10.1016/j.tet.2012.06.009
49. Banik, B. K.; Banik, I.; Becker, F. F. *Bioorg. Med. Chem.* **2005**, *13*, 3611. http://dx.doi.org/10.1016/j.bmc.2005.03.044
50. Delpiccolo, C. M. L.; Testero, S. A.; Leyes, F. N.; Boggian, D. B.; Camacho, C. M.; Mata, E. G. *Tetrahedron* **2012**, *68*, 10780. http://dx.doi.org/10.1016/j.tet.2012.01.072

 ©ARKAT-USA, Inc.

51. Zhang, Z.; Liu,Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330. http://dx.doi.org/10.1021/ja107351d
52. Duguet, N.; Donaldson, A.; Leckie, S. M.; Kallstrom, E. A.; Campbell, C. D.; Shapland, P.; Brown, T. B.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron: Asymmetry* **2010**, *21*, 601. http://dx.doi.org/10.1016/j.tetasy.2010.03.002
53. Duguet, N.; Donaldson, A.; Leckie, S. M.; Douglas, J.; Shapland, P.; Brown, T. B.; Slawin, A. M. Z.; Smith, A. D.; Churchil, G. *Tetrahedron: Asymmetry* **2010**, *21*, 582. http://dx.doi.org/10.1016/j.tetasy.2010.03.001
54. Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. http://dx.doi.org/10.1039/b800857b
55. Zhang, Y-R.; He, L.; Wu, X.; Shao, P-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. http://dx.doi.org/10.1021/ol702759b
56. Abraham, C. J.; Paull, D. H.; Dogo-Isonagie, C.; Lectka, T. *Synlett* **2009**, 1651.
57. D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4575. http://dx.doi.org/10.1016/j.tet.2008.03.006
58. Singh, P.; Sachdeva, S.; Raj, R.; Kumar, V.; Mahajan, M. P.; Nasser, S.; Vivas, L.; Gut, J.; Rosenthal, P. J.; Feng, T.-S.; Chibale, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4561. http://dx.doi.org/10.1016/j.bmcl.2011.05.119
59. Singh, G. S.; Pandeya, S. N. *J. Chem. Engg. Data* **1987**, *32*, 278. http://dx.doi.org/10.1021/je00048a037
60. Qi, H.; Yang, Z.; Xu, J. *Synthesis* **2011**, 723.
61. Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. http://dx.doi.org/10.1002/1099-0690(200207)2002:14<2193::AID-EJOC2193>3.0.CO;2-D
62. Singh, G. S.; Al-Kahraman, Y. M. S. A.; Mpadi, D.; Yasinzai, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5704. http://dx.doi.org/10.1016/j.bmcl.2012.06.081
63. Singh, G. S.; Al-Kahraman, Y. M. S. A.; Mpadi, D.; Yasinzai, M. *J. Heterocycl. Chem.* **2013**, in press.
64. Singh, G. S.; Mbukwa, E.; Pheko, T. *Arkivoc* **2007**, *ix*, 80.
65. Boyer, N.; Gloanec, P.; Nanteuil, G. D.; Jubault, P.; Quirion, J-C. *Tetrahedron* **2007**, *63*, 12352. http://dx.doi.org/10.1016/j.tet.2007.09.058
66. Tarui, A.; Ozaki, D.; Nakajima, N.; Yokota, Y.; Sokeirik, Y. S.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, *49*, 3839. http://dx.doi.org/10.1016/j.tetlet.2008.04.101
67. Soengas, R. G.; Segade, Y.; Jimenez, C.; Rodriguez, J. *Tetrahedron* **2011**, *67*, 2617. http://dx.doi.org/10.1016/j.tet.2011.02.006

 ©ARKAT-USA, Inc.

68. Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 2000. http://dx.doi.org/10.1016/j.tetlet.2010.02.023
69. Gembus, V.; Poisson, T.; Oudeyer, S.; Marsais, F.; Levacher, V. *Synlett* **2009**, 2437.
70. Michel, K.; Frohlich, R.; Wurthwein, E-U. *Eur. J. Org. Chem.* **2009**, 5653. http://dx.doi.org/10.1002/ejoc.200900864
71. Boyer, N.; Gloanec, P.; Nanteuil, G. D.; Jubault, P.; Quirion, J. C. *Eur. J. Org. Chem.* **2008** 4277. http://dx.doi.org/10.1002/ejoc.200800363
72. Michalak, M.; Stodulski, M.; Stecko, S.; Mames, A.; Panfil, I.; Soluch, M.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2011**, *76*, 6931. http://dx.doi.org/10.1021/jo2010846
73. Wu, G.; Wong, Y.; Chen, X.; Ding, Z. *J. Org. Chem.* **1999**, *64*, 3714. http://dx.doi.org/10.1021/jo990428k
74. Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, *10*, 3477. http://dx.doi.org/10.1021/ol801257j
75. McKay, C. S.; Kennedy, D. C.; Pezacki, J. P. *Tetrahedron Lett.* **2009**, *50*, 1893. http://dx.doi.org/10.1016/j.tetlet.2009.02.035
76. Michalak, M.; Stodulski, M.; Stecko, S.; Woznica, M.; Staszewska-Krajewska, O.; Kalicki, P.; Furman, B.; Frelek, J.; Chmielewski, M. *Tetrahedron* **2012**, *68*, 10806. http://dx.doi.org/10.1016/j.tet.2011.11.007
77. Coyne, A. G.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 199. http://dx.doi.org/10.1016/j.tetasy.2007.01.006
78. Chen, J-H.; Liao, S-H.; Sun, X-L.; Shen, Q.; Tang, Y. *Tetrahedron* **2012**, *68*, 5042. http://dx.doi.org/10.1016/j.tet.2012.04.049
79. Saito, T.; Kikuchi, T.; Tanabe, H.; Yahiro, J.; Otani, T. *Tetrahedron Lett.* **2009**, *50*, 4969. http://dx.doi.org/10.1016/j.tetlet.2009.06.050
80. Baeza, B.; Casarrubios, L.; Sierra, M. A. *Chem. Eur. J.* **2013**, *19*, 11536. http://dx.doi.org/10.1002/chem.201301114
81. Lee, S. H. *Bull. Korean Chem. Soc.* **2013**, *34*, 121. http://dx.doi.org/10.5012/bkcs.2013.34.1.121
82. Troisi, L.; Ronzini, L.; Granito, C.; Vitis, L. D.; Pindinelli, E. *Tetrahedron* **2006**, *62*, 1564. http://dx.doi.org/10.1016/j.tet.2005.11.007
83. Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A.;Tanaka, H. *Tetrahedron Lett.* **1993**, *34*, 6553. http://dx.doi.org/10.1016/0040-4039(93)88102-O
84. Tanaka, H.; Hai, A.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem.* **1994**, *59*, 3040. http://dx.doi.org/10.1021/jo00090a023
85. Troisi, L.; Granito, C.; Pindinelli, E. *Tetrahedron* **2008**, *64*, 11632.

 ©ARKAT-USA, Inc.

http://dx.doi.org/10.1016/j.tet.2008.10.027
86. Xie, P.; Qian, B.; Huang, H.; Xia, C. *Tetrahedron Lett.* **2012**, *53*, 1613. http://dx.doi.org/10.1016/j.tetlet.2012.01.073
87. Troisi, L.; Pindinelli, E.; Strusi, V.; Trinchera, P. *Tetrahedron: Asymmetry* **2009**, *20*, 368. http://dx.doi.org/10.1016/j.tetasy.2009.01.012
88. Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S. P.; Aggarwal, V. K. *Chem. Commun.* **2010**, 267. http://dx.doi.org/10.1039/b920564k
89. Huang, L.; Zhao, W.; Staples, R. J.; Wulff, W. D. *Chem. Sci.* **2013**, 4, 622. http://dx.doi.org/10.1039/c2sc21240d
90. Guerrini, A.; Varchi, G.; Samori, C.; Daniele, R.; Arturo, B. *Tetrahedron Lett.* **2007**, *48*, 5081. http://dx.doi.org/10.1016/j.tetlet.2007.05.087
91. Dema, H. K.; Foubelo, F.; Yus, M. *Helvetica Chim. Acta* **2012**, *95*, 1790. http://dx.doi.org/10.1002/hlca.201200303
92. Kashikura, W.; Mori, K.; Akiyama, T. *Org. Lett.* **2011**, *13*, 1860. http://dx.doi.org/10.1021/ol200374m
93. Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8700. http://dx.doi.org/10.1002/anie.200803819
94. Jakowiecki, J.; Loska, R.; Makosza, M. *J. Org. Chem.* **2008**, *73*, 5436. http://dx.doi.org/10.1021/jo800721w
95. Hachiya, I.; Yoshitomi, T.; Yamaguchi, Y.; Shimizu, M. *Org. Lett.* **2009**,*11*, 3266. http://dx.doi.org/10.1021/ol901192y
96. Vaske, Y. S. M.; Mahoney, M. E.; Konopelski, J. P.; Rogow, D. L.; McDonald, W. J. *J. Am. Chem. Soc.* **2010**, *132*, 11379. http://dx.doi.org/10.1021/ja1050023
97. Gerstenberger, B. S.; Lin, J. Z.; Mimieux, Y. S.; Brown, L. E.; Oliver, A. G.; Konopelski, J. P. *Org. Lett.* **2008**, *10*, 369. http://dx.doi.org/10.1021/ol7025922
98. Lu, X.; Long, T. E. *Tetrahedron Lett.* **2011**, *52*, 5051. http://dx.doi.org/10.1016/j.tetlet.2011.07.085
99. Yang, Y.; Xiang, D.; Zhao, X.; Liang, Y.; Huang, J.; Dong, D. *Tetrahedron* **2008**, *64*, 4959. http://dx.doi.org/10.1016/j.tet.2008.03.093
100. Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. http://dx.doi.org/10.1021/ol801545a
101. Perez-Faginas, P.; Aranda, M. T.; Garcia-Lopez, M. T.; Francesch, A.; Cuevas, C.; Gonzalez-Muniz, R. *Eur. J. Med. Chem.* **2011**, *46*, 5108. http://dx.doi.org/10.1016/j.ejmech.2011.08.025

