Review

Novel Syntheses of Azetidines and Azetidinones

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Novel Syntheses of Azetidines and Azetidinones

Alberto Brandi,* Stefano Cicchi, and Franca M. Cordero

Dipartimento di Chimica Organica "Ugo Schiff", Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Biologicamente Attivi - HeteroBioLab, Università degli Studi di Firenze, via della Lastruccia 13, 50019 Sesto F.no (FI), Italy

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Contents

1. Introduction

Four-membered monocyclic aza-heterocycles,[1] despite their indisputable importance as bioactive compounds and pharmaceutical tools, have received by the chemical community little interest compared to the higher homologous counterparts. The greatest interest was obviously gathered by azetidine-2-ones (β-lactams) for their key role in antibacterial activity, but still the main object of study was the synthesis of bicyclic fused compounds for their relationship with natural antibacterial agents. The lower general interest in azetidines is probably due to their strained nature and the difficulty of formation of the four-membered ring, thereof. For simple azetidines, for example, the reduction of β-lactams is still one of the most used methods for their synthesis. Nevertheless, an overview of the literature shows that derivatives of these heterocyclic rings found diffuse applications in medicinal chemistry as pharmacological tools, in peptidomimetics as non-natural amino acids, and in numerous natural products.

This review will, therefore, address the most recent methods for the synthesis of these four-membered ring systems, focusing on the stereoselective methods. For azetidines and azetidine-3-ones, the highlights of the literature from 1990 will be covered, whereas for azetidine-2-ones (β-lactams), because of the higher literature coverage, the literature since 2000 will be considered, for both subjects until the most recent of early 2008.

2. Azetidines

Azetidines are an important class of aza-heterocyclic compounds with remarkable biological activities, which makes them an interesting synthetic topic. Compared to their importance, a relatively low number of reviews, albeit very broad and complete,[2] on their synthesis has appeared. In particular, what is remarkable is the lack of profuse general methods for the synthesis of enantiopure azetidines.[3] On the other hand, the azetidine ring finds a wide application as a pharmacological tool in many drugs or bioactive compounds, usually in medicinal chemistry structure activity studies. The number of only the most recent manuscripts[4] gives evidence

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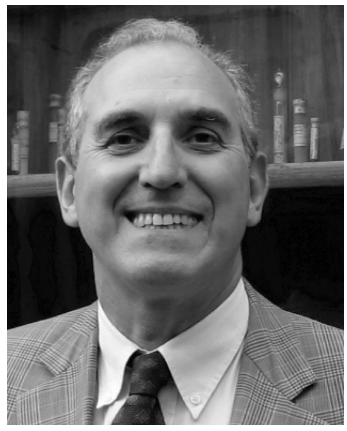


Alberto Brandi was born in 1951. In 1975, he received his Doctor in Chemistry from the University of Florence, and he became a CNR fellow in 1978. In 1980 he moved to Ricercatore Universitario at the Department of Organic Chemistry of University of Florence. From 1982 to 1984, he was a NATO fellow with Professor Barry M. Trost at the University of Wisconsin-Madison. In 1987, he became Associate Professor at the University of Basilicata-Potenza. In 1990, he moved back to the University of Florence where, in 1994, he became a Professor of Organic Chemistry in the Faculty of Science. From 2001−2006 he was Head of the Department of Organic Chemistry "U. Schiff". In 2007, he became Director of Master Degree on "Innovative Synthetic Methodologies in Organic Chemistry". He has received numerous awards, including a Fellowship, Osaka City University, Japan, 1994; "Prix Franco-Italien" of the French Chemical Society, 2005; and Prize for Research of the Organic Chemistry Division of Italian Chemical Society, 2007. He is author of over 180 original papers and reviews and more than 60 invited conferences in national and international congresses and Italian and international universities. His recent research deals with stereoselective 1,3-dipolar cycloadditions of nitrones for the syntheses of alkaloids and aza-heterocycles; chemistry of spirocyclopropane heterocycles; asymmetric synthesis of biologically active compounds, including glycosidase inhibitors, sugar mimetics, β-lactams, and amino acids; synthesis of peptidomimetics and peptides; and synthesis of dendrimeric materials.

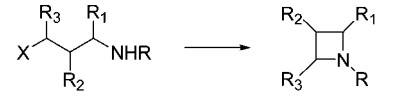
Stefano Cicchi, born in Firenze in 1963, is a researcher at the Organic Chemistry Department of the University of Firenze. He received his Laurea in Chemistry in 1989 from the University of Firenze and, in 1992, his doctoral degree in synthetic organic chemistry with work on 1,3-dipolar cycloaddition reactions of nitrones with phosphinylalkenes. He was CNR fellow from 1993 to 1995 with Dr. Claudio Bianchini (ICCOM-CNR, Firenze). He spent a research period in the laboratories of Prof. Bernd Giese (Basel, Switzerland, 1991) and Prof. Pedro Merino (Zaragoza, Spain, 2002). His research interests concern new synthetic methods and strategies for the synthesis of heterocycles with biological activity and the synthesis and study of new molecular and supramolecular materials.

of the large use of this ring system in the synthesis of bioactive compounds.

The most recent methods of synthesis of the azetidine ring will be examined. A few more important classes of azetidine compounds will be analyzed separately, evidencing the most recent and selective ways of access.

Franca M. Cordero received her Laurea degree in chemistry (in 1988) and her Ph.D. in synthetic organic chemistry in 1992, from the University of Firenze. She was researcher at the Department of Organic Chemistry, University of Firenze, during 1994−2004. Since 2005, she has been associate professor of organic chemistry at the Faculty of Science, University of Firenze. She joined Prof. Trost's group at Stanford University (U.S.A) for one year in 1991 and Prof. J. Salaün's group at the University of Paris—Sud (France) for some months in 1997. Her research interests are in development and application of new synthetic methods and strategies for the synthesis of biologically active aza-heterocyclic compounds and peptidomimetics; stereoselective synthesis based on 1,3-dipolar cycloaddition reactions; and chemistry of spirocyclopropane heterocycles.

Scheme 1



2.1. Cyclizations by Nucleophilic Substitution of Amine Nucleophiles

2.1.1. Halides, Sulfonic Esters, Triflates, Etc., Leaving Groups

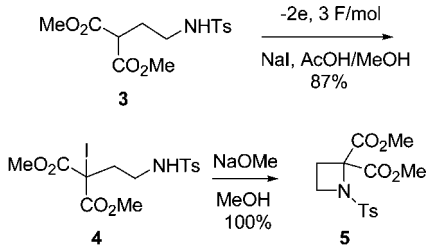
Cyclization of a preformed chain by nucleophilic displacement of a leaving group (X, Scheme 1) by a nitrogen nucleophile is, by far, the most common method to produce azetidines. Amines are the most common nitrogen nucleophiles, as the only other example is limited to hydroxylamines.[5] One common drawback of the reaction is the elimination of HX moiety that competes with the cyclization, apparently due to the strain nature of the forming azetidine ring.

Chloride[6] and bromide[7,6j] are the most common halide leaving groups encountered, being as much reactive and more available than iodides.[8,7i] However, the iodomalonate **4**, formed by anodic oxidation of I^-, underwent a quantitative cyclization to azetidine **5** (Scheme 2).[9]

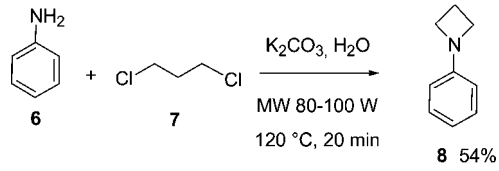
The cyclization of aniline (**6**) with 1,3-dichloropropane (**7**) has been recently carried out in water by the assistance of microwaves (80−100 W), affording *N*-Ph-azetidine **8** in 54% yield (Scheme 3).[6a]

Traditional protocols in the presence of alcoholic intermediates involve the transformation of the alcohol in sulfonic ester, mainly mesylate,[10,7p,8c] tosylate,[11,6j,7j,p] and triflates,[12] followed by base mediated cyclization. Triflates, albeit the

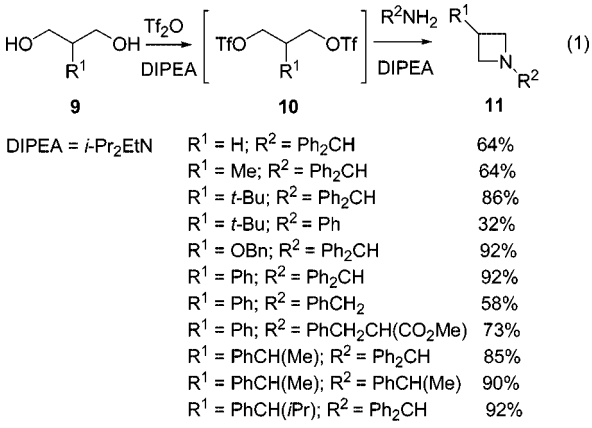
Scheme 2



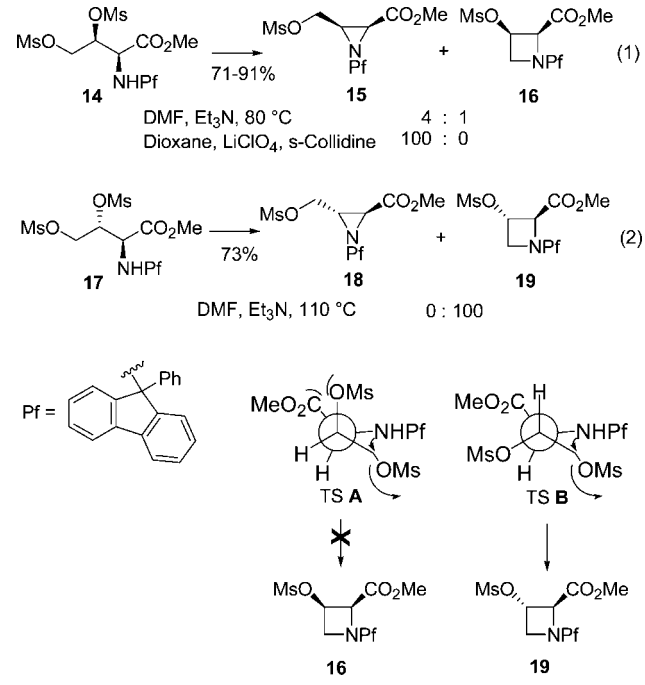
Scheme 3



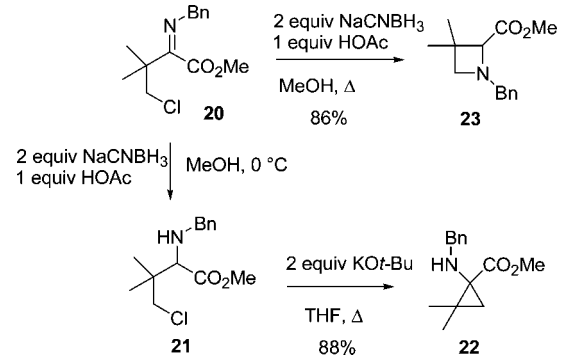
Scheme 4



Scheme 5



Scheme 6



less addressed, are the most reactive leaving groups, allowing the cyclization to be run in one pot. Hillier and co-worker[12b] proved their superiority over tosylates, especially in the presence of bulky substituents, in the synthesis of 1,3-substituted azetidines **11** from 2-substituted-1,3-propanediols **9** in a one-pot reaction (Scheme 4, eq 1). By this method, pentaerythritol **12** gave the spirocyclic azetidine dimer **13** in 35% yield (Scheme 4, eq 2).

The phenylselenonyl group can act efficiently as a leaving group.[13] Very recently, the method has been applied to the synthesis of a variety of enantiomerically pure azetidines with yields ranging from 44 to 80%.[13b] Only one example of a cyclic sulfate is recorded,[14] as well as diphenylsulfonium[15] and azide[16] as leaving groups.

A competition between cyclization to a three-membered aziridine **15** instead of azetidine **16** (Scheme 5, eq 1) was observed as a result of unfavorable steric interaction in the cyclization of dimesylate **14**, as evident from the transition state **A** (Scheme 5).[10e] Isomer **17** afforded exclusively *trans*-substituted azetidine **19** (Scheme 5, eq 2).

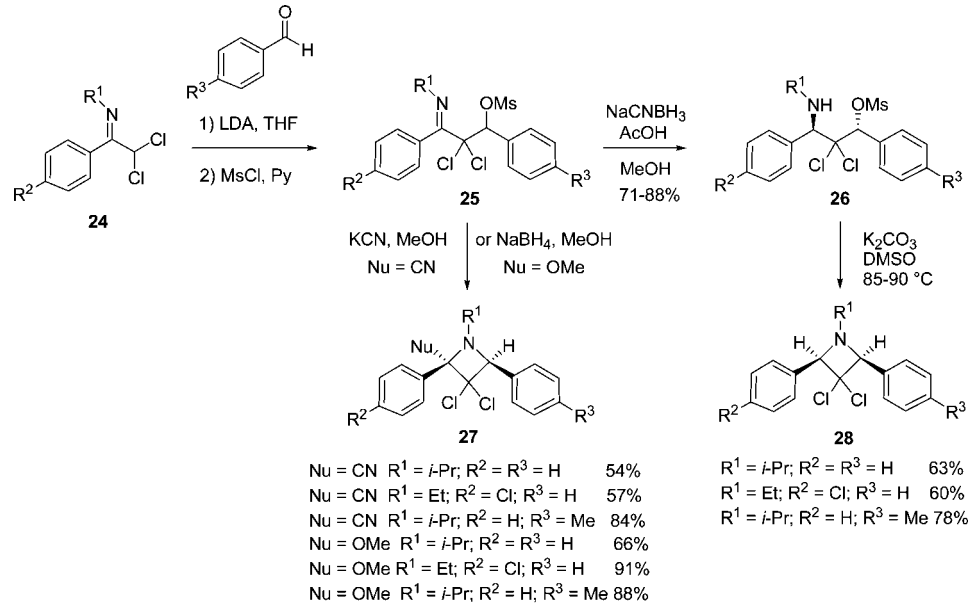
Another competition might occur between the formation of an azetidine ring and a cyclopropane ring, as shown by De Kimpe and co-workers.[6f] When acidic protons are present, like in compound **21**, the use of a base can lead to the formation of the cyclopropane amino ester **22**. Efficient formation of the azetidine occurs under heating without any additional base, directly during the reduction of imine **20**, because of the sufficient nucleophilicity of the secondary nitrogen (Scheme 6).

De Kimpe's group provided the synthesis of uncommon 3,3-dichloroazetidines **27** and **28** (Scheme 7)[10g] and 3-fluoroazetidines **31** (Scheme 8)[7b] starting from imines.

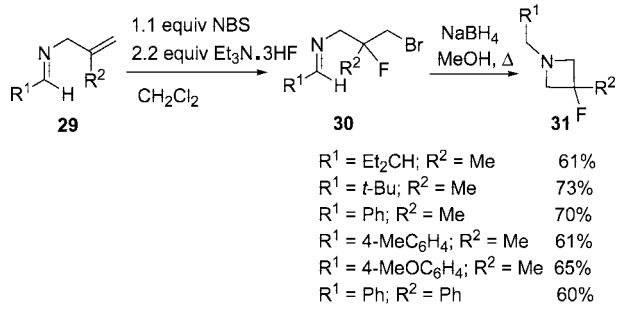
Concellón and co-workers developed an efficient protocol for the synthesis of enantiopure azetidinium salts **34a**,**c**, starting from dibenzylamino aldehydes **32a**,**c**, through samarium mediated iodomethylation, which occurs with good diastereoselectivity (Scheme 9).[8b,c] By the same group,[6e] addition of ester enolates **36** to analogous *N*-dibenzylamino ketones **35** gave enantiopure azetidinylium acetates **38** in excellent yields and stereoselectivity, which can be hydrogenolysed quantitatively to the azetidinyl acetate **39** (Scheme 10).

Several bis(hydroxymethyl)azetidine-1-yl-pyrimidine nucleosides **43**, analogs of oxetanocin-A, were synthesized via construction of the nucleobase on the unstable 1-aminoazetidine **42** prepared from (+)-diethyltartrate (DET) (Scheme 11).[10m] Monosaccharide-fused azetidines were synthesized as pharmacological tools. The 3-amino-3-deoxy furanose derivative **46** is an important intermediate for the synthesis of bicyclic analogs of AZT (Scheme 12).[11c]

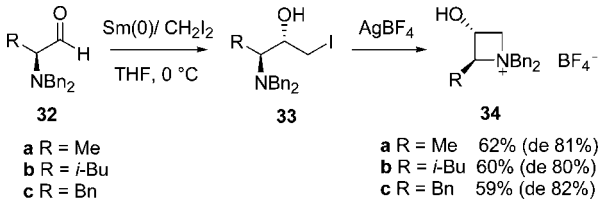
Scheme 7



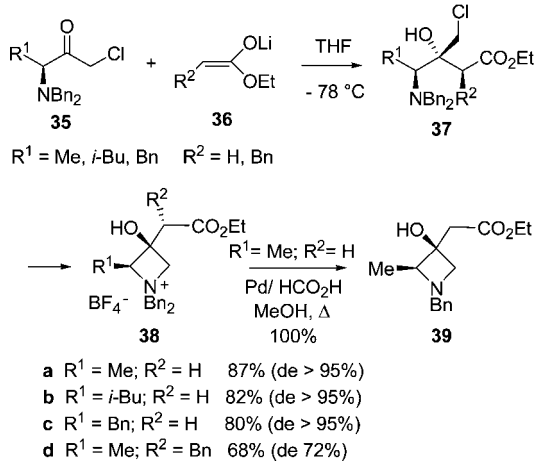
Scheme 8



Scheme 9



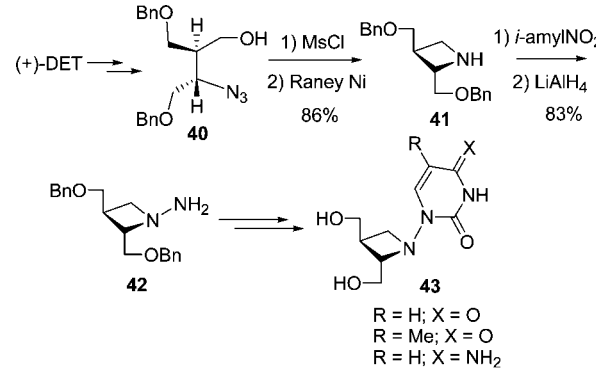
Scheme 10



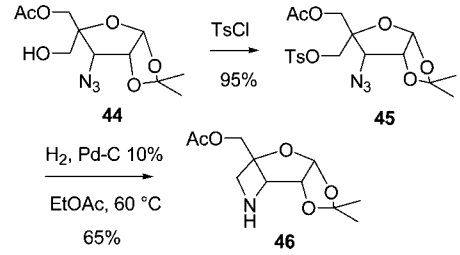
Primary amines reacted upon 4,6-ditosylates of glucopyranosides **47** to give compounds **48a**,**c**, with an azetidine ring formed between C4 and C6 of the pyranose ring, in good yields. Interestingly, corresponding mannopyranosides led to the uncyclized 4,6-diamino-4,6-dideoxy compounds (Scheme 13).[11f]

An azetidine isostere **52** of the oxetane-type taxane 1-deoxy-2-debenzoyloxy-4-deacetylbaccatin VI was synthesized starting from the alkaloid 2′-deacetoxyaustrospicatine **49** (Scheme 14).[10i]

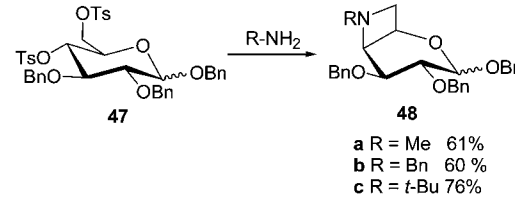
Scheme 11



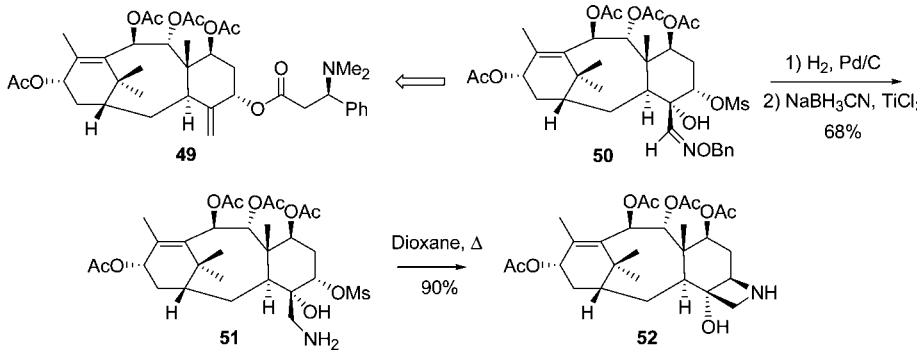
Scheme 12



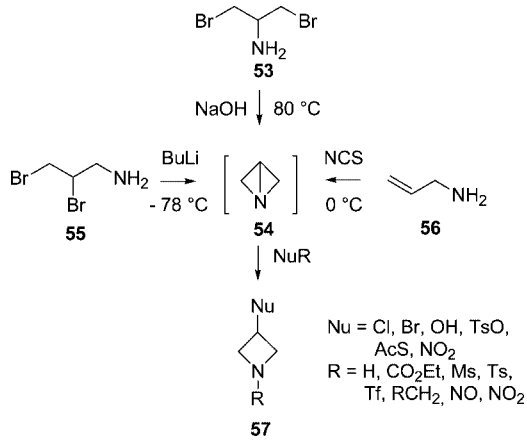
Scheme 13



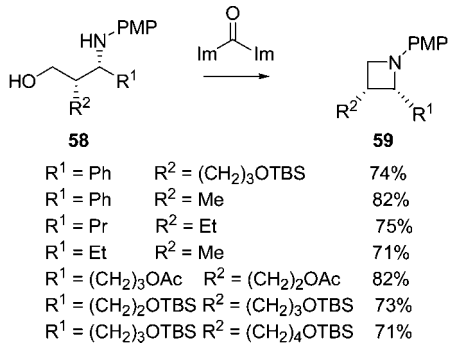
Scheme 14



Scheme 15



Scheme 16

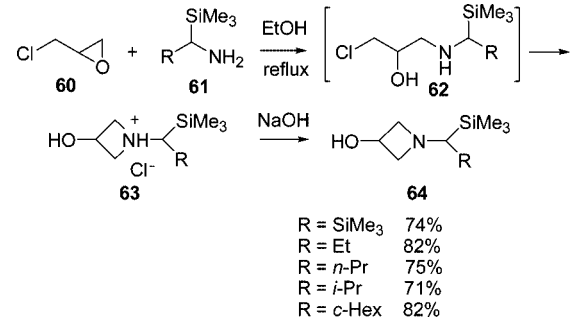


R^1 = Ph	R^2 = $(CH_2)_3OTBS$	74%
R^1 = Ph	R^2 = Me	82%
R^1 = Pr	R^2 = Et	75%
R^1 = Et	R^2 = Me	71%
R^1 = $(CH_2)_3OAc$	R^2 = $(CH_2)_2OAc$	82%
R^1 = $(CH_2)_2OTBS$	R^2 = $(CH_2)_3OTBS$	73%
R^1 = $(CH_2)_3OTBS$	R^2 = $(CH_2)_4OTBS$	71%

The efficient formation of azetidines through the intermediacy of an extremely strained molecule, 1-azabicyclo[1.1.0]butane (**54**),[17] needs a special remark (Scheme 15).[18] Compound **54** is, in turn, obtained indifferently from 1,3-dibromo-**53**,[19] or 1,2-dibromopropylamines (**55**),[20] or allylamine (**56**) and NCS. Several nucleophiles were added to the strained 1-azabicyclo[1.1.0]butane, forming 3 substituted azetidines **57** quite efficiently (Scheme 15).[17−20] The method revealed useful for the synthesis of the new energetic material 1,3,3-trinitroazetidine.[19a] 3-Phenyl-1-azabicyclo[1.1.0]butane gave 3-chloro-3-azetidine-1-carbodithioates by reaction with chlorodithioformates.[21]

Other methods of cyclization involve Mitsunobu activation of the hydroxyl group.[22]Recently, an efficient novel cyclization of γ-amino alcohols **58**, obtained by a stereoselective Mannich reaction, mediated by 1,1′-carbonyldiimidazole (CDI) led to an efficient synthesis of enantiopure *cis*-substituted azetidines **59** (Scheme 16).[23] Also one example of *trans*-substituted azetidine is reported.

Scheme 17



R = $SiMe_3$	74%
R = Et	82%
R = *n*-Pr	75%
R = *i*-Pr	71%
R = *c*-Hex	82%

2.1.2. Opening of Epoxides

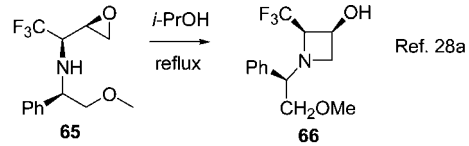
The base induced intramolecular cyclization of *N*-alkylamino oxiranes continues to be an important synthetic route to the azetidine ring system, in particular azetidin-3-ols and azetidin-3-ones. The original Gartner's method consisted of condensation of primary amines with epichlorohydrine **60** under heating (see, for example, Scheme 17),[24] leading to a straightforward synthesis of 1-alkyl-3-azetidinols, albeit in moderate yields, and with the limitation of the poor reactivity of sterically bulky amines. Several more recent examples using this procedure were reported.[25]

The use of α-silylated amines **61** provides good yields of azetidinols **64** (Scheme 17).[26] Similar reactivity is shown by 2-(1-bromoalkyl)oxiranes.[27] The mechanism of the reaction requires some comment. The process proceeds rather with the opening of the epoxide by the amine, i.e., to give intermediate **62**, followed by cyclization to azetidine by displacement of the halide. The formation of aminoalkyl oxiranes (as **65** or **68**, Scheme 18), by primary displacement of the halide, seems to hamper the further cyclization to azetidines.[11e,25i,26] However, these findings are contradicted by more recent results (Scheme 18), where azetidines **66** and **69** were obtained from aminoalkyl oxiranes by simple heating.[28] In one case, the rearrangement ran more smoothly under $MgBr_2$ catalysis.[29]

2.1.3. Opening of Aziridines

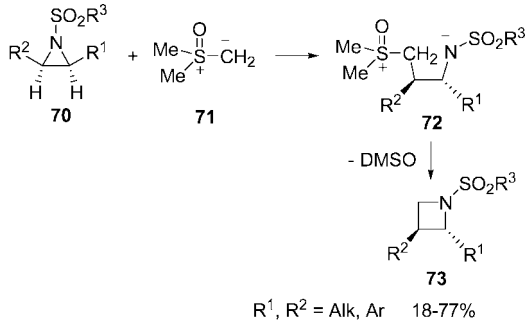
Nadir's group intensely contributed to the synthesis of azetidines through the opening of aziridines. They developed a process involving the opening of aziridines **70** by dimethylsulfoxonium methylide **71** followed by 4-*exo-tet* ring closure of intermediate **72** with dimethyl sulfoxide (DMSO) extrusion (Scheme 19).[30] The reaction is stereospecific, as the *cis*-aziridines yield the *trans*-azetidines **73** and the *trans*-aziridines yield the *cis*-azetidines. This stereochemical course is interpreted in terms of an S_N2/1,4-elimination

Scheme 18



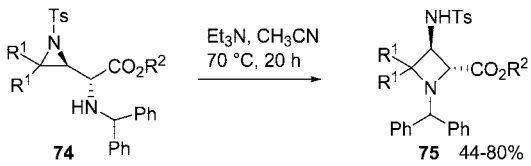
R = *n*-Bu	40%
R = *t*-Bu	85%
R = *i*-Pr	47%
R = Allyl	50%
R = Bn	56%
R = Ph_2CH	72%
R = $HOCH_2CH_2$	26%

Scheme 19



R^1, R^2 = Alk, Ar 18-77%

Scheme 20



R^1= Me, Et; R^1-R^1= *c*-Hex
R^2= Me, Et, *t*-Bu

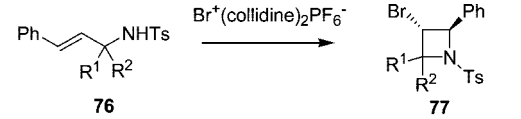
mechanism.[30c] Several alkyl and aryl 2,3-substituted- and 2,3-disubstituted-*N*-arylsulfonylazetidines were prepared in fair-to-good yields. Recently, the synthesis was carried out using microwave irradiation in solvent-free conditions on alumina as the solid support.[30f] Dimethylsulfonium ethoxycarbonylmethylide also gives a similar reaction.[31]

1-Arylsulfonyl-2-(halomethyl)aziridines, by opening with amines, gave 3-aminoazetidines, albeit in moderate yields.[32] More recently, *anti*-aziridino amino esters **74** were thermally rearranged upon treatment with Et_3N to *trans*-*N*-protected alkyl-3-aminoazetidine-2-carboxylic esters **75** (Scheme 20).[33] Absence of the base leads to lower rearrangement yields. Interestingly, *syn*-aziridino amino esters failed to give rearrangement to azetidines.

2.1.4. Opening of Bromonium, Iodonium, and Seleniranium Intermediates

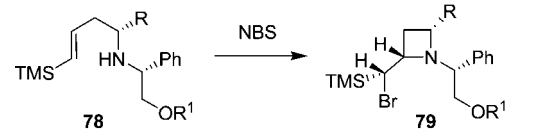
N-Tosyl-cynnamilamides **76** gave with $Br^+(collidine)_2PF_6^-$, chemoselectively, azetidines **77** by 4-*endo* cyclizations (Scheme 21).[34]

Scheme 21



R^1 = R^2 = H	71%
R^1 = Ph; R^2 = H	64%
R^1 = *i*-Pr; R^2 = H	80% (11:1)
R^1 = Me; R^2 = H	83% (4:1)
R^1 = R^2 = Me	95%

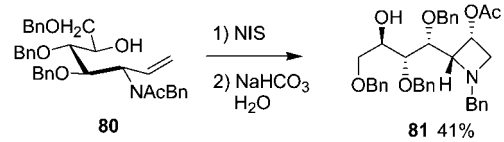
Scheme 22



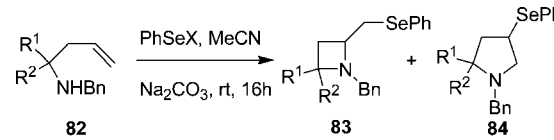
R^1= H
R^1= Me

	R^1= H	R^1= Me
R = Ph	75%	52%
R = Pr	70%	39%
R = *i*-Pr	55%	43%
R = *t*-Bu	53%	66%

Scheme 23



Scheme 24



R^1 = Me, Et, *i*-Pr, Et_2CH, *t*-Bu, Ph
R^2 = H, Me
R^1-R^2 = -$(CH_2)_5$-

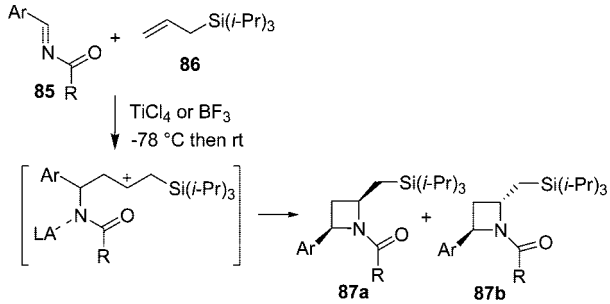
Stereochemical results suggested a carbocation intermediate. No reaction occurred in the absence of the phenyl substituent on the allylamine, nor other protecting groups of the amine.

Optically pure β-amino alcohols or methyl ethers **78**, containing a homoallylvinylsilane moiety, treated with *N*-bromosuccinimide (NBS), provide fair-to-good yields of azetidines **79** (Scheme 22) in a totally regio- and diastereoselective manner.[35]

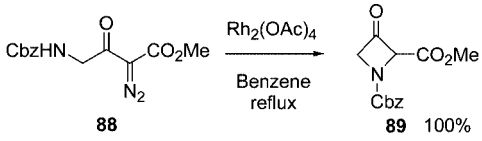
A reinvestigation[36] of the iodocyclization of a 1,2,3-trideoxy-D-*gluco*-hept-1-enitol **80** demonstrates the formation of an azetidine imine alditol **81** (Scheme 23). An *N*-tosyl-2-iodomethylazetidine was obtained in poor yield by treatment of the homoallyl-*N*-tosylamide with *tert*-butyl hypoiodite.[37]

The formation of azetidines by nucleophilic opening of seleniranium intermediates was observed for the first time.[38] Homoallyl benzylamines **82** with PhSeX (X = Cl, Br, I) in CH_3CN and Na_2CO_3 at room temperature (rt) afforded mixtures of azetidines **83** and pyrrolidines **84**, deriving from 4-*exo*-*trig* and 5-*endo*-*trig* cyclizations, respectively (Scheme 24). α,α-Disubstituted homoallylic amines gave exclusively azetidines, also favored by the use of PhSeI or PhSeBr instead of PhSeCl. The use of an excess of PhSeX induced an isomerization of the mixture, leading preferentially to pyrrolidines.[38a]

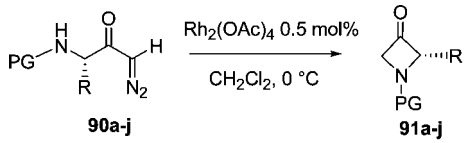
Scheme 25



Scheme 26



Scheme 27



a: R = *t*-BuPh$_2$SiOCH$_2$, PG = Boc	67%	Ref. 43b
b: R = PhCH$_2$, PG = Cbz	70%	Ref. 43c
c: R = Me, PG = Cbz	68%	Ref. 43c
d: R = Me, PG = Boc	59%	Ref. 43d
e: R = *i*-Pr, PG = Cbz	50%	Ref. 43d
f: R = PhCH$_2$, PG = Boc	63%	Ref. 43d
g: R = CbzNH(CH$_2$)$_4$, PG = Cbz	50%	Ref. 43d
h: R = CbzOCH$_2$, PG = Boc	47%	Ref. 43d
i: R = *i*-Bu, PG = EtOCO	62%	Ref. 43e
j: R = Me$_2$NCO(CH$_2$)$_2$, PG = Boc	52%	Ref. 43f

2.1.5. Electrophilic Attack on C═C

The reaction of *tert*-butylaminomethylbenzotriazole with allyltrimethylsilane in the presence of $AlCl_3$ afforded *N*-*tert*-butyl-2-trimethylsilylazetidine via cyclization on a carbocationic intermediate.[39] A $TiCl_4$ (or BF_3) catalyzed reaction of *N*-acylaldimines **85** with allyltriisopropylsilane **86** gave azetidines **87a**,**b** with poor diastereoselectivity (Scheme 25).[40]

The *N*-acyl protecting group and the bulkyness of the silicon substituent are key factors for the cyclization to occur. *N*-Ethoxycarbonylaldimine and allyltrimethylsilane gave exclusively, or preferentially, homoallylamines.

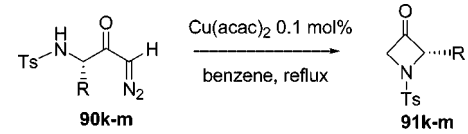
2.1.6. NH Insertions in Diazo Compounds

The metal-catalyzed intramolecular NH insertion of diazo compounds has received considerable attention, mainly regarding amide NH bonds, and has led to the synthesis of fused β-lactams.[41] After the first example by Rapoport[42] of $Rh_2(OAc)_4$ catalyzed intramolecular N−H insertion of α-diazo β-chetoesters **88** to azetidine-3-one **89** (Scheme 26), several other examples have followed since.[43]

Amino acids provide an excellent starting point for the synthesis of optically pure 2-substituted azetidine-3-ones **91a**−**j** (Scheme 27).[41,43b−g]

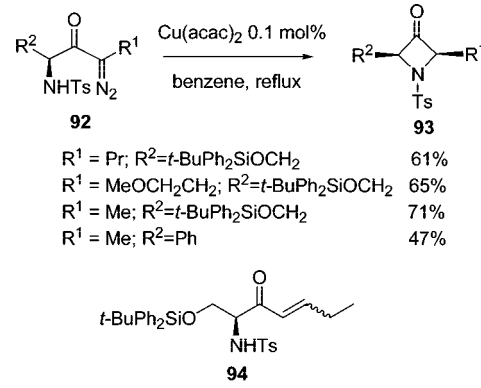
Cu(acac)$_2$ was also used as the catalyst with *N*-Ts protected amino acids **90k**−**m**, with somewhat lower yields (Scheme 28).[43g] Correia and co-workers[43i,j] recently extended this chemistry to the synthesis of 2,4-disubstituted azetidine-3-ones **93**, finding Cu(acac)$_2$ catalyst and *N*-Ts diazoketones **92** to be the best reagents (Scheme 29).

Scheme 28

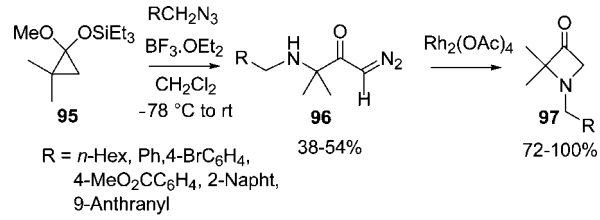


k: R = Me 34%
l: R = PhCH$_2$ 45%
m: R = MeS(CH$_2$)$_2$ 57%

Scheme 29



Scheme 30



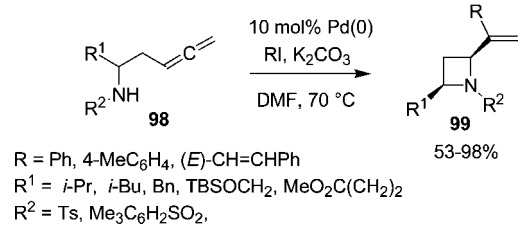
Diastereomeric olefin side products, like **94**, were obtained in yields around 20% as a result of a β-hydride elimination of the intermediate organometal. The yield and diastereomeric ratio of olefinic side products vary greatly with respect to the catalyst employed. Rh catalyst favors the formation of olefin compound, with preference of the *Z* diastereoisomer. It is noteworthy that the high stereoselectivity of the reaction leads exclusively to *cis*-2,4-disubstituted azetidine-3-ones **93**, likely deriving from a transition state in which the bulky metal ML_n and the alkyl group are preferred in an *anti* relationship.

