CHEMICAL REVIEWS

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α-Amido Sulfones as Stable Precursors of Reactive *N*-Acylimino Derivatives

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Marino Petrini received his Laurea degree in Chemistry in 1980 (University of Camerino). In 1983, he became Research Associate in Organic Chemistry at the University of Camerino, and during the period 1987–1988, he was a visiting scientist at the University of Montreal (Prof. S. Hanessian). In 1992, he was appointed Associate Professor and then (in 2004) Full Professor in Organic Chemistry at the University of Camerino. His research interests mainly deal with the following topics: synthesis and reactivity of aliphatic and aromatic nitrocompounds, reactivity of organometallic reagents toward carbon and nitrogen electrophiles, synthesis of natural products features of enhanced biological activity, and synthesis and reactivity of imino derivatives.

1. Introduction

Nucleophilic addition to carbon−nitrogen double bonds is one of the most practiced methods for the synthesis of nitrogen derivatives.[1−4] In terms of reactivity, a logical comparison with the carbonyl group immediately evidences a lower electrophilicity of the azomethine carbon that introduces several limitations in the utlilization of these unsaturated derivatives. The most serious side process that often occurs working with C=X derivatives is a competitive enolization that definitively hampers any efficient addition. To overcome this problem, various synthetic efforts have been done as the development of new nucleophilic systems was endowed with a consistent reactivity but featured by a low basicity. Organocerium, alkyl cuprates, and other allyl-based organometallic reagents have been successfully used with a variety of imino derivatives.[5−7] In a complementary approach, it is also possible to modify the electrophilic aptitude of the C=N bond through a proper choice of the nitrogen-linked group. Coordination of the nitrogen lone pair with Lewis acids can have a beneficial effect on the reactivity of the imino derivative, although several nucleophilic reagents are often incompatible with the presence of these acidic activators.[8] Electron-withdrawing substituents at the nitrogen atom are also able to exert a marked enhancement of the reactivity of the imino derivative. In this

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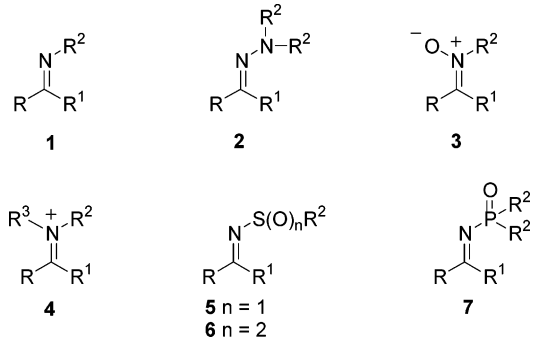
Scheme 1

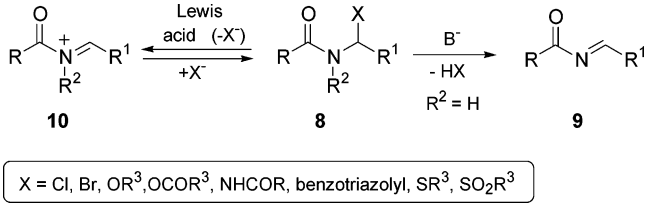


context, it is important to remark that when optically active activating groups are employed, a stereocontrolled addition of the nucleophilic reagent can be easily achieved.[9] When primary amines are the final targets of the synthetic procedure, an easy cleavage of the activating group on nitrogen is often desirable. This is not always a trivial task, and an outlook of the most important synthetically useful imino derivatives, currently used in many conventional preparative processes, is displayed in Scheme 1. Alkyl or arylimines **1** and hydrazones **2** are sufficiently stable to be prepared and stored at least for some days in proper conditions.

However, these derivatives are not particularly reactive and removal of the nitrogen-linked group after the addition is often troublesome. Nitrones **3**, which can be considered as imine *N*-oxides, are more reactive than simple imines, and their reaction with nucleophilic reagents affords secondary hydroxylamines.[10,11] Nitrones can be prepared using several synthetic procedures, but their stability is strongly affected by the nature of substituents present in the structure. A consistent increase in the reactivity can be realized moving to iminium ions **4** that are obtained by *N*-alkylation of imines or acid-promoted elimination of suitable tertiary amines. These unstable, reactive cations are the electrophilic reagents involved in the Mannich reaction, a very popular procedure mainly used for the synthesis of β-dialkylamino carbonyl derivatives.[12−15] *N*-Sulfinylimines **5** (R^2 = *t*-Bu, *p*-tolyl) join the activating properties of the sulfinyl group with its configurational stability that provides a high diastereofacial selectivity for nucleophilic additions.[16,17] *N*-Tosylimines **6** (R^2 = *p*-tolyl) obtained from aromatic aldehydes are quite stable compounds, while the same derivatives obtained from aliphatic aldehydes must be freshly prepared and used immediately in order to avoid a rapid decomposition or a quick tautomerization to the more stable enamino derivative.[18] Recently, *N*-phosphinoylimines **7** have gained a particular importance in some catalytic processes leading to the preparation of enantioenriched primary amines.[19−22] Finally, *N*-acylimines **9**[23] and *N*-acyliminium ions **10**[24−30] are very electrophilic substrates although they are too unstable to be prepared and stored in whatever extent. Therefore, they must be formed in situ from suitable precursors **8** by means of an elimination process promoted by basic or acid reagents (Scheme 2).

Compounds of type **8** are often referred as amidoalkylating reagents and are featured by a good

Scheme 2



leaving group X that can be easily eliminated in proper conditions.[31] *N*-Acylimines **9** are obtained from compound **8** using a base of suitable strenght that ensures the irreversiblility of the elimination process. The equilibrium in which the *N*-acyliminium ion **10** is involved strongly depends on the acid promoter (usually a Lewis acid) and the nature of the acyl group on the nitrogen atom. As a matter of fact, cation stabilization is higher when the acyl moiety is a carbamate (**10**, R=OR^3) rather than an amide probably because of the increased availability of the carbamate nitrogen lone pair. At this point, it is clearly evident that a prompt access to α-substituted amides **8** is mandatory for the success of all procedures involving reactive intermediates **9** and **10**. α-Haloamides (**8**, X=Cl,Br) have found only occasional utilization as electrophilic substrates because of their instability.[32] α-Oxygenated amides and carbamates (**8**, X=OR^3, $OCOR^3$) are the most exploited precursors for both *N*-acylimines **9** and *N*-acyliminium ions **10**. These derivatives are quite stable compounds and can be prepared by electrochemical oxidation of amides, partial reduction of imides, and other reactions on imines.[28] Bisamides (**8**, X=NHCOR) have been mainly used in cycloaddition reactions,[33] although these compounds are also probable intermediates in the three-component synthesis of *N*-protected homoallylamines obtained mixing an aldehyde with a carbamate in the presence of allyltrimethylsilane and a Lewis acid.[34−36] α-Amidoalkyl benzotriazoles (**8**, X=benzotriazolyl) are readily prepared and are effective precursors of reactive intermediates **9** and **10**.[37] Arylthio frameworks are poor leaving groups that need strong electrophilic reagents to be eliminated from the corresponding *N*,*S*-acetals (**8**, X=SAr). On the contrary, the ability of the RSO_2 group to act as a good leaving group in elimination reactions is well-documented.[38] Therefore, the utilization of α-amido sulfones (**8**, X=SO_2R) as forerunners of *N*-acylimines **9** and *N*-acyliminium ions **10** takes advantage of the great stability of these precursors, which are mostly solid compounds, and of the prompt reactivity displayed both in acidic and in basic conditions. The aim of this review is to survey the synthetic opportunities offered by α-amido sulfones as precursors of reactive imino derivatives since their early discovery 40 years ago. In addition, the utilization of α-amido sulfones in processes other than the generation of *N*-acylimino derivatives, although limited in number, will be also considered.

2. Open Chain α-Amido Sulfones

2.1. General Syntheses

The three-components coupling leading to the synthesis of α-amido sulfones was pioneered by Engberts

Scheme 3

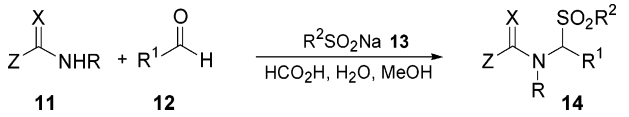
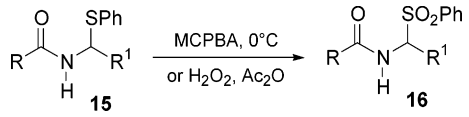


Table 1. Synthesis of α-Amido Sulfones 14 by Three-Components Coupling

	amido derivative **11**			aldehyde **12**	sulfinate **13**	sulfone **14**	
entry	X	Z	R	R^1	R^2	yield (%)	ref
1	O	OEt	H	H	Et	70	39
2	O	OEt	H	H	Ph	95	40
3	O	OEt	H	H	4-MePh	79	40
4	O	OEt	H	H	4-MeOPh	88	40
5	O	OEt	H	H	$PhCH_2$	85	40
6	O	OEt	H	Ph	4-MePh	70	40
7	O	OEt	H	3-ClPh	4-MePh	81	40
8	O	OEt	H	3-NO_2Ph	4-MePh	76	40
9	O	OEt	H	Me	4-MePh	83	40
10	O	OEt	H	*n*-Pr	4-MePh	87	40
11	O	OEt	Me	H	4-MePh	85	41
12	O	OEt	Me	*n*-Pr	4-MePh	83	41
13	O	OEt	$PhCH_2$	H	4-MePh	68	41
14	O	Me	H	H	4-MePh	83	41
15	O	Ph	H	H	4-MePh	74	42
16	O	$-(CH_2)_4-$		H	4-MePh	68	42
17	O	SEt	H	Et	4-MePh	92	41
18	O	SEt	H	Ph	4-MePh	95	41
19	O	NMe_2	H	H	4-MePh	79	43
20	S	OEt	H	Et	4-MePh	60	41
21	S	OEt	H	4-MePh	4-MePh	72	41
22	S	NMe_2	H	*n*-Pr	4-MePh	72	43
24	S	SEt	H	Et	4-MePh	84	41