 ©ARKAT-USA, Inc.

102. Perez-Faginas, P.; Alkorta, I.; Garcıa-Lopez, M. T.; Gonzalez-Muniz, R. *Tetrahedron Lett.* **2008**, *49*, 215. http://dx.doi.org/10.1016/j.tetlet.2007.11.099
103. Sotgiu, G.; Chiarotto, I.; Feroci, M.; Orsini, M.; Rossi, L.; Inesi, A. *Electrochim. Acta* **2008**, *53*, 7852. http://dx.doi.org/10.1016/j.electacta.2008.05.054
104. Sakamoto, M.; Kawanishi, H.; Mino, T.; Fujita, T. *Chem. Commun.* **2008**, 2132. http://dx.doi.org/10.1039/b801524d
105. Candeias, N. R.; Gois, P. M. P.; Veiros, L. F.; Afonso, C. A. M. *J. Org. Chem.* **2008**, *73*, 5926. http://dx.doi.org/10.1021/jo800980c
106. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. http://dx.doi.org/10.1021/cr100233r
107. Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 633. http://dx.doi.org/10.1021/cc100035q
108. Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Shestopaqlov, A. M. *J. Comb. Chem.* **2009**, *11*, 914. http://dx.doi.org/10.1021/cc900076j
109. Vishwanatha, T. M.; Narendra, N.; Sureshbabu, V. V. *Tetrahedron Lett.* **2011**, *52*, 5620. http://dx.doi.org/10.1016/j.tetlet.2011.08.090
110. Gupta, A. K.; Mukherjee, M.; Wulff, W. D. *Org. Lett.* **2011**, *13*, 5866. http://dx.doi.org/10.1021/ol202472z
111. Aronica, L. A.; Valentini, G.; Caporusso, A. M.; Salvadori, P. *Tetrahedron* **2007**, *63*, 6843. http://dx.doi.org/10.1016/j.tet.2007.04.064
112. Aronica, L. A.; Caporusso, A. M.; Evangelisti, C.; Botavina, M.; Alberto, G.; Martra, G. *J. Organometall. Chem.* **2012**, *700*, 20. http://dx.doi.org/10.1016/j.jorganchem.2011.11.008
113. Ceric, H.; Sindler-Kulyk, M.; Kovacevic, M.; Peric, M.; Zivkovic, A. *Bioorg. Med. Chem.* **2010**, *18*, 3053. http://dx.doi.org/10.1016/j.bmc.2010.03.045

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Girija S. Singh was born in Sasaram (Bihar), India. He received his B. Sc. and M. Sc. degrees from the U. P. College (then Gorakhpur University), Varanasi, India, in 1977 and 1979, respectively. He received his Ph. D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines and hydrazones in October, 1984. Since then he has occupied teaching and research positions in various universities such as Banaras Hindu University, India (JRF, SRF, PDF, Research Associate, Pool-Officer, Reader), Osaka University, Japan (PDF), University of Zambia (Lecturer), and University of Botswana (Lecturer, Senior Lecturer, Associate Professor). He is currently working as Professor of Chemistry at the University of Botswana. He has authored eighty five publications in books and in peer-reviewed journals. He is member of the American Chemical Society, Chemical Research Society of India, and Indian Chemical Society. He is on the editorial board of over half a dozen chemistry journals. His research interests include the study of synthesis and reactivity of biologically important heterocycles, reactions of carbenoids, metal-catalyzed oxidations and organic chemistry education.

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