Aminodiazomethyl ketones **96** leading to azetidinones **97** were synthesized by a new method from alkyl azides and a cyclopropanone methyltriethylsilyl ketal **95** under BF_3 catalysis (Scheme 30).[43h]

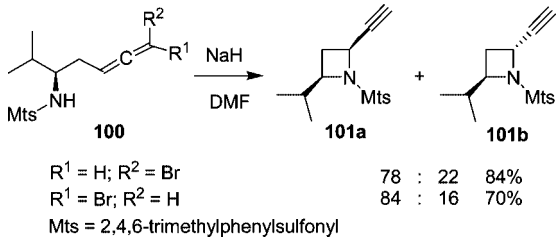
2.1.7. Pd Catalyzed Cyclizations

Allenes bearing a tosylamino group on the chain undergo Pd catalyzed coupling-cyclizations to aza-heterocycles with phenyliodonium salts[44] or organic halides.[45−47] In these reactions, the amino allene undergoes carbopalladation at the central sp-carbon atom to form a π-allyl palladium intermediate, which is followed by intramolecular 4-*exo* and 4-*endo* cyclization of nitrogen. In the case of 5-tosylamino-1,2-pentadiene, a 2:1 mixture of the vinyl azetidine ring and the tetrahydropyridine was obtained.[44] The method, using allenyl

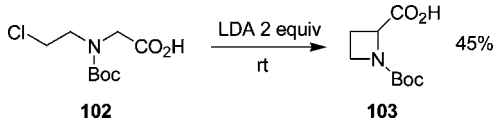
Scheme 31



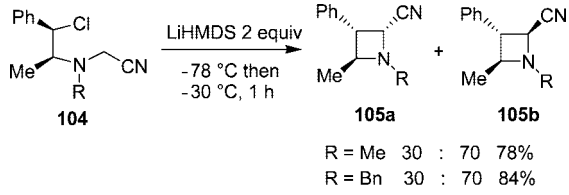
Scheme 32



Scheme 33



Scheme 34



modified amino acids, was applied to the synthesis of enantiopure azetidine-2-carboxylates. The ratio in favor of the azetidine reached as much as 95:5.[45] Similar optically pure amino acid derived β-amino allenes **98**, by choosing the appropriate solvent and nitrogen protecting group, gave exclusively the *cis*-substituted vinyl azetidines **99** with excellent stereoselectivity and yield (Scheme 31).[46]

Interestingly, similar Br substituted allenes **100** give *cis*- and *trans*-2-ethynylazetidines **101a**,**b** with good yield and stereoselectivity by treatment with NaH (Scheme 32).[48]

2.2. Cyclizations by C−C Bond formation

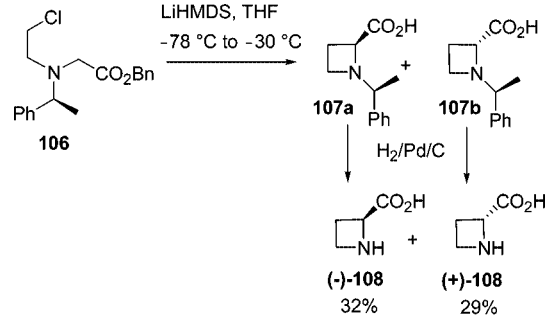
2.2.1. Nucleophilic Displacement of Halides

Boc protected azetidine-2-carboxylic acid **103** was synthesized from *N*-(ω-chloroethyl)-Boc-glycine **102** by treatment with 2 equiv of LDA at room temperature (Scheme 33).[49] Racemic 2-phenyl azetidine-2-carboxylic acids were similarly synthesized from phenylglycine esters.[50]

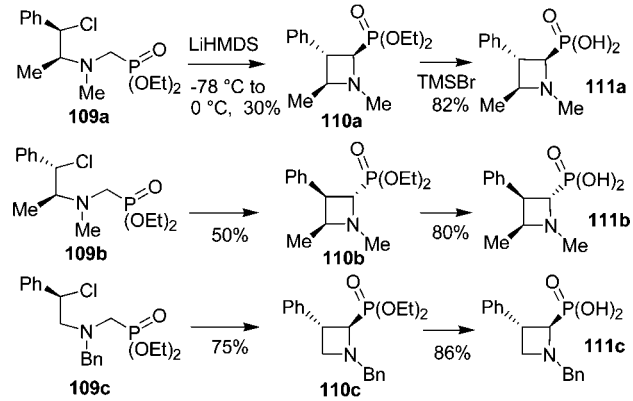
The Couty group nicely developed this carbanion chemistry for the synthesis of enantiopure 2-cyano azetidines **105a**,**b**, precursors of 2-acyl azetidines or 2-carboxylic acid and derivatives, starting from ephedrine or phenylglycinol precursors (Scheme 34).[51]

Interestingly, by keeping the reaction longer at −30 °C, the ratio in favor of isomer **105b** increased to 92:8.[51c] Both enantiomers of azetidine-2-carboxylic acid **108** were obtained by intramolecular alkylation using optically pure α-methylbenzylamine derived glycine esters **106** (Scheme 35).[52]

Scheme 35



Scheme 36



Starting from proline ester derivatives, strained azabicyclo-[3.2.0]heptanes are obtained in good yields.[53] With the same chemistry applied to phosphonates **106a**−**c** azetidine 2-phosphonic acids **107a**−**c** were obtained with complete diastereoselectivity (Scheme 36).[54] Azetidines **105** can be alkylated to form azetidinium salts, which, by treatment with base, produce strained azetidinium ylides able to undergo cyclopropanation and epoxidation reactions.[55]

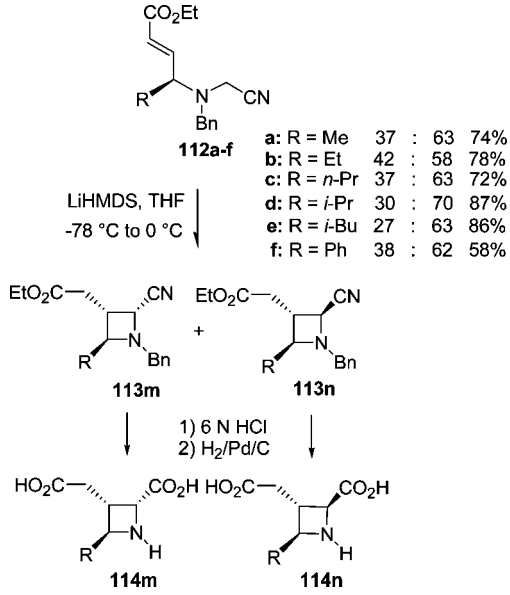
A series of constrained analogues of glutamic acid **114a** and **114b** were also obtained, by the same group, through intramolecular Michael additions of nitriles **112a**−**f**, followed by hydrolysis and deprotection of intermediates **113m** and **113n** (Scheme 37).[56] The Michael addition occurred with moderate stereoselectivity, except in one case, by replacing the nitrile group with a *tert*-butyl ester group, and it was thermodynamically controlled.

2.2.2. Cyclizations Involving C═O Group

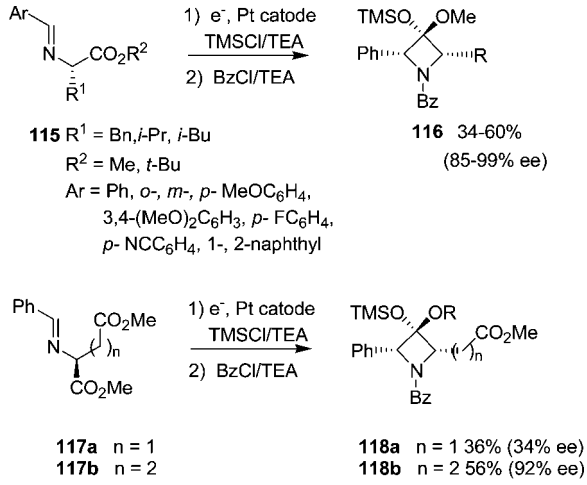
Electroreductive intramolecular cross-coupling of imines with alkoxycarbonyl compounds is an interesting method for the synthesis of azetidines. Enantiomerically pure or enriched azetidin-2-ones **116** were obtained by electroreduction of enantiopure aromatic α-iminoesters, prepared from α-aminoacids, in fair yields (Scheme 38).[57] TMSCl was indispensable to promote the electroreductive intramolecular coupling. Some racemization occurred under the conditions of electroreduction (0.3 M solution of Bu_4NClO_4/THF, TMSCl, and triethylamine (TEA)).

When a second ester group is present on the substrate, the formation of azetidine-3-one mixed ketal **118b** is preferred for glutamic acid derivative **117b** ($n = 2$) over the six-membered cyclized product, as calculated also by density functional theory (DFT) method.[57a] Aspartic acid derivative **117a** ($n = 1$) gave, besides azetidine-3-one mixed ketal **118a**, diastereomeric pyrrolidin-3-ones.

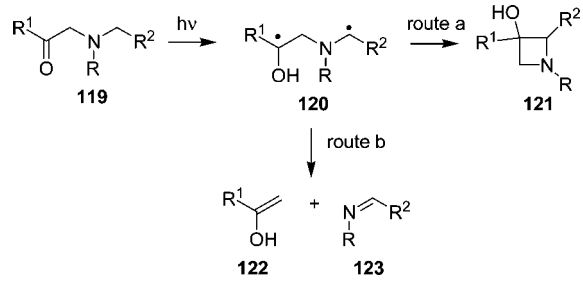
Scheme 37



Scheme 38



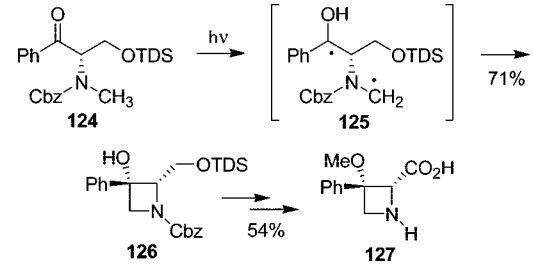
Scheme 39



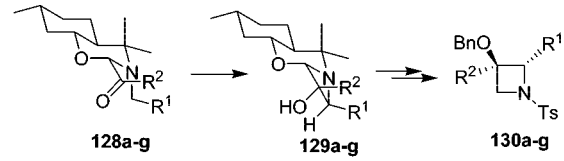
The photochemical activation by irradiation of appropriate aminoketones **119** leads to an intramolecular cyclization, to form azetidinols **121** as reaction intermediates or final products, known as Yang cyclization (Scheme 39).[58] The success of the process depends on several factors that can drive the reaction path chemoselectively toward the cyclization of the diradical intermediate **120** (route a) rather than a Norrish-Type-II cleavage (Scheme 39, route b).

Several examples of the application of this chemistry have been reported.[59] An efficient stereoselective synthesis of an enantiopure azetidine-2-carboxylic acid **127** (and its enantiomer) was achieved starting from the amino ketone **124**,

Scheme 40

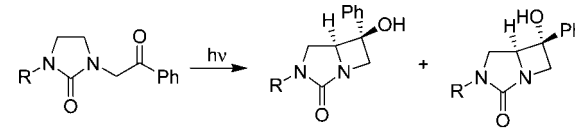


Scheme 41



a: R^1 = -CH=CH_2, R^2 = H 50% (82:18)
b: R^1 = -CH=CH_2, R^2 = Ph 56% (79:21)
c: R^1 = -CPh=CHEt, R^2 = Ph 27% (94:6)
d: R^1 = Ph, R^2 = Ph 60% (> 96%)
e: R^1 = Ph, R^2 = 4-$MeOC_6H_4$ 58% (> 96%)
f: R^1 =-Ph, R^2 = 2-Furyl 55% (> 96%)
g: R^1 = 3,4-$(MeO)_2$Ph, R^2 = Ph 56% (> 96%)

Scheme 42



which was designed to avoid photochemical fragmentation (Scheme 40).[59a]

The process found more applications in the formation of bicyclic fused azetidines, likely because substrates are less prone to fragmentation.[59c−h] Pedrosa and co-workers[59c] devised a method for the synthesis of enantiopure azetidinols **130a−g** by using enantiopure scaffolds **128a−g**, derived from menthol, which contain the two photoreactive chains undergoing photocyclization and can eventually be removed (Scheme 41).

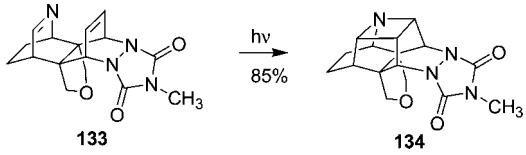
The diastereoselectivity of the cyclization is dependent on the nature of the substituents at the nitrogen atom. *N*-Benzyl derivatives were totally diastereoselective, leading to a single diastereoisomer. Bach and co-workers[59d] proposed a Norrish−Yang cyclization of *N*-(*ω*-oxo-*ω*-phenylalkyl)-substituted imidazolidinones **131** to fused azetidines **132a**,**b** in solution and in the solid state (Scheme 42).

As compound **131** (R = Ac) crystallizes in a chiral space group, a suitable homochiral crystal was also irradiated in the solid state to study the enantioselectivity of the process. At low conversion (1%), a high diastereomeric ratio (*exo*/*endo* = 94:6) of the product was observed, and the major *exo* isomer showed a 78% ee. The ratio drops to 87:13 and ee drops to 28% at 36% conversion.

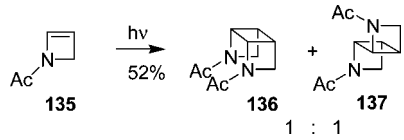
2.3. Cycloadditions

The cycloaddition chemistry for four-membered heterocycles involves mainly the synthesis of *β*-lactams, from which azetidines are obtained by reduction (see below). There

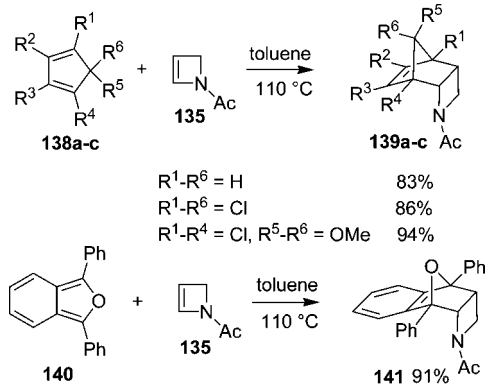
Scheme 43



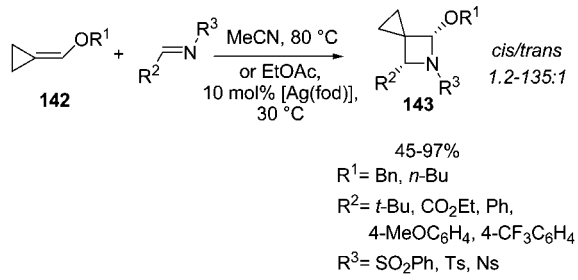
Scheme 44



Scheme 45



Scheme 46



are relatively few examples of cycloaddition reactions of imines and alkenes leading directly to the azetidine ring.[60−62]

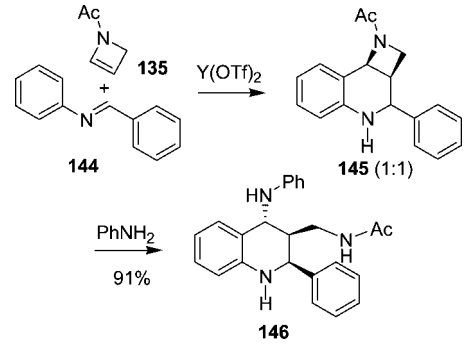
The Prinzbach group[61] has extensively studied the intramolecular [2 + 2]-photocycloadditions of rigid imine/ene systems **133** leading to cage compounds **134** (Scheme 43).

Dave and co-workers[62a] studied the photodimerization of *N*-acetyl-2-azetine **135**, obtaining both possible head-to-head dimers diazatricyclooctanes **136** and **137** with *syn* and *anti* geometry, respectively (Scheme 44).

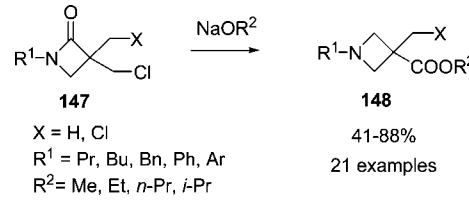
N-Acetyl-2-azetine **135** was employed by the same group[62b] with cyclic dienes **138a**−**c** and **140** in Diels−Alder reactions, which occurred easily in high yields (Scheme 45).

Cycloadditions of imines to enol ethers have rarely been employed. In fact, Scheeren and co-workers reported that [2 + 2]-cycloadditions of imines to enol ethers require high pressure (12 kbar).[60b] Because of their ring strain, however, (alkoxymethylene)cyclopropanes **142** are excellent substrates for cycloadditions. Thermal cycloaddition in acetonitrile at 80 °C gave spirocyclopropane azetidines **143** in very good yields (Scheme 46).[63]The [Ag(fod)] (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) catalyzed [2 + 2]-cycloaddition allowed the reaction to proceed at lower temperature (30 °C), with somewhat lower yields but higher diastereoselectivity. A strong preference for the *cis* diastereoisomers of the products **143** is observed, which is fully consistent with the proposed two-step mechanism of the process.

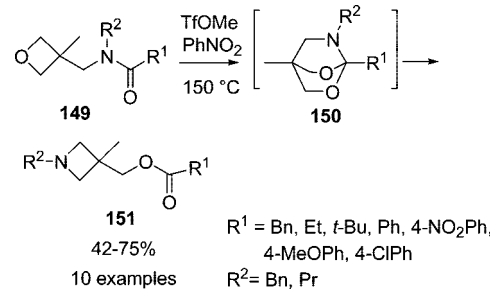
Scheme 47



Scheme 48



Scheme 49



A Lewis acid catalyzed [4 + 2]-cycloaddition of *N*-acetyl-2-azetine **135** with imines of aromatic amines was also reported, on the way of the synthesis of functionalized tetrahydroquinolines **146** by opening of the azetidine ring of **145**.[62c] One example is reported in Scheme 47.

2.4. Ring Rearrangements

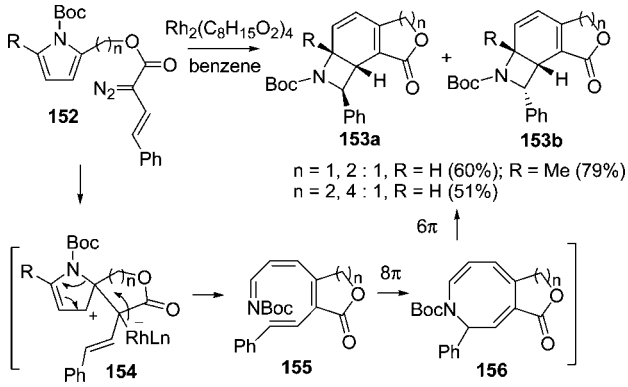
2.4.1. Rearrangements of Four-Membered Rings

3-(Chloromethyl)azetidin-2-ones **147**, 3-methyl- or 3-chloromethyl substituted, efficiently rearrange to azetidine-3-carboxylic acid esters **148** on treatment with alkoxides. Numerous examples are reported with yields ranging from 41 to 88% (Scheme 48).[64]

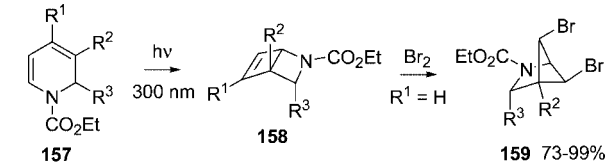
Oxetane amides **149** undergo a new synthesis of (3-azetidinyl)methanol esters **151** by an acid-catalyzed rearrangement at 150 °C of intermediates **150** (Scheme 49).[65]

Although the scope of the reaction is limited by the vigorous reaction conditions and, apparently, the necessary bulkiness of the R^1 and R^2 substituents, the method offers an interesting alternative to the most common procedures. Oxaziridines, and their precursor nitrones, of hexahydroindoles have been rearranged, applying the known photochemical rearrangement of oxaziridines,[66] to fused azetidines, 1-azabicyclo[5.2.0]nonan-2-ones.[67] The method has been employed for the synthesis of novel nonpeptide RGD mimetics.

Scheme 50

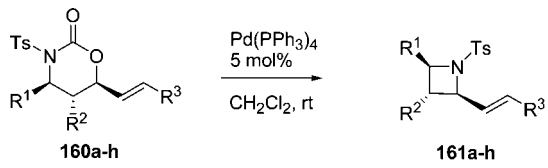


Scheme 51



$R^1 = R^2 = R^3 = H$	50%
$R^2 = R^3 = H$; $R^1 = CH_2OH$	17%
$R^2 = R^3 = H$; $R^1 = Me$	25%
$R^1 = R^3 = H$; $R^2 = Me$	16%
$R^1 = R^2 = H$; $R^3 = Me$	21%
$R^1 = H$; $R^2 = R^3 = Me$	13%
$R^1 = R^2 = H$; $R^3 = Ph$	15%

Scheme 52



a: $R^1 = R^3 = H$; $R^2 = Ph$	74% (16:1)
b: $R^2 = R^3 = Ph$; $R^1 = H$	62% (>19:1)
c: $R^1 = R^3 = H$; $R^2 = Bn$	60% (8.5:1)
d: $R^1 = R^3 = H$; $R^2 = i\text{-Pr}$	93% (>19:1)
e: $R^1 = R^3 = H$; $R^2 = 4\text{-}ClC_6H_4$	78% (>19:1)
f: $R^1 = R^3 = H$; $R^2 = 4\text{-}MeOC_6H_4$	84% (14:1)
g: $R^1 = Ph$; $R^2 = R^3 = H$	92% (>19:1)
h: $R^1 = Me$; $R^2 = R^3 = H$	78% (8:1)

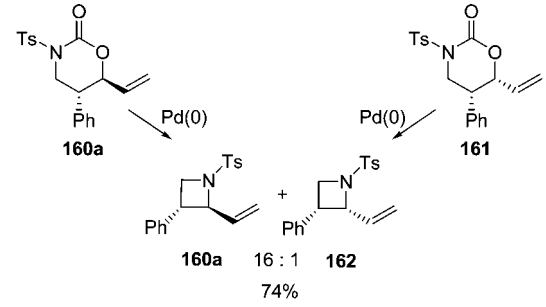
2.4.2. Rearrangements of Larger Rings

Among ring rearrangements, ring contractions represent a group of interesting reactions for the synthesis of less common azetidines.[68−71] The well-known electrocyclic ring contraction[72] of l-aza-2,4,6-cyclooctatriene systems **156** found new examples of the synthesis of benzofused azetidines (7-azabicyclo[4.2.0]octadienes) **153a**,**b** through a rhodium(II) catalyzed intramolecular domino reaction of vinyldiazomethanes substituted pyrroles **152** (Scheme 50).[69]

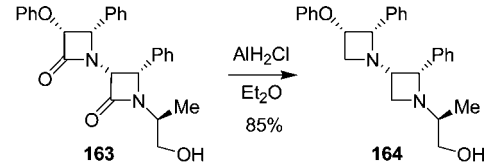
Krow[70] and co-workers extensively investigated the known[73] synthesis of 2-azabicyclo[2.2.0]hex-5-enes **158** by photochemical electrocyclic ring contraction of dihydropyridines **157** (Scheme 51). The main scope of the study is the further rearrangement of 2-azabicyclo[2.2.0]hex-5-enes to 2-azabicyclo[2.1.1]hexanes **159**.

A very efficient method for the synthesis of valuable 2-vinylazetidines **161** is the Pd(0) catalyzed decarboxylative ring contraction[71] of vinyloxazinones **160** (Scheme 52).[74]

Scheme 53



Scheme 54



The mechanism of the ring contraction involves the formation of a π-allyl Pd complex, by extrusion of CO_2, followed by nucleophilic attack of the nitrogen to form the azetidine ring. A fast epimerization through a $\pi-\sigma-\pi$ allyl interconversion must occur in the process with vinyl-unsubstituted substrates, as the two diastereoisomers **160a** and **161** gave the same product mixture of azetidine **160a** and **162** in a 16:1 ratio (Scheme 53).

2.5. Reduction of Azetidin-2-ones

The synthesis of azetidines by reduction of azetidin-2-ones (β-lactams) is among the most used methods, because of the easy availability of these compounds and the facile reduction process. Reduction of *N*-substituted azetidin-2-ones to *N*-substituted azetidines is generally accomplished rapidly and in good yield with diborane in tetrahydrofuran, $LiAlH_4$, and Raney nickel or, more efficiently, with alanes in ether. The stereochemistry of the ring substituents is retained under the reaction conditions. 3-Aminopropanol derivatives, formed by reductive ring cleavage, are sometimes obtained as byproducts in diborane, $LiAlH_4$, and Raney nickel reductions, but not in alane reductions. Several significant examples appeared recently.[75−78] Ojima and co-workers were the first to discover the potency and selectivity of DIBAL-H and chloroalanes (AlH_2Cl or $AlHCl_2$) in reductions of β-lactams.[75e] He applied these conditions to an extremely large variety of substrates showing the generality and efficiency of the process.[75] As an example of the efficiency of the reduction, the reduction of bis-β-lactam **163** to bis-azetidine **164** is shown in Scheme 54.

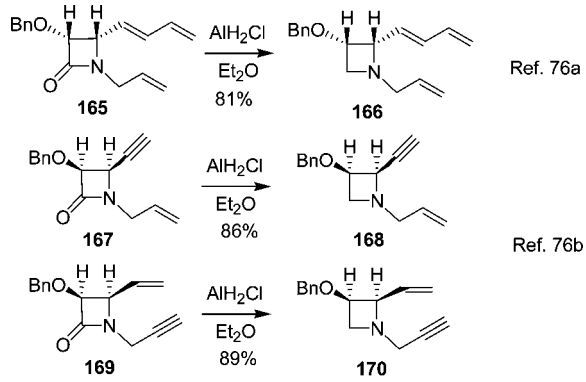
Alcaide and co-workers[76] applied more recently the chloroalane reduction method to a large series of monocyclic and polycyclic β-lactams (Scheme 55).

It is worth noting the high chemoselectivity of these reductions, as the amide bond is reduced selectively in the presence of conjugated double bonds (**165**),[76a] double triple bonds (**167**, **169**),[76a,b] and other functionalities sensible to reduction conditions (Scheme 56, eqs 1−3).[76c,d]

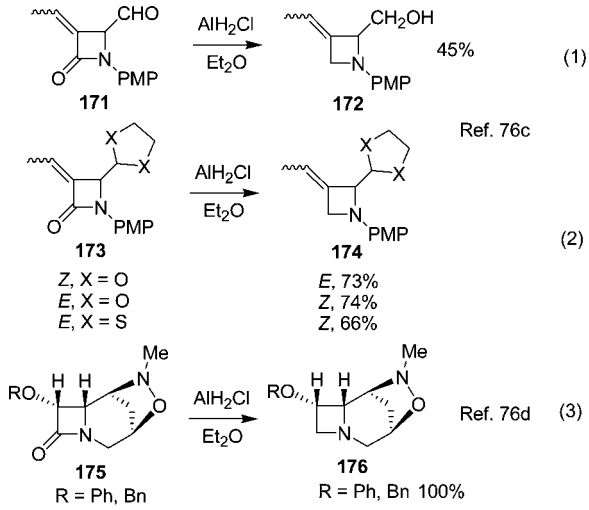
2-Azetidine carboxaldehyde acetals and thioacetals **177**, in contrast, under reduction conditions underwent a Lewis acid catalyzed ring enlargement to 2,3,4-substituted pyrrolidines **178** (Scheme 57).[76e]

De Kimpe and co-workers[77a,b] have recently used the methodology for the synthesis of 3-chloro- and 3,3-dichlo-

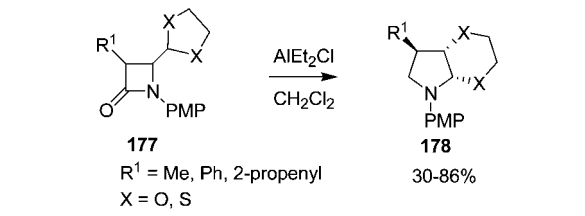
Scheme 55



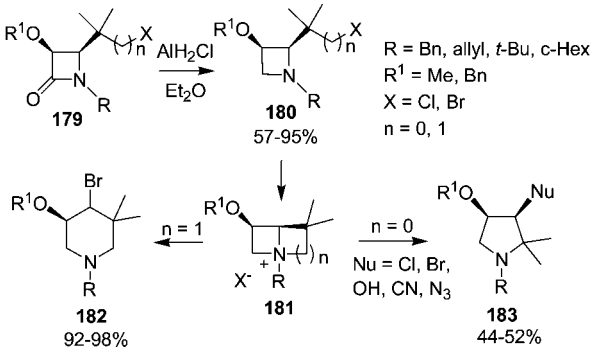
Scheme 56



Scheme 57



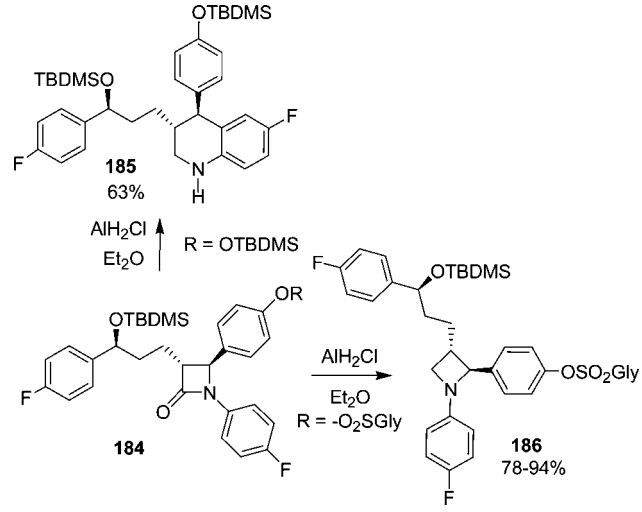
Scheme 58



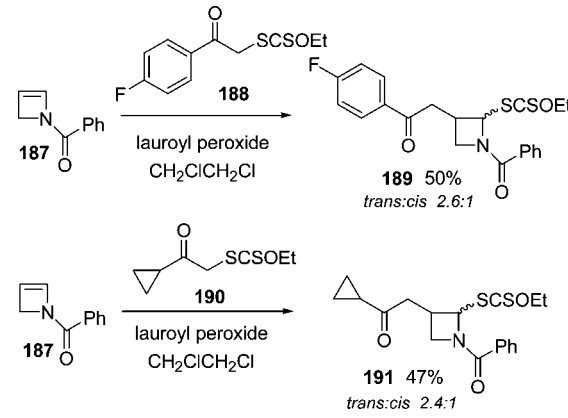
roazetidines. 2-(1-Haloalkyl)- and 2-(2-bromoalkyl)azetidines **180**, precursors for a new azetidine ring transformation to piperidines **182** and pyrrolidines **183** via bicyclic azetidinium salt **181**, were synthesized in a similar manner from the corresponding azetidine-2-ones **179** (Scheme 58).[77c]

The instability, and tendency to opening of the azetidine ring, in the presence of Lewis acids during the reduction

Scheme 59



Scheme 60



with alanes was observed also by Carreira and co-workers[78a] in the synthesis of cholesterol absorption inhibitors, like **186**. The electron-rich phenyl C-4 substituent of the β-lactam **184** favors rearrangement of the formed azetidine to tetrahydroquinoline **185** (Scheme 59).

Only by transforming the group in electron-withdrawing through a sulfonyl ester does the reduction to azetidine perform nicely. Sulfonylated azetidine glycosides **186** are potent cholesterol absorption inhibitors.[78b]

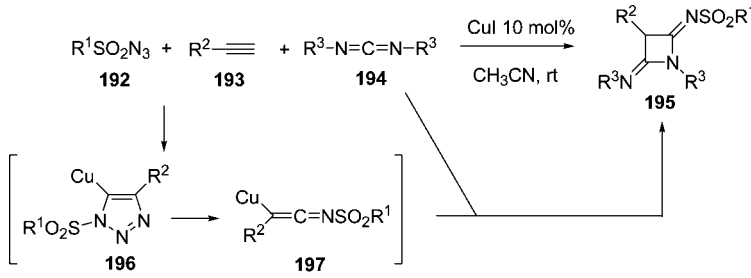
2.6. Miscellaneous Syntheses

One example of the cyclization of ethyl ester of 4-azidoboronic acid in the presence of BCl_3 leads to azetidine in low yield (31%).[79] The novel radical addition[25g] of xanthates **188** and **190** to azetine **187** produced new azetidines **189** and **191** in fair yields.[80] The *trans* isomer predominates in both cases. (Scheme 60).

The multicomponent copper-catalyzed reaction of sulfonylazides **192**, alkynes **193**, and carbodiimides **194** gave 2-(sulfonylimino)-4-(alkylimino)azetidines **195** very efficiently (Scheme 61).[81] The triazole **196**, formed by addition of sulfonylazides **192** and alkynes **193,** is the presumed intermediate that extrudes nitrogen to form the chetenimine **197**, which undergoes [2 + 2]-addition to the carbodiimides **194**.

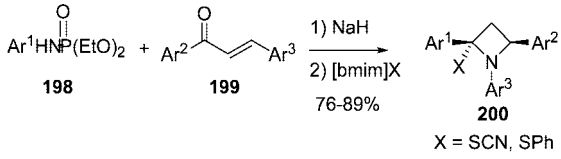
An efficient synthesis of 1,2,5-triaryl substituted azetidines **200** by the aza-Michael addition of diethyl *N*-arylphosphoramidates **198** to chalcones **199** was recently reported. The

Scheme 61



R^1 = Me; R^2 = Pentyl; R^3 = C_6H_{11}	76%	R^1 = 4-MeC_6H_4; R^2 =Ph; R^3 = *c*-Hex	94%
R^1 = Me; R^2 = 4-MeC_6H_4; R^3 = *c*-Hex	77%	R^1 = 4-MeC_6H_4; R^2 =4-MeC_6H_4; R^3 = *c*-Hex	87%
R^1 = Ph; R^2 = Ph; R^3 = C_6H_{11}	91%	R^1 = 4-MeC_6H_4; R^2 =CO_2Et; R^3 = *c*-Hex	93%
R^1 = Ph; R^2 = CO_2Et; R^3 = *i*-Pr	95%	R^1 = 4-MeC_6H_4; R^2 =Butyl; R^3 = *c*-Hex	65%
R^1 = Ph; R^2 = 4-MeOC_6H_4;R^3 = *i*-Pr	88%	R^1 = 4-MeC_6H_4; R^2 =Pentyl; R^3 = *c*-Hex	71%
R^1 = Ph; R^2 = 4-EtC_6H_4;R^3 = *i*-Pr	79%	R^1 = 4-MeC_6H_4; R^2 =Ph; R^3 = *i*-Pr	88%
R^1 = Ph; R^2 = 4-PrC_6H_4;R^3 = *i*-Pr	81%	R^1 = 4-MeC_6H_4; R^2 =CO_2Et; R^3 = *i*-Pr	95%
R^1 = Ph; R^2 = 4-BuC_6H_4;R^3 = *i*-Pr	83%	R^1 = 4-ClC_6H_4; R^2 =Ph; R^3 = *i*-Pr	84%
		R^1 = 4-ClC_6H_4; R^2 =Ph; R^3 = *c*-Hex	86%
		R^1 = 4-ClC_6H_4; R^2 =TMS; R^3 = *c*-Hex	76%

Scheme 62



cyclization to azetidines is induced by anions (X = PhS^-, NCS^-) of a task-specific ionic liquid [bmim]X (Scheme 62).[82]

2.7. Important Classes of Compounds

2.7.1. Natural Products

Natural compounds containing the azetidine ring as a substructure, apart from β-lactams, are somewhat rare. They include compounds from the mugineic acid class (**201** and **202**),[83] to penaresidin/penazetidine class (**203**−**205**),[84,85] and a series of peptidyl polyoxins **206a**−**d**,[86] although new compounds, like calydaphninone **207**, are being recently isolated (see Chart 1).[87]

Mugineic acid and analogues **201** are phytosiderophores, which are produced in higher plants as iron-chelating amino acids and promote uptake and transport of iron required for the chlorophyl biosynthesis. Mugineic acid is isolated from wheat or roots of barley, whereas nicotianamine **202** is found in solanaceous plants, e.g., tobacco leaves. The key structural feature of the compounds is the presence of an azetidine-2-carboxylic acid *N*-linked to a peptidic chain. The strategy for the synthesis of the compounds, pursued by the group of Shioiri and Hamada,[83] has been devoted mainly to the formation of the pseudopeptide chain to be coupled with azetidine-2-carboxylic acid, as shown in Scheme 63 for the synthesis of 2′-deoxymugineic acid **213**.[83b]

The reductive amination of aldehyde **209**, derived from *p*-methoxycinnamate, with amine **208**, derived from β-tyrosine, followed by reduction, led to the formation of the chain of natural compounds **201**−**202**, where the carboxylic groups were installed by a $RuCl_3$ oxidation of the *p*-methoxyphenyl groups of **209**. Reductive coupling of the aldehyde **211** with azetidine-2-carboxylic acid *t*-butyl ester **212** gives 2′-deoxymugineic acid **213**. Replacing aldehyde **211** with an appropriate amino aldehyde **214** leads to the synthesis of nicotianamine **202** (Scheme 63).[83b]

Another more recent synthesis utilizes the key intermediate **216** to synthesize, in a straightforward way, both nicotianamine **202** and 2′-deoxymugineic acid **213** by reductive condensation of **212** with aldehydes **215** and **217**, respectively, which were obtained from aspartic and malic acid, respectively (Scheme 64).[83a]

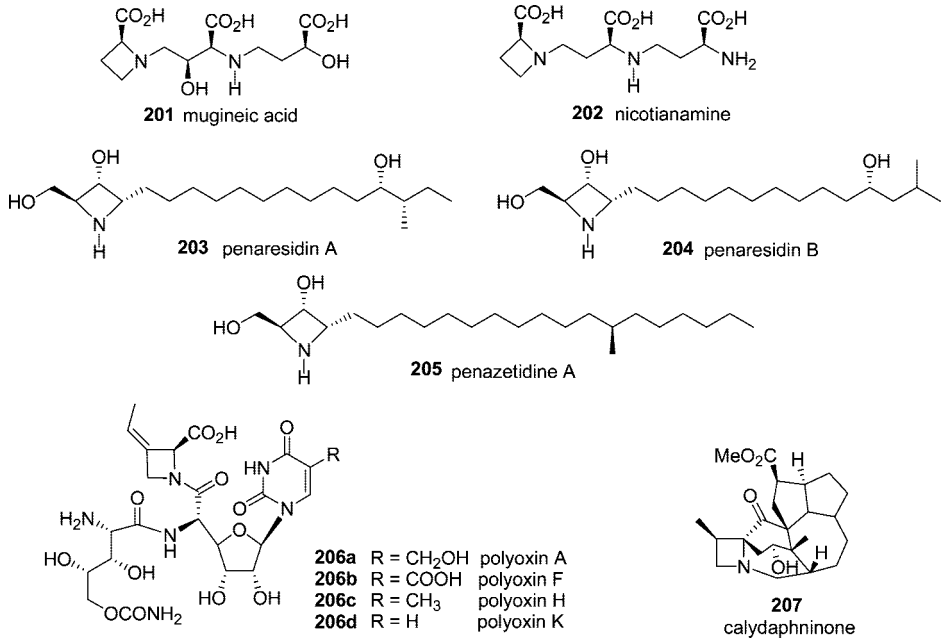
Penaresidin A (**203**) and B (**204**)[84] and penazetidine A (**205**)[85] alkaloids, isolated from marine sponges of the genus *Penares*, are sphingosine-derived azetidine alkaloids possessing potent bioactivity. Compounds **203** and **204** have an actomyosin ATPase-activating activity, and compound **205** has a protein Kinase C inhibitory activity. Mori's group[88] carried out the first synthesis of Penaresidin A (**203**) to determine the correct absolute configuration of the natural compounds. The synthesis started from the alkyne **219**, incorporating the chain obtained from the epoxide **218**, and in 11 steps constructed the azetidine moiety through modification of an incorporated Garner's aldehyde (Scheme 65).