Scheme 4

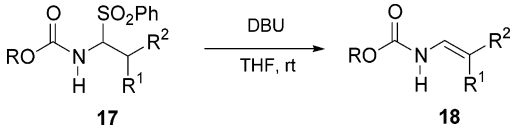


and Strating who in 1964 obtained a number of these sulfones by mixing ethyl carbamate, formaldehyde, and sodium sulfinates in acidic conditions.[39] Later on, the same authors prepared several amidosulfonyl derivatives **14** starting from suitable nitrogenated compounds **11**, alkyl or aryl aldehydes **12**, and sodium sulfinates **13** (Scheme 3 and Table 1).[40−43]

The obtained sulfones **14** are mostly stable solids that often precipitate from the reaction mixture and are easily recovered by a simple filtration. The classical procedure usually gives poor results when formamide is used to prepare sulfones **14**;[44,45] however, a slight modification in the reaction conditions allows a proper preparation of these amido derivatives.[46] Alternatively, α-amido sulfones **16** can be obtained by oxidation of the corresponding sulfides **15**[47] using hydrogen peroxide or MCPBA (Scheme 4).[48−50]

Other methods such as the substitution of chloride anion with sulfinates in *N*-acyl-α-chloro glycines or the rearrangement of α-sulfonylacyl azides have found only a narrow application in the chemistry of α-amido sulfones.[51,52] Reaction of nitrogen derivatives such as oximes, hydroxamic acids, and amines with aldehydes and sulfinic acids has been exploited, but the corresponding sulfones although prepared in good yield have not found any application in synthesis.[53,54]

Scheme 5



2.2. α-Amido Sulfones as Precursors of *N*-Acylimines

Base-assisted elimination of benzenesulfinic acid from sulfones **17** leads to the formation of reactive *N*-acylimines that promptly react with nucleophilic reagents to give the corresponding addition product. The whole process can be considered as a tandem elimination−addition reaction that can be carried out using a suitable base−nucleophile couple. Frequently, the nucleophilic reagent is basic enough to promote the elimination step so that an excess of this reagent alone ensures a rapid formation of the final product. Heteronucleophiles as well as carbanionic reagents can be made to react with α-amido sulfones, thus giving the opportunity to prepare a large array of amino derivatives. These target molecules can be produced in both racemic and enantiopure form exploiting diastereo and enantioselective processes. The utilization of basic systems with poor nucleophilic character such as DBU initially produces the corresponding *N*-acylimine that rapidly tautomerizes to the more stable enecarbamate with a marked preference for the *Z* stereoisomer (Scheme 5 and Table 2).[55]

Condensation of aldehydes **19** with arylsulfonylamides **20** in the presence of sodium 4-toluenesulfinate leads to the formation of the corresponding *N*-arylsulfonylamido sulfones **21** (Scheme 6).[56] These sulfones are quite unstable derivatives but can be profitably converted into *N*-sulfonyl aldimines **22** upon reaction with $NaHCO_3$ in a biphasic system H_2O/CH_2Cl_2.

2.2.1. Reaction with Organometallic Reagents and Other Nonstabilized Carbanions

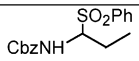
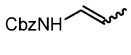
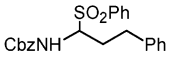
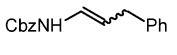
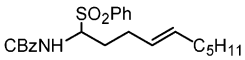
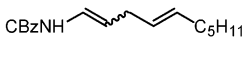
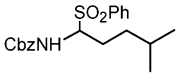
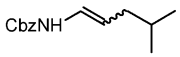
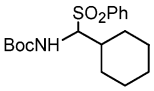
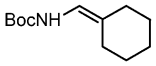
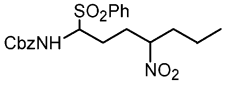
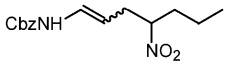
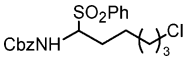
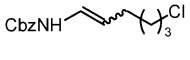
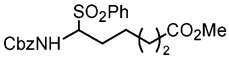
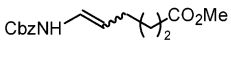
The reaction of fluorinated sulfones **23** with vinylmagnesium bromide **24** represents one of the first examples of the application of these compounds as *N*-acylimino derivatives in the addition reaction with carbanions (Scheme 7).[57] The obtained adducts **25** can be converted into the corresponding amino acids **26** by an oxidative cleavage of the double bond followed by the hydrolysis of the amido group.

A related procedure allows the preparation of partially fluorinated compounds as racemic 3,3-difluoro alanine.[58] Sulfones **27** obtained from enolizable aldehydes and carbamates react with the same Grignard reagent **24** providing an efficient entry to various *N*-protected homoallylamines **28** (Scheme 8).[59]

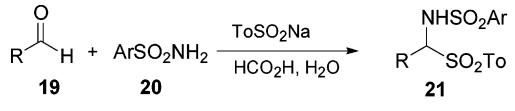
Analogously, functionalized 1-alkynyllithium reagents **29** react with sulfones **27** at low temperature giving *N*-carbamoylpropargylamines **31**. The same products can be otained by reaction of **27** (R^1 = aryl) with terminal alkynes **30** in the presence of CuBr in water under sonication (Scheme 9 and Table 3).[59,60]

Fully protected 1,2-amino alcohols **33** are prepared by reaction of sulfones **27** with benzyloxymethyllithium **32** (Scheme 10).[61] A suitable choice of the

Table 2. Synthesis of Enecarbamates 18 from α-Amido Sulfones 17

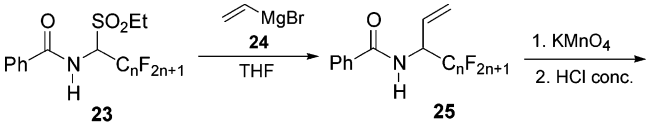
entry	sulfone **17**	enecarbamate **18**	*E:Z*	yield (%)
1			10:90	80
2			20:80	71
3			27:73	78
4			30.70	67
5				75
6			20:80	89
7			17 :83	90
8			16 :84	64

Scheme 6



R	Ar	**22** yield (%)
t-Bu	4-MePh	78
c-C_6H_{11}	Ph	74
i-Pr	Ph	55
Ph	4-MePh	63

Scheme 7

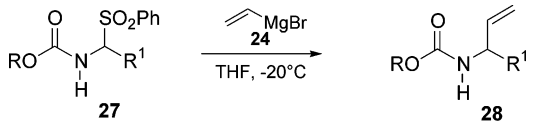


n	**25** yield (%)	**26** yield (%)
1	73	69
2	76	51
3	62	44

carbamoyl group in sulfone **27** (e.g., R = *t*-Bu) allows a selective regeneration of the amino and the hydroxy groups.

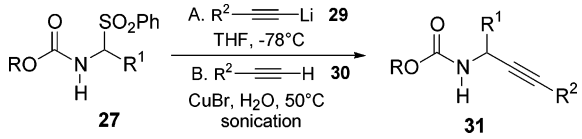
Recently, the first example of utilization of α-amidoaryltolyl sulfones **34** in the asymmetric catalytic ethyl transfer leading to optically active arylpropyl-*N*-formylamines **37** was reported (Scheme 11 and Table 4).[62] This highly enantioselective addition is catalyzed by [2.2]-paracyclophane-*N*,*O*-ligand **35** and most notably is carried out at temperatures ranging from −15 to 20 °C. Similar results can be obtained using a zinc complex between chiral BINOL derivatives and 1,2-diimines **36**.[63]

Scheme 8



R	R^1	**28** yield (%)
Bn	*n*-$C_5H_{11}CH{=}CH(CH_2)_2$	92
Bn	$Ph(CH_2)_2$	90
t-Bu	$BnO(CH_2)_4$	85
t-Bu	Ph	93

Scheme 9



A related procedure allowed the asymmetric catalytic aryl transfer on the same substrates **34** using a structurally similar catalyst **38** to afford diarylmethyl-*N*-formylamines **39** (Scheme 12).[64]

Deprotection of the formyl group in acidic conditions (concentrated HCl, MeOH, 50 °C) ensures the formation of the corresponding optically active amines racemization free and in good yield. The *N*-acyl group in α-amido sulfones **27** and **34** can be replaced by the *N*-phosphinoyl group that displays a comparable efficiency in assisting the base-promoted elimination of the arylsulfonyl group. Phosphinoylalkyl sulfones **41** can be prepared coupling an aldehyde **19** with diphenylphosphinic amide **40** in the presence of *p*-toluenesulfinic acid (Scheme 13 and Table 5).[65,66]

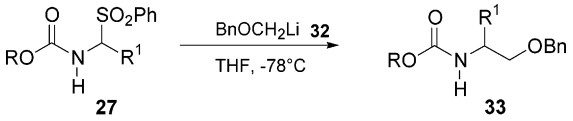
Sulfones **41** react with diethylzinc in the presence of the chiral catalyst **42** to afford the corresponding optically active arylpropyl-*N*-phosphinoylamines **43**

Table 3. Synthesis of Propargylamines 31 by Reaction of Sulfones 27 with Alkynyllithiums 29 or Alkynes 30

entry	R	R^1	R^2	method[a]	propargylamine **31** yield (%)	ref
1	*t*-Bu	Ph	Ph	A	78	59
2	*t*-Bu	Ph	Ph	B	15	60
3	Bn	*n*-C_7H_{15}	CO_2Me	A	75	59
4	Bn	$Ph(CH_2)_2$	$MOMOCH_2$	A	70	59
5	*t*-Bu	$BnO(CH_2)_4$	Ph	A	68	59
6	*t*-Bu	$Ph(CH_2)_2$	*n*-Bu	A	89	59
7	*t*-Bu	$Ph(CH_2)_2$	Me_3Si	A	77	59
8	*n*-Bu	4-MePh	Ph	B	70	60
9	*n*-Bu	1-naphthyl	Ph	B	71	60

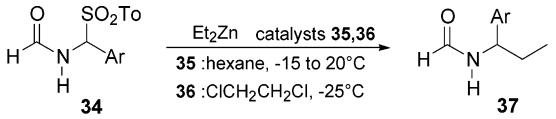
[a] Method A: alkynyllithium, THF, −78 °C. Method B: alkyne, CuBr, water, sonication, 50 °C.