The synthesis of penazetidine A (**205**) by the same authors followed the same synthetic scheme.[88b] Yoda and coworkers[89] synthesized Penaresidin B (**204**) in two different ways, producing the azetidine ring via conversion of lactams. The more recent strategy is reported in Scheme 66.[89a]

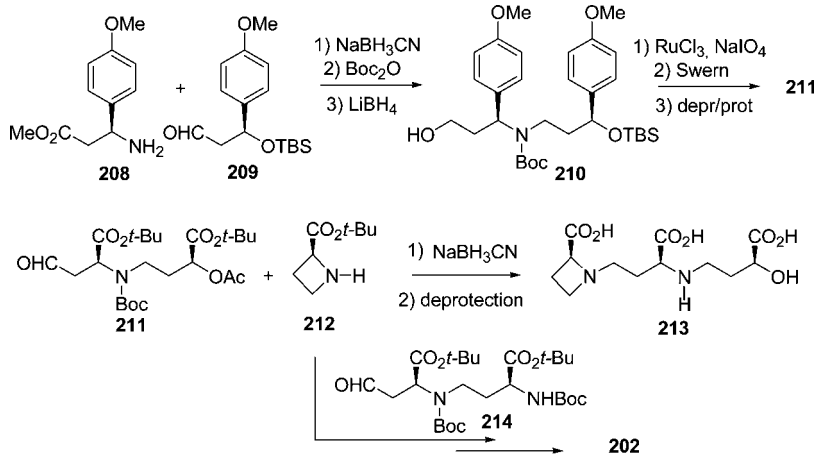
The key precursor **223** for the azetidine moiety is obtained in five steps from the alkyne **221** and the aminoglycoside **222**. Other syntheses, mainly differentiating in the construction of the azetidine moiety, led to the synthesis of natural compounds and their analogues.[90]

Polyoximic acid **229** is a degradation product of polyoxins **206**, a total of 15 compounds that are potent inhibitors of chitin synthetase.[86] It was originally designated as *trans*-3-ethylidene-L-azetidine-2-carboxylic acid, and several total syntheses referred to this stereoisomer,[43a,86,91] but the work of Hanessian and co-workers[43b,c] revealed the correct *Z* structure. The key step in the synthesis is the formation of the azetidine ring **225** by Rh catalyzed carbene insertion into the N−H bond of a diazoketone **224** derived from D-serine. A *Z*-stereoselective Wittig reaction of a Weinreb amide stabilized ylide **226** on the formed azetidinone **225** follows.

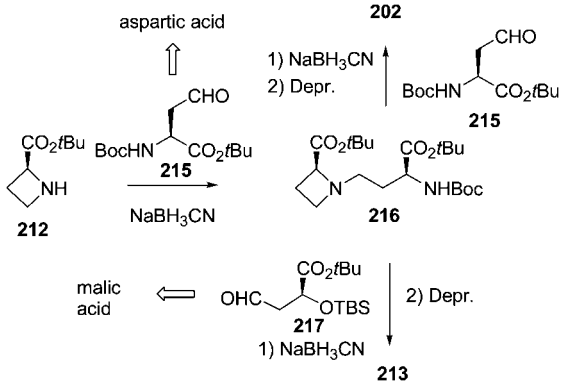
Chart 1



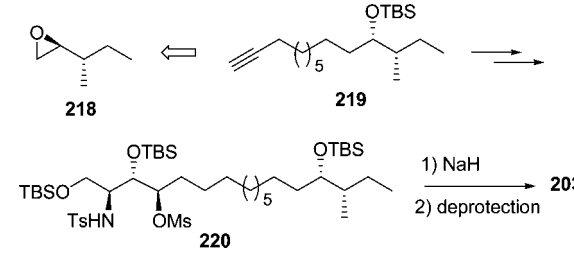
Scheme 63



Scheme 64



Scheme 65



Further reduction of azetidinylene amide **227a** and deprotection/oxidation steps give *cis*-polyoximic acid **229** (Scheme 67).

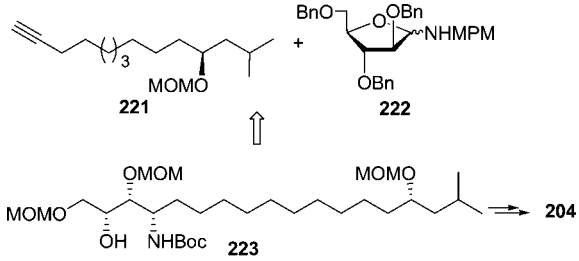
2.7.2. Azetidine Carboxylic Acids

Parent azetidin-2-carboxylic acid and derivatives have been synthesized by several groups as rigid analogues of amino acids and employed in numerous medicinal chemistry studies. Together with examples reported in other part of the review, here are reported some significant examples of these compounds and their reactivity.[92]

Kozikowski and co-workers[92a,c] have synthesized a series of optically pure rigidified glutamate analogues **230**, **231**, **232**, and derivatives, with potent activity on the glutamate receptors. Yamamoto and co-workers have synthesized again amino acid **230** by the same procedure using optically pure 1-phenylethylamine (see Chart 2).[7m]

Correia and Burtoloso[92d] recently provided an alternative synthesis to the rigid glutamic acid analog **231** ($n = 1$)

Scheme 66



Scheme 67

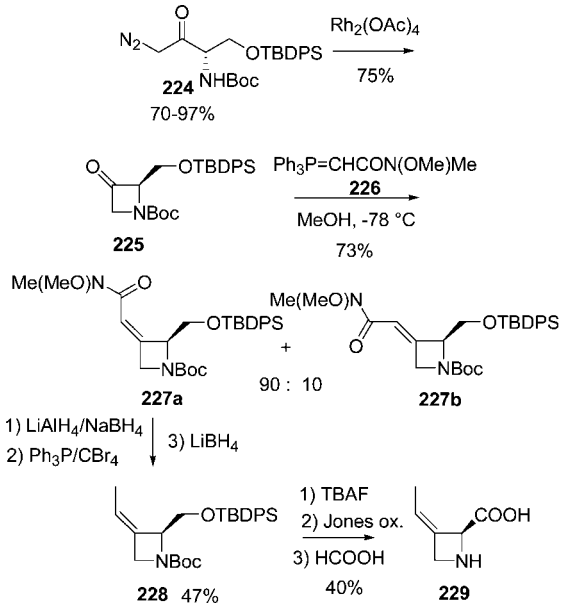
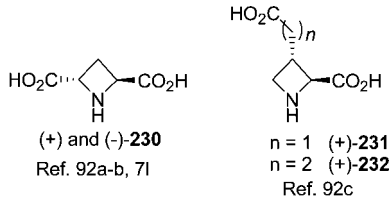
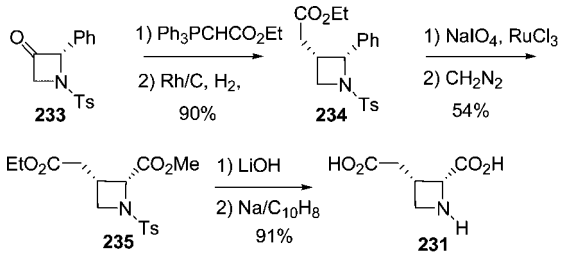


Chart 2



Scheme 68

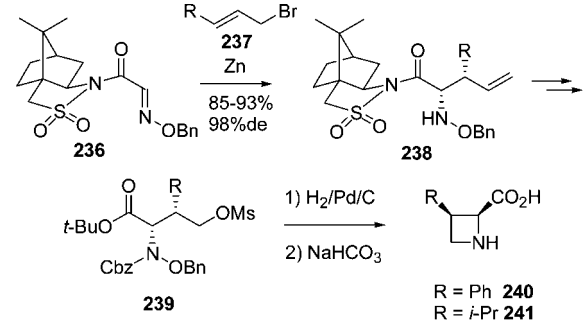


starting from optically pure 2-phenylazetidin-3-one **233** (Scheme 68).

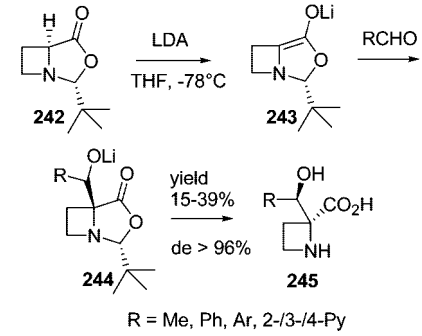
Hanessian and co-workers[92e] have synthesized conformationally constrained analogues of phenylalanine **240** and leucine **241** by a zinc-mediated asymmetric addition of allylic bromides **237** to camphor sultam derivative of glyoxylic acid *O*-benzyl oxime **236** (Scheme 69).

Seebach and co-workers[93] have stereoselectively alkylated the carbanion **243** of oxazolidinone **242**, derived from (*S*)-2-azetidine carboxylic acid, with aldehydes (Scheme 70). The reaction, resembling that of the homologous proline, provides 2-hydroxyalkylated azetidine-2-carboxylic acids **245** (formally D-*allo*-threonines) with *R*,*R*-configuration. An efficient enzymatic resolution of methyl *N*-alkylazetidine-2-carboxylates by *Candida antartica* lipase-mediated ammoniolysis has been reported.[94]

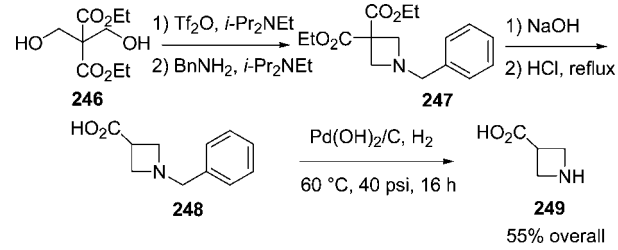
Scheme 69



Scheme 70



Scheme 71

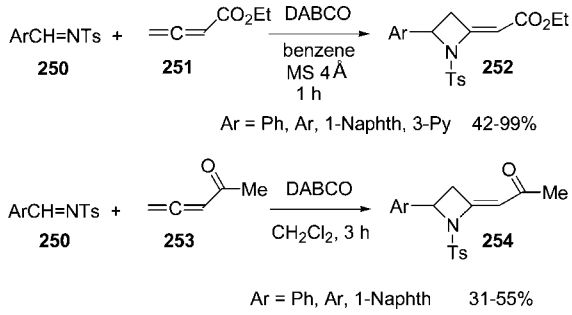


Azetidine-3-carboxylic acid (**249**) is an important β-amino acid used for the preparation of a variety of pharmaceutically active compounds, including CCR5 receptor modulators, procollagen C-proteinase inhibitors, tryptase inhibitors, IL-5 inhibitors, and others.[12a] However, only one literature report has appeared on the preparation of this compound based on a condensation of epichlorhydrin and benzhydrylamine followed by a cyanide displacement.[95] A more efficient recent synthesis[12a] utilizes the cyclization of benzylamine on an activated diethylbis(hydroxymethyl)malonate **246**. Simple hydrolysis and decarboxylation provide the azetidine-3-carboxylic acid **249** in 55% overall yield (Scheme 71).

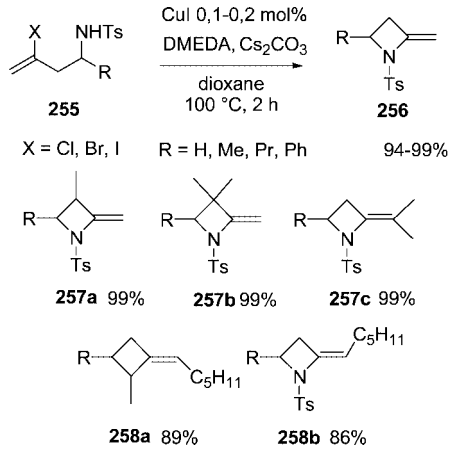
2.7.3. Exomethylene Azetidines

2-*Exo*-methylene azetidines have been the object of interest as entries to β-lactams through ozonolysis. An aza-Baylis−Hillman reaction of *N*-tosylated aryl aldimines **250** with ethyl 2,3-butadienoate **251** or penta-3,4-dien-2-one **253** under catalysis of DABCO undergoes an efficient synthesis of azetinylidene ethyl carboxylates **252** or ketones **254** (Scheme 72). The yields with ketone are sensibly lower because of the formation of unidentified side products.[96]

Scheme 72



Scheme 73



The behavior of DABCO as the Lewis base promoter is to be considered abnormal, because other bases show no catalytic activity for this reaction. DMAP furnishes dihydropyridines with the intervention of 2 equiv of aldimines in slightly different conditions, and phosphines give pyrrolines.[96] Similar 4-trifluoromethylazetinylidene carboxylates were obtained by Wittig reaction of corresponding β-lactams.[97]

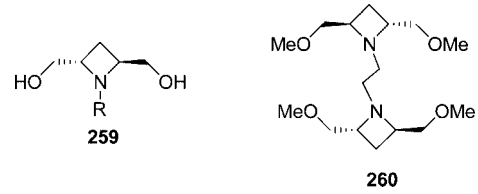
The cyclization of enamines by nucleophilic displacement of chloride, previously reported by De Kimpe's group,[98] has been recently complemented by the CuI catalyzed cyclization of *N*-tosyl-3-halobutenylamines **251** (Scheme 73).[99] Excellent yields of *exo*-methylene azetidines **256**−**258** were obtained, also with a complete control of the stereoselectivity in the case of alkene substituted starting materials.

2.7.4. Ligands for Metal-Catalyzed Reactions and Chiral Auxiliaries

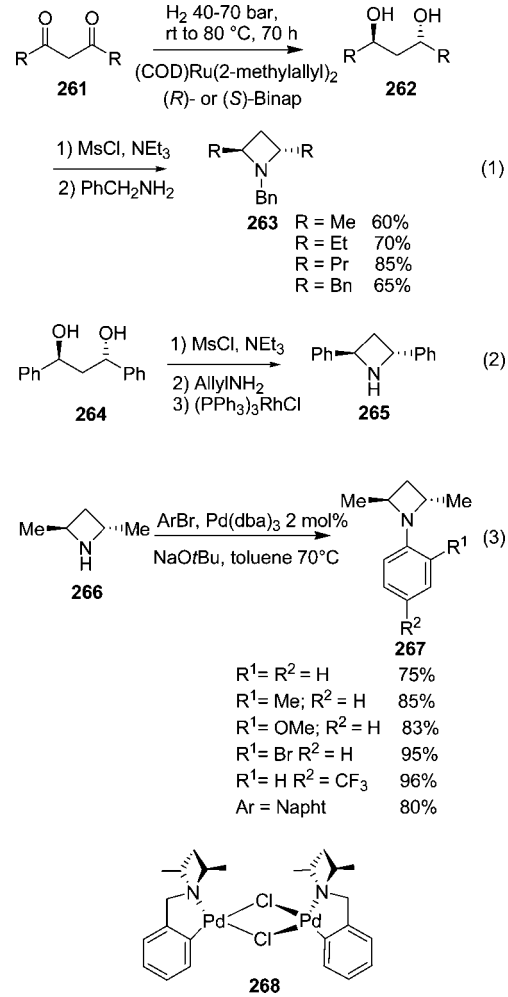
A great deal of effort has been devoted to the synthesis of optically pure azetidines as ligands for metal-catalyzed reactions or chiral auxiliaries.[6j,7n,10c,d,g,14,94,100] One principal target of several groups is the synthesis of C_2-symmetric azetidines.[7m,n,10c,d,g,14,100c,d] Among these, azetidine diols **259** were the main goal of Yamamoto's[7m] and Guanti's[100c] groups, who engaged themselves in their enantioselective synthesis (see Chart 3).

Yamamoto and co-workers[7m] obtained optically pure diols **259** by reduction of optically pure diesters and used the methyl and benzyl ethers of the diol as chiral auxiliaries in the asymmetric alkylation of the derived propionamides with good diastereoselectivity (79 and 81% de, respectively). Guanti and co-workers[100c] proposed an elegant enzymatic resolution of racemic diol **259** using S-PPL (porcine pancreatic lipase) immobilized on celite.

Chart 3



Scheme 74



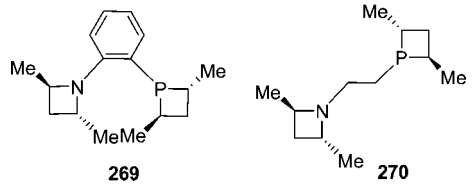
The bidentate ligand **260**, containing the same azetidine diol moiety, was synthesized by Shi and co-workers.[100d] Its catalytic ability on asymmetric induction has been examined in the cyclopropanation of styrene by diazoacetate catalyzed by copper(I), but stereoselectivity and enantioselectivity was only poor (20−34% ee).

Genet and co-workers[10d] have synthesized several C_2-symmetric azetidines **263**, by displacement of optically pure dimesylates of *anti*-1,3-diol **262,** as new ligands for Pd catalyzed organic reactions (Scheme 74, eq 1).

Yamada and co-workers,[10c] by a similar procedure, synthesized the C_2-symmetric 2,4-diphenyl azetidine **265** (Scheme 74, eq 2). This process is much less efficient for the production of *N*-arylated azetidines **267**. These can be efficiently produced by palladium-catalyzed coupling of preformed azetidines with aryl bromides (Scheme 74, eq 3).[10d]

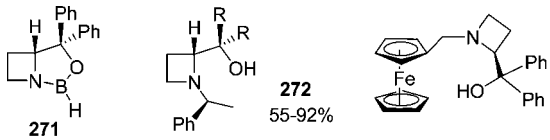
A Pd complex **268**, an intermediate of the synthesis, was isolated and characterized. The same authors synthesized the

Chart 4



269 **270**

Chart 5

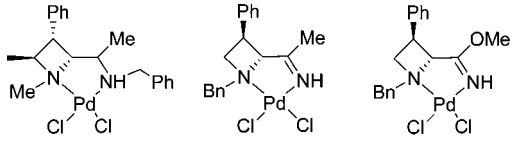


271 **272** 55-92%

R = Me, 1-Hept, c-Hex, Ph, 4-Tol, 2-Naphth

273

Chart 6



274 **275** **276**

P−N heterobidentate ligands **269** and **270** bearing phosphetane and azetidine rings (see Chart 4).[14]

Four-membered fused oxazaborolidine **271**, azetidine analogues of Corey reduction catalyst,[101] were synthesized in both enantiomeric forms from azetidine-2-carboxylates.[100e] The oxazaborolidine showed an excellent reactivity and enantioselectivity in the reduction of prochiral ketones with borane (0.1 equiv of catalyst, yield > 90%, 95−97% ee) (see Chart 5).

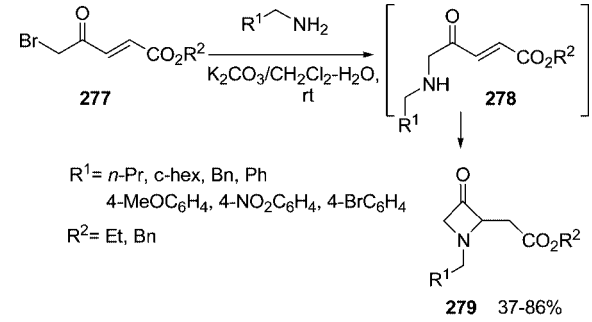
Similar ligands **272**, with various R groups, were synthesized in good yields (55−92%) as chiral ligand for BBr_3 catalyzed Diels−Alder reaction.[94] *N*-ferrocenylmethyl azetidin-2-yl(diphenyl)methanol **273** catalyzed the enantioselective ethylation and arylation of arylaldehydes with enantioselectivities up to 98.4% ee and 95.7% ee, respectively.[102] Similar excellent catalytic activities have a new series of enantiopure *cis*-3-hydroxyazetidines prepared from (*R*)-1-phenylethylamine.[103]

Finally, the synthesis of new palladium(II) complexes bearing sterically congested azetidine ligands was developed by Couty and co-workers.[100a] Diamine, aminoimine, and aminoimidate ligands provided bidentate palladium(II) complexes **274**, **275**, and **276**, respectively, whose structures were confirmed by X-ray analyses. The complexes revealed very efficient catalyst for Suzuki cross-coupling of aromatic halides (yields 77−87%, 0.1% catalyst) (see Chart 6).

3. Azetidin-3-ones

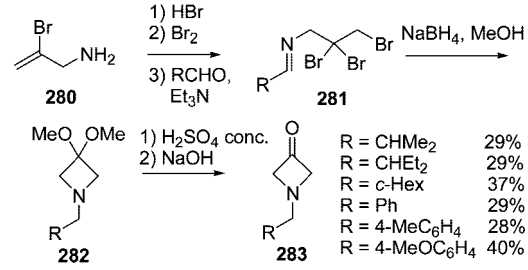
Azetidin-3-ones have been the object of wide interest since they are important intermediates for the synthesis of numerous azetidine derivatives.[104] A collection of the most common methods for their synthesis is nicely reported in refs 43d, 91b, and 104, mainly including cyclizations of aminohalogenoketones, oxidations of azetidinols, or, more efficiently, α-diazo ketones, and several examples of their syntheses have been reported in section 2.1.6 of this review. More recent examples provide novel straightforward syntheses of azetidine-3-ones by intramolecular bromide displacements.

Scheme 75



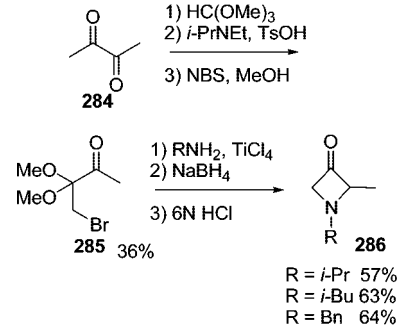
277 **278** **279** 37-86%

Scheme 76



280 **281** **282** **283**

Scheme 77



284 **285** 36% **286**

N-Substituted azetidin-3-ones **279** are obtained in a one-pot methodology by treatment of primary amines with alkyl 5-bromo-4-oxopent-2-enoates **277** (Scheme 75).[105]

The mechanism of the reaction probably involves the tandem displacement of bromine followed by 4-*exo*-*trig* ring closure of **278**. Chiral phenylethylamine provides only poor diastereoselectivity in the process.

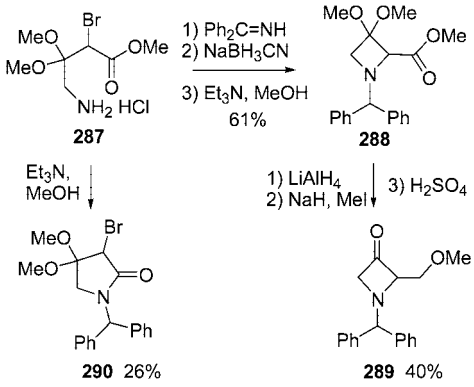
De Kimpe's group[106] has developed new syntheses of *N*-substituted azetidine-3-ones. Compounds **283** are obtained in six simple steps and 30−40% overall yield from 2-bromoallylamine **280** (Scheme 76).[106a]

2-Methyl-*N*-alkyl azetidine-3-ones **285** were synthesized from butane-2,3-dione **283** in six simple steps and similar overall yield (Scheme 77).[106b]

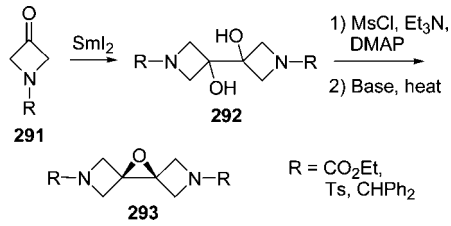
The characteristic feature of these syntheses, and of the following regarding 2-methoxymethyl azetidine-3-one **289** (Scheme 78),[106c] is the introduction of the nitrogen as an imine that undergoes reduction and cyclization. The further reduction of the ester function in **288** provides the methylenoxy side chain of azetidine-3-one **289**.

Interestingly, in the cyclization step, a competition between bromide displacement and nucleophilic attack on the methoxycarbonyl function occurs, leading to a 26% yield of lactam **290**. Changing the conditions for cyclization from Et_3N in MeOH to a saturated aqueous solution of $NaHCO_3$ leads to exclusive formation of the lactam **290**.

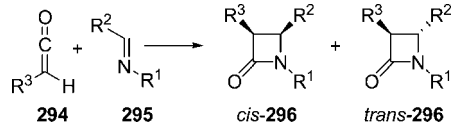
Scheme 78



Scheme 79



Scheme 80



An interesting samarium iodide promoted coupling of *N*-substituted azetidine-3-ones **291** produced the corresponding pinacols **292** that, through their mesylates, were transformed in the corresponding spirocyclic oxiranes **293** (Scheme 79).[107] A computational study of puckering potential and thermodynamic properties of 3-azetidinone has been carried out.[108]

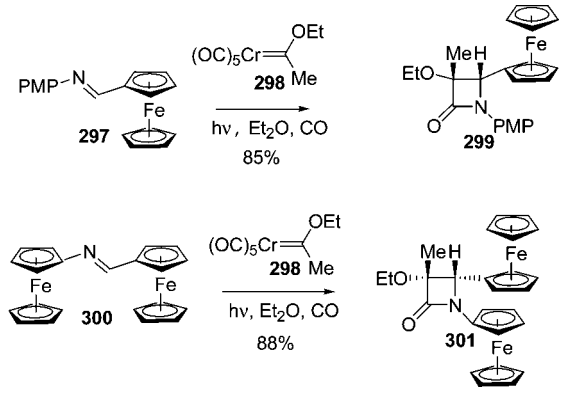
4. Azetidin-2-ones

Azetidin-2-ones (β-lactams) represent a very important class of compounds because of their well-known biological activity[109] and their usefulness as intermediates in organic synthesis.[110] Many synthetic methods were developed for the formation of the β-lactam ring including [2 + 2]-cycloadditions, cyclization reaction, carbene insertion reactions, and rearrangement of heterocyclic compounds.[111,1,109f] In this review, the recent methods of synthesis of the azetidin-2-one ring, besides some of the most remarkable advances in the more classical approaches, are reported.

4.1. Imines Plus Ketenes: The Staudinger Reaction

The Staudinger reaction, reactions of ketenes with imines, is probably the most important synthetic tool to access β-lactams. Since its discovery by Staudinger,[112] this reaction has long been studied experimentally and theoretically to understand its mechanism(s) and the rationale for the stereoselectivity, and it has been applied to the synthesis of a wide variety of β-lactam structures (Scheme 80). This reaction is still nowadays one of the best means for the synthesis of β-lactams.[111c]

Scheme 81



4.1.1. Methods for the in situ Preparation of the Ketene Reagent

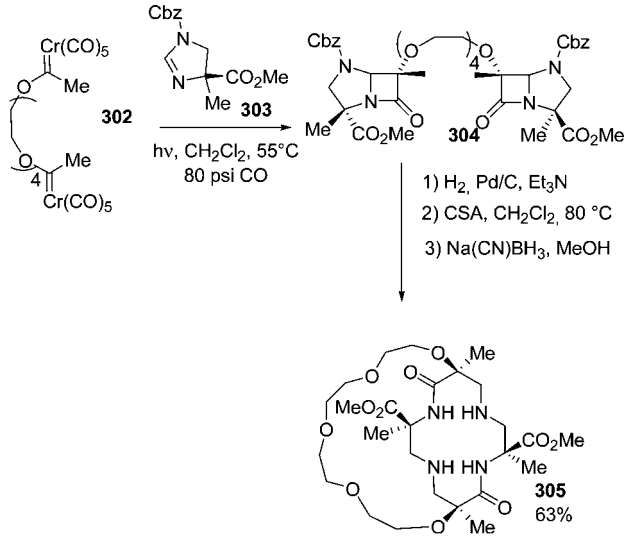
The crucial point of the reaction is the use of highly reactive ketenes, which have to be often produced in situ,[113] with some remarkable exceptions of stable ketenes as diphenyl ketene[114] and (trimethylsilyl)ketene.[115] The most common method for the in situ production of the ketene derivatives is the simple reaction of an acyl chloride with a base, generally a tertiary amine. The reaction conditions are generally mild (−10 °C to room temperature).[116] Very recently, the use of the Vilsmeier reagent was reported as an efficient activator of carboxylic acids,[117] as well as *N*,*N*′-carbonyl diimidazole[118] and triphosgene.[119] If the reaction between an acyl chloride and an aromatic imine is performed in ionic liquids, and in the presence of $Yb(OTf)_2$, the addition of a base is not necessary for the reaction to occur, with remarkable selectivity toward the *trans* adduct.[120] Also, a solvent-free procedure, under microwave irradiation, was described.[121]

Since the first observations by Hegedus[122] that Cr and Mo Fischer carbene complexes, when exposed to sunlight in the presence of an imine, formed a β-lactam in almost quantitative yield, this method has found application as a general synthesis of β-lactams. The intermediacy of ketene-like species formed by the reversible insertion of a *cis*-CO ligand into the M=C bond was postulated on the basis of indirect evidence.[123] More recently computational and experimental studies by Cossìo and Sierra suggested that the irradiation gives place to an equilibrium with a metallacyclopropanone structure that, in the presence of a ketenophile, forms the β-lactam.[124] Ferrocene substituted 2-azetidinones were obtained by reacting ethoxychromium(0)carbene complex **298** with imine **297** and **300** under irradiation. In this case, the reaction afforded selectively azetidinones **299** and **301** in good yields (Schemes 81 and 82).[125]

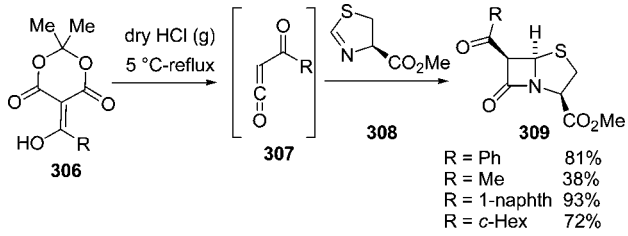
This approach was also extended to polycyclic aromatic substituents on the carbene reagent, and the presence of a coordinating group was revealed to be deleterious for the cycloaddition.[126] Toward the synthesis of cyclam derivatives, a useful intermediate was obtained using the reaction of the bis-carbene complex **302** with protected imidazoline **303**. The bis-azapenam **304**, upon deprotection and acid treatment, afforded the basket dioxocyclam **305**.[127]

Meldrum's acid derivatives, like **306**, are precursors of an acylketene **307** that can be used in Staudinger reactions.[128] Recent examples are offered by the synthesis of penam derivatives by the reaction of derivatives **306** with Δ^2-thiazoline **308** obtained from L-cysteine methyl ester hydro-

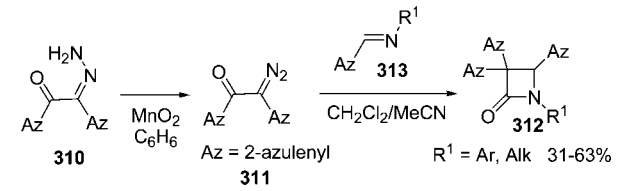
Scheme 82



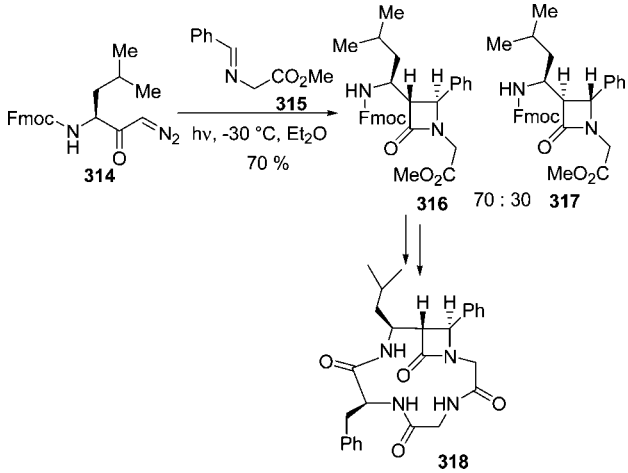
Scheme 83



Scheme 84



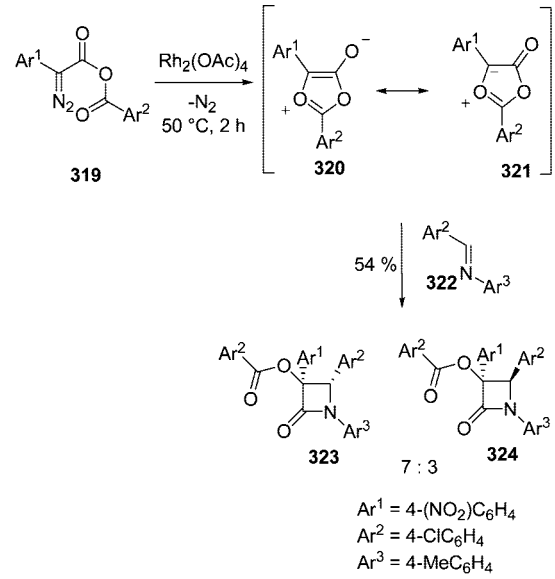
Scheme 85



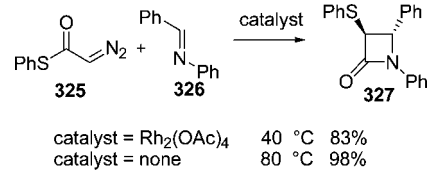
chloride. The reaction occurs in dry benzene with gaseous HCl affording the corresponding penams **309** in good yields (Scheme 83).[129] More recently, some mechanistic evidence was disclosed to confirm the α-oxoketene pathway through kinetic studies.[130]

Diazoketones can decompose under thermal condition, irradiation, or Rh catalysis to afford the corresponding ketene through a Wolff rearrangement.[131] Some recent examples

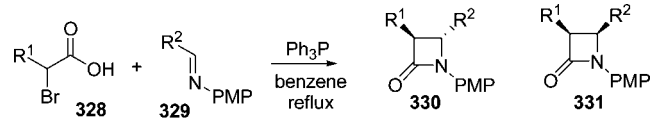
Scheme 86



Scheme 87



Scheme 88



		yield	*trans/cis*
R^1 = Ph	R^2 = 4-(MeO)C_6H_4	82%	>95:5
R^1 = Ph	R^2 = Ph	98%	95:5
R^1 = Ph	R^2 = 4-ClC_6H_4	100%	91:9
R^1 = Ph	R^2 = 4-(NO$_2$)C_6H_4	100%	88:12
R^1 = Me	R^2 = 4-ClC_6H_4	26%	79:21

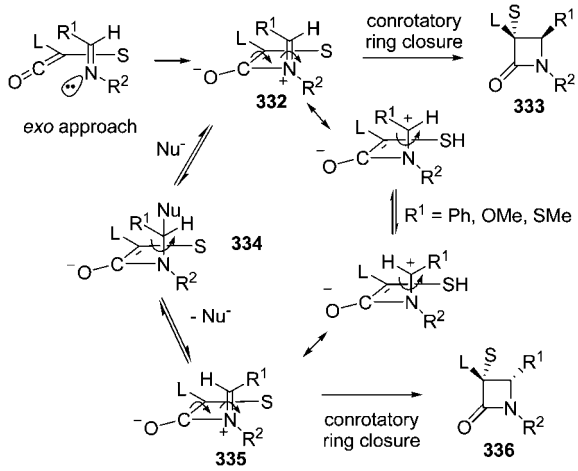
can illustrate this reactivity. Di(2-azulenyl)ethanedione monohydrazone (**310**) was oxidized with MnO_2 to the α-diazoketone **311** that, upon heating in the presence of imines, afforded the corresponding β-lactams **312** (Scheme 84).[132]

Analogously, the same reaction can be performed by microwave irradiation[133] or by vapor-phase pyrolysis.[134] The decomposition of the diazoketone can be also accomplished by irradiation at low temperature. This last approach was used for the synthesis of the β-lactam cyclopeptide analogue **318** (Scheme 85).[135]

A recent example of the use of $Rh_2(OAc)_4$ for the degradation of a α-diazocarbonyl derivative is offered by the reaction of phenyldiazoacetic anhydride **319**. The decomposition of compound **319** gave origin to the mesoionic derivative **320**, which reacted with amine **322** to afford β-lactams **323** and **324** in moderate yield (Scheme 86).[136]

Another mesoionic compound, although obtained with a different approach, found application in the synthesis of C-3 spirofused β-lactams.[137] The catalysis of Rh complex is also effective in promoting a thia-Wolff rearrangement, trans-

Scheme 89



forming α-diazo thiol esters, such as **325**, into thiosubstituted ketenes.[138] However, the same reaction can be performed without the use of the catalyst, increasing the temperature as shown in the next example for the diastereoselective preparation of **327** (Scheme 87).[139]

The reaction between α-bromocarboxylic acids and imine can be mediated by triphenylphosphine. The reaction occurs in refluxing benzene with a moderate-to-quantitative yield and a remarkable selectivity toward the *trans* stereoisomer. This selectivity and the mechanism proposed by the authors suggest that this might not be a real Staudinger reaction (Scheme 88).[140]

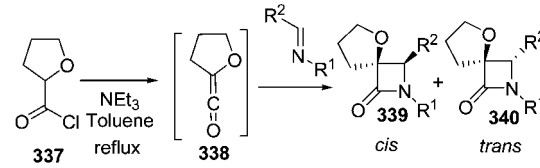
4.1.2. Reaction Mechanism and Control of the Stereoselectivity

Concerning the comprehension of the mechanism of the Staudinger reaction, probably the best qualitative description of one possible mechanism was offered by Hegedus.[141] It is suggested that the imine, the nucleophile, attacks the lowest unoccupied molecular orbital (LUMO) of the ketene carbonyl group coplanar to the ketene substituents. The attack occurs on the less hindered side (*exo* approach), with the plane of the imine perpendicular to that of ketene, generating the zwitterionic intermediate **332** (Scheme 89).

This intermediate was detected and characterized by IR spectroscopy.[142] Rotation of the imine into the plane of the ketene in concurrence with a conrotatory ring closure produces the β-lactam **333** in which the imine R^1 group and the L group of the ketene are *cis*. When the substituents on the sp^2 carbon of the imine (R^1 in the scheme) can stabilize positive charge, the zwitterionic intermediate may undergo isomerization to the *cis* form of the iminium bond, producing the more stable *trans*-β-lactam **336**. Isomerization of the zwitterionic intermediate can also occur by addition of nucleophiles to the zwitterions followed by rotation and elimination. The relative rates of each of these processes determine the stereochemical outcome of any particular ketene/imine reaction. Using a cyclic imine, the *cis* geometry is forced by the ring; thus, cyclic imines generally give β-lactams possessing a *trans* geometry.

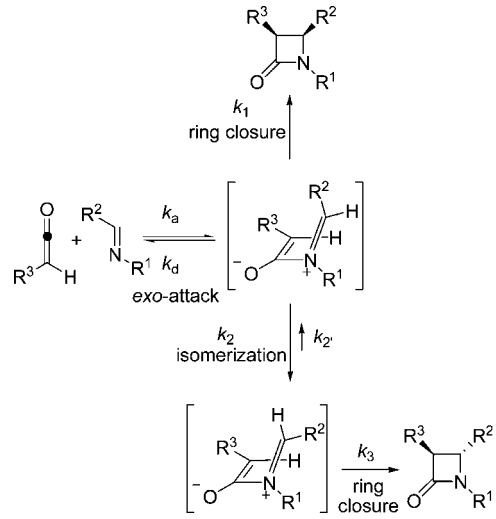
In the following years, an effort was made to give a more detailed theoretical framework to this reaction. Ab initio calculations verified the presence of the zwitterionic intermediate and an electrocyclic conrotatory ring closure which appeared to be the rate-determining step.[143] Subsequent studies[144] confirmed the two-step nature of the process and evidenced some similarities with the model proposed by Houk for the conrotatory electrocyclic reaction of cyclobutenes.[145] The authors rationalized the stereochemical result on the basis of the configuration (*Z* or *E*) of the starting imine and upon the *exo* or *endo* approach between the two reagents.

Scheme 90



R^1 = PMP, R^2 = PMP	15 : 1	76
R^1 = Ph, R^2 = PMP	12 : 1	75
R^1 = 2-furyl, R^2 = PMP	8 : 1	64
R^1 = Ph, R^2 = Me	14 : 1	66
R^1 =4-$(NO_2)C_6H_4$, R^2 = Ph	1 : 4	58

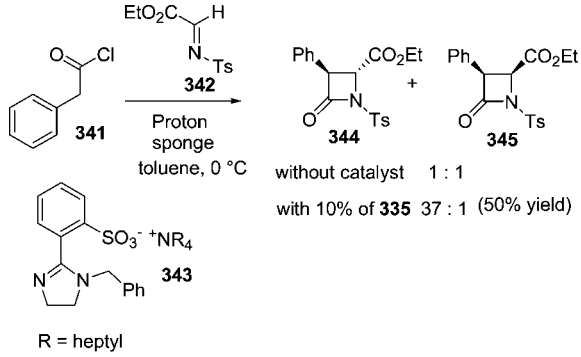
Scheme 91



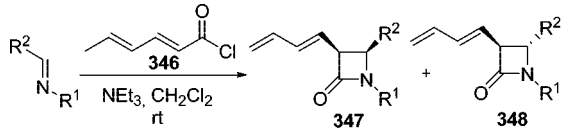
Recently, a new study by Xu's group[148] proposed a new rationale to justify the stereochemical outcome of the reaction, revisiting the model described by Hegedus and pointing out the kinetic origin of the *cis*/*trans* ratio of β-lactam products. The proposed pathway for the formation of the final β-lactam is described below (Scheme 91).

This model is based on the consideration that the *exo*-attack is generally favored. Indeed,for the most frequently used monosubstituted ketenes, the *exo*-attack is exclusive. The final stereochemical outcome is influenced by the nature of the ketenes and the imines, since it is the result of the competition of the direct ring closure (k_1) and the isomerization of the imine moiety (k_2). The k_1/k_2 ratio determines the *cis*/*trans* ratio of the β-lactam products. The authors propose, according also to observations present in precedent works,[149,144a] that the ring-closure step could be more conveniently viewed as an intramolecular nucleophilic addition of an enolate to the imine moiety rather than an electrocyclic process. Electron-donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ring closure (increasing k_1), leading to a preference

Scheme 92



Scheme 93



R^1 = Ph	R^2 = Ph	> 5 : 95
R^1 = Ph	R^2 = 4-MeC_6H_4	> 5 : 95
R^1 = 4-MeC_6H_4	R^2 = Ph	> 5 : 95
R^1 = 4-MeC_6H_4	R^2 = 4-MeC_6H_4	> 5 : 95
R^1 = *c*-Hex	R^2 = Ph	> 95 : 5
R^1 = *c*-Hex	R^2 = 4-MeC_6H_4	> 95 : 5

for *cis*-β-lactam formation. On the other hand, electron-withdrawing ketene substituents and electron-donating imine substituents decrease the k_1 value and favor the isomerization process, leading to a preference for the *trans*-β-lactam formation. The electronic effect of the substituents on the isomerization is a minor factor in stereoselectivity. Finally, after a comparison of the same reactions performed under different conditions, the same authors suggested that there is no influence of microwaves[150] or photoirradiation in the stereoselectivity of the Staudinger reactions.[151]

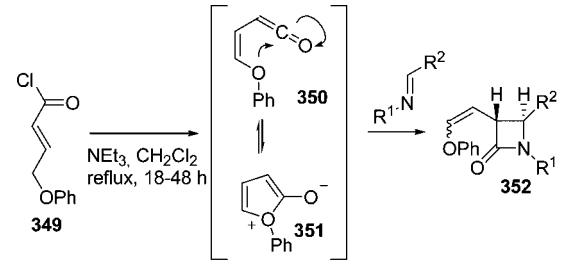
The stereoselectivity is influenced also by the nature of the solvent since nonpolar solvents favor the formation of *cis*-β-lactams, while polar solvents favor the formation of the *trans* ones. Also, the way the ketene is formed, and the order of addition of the reagents, appears to influence the stereochemical outcome.[152] The presence of orbital interactions (p$-\pi$ or $\pi-\pi$) between the ketene and the imine reagents influences the stereochemical outcome as well as temperature.[153]

A very effective procedure to obtain *trans*-β-lactams was developed by Lectka and co-workers by using the salt **343** as an anionic nucleophilic catalyst. The ionic nature of the catalyst is proposed as the reason for the observed selectivity (Scheme 92). Actually, this procedure does not work efficiently with aliphatic acyl chlorides.[154]

The use of sorbyl chloride **346** as a precursor of butadienylketene afforded some interesting results concerning the diastereoselectivity. When the Staudinger reaction was performed with *N*-aryl imines, it afforded exclusively the *trans* adduct, while the use of *N*-alkyl imines afforded exclusively the *cis* β-lactam (Scheme 93).[155]

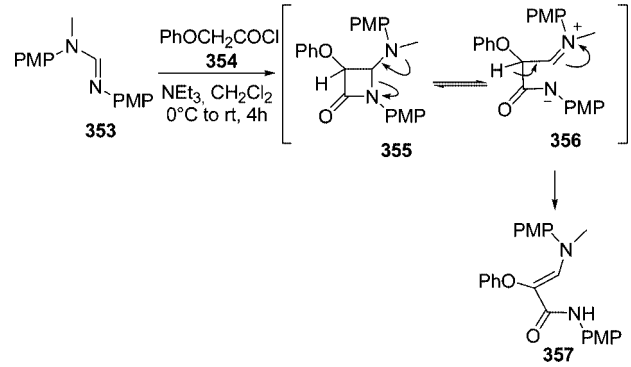
The *trans* selectivity is also obtained in Staudinger reactions between imines and vinylketenes possessing a γ-heteroatom. The vinyl side-chain stereoselectively adopts the *Z*-configuration to stabilize the vinylketene and produces exclusively *trans*-3-vinyl-β-lactams (Scheme 94).[156]

Scheme 94

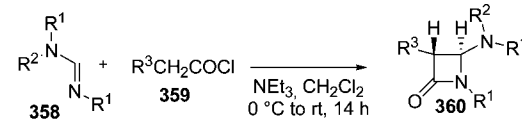


R^1 = R^2 = 4-MeC_6H_4	77%
R^1 = 4-MeC_6H_4 R^2 = Ph	80%
R^1 = R^2 = Ph	75%
R^1 = Ph R^2 = 4-MeC_6H_4	73%
R^1 = 4-MeC_6H_4 R^2 = CO_2Me	70%

Scheme 95



Scheme 96



R^1 = Ph R^2 = PhCO R^3 = PhO	72%
R^1 = Ph R^2 = 4-$NO_2C_6H_4CO$ R^3 = PhO	68%
R^1 = 4-MeC_6H_4 R^2 = Ts R^3 = PhO	80%
R^1 = 4-MeC_6H_4 R^2 = Ts R^3 = PhthN	89%

4.1.3. Special Classes of Azetidin-2-ones

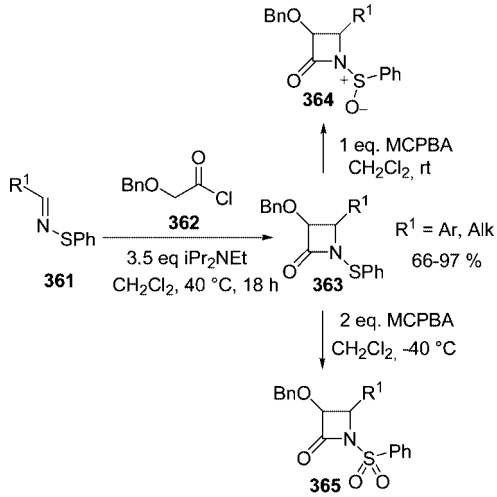
Very few examples of the synthesis of 4-amino-β-lactams are known because of their instability. These compounds undergo ring cleavage mainly by the fission of C3$-$C4 bond. Another possible mechanism of ring cleavage was observed when a hydrogen atom was present on C3 and was ascribed to the mesomeric effect of the *exo*-cyclic nitrogen atom, as shown in Scheme 95.

This difficulty can be compensated for by using, as starting reagents, trisubstituted amidines bearing electron-withdrawing substituents on enamino nitrogen. The reaction afforded in good yield exclusively *trans*-adducts **360** (Scheme 96).[157]

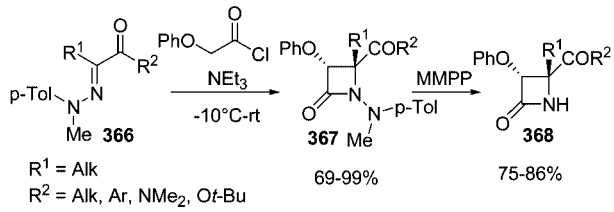
The use of *N*-sulfenylimines afforded the corresponding *N*-sulfenyl-β-lactams as mixtures of *cis*$-$*trans* adducts. The interest in this approach is related to the ability to vary the oxidation state of the sulfur atom, varying, accordingly, the reactivity of the β-lactam ring (Scheme 97).[158]

Also α-oxohydrazones have been used as imine components to obtain 4-functionalized azetidinones. The final lactams were subsequently easily deprotected at the nitrogen

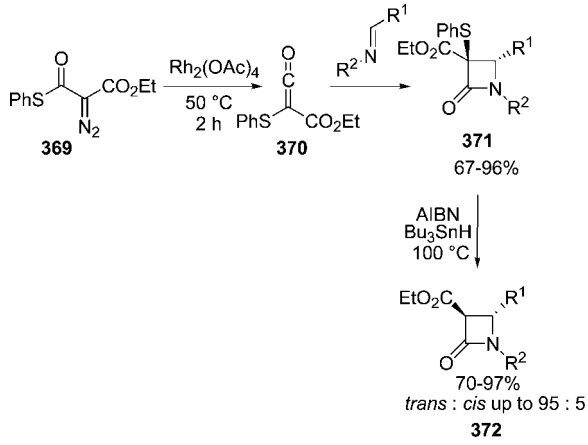
Scheme 97



Scheme 98



Scheme 99



atom by oxidation with magnesium monoperoxyphthalate (MMPP) (Scheme 98).[159]

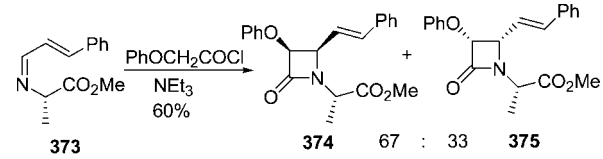
3-Alkoxycarbonyl β-lactams have been obtained using the Staudinger reaction of ethoxycarbonyl(phenylthio)ketene with various imines. The ketene was formed through a thia-Wolff rearrangement of compound **369** under the catalysis of $Rh_2(OAc)_2$. The subsequent desulfurization of **371** afforded the final lactam with good yields and diastereoselectivity. The reaction was performed with a large number of acyclic and cyclic imines (Scheme 99).[160]

4.1.4. Asymmetric Synthesis

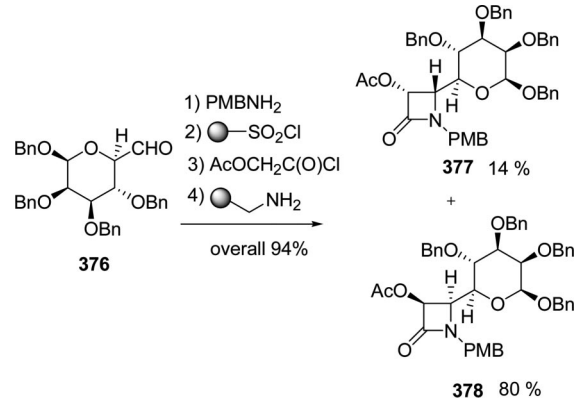
Many examples of the synthesis of optically active β-lactams by the Staudinger reaction are reported in the literature, and the argument has been already reviewed[161] and also tackled on a theoretical basis.[162]

The chiral imine **373** derived from L-alanine methyl ester and cinnamaldehyde was used with phenoxyacetylchloride

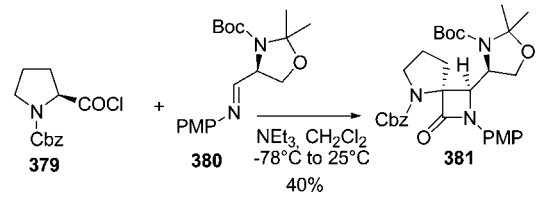
Scheme 100



Scheme 101



Scheme 102



and afforded a mixture of the two diastereoisomers **374** and **375** with a low selectivity (Scheme 100).[163]

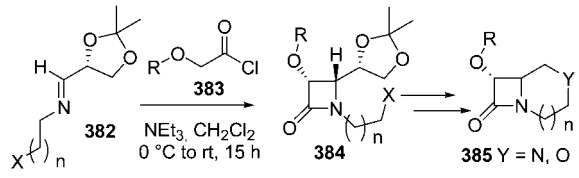
A collection of 4-(*C*-galactosyl)- and 4-(*C*-ribosyl)-β-lactams was prepared by the Staudinger reaction in a one-pot procedure starting from a formyl *C*-glycoside, a primary amine, and a substituted acetylchloride in the presence of triethylamine. The reactions were performed using resin-supported scavengers for the removal of the excess reagents (Scheme 101).[164] A similar approach was also exploited by other authors.[165]

Chiral imine **380** found applications in reactions with cyclic ketenes derived from proline. The reaction is extremely selective, and the authors rationalized this result through density-functional calculations (Scheme 102).[166]

N-alkylimines **374** derived from (*R*)-glyceraldehyde acetonide were employed in cycloadditions with alkoxyketenes to afford the corresponding 2-azetidinones. These compounds were subsequently elaborated to afford new bicyclic β-lactams **377** (Scheme 103).[167]

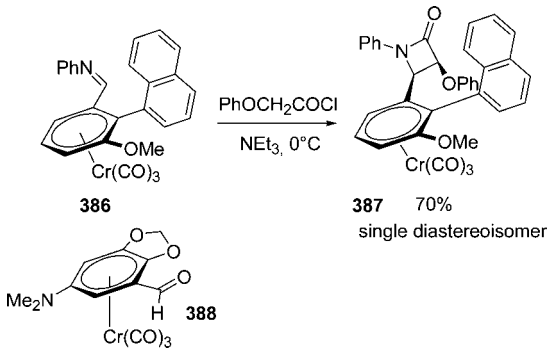
An enantiopure 2,3-dihydrobenzoxazepine was used in the formal cycloaddition with phthalimido ketene, affording, with high selectivity, the corresponding tricyclic 2-azetidinone.[168] Similarly chiral 5,6-dihydropyrazin-2-(1*H*)-ones were used for the synthesis of fused oxopiperazino-β-lactams.[169] Some examples of the use of tricarbonylchromium complexes for the asymmetric synthesis of 2-azetidinones are present in the literature.[170] The group of Uemura reported the use of the axially chiral biaryl derivative **386** for the synthesis of the enantiopure 2-azetidinones **387** through a very selective and efficient reaction (Scheme 104).[171] Analogously, aldehyde **388** was a precursor for imines used in Staudinger reactions with acetoxyketene to afford new enantiopure azetidinones.[172]

Scheme 103

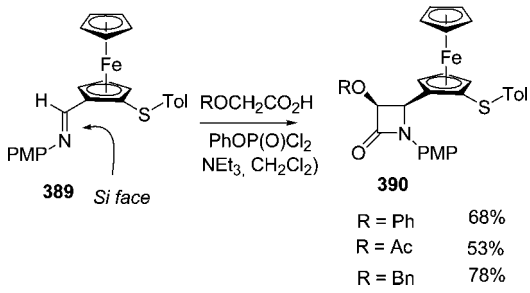


			yield	de
R = Bn	n = 1	X = Cl	86	87
R = Ph	n = 1	X = Cl	87	88
R = Me	n = 1	X = Cl	81	83
R = Bn	n = 2	X = Br	77	88
R = Me	n = 2	X = Br	75	91

Scheme 104



Scheme 105

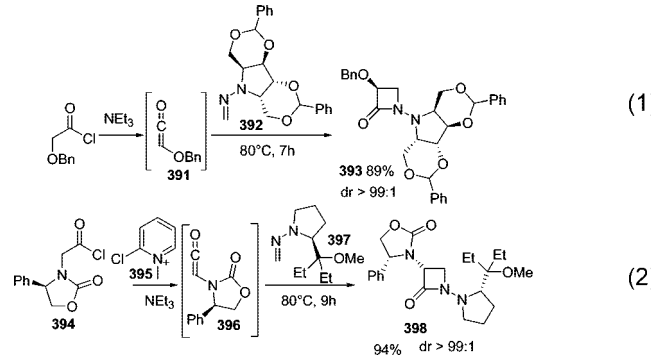


The planar-chiral ferrocenylimine **389** was used in the stereoselective synthesis of the 2-azetidinones **390**, affording exclusively the *cis* adduct derived from the approach to the less-hindered diastereotopic face of the imine double bond (Scheme 105).[173]

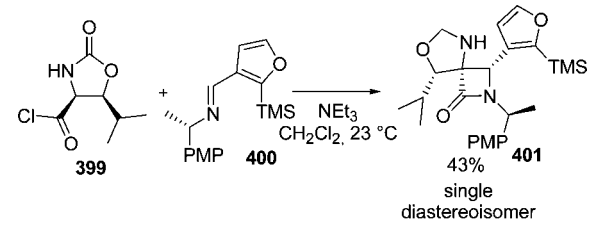
The use of the Staudinger reaction for the synthesis of 4-unsubstituted 2-azetidinones is not viable, since it would require the use of formaldehyde-derived imines that are prone to oligomerize under the reaction conditions. An efficient alternative is offered by the use of formaldehyde *N*,*N*-dialkylhydrazones.[174] These reagents are more stable and also offer the possibility to use the extra nitrogen atom as a tool for inserting a chiral auxiliary to be used in diastereoselective reactions. The high efficiency of this approach is demonstrated by the synthesis of 2-azetidinones **393** and **398** (Scheme 106).

The second reaction is an example of a double asymmetric induction between the two chiral reagents. The same procedure was subsequently applied also to the synthesis of 4-substituted 2-azetidinones starting from higher aldehydes.[175] A double asymmetric induction was also used by Corey in the synthesis of β-lactam **401**, an intermediate toward a β-lactam related to salinosporamide A and omuralide (Scheme 107).[176]

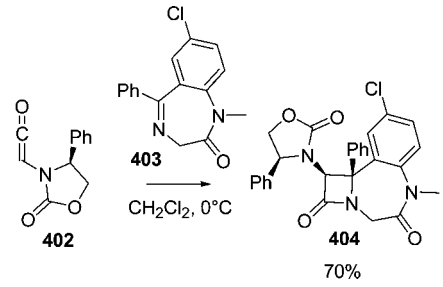
Scheme 106



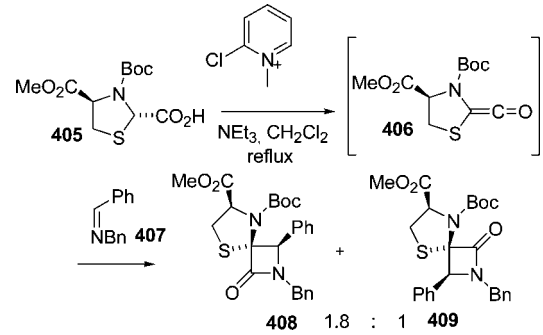
Scheme 107



Scheme 108



Scheme 109



Optically active ketene **402** was used in Staudinger reactions with cyclic imines to afford polycyclic 2-azetidinones incorporating 1,4-benzodiazepines **404** (Scheme 108).[177]

The enantiopure cyclic ketene **406**, obtained from 1,3-thiazolidine derivatives,[178,137] underwent the formal cycloaddition with *C*-phenyl-*N*-phenyl imine, affording two diastereoisomers derived from the different approach of the imine to the two diastereotopic faces of the ketene (Scheme 109).[179]

In a similar approach, the residual stereogenic center present in the ketene derived from 4-hydroxyproline was revealed to be efficient in determining the stereoselectivity of the formal cycloaddition with achiral imines.[180] The ephedrine derived acid **410** was used as a precursor of a chiral ketene (see Figure 1). Although the diastereoselectivity

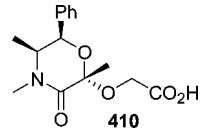
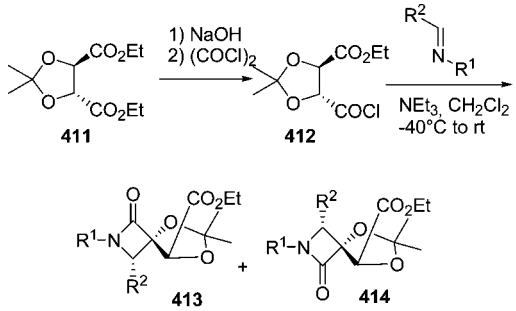
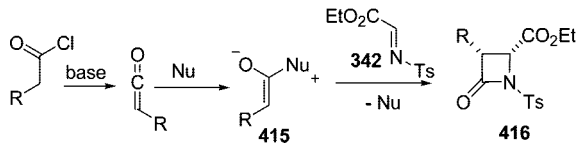


Figure 1. Ephedrine-derived acid **410**.

Scheme 110



Scheme 111



obtained is poor, the ketal moiety allowed the easy removal, after separation of the diastereomeric mixture, and recycle of the chiral auxiliary for the synthesis of enantiopure 3-hydroxy-4-aryl-2-azetidinones.[181]

Also very recently, tartaric acid was used as a precursor of a chiral ketene. The C_2 symmetric nature of the acetonide **411** allowed the partial saponification and transformation into the monoacylchloride **412**. The Staudinger reaction afforded the spiro-β-lactams **413** and **414** in a 60:40 ratio (Scheme 110). Both diastereoisomers derived from the exclusive approach of the imine to the side opposite to the oxygen atom. The authors justify this result on the basis of the torquoelectronic effect of the oxygen substituent.[182]

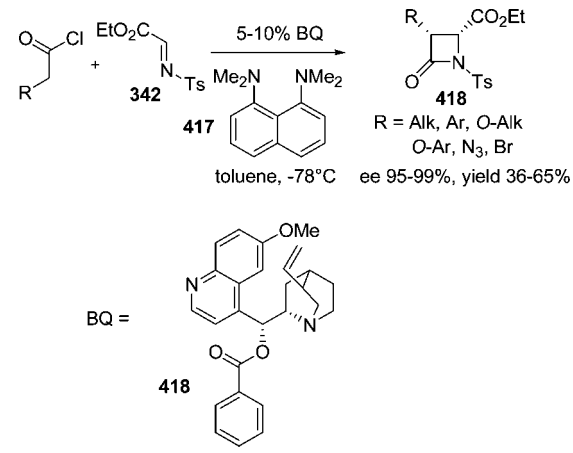
Tosylimine **342** was the substrate of choice for an enantioselective approach to β-lactams through a modified Staudinger reaction, still developed by the group of Lectka.[183] Tosylimine **342** reacts sluggishly with ketenes, but the reaction can be catalyzed by tertiary amines.[184] The amine undergoes nucleophilic addition to the ketene to form the zwitterionic enolate **415** that finally reacts with the imine **342** to afford the desired β-lactam **416** (Scheme 111).

The use of benzoyl quinine (BQ, **418**), a chiral alkaloid, allowed the obtainment of the final lactam in excellent enantioselectivity and good yields (Scheme 112).

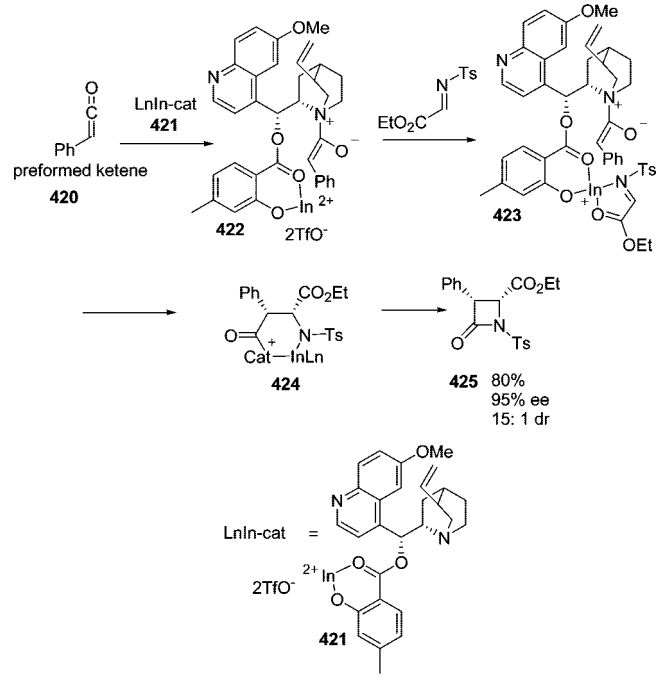
The proton sponge **417** was used as a stoichiometric base since it did not interfere with the ketene because of its low nucleophilicity. Other stoichiometric bases have been used, such as bicarbonate[185] or sodium hydride.[186] The addition of a chiral Lewis acid increased the yield and the enantioselectivity of the process.[187]

Finally, the overall process was optimized, increasing the yield of the β-lactam by varying the structure of the chiral base and introducing a catalytic amount of $In(OTf)_3$, which enhanced the reactivity of the imine counterpart. In this way,

Scheme 112



Scheme 113



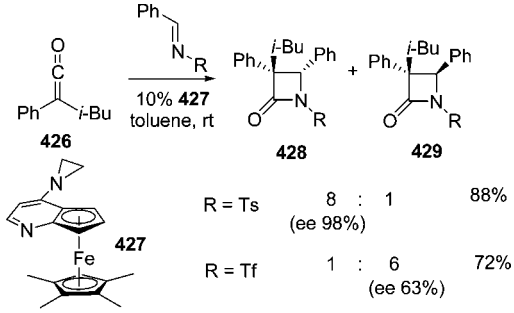
a bifunctional asymmetric catalysis process was obtained as described in scheme 113.[188]

This approach has been recently extended to the use of arylimine.[189] In this case, the catalyst was a silylated derivative of quinine and required a hindered lanthanide complex to afford high ee.

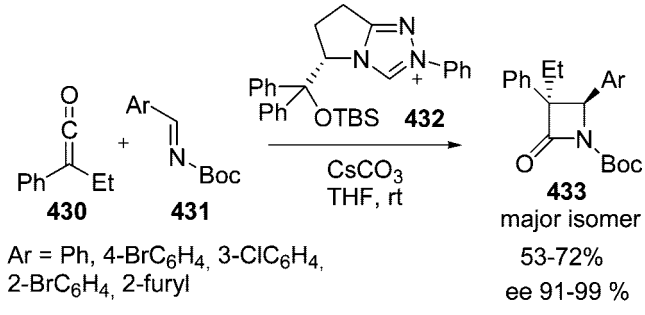
A similar approach was followed by Fu and co-workers using a planar-chiral nucleophile obtained from ferrocene derivative **427**.[190] This catalyst was revealed to be particularly useful with cyclic and disubstituted ketenes, both symmetrical and unsymmetrical, and the imine counterpart is again represented by the tosylimine derivative (Scheme 114).

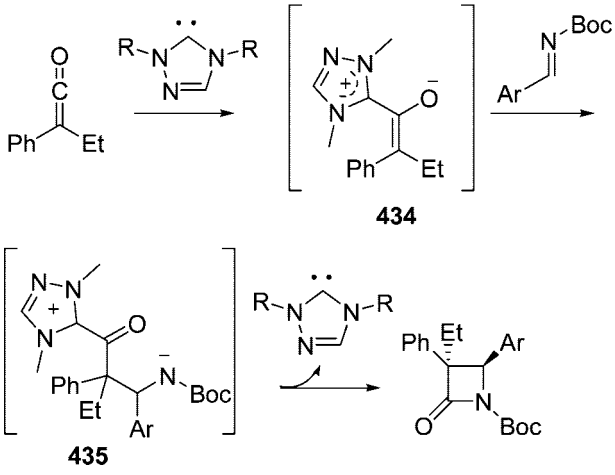
The stereoselectivity is influenced by the nature of the substituent on the nitrogen atom of the imine. A tosyl group gives the *cis* diastereoisomer as the major one, whereas the triflic imine derivative affords the *trans* adduct as the major one.[191] Finally, very recently, a carbene catalyzed enantioselective version of the Staudinger reaction has been described. Again, the action of the catalyst is supposed to be related to the formation of an intermediate derived from the nucleophilic attack of the catalyst on the ketene as

Scheme 114

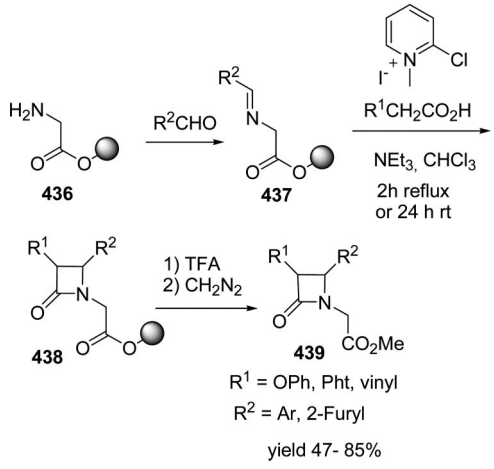


Scheme 115



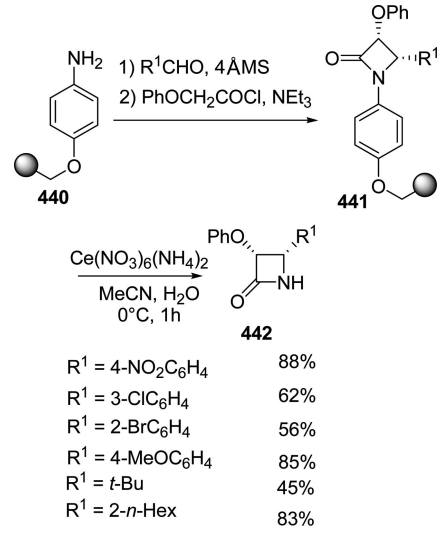


Scheme 116

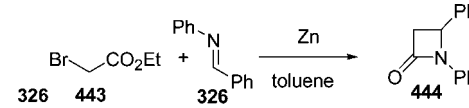


described in Schemes 115 and 116.[192] However, the same authors do not exclude an alternative mechanism involving a nucleophilic addition of the catalyst to the imine counterpart.

Scheme 117



Scheme 118



4.1.5. Solid-Phase Synthesis

Several examples are known of the application of the Staudinger reaction in solid-phase syntheses, or polymer-supported liquid-phase syntheses, of β-lactams.[193] The Mata group has developed a solid-phase synthesis of di- and trisubstituted β-lactams using a Wang resin functionalized with the imine reagent. The ketene was produced in situ starting from the carboxylic acid and the Mukaiyama's reagent (Scheme 116).

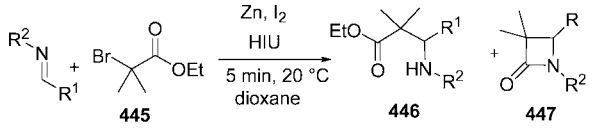
The authors tested several resins, but the best results were obtained with the Wang resin, and the Mukaiyama's reagent revealed the most efficient and user-friendly reagent for the in situ production of the ketene.[194] The same authors extended this approach to the synthesis of 1,3,4-trisubstituted β-thiolactams[195] and, more recently, to the production of C3 anchored monocyclic β-lactam derivatives.[196] A complementary approach was described by Taddei and co-workers,[197] anchoring the Mukaiyama's reagent onto a Merrifield resin through a 6-aminocaproic acid spacer. Because of the reduced reactivity of the salt, it was revealed to be necessary to use sonication for 2 h. A benzyloxyaniline functionalized tentagel-resin was used for a solid-phase synthesis of *N*-unsubstituted 2-azetidinones.[198] The spacer was designed to be removed using ceric ammonium nitrate as the cleaving reagent (Schemes 117 and 118).

4.2. Enolate−Imine Condensation[199]

The first example of this synthetic approach to β-lactams was described by Gilman and Speeter (after whom the reaction is named) in 1943. They described the condensation of the Reformatsky reagent derived from ethyl-α-bromoacetate with *N*-phenylbenzaldimine.[200] Actually, under the name of Gilman−Speeter reaction, several kinds of conditions are described using zinc, lithium, aluminum, tin boron, zirconium, and titanium enolates, although most of these approaches end up producing the β-aminoesters.

Although the use of zinc enolates was the first to be described, still several recent examples of this reaction are

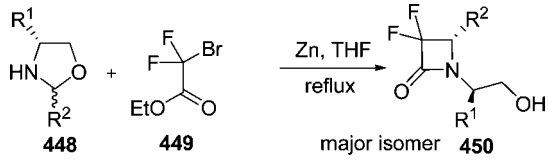
Scheme 119



445 446 447

R^1	R^2	yield (%)	
Ph	Ph		94
4-ClC_6H_4	Ph		72
4-$MeOC_6H_4$	Ph		86
4-$CF_3C_6H_4$	Ph		79
4-$Me_2NC_6H_4$	Ph		72
Ph	4-$MeOC_6H_4$		79
Ph	4-$CF_3C_6H_4$	82	
Ph	2-$MeOC_6H_4$	92	
Ph	2-EtC_6H_4		82
Ph	*t*-Bu		93
Ph	Bn		92
Ph	$SO_2C_6H_4$	98	

Scheme 120



448 449 major isomer 450

R^1	R^2	yield	diastereomeric ratio
Ph	Ph	65	>99:1
Et	Ph	69	98:2
Et	*n*-C_5H_{11}	35	95:5
Et	2-furyl	62	92:8
Et		32	98:2

known. Often the reaction gave origin to mixtures of β-lactams and β-aminoesters (Scheme 119).[201] The use of high-intensity ultrasounds afforded in good yield mixtures of these two products, with their ratio depending on the structural characteristics of the imine and the α-bromoester.[202]

The reaction was also extended to the use of chiral 1,3-oxazolidines, which afforded the corresponding β-lactams with high diastereoselectivity (Scheme 120).[203]

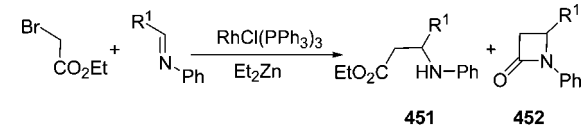
The high level of diastereoselectivity was rationalized on the basis of the formation of a strongly rigid intermediate in which the zinc atom of the alcoholate is complexed by the nitrogen atom. γ-Fluorinated derivatives of acrylates reacted efficiently with aromatic imines to afford the corresponding β-lactams as the main products.[204]

The Reformatsky reaction can also be catalyzed by $RhCl(PPh_3)_3$. With this methodology, the use of a different solvent and temperature allowed for the selective obtainment of the β-aminoester or the corresponding β-lactam (Scheme 121).[205]

Analogously, titanium complexes can act as catalyst in the presence of a stoichiometric amount of Zn metal.[206] Zn can be substituted with In powder, and a series of ferrocenylimines reacted with ethyl bromoacetate in the presence of In (Scheme 122).[207]

The Reformatsky procedure can be extended also to imide **445**,[208] which offered also the chance to perform an enantioselective synthesis of *trans*-β-lactams.[209] This approach is particularly remarkable since, generally, the

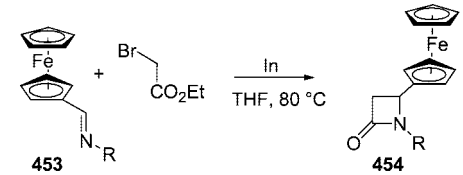
Scheme 121



451 452

R^1	THF 0 °C	Toluene 40 °C
Ph	70	65
2-$MeOC_6H_4$	61	49
3-$MeOC_6H_4$	62	63
cynnamyl	43	

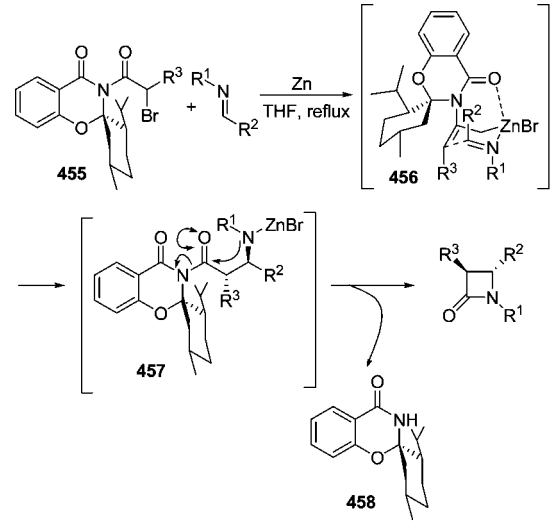
Scheme 122



453 454

R = Ar, Alk 41-66%

Scheme 123



455 456 457 458

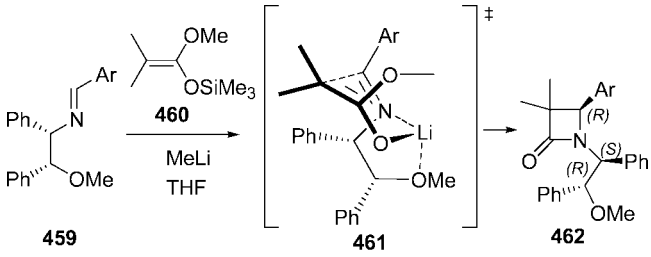
R^1	R^2	R^3	e.e. (%)	yield (%)
Ph	Ph	Me	85	65
Ph	4-ClC_6H_4	Me	80	73
4-ClC_6H_4	Ph	Et	86	63
Ph	*trans*-Styryl	Me	75	79
Ph	*trans*-Styryl	Et	78	70

Gilman−Speeter reaction affords mixtures of *cis*- and *trans*-β-lactams with the *cis* isomer being the major one. This *trans*-selectivity, as well as the enantioselectivity, was rationalized with the formation of the Zn complex **446** (Scheme 123).

Amine-free lithium enolates can be obtained by treating silylketene acetals with MeLi. The reaction of the lithium enolates with a chiral imine afforded the corresponding β-lactams with high diastereoselectivity, which was rationalized by the formation of the transition state **461** (Scheme 124).[210]

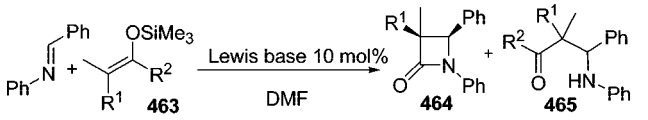
Also, lithium acetate or methoxide, *N*-lithio-2-pyrrolidone, potassium phtalimide,[211] and tris(2,4,6-trimethoxyphenyl)phosphine[212] were revealed to be proper Lewis bases for the Mannich-type addition and cyclization of aldimines and ketenesilyl acetals (Scheme 125). Mixtures of β-lactams **464** with the corresponding β-aminoester were obtained, but

Scheme 124



Ar	Reaction conditions	yield (%)	dr
Ph	0 °C, 24 h	81	98:2
4-$MeOC_6H_4$	rt, 24 h	76	99:1
4-ClC_6H_4	0 °C, 7 h	79	98 : 2

Scheme 125



R^1	R^2	base	temperature	Yield (%) 464	Yield (%) 465	ref
Me	OMe	AcOLi	rt	95	-	211
Me	OMe	AcOLi	-45	83	15	211
Me	OMe	2-pyrrolidone Li	rt	98	-	211
Me	OMe	Phthalimide K	rt	98	-	211
Me	OMe	Phthalimide K	-45	32	49	211
Me	OMe	MeOLi	rt	98	-	211
Me	OMe	MeOLi	-45	38	22	211
H	S*t*-Bu	PhOLi	rt	96 (88:12)	-	213
H	S*t*-Bu	PhOLi	-45	32 (98:2)	-	213
H	SEt	PhOLi	-45	91(95:5)	-	213
H	SEt	$PhONBu_4$	-45	96 97:3)	-	213

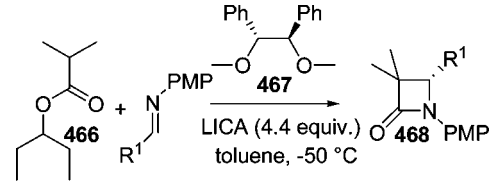
usually the β-lactam is the main product, and in some cases the only one. The same reaction was revealed to be even more efficient and also stereoselective when using trimethylsilylenolate from *S*-ethyl thioates with lithium phenoxide (Scheme 125).[213]

The first example of a direct catalytic enantioselective[111d] synthesis of β-lactams was reported by Tomioka and coworkers, who achieved a catalytic asymmetric Gilman−Speeter reaction.[214d] The reaction of pent-3-yl-2-methylpropanoate with imine in the presence of a catalytic amount of the enantiomerically pure ether ligands **467** resulted in a ternary complex reagent **469** [containing an achiral lithium amide (LICA), the ester enolate, and the ligand **467**] that afforded β-lactam **468** in high yield and good enantiomeric excess (Scheme 126).