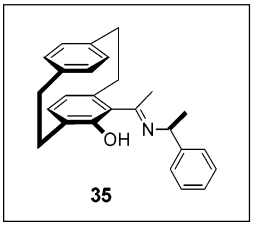
Scheme 10



R	R^1	**33** yield (%)
Bn	Ph	87
t-Bu	4-MeOPh	80
t-Bu	*i*-Pr	81
Bn	*t*-Bu	91

Scheme 11





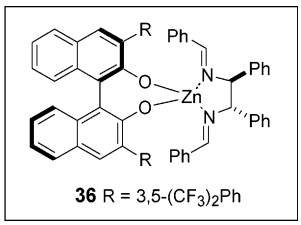
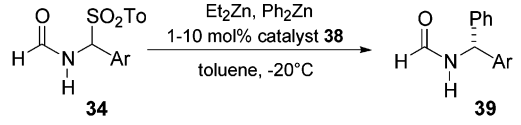


Table 4. Enantioselective Addition of Diethylzinc to Sulfones 34 Mediated by Chiral Catalysts 35 and 36

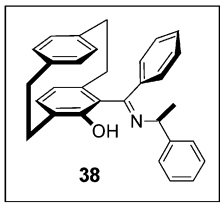
entry	Ar	catalyst	formamide **37** yield (%)	ee (%)
1	Ph	**35**	99	95(*R*)
2	Ph	**36**	91	83(*S*)
3	4-ClPh	**35**	99	89(*R*)
4	4-ClPh	**36**	80	90(*S*)
5	4-MeOPh	**35**	97	95(*R*)
6	4-MeOPh	**36**	91	71(*S*)
7	4-MePh	**35**	99	95(*R*)
8	4-MePh	**36**	78	86(*S*)
9	2,6-Cl_2Ph	**35**	98	95(*R*)
10	4-*t*-BuPh	**35**	99	75(*R*)
11	4-MeO_2CPh	**35**	90	94(*R*)
12	3-BrPh	**36**	90	93(*S*)
13	4-CNPh	**36**	75	94(*S*)
14	4-CF_3Ph	**36**	86	92(*S*)

in good yield and ees. The nature of the *O*-protecting group in sulfones **41** obtained from α-hydroxy aldehydes plays a fundamental role in the efficiency of the procedure (Table 5, entries 7−12). Lowering the

Scheme 12



entry	Ar	**39** yield (%)	ee (%)
a	4-MePh	99	97
b	4-ClPh	99	94
c	4-MeOPh	99	97
d	3-MePh	98	89
e	2,6-Cl_2Ph	99	95
f	4-*t*-BuPh	98	96
g	4-MeO_2CPh	99	95



Scheme 13

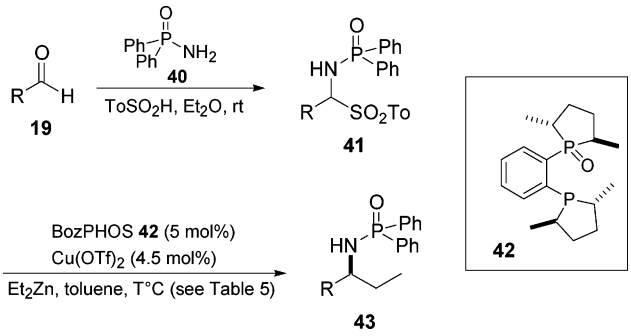


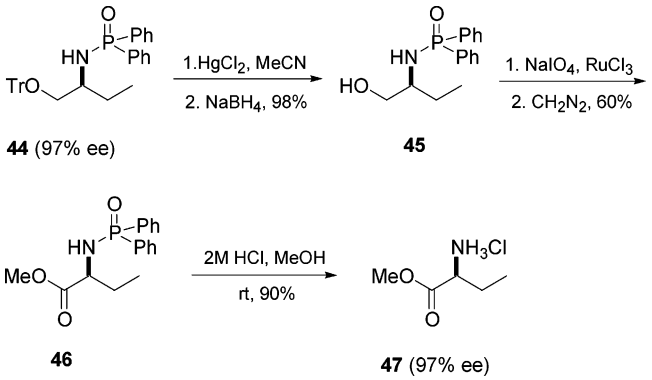
Table 5. Enantioselective Addition of Diethylzinc to *N*-Phosphinoyl Sulfones 41 Mediated by Chiral Catalysts 42

entry	R	sulfone **41** yield (%)	*T* (°C)	amine **43** yield (%)	ee (%)
1	Ph	71	−20	87	97
2	*c*-C_5H_{11}	95	−20	92	95
3	$Ph(CH_2)_2$	97	−20	98	96
4	C_6H_{13}	87	−20	98	95
5	*i*-Pr	88	−20	86	96
6	Me	91	−20	97	90
7	$BnOCH_2$	97	−20	95	84
8			−60	83	89
9	$TrOCH_2$	70	−60	84	97
10			−78	89	75
11	$PivOCH_2$	54	0	51	92
12			−20	69	87

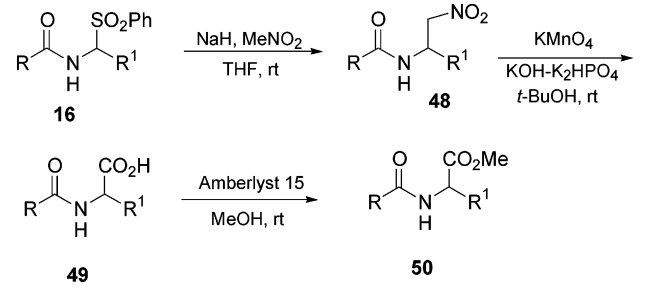
reaction temperature generally has a beneficial effect on the enantioselectivity of the process (Table 5, entries 7 and 8). However, quite surprisingly, some common *O*-protecting groups such as trityl and pivaloyl show an opposite trend since the ee values decrease upon lowering the temperature (Table 5, entries 9−12). Leaving groups other than *p*-toluenesulfonyl (e.g., succinoyl, benzotriazolyl, phenoxide, and methoxide) have been tested for this procedure. Phosphinoylphenyl benzotriazole only gives comparable results to sulfones **41** in terms of ee (96%), although the yield of the resulting adduct **43** is rather modest (38%).

Optically active amino alcohol derivative **44** upon selective removal of the trityl protecting group gives alcohol **45** that can be oxidized and methylated to amino ester derivative **46** (Scheme 14). Deprotection of the amino group in ester **46** can be realized under milder conditions as compared to formyl derivatives

Scheme 14



Scheme 15



37 and **39** giving amino ester **47** in good yield without any loss of the enantiomeric purity.

2.2.2. Reaction with Stabilized Carbanions

Stabilized carbanions are widely used as nucleophilic reagents in synthesis since they are easily prepared from functionalized precursors and obviously retain the activating functional group in the final molecule. Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position (cf. pk_a $MeNO_2$ = 10). Nitromethane anion reacts with α-amido sulfones **16** giving nitro derivatives **48** that can be readily converted into carboxylic acids **49** using alkaline $KMnO_4$ solutions and, after methylation, give *N*-acyl-α-amino acid esters **50** (Scheme 15 and Table 6).[67]

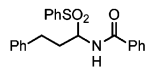
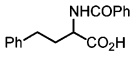
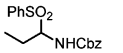
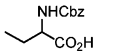
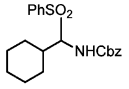
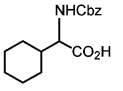
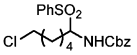
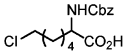
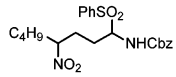
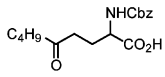
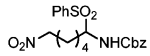
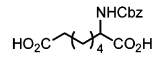
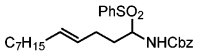
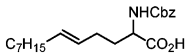
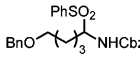
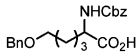
This procedure can be extended to optically active α-amidoalkylphenyl sulfones **53** obtained with high diastereoselectivity from (*R*)-2,3-*O*-isopropylidene gliceraldehyde **51** and carbamates **52** (Scheme 16).[68]

Chiral sulfones **53** react with the anion of nitromethane at room temperature with high diastereofacial preference for the *si* side on the intermediate *N*-acylimine **54**, giving preferentially the anti adducts **55** that upon Nef conversion and esterification produce β-hydroxy-α-amino acid esters **56** (Scheme 17).

This strategy can also be applied, starting from sulfone **57**, to the preparation of polyoxamic acid derivative **58**, which is an intermediate in the synthesis of polyoxins **59**, a known class of antibiotic derivatives (Scheme 18).

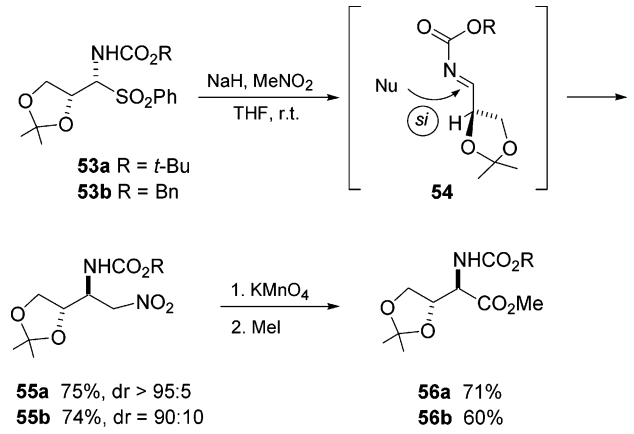
Optically active α-amido sulfone **60** prepared from L-prolinal affords 1,2-diamino acid derivative **61** by the usual procedure (Scheme 19).