The same authors developed several different chiral ethereal ligands that favored the formation of a binary complex without the need of the excess of LICA necessary in the preceding version of the reaction. The amines **470**−**473** gave the corresponding complexes **474**−**477** (see Chart 7).[214a]

These ligands, as well as some bis-oxazolines,[215] were revealed to be more efficient in the catalysis of the reaction, although the enantiomeric excesses did not improve markedly. More recently, the same methodology using ligands **470** and **473** and LDA was applied to the reaction of enolate obtained from silyl protected glycolates and imines with high yields but low enantioselectivity.[216] Better results were obtained combining the use of chiral ethereal and aminoethereal ligand **470** and **473** with the presence of the enolate

Scheme 126



R^1	yield (%)	ee (%)
Ph	85	88
4-$MeOC_6H_5$	80	70
1-Naph	40	75
2-Naph	85	90
Stiryl	40	75
$PhCH_2CH_2$	80	90

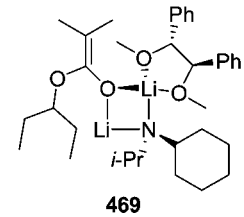
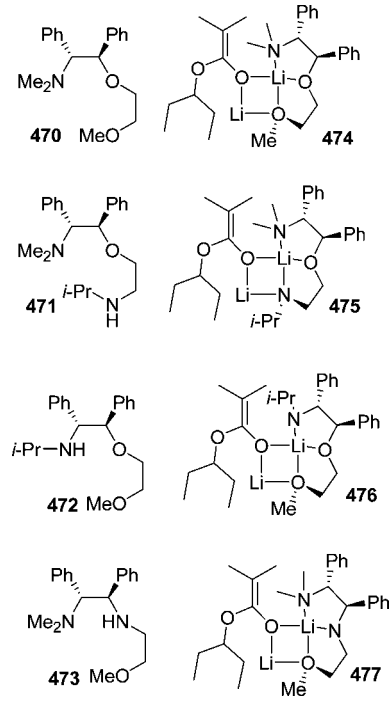


Chart 7

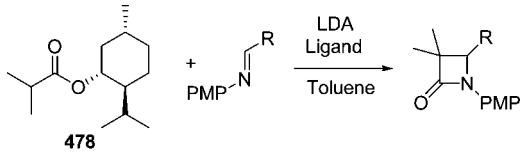


derived from menthyl isobutyrate **478**. In this case, the enantiomeric ratio raised up to 97:3 (Scheme 127).[217]

A few examples of the solid-supported synthesis of β-lactams through the enolate−imine reaction have been described. The benzylamine resin **479** was modified with a triazene linker to afford the supported esters **480** and **483**. Treating ester **480** with 1.2 equiv of LiHMDS and subsequently with *C*,*N*-diaryl imines afforded the corresponding β-lactam derivatives. Ester **483** with an excess of LiHMDS afforded the corresponding dianion, which was transformed into β-lactam derivatives. The traceless triazene junction was finally removed (Scheme 128).[218]

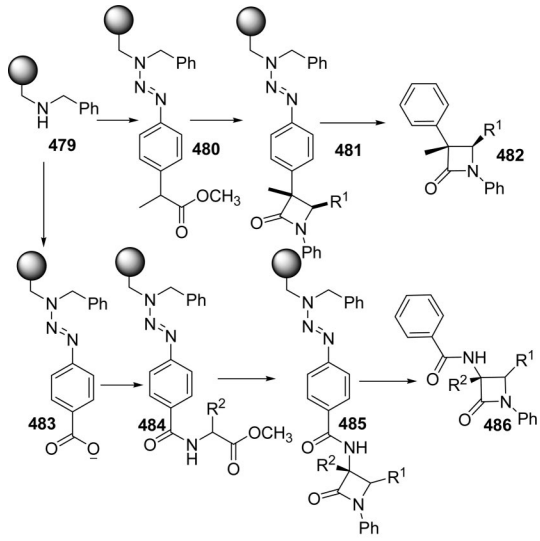
Functionalized carbosilane dendritic species demonstrated useful soluble supports for the stereo- and enantioselective synthesis of β-lactams. The proper derivatization of the

Scheme 127



ester	R	Ligand	temp (°C)	er	yield
478	Ph	none	rt	75 : 25	95
478	Ph	**470**	-10	88 : 12	99
ent-**478**	Ph	**470**	-10	64: 36	85
478	Ph	**473**	-35	97 : 3	93
ent-**478**	Ph	**473**	-20	54 : 48	95
478	stiryl	**470**	-20	96 : 4	62
478	stiryl	**473**	-20	95 : 5	34
478	$PhCH_2CH_2$	**473**	-20	74 : 26	74
478	$PhCH_2CH_2$	**473**	-20	76 : 24	86

Scheme 128



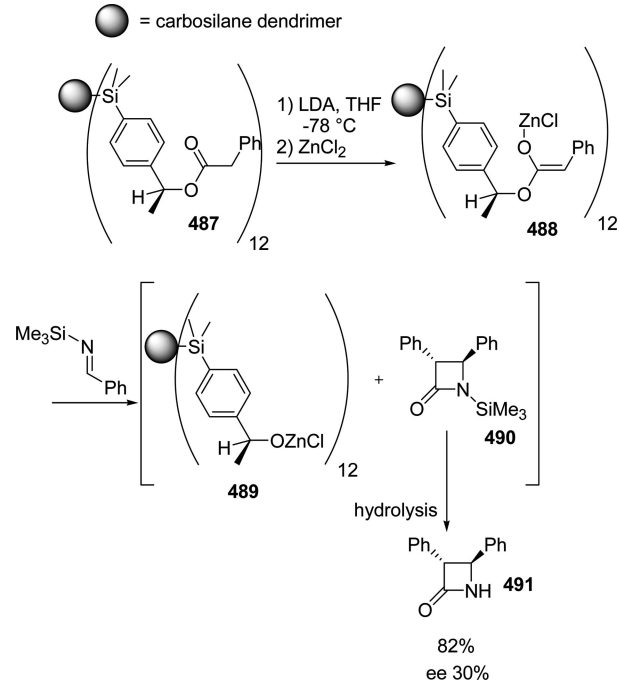
Compound	R^1	R^2	Loading	yield (%)	*cis:trans*
480	Ph	-	94	35	78:22
480	4-$OMeC_6H_4$	-	68	46	83:17
480	4-ClC_6H_4	-	74	65	80:20
480	3-(C_6H_5O) C_6H_4	-	72	92	74:26
480	1-Naph	-	96	73	>98:2
484	Ph	CH_3	96	54	>98:2
484	Ph	*i*-Pr	89	26	>98:2
484	4-ClC_6H_4	CH_3	95	54	>98:2
484	3-(PhO) C_6H_4	CH_3	97	71	96:4
484	1-Naph	CH_3	97	61	95:5

dendritic species **487** afforded the Zn enolate **488** that reacted with an imine to afford directly the β-lactam **491** as a single *trans*-isomer and 30% ee (Scheme 129).[219] The use of this carbosilane dendrimer allowed the use of nanofiltration techniques for the separation and recycling of the dendritic support. Wang and co-workers also applied soluble polymer supports to the Reformatsky procedure of α-bromoimide with good results.[220]

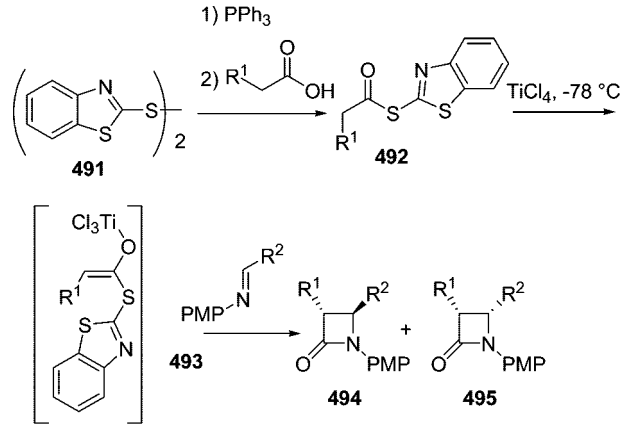
Thioesters are ideal enolate precursor for β-lactam synthesis since they possess several of the features required for this reaction. They are easily enolized (also in a highly stereoselective fashion), and the sulfide group is a better leaving group with respect to the alkoxide group. For this reason, thioesters have been widely used to prepare titanium, tin, aluminum, and boron enolates of thioesters. This application has been recently reviewed in detail, and only one new contribution will be discussed.[221]

2,2′-Dibenzothiazolyl disulfide was revealed to be a versatile reagent for the formation of thioesters **492**. These

Scheme 129



Scheme 130



R^1	R^2	**495** : **494**	yield (%)
Ph	Ph	75:25	85
Ph	piperonyl	>98:2	70
Me	piperonyl	20:80	65
PhS	Ph	<2:98	72
PhS	piperonyl	2:98	75
Phth	Ph	<2:98	70
Ph	cynnamyl	>98:2	75

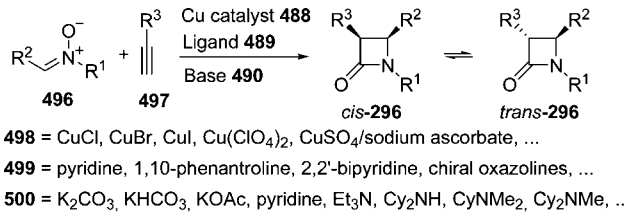
substrates react with titanium tetrachloride to afford the corresponding enolates **493**, which react with imines to afford efficiently β-lactams **494** and **495** (Scheme 130).[222]

Recently, silyl ketene thioacetal,s[223] derived from 2-pyridyl thioesters,[224] were used in a Sc(OTf)3-catalyzed reaction with imines to afford β-lactams[225] The use of $Sc(OTf)_3$ allowed the development of a catalyzed, solvent-free process.

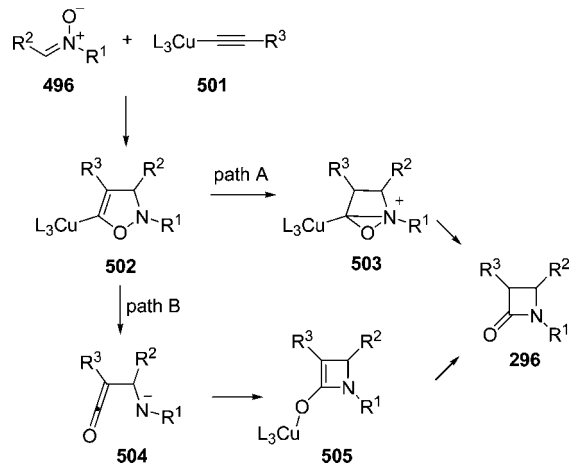
4.3. Kinugasa Reaction

The reaction of nitrones with terminal alkynes catalized by Cu(I), known as the Kinugasa reaction, is a relatively new and unexplored approach to β-lactams. Usually, the kinetic favored *cis*-3,4-disubstituted β-lactam *cis*-**293** is mainly obtained, but depending on the reaction conditions

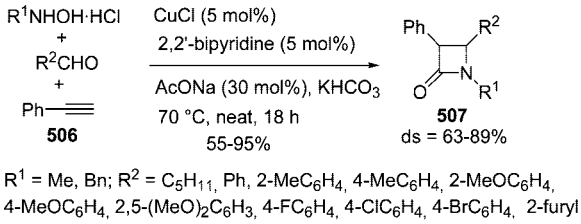
Scheme 131



Scheme 132



Scheme 133



and the substitution pattern, epimerization to the thermodynamically more stable *trans*-isomer can occur (Scheme 131).[226]

Two mechanisms have been proposed for this highly versatile and efficient methodology, both considering an initial [3 + 2]-cycloaddition between the nitrone **496** and the in situ formed copper acetylide complex **501.** Then, the intermediate isoxazoline **502** rearranges to the final azetidinone **296**, passing through the bicyclic oxaziridine **503** (Scheme 132, path A) or the ketene **504** (Scheme 132, path B).[227]

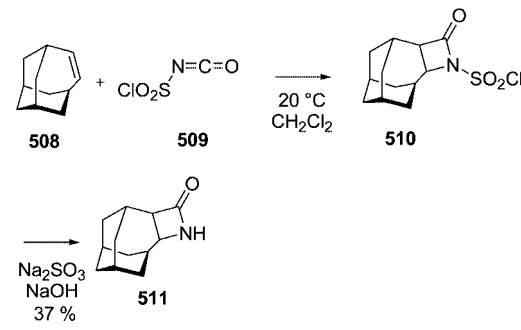
Since its discovery in 1972,[228] several aspects of this reaction have been addressed including modifications of the reaction conditions, the intramolecular version, and its diastereo- and enantioselectivity, which were achieved using either chiral auxiliaries and chiral ligands. A three-component synthesis of β-lactams **507** from *N*-substituted hydroxylamines, aldehydes, and phenylacetylene (**506**) in the presence of catalytic amounts of CuCl, 2,2′-bipyridine, and AcONa was also studied (Scheme 133).[229]

The most significant achievements in the field have been very recently and comprehensively reviewed[226] and, therefore, are not discussed here.

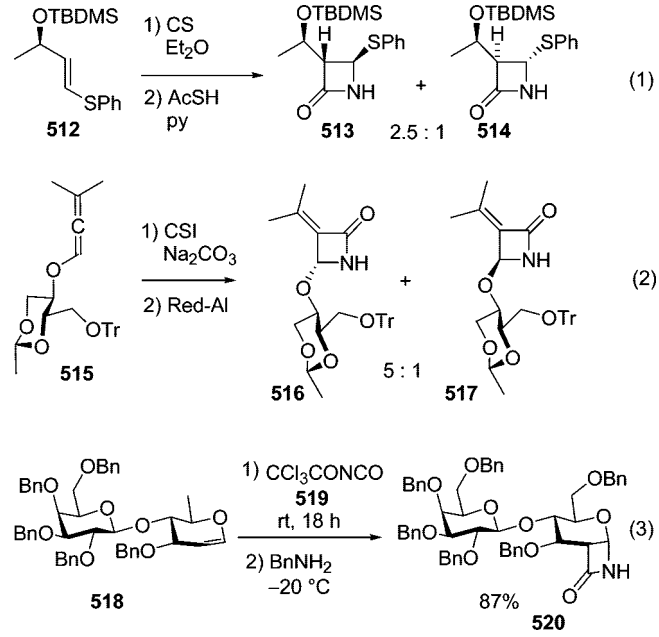
4.4. Isocyanate Cycloaddition

The [2 + 2]-cycloaddition of isocyanates to alkenes provides an easy route to β-lactams. The most used isocyanate is chlorosulfonylisocyanate (**509**, CSI) because of its exceptionally high reactivity. Furthermore, the resulting β-lactams can easily be converted into the *N*-unsubstituted derivatives by reducing treatment under basic conditions (Scheme 134).[230]

Scheme 134



Scheme 135

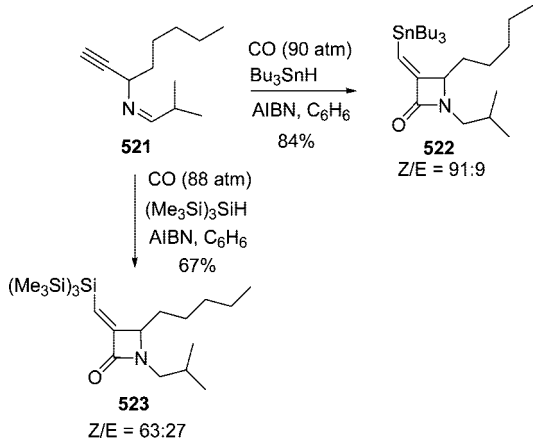


This reaction is mechanistically related to the addition of ketenes. Formally thermally not allowed, the low-energy orthogonal π-bond of the cumulene renders concerted thermal [2 + 2]-addition energetically feasible. Ab initio calculations predict that the [2 + 2]-reaction takes place through a concerted suprafacial mechanism.[231]

More recently, some attention has been devoted to the control of the stereochemistry in cycloaddition to chiral alkenes. The cycloaddition of CSI to chiral *E*-vinylsulfide **502** afforded a 2.5:1 diastereomeric mixture of phenylthioazetidinones after the reductive removal of the *N*-chlorosulfonyl group of the adduct (Scheme 135, eq 1).[232]

Chmielewski's group has thoroughly studied the stereoselectivity of the reaction of CSI with chiral vinyl ethers, derived from carbohydrates, for the production of mono- and bicyclic β-lactams.[233] This approach was also revealed to be useful in solid-phase synthesis.[234] More recently, this study was also extended to chiral alkoxyallene **515** (Scheme 135, eq 2).[235] Trichloroacetyl isocyanate **519** was added to glycal to obtain 1-oxabicyclic β-lactam **520** with good selectivity and yield (Scheme 135, eq 3).[236] The trichloroacetyl group was removed using benzylamine.

Scheme 136



4.5. [3 + 1]-Annulation

Free-radical mediated stannylcarbonylation of azaenynes with tributyltin hydride and carbon monoxide appears to be a useful method for the synthesis of 3-(stannylmethylene)-2-azetidinones. For example, imine **521** was converted to azetidinone **522** in 84% yield (Scheme 136).[237] Analogously, 3-silylmethylene derivatives such as **523** and 3-thiomethylene lactams were obtained using tris(trimethylsilyl)silane and hexanethiol, respectively, as radical mediators.[238]

4.6. Cyclizations

4.6.1. N−C2 Cyclization

A common approach to the azetidinone ring is based on the cyclization of β-amino acids and esters. In situ activation of the carboxylic acid group can be achieved using conventional amide coupling reagents such as carbodiimides, 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent), and the redox couple di(2-pyridinyl) disulfide/triphenylphosphine.[239]

Recently, Sharma et al. have investigated the efficiency of some coupling reagents in promoting the cyclization of β-amino acids. Disulfide reagents such as di(1,3-benzothiazol-2-yl) disulfide and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent), (chloromethylene)dimethylammonium chloride, and phosphoryl chloride promoted the cyclodehydration of β-amino acids **524** under mild conditions, affording the corresponding monobactams **525** in good yields (Table 1).[240]

The cyclization of β-amino acids mediated by phenylphosponic dichloride [$PhP(O)Cl_2$] in TEA was found to afford β-lactams and cyclo-β-dipeptides in different ratios depending on the reaction conditions and the substitution pattern.[241] Usually, the formation of particularly strained azetidinones from the corresponding β-amino acids is more difficult and the yields strongly depend on the reaction conditions and the substitution pattern. For example, β-amino acids **526a** and **526b** were cyclized in low yields using different standard coupling reagents. However, the *N*-methyl dihydro-2*H*-indol-2-one derivative **526c** afforded the corresponding spiro-β-lactams **527c** in good yield by treatment with tris(2-oxo-3-benzoxazolinyl)phosphine oxide and TEA in boiling CH_3CN (Table 2).[242]

Tris(2-oxo-3-benzoxazolinyl)phosphine oxide was also one of the best coupling reagents in the cyclization of amino acids **528** to carbapenam-3-carboxylates **529** (Scheme 137). The discrepancies in the yield values reported by different authors for the synthesis of **529** under similar conditions can probably be ascribed to its instability.[243]

β-Amino acids were converted to substituted azetidinones through intramolecular multicomponent Ugi reaction (see section 4.6.1.1).

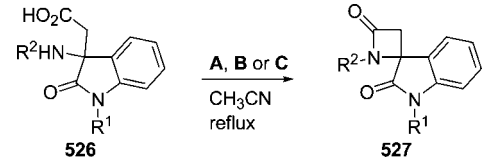
An alternative approach to the β-lactam ring is based on cyclization of β-amino esters in the presence of a base such

Table 1. Intramolecular Coupling of β-Amino Acids 524

	R^1	R^2	R^3	R^4	yield[a] (%) A	B	C	D
a	H	H	H	H	54	76	77	
b	H	H	H	Bn	80	80	85	
c	H	Me	H	Bn	83	79	82	83
d	H	Me	H	CH_2Bn	85	82	84	
e	H	Me	H	*n*-Bu	75	81	86	76
f	H	Me	H	*i*-Bu	82	78	80	77
g	H	Me	H	CH_2CH_2OH	83	79	80	78
h	H	Me	H	$CH_2CH(OH)Me$	79	82	82	74
i	Me	H	H	Bn	85	85	82	82
j	Me	H	H	CH_2Bn	86	81	81	
k	Me	H	H	*n*-Bu	73	82	82	
l	Me	H	H	*i*-Bu	81	80	83	78
m	Me	H	H	CH_2CH_2OH	82	83	82	79
n	Me	H	H	$CH_2CH(OH)Me$	84	84	84	
o	H	Ph	H	Bn	80	81	75	79
p	H	Ph	H	H	54	82	83	73
q	H	piperonyl	H	H	50	80	83	
r	H	4-$MeOC_6H_4$	H	H	51	79	81	
s	Me	H	4-MeC_6H_4	4-MeC_6H_4	79	75		
t	Et	Me	H	Bn	75	70		
u	Bn	Me	H	Bn	73	69		
v	BnO	Ph	H	Bn	70	77		

[a] Reaction conditions: (A) (i) di(1,3-benzothiazol-2-yl) disulfide, Ph_3P, CH_2Cl_2 (0.07 M), 25−30 °C; (ii) TEA.[240c] (B) (i) Lawesson's reagent, TEA, CH_2Cl_2 (0.01 M), 25−30 °C; (ii) TEA, 0 °C to 25−30 °C.[240c] (C) (i) (chloromethylene)dimethylammonium chloride, CH_3CN (0.01 M), 0 °C; (ii) TEA, 0 °C to rt.[240b] (D) $POCl_3$, TEA, CH_2Cl_2 (0.04 M), 0 °C to rt.[240a]

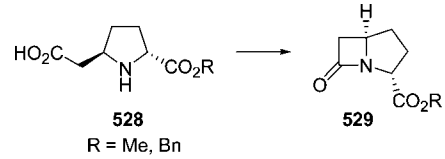
Table 2. Formation of Spiroazetidinones 527[242]



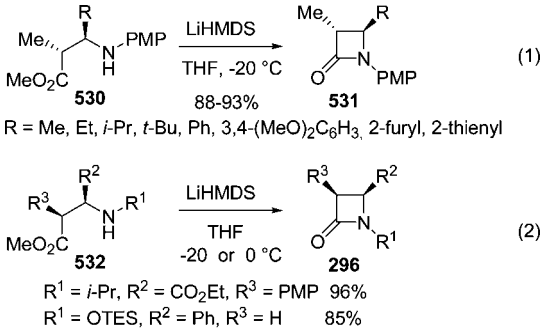
	R^1	R^2	yield[a] (%) A	B	C
a	H	H	13	16	39
b	H	4-$MeOC_6H_4$	15	20	26
c	Me	H	13	16	70

[a] Coupling reagents: (A) $(PyS)_2$, Ph_3P; (B) 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent); (C) tris(2-oxo-3-benzoxazolinyl)phosphine oxide, TEA.

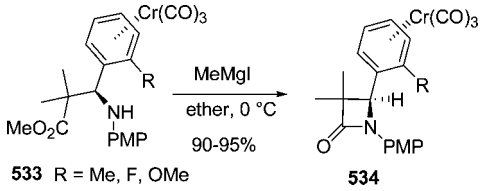
Scheme 137



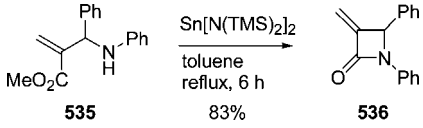
Scheme 138



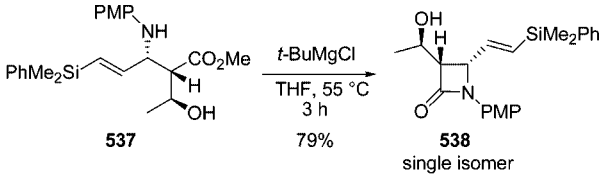
Scheme 139



Scheme 140



Scheme 141



as EtMgBr, MeMgI, *n*-BuLi, *t*-BuOK, LiHMDS, LiOH, KOH, etc. For example, chiral amino esters **530** and **532** in the presence of LiHMDS gave β-lactams **531** and **296**, respectively, in high yields and with retention of the relative and absolute configurations of the stereocenters (Scheme 138).[244]

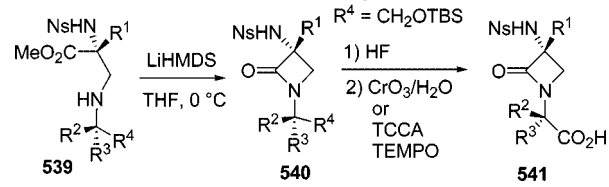
Sarkar et al. reported the cyclization of β-amino esters **533** in the presence of MeMgI. The expected $Cr(CO)_3$-complexed 4-aryl-azetidinones **534** were obtained in high yields and with no loss of diastereomeric purity (Scheme 139).[245]

In some cases, a strong dependence of these reactions on the substrate substitution pattern and the reaction conditions was observed. For example, several bases in different solvents failed to cyclize **535**, whereas 3-methylene azetidinone **536** was obtained in 83% yield using $Sn[N(TMS)_2]_2$ in refluxing toluene (Scheme 140).[246]

The β-amino ester **537** was converted to the *cis*-disubstituted β-lactam **538** in 79% yield and complete diastereoselectivity by treatment with *t*-BuMgCl in tetrahydrofuran (THF) at 55 °C for 3 h (Scheme 141). Prolonged reaction times or using *i*-PrMgCl as base afforded a *cis/trans* diastereomeric mixture of **538**.[247]

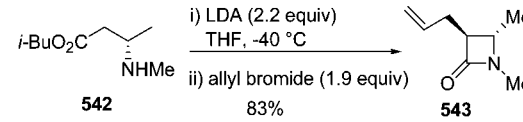
Pseudodipeptides **539a** and **539b** failed to cyclize to β-lactams by treatment with LiHDMS probably because of the presence of an enolizable ester moiety (Table 3). Actually, the reduced α,β-diamino esters **539c**−**539j** smoothly underwent the LiHMDS-promoted intramolecular aminolysis

Table 3. Base-Induced Cyclization of β-Amino Esters 539[248]

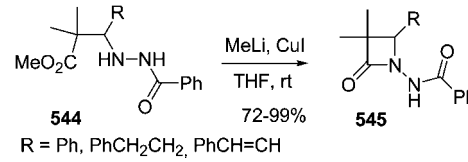


	R^1	R^2	R^3	R^4	**540** yield (%)	**541** byield (%)
a	Bn	H	H	CO_2Bn		
b	Bn	H	Me	CO_2Bn		
c	Bn	H	H	CH_2OTBS	95	81
d	Bn	H	Me	CH_2OTBS	92	89
e	Bn	Me	H	CH_2OTBS	90	90
f	Bn	H	Ph	CH_2OTBS	97	60
h	Bn	Ph	H	CH_2OTBS	93	60
i	Me	H	H	CH_2OTBS	60	90
j	Me	*i*-Pr	H	CH_2OTBS	98	80

Scheme 142



Scheme 143



to the corresponding azetidinones **540**, which, in turn, were converted into the [3-amino-2-oxoazetidin-1-yl]propanoic acids **541** in good overall yields (Table 3).[248]

A large-scale synthesis (60 g) of the (3*S*,4*S*)-3-allyl-1,4-dimethylazetidin-2-one (**543**) was achieved by one-pot cyclization and stereocontrolled alkylation of the β-amino ester **542** through the formation of a dianion intermediate (Scheme 142).[249]

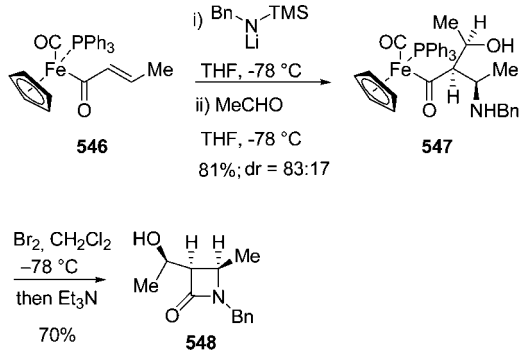
Analogously to β-amino esters, β-hydrazino esters can cyclize under basic conditions. For example, *N*-benzoyl derivatives **544** afforded the corresponding β-lactams **545** in 72−99% yield (Scheme 143).[250]

Some *cis*- and *trans*-disubstituted monobactams, including synthetic precursors of racemic olivanic acid and tienamycin, have been synthesized by cyclization of β-amino acyl iron complexes such as **547** by oxidative decomplexation with bromine. The substrates were obtained by conjugate addition of lithium amides to α,β-unsaturated acyl iron complexes followed by in situ treatment of the enolate with acetaldehyde (Scheme 144).[251]

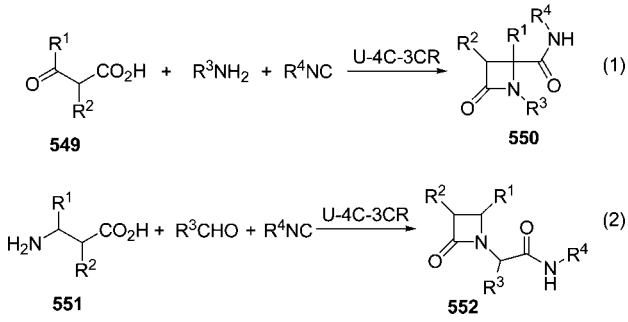
4.6.1.1. Multicomponent Reactions. Variations of the multicomponent Ugi reaction involving an amine, a carbonyl compound, an isocyanide, and a carboxylic acid were used to prepare substituted β-lactams in a convergent fashion. In particular, β-keto acids **549** and β-amino acids **551** acted as bifunctional reagents in an Ugi four-center three-component reaction (U-4C-3CR), leading to small libraries of mono- and polycyclic azetidinones **550** and **552** (Scheme 145).[252] Significant rate enhancements were observed when the U-4C-3CRs were performed in water or aqueous glucose solution.[252c−f]

When β-aminothiocarboxylic acids were reacted with aldehydes and 3-dimethylamino-2-isocyanoacrylates, a thia-

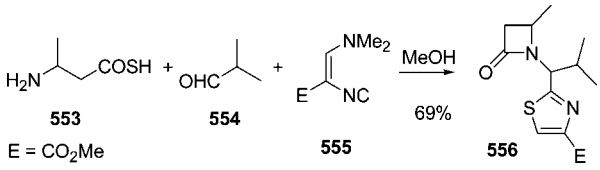
Scheme 144



Scheme 145



Scheme 146



zole ring was also formed and 1-(1,3-thiazol-2-yl-methyl)-azetidin-2-ones such as **556** were obtained (Scheme 146).[253]

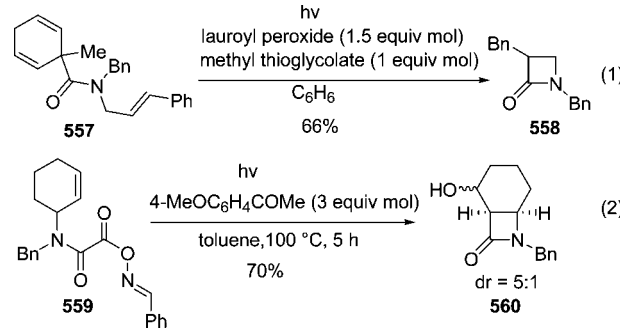
4.6.2. C2−C3 Cyclization

Cyclization by C2−C3 bond formation is a quite uncommon β-lactam synthesis. The more studied of this type is cyclization of carbamoyl radicals. Recently, *N*-allyl aminoacyl radicals able to undergo 4-*exo-trig* ring closure were generated from 1-methyl-2,5-cyclohexadiene-1-carboxamides and from oxime oxalate amides by photolysis. Up to now, these processes afforded β-lactams such as **558** and **560** in moderate yields (up to 66−70%). Depending on the reaction conditions and the stability of the intermediate cyclized radicals, hydroxylated derivatives could be obtained (Scheme 147).[254] The kinetics of cyclization of carbamoil radicals generated by oxime oxalate amides were studied by electron paramagnetic resonance (EPR) spectroscopy and DFT computations.[255]

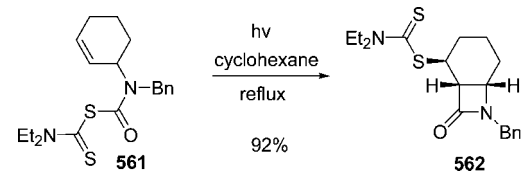
N,*N*-Dialkyl dithiocarbamates were used in place of xanthates in group transfer radical cyclization reactions of carbamoyl radicals. For example, β-lactam **552** was obtained as a single diastereomer in 92% yield by irradiation of **551** (Scheme 148).[256]

Radical cyclization of haloenamides with Cu(I) or Ru(II) complexes was investigated. Depending on the reaction conditions and the metal oxidant used, the kinetically favored β-lactams or the thermodynamically more stable γ-lactams were regioselectively formed.[257]

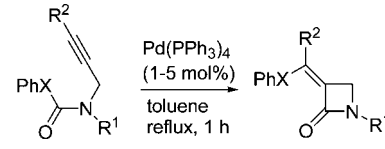
Scheme 147



Scheme 148

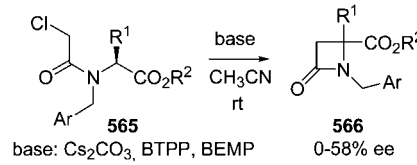


Scheme 149

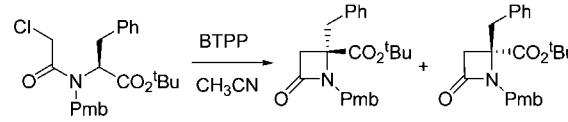


X	R^1	R^2	Yield (%)	*E*/*Z*
Se	Me	H	74-81	0/100
Se	*n*-Bu	H	60	2/98
Se	Bn	H	59	3/97
Se	Bn	Et	88	3/97
Se	Me	4-ClC_6H_4	76	11/89
S	Me	H	72	0/100

Scheme 150



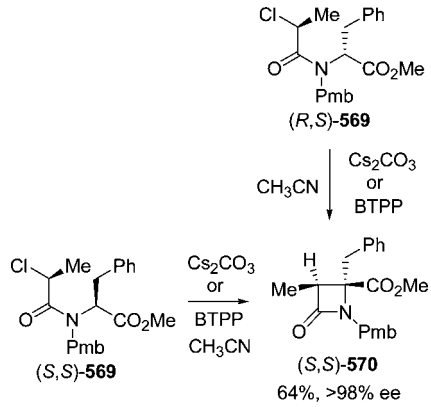
Scheme 151



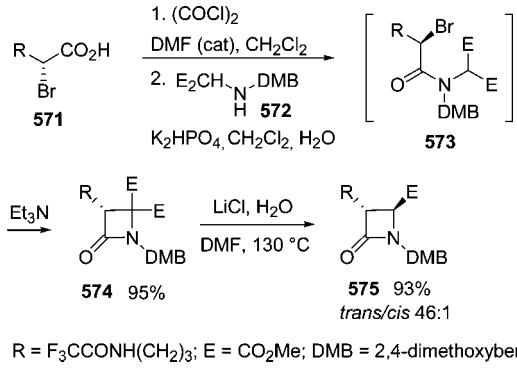
Additive	mol%	yield%	(*S*)-**568** : (*R*)-**568**
–		73	76 : 24
(–)-TADDOL	10	71	85 : 15
(+)-TADDOL	10	67	81 : 19
(±)-TADDOL	10	81	79 : 21
(–)-TADDOL	50	68	91 : 9

Fujiwara and Kambe prepared 3-alkylidene-β-lactams **564** by intramolecular selenocarbamoylation of alkynes catalized by Pd (1−5 mol %). Both terminal and internal alkynes afforded **564** in good yields. Competitive cyclization of a carbamoselenoate bearing both *N*-(2-propynyl) and *N*-(4-pentynyl) showed that the formation of the four-membered ring is kinetically favored over the six-membered lactam. An analogous example of intramolecular thiocarbamoylation

Scheme 152

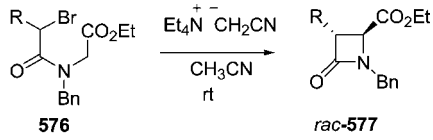


Scheme 153



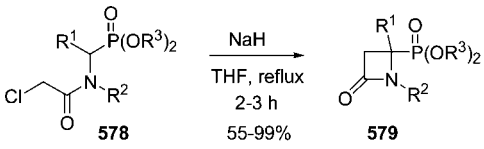
R = $F_3CCONH(CH_2)_3$; E = CO_2Me; DMB = 2,4-dimethoxybenzyl

Scheme 154



R	yield%	*cis/trans* ratio
Me	84	91 : 9
Et	90	90 : 10
i-Pr	75	87 : 13
n-Bu	85	93 : 7
c-C_5H_9	57	90 : 10
c-Hex	63	91 : 9

Scheme 155



R^1 = Ph, Furyl, Cinnamyl; R^2 = Ph, Bn, Allyl, *i*-Pr, Naphth; R^3 = Me, Et

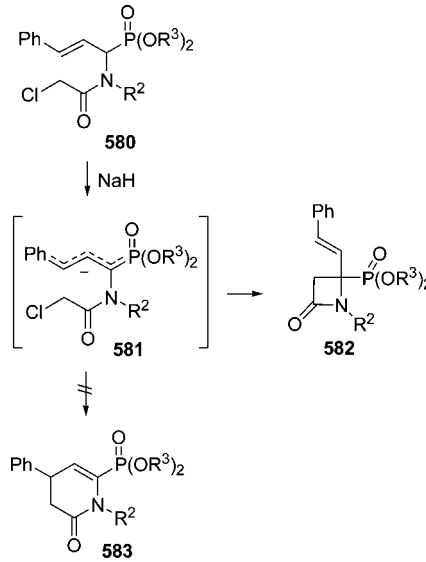
to thio-substituted 3-methylidene azetidinone was also reported (Scheme 149).[258]

4.6.3. C3−C4 Cyclization

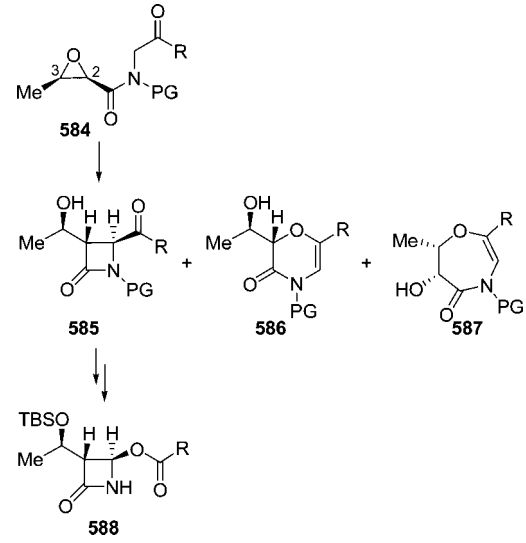
The C3−C4 bond formation can involve either radical or ionic intermediates. Usually the stereochemistry control is a major concern in these reactions, and the development of known and new methodologies continue to attract attention.

Base-assisted intramolecular alkylation of *N*-chloroacetyl α-amino acid derivatives **565** to 1,4,4-trisubstituted 2-azetidinones **566** was thoroughly explored by González-Muñiz's group (Scheme 150).[259] Generally, the best results were

Scheme 156



Scheme 157



obtained using bases such as Cs_2CO_3 or more exotic ones like *tert*-butylimino tri(pyrrolidino)phosphorane (BTPP) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) in acetonitrile solution. The intramolecular alkylation occurs with some chirality memory of the enolate intermediates as a modest enantioselectivity (0−58% ee) is observed, strongly depending on the nature of the amino acid side chain R^1 and the base and the solvent used.

In the cyclization of phenylalanine derivatives, the memory of chirality effect was enhanced in the presence of 2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-L-threitol (TADDOL) and its enantiomer. The extent and sign of the enantioselectivity was practically independent of the configuration of the additive, as shown in Scheme 151.[260]

The effect on stereoselectivity of additional stereogenic centers in the acyclic substrate was also studied. The introduction of a suitable chiral auxiliary on the carboxylic group in **565** allowed the synthesis of β-lactam derivatives with good stereoselectivity.[261]

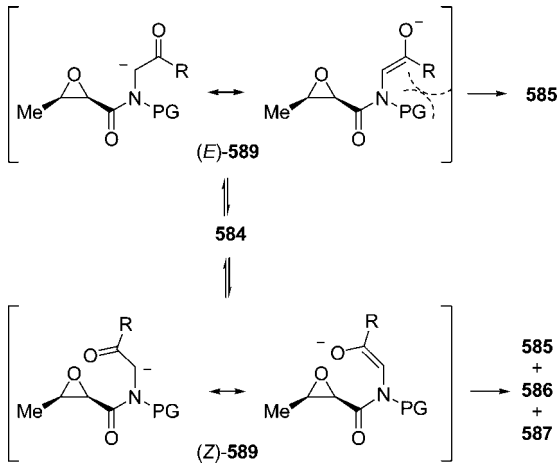
A high diastereoselectivity was observed with derivatives of enantiopure 2-chloropropionic acid. In this case, the configuration of the newly formed quaternary stereocenter

Table 4. Cyclization of Epoxybutyramides 584[268]

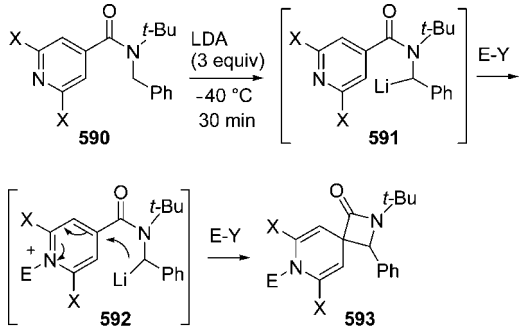
entry	SM	PG	R	rxn cond.[a]	product ratio[b] (rel %) 585	586	587	other	585 yield
1	**584a**	4-$MeOC_6H_4$	Ph	A	100				76%
2	**584b**	4-$MeOC_6H_4$	*t*-Bu	A	100				81%
3	**584c**	Ph_2CH	Ph	A	16	56	21	7	
4		Ph_2CH	Ph	B	57	21	20	2	
5	**584d**	Ph_2CH	*t*-Bu	A	55	35	8	2	
6		Ph_2CH	*t*-Bu	B	100				
7	**584e**	Ph_2CH	2-$MeOC_6H_4$	B	31	12	57		
8	**584f**	Ph_2CH	*i*-Pr	B	85	15			
9	**584g**	Ph_2CH	*c*-Pr	B	88		7		82%
10	**584h**	Ph_2CH	H	A		76	24		
11		Ph_2CH	H	B	2	98			

[a] (A) K_2CO_3, 100 °C, DMF, 18 h; (B) LiHMDS, 0 °C, THF, 3 h. [b] Determined by ^1H NMR spectroscopy of the crude mixtures.

Scheme 158



Scheme 159

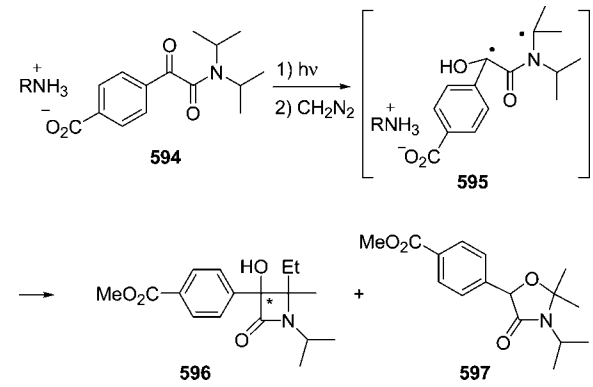


X	E-Y	Yield (%)
H	MeO_2C-Cl	91
H	BnO_2C-Cl	81
H	Bz-Cl	86
H	Me-OTf	82
Cl	MeO_2C-Cl	83
Cl	BzCl	39

was completely determined by the propionic acid configuration without any influence of the amino acid moiety. For example, diastereomeric (*S*,*S*)-**569** and (*R*,*S*)-**569** gave the same 3,4-*cis* β-lactam (*S*,*S*)-**570** with 64% yield and >98% ee (Scheme 152). Similarly, base-promoted cyclization of (*R*,*R*)-**569** and (*S*,*R*)-**569** afforded the enantiomeric 1,3,4,4-tetrasubstitued 2-azetidinone (*R*,*R*)-**570**.[262] The solid-phase synthesis of 1,4,4-trisubstituted 2-azetidinones by base-assisted cyclization of supported *N*-chloroacetyl α-amino acids has also been reported.[263]

Azetidinone **574** was prepared by in situ generation of amide **573** from the acid chloride of **571** and amine **572** in

Scheme 160



the presence of $KHPO_4$ as base, followed by addition of an excess of triethylamine to promote the intramolecular cyclization (Scheme 153).[264] Under these conditions, the overall process occurred with inversion of configuration without any detectable racemization. The two-base, one-pot protocol was shown to be more convenient than performing both the acylation and cyclization steps in the presence of the same base such as triethylamine, diisopropylethylamine, or *N*-methylpiperidine. The C4 geminal diester **574** underwent highly *trans*-diastereoselective dealkoxycarbonylation by treatment with LiCl in DMF/H_2O at 130 °C (93% yield and 98% ds). The unprecedented degree of selectivity was ascribed to the presence of the trifluoroacetamide group, which can act as an intramolecular proton source. The 3,4-*trans*-azetidinone **575** was then converted into the tryptase inhibitor BMS-262084 in optically pure form (ee > 99%).

Electrogenerated bases were used to induce cyclization of bromoamides **576**. Addition of racemic **576** to a solution of cyanomethyl anion, generated by galvanostatic cathodic reduction of a solution of Et_4NPF_6 in acetonitrile, afforded 3,4-*cis*-azetidinones **577** in good yields and high diastereoselectivity. Complete conversion of the substrate required two moles of electrons per mole of bromoamide (2 F/mol) (Scheme 154).[265]

Chloroamidophosphonates **578** gave phosphono-β-lactams **579** in good yield by treatment with NaH to induce the ring closure (Scheme 155). Unexpectedly, the ring-closure reaction of *N*-chloroacetyl-1-aminoalkenyl phosphonates **580** exclusively leads to the azetidinones **582** without formation of the six-membered lactams **583** (Scheme 156).[266]

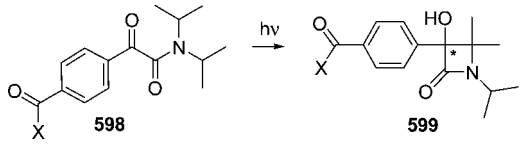
Ab initio calculations showed that the remarkable selectivity associated with this intramolecular reaction was primarily due to a restricted rotation around the C−N bond, which

Table 5. Solid-State and Solution Irradiation of Salts 594 (Ionic Chiral Auxiliary Method)

entry	RNH_2	rxn cond.[a]	convs (%)	**596** (%)	ee (%)	**597** (%)	ref
1	L-prolinamide	A	99	94	99	2	271a,b
2		B	99	91	>99	nr[b]	271a,b
3		C	nr[b]	nr[b]	7	nr[b]	271a
4	(*R*)-bornylamine	A	100	92	96	7	271b
5	(*S*)-1-aminoindan	A	100	94	89	5	271b
6	(*S*)-1-phenylethylamine	A	52	nr[b]	18	nr[b]	271a
7		A	99	79	3	10	271a,b
8	(1*R*,2*S*)-1-amino-2-indanol	A	23	15	91	1	271b
9		A	98	75	45	10	271b

[a] Photocyclization was conducted at rt followed by diazomethane work up: (A) irradiation under nitrogen of a 5 mg sample of the crystalline salt sandwiched between Pyrex microscope slides; (B) irradiation of a degassed hexane suspension of 500 mg of the salt; (C) irradiation of a deoxygenated CH_3CN solution of the salt. [b] nr = not reported.

Scheme 161



prevents the ambident allylic anion **581** from reaching the conformer suitable for six-membered ring formation (Scheme 156).[267]

Marchand-Brynaert et al.[268] revisited the approach to valuable carbapenem precursors **588** previously used by Hanessian[269] (Scheme 157 and Table 4, entries 1 and 2) and based on cyclization of the epoxybutyramide **584** derived from L-threonine and a Bayer−Villiger oxidation (B−V). Replacement of the PMP N-protecting group with the benzhydryl one caused the loss of regioselectivity in the K_2CO_3-promoted cyclization in hot dimethylformamide (DMF) (Scheme 157 and Table 4, entries 3, 5, and 10). Either the nature of the base, the countercation, the solvent, or the R group affected the enolate *C*-/*O*-alkylation selectivity. Formation of azetidinone was favored in the presence of a hard cation (Li_2CO_3 vs K_2CO_3) in a less polar solvent (THF vs DMF). Furthermore, *C*-alkylation was favored by the presence of bulky substituent (steric effect) (R = *t*-Bu, *c*-Pr, *i*-Pr vs H), while the presence of an aryl group increased the ratio of *O*-alkylation (electronic effect) (R = Ph, 2-$MeOC_6H_4$).

The proposed rationalization of the effect of the N-protecting group on the cyclization selectivity was based on (*E*)-**589** and (*Z*)-**589** enolates ratio. The (*E*)-enolate could only provide the four-membered heterocycle **585**, while the (*Z*)-enolate could undergo intramolecular *C*- and *O*-alkylation to **585** and **586**, **587**, respectively (Scheme 158). With PG = PMP, the 4-*exo*-*tet* process was observed in all cases, because of the formation of the sole enolate (*E*)-**589**. With the nonconjugated and bulkier benzhydryl group, (*E*)-**589** is probably less stable than (*Z*)-**589**, because of steric interactions between the PG and R groups. Thus, under reversible conditions of enolate formation (K_2CO_3, DMF, Δ), the reaction should proceed mostly via the (*Z*)-enolate, giving three kinds of cyclized products. On the other hand, under nonreversible conditions of enolate formation (LiHMDS, THF, 0 °C), the (*E*)-enolate should be formed more rapidly, giving the expected azetidinone as the major (or unique) product.

Azetidinones **585** were obtained exclusively as the *trans*-stereoisomers through a clean S_N2 mechanism with inversion of configuration of epoxide C2 and control of the absolute configuration of the new generated stereocenter. Eventually, **585g** was converted into **588g** by removal of the benzhydryl group, B−V oxidation with *m*CPBA, and protection of the hydroxy group with TBSCl in 69% overall yield.

Acylation and alkylation of lithiated *N*-benzylisonicotinamides **591** trigger a dearomatizing 4-*exo*-cyclization to spiroazetidinones **593** (Scheme 159). Remarkably, the electrophile attacks **591** at the pyridine nitrogen rather than the organolithium center, presumably for steric reasons. When MeI was used as an electrophile, mixtures of products resulting from *N*- and *C*-alkylation were obtained.[270]

Several approaches to stereoselective photocyclization of α-oxoamides **594** to β-lactams **596** have been analyzed. In particular, both the use of ionic and covalent chiral auxiliaries leads to high levels of asymmetric induction in the crystalline state.[271]

Irradiation of crystalline salts of the achiral 4-[(diisopropylamino)(oxo)acetyl]benzoic acid with an enantiopure amine (solid-state ionic chiral auxiliary method) afforded, after esterification with diazomethane, optically active 3-hydroxyazetidinone **596** along with small amounts of oxazolidinone **597** (Scheme 160 and Table 5). L-Prolinamide proved to be the best chiral auxiliary, giving essentially enantiopure **596** in high yield (>90%) by irradiation of the corresponding salt **594** (RNH_2 = L-prolinamide) either in the pure solid state (5 mg scale) or in hexane suspension (500 mg scale) (Table 5, entries 1 and 2). The crystalline state of the irradiated sample was proved to be important. Actually, negligible enantioselectivity was obtained by photolysis of MeOH or CH_3CN solution of the salt (Table 5, entry 3). In some cases, the enantiomeric excess of the β-lactam **596** varied with the extent of conversion of the starting material **594** (Table 5, entries 6−9). This was probably due to the occurrence of conformational isomerism in the crystals of the corresponding salt **594**.[271a,b]

Other approaches consist of irradiating covalent chiral auxiliary-containing α-oxoamides **598** in pure crystalline state (solid-state covalent chiral auxiliary method) or in zeolites and cyclodextrins (Scheme 161).

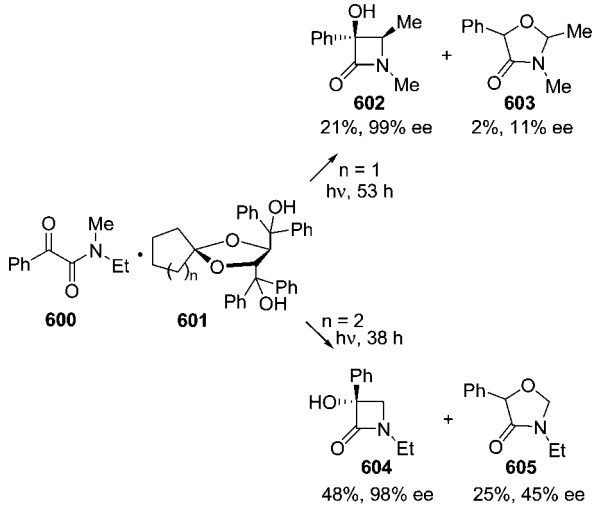
Solid-state irradiation of **598** was highly diastereoselective when a suitable chiral auxiliary was used, whereas photolysis of the same substrate in solution was poorly stereoselective (Scheme 161 and Table 6). Phenylethylamide derivative **598** (X = PhMeCH) gave the corresponding β-lactam with >99% de even at 100% conversion (Table 6, entry 1). Using other chiral auxiliaries, the de of the product **598** decreased progressively with conversion (Table 6, entries 5, 6, 9, and 10). X-ray structural studies of crystals of α-oxoamides **598** showed that the crystal lattice preorganizes the reactant molecules toward a single diasteromer of the β-lactam and

Table 6. Solid-State and Solution Irradiation of α-Oxoamides 598 (Covalent Chiral Auxiliary Method)

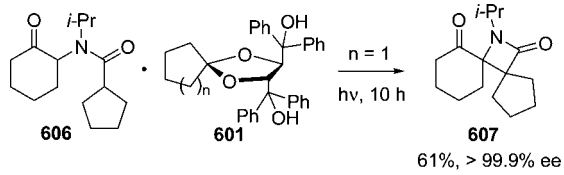
entry	XH	rxn cond.[a]	convs (%)	**599** de (%)	ref
1	(*R*)-1-phenylethylamine	A	98	>99	271b,d
2		C		2 (MeOH) 28 (C_6H_6)	271d,b
3		D (NaY)		62	271c,b
4		E(β-CD)		87	271b
5	(*R*)-3-methyl-2-bythylamine	A	22	96	271d
6		A	100	79	271d
7		C		2	271d
8		D (NaY)		30	271c
9	(1*R*,2*S*)-ephedrine	A	70	91	271d
10		A	100	87	271d
11		C		3	271d
12	(2*R*)-2-phenyl-1-propanol	A	98	84	271b
13		B	94	95	271b
14	L-phenylalanine methyl ester	A	80	76	271b
15		C		2 (MeOH) 5 (C_6H_6)	271b
16		D (NaY)		82	271b
17		E(β-CD)		12	271b

[a] Photocyclizations of (A) neat polycrystals; (B) crystals suspended in H_2O; (C) a CH_3CN or C_6H_6 solution of the oxoamide; (D) the oxoamide within zeolite (MY, M = alkali metal ion); (E) the oxoamide within cyclodextrin (CD).

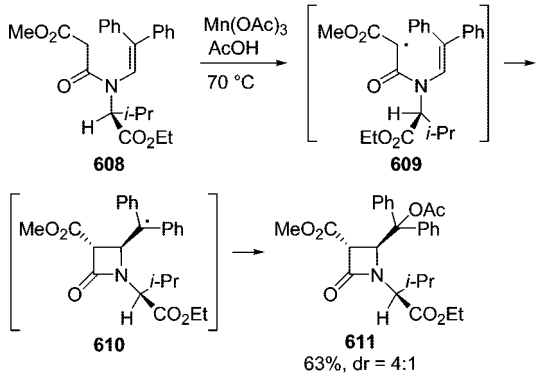
Scheme 162



Scheme 163

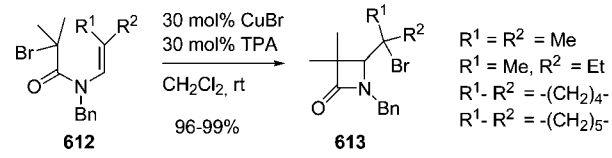


Scheme 164

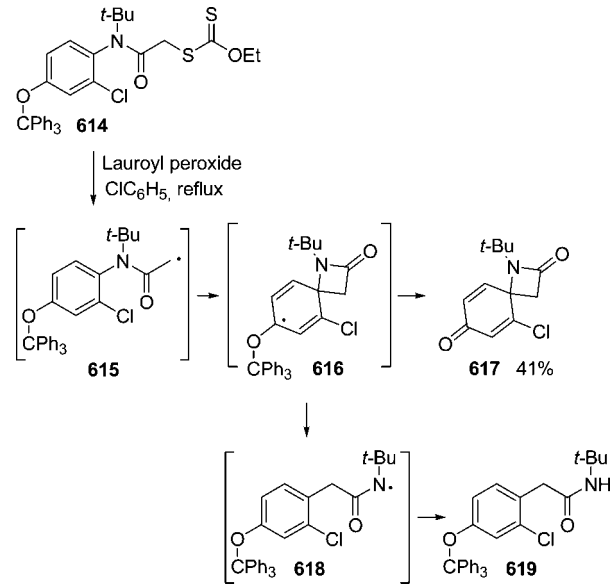


forbids large motions of the 1,4-diradical intermediate, which would lose the stereochemical memory.[271d]

Scheme 165



Scheme 166



Photochemical rearrangement of covalent chiral auxiliary-containing α-oxoamides **598** in the interior cavities of zeolites (MY, M = alkali metal ion) and as crystalline 1:1 complexes with cyclodextrins (CDs) was also studied. In some cases, good levels of asymmetric induction were observed, but they were generally lower than those obtained in the pure crystalline state (Table 6, entries 3, 4, 8, and 16).

Photorearrangement of achiral oxoamides **594** in "chirally modified" zeolites, i.e., zeolites preloaded with an enantiopure external chiral inductor such as ephedrine, norephedrine, menthol, and 1-phenylethylamine afforded the corresponding β-lactams with low enantioselectivity (up to 44% ee).[271b]

Highly regio- and enantioselective photocyclization of *N*-ethyl-*N*-methyl-2-oxo-2-phenylacetamide **600** was achieved

by irradiation of a 1:1 inclusion complex of **600** with optically active hosts **601** in the solid state (Scheme 162).[272] Five- and six-membered hosts **601** ($n = 1, 2$) induced reversed regioselectivity, and β-lactams **602** and **603** were obtained with opposite absolute configuration at the C3 stereocenter. X-ray structure analyses of the inclusion complexes showed that the observed selectivities were due to different conformations adopted by **600** in the crystals.

A study on photochemical behavior of *N*-trimethylsilylmethyl- and *N*-tributylstannylmethyl-substituted α-ketoamides in solution was reported.[273] Photoreaction of a 1:1 inclusion crystal of amide **606** with **601** ($n = 1$) gave optically pure azetidinone **607** in 61% yield (Scheme 163).[274]

Some enamides prepared from enantiopure α-amino esters underwent diastereoselective Mn(III)-mediated 4-*exo*-*trig* cyclization. For example, the Val derivative **608** afforded the *trans*-azetidinones **609** in 4:1 diastereomeric ratio (Scheme 164).[275]

Regiochemistry in radical cyclizations of 2-halide-*N*-vinylacetamide derivatives has also been studied.[276] Complete regioselectivity was observed in the atom transfer radical cyclization of bromoenamides **612** mediated by the *N*,*N*,*N*-tris(pyridin-2-ylmethyl)amine (TPA)−CuBr complex that afforded β-lactams **613** in high yields with no formation of γ-lactams (Scheme 165).[276a]

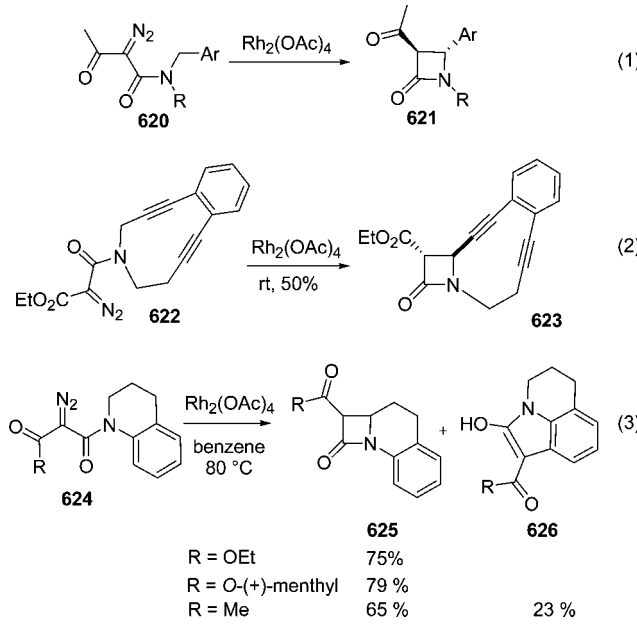
The formation of the spiroazetidinone **617** was useful to prove that radicals of *o*-substituted acetanilides undergo Smiles rearrangement through the formation of four-membered cyclic intermediates.[277] In particular, when xanthate **614** was treated with a peroxide in refluxing chlorobenzene, it afforded **617** as the main product along with only traces of the Smiles product **619** (Scheme 166). In this case, the elimination of the stabilized triphenylmethyl radical from intermediate **616** justified the favored formation of derivative **617**.

4.6.3.1. Metal-Catalyzed C−H Insertion. Diazoacetoacetamides and related diazo compounds undergo Rh(II) catalyzed decomposition to form β-lactams in high yield and good stereocontrol. The reaction proceeds through the formation of a metallocarbenoid. A stable dirhodium tetracarboxylate carbenoid was isolated and its structure analyzed. This complex was revealed to be able to catalyze the β-lactam formation from a diazoacetoacetamide.[278] This approach was used for the synthesis of β-lactam fused cyclic enediynes **623** (Scheme 167, eq 2).[279] The main features of the reaction have been defined and often give mixture of five- and four-membered lactams.[280] Most recent examples are directed toward the application of the reaction to new substrates.[281]

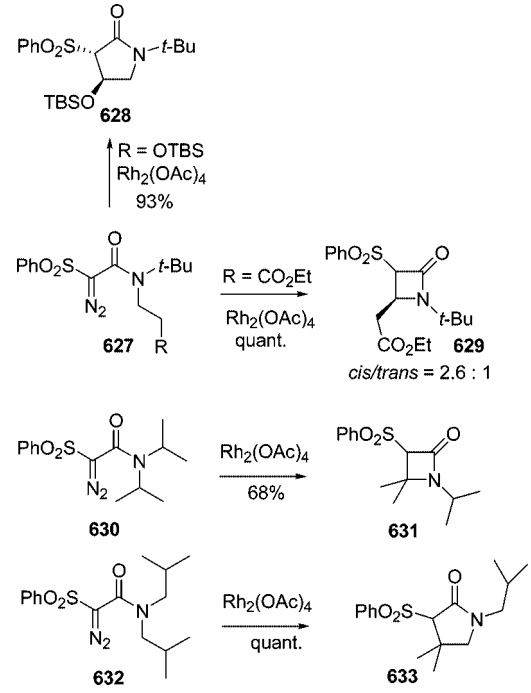
Quinoline β-lactams **625** were obtained by the Rh(II) catalyzed decomposition of the corresponding α-diazoamides (Scheme 167, eq 3). The formation of the β-lactam as the sole product was justified on the basis of steric and stereoelectronic effects as shown also by the less selective behavior of ketone **624** (R = Me).[282]

Also α-diazo-α-(phenylsufonyl)acetamides can undergo the rhodium(II) catalyzed C−H insertion to afford β-lactams, although this reaction was reported as a side reaction for the formation of γ-lactams. The reaction was revealed to be sensitive to stereoelectronic effects (Scheme 168).[283] Similar behavior was described for α-diazo-α-(dialkylphosphoryl)-acetamides for the synthesis of phosphoryl substituted β- and γ-lactams.[284]

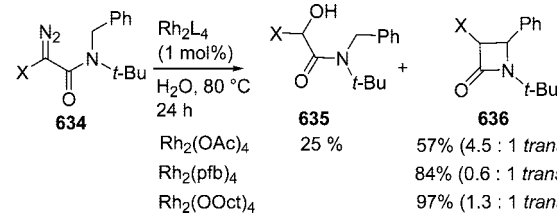
Scheme 167



Scheme 168

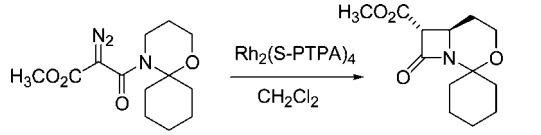


Scheme 169

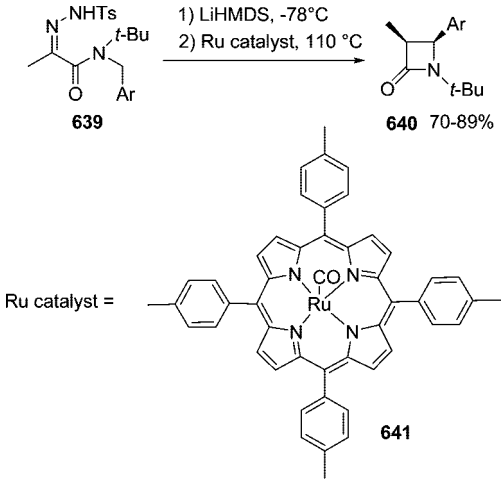


This reaction can also be performed in water or ionic liquids.[285] The advantage of using water as the reaction medium consists of the solubility and stability of the catalyst that makes its recycle easier. For reactions in water, it was revealed to be more efficient to use less polar Rh(II) catalyst as well as less polar substituents on the amide groups (Scheme 169).[286]

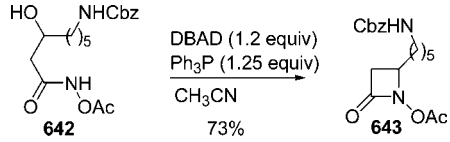
Scheme 170



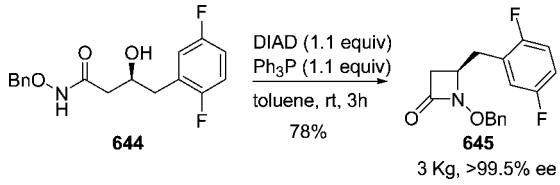
Scheme 171



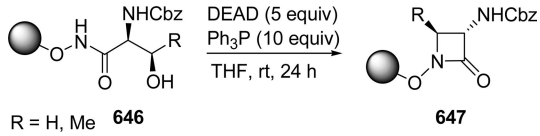
Scheme 172



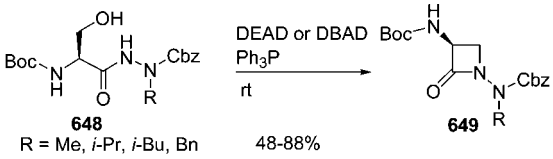
Scheme 173



Scheme 174



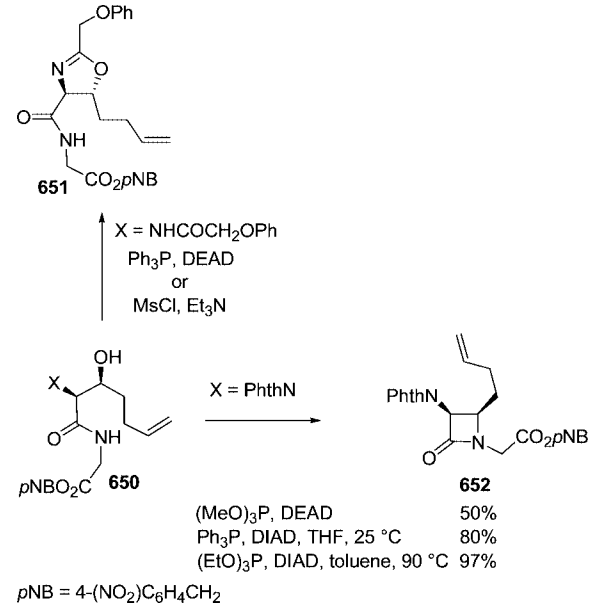
Scheme 175



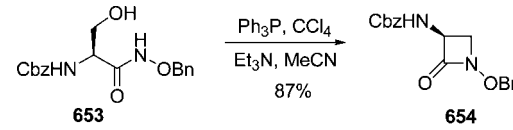
A few examples of the enantioselective version of this reaction are reported using enantiopure Rh(II) catalysts. Dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate [Rh_2(S-PTPA)$_4$] induced an interesting level of enantioselectivity in the reaction of α-diazoamide **637** to afford *β*-lactam **638** (Scheme 170). [287]

More recently, the same authors developed another analogous catalyst based on an atropisomeric biaryl backbone.[288] Also, Ru(I) complexes like [$RuCl_2$(p-cymene)]$_2$[289]

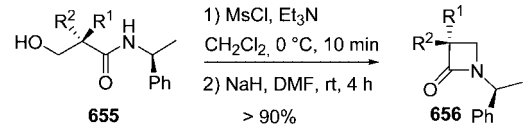
Scheme 176



Scheme 177



Scheme 178



R^1 = H, R^2 = Me, *i*-Pr, Bn; R^1 = Me, *i*-Pr, Bn, R^2 = H;
R^1 = Me, R^2 = Bn, *n*-Bu; R^1 = Bn, *n*-Bu, R^2 = Me

and several others[290] were revealed to be able to catalyze the carbenoid C−H insertion of α-diazoacetamides, however, with the same problem of selectivity between *β*- and *γ*-lactams already evidenced with Rh catalysts.

Ruthenium porphyrin **641** effectively catalyzed the transformation of lithium tosylhydrazone salts **639** into the corresponding *β*-lactams. It is remarkable that the stereoselectivity of this reaction, i.e., exclusively *cis*-lactam was obtained, is complementary to the one catalyzed by Rh complexes, which are known to afford the *trans*-*β*-lactams (Scheme 171).[291]

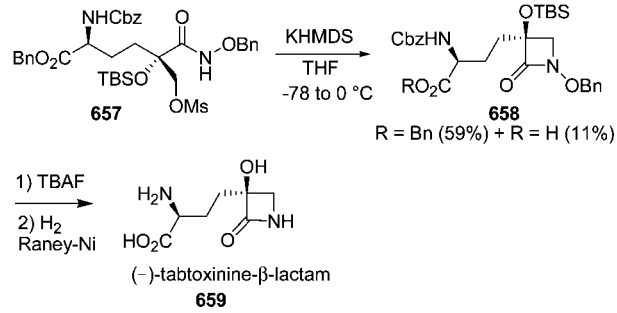
4.6.4. N−C4 Cyclization

The most commonly used approach to *β*-lactams by N−C4 bond formation is the cyclization of activated *β*-hydroxy amides.[292] Ring closure is performed in one step using the Mitsunobu protocol and related reactions, or by a two-step procedure where the alcohol is first converted into a good leaving group such as a mesylate, which is then displaced by the amidic nitrogen under basic conditions.

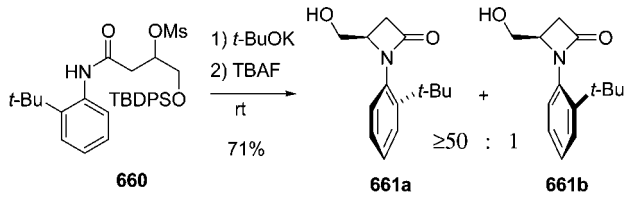
For example, hydroxamate **642** provided 1-(acetyloxy)azetidin-2-one **643** in good yield by treatment with PPh_3 and di-*tert*-butyl azodicarboxylate (DBAD) (Scheme 172).[293]

Optically active 1-(benzyloxy)azetidin-2-one **645** was prepared on a multi-kg scale from **644**. Cyclization occurred with complete inversion of configuration. The elimination

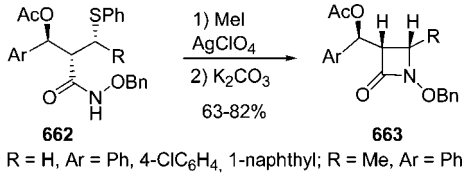
Scheme 179



Scheme 180



Scheme 181



side reaction was reduced to less than 3% when the reaction was carried out in toluene, whereas a large amount of styrene derivative was obtained when THF was used as a solvent (Scheme 173).[294]

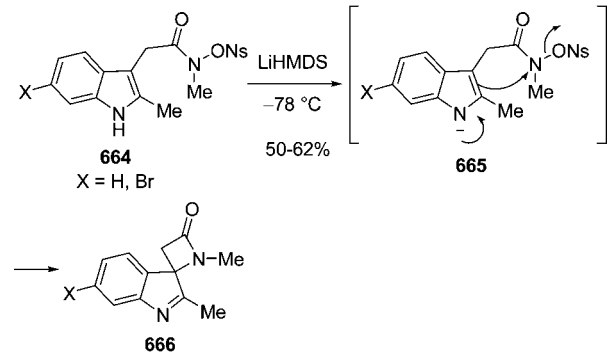
The method was successfully extended also to the synthesis of azetidinones on solid phase. In particular, polystyrene supported hydroxamates such as **646** underwent cyclization in THF with high conversions (Scheme 174). The supported β-lactams could be easily separated from the excess reagents and byproducts and then coupled on resin with amino acids. Eventually, the product was removed from the resin by reductive cleavage with SmI_2 to give the *N*-unsubstituted azetidinone. Alternatively, acidic cleavage of the trityl linker yields the corresponding 1-hydroxy-β-lactam.[295]

As well as *N*-hydroxyamides, acyl hydrazides are suitable acidic nucleophiles to undergo intramolecular Mitsunobu reaction. For example, 3-hydroxy derivatives **648** have been cyclized to β-lactams **649** (Scheme 175).[296]

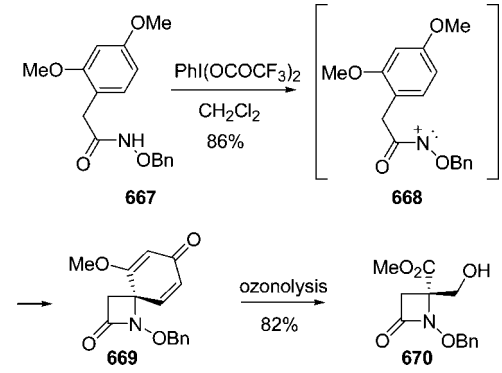
Unactivated amides are less reactive and cyclization efficiency can be strongly affected by substitution pattern and reaction conditions, as shown by the examples in Scheme 176. In the presence of the (phenoxyacetyl)amino on Cα (**650**, X = $NHCOCH_2OPh$), the formation of oxazoline **651** was favored under standard Mitsunobu conditions and by mesylation. The phthalimido group was a more suitable protecting group for the α-nitrogen, and **650** (X = NHPhTh) was converted into lactam **652** with excellent yield by treatment with triethyl phosphate and diisopropylazodicarboxylate (DIAD) in toluene at 90 °C (Scheme 176). Other reagents, solvents, and reaction conditions tested in cyclization of **650** were shown to be less convenient and selective.[297]

As an alternative, CCl_4 and triethylamine can be used in place of the azodicarboxylate reagent as first proposed by Miller. For example, the serine derivative **653** was converted to **654** in 87%

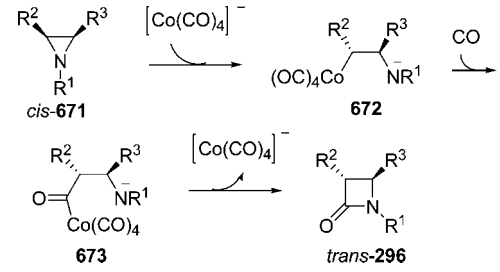
Scheme 182



Scheme 183



Scheme 184



yield (Scheme 177). These reagents were found to be more convenient especially for large-scale preparation because of the easy and fast product separation.[298]

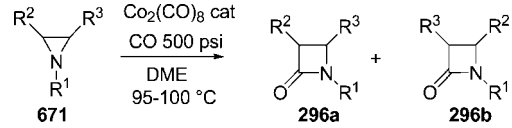
The two-step process, mesylation followed by base-induced cyclization, applied to enantiopure 3-hydroxypropanamides **655** afforded β-lactams **656** in excellent overall yields (Scheme 178). With the same substrates, the Mitsunobu reaction was effective only in the case of 2,2-disubstituted derivatives (**655**, $R^1 \neq H$ and $R^2 \neq H$).[299]

In the presence of KHMDS, compound **657** was converted into **658**, a synthetic precursor of the phytopathogenic tabtoxinine-β-lactam **659** (Scheme 179).[300]

The same approach was also applied to an atroposelective synthesis of *N-ortho-t*-butylphenyl β-lactam **661a** (Scheme 180).[301]

N-(Benzyloxy)-3-(phenylsulfanyl)propanamides **662** were stereoselectively cyclized to azetidinones **663** by conversion of the phenylsulfanyl moiety to sulfonium group followed by intramolecular S_N2 reaction under basic conditions. In all cases, the reaction afforded a sole diastereoisomer without any epimerization of the contiguous stereocenters (Scheme 181).[302] Cyclization of *N*-monosubstituted 3-bromopropanamides to β-lactams in the presence of electrogenerated anions has also been studied.[303]

Table 7. Cobalt Carbonyl-Catalyzed Carbonylation of Aziridines



	aziridine				β-lactams			
entry		R^1	R^2	R^3		**296a/296b**	yield (%)	ref
1		Bn	H	Me		100	90[a] (50)[b]	307d
2		Bn	H	CH_2OTBS		100	40	307b
3	*cis*	Bn	Me	CH_2OTBS	*trans*	92:8 (95:5)[a]	99.8 (95)[a]	307a,d
4	*trans*	Bn	Me	CH_2OTBS	*cis*	88:12	63	307a
5	*cis*	Bn	Me	CH_2OH	*trans*	100	84	307b
6	*trans*	Bn	Me	CH_2OH				307b
7	*cis*	Bn	Me	CH_2OAc	*trans*	86:14	82	307b
8	*cis*	Bn	Et	CH_2OTBS	*trans*	83:17	98	307b
9	*trans*	Bn	Et	CH_2OTBS	*cis*	73:27	60	307b
10	*cis*	Bn	Ph	CH_2OTBS	*trans*	100	95	307b
11	*trans*	Bn	Ph	CH_2OTBS	*cis*	100	40	307b
12	*cis*	Bn	Ph	CH_2OH	*trans*	100	79	307b
13	*trans*	Bn	Ph	CH_2OH	[c]	[c]	[c]	307b
14	*cis*	Bn	Ph	CH_2OAc	*trans*	100	86	307b
15	*cis*	Bn	Ph	CH_2NH_2	*trans*	100	68	307b
16	*cis*	Bn	Ph	CO_2Me				307b
17	*cis*	Bn	Ph	COMe				307b
18	*cis*	Bn	Ph	CHO				307b
19	*cis*	Bn	CH_2OTBS	CH_2OTBS	*trans*	100	90	307b
20	*cis*	Bn	$-(CH_2)_4-$		*trans*	100	80[a] (<5)[b]	307d
21	*trans*	Bn	CF_3	CH_2OTBS				307b
22		H	Ph	CH_2OTBS				307b
23	*cis*	CH_2CO_2Et	Ph	CH_2OTBS	*trans*	100	63	307b
24	*cis*	COMe	Ph	CH_2OTBS				307b
25	*cis*	*n*-Bu	$SiMe_3$	*n*-Bu	*trans*	100	74	307a
26	*cis*	Ts	$SiMe_3$	*n*-Bu				307a
27		Ts	H	Me		100	35[a] (99)[b]	307d

[a] Catalyst = $[(C_5H_5)_2Ti(THF)_2][Co(CO)_4]$; CO (900 psi), 60−90 °C. [b] Catalyst = $[(salph)Al(THF)_2][Co(CO)_4]$; CO (900 psi), 60−90 °C; [salph = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)phenylenediamine]. [c] *trans*-4-(Benzylamino)-3-methyldihydrofuran-2(3*H*)-one was recovered in 64% yield.