Table 6. Base-Assisted Substitutions of Sulfones 16 into Nitro Derivatives 48 and Their Conversion to α-Amino Acids 49

entry	sulfone **16**	nitrocompound **48** yield (%)	amino acid **49**	yield (%) (methyl ester **50**)
a		87		90 (95)
b		78		81 (93)
c		90		88 (97)
d		77		85 (92)
e		80		83 (90)
f		83		78 (92)
g		85		72[a] (91)
h		79		70[a] (88)

Scheme 16

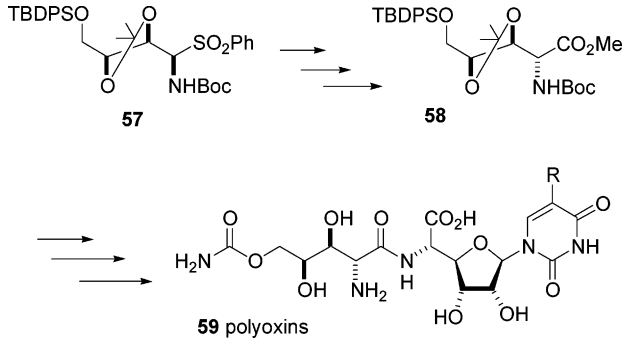
Scheme 17



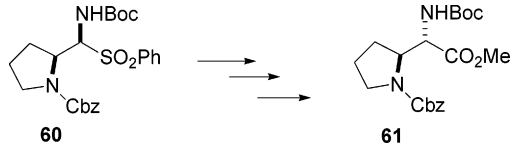
The reaction of ethyl *N*-carbamoyltosylglycinates **62** with nitroalkanes **63** follows a different pathway since the intermediate addition product **64** suffers a base-promoted elimination of HNO_2 giving dehydroamino acids **65** of predominantly *Z* configuration (Scheme 20 and Table 7).[69,70]

The anion of *tert*-butyl acetoacetate **67** reacts with sulfones **66** in the usual way giving the addition products **68** that upon hydrolysis and decarboxylation afford β-aminomethyl ketones **69** as hydrochloride salts (Scheme 21).[71,72]

Scheme 18



Scheme 19



Scheme 20

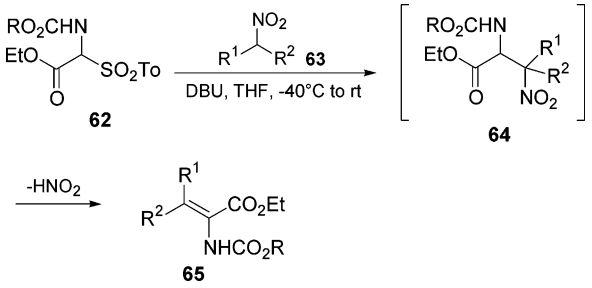
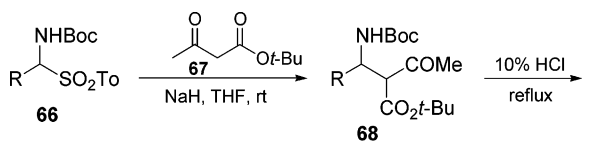


Table 7. Synthesis of Dehydroamino Acid Esters 65 by Reaction of Tosylglycinates 62 with Nitroalkanes 63

entry	R	R^1	R^2	amino ester **65** yield (%)	*Z/E*
1	Bn	Me	H	78	97/3
2	Bn	Me	Me	68	
3	Bn	$CbzNH(CH_2)_2$	H	79	100/0
4	Bn	CO_2Et	H	54	64/36
5	Bn	Ph	H	73	97/3
6	*t*-Bu	Me	Me	68	
7	*t*-Bu	$BocNH(CH_2)_2$	H	76	100/0
8	*t*-Bu	$MeSCH_2$	H	83	90/10
9	*t*-Bu	4-MeOPh	H	70	95/5

Scheme 21



R	**69** yield (%)
H	86
n-Pr	77
i-Pr	83
Ph	66

The utilization of Reformatsky and allylzinc reagents presents some evident advantages over other metal enolates and allylmetal derivatives. Indeed, these reactive compounds can be generated in situ by reaction of the appropriate α-bromo ester or allyl bromide with activated zinc at room temperature.[73] Sulfones **70** react with Reformatsky reagents pre-

Scheme 22

pared from α-bromo esters or ketones **71** with modest syn selectivity to give the corresponding *β-N*-carbamoylamino esters or ketones **72** (Scheme 22 and Table 8).[74,75]

Allyl bromides **73** react in the presence of activated zinc with sulfones **70** giving homoallylamino derivatives **74** (Scheme 23 and Table 9).[75] Particularly, the utilization of 3-bromo-1-acetoxy-1-propene **73** (R^2 = OAc) allows a new diastereoselective entry to fully protected *anti*-1,2-amino alcohols (Table 9, entries 4−7).

The organozinc reagent obtained from 2-bromomethylacrylate **76** adds to sulfones **75** giving α-methylidene-*γ*-amino ester derivatives **77** (Scheme 24). The low nucleophilicity of the carbamoyl nitrogen in compounds **77** avoids any spontaneous cyclization to the corresponding 3-methylidene lactams **78**. However, ring closure to lactams **78** can be promoted by trimethylaluminum in toluene.

Reaction of Reformatsky reagents can also be applied to optically active sulfones **53** and **60** leading to the diastereoselective synthesis of the corresponding homoallylamines and *N*-carbamoylamino esters **79**−**82** (Scheme 25).[76]

Lithium enolate of ethyl acetate **83** gives the best results in terms of chemical yield and diastereoselectivity in the reaction with sulfone **60**. Further synthetic transformations on *β*-amino ester derivative **84** allow the enantioselective synthesis of (−)-1-aminopyrrolizidine **87**, a central intermediate for the preparation of various biologically active substances (Scheme 26).

α-Amido sulfones are particularly suitable for generation of *N*-acylimines that are prone to tautomerization to the parent enecarbamate, but their utilization is also instrumental for the synthesis of certain arylaldehyde *N*-acylimines that are difficult to prepare by direct condensation. Benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **89** is more conveniently prepared in pure form by reaction of sulfone **88** with K_2CO_3 (Scheme 27). Filtration of the insoluble salts affords pure imine **89** that upon reaction with lithium enolate of amide **90** and cleavage of the chiral auxiliary leads with high diastereoselectivity to acid **91** that constitutes the side chain framework of docetaxel (Taxotere).[77]

The lithium enolate of camphor-derived ketone **93** is particularly effective in the reaction with sulfones **92** giving the *β*-amino keto derivative **94** with high diastereoselectivity (Scheme 28 and Table 10).[78] Oxidative cleavage of the chiral auxiliary with CAN affords *N*-carbamoyl-*β*-amino acid derivatives **95** in good yields.

This procedure can be successfully applied to the synthesis of *C*-glycoalkyl-*β*-amino acids **97** as well as other *β*-peptides and α,*β*-peptides (Scheme 29).[79]

An effective source of chiral enol ethers is represented by α-silylated TMS enol ethers **98** that react

Table 8. Synthesis of β-Amino Esters and Ketones 72 by Reaction of Sulfones 70 with Reformatsky Reagents

entry	R	R^1	R^2	R^3	method[a]	*syn*:*anti*	amino derivative **72** yield (%)	ref
1	Me_2CHCH_2	Bn	H	OEt	A		75	74
2	Me_2CHCH_2	Bn	Me	OEt	A	72:28	82	74
3	$Ph(CH_2)_2$	*t*-Bu	Et	OEt	A	55:45	70	74
4	*c*-C_6H_{11}	*t*-Bu	Et	OEt	A	75:25	79	74
5	Et	Bn	Ph	OEt	A	92:8	78	74
6	$Cl(CH_2)_5$	Bn	Me	OMe	A	65:35	83	74
7	*n*-C_7H_{15}	Bn	H	2-furyl	B		65	75
8	$Ph(CH_2)_2$	*t*-Bu	H	Ph	B		85	75
9	$Ph(CH_2)_2$	*t*-Bu	H	Me	B		72	75
10	Me_2CHCH_2	Bn	H	Ph	B		64	75

[a] A: Zn−Cu couple, dichloromethane, room temperature. B: Zn activated, THF, room temperature.

Scheme 23

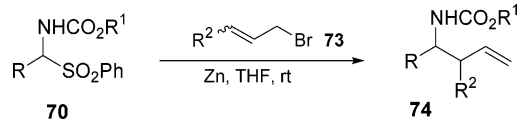
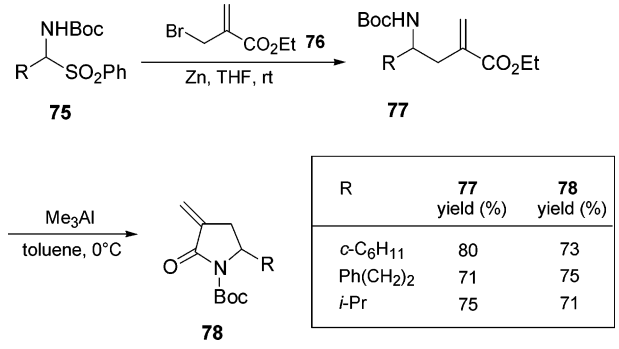


Table 9. Reaction of Sulfones 70 with Allylzinc Reagents

entry	R	R^1	R^2	*syn*:*anti*	homoallylamine **74** yield (%)
1	*n*-C_7H_{15}	Bn	H		99
2	CH_2=$CH(CH_2)_7$	Me	H		75
3	$Ph(CH_2)_2$	Bn	H		80
4	CH_2=$CH(CH_2)_7$	*t*-Bu	OAc	20:80	77
5	*i*-Pr	*t*-Bu	OAc	10:90	76
6	$Ph(CH_2)_2$	*t*-Bu	OAc	15:85	78
7	Ph	*t*-Bu	OAc	5:95	88

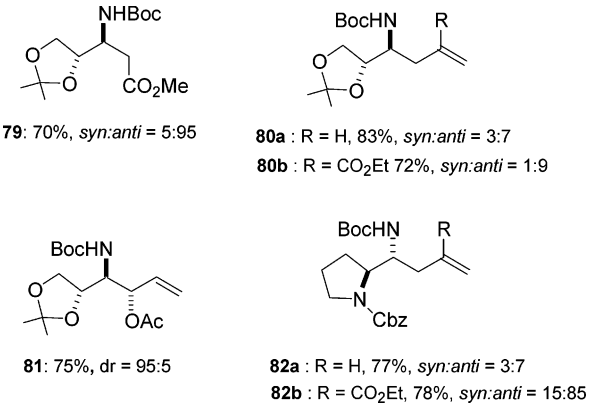
Scheme 24



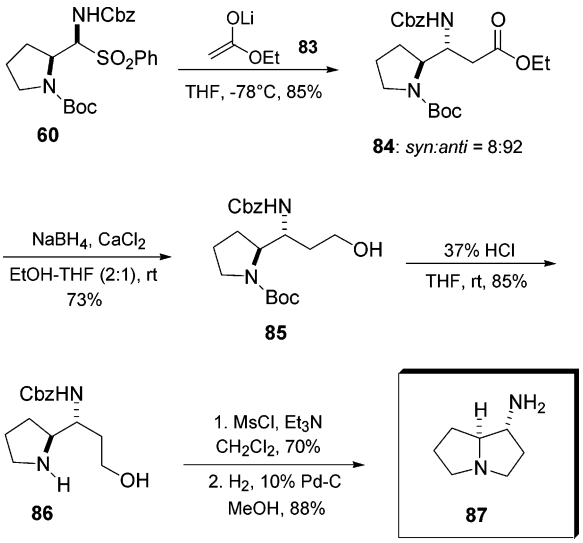
with *N*-acylimines prepared in situ from sulfones **99** and in the presence of $TiCl_4$ (Scheme 30).[80] The chiral silylated group in adducts **100** can be removed using fluoride salts, and finally, β-amino ketones **101** are obtained in high yield and diastereoselectivity.