Finally, oxoindole spirofused azetidinones **666** were prepared by nucleophilic substitution at the amide nitrogen with the indole C3 (Scheme 182),[304] whereas spirolactam **669** was achieved by nitrenium ion spirocyclization and then converted into the 4,4-disubstituted azetidinone **670** by ozonolysis followed by aldehyde reduction (Scheme 183).[305]

4.7. From Heterocyclic Compounds

4.7.1. Aziridines

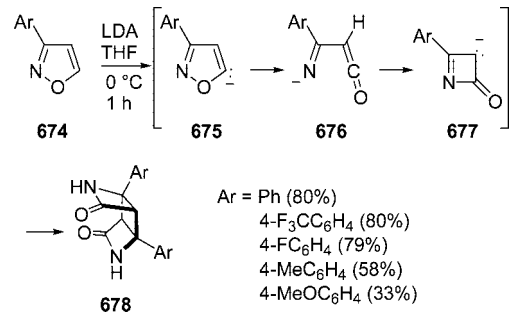
Recently, new developments in transition metal mediated carbonylative ring expansion of aziridines **671** to β-lactams **296** have been reported.[306] Carbonylation catalyzed by cobalt carbonyl under CO pressure goes through nucleophilic ring opening by the tetracarbonyl cobaltate anion $[Co(CO)_4]^-$, followed by CO insertion and ring closure to azetidinone (Scheme 184).

The process is highly regioselective and stereospecific. In particular, the CO insertion occurs preferentially on the less hindered and/or more electrophilic ring carbon, and the ring opening takes place with inversion of configuration. Accordingly, *trans*-β-lactams *trans*-**296** were obtained from *cis*-azetidines *cis*-**671** and *cis*-β-lactams were obtained from *trans*-azetidines.

The effects of stereochemistry and ring substituents have been analyzed (Table 7).[307] For example, carbonylation of *cis*-aziridines was more regioselective and efficient than carbonylation of the corresponding *trans*-isomers (Table 7, entries 3−6 and 8−13).

Carbonylation of 2-alkyl-3-phenyl- and 2-butyl-3-(trimethylsilyl)aziridine occurred exclusively at the benzylic and

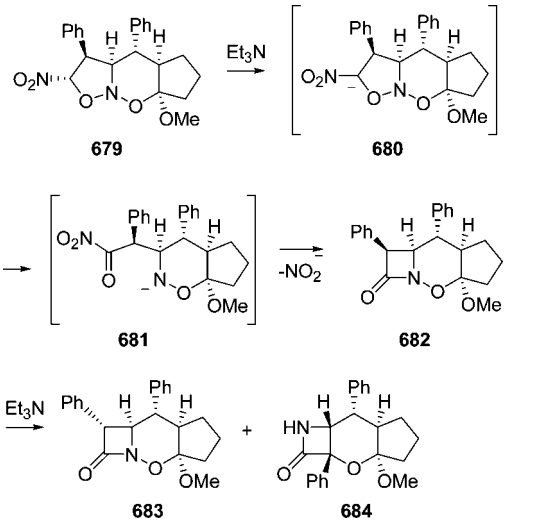
Scheme 185



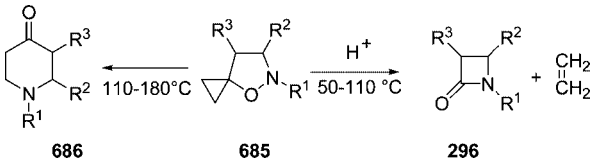
the silicon-bearing carbon, respectively (Table 7, entries 10−12, 14, 15, 23, and 25). Usually, electron-withdrawing substituents on ring carbon and nitrogen are detrimental for β-lactam formation (Table 7, entries 16−18 and 26). Analogously to $Co_2(CO)_8$, suitable [Lewis Acid][$Co(CO)_4$] complexes catalyze the regio- and stereoselective carbonylation of aziridines to β-lactams (Table 7, entries 1, 3, 20, and 27). In some cases, these discrete catalysts were shown to be very efficient. For example, 2-methyl-1-[(4-methylphenyl)sulfonyl]aziridine could be quantitatively converted into the corresponding *N*-tosyl 4-methylazetidinone by carbonylation under higher pressure of CO (900 psi) at 90 °C in the presence of a catalytic amount (5 mol %) of $[(salph)Al(THF)_2][Co(CO)_4]$ (Table 7, entry 27).

Rhodium-complexed dendrimers, supported on resin, were evaluated as catalysts for the carbonylation of aziridines. The dendritic catalysts, which showed comparable activity to the homogeneous analogue, could be recovered by simple

Scheme 186



Scheme 187



filtration and recycled without significant loss of activity.[308] Theoretical studies on the mechanism and selectivity of rhodium and cobalt carbonyl-catalyzed carbonylative ring expansion of aziridines have been reported.[309]

4.7.2. Isoxazoles and Related Compounds

Examples of β-lactams formation by ring contraction of isoxazole derivatives, such as 5-nitroisoxazolidines under heating, irradiation, or basic conditions,[310] 5,5-difluoroisoxazolidines with Raney nickel,[311] 5-phenylthioisoxazolidines with BuLi,[312] 5-cyanobicycloisoxazolidines with LDA,[313] and 5-(trimethylsilyl)isoxazolines with TBAF,[314] have been known for a long time. Recently, new examples of direct formation of β-lactams from isoxazole derivatives have been disclosed. 3-Arylisoxazoles **674** were converted into cage-shaped bis-β-lactams **678** by treatment with non-nucleophilic bases such as LDA, LHDMS, and LTMP. The process goes through C5 deprotonation, followed, in sequence, by ring opening to iminoketene **676**, cyclization to azetidinone anion **677**, and dimerization to **678** (Scheme 185).[315] The presence of EDG on the aryl group and the use of bases with noncoordinating cations were shown to lower the yield of **678** in favor of fragmentation products.

Analogously to 5-nitroisoxazolidines,[310] 2-nitrohexahydroisoxazolo[2,3-*b*][1,2]oxazines, obtained by tandem [4 + 2]/[3 + 2]-cycloaddition of enol ethers and β-nitrostirene, undergo a base-induced ring contraction to azetidinones through C5 deprotonation, N−O bond cleavage, and intramolecular substitution with loss of a nitrite anion.[316] For example, treatment of the nitroso acetal **679** with triethylamine at 0 °C afforded the *N*-organyloxy β-lactam **682** in 74% yield. In the presence of the amine at room temperature, **682** slowly rearranged to a mixture of β-lactams **683** and **684** (Scheme 186). A mechanism was proposed for the isomerization of *N*-organyloxy β-lactams to 3-organyloxy β-lactams.[316]

5-Spirocyclopropane isoxazolidines **685** (SPIXs) are very versatile intermediates that can be selectively converted into different heterocycles depending on the substitution pattern and the reaction conditions.[317] The peculiar chemistry of these compounds, easily prepared by 1,3-dipolar cycloaddition of nitrones with methylene cyclopropane derivatives, originates from the presence of the highly strained cyclopropane ring spirofused at the adjacent position of the relatively weak N−O bond. Thermally induced ring expansion of SPIXs to 4-tetrahydropipridones **686** (Brandi−Guarna reaction) is well-known and was applied to the synthesis of several natural alkaloids and related compounds (Scheme 187).[318]

More recently, a new general process leading to β-lactam formation has been discovered by heating SPIX in the presence of protic acids.[319] The process is chemoselective and occurs in the presence of 1 equiv, or a slight excess, of a protic acid such as TFA and *p*-TsOH at 50−110 °C in different kind of solvents (CH_3CN, toluene, and EtOH) (Scheme 187).

The proposed mechanism for the acidic thermal rearrangement considers the homolysis of the isoxazolidinium N−O bond followed by opening of the three-membered ring with strain relief and formation of a strong C=O double bond. Eventually, the four-membered ring closure and ethylene elimination leads to the observed product (Scheme 188).[320]

A nice aspect of this transformation is that the isoxazolidine stereocenters are fully preserved during the ring contraction. Accordingly, it is possible to take advantage of the highly stereoselective cycloaddition step to set up the azetidinone relative and absolute configuration.

Up to now, the scope of the reaction has been investigated by the synthesis of a series of variously substituted mono- and polycyclic azetidinone derivatives (Table 8). Examples of *cis*- and *trans*-3,4-disubstituted β-lactams were stereospecifically produced from the corresponding SPIXs (Table 8, entries 4−7), and enantiopure 3,4-*cis*-fused derivated were formed starting from amino acids such as alanine, valine, tryptophan, and proline, through an intramolecolar nitrone cycloaddition followed by the acid-induced ring contraction (Table 8, entries 16−19).

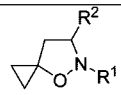
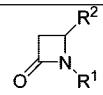
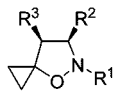
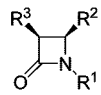
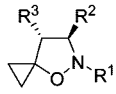
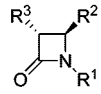
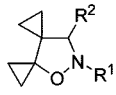
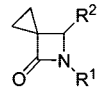
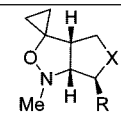
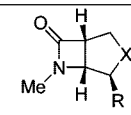
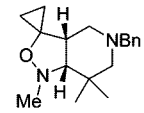
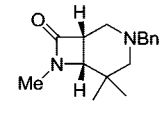
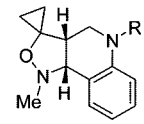
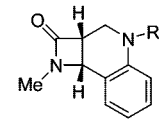
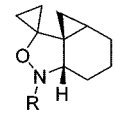
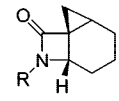
The reaction can be applied to bicyclopropylidene adducts providing an easy access to highly strained 3-spirocyclopropane β-lactams (Table 8, entries 8−13, 24, and 25). The spirofused derivatives **692** were also prepared via a one-pot three-component cascade reaction from *N*-substituted hydroxylamine salts, aldehydes, and bicyclopropylidene (**691**) in the presence of acetate under microwave heating (Scheme 189).[324]

Some highly reactive β-lactams were found to spontaneously undergo trifluoroacetolysis of the amide bond under the reaction conditions. For example, β-homoprolines such as **695** and the bicyclic β-amino acid **679** were directly obtained by acidic treatment of isoxazolidines **693** and **696**, respectively, through the intermediate formation of carbapename **694** and the highly strained tricyclic β-lactam **697** (Scheme 190).[325]

5. Concluding Remarks

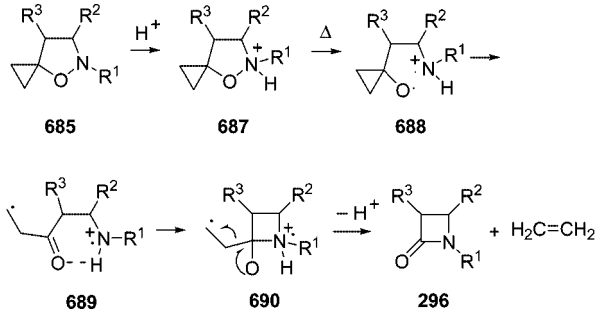
The impressive summary of new research described in the review regarding four-membered aza-heterocyclic compounds attests the importance they assume in the chemistry of organic compounds. The recent syntheses of these ring systems have much profited from the most modern synthetic

Table 8. Examples of β-Lactams Synthesized by Acidic Ring Contraction of SPIXs[a]

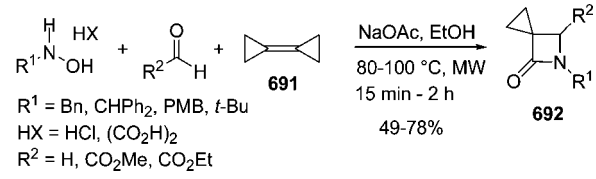
Entry	SPIX	β-lactam	Yield (%)	Ref
				
1	R^1= Me, R^2 = 2-ClC_6H_4		56	325a
2	R^1= Bn, R^2 = CO_2Et		91	325a
3	R^1= (*R*)-CHMePh, R^2 = CO_2Et		61	325a
				
4	(*rac*), R^1= Me, R^2 = Ph, R^3 = CO_2Me		30	325a
5	(*rac*), R^1= Bn, R^2 = Ph, R^3 = CH_2OH		67	325a
				
6	(*rac*), R^1= Me, R^2 = Ph, R^3 = CO_2Me		29	325a
7	(*rac*), R^1= Bn, R^2 = Ph, R^3 = CH_2OH		78	325a
				
8	R^1= Me, R^2 = Ph		96	321
9	R^1= Me, R^2 = 2-Py		96	321
10	R^1= Bn, R^2 = Ph		75	321
11	R^1= Bn, R^2 = CO_2Me		78	321
12	R^1= Bn, R^2 = CN		75	321
13	R^1= PMB, R^2 = CN		94	321
				
14	(*rac, dr=1:1-2*), X = CHOAc, R = H		63-92	320
15	(*dr>92:8*), X = CHO-(*S*)-*O*-Ac-lactyl		66	322
16	X = NTs, R = Me		60	319
17	X = NTs, R = *i*-Pr		63	320
18	X = NTs, R = CH_2-3-indolyl		57	320
19	X, R = $NCH_2CH_2CH_2$		47	320
20	(*rac*), X = O, R = H		60	320
				
21	(*rac*)		87	320
				
22	(*rac*), R = Ns		72	320
23	(*rac*), R = Ts		60	320
				
24	(*rac*), R = Me		66	325b,323
25	(*rac*), R = Bn		50	325b

[a] Solvent = toluene, CH_3CN; temperature = 50−110 °C; acid = TFA, pTsOH, 1−2 equiv; 2 min−12 h.

Scheme 188

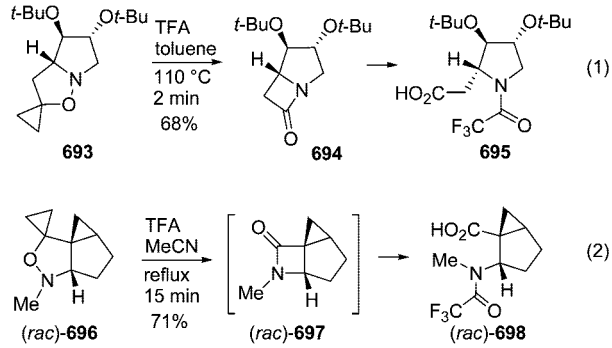


Scheme 189



methods derived from other fields of organic synthesis. In this sense, the biggest impact has been offered by the explosion, in recent years, of transition metal catalysis. Nevertheless, the challenge enforced by the four-membered ring formation has encouraged the researchers to modify or render more efficient the synthetic methodologies, with a consecutive feedback to other synthetic tasks. The main challenge for the future remains still the design of general methods for the obtainment of enantiopure compounds, and, in particular, the extension of the most efficient recent methods described to asymmetric synthesis, with special attention to transition metal catalyzed reactions.

Scheme 190



6. References

(1) For the most recent review on the subject, see: Singh, G. S.; D'hooghe, M.; De Kimpe, N. Azetidines, Azetines and Azetes: Monocyclic. In *Comprehensive Heterocyclic Chemistry III*; Stevens, C. V., Ed.; Elsevier: Oxford, U.K., 2008; Vol. 2, Chapter 2.01, p 1.

(2) (a) De Kimpe, N. 3- and 4-membered rings, with all fused systems containing 3- and 4-membered rings. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, U.K., 1996; Vol. 1B, Chapter 1.18, p 507. (b) Davies, D. E.; Starr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, U.K., 1984; Vol. 7, Part 5, p 237. (c) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds−Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 2, p 1. (d) Kurteva, V. Modern aspects of azetidine synthesis. In *Modern Approaches to the Synthesis of O- and N- Heterocycles*; Kaufman, T., Larghi, E., Eds.; Research Signpost: Kerala, India, 2007; Vol. 3, pp 45−71. (e) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

(3) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133–148.

(4) For selected recent reports on bioactive compounds containing the azetidine ring, see: (a) Evans, G. B.; Fumeaux, R. H.; Greatrex, B.; Murkin, A. S.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2008**, *51*, 948. (b) Honcharenko, D.; Barman, J.; Varghese, O. P.; Chattopadhyaya, J. *Biochemistry* **2007**, *46*, 5635. (c) Slade, J.; Bajwa, J.; Liu, H.; Parker, D.; Vivelo, J.; Chen, G. P.; Calienni, J.; Villhauer, E.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2007**, *11*, 825. (d) Ikee, Y.; Hashimoto, K.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 942. (e) Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Gillard, M.; Quere, L.; Stebbins, K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3077. (f) Kolocouris, N.; Zoidis, G.; Foscolos, G. B.; Fytas, G.; Prathalingham, S. R.; Kelly, J. M.; Naesens, L.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4358. (g) Yeh, C. H.; Wu, S. J.; Tsai, Y. F.; Chen, H. Y.; Lin, C. Y. *Plant Science* **2007**, *172*, 1124.

(5) (a) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1983**, *48*, 4043. (b) van Elburg, P. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *Tetrahedron Lett.* **1985**, 2809.

(6) Chloride leaving group: (a) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (b) Jin, J. Y.; Wu, X.; Tian, G. R. *Synth. Commun.* **2005**, *35*, 2535. (c) Blizzard, T. A.; DiNinno, F.; Morgan, J. D.; Chen, H. Y.; Wu, J. Y.; Gude, C.; Kim, S.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L.-Y.; Hayes, E. C.; DaSilva, C. A.; Tang, W.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3861. (d) Bell, T. W.; Choi, H.-J.; Harte, W.; Drew, M. G. B. *J. Am. Chem. Soc.* **2003**, *125*, 12196. (e) Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1299. (f) De Kimpe, N.; Boeykens, M.; Tourwé, D. *Tetrahedron* **1998**, *54*, 2619. (g) Olivo, H. F.; Hemenway, M. S.; Gezginci, M. H. *Tetrahedron Lett.* **1998**, *39*, 1309. (h) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S.; Kurihara, T. *Tetrahedron* **1996**, *52*, 14563. (i) De Kimpe, N.; Stevens, C. *Synthesis* **1993**, 89. (j) Huszthy, P.; Bradshaw, J. S.; Krakowiak, K. E.; Wang, T.; Dalley, N. K. *J. Heterocycl. Chem.* **1993**, *30*, 1197. (k) Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 2937. (l) Sulmon, P.; De Kimpe, N.; Schamp, N.; Tinant, B.; Declercq, J.-P. *Tetrahedron* **1988**, *44*, 3653. (m) Higgins, R. H.; Watson, M. R.; Faircloth, W. J.; Eaton, Q. L.; Jenkins, H., Jr *J. Heterocycl. Chem.* **1988**, *25*, 383. (n) Causey, D. H.; Mays, R. P.; Shamblee, D. A.; Lo, Y. S. *Synth. Commun.* **1988**, *18*, 205. (o) Higgins, R. H. *J. Heterocycl. Chem.* **1987**, *24*, 1489. (p) Higgins, R. H.; Eaton, Q. L.; Worth, L., Jr.; Peterson, M. V. *J. Heterocycl. Chem.* **1987**, *24*, 255. (q) Kobor, J.; Fülöp, F.; Bernath, G.; Sohar, P. *Tetrahedron* **1987**, 1887. (r) Bernath, G.; Kobor, J.; Fülöp, F.; Sohar, P.; Argay, G.; Kalman, A. *Tetrahedron* **1986**, 5139.

(7) Bromide leaving group: (a) Ma, S. H.; Yoon, D. H.; Ha, H. J.; Lee, W. K *Tetrahedron Lett.* **2007**, *48*, 269. (b) Van Brabandt, W.; Verniest, G.; De Smaele, D.; Duvey, G.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7100. (c) Matsuo, K.; Shichida, Y.; Nishida, H.; Nakata, S.; Okubo, M. *J. Phys. Org. Chem.* **2004**, *7*, 9. (d) D'hooghe, M.; Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 2703. (e) Wu, W.-L.; Caplen, M. A.; Domalski, M. S.; Zhang, H.; Fawzi, A.; Burnett, D. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3157. (f) Lai, G. *Synth. Commun.* **2001**, *31*, 565. (g) Starmans, W. A. J.; Walgers, R.W. A.; Thijs, L.; de Gelder, R; Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991. (h) Ciapetti, P.; Mann, A.; Shoenfelder, A.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3843. (i) Zhao, L.; Matsuyama, H.; Iyoda, M. *Chem. Lett.* **1996**, 827. (j) Axenrod, T.; Watnick, C.; Yazdekhasti, H.; Dave, P. R. *J. Org. Chem.* **1995**, *60*, 1959. (k) De Kimpe, N.; De Smaele, D. *Tetrahedron* **1995**, *51*, 5465. (l) De Kimpe, N.; De Smaele, D. *Tetrahedron Lett.* **1994**, *35*, 8023. (m) Hoshino, J.; Hiraoka, J.; Hata, Y.; Sawada, S.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 693. (n) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2921. (o) Dolle, R. E.; Li, C. S.; Shaw, A. N. *Tetrahedron Lett.* **1989**, *30*, 4723. (p) Juaristi, E.; Madrigal, D. *Tetrahedron* **1989**, *45*, 629.

(8) (a) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A *Tetrahedron Lett.* **2006**, *47*, 5393–5397. (b) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902. (c) Concellón, J. M.; Bernad, P. L.; Perez-Andres, J. A. *Tetrahedron Lett.* **2000**, *41*, 1231. (d) Ivanova, M. E.; Kurteva, V. B.; Lyapova, M. J.; Pojarlieff, I. G. *J. Chem. Res. Synop.* **1998**, 658.

(9) Shono, T.; Matsumura, Y.; Katoh, S.; Ohshita, J. *Chem. Lett.* **1988**, 1065.

(10) (a) Sayago, F. J.; Pradera, M. Á.; Gasch, C.; Fuentes, J. *Tetrahedron* **2006**, *62*, 915. (b) Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1434. (c) Ogier, L.; Turpin, F.; Baldwin, R. M.; Riché, F.; Law, H.; Innis, R. B.; Tamagnan, G. *J. Org. Chem.* **2002**, *67*, 3637. (d) Marinetti, A.; Hubert, P.; Genet, J.-P. *Eur. J. Org. Chem.* **2000**, 1815. (e) Fernández-Megía, E.; Montaos, M. A.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 6780. (f) Roos, G. H. P.; Donovan, A. R. *Tetrahedron: Asymmetry* **1999**, *10*, 991. (g) Aelterman, W.; De Kimpe, N.; Declercq, J.-P. *J. Org. Chem.* **1998**, *63*, 6. (h) Chou, S.-S. P.; Yu, Y.-J. *Tetrahedron Lett.* **1997**, *38*, 4803. (i) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett.* **1996**, 3203. (j) Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.-S. *Tetrahedron* **1996**, *52*, 3095. (k) Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Org. Chem.* **1996**, *61*, 5659. (l) Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K.; Terada, Y. *Tetrahedron* **1994**, *50*, 13335. (m) Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2083. (n) Dureault, A.; Portal, M.; Carreaux, F.; Depezay, J. C. *Tetrahedron* **1993**, *49*, 4201. (o) Giudicelli, M.-B.; Picq, D.; Anker, D. *Tetrahedron* **1992**, *48*, 6033. (p) Poch, M.; Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935. (q) Jacquet, J.-P.; Bouzard, D.; Kiechel, J.-R.; Remuzon, P. *Tetrahedron Lett.* **1991**, *32*, 1565.

(11) Tosylate leaving group: (a) Ghorai, M. K.; Kumar, A.; Halder, S *Tetrahedron* **2007**, *63*, 4779–4787. (b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 2471. (c) Prasad, A. K.; Roy, S.; Kumar, R.; Kalra, N.; Wengel, J.; Olsen, C. E.; Cholli, A. L.; Samuelson, L. A.; Kumar, J.; Watterson, A. C.; Gross, R. A.; Parmar, V. S. *Tetrahedron* **2003**, *59*, 1333. (d) Chong, J. M.; Sokoll, K. K. *Synth. Commun.* **1995**, *25*, 603. (e) Froehlich, J.; Sauter, F.; Blasl, K. *Heterocycles* **1994**, *37*, 1879. (f) Michaud, T.; Chanet-Ray, J.; Chou, S.; Gelas, J. *Carbohydr. Res.* **1997**, *299*, 253.

(12) (a) Miller, R. A.; Lang, F.; Marcune, B.; Zewge, D.; Song, Z. J.; Karady, S. *Synth. Commun.* **2003**, *33*, 3347. (b) Hillier, M. C.; Chen, C.-Y. *J. Org. Chem.* **2006**, *71*, 7885.

(13) (a) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 4017. (b) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Org. Biomol. Chem.* **2007**, *5*, 3510.

(14) Marinetti, A.; Jus, S.; Labrue, F.; Lemarchand, A.; Genet, J.-P.; Ricard, L. *Synthesis* **2001**, 2095.

(15) Yamanaka, H.; Yamane, Y.; Mukaiyama, T. *Heterocycles* **2004**, *63*, 2813.

(16) Kurteva, V. B.; Lyapova; M. J, *ARKIVOC* **2005**, 8.

(17) Funke, W. *Angew. Chem., Int. Ed. Engl.* **1969**, *80*, 70.

(18) Bartnik, R.; Cal, D.; Marchand, A. P.; Alihodzic, S.; Devasagayaraj, A. *Synth. Commun.* **1998**, *28*, 3949.

(19) (a) Marchand, A. P.; Rajagopal, D.; Bott, S. G.; Archibald, T. G. *J. Org. Chem.* **1995**, *60*, 4943. (b) Marchand, A. P.; Rajagopal, D.; Bott, S. G.; Archibald, T. G. *J. Org. Chem.* **1994**, *59*, 1608.

(20) (a) Hayashi, K.; Hiki, S.; Kumagai, T.; Nagao, Y. *Heterocycles* **2002**, *56*, 433. (b) Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T.; Tamai, S.; Abe, T.; Nagao, Y. *Tetrahedron Lett.* **1999**, *40*, 3761.

(21) Woznicka, M.; Urbaniak, K.; Mloston, G.; Heimgartner, H *Heterocycles* **2006**, *69*, 351.

(22) (a) Enders, D.; Gries, J. *Synthesis* **2005**, 3508. (b) Enders, D.; Gries, J.; Kim, Z.-S. *Eur. J. Org. Chem.* **2004**, 4471. (c) Bhanu Prasad, A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829. (d) Ohno, H.; Hamaguchi, H.; Tanaka, T. *J. Org. Chem.* **2001**, *66*, 1867. (e) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044.

(23) (a) de Figueiredo, R. M.; Froehlich, R.; Christmann, M. *J. Org. Chem.* **2006**, *71*, 4147. (b) Münch, A.; Wendt, B.; Christmann, M. *Synlett* **2004**, 2751.

(24) Gaertner, V. R. *J. Org. Chem.* **1967**, *32*, 2972.

(25) (a) Vuilhorgne, M.; Commerçon, A.; Mignani, S. *Chem. Lett.* **1999**, *28*, 605. (b) Carruthers, N. I.; Wong, S.-C.; Chan, T.-M. *J. Chem. Res., Synop.* **1996**, 430. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (d) Katritzky, A. R.; Cundy, D. J.; Chen, J. *J. Heterocycl. Chem.* **1994**, *31*, 271. (e) Kozikowski, A. P.; Fauq, A. H. *Synlett* **1991**, 783. (f) Archibald, T. G.; Gilardi, R.; Baum, K.; George, C. *J. Org. Chem.* **1990**, *55*, 2920. (g) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729. (h) Laguerre, M.; Boyer, C.; Leger, J. M.; Carpy, A. *Can. J. Chem.* **1989**, *67*, 1514. (i) Buriks, R. S.; Lovett, E. G. *J. Org. Chem.* **1987**, *52*, 5247.

(26) Constantieux, T.; Grelier, S.; Picard, J.-P. *Synlett* **1998**, 510.

(27) (a) Higgins, R. H.; Faircloth, W. J.; Baughman, R. G.; Eaton, Q. L. *J. Org. Chem.* **1994**, *59*, 2172. (b) Toda, T.; Karikomi, M.; Ohshima, M.; Yoshida, M. *Heterocycles* **1992**, *33*, 511.

(28) (a) Ngoc Tam, T. N.; Magueur, G.; Ourévitch, M.; Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2005**, *70*, 699. (b) Oh, C. H.; Rhim, C. Y.; You, C. H.; Cho, J. R. *Synth. Commun.* **2003**, *33*, 4297. (c) Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem.* **2006**, *45*, 3146.

(29) Karikomi, M.; Arai, K.; Toda, T. *Tetrahedron Lett.* **1997**, *38*, 6059.

(30) (a) Nadir, U. K; Arora, A *Indian J. Chem., Sect. B* **1998**, *37B*, 163. (b) Nadir, U. K.; Arora, A *Indian J. Chem., Sect. B* **1993**, *32B*, 297. (c) Nadir, U. K.; Sharma, Ms. R. L.; Koul, V. K. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 2015. (d) Nadir, U. K.; Sharma, R. L.; Koul, V. K. *Tetrahedron* **1989**, *45*, 1851. (e) Nadir, U. K.; Koul, V. K. *Synthesis* **1983**, 554. (f) Malik, S.; Nadir, U. K. *Synlett* **2008**, 108.

(31) Nadir, U. K.; Arora, A. *J. Chem. Soc., Perkin Trans.* **1995**, *1*, 2605.

(32) Karikomi, M.; De Kimpe, N. *Tetrahedron Lett.* **2000**, *41*, 10295.

(33) Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399.

(34) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, 3007.

(35) (a) Banide, E.; Lemau de Talance, V.; Schmidt, G.; Lubin, H.; Comesse, S.; Dechoux, L.; Hamon, L.; Kadouri-Puchot, C. *Eur. J. Org. Chem.* **2007**, 4517. (b) Lemau de Talance, V.; Banide, E.; Bertin, B.; Comesse, S.; Kadouri-Puchot, C. *Tetrahedron Lett.* **2005**, *46*, 8023.

(36) Eniade, A.; Martin, O. R. *Carbohydr. Res.* **2002**, *337*, 273.

(37) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 3335.

(38) (a) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995. (b) Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393.

(39) Churlaud, C.; Pornet, J.; Oniciu, D. C.; Katritzky, A. R. *Organometallics* **1999**, *18*, 4270.

(40) Uyehara, T.; Yuuki, M.; Masaki, H.; Matsumoto, M.; Ueno, M.; Sato, T. *Chem. Lett.* **1995**, 789.

(41) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091.

(42) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.

(43) (a) Emmer, G. *Tetrahedron* **1992**, *48*, 7165–7172. (b) Hanessian, S.; Fu, J.; Chiara, J. L.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157. (c) Hanessian, S.; Fu, J. *Can. J. Chem.* **2001**, *79*, 1812. (d) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238. (e) Sengupta, S.; Das, D. *Synth. Commun.* **1998**, *28*, 403. (f) Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 3169. (g) Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2277. (h) Desai, P.; Aubé, J. *Org. Lett.* **2000**, *2*, 1657. (i) Burtoloso, A. C. B.; Correia, C. R. D. *Tetrahedron Lett.* **2004**, *45*, 3355. (j) Burtoloso, A. C. B.; Correia, C. R. D. *J. Organomet. Chem.* **2005**, *690*, 5636.

(44) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324.

(45) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717.

(46) (a) Anzai, M.; Toda, A.; Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 7393. (b) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904.

(47) (a) Ma, S.; Yu, F.; Li, J.; Gao, W. *Chem.—Eur. J.* **2007**, *13*, 247. (b) Ma, S.; Gao, W. *Org. Lett.* **2002**, *4*, 2989.

(48) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255.

(49) De Nicola, A.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1994**, 879.

(50) Blythin, D. J.; Green, M. J.; Lauzon, M. J. R.; Shue, H.-J. *J. Org. Chem.* **1994**, *59*, 6098.

(51) (a) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297. (b) Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619. (c) Couty, F.; Evano, G.; Rabasso, N. *Tetrahedron: Asymmetry* **2003**, *14*, 2407.

(52) Couty, F.; Evano, G.; Vargas-Sanchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028.

(53) Sivaprakasam, M.; Couty, F.; David, O.; Marrot, J.; Sridhar, R.; Srinivas, B.; Rao, K. R. *Eur. J. Org. Chem.* **2007**, 5734.

(54) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2002**, *43*, 4633.

(55) (a) Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058. (b) Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* **2007**, 2500. (c) Couty, F.; David, O.; Durrat, F. *Tetrahedron Lett.* **2007**, *48*, 1027.

(56) (a) Carlin-Sinclair, A.; Couty, F.; Rabasso, N. *Synlett* **2003**, 726–728. (b) Bräuner-Osborne, H.; Bunch, L.; Chopin, N.; Couty, F.; Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. *Org. Biomol. Chem.* **2005**, *3*, 3926.

(57) (a) Kise, N.; Hirano, Y.; Tanaka, Y. *Org. Lett.* **2006**, *8*, 1323. (b) Kise, N.; Ozaki, H.; Moriyama, N.; Kitagishi, Y.; Ueda, N. *J. Am. Chem. Soc.* **2003**, *125*, 11591. (c) Shono, T.; K, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191.

(58) Yang, N. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913.

(59) (a) Wessig, P.; Schwarz, J. *Helv. Chim. Acta* **1998**, *81*, 1803. (b) Lee, Y. J.; Ling, R.; Mariano, P. S.; Yoon, U. C.; Kim, D. U.; Oh, S. W. *J. Org. Chem.* **1996**, *61*, 3304. (c) Pedrosa, R.; Andres, C.; Nieto, J.; Del Pozo, S. *J. Org. Chem.* **2005**, *70*, 1408. (d) Bach, T; Aechtner, T.; Neumüller, B. *Chem.—Eur. J.* **2002**, *8*, 2464. (e) Toda, F.; Tanaka, K.; Kakinoki, O.; Kawakami, T. *J. Org. Chem.* **1993**, *58*, 3783. (f) Ouazzani-Chadi, L.; Quirion, J.-C.; Troin, Y.; Gramain, J.-C. *Tetrahedron* **1990**, *46*, 7751. (g) Jeon, Y. T.; Lee, C.-P.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8847. (h) Khim, S.-K.; Cederstrom, E.; Ferri, D. C.; Mariano, P. S. *Tetrahedron* **1996**, *52*, 3195.

(60) (a) Schrader, T.; Steglich, W. *Synthesis* **1990**, 1153. (b) Aben, R. W. M.; Smit, R.; Scheeren, J. W. *J. Org. Chem.* **1987**, *52*, 365. (c) Nishio, T.; Omote, Y. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 2611. (d) Cabral, J.; Laszlo, P.; Montaufier, M. T. *Tetrahedron Lett.* **1988**, *29*, 547. (e) Nishio, T. *J. Org. Chem.* **1984**, *49*, 827. (f) Golankiewicz, K.; Jankowska, J.; Koroniak, H. *Heterocycles* **1984**, *22*, 67. (g) Jankowska, J.; Koroniak, H.; Golankiewicz, K. *Heterocycles* **1984**, *22*, 1363.

(61) (a) Fischer, G.; Fritz, H.; Rihs, G.; Hunkler, D.; Exner, K.; Knothe, L.; Prinzbach, H. *Eur. J. Org. Chem.* **2000**, 743. (b) Trupp, B.; Fritz, H.; Prinzbach, H.; Irngartinger, H.; Reifenstahl, U. *Chem. Ber.* **1991**, 1777. (c) Trupp, B.; Fritz, H.; Prinzbach, H. *Angew. Chem.* **1989**, 1381. (d) Marterer, W.; Prinzbach, H.; Rihs, G.; Wirz, J.; Lecoultre, J.; Heilbronner, E. *Helv. Chim. Acta* **1988**, *71*, 1937. (e) Fischer, G.; Fritz, H.; Prinzbach, H. *Tetrahedron Lett.* **1986**, *27*, 1269.

(62) (a) Dave, P. R.; Duddu, R.; Li, J.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1998**, *39*, 5481. (b) Dave, P. R.; Duddu, R.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1999**, *40*, 443. (c) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun.* **2002**, 444.

(63) Nakamura, I.; Nemoto, T.; Yamamoto, Y.; de Meijere, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5176.

(64) Bartholomew, D.; Stocks, M. J. *Tetrahedron Lett.* **1991**, *32*, 4795.

(65) (a) Kanoh, S.; Naka, M.; Nishimura, T.; Motoi, M. *Tetrahedron* **2002**, *58*, 7049. (b) Kanoh, S.; Nishimura, T.; Kita, Y.; Ogawa, H.; Motoi, M.; Takani, M.; Tanaka, T. *J. Org. Chem.* **2000**, *65*, 2253.

(66) (a) Black, D; St, C.; Johnstone, L. M. *Aust. J. Chem.* **1984**, *37*, 577. (b) Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1985**, *26*, 4115.

(67) (a) Bourguet, E.; Banères, J.-L.; Parello, J.; Lusinchi, X.; Girard, J.-P.; Vidal, J.-P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1561. (b) Bourguet, E.; Banères, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declercq, J.-P. *Org. Lett.* **2001**, *3*, 3067.

(68) (a) Varlamov, A. V.; Sidorenko, N. V.; Zubkov, F. I.; Chernyshev, A. I.; Turchin, K. F. *Chem. Heterocycl. Compd.* **2004**, *40*, 1097. (b) Lee, S. I.; Seung, S. U.; Choi, M. R.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett.* **2003**, *44*, 4705. (c) Barluenga, J.; Sanz, R.; Fañanás, F. J. *J. Org. Chem.* **1997**, *62*, 5953. (d) Gilardi, R.; George, C.; Karle, J.; Eaton, P. E.; Fisher, A. M. *J. Heterocycl. Chem.* **1993**, *30*, 1385. (e) Baxter, E. W.; Labaree, D.; Chao, S.; Mariano, P. S. *J. Org. Chem.* **1989**, *54*, 2893. (f) Davies, J. W.; Malpass, J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 686.