The utilization of a carbamate resin allows the preparation of polymer-bound α-carbamoyl sulfones **102** that react with ester enolates, allylzinc reagents, and Grignard reagents to give the corresponding addition products. Particularly, reaction with ketone enolates **103** affords resin-linked β-amino ketones **104** that can be cleaved using Me_2S−BF_3·Et_2O (for aryl ketones) or $ZnBr_2$ (for alkyl ketones) giving, after benzoylation, *N*-acyl-β-amino ketones **105**. Alternatively, ketones **104** can be reduced to the parent β-hydroxy amino derivatives **106** that by intramolecular nucleophilic displacement leads to 1,3-oxazinan-2-ones **107** (Scheme 31).[81]

Scheme 25



Scheme 26

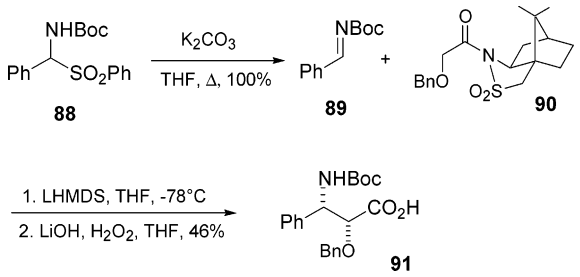


N-Formylarylimines derived from sulfones **34** are reactive enough to produce *N*-formyl-β-amino esters **109** upon reaction with ketene diethyl acetate **108** (Scheme 32).[82]

Chiral α-diazocarbonyl derivatives can be deprotonated at the 2-position and made to react with various aryl *N*-tosylimines. However, reaction of diazo compound **110** with aliphatic *N*-tosylimines is possible only using *N*-tosylbutyltolyl sulfone **111** that in basic conditions is transformed into the corresponding *N*-tosylbutylimine giving adduct **112** (Scheme 33).[83]

A Strecker-like synthesis of *N*-Boc-α-amino nitriles **113** can be realized by reaction of sulfones **75** with

Scheme 27



Scheme 28

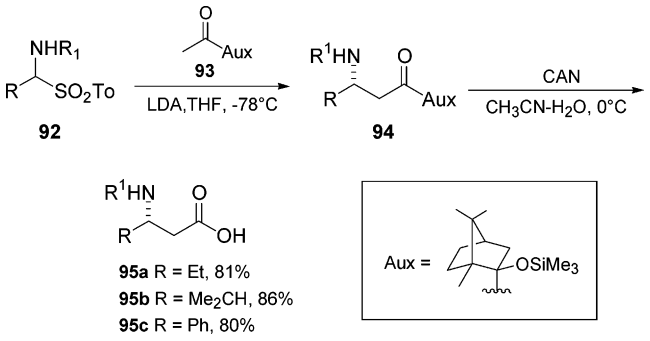
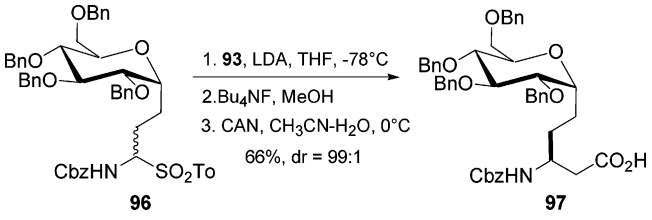


Table 10. Diastereoselective Synthesis of β-Amino Ketones 94 Using Chiral Ketone 93

entry	R	R^1	amino ketone **94** yield (%)	d.r
1	Et	Cbz	94	98:2
2	*n*-Pr	Boc	60	99:1
3	*i*-Pr	Cbz	82	98:2
4	$Ph(CH_2)_2$	Cbz	90	98:2
5	Ph	Boc	72	99:1
6	*c*-C_6H_{11}	Cbz	81	98:2
7	$BnO(CH_2)_2$	Cbz	55	97:3

Scheme 29

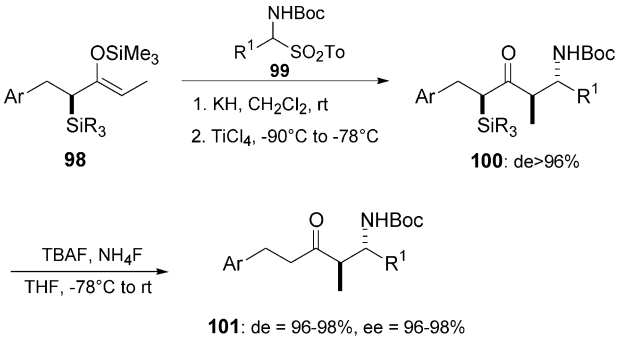


KCN under phase transfer conditions. Cyanide ion is basic enough to promote elimination in sulfone **75** leading to the parent *N*-acylimine (Scheme 34).[84]

Reaction of metalated nitriles with imino derivatives is a rather uncommon process probably because of the poor reactivity of *N*-alkylimines toward these nucleophiles. Lithiated nitriles **115** add quite efficiently to sulfones **114** giving the corresponding *N*-carbamoyl-β-amino nitriles **116** with a certain preference for the syn diastereomer (Scheme 35 and Table 11).[85]

Reduction of the cyano group in nitriles **116** using $LiAlH_4-AlCl_3$ allows the preparation of *N*-carbamoyl-1,3-diamino derivatives **117**. A synthetic strategy to the preparation of symmetrically substituted porphyrins involves the preparation of functionalized pyrrole derivatives **122** (Scheme 36).[86] These heterocyclic compounds are prepared by reaction of sulfone **118** with methylmagnesium bromide that at very low

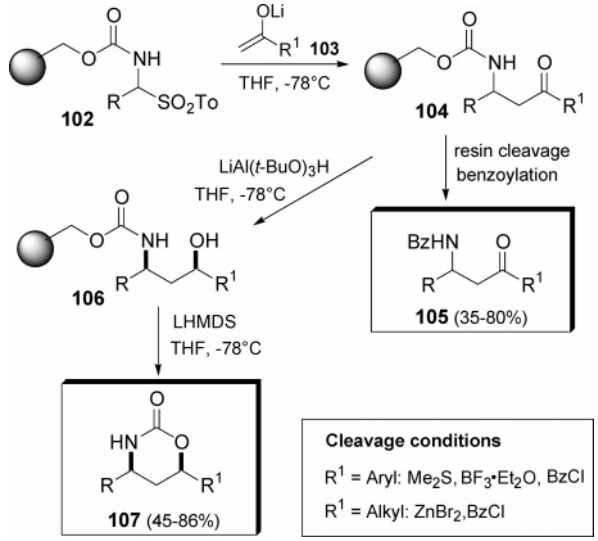
Scheme 30



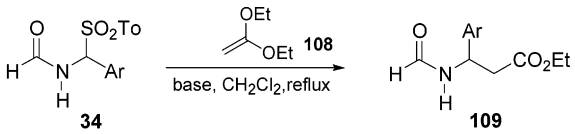
Ar = 4-BrC_6H_4
R_3Si = thexylMe_2Si

entry	R^1	**100** yield (%)	**101** yield (%)
a	Ph	90	95
b	4-MeOPh	89	93
c	2-furyl	88	94
d	4-MePh	92	92

Scheme 31



Scheme 32

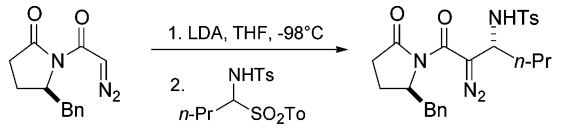


entry	Ar	base	**109** yield (%)
a	Ph	Cs_2CO_3	90
b	4-NO_2Ph	Et_3N	77
c	4-MeOPh	Et_3N	67
d	4-OHPh	Et_3N	62

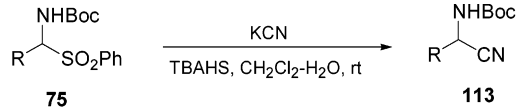
temperature (−100 °C) acts selectively as a base generating the *N*-mesylimine **119** that reacts with lithiated sulfones **120** to give adducts **121**. Crude compounds **121** are converted into pyrroles **122** upon cleavage of the acetal group followed by ring closure−aromatization.

Reaction of lithiated chiral sulfoxide **124** with sulfone **123** affords adduct (4*R*,5*S*)-**125** as the main component of the diastereomeric mixture (Scheme 37).[87,88] After separation, this sulfoxide undergoes to

Scheme 33



Scheme 34



entry	R	113 yield (%)	entry	R	113 yield (%)
a	Ph	73	**e**	*i*-Pr	81
b	4-FPh	83	**f**	*t*-Bu	82
c	2-furyl	84	**g**	$PhCH_2$	81
d	4-*t*-BuPh	78	**h**	*c*-C_6H_{11}	85

Scheme 35

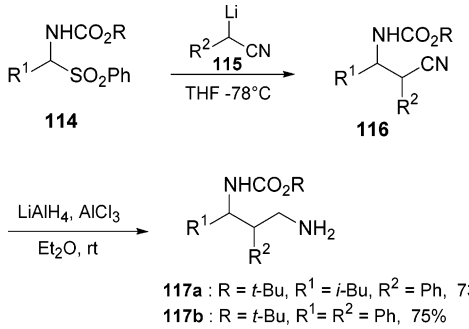
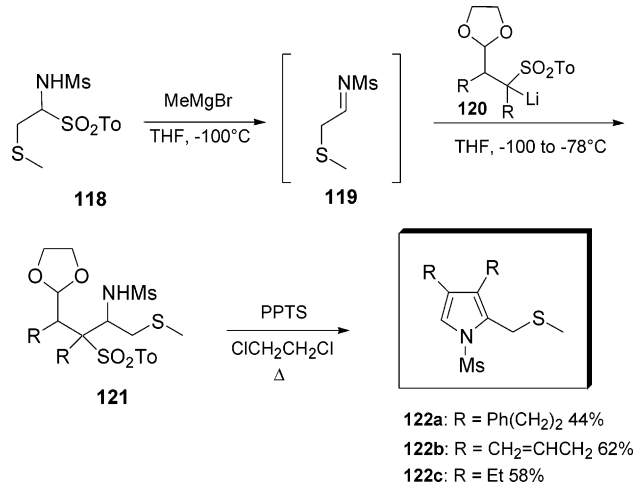


Table 11. Synthesis of β-Amino Nitriles 116 by Reaction of Sulfones 114 with Lithiated Nitriles 115

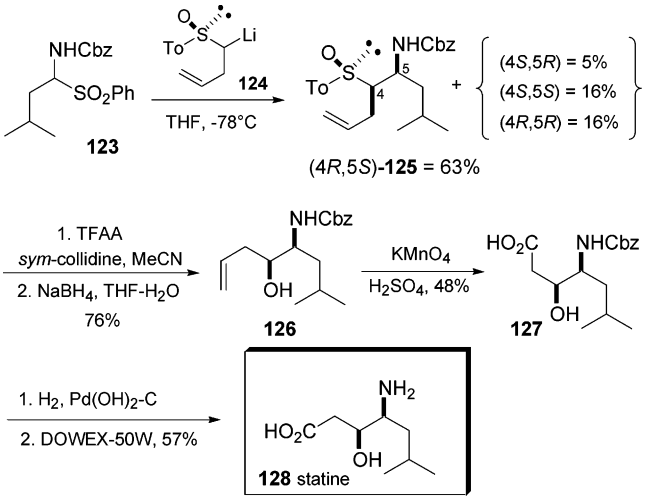
entry	R	R^1	R^2	amino nitrile **116** *syn:anti*	yield (%)
1	Bn	$Ph(CH_2)_2$	H		70
2	Bn	$Ph(CH_2)_2$	Ph	75:25	62
3	Bn	$Ph(CH_2)_2$		80:20	60
4	Bn	$Ph(CH_2)_2$	2-MeOPh	60:40	68
5	*t*-Bu	$Ph(CH_2)_2$	H		91
6	Bn	*c*-C_6H_{11}	Ph	70:30	95
7	Bn	Me_2CHCH_2	Ph	70:30	90
8	*t*-Bu	Ph	Ph	90:10	87
9	Bn	Ph	1-naphthyl	95:5	95
10	Bn	Ph	Me	70:30	60

a "nonoxidative" Pummerer reaction (NOPR) that provides an effective entry to *N*-carbamoylamino alcohol **126**. In this context, it is interesting to observe that the presence of a carbamoyl protecting group on the nitrogen atom is mandatory for a successfully NOPR process since other groups such as PMP give rise to a totally different outcome. Oxidative cleavage of the double bond and removal of the Cbz protection complete the synthesis of the nonproteinogenic amino acid (3*S*,4*S*)-statine **128**. A related strategy can be applied to the stereoselective synthesis of vicinal chloroamine **129** and aziridine **130** exploiting a "nonoxidative" chloro-Pummerer reaction (NOCPR) on sulfoxide **125** followed by an

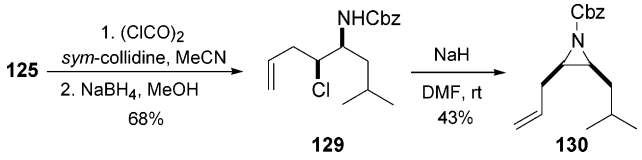
Scheme 36



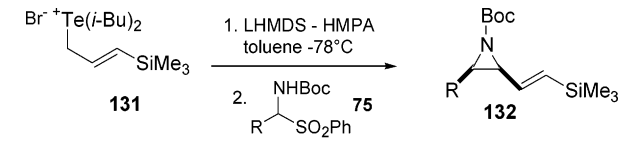
Scheme 37



Scheme 38



Scheme 39



entry	R	132 yield (%)	*trans:cis*
a	Me_2CH	77	9:91
b	*c*-C_5H_{11}	71	7:93
c	*n*-Bu	50	14:86

intramolecular nucleophilic displacement (Scheme 38).[89,90]

cis-Vinylaziridines **132** can also be prepared in a stereoselective fashion by reaction of a telluronium allylide, obtained from the corresponding salt **131**, with α-amido sulfones **75** (Scheme 39).[91] Reaction of the same ylide with *N*-arylimines leads to the formation of *trans*-*N*-arylaziridines.

Scheme 40

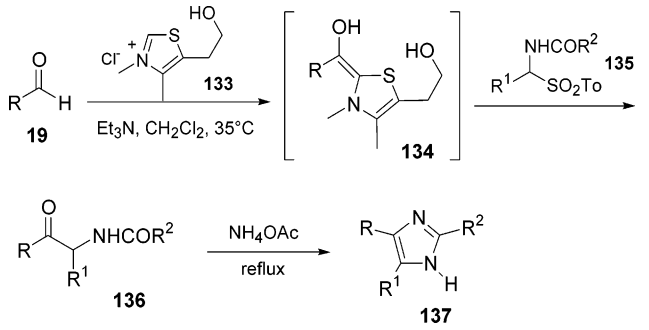


Table 12. Thiazolium-Catalyzed Addition of Aldehydes 19 to Sulfones 135

entry	R	R^1	R^2	ketone **136** yield (%)
1	4-pyridyl	Ph	H	86
2	4-pyridyl	Ph	*c*-C_6H_{11}	98
3	4-pyridyl	Ph	BnO	96
4	4-pyridyl	*c*-C_6H_{11}	Ph	90
5	4-pyridyl	4-FPh	*c*-C_6H_{11}	76
6	Ph	Ph	*t*-BuO	75
7	2-BrPh	Ph	*t*-BuO	86
8	4-CNPh	Ph	*t*-BuO	80
9	2-furyl	Ph	*t*-BuO	73
10	Me	Ph	*t*-BuO	62
11	$BnO(CH_2)_2$	Ph	*t*-BuO	75
12	PhCH=CH	Ph	*c*-C_6H_{11}	80

Thiazolium-catalyzed processes allow the utilization of aldehydes as acyl−anion equivalents in addition reactions with electrophilic substrates.[92] Aldehydes **19** react with thiazolium salt **133** giving intermediate thiazole-enamines **134** that in the presence of sulfones **135** afford the corresponding *N*-acylamino ketones **136** (Scheme 40 and Table 12).[93] Compounds **136** can be converted into substituted imidazoles **137** by reaction with NH_4OAc or a primary amine in a "one pot" procedure.[94]

An enantioselective version of this process involves the reaction of arylaldehydes **138** with amido sulfones **139** mediated by chiral thiazolylalanine-derived catalyst **140** (Scheme 41 and Table 13).[95] 2-*N*-Acylamino ketones **141** are obtained in usually good yield with interesting values of ee that can be greatly improved (>98%) after a single crystallization.

2.2.3. Reaction with Heteronucleophiles and Reducing Agents

Nucleophiles other than carbanions can be used in the reaction with α-amido sulfones. Amines, alkoxides, thiolates, and phosphites react efficiently with sulfones **142** to give the corresponding addition products **143** (Scheme 42 and Table 14).[48,96−100]

Reduction of the intermediate *N*-acylimine obtained from α-amido sulfones **142** can be realized using $NaBH_4$ leading to the synthesis of the corresponding *N*-acylamines **144** (Scheme 43 and Table 15).[101]

Complete reduction of the imino and acyl groups in α-amido sulfones **16** is needed for a stronger reducing agent such as $NaBH_3OAc$, and this procedure allows a straightforward synthesis of secondary amines **145** (Scheme 44 and Table 16).[102] Some functional groups such as fluorine atoms are retained, while, quite interestingly, isolated double bonds are reduced by the reagent (Table 16, entry 5).

Scheme 41

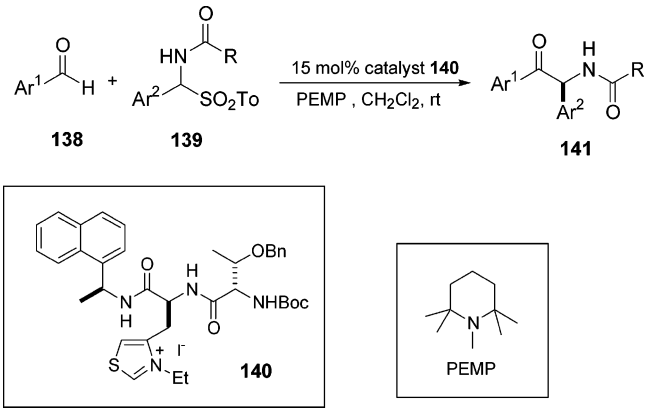
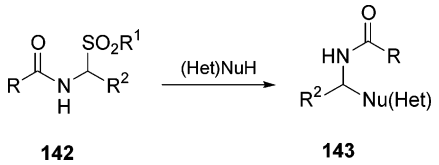


Table 13. Enantioselective Addition of Arylaldehydes 138 to Sulfones 139 Mediated by Chiral Catalyst 140

entry	Ar^1	Ar^2	R	ketone **141** yield (%)	ee (%)
1	4-ClPh	Ph	Ph	100	76
2	4-ClPh	4-MeOPh	Ph	91	85
3	3-NO_2Ph	4-MeOPh	Ph	77	82
4	3-NO_2Ph	4-MeOPh	*i*-Pr	63	79
5	4-ClPh	Ph	*i*-Pr	97	75
6	4-ClPh	3,4-MeOPh	Ph	80	81
7	Ph	Ph	Ph	15	83

Scheme 42



The reaction of ethyl *N*-carbamoyl-α-tosylglycinates **62** with aldehydes **12** in the presence of Bu_3P represents an efficient entry to α,β-didehydroamino acid derivatives **146** that are formed with enhanced *Z* stereoselectivity (Scheme 45 and Table 17).[103] Bu_3P is responsible for the initial formation of *N*-acylimine **147** that reacts with a further equivalent of phosphine to afford the adduct **148**. Intermediate **148** is in equilibrium with ylide **149** that in the presence of an aldehyde **12** gives the corresponding addition product **150**. Elimination of Bu_3PO from **150** leads to the unsaturated amino acid derivative **146**.

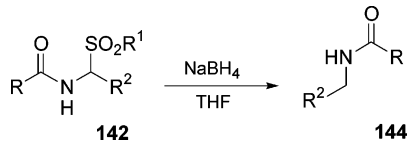
2.3. α-Amido Sulfones as Precursors of *N*-Acyliminium Ions

As previously stated, conversion of α-amido sulfones into *N*-acyliminium ions occurs in the presence of Lewis acids that provide the elimination of the phenylsulfonyl group. The utilization of linear or exocyclic α-amido sulfones for the generation of highly reactive *N*-acyliminium ions has not been recognized until very recent years. Chiral exocyclic α-amido sulfones **152** have been prepared from ephedrine-derived imidazolidin-2-one **151** by Pearson et al. as single diastereomers and used in order to prepare chiral organolithium derivatives (vide infra) (Scheme 46).[104]

Table 14. Reaction of Various Heteronucleophiles with Sulfones 142

entry	R	R^1	R^2	(Het)NuH/ base or NuNa	acylamine **143** yield (%)	ref
1	Ph	Et	CF_3	PhOH/Et_3N	85	48
2	Me	Et	CF_3	EtOH/ Et_3N	69	97
3	*t*-Bu	Ph	Ph	MeONa	98	96
4	*t*-Bu	Ph	4-MeOPh	MeONa	78	96
5	*t*-Bu	Ph	4-CF_3Ph	MeONa	79	96
6	*t*-Bu	Ph	*t*-Bu	MeONa	75	96
7	*t*-Bu	Ph	4-NO_2Ph	MeONa	94	96
8	BnO	Et	CF_3	4-NO_2PhSH/Et_3N	91	48
9	Ph	Et	CF_3	Cbz-L-Cys-Gly-OEt/Et_3N	79	97
10	BnO	Et	CF_3	$PhCH_2NH_2$	97	48
11	BnO	Et	CF_3	$EtO_2CCH_2NH_2$	97	48
12	Me	Et	CF_3	imidazole	89	97
13	Ph	Et	CF_3	Ph_3CNHNH_2	81	97
14	EtO	4-MePh	4-MePh	morpholine	78	98
15	Ph	4-MePh	H	$MeNHNO_2$/Et_3N	89	99
16	*t*-Bu	4-MePh	*i*-Bu	$(EtO)_2P(O)H$/NaH	83	100
17	*t*-Bu	4-MePh	Ph	$(EtO)_2P(O)H$/NaH	65	100

Scheme 43

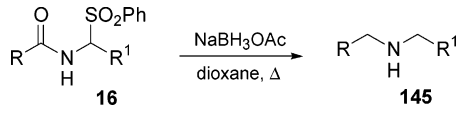


142 144

Table 15. Reduction of Sulfones 142 to the Corresponding *N*-Protected Primary Amines 144

entry	R	R^1	R^2	acylamine **144** yield (%)	ref
1	Ph	Et	CF_3CH_2	92	48
2	EtO	4-MePh	Me	45	97
3	*t*-BuO	4-MePh	Ph	65	101
4	*t*-BuO	4-MePh	2-furyl	54	101
5	*t*-BuO	4-MePh	Me	76	101
6	*t*-BuO	4-MePh	*c*-C_6H_{11}	80	101

Scheme 44



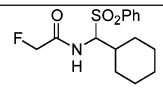
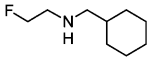
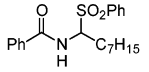
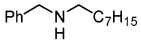
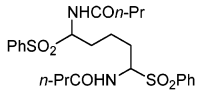
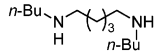
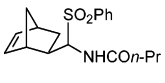
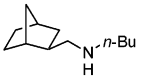
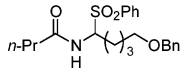
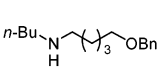
16 145

In the presence of $SnCl_4$, sulfones **152** are converted into the corresponding *N*-acyliminium ions **153** that react with allyltrimethylsilane **154** and silyl enol ethers **155** to afford the corresponding addition products **156** and **157** (Scheme 47 and Table 18).[105]

The imidazolidin-2-one ring in compounds **156** and **157** has been proved to be resistant to cleavage under different conditions; therefore, these derivatives are not suitable for the preparation of enantioenriched homoallylamines or β-amino ketones. Although the classical conditions ($PhSO_2Na$, H_2O, HCO_2H) fail to give the corresponding α-amido sulfone using chiral oxazolidin-2-ones **158**, a modification of the reaction conditions ($PhSO_2H$, CH_2Cl_2) allows an efficent entry to sulfones **160** as a mixture of diastereomers (Scheme 48 and Table 19).[106, 107]

Chiral α-amido sulfones **160** react with allyltrimethylsilane **154** and electron rich aromatics **161** in the presence of $TiCl_4$ to afford the corresponding adducts **162** and **163** that upon cleavage of the oxazolidin-2-one ring using Li/NH_3 and carbamoylation of the amino group give homoallylamine and benzylamine derivatives **164** and **165** (Scheme 49 and Table 20). The sense of asymmetric induction observed in compounds **164** and **165** is opposite to that obtained in derivatives **156** and **157** although semiempirical calculations (PM3) made on the intermediate *N*-acyliminium ion obtained from **160** show that the *E* stereoisomer is more stable than the *Z* one.[106]

Table 16. Synthesis of Secondary Amines 145 by Complete Reduction of Sulfones 16

entry	sulfone **16**	amine **145**	yield (%)
1			88
2			91
3			87
5			96
6			81

Scheme 45

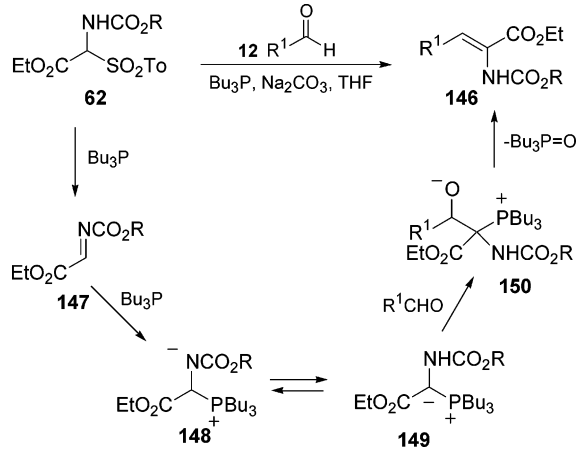
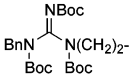
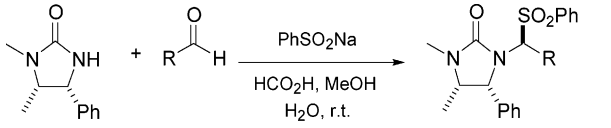


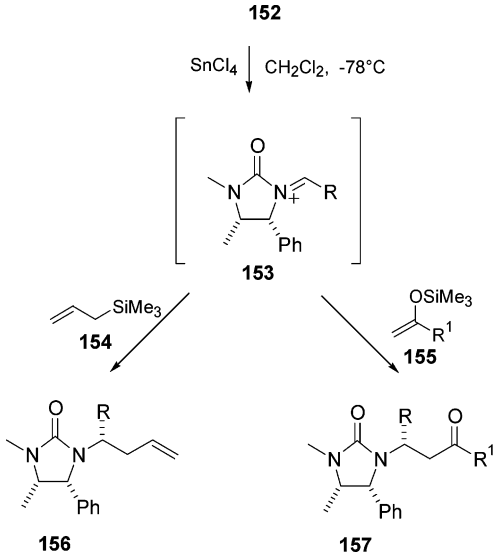
Table 17. Coupling of Tosylglycinates 62 with Aldehydes 12

entry	R	R^1	ester **146** yield (%)	*Z:E*
1	*t*-Bu	Et	82	90:10
2	*t*-Bu	*i*-Pr	84	93 :7
3	Bn	*i*-Pr	76	84:16
4	*t*-Bu	Ph	79	100 :0
5	Bn	4-MeOPh	77	93:7
6	*t*-Bu	$O_2N(CH_2)_3$	84	89 :11
7	*t*-Bu		84	100:0
8	*t*-Bu		77	100:0
9	*t*-Bu		79	100:0
10	*t*-Bu		94	95:5

Scheme 46



Scheme 47



Chiral sulfones obtained from optically active 4-benzyloxazolidin-2-one can undergo an intramolecular ring closure upon formation of the corresponding *N*-acyliminium ion.[107] This synthetic approach can be used for the synthesis of aza-analogues of the anticancer drug podophyllotoxin. The reaction of Garner's aldehyde **166** with Grignard reagent **167** gives alcohol **168** with enhanced anti stereoselectivity (Scheme 50).[108] Acetylation of the hydroxy group and

Table 18. Diastereoselective Addition of Silyl Derivatives 154 and 155 to Chiral *N*-Acyliminium Ions Generated from Sulfones 152

entry	R	R^1	d.r	alkene **156** yield (%)	ketone **157** yield (%)
1	Et		95:5	74	
2	$Ph(CH_2)_2$		95:5	70	
3	$Cl(CH_2)_5$		93:7	70	
4	$BnO(CH_2)_4$		95:5	80	
5	$C_5H_{11}CH{=}CH(CH_2)_2$		93:7	72	
6	$Ph(CH_2)_2$	2-furyl	99:1		91
8	*n*-C_7H_{15}	2-furyl	98:2		70
7	Me_2CHCH_2	Ph	99:1		97
9	$BnO(CH_2)_4$	Ph	99:1		98
10	$Cl(CH_2)_5$	Ph	98:2		87

Scheme 48

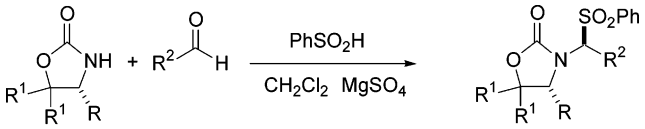


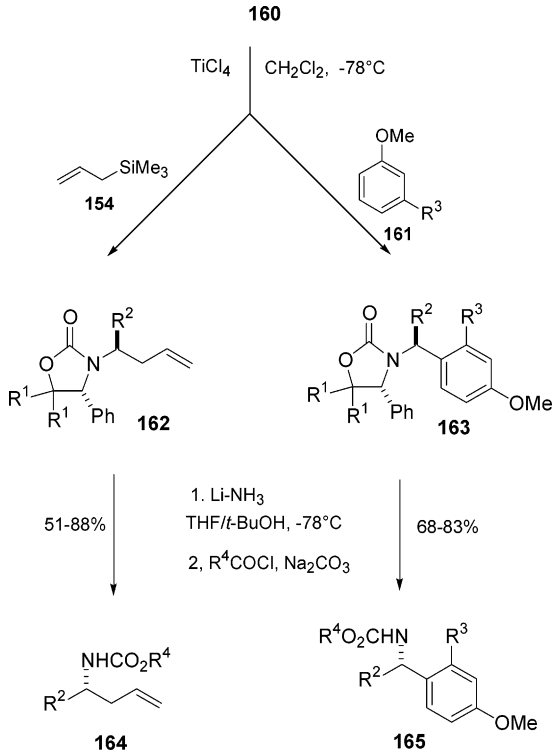
Table 19. Synthesis of Chiral Sulfones 160 from Optically Active Oxazolidin-2-ones 158

entry	R	R^1	R^2	sulfone **160** yield (%)	d.r	ref
1	Ph	H	Et	95	85:15	106
2	Ph	H	$Ph(CH_2)_2$	68	90:10	106
3	Ph	H	$Cl(CH_2)_5$	72	90:10	106
4	Ph	H	Me_2CH	70	80:20	106
5	Ph	Me	Me_2CHCH_2	75	80:20	106
6	Ph	Me	*n*-C_7H_{15}	95	75:25	106
7	Ph	Ph	Me_2CHCH_2	68	80:20	106
8	Bn	H	*n*-C_3H_7	98	75:25	107
9	Bn	H	$Ph(CH_2)_2$	75	65:35	107
10	Bn	H	$BnO(CH_2)_4$	65	80:20	107

hydrolysis of the oxazolidine ring provides alcohol **169** that is then converted into oxazolidin-2-one **170**. α-Amido sulfones **171** obtained from compound **170** upon treatment with $TiCl_4$ give tricyclic derivatives **172** as single diastereomers. In these conditions, a cleavage of the acetoxy group with a concurrent epimerization at C-4 is also observed. Linear α-amidoalkylphenyl sulfones **16** usually employed for the generation of *N*-acylimines can also be converted into *N*-acyliminium ions **173** by reaction with $TiCl_4$ at low temperature (Scheme 51).[109] The real structure of the *N*-acyliminium ion **173** involved in this reaction is obviously unknown; the nitrogen atom could be linked to a hydrogen or to the Lewis acid since two equivalents of $TiCl_4$ are employed in the reaction. The reaction of **173** with different nucleophiles **174** leads to the expected adducts **175** (Table 21). This procedure is particularly effective when the α-amido sulfone contains some functional groups that are incompatible with the utilization of strong nucleophiles as organometallic reagents with *N*-acylimines as intermediates (Table 21, entries 1−3).

Furthermore, bisamido sulfones as **176** can undergo to a double allylation giving compound **177**, using a procedure that involves addition of $TiCl_4$ and allyltrimethylsilane in two distinct steps without the isolation of the monoallyl derivative (Scheme 52).

Scheme 49

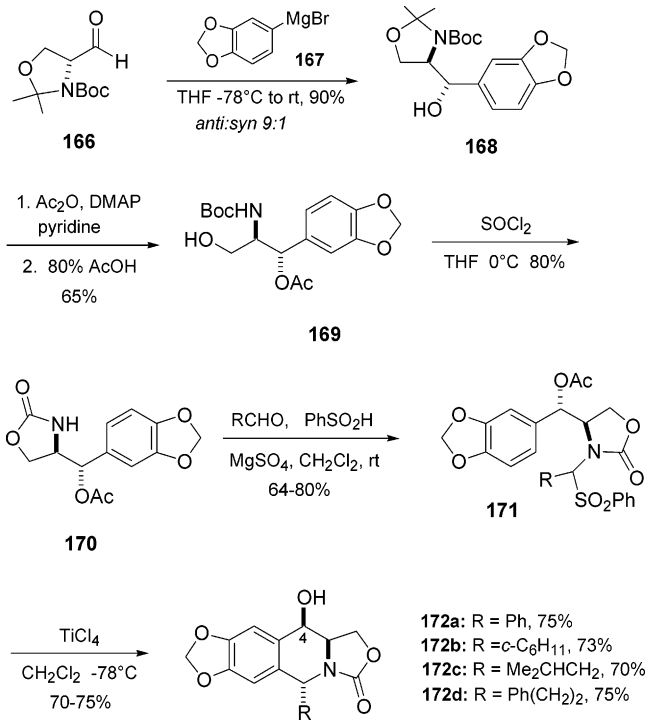


2.4. Other Applications

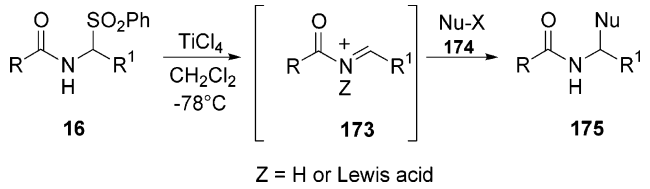
The phenylsulfonyl group is involved in a consistent number of synthetic transformations, enabling the preparation of a vast array of functionalized products.[110] Although α-amido sulfones are mainly used as precursors of *N*-acylimino species, the sulfonyl group in these derivatives can promote the formation of α-stabilized carbanions and other useful reactive intermediates. Chiral imidazolidin-2-one-derived sulfones **152** can be converted into the corresponding tributylstannyl derivatives **178**, in a process that probably involves a SET mechanism, with complete retention of the original configuration of the exocyclic stereocenter (Scheme 53).[104] Transmetalation of compounds **178** provides the corresponding chiral organolithium reagents **179** that upon reaction with various electrophiles afford the corresponding addition products **180** with usually high diastereoselectivity (Table 22).

Reaction of sulfones **181** with two equivalents of *n*-BuLi at −90 °C does not result in the elimination of the tosyl group but in the formation of the corresponding dianions **182** (Scheme 54).[111−113] These dianions can be trapped with electrophiles giving the

Scheme 50



Scheme 51



addition products that upon elimination of sulfinate anions afford enamides **183**.

Similarly, monolithiated *N*-disubstituted sulfones **185** obtained from compounds **184** when made to react with electrophiles give the substitution products **186** (Scheme 55 and Table 23). The sulfonyl group in compounds **186** can be reductively removed giving derivatives **187** or eliminated to afford enamides.

Palladium-catalyzed allylation of sulfone **188** using allyl carbonates **189** affords compounds **190** that can be successively desulfonylated to homoallylamino acid ethyl esters **191** (Scheme 56).[114] Substituted allyl carbonates usually give better yields of the corresponding adducts than simple allyl carbonate. Vinyloxirane can also be employed as allylating agent with sulfone **188** giving the corresponding ω-hydroxy ester derivative **191** (R^1 = H, R = CH_2OH, 72% yield).

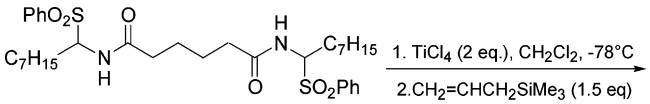
Table 20. Distereoselective Addition of Allylsilane 154 and Aromatics 161 to Chiral *N*-Acyliminium Ions Generated from Sulfones 160

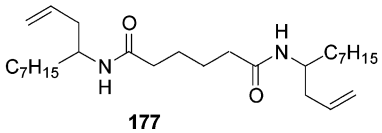
entry	R^1	R^2	R^3	alkene **162** yield (%)	d.r	aryl derivative **163** yield (%)	d.r
1	H	Et	H	73	70:30	65	70:30
2	H	$Ph(CH_2)_2$	H	66	80:20		
5	Me	Me_2CHCH_2	H	93	90:10		
6	Me	Me_2CH	H	73	95:5		
7	Me	$Ph(CH_2)_2$	H	78	85:15		
8	Me	*n*-C_7H_{15}	H	79	90:10		
9	Me	Ph	H			73	95:5
10	Me	$BnO(CH_2)_4$	OMe			62	70:30

Table 21. Addition of Nucleophiles 175 to α-Amido Sulfones 16 Promoted by $TiCl_4$

entry	R	R^1	Nu-X **174**	Nu	adduct **175** yield (%)
1	$Cl(CH_2)_2$	$Ph(CH_2)_2$	CH_2=$CHCH_2SiMe_3$	CH_2=$CHCH_2$	77
2	FCH_2	$Ph(CH_2)_2$	CH_2=$CHCH_2SiMe_3$	CH_2=$CHCH_2$	80
3	CH_2=CH	$Ph(CH_2)_2$	CH_2=$CHCH_2SiMe_3$	CH_2=$CHCH_2$	81
4	BnO	$BnO(CH_