(69) (a) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. J. *J. Org. Chem.* **1996**, *61*, 2305. (b) Davies, H. M. L.; Matasi, J. J. *Tetrahedron Lett.* **1994**, *35*, 5209.

(70) (a) Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590. (b) Krow, G. R.; Lester, W. S.; Lin, G.; Fang, Y.; Carroll, P. J. *J. Org. Chem.* **2003**, *68*, 1626. (c) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Liu, N.; Yuan, J.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Zacharias, D. *J. Org. Chem.* **2001**, *66*, 1805. (d) Krow, G. R.; Yuan, J.; Fang, Y.; Meyer, M. D.; Anderson, D. J.; Campbell, J. E.; Carroll, P. J. *Tetrahedron* **2000**, *56*, 9227. (e) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558.

(71) Wang, C.; Tunge, J. A. *Org. Lett.* **2006**, *8*, 3211.

(72) Paquette, L. A.; Kakihana, T.; Kelly, J. F. *J. Org. Chem.* **1971**, *36*, 435.

(73) Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677.

(74) (a) Bando, T.; Harayama, H.; Fukazawa, Y.; Shiro, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1994**, *59*, 1465. (b) Tamaru, Y.; Bando, T.; Kawamura, Y.; Okamura, K.; Yoshida, Z.-i.; Shiro, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1498. (c) Tamaru, Y.; Hojo, M.; Yoshida, Z.-I. *J. Org. Chem.* **1988**, *53*, 5731.

(75) (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263. (b) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798. (c) Ojima, I.; Yamato, T.; Nakahashi, K. *Tetrahedron Lett.* **1985**, *26*, 2035. (d) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339.

(76) (a) Alcaide, B.; Almendros, P.; Salgado, N. R. *J. Org. Chem.* **2000**, *65*, 3310. (b) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. (c) Alcaide, B.; Esteban, G; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1994**, *59*, 7994. (d) Alcaide, B.; Saez, E. *Eur. J. Org. Chem.* **2005**, 1680. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem.* **1999**, *64*, 9596. (f) Alcaide, B; Salgado, N. R.; Sierra, M. A *Tetrahedron Lett.* **1998**, *39*, 467.

(77) (a) Van Driessche, B.; Van Brabandt, W.; D'Hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 6882. (b) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075. (c) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105.

(78) (a) Kvärnö, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 1145. (b) Kvärnö, L.; Werder, M.; Hauser, H.; Carreira, E. M. *J. Med. Chem.* **2005**, *48*, 6035. (c) Hartmann, R. W.; Hector, M.; Wachall, B. G.; Palusczak, A.; Palzer, M.; Huch, V.; Veith, M. *J. Med. Chem.* **2000**, *43*, 4437. (d) Receveur, J.-M.; Bryans, J. S.; Field, M. J.; Singh, L.; Horwell, D. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2329. (e) Holladay, M. W.; Bai, H.; Li, Y.; Lin, N.-H.; Daanen, J. F.; Ryther, K. B.; Wasicak, J. T.; Kincaid, J. F.; He, Y.; Hettinger, A.-M.; Huang, P.; Anderson, D. J.; Bannon, A. W.; Buckley, M. J.; Campbell, J. E.; Donnelly-Roberts, D. L.; Gunther, K. L.; Kim, D. J. B.; Kuntzweiler, T. A.; Sullivan, J. P.; Decker, M. W.; Arneric, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2797. (f) Lynch, J. K.; Holladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.-N.; Morton, H. E.; Dickman, D. A.; Arnold, W.; King, S. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2791. (g) Krämer, B; Franz, T.; Picasso, S.; Pruschek, P.; Jaeger, V *Synlett* **1997**, 295. (h) Suga, H.; Tanimoto, N.; Sinskey, A. J.; Masamune, S. *J. Am. Chem. Soc.* **1994**, *116*, 11197. (i) Hassner, A.; Wiegand, N. *J. Org. Chem.* **1986**, *51*, 3652. (j) Verkoyen, C.; Rademacher, P. *Chem. Ber.* **1985**, *118*, 653. (k) Jackson, M. B.; Mander, L. N.; Spotswood, T. M. *Aust. J. Chem.* **1983**, *36*, 779.

(79) Jego, J. M.; Carboni, B.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1992**, *129*, 554.

(80) Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.

(81) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585.

(82) Yadav, L. D. S.; Patel, R.; Srivastava, V. P. *Synett* **2008**, 583.

(83) (a) Shioiri, T.; Irako, N.; Sakakibara, S.; Matsuura, F.; Hamada, Y. *Heterocycles* **1997**, *44*, 519–530. (b) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 9457. (c) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265. (d) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1993**, *49*, 8211. (e) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 7917. (f) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 7921.

(84) (a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (b) Kobayashi, J.; Tsuda, M.; Cheng, J.; Ishibashi, M.; Takikawa, H.; Mori, K. *Tetrahedron Lett.* **1996**, *37*, 6775.

(85) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447.

(86) (a) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron Lett.* **1980**, *21*, 3395. (b) Isono, K; Funayama, K.; Suhadolnik, R. J. *Biochemistry* **1975**, *14*, 2992. (c) Isono, K; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (d) Isono, K; Suzuki, S. *Tetrahedron Lett.* **1968**, *9*, 1133.

(87) Di, Y.-T.; He, H.-P.; Wang, Y.-S.; Li, L.-B.; Lu, Y.; Gong, J.-B.; Fang, X.; Kong, N.-C.; Li, S.-L.; Zhu, H.-J.; Hao, X.-J. *Org. Lett.* **2007**, *9*, 1355.

(88) (a) Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 97. (b) Yajima, A; Takikawa, H.; Mori, K. *Liebigs Ann.* **1996**, 1083. (c) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689.

(89) (a) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977–979. (b) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283.

(90) (a) Ohshita, K.; Ishiyama, H.; Takahashi, Y.; Ito, J.; Mikami, Y.; Kobayashi, J. *Bioorg. Med. Chem.* **2007**, *15*, 4910. (b) Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett.* **1999**, *40*, 337. (c) Lin, G.-Q.; Liu, D.-G. *Heterocycles* **1998**, *47*, 337. (d) Beauhaire, J.; Ducrot, P.-H. *C. R. Acad. Sci., Ser. IIc: Chim.* **1999**, *2*, 477. (e) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813. (f) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841.

(91) (a) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1025. (b) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1035. (c) Hanessian, S.; Fu, J.-M.; Tu, Y.; Isono, K. *Tetrahedron Lett.* **1993**, *34*, 4153.

(92) (a) Kozikowski, A. P.; Tuckmantel, W.; Liao, Y.; Manev, H.; Ikonomovic, S.; Wroblewski, J. T. *J. Med. Chem.* **1993**, *36*, 2706. (b) Kozikowski, A. P.; Tuckmantel, W.; Reynolds, I. J.; Wroblewski, J. T. *J. Med. Chem.* **1990**, *33*, 1561. (c) Kozikowski, A. P.; Liao, Y.; Tueckmantel, W.; Wang, S.; Pshenichkin, S.; Surin, A.; Thomsen, C.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2559. (d) Burtoloso, A. C. B.; Correia, C. R. D. *Synlett* **2005**, 1559. (e) Hanessian, S.; Bernstein, N.; Yang, R.-Y.; Maguire, R. *Bioorg. Med. Chem. Lett.* **1999**, 1437. (f) Mangelinckx, S.; Boeykens, M.; Vliegen, M.; Van der Eycken, J.; De Kimpe, N. *Tetrahedron Lett.* **2005**, *46*, 525. (g) Sajjadi, Z.; Lubell, W. D. *J. Pept. Res.* **2005**, *65*, 298.

(93) Seebach, D.; Vettiger, T.; Mueller, H. M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687.

(94) Starmans, W. A.; Doppen, R. G.; Thijs, L.; Zwanenburg, B. *Tetrahedron: Asymmetry* **1998**, *9*, 429.

(95) Anderson, A. G.; Lok, R. *J. Org. Chem.* **1972**, *37*, 3953.

(96) (a) Zhao, G. L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975. (b) Zhao, G. L.; Huang, J.-W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737.

(97) Jiang, J.; Shah, H.; DeVita, R. J. *Org. Lett.* **2003**, *5*, 4101.

(98) (a) Sulmon, P.; De Kimpe, N.; Schamp, N. *J. Org. Chem.* **1988**, *53*, 4462. (b) Sulmon, P.; De Kimpe, N.; Schamp, N. *J. Chem. Soc., Chem. Commun.* **1985**, 715.

(99) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365.

(100) (a) Keller, L.; Sanchez, M. V.; Prim, D.; Couty, F.; Evano, G.; Marrot, J. *J. Organomet. Chem.* **2005**, *690*, 2306. (b) Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2004**, 3893. (c) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 605. (d) Shi, M.; Jiang, J.-K.; Shen, Y.-M.; Feng, Y.-S. *J. Chem. Res., Synop.* **2001**, 375. (e) Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. *Tetrahedron: Asymmetry* **1992**, *3*, 859.

(101) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(102) Wang, M.-C.; Zhao, W.-X.; Wang, X.-D.; Song, M.-P. *Synlett* **2007**, 3443.

(103) Zhang, Z.; Li, M.; Zi, G. *Chirality* **2007**, *19*, 802.

(104) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29.

(105) Gérard, S.; Raoul, M.; Sapi, J. *Eur. J. Org. Chem.* **2006**, 2440.

(106) (a) De Smaele, D.; Dejaegher, Y.; Duvey, G.; De Kimpe, N. *Tetrahedron Lett.* **2001**, 2373. (b) Salgado, A.; Dejaegher, Y.; Verniest, G.; Boeykens, M.; Gauthier, C.; Lopin, C.; Tehrani, K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231. (c) Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.-P.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763.

(107) Marchand, A. P.; Devasagayaraj, A.; Bott, S. G. *Heterocycles* **1998**, *49*, 149.

(108) Vansteenkiste, P.; Van Speybroeck, V.; Verniest, G.; De Kimpe, N.; Waroquier, M. *J. Phys. Chem. A* **2007**, *111*, 2797.

(109) For a selection of recent reviews on the biological activity of β-lactams, see: (a) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072. (b) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69. (c) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 93. (d) Buynak, J. D. *Curr. Med. Chem.* **2004**, *11*, 1951. (e) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, *10*, 1741. (f) Kidwai, M.; Sapra, P.; Bhushan, K. R. *Curr. Med. Chem.* **1999**, *6*, 195.

(110) For selected reviews on the "β-lactam synthon method", see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (b) Deshmukh, A.R.A.S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**,

11, 1889. (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (d) Ojima, I. F.; Delaloge, F *Chem. Soc. Rev* **1997**, *26*, 377.
(111) For some previous general reviews on the topic, see: (a) Coates, C.; Kabir, J.; Turos, E. *Sci. Synth.* **2005**, *21*, 609. (b) Walton, J. C. *Top. Curr. Chem.* **2006**, *264*, 163. (c) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631. (d) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377. (e) Gòmez-Gallego, M.; Mancheño, M. J.; Sierra, A. M. *Tetrahedron* **2000**, *56*, 5743. (f) Barrett, A. G. M.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615.
(112) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.
(113) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563.
(114) Staudinger, H. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1735.
(115) Pelotier, B.; Rajzmann, M.; Pons, J.-M.; Campomanes, P.; Lòpez, R.; Sordo, T. L. *Eur. J. Org. Chem.* **2005**, 2599.
(116) (a) Arumugam, N.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 8855–8857. (b) Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, *48*, 7140.
(117) Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, *48*, 8712.
(118) Nahmany, M.; Melman, A. *J. Org. Chem.* **2006**, *71*, 5804.
(119) Krishnawamy, D.; Govande, V. V.; Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2002**, *58*, 2215.
(120) Chen, R.; Yang, B.; Su, W. *Synth. Commun.* **2006**, *36*, 3167.
(121) Dandia, A.; Singh, R.; Sharma, P. *Heteroatom Chem.* **2003**, *14*, 468.
(122) (a) McGuire, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538. (b) Hegedus, L. S.; McGuire, L. M.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680.
(123) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.
(124) (a) Arrieta, A.; Cossìo, F. P.; Fernàndez, I.; Gòmez-Gallego, M.; Lecea, B.; Mancheno, M. J.; Sierra, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 11509. (b) Fernàndez, I.; Sierra, M. A.; Gòmez-Gallego, M.; Mancheno, M. J.; Cossìo, F. P. *Chem.—Eur. J.* **2005**, *11*, 5988.
(125) Sierra, M. A.; Mancheno, M. J.; Vicente, R.; Gòmez-Gallego, M. *J. Org. Chem.* **2001**, *66*, 8920.
(126) Woodgate, P. D.; Sutherland, H. S.; Rickard, C. E. F. *J. Organomet. Chem.* **2002**, *629*, 114.
(127) Brugel, T. A.; Hegedus, L. S. *J. Org. Chem.* **2003**, *68*, 8409.
(128) (a) Yamamoto, Y.; Watanabe, Y.; Ohnishi, S. *Chem. Pharm. Bull.* **1987**, *35*, 1860. (b) Yamamoto, Y.; Watanabe, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1871.
(129) Emtenas, H.; Soto, G.; Hultgren, S. J.; Marshall, G. R.; Almqvist, F. *Org. Lett.* **2000**, *2*, 2065.
(130) Xu, F.; Armstrong, J. D., III; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002.
(131) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129.
(132) Ito, S.; Hazamaki, H.; Hirasawa, Y.; Ohta, A.; Fujimori, K.; Tanaka, N.; Shiro, M. *Heterocycles* **2004**, *62*, 463.
(133) Linder, M. R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849.
(134) Sugimura, T.; Tei, T.; Okuyama, T. *Tetrahedron Lett.* **2003**, *44*, 3115.
(135) Maier, T. C.; Podlech, J. *Eur. J. Org. Chem.* **2004**, 4379.
(136) Hamaguchi, M.; Tomida, N.; Iyama, Y.; Oshima, T. *J. Org. Chem.* **2006**, *71*, 5162.
(137) Cremonesi, G.; Dalla Croce, P.; La Rosa, C. *Tetrahedron* **2004**, *60*, 93.
(138) Danheiser, R. L.; Okamoto, I.; Lawlor, M. D.; Lee, T. W. *Org. Synth.* **2003**, *80*, 160.
(139) Jiao, L.; Zhang, Q.; Zhang, S.; Xu, J. *Synthesis* **2006**, 659.
(140) Kikuchi, S.; Hashimoto, Y. *Heterocycles* **2006**, *68*, 453.
(141) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.
(142) Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W *J. Org. Chem.* **1982**, *47*, 2233.
(143) Sordo, J. A.; Gonzalez, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249.
(144) (a) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (b) Arrieta, A.; Lecea, B.; Cossìo, F. P. *J. Org. Chem.* **1998**, *63*, 5869.
(145) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(146) Alonso, E.; Lòpez-Ortiz, F.; del Pozo, C.; Peralta, E.; Macìas, A.; Gonzàlez, J. *J. Org. Chem.* **2001**, *66*, 6333.
(147) Alonso, E.; del Pozo, C.; Gonzàlez, J. *J. Chem. Soc., Perkin Trans. I* **2002**, 571.
(148) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.
(149) Brady, W. T.; Gu, Y. Q. *J. Org. Chem.* **1989**, *54*, 2838.
(150) Hu, L.; Wang, Y.; Li, B.; Du, D.-M.; Xu, J. *Tetrahedron* **2007**, *63*, 9387.
(151) Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334.
(152) Wang, Y.; Liang, Y.; Jiao, L.; Du, D. M.; Xu, J. *J. Org. Chem.* **2006**, *71*, 6983.
(153) Li, B.; Wang, Y.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 990.
(154) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461.
(155) Sharma, A. K.; Kumar, R. S.; Mahajan, M. P. *Heterocycles* **2000**, *52*, 603.
(156) Shaikh, A. L.; Puranik, V. G.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2006**, 5993.
(157) Thiagarajan, K.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **2000**, *56*, 7811.
(158) Coantic, S.; Mouysset, D.; Mignani, S.; Tabart, S.; Stella, L. *Tetrahedron* **2007**, *63*, 3205.
(159) Bianchi, L.; Dell'Erba, C.; Maccagno, M.; Mugnoli, A.; Novi, M.; Petrillo, G.; Sancassan, F.; Tavani, C. *Tetrahedron* **2003**, *59*, 10195.
(160) Jiao, L.; Zhang, Q.; Liang, Y.; Zhang, S.; Xu, J. *J. Org. Chem.* **2006**, *71*, 815.
(161) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.
(162) (a) Cossìo, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (b) Palomo, C.; Cossìo, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Romàn, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.
(163) Del Buttero, P.; Molteni, G. *Tetrahedron:Asymmetry* **2006**, *17*, 1319.
(164) (a) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *Adv. Synth. Catal.* **2004**, *346*, 1355. (b) Dondoni, A.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451.
(165) (a) Arun, M.; Joshi, S. N.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2003**, *59*, 2309. (b) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603.
(166) Macias, A.; Alonso, E.; del Pozo, C.; Venturini, A.; Gonzalez, J. *J. Org. Chem.* **2004**, *69*, 7004.
(167) Van Brabandt, W.; Vanwalleghem, M.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7083.
(168) Del Buttero, P.; Molteni, G.; Papagni, A.; Miozzo, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2555.
(169) Viso, A.; de la Pradilla, F.; Flores, A. *Tetrahedron Lett.* **2006**, *47*, 8911.
(170) Del Buttero, P.; Baldoli, C.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1927.
(171) (a) Kamikawa, K.; Sakamoto, T.; Tanaka, Y.; Uemura, M. *J. Org. Chem.* **2003**, *68*, 9356. (b) Tanaka, Y.; Sakamoto, T.; Kamikawa, K.; Uemura, M. *Synlett* **2003**, 519.
(172) Costa, M. F.; da Costa, M. R. G.; Curto, M. J. M.; Magrinho, M.; Damas, A. M.; Gales, L. *J. Organomet. Chem.* **2001**, *623*, 27.
(173) (a) Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Dessole, G.; Fochi, M.; Ricci, A. *Eur. J. Org. Chem.* **2005**, 3326. (b) Bonini, B. F.; Femoni, C.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **2001**, 1092.
(174) Fernàndez, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893–2897.
(175) (a) Fernandez, R.; Ferrete, A.; Lassaletta, J. M.; Lllera, J. M.; Martìn-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831. (b) Dìez, E.; Fernàndez, R.; Marquès-Lopez, E.; Martìn-Zamora, E.; Lassaletta, J. M. *Org. Lett.* **2004**, *6*, 2749.
(176) Hogan, P. C.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 15386.
(177) del Pozo, C.; Macìas, A.; Lòpez-Ortiz, F.; Maestro, M. a.; Alonso, E.; Gonzàlez, J. *Eur. J. Org. Chem.* **2004**, 535.
(178) Cremonesi, G.; Dalla Croce, P.; La Rosa, C. *Helv. Chim. Acta* **2005**, *88*, 1580.
(179) Cremonesi, G.; Dalla Croce, P.; Fontana, F.; Forni, A.; La Rosa, C. *Tetrahedron: Asymmetry* **2005**, *16*, 3371.
(180) Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766.
(181) Shinkre, B. A.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron: Asymmetry* **2003**, *14*, 453.
(182) Chincholkar, P. M.; Puranik, V. G.; Deshmukh, A. R. A. S. *Synlett* **2007**, 2242.
(183) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (b) Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351.
(184) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
(185) Shah, M. H; France, S; Lectka, T *Synlett* **2003**, 1937.
(186) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627.
(187) (a) Wack, H.; France, S.; Hafez, A. M.; Drury, W. J., III; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, *69*, 4531. (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592. (c) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
(188) (a) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *9*, 1603. (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.
(189) Huang, Y.; Calter, M. A. *Tetrahedron Lett.* **2007**, *48*, 1657.
(190) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.

(191) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.
(192) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.
(193) (a) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. *Tetrahedron Lett.* **2000**, *41*, 8621. (b) Wills, A. J.; Krishnan-Ghosh, Y.; Balasubramanian, S. *J. Org. Chem.* **2002**, *67*, 6646. (c) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron Lett.* **2004**, *45*, 4085. (d) Testero, S. A.; Mata, E. G. *Org. Lett.* **2006**, *8*, 4783. (e) Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett.* **2002**, *43*, 9445. (f) Gupta, P.; Singh, S. K.; Pathak, A.; Kundu, B. *Tetrahedron* **2002**, *58*, 10469. (g) Le Roy, I.; Mouysset, D.; Mignani, S.; Vuilhorgne, M.; Stella, L. *Tetrahedron* **2003**, *59*, 3719. (h) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G *Synthesis* **2005**, 530.
(194) (a) Delpiccolo, C. M.; Fraga, M. A.; Mata, E. G. *J. Comb. Chem.* **2003**, *5*, 208. (b) Delpiccolo, C. M.; Mendez, L.; Fraga, M. A.; Mata, E. G. *J. Comb. Chem.* **2005**, *7*, 331.
(195) Méndez, L.; Delpiccolo, C. M. L.; Mata, E. G. *Synlett* **2005**, 1563.
(196) Mèndez, L.; Testero, S. A.; Mata, E. G. *J. Comb. Chem.* **2007**, *9*, 189.
(197) Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **2004**, *69*, 9316.
(198) Gordon, K. H.; Balasubramanian, S. *Org. Lett.* **2001**, *3*, 53.
(199) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447.
(200) Gilman, H.; Speeter, H. *J. Am. Chem. Soc.* **1943**, *65*, 2250.
(201) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *111*, 77.
(202) Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035.
(203) (a) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461. (b) Gouge, V.; Jubault, P.; Quirion, J.-C. *Tetrahedron Lett.* **2004**, *45*, 773.
(204) Peng, W.; Zhao, J.; Zhu, S. *Synlett* **2006**, 296.
(205) Kanai, K.; Wakabayashi, H.; Honda, T. *Heterocycles* **2002**, *58*, 47.
(206) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611.
(207) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, *53*, 2769.
(208) Jan, S.-Z.; Ma, C.; Wang, Y.-G. *Synthesis* **2005**, 725.
(209) Yuan, Q.; Jian, S.-Z.; Wang, Y.-G. *Synlett* **2006**, 1113.
(210) Hashimoto, Y.; Ogasawara, T.; Hayashi, M.; Saigo, K. *Heterocycles* **2000**, *52*, 1001.
(211) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 216.
(212) Matsukawa, S.; Obu, K. *Chem. Lett.* **2004**, 1626.
(213) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, 994.
(214) (a) Hussein, M.; A.; Iida, A.; Tomioka, K *Tetrahedron* **1999**, *55*, 11219. (b) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715. (c) Kambara, T.; Hussein, M. A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1998**, *39*, 9055. (d) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060.
(215) Kanibara, T.; Tomioka, K. *Chem. Pharm. Bull.* **2000**, *48*, 1577.
(216) Fujieda, H.; Hata, S.; Yamada, K.-I.; Tomioka, K. *Heterocycles* **2005**, *66*, 603.
(217) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, 1471.
(218) (a) Schunk, S.; Enders, D. *Org. Lett.* **2000**, *2*, 907. (b) Schunk, S.; Enders, D. *J. Org. Chem.* **2002**, *67*, 8034.
(219) Hovestad, N. J.; Ford, A.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **2000**, *65*, 6338.
(220) (a) Jian, S.-Z.; Wang, Y.-G. *Chem. Lett.* **2004**, *33*, 866. (b) Jian, S.-Z.; Yuan, Q.; Wang, Y.-G. *Synthesis* **2006**, 1829.
(221) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563.
(222) Sharma, S. D.; Kanwar, S. *Synlett* **2004**, 2824.
(223) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1996**, *52*, 2573.
(224) For the use of 2-pyridylthioester enolates with imines, see:(a) Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025. (b) Annunziata, R.; Benaglia, A.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 5821. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Molteni, V. *Tetrahedron* **1995**, *51*, 8941.
(225) Benaglia, M.; Cozzi, M.; Puglisi, A. *Eur. J. Org. Chem.* **2007**, 2865.
(226) (a) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198. (b) Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. *Synlett* **2007**, 2321.
(227) (a) Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382. (b) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576.
(228) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.
(229) Zhao, L.; Li, C.-J. *Chem. Asian J.* **2006**, *1*−*2*, 203.
(230) (a) Gyarmaty, Z. Cs.; Liljeblad, A.; Argay, G.; Kàlmàn, A.; Bernath, G.; Kanerva, L. T. *Adv. Synth. Catal.* **2004**, *346*, 566. (b) Tanaka, M.; Oba, M.; Ichiki, T.; Suemune, H. *Chem. Pharm. Bull.* **2001**, *49*, 1178.
(231) Cossío, F. P.; Lecea, B.; Lopez, X.; Roa, G.; Arrieta, A.; Ugalde, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1450.
(232) Lee, K.-I.; Yoon, T.-H.; Shim, Y.-K.; Kim, W.-J. *Bull. Korean Chem. Soc.* **2001**, *22*, 939.
(233) (a) Borsuk, K.; Kazimierski, A.; Solecka, J.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Carbohydr. Res.* **2002**, *337*, 2005. (b) Borsuk, K.; Grzeszczk, B.; Szczukiewicz, P.; Przykorska, B.; Frelek, J.; Chmielewski, M. *Chirality* **2004**, *16*, 414. (c) Cierpucha, M.; Solecka, J.; Frelek, J.; Szczukiewicz, P.; Chmielewski, M. *Bioorg. Med. Chem.* **2004**, *12*, 405.
(234) (a) Lysek, R.; Furman, B.; Cierpucha, M.; Grzeszczyk, B.; Matyjasek, L.; Chmielewski, M. *Eur. J. Org. Chem.* **2002**, 2377. (b) Lysek, R.; Grzeszczyk, B.; Furman, B.; Chmielewski, M. *Eur. J. Org. Chem.* **2004**, 4177.
(235) (a) Thanh Dahn, T.; Bocian, W.; Kozerski, L.; Szczukiewicz, P.; Frelek, J.; Chmielewski, M. *Eur. J. Org. Chem.* **2005**, 429. (b) Thanh Dahn, T.; Borsuk, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2006**, 10928.
(236) Ruhela, D.; Chatterjee, P.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2005**, *3*, 1043.
(237) Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632.
(238) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262.
(239) For a selection of recent examples of the use of these reagents, see: (a) Turner, J. J.; Sikkema, F. D.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Synlett* **2001**, 1727. (b) Lee, J. C.; Kim, G. T.; Shim, Y. K.; Kang, S. H. *Tetrahedron Lett.* **2001**, *42*, 4519. (c) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 3106. (d) Vassiliou, S.; Dimitropoulos, C.; Magriotis, P. A. *Synlett* **2003**, 2398. (e) Whisler, M. C.; Beak, P. *J. Org. Chem.* **2003**, *68*, 1207. (f) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253. (g) Pandey, G.; Dumbre, S. G.; Khan, M. I.; Shabab, M.; Puranik, V. G. *Tetrahedron Lett.* **2006**, *47*, 7923.
(240) (a) Sharma, S. D.; Anand, R. D.; Kaur, G. *Synth. Commun.* **2004**, *34*, 1855. (b) Kanwar, S.; Sharma, S. D. *J. Chem. Res.* **2005**, 705. (c) Kanwar, S.; Sharma, S. D. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1748.
(241) Escalante, J.; González-Tototzin, M. A.; Aviña, J.; Muñoz-Muñiz, O.; Juaristi, E. *Tetrahedron* **2001**, *57*, 1883.
(242) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440.
(243) (a) Nagasaka, T.; Tsukada, A.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 2015. (b) Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93. (c) Bycroft, B. W.; Chhabra, S. R.; Kellam, B.; Smith, P. *Tetrahedron Lett.* **2003**, *44*, 973. (d) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Peregrina, J. M. *J. Org. Chem.* **2003**, *68*, 2889. (e) Stapon, A.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc.* **2003**, *125*, 8486.
(244) (a) Kim, S.-C.; Kim, H.-K. *Bull. Korean Chem. Soc.* **2000**, *21*, 1047. (b) Notz, W.; Tanaka, F.; Watanabe, S.-i.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F, III *J. Org. Chem.* **2003**, *68*, 9624. (c) Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, 4065.
(245) Maity, B. C.; Puranik, V. G.; Sarkar, A. *Synlett* **2002**, 504.
(246) Chen, H.-Y.; Patkar, L. N.; Ueng, S.-H.; Lin, C.-C.; Lee, A. S.-Y. *Synlett* **2005**, 2035.
(247) Shimizu, M.; Tachi, M.; Fukushima, S.; Hachiya, I. *Heterocycles* **2005**, *66*, 75.
(248) Palomo, C.; Aizpurua, J. M.; Balentovà, E.; Jimenez, A.; Oyarbide, J.; Fratila, R. M.; Miranda, J. I. *Org. Lett.* **2007**, *9*, 101.
(249) Fleck, T. J.; McWhorter, W. W., Jr.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612.
(250) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143.
(251) Davies, S. G.; Dupont, J.; Easton, R. J. C.; Ichihara, O.; McKenna, J. M.; Smith, A. D.; de Sousa, J. A. A. *J. Organomet. Chem.* **2004**, *689*, 4184.
(252) (a) Gedey, S.; Van der Eycken, J.; Fülöp, F. *Org. Lett.* **2002**, *4*, 1967. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587. (c) Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444. (d) Pirrung, M. C.; Das Sarma, K. *Synlett* **2004**, 1425. (e) Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456. (f) Kanizsai, I.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Tetrahedron Lett.* **2006**, *47*, 9113.
(253) Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett.* **2002**, *43*, 689.

(254) (a) Bella, A. F.; Jackson, L. V.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 421. (b) Scanlan, E. M.; Slawin, A. M. Z.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 716.
(255) Scanlan, E. M.; Walton, J. C. *Helv. Chim. Acta* **2006**, *89*, 2133.
(256) Grainger, R. S.; Innocenti, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3445.
(257) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901.
(258) Toyofuku, M.; Fujiwara, S.-i.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 9706.
(259) (a) Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2001**, *66*, 3538. (b) Bonache, M. A.; Gerona-Navarro, G.; Martín-Martínez, M.; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Synlett* **2003**, 1007. (c) Bonache, M. A.; Gerona-Navarro, G.; García-Aparicio, C.; Alías, M.; Martín-Martínez, M.; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Tetrahedron: Asymmetry* **2003**, *14*, 2161. (d) Bonache, M. A.; Cativiela, C.; García-López, M. T.; González-Muñiz, R. *Tetrahedron Lett.* **2006**, *47*, 5883.
(260) Bonache, M. A.; López, P.; Martín-Martínez, M.; García-López, M. T.; Cativiela, C.; González-Muñiz, R. *Tetrahedron* **2006**, *62*, 130.
(261) Gerona-Navarro, G.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2002**, *67*, 395.
(262) Pérez-Faginas, P.; O'Reilly, F.; O'Byrne, A.; García-Aparicio, C.; Martín-Martínez, M.; Pérez de Vega, M. J.; García-López, M. T.; González-Muñiz, R *Org. Lett.* **2007**, *9*, 1593.
(263) Gerona-Navarro, G.; Royo, M.; García-López, M. T.; Albericio, F.; González-Muñiz, R. *Mol. Diversity* **2003**, *6*, 75.
(264) Qian, X.; Zheng, B.; Burke, B.; Saindane, M. T.; Kronenthal, D. R. *J. Org. Chem.* **2002**, *67*, 3595.
(265) Feroci, M.; Lessard, J.; Orsini, M.; Inesi, A. *Tetrahedron Lett.* **2005**, *46*, 8517.
(266) (a) Stevens, C. V.; Vekemans, W.; Moonen, K.; Rammeloo, T. *Tetrahedron Lett.* **2003**, *44*, 1619. (b) Moonen, K.; Stevens, C. V. *Synthesis* **2005**, 3603.
(267) Van Speybroeck, V.; Moonen, K.; Hemelsoet, K.; Stevens, C. V.; Waroquier, M. *J. Am. Chem. Soc.* **2006**, *128*, 8468.
(268) Laurent, M.; Cérésiat, M.; Marchand-Brynaert, J. *Eur. J. Org. Chem.* **2006**, 3755.
(269) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438.
(270) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.
(271) (a) Scheffer, J. R.; Wang, K. *Synthesis* **2001**, 1253. (b) Natarajan, A.; Wang, K.; Ramamurthy, V.; Scheffer, J. R.; Patrick, B. *Org. Lett.* **2002**, *4*, 1443. (c) Kaanumalle, L. S.; Sivaguru, J.; Arunkumar, N.; Karthikeyan, S.; Ramamurthy, V. *Chem. Commun.* **2003**, 116. (d) Natarajan, A.; Mague, J. T.; Ramamurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 3568.
(272) Ohba, S.; Hosomi, H.; Tanaka, K.; Miyamoto, H.; Toda, F. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2075.
(273) Wang, R.; Chen, C.; Duesler, E.; Mariano, P. S.; Yoon, U. C. *J. Org. Chem.* **2004**, *69*, 1215.
(274) Toda, F.; Miyamoto, H.; Inoue, M.; Yasaka, S.; Matijasic, I. *J. Org. Chem.* **2000**, *65*, 2728.
(275) D'Annibale, A.; Nanni, D.; Trogolo, C.; Umani, F. *Org. Lett.* **2000**, *2*, 401.
(276) (a) Clark, A. J.; Battle, G. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409. (b) Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron* **2001**, *57*, 7629.
(277) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817.
(278) Snyder, J. P.; Padwa Stengel, T.; Arduengo, A. J., III; Jockish, A.; Kim, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 11318.
(279) Basak, A.; Mandal, S. *Tetrahedron Lett.* **2002**, *43*, 4241.
(280) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773. (c) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137.
(281) (a) Wee, A. G. H.; Duncan, S. C. *Tetrahedron Lett.* **2002**, *43*, 6173. (b) Doyle, M. P.; Hu, W.; Wee, A. G. H.; Wang, Z.; Duncan, S. C. *Org. Lett.* **2003**, *5*, 407. (c) Wee, A. G. H.; Duncan, S. C. *J. Org. Chem.* **2005**, *70*, 8372. (d) Wee, A. G. H.; Duncan, S. C.; Fan, G.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 297.
(282) Muroni, D.; Saba, A. *Arkivoc* **2005**, *xiii*, 1.
(283) (a) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539. (b) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259. (c) Flanigan, D. L.; Yoon, C. H.; Jung, K. W. *Tetrahedron Lett.* **2005**, *46*, 143.
(284) (a) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798. (b) Gois, P. M. P.; Candeias, N. R.; Afonso, C. A. M. *J. Mol. Catal., A: Chem.* **2005**, *227*, 17.
(285) Gois, P. M. P.; Afonso, C. a. M. *Tetrahedron Lett.* **2003**, *44*, 6571.
(286) (a) Candeias, N. R.; Gois, P. M.; Afonso, C. A. M. *Chem. Commun.* **2005**, 391. (b) Candeias, N. R.; Gois, P. M.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489.
(287) Anada, M.; Kitagaki, S.; Hashimoto, S. *Heterocycles* **2000**, *52*, 875.
(288) Hikichi, K.; Kitagaki, S.; Anada, M.; Nakamura, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Heterocycles* **2003**, *61*, 391.
(289) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081.
(290) Grohmann, M.; Maas, G. *Tetrahedron* **2007**, *63*, 12172.
(291) Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535.
(292) For a previous review, see:(a) Miller, M. J. *Chem. Soc. Rev.* **1986**, *19*, 49.
(293) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 35.
(294) Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949.
(295) Meloni, M. M.; Taddei, M. *Org. Lett.* **2001**, *3*, 337.
(296) Malachowski, W. P.; Tie, C.; Wang, K.; Broadrup, R. L. *J. Org. Chem.* **2002**, *67*, 8962.
(297) (a) Misner, J. W; Fisher, J. W.; Gardner, J. P.; Pedersen, S. W.; Trinkle, K. L.; Jackson, B. G.; Zhang, T. Y. *Tetrahedron Lett.* **2003**, 5991. (b) Jackson, B. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reinhard, M.; Kroeff, E. P.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y. *Tetrahedron* **2000**, *56*, 5667.
(298) Strazzolini, P.; Dall'Arche, M. G.; Zossi, M.; Pavsler, A. *Eur. J. Org. Chem.* **2004**, 4710.
(299) Lee, H. S.; Park, J. D.; Kim, D. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 467.
(300) Kiyota, H.; Takai, T.; Saitoh, M.; Nakayama, O.; Oritani, T.; Kuwahara, S. *Tetrahedron Lett.* **2004**, *45*, 8191.
(301) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539.
(302) Kamimura, A.; Morita, R.; Matsuura, K.; Mitsudera, H.; Shirai, M. *Tetrahedron* **2003**, *59*, 9931.
(303) Feroci, M.; Orsini, M.; Palombi, L.; Rossi, L.; Inesi, A. *Electrochim. Acta* **2005**, *50*, 2029.
(304) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025.
(305) (a) Wardrop, D. J. B.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271. (b) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *59*, 149.
(306) For a previous review on the topic, see: Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414.
(307) (a) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (b) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801. (c) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2445. (d) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781.
(308) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558.
(309) (a) Ardura, D.; López, R.; Sordo, T. L. *J. Org. Chem.* **2006**, *71*, 7315. (b) Ardura, D.; López, R. *J. Org. Chem.* **2007**, *72*, 3259.
(310) (a) Padwa, A.; Koeheler, K. F.; Rodriguez, A. *J. Am. Chem. Soc.* **1981**, *103*, 4974. (b) Padwa, A.; Koeheler, K. F.; Rodriguez, A. *J. Org. Chem.* **1984**, *49*, 282.
(311) Purrington, S. T.; Sheu, K.-W. *Tetrahedron Lett.* **1992**, *33*, 3289.
(312) Di Nunno, L.; Scilimati, A. *Tetrahedron* **1993**, *49*, 10965.
(313) Aurich, H. G.; Quintero, J.-L. R. *Tetrahedron* **1994**, *50*, 3943.
(314) Ahn, C.; Kennington, J. W., Jr.; DeShong, P. *J. Org. Chem.* **1994**, *59*, 6282.
(315) Di Nunno, L.; Vitale, P.; Scilimati, A.; Simone, L.; Capitelli, F. *Tetrahedron* **2007**, *63*, 12388.
(316) van Berkom, L. W. A.; Kuster, G. J. T.; de Gelder, R.; Scheeren, H. W. *Eur. J. Org. Chem.* **2004**, 4397.
(317) Cordero, F. M.; De Sarlo, F.; Brandi, A. *Monatsh. Chem.* **2004**, *135*, 649.
(318) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.
(319) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, *122*, 8075.
(320) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Paschetta, V.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Org. Chem.* **2003**, *68*, 3271.
(321) Zanobini, A.; Gensini, M.; Magull, J.; Vidoviæ, D.; Kozhushkov, S. I.; Brandi, A. *Eur. J. Org. Chem.* **2004**, 4158.
(322) Paschetta, V.; Cordero, F.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaün, J. *Syn. Lett.* **2001**, 1233.
(323) Marradi, M.; Brandi, A.; de Meijere, A. *Synlett* **2006**, 1125.
(324) Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 1251.
(325) (a) Cordero, F. M.; Salvati, M.; Pisaneschi, F.; Brandi, A. *Eur. J. Org. Chem.* **2004**, 2205. (b) Marradi, M.; Brandi, A.; Magull, J.; Schill, H.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 5485.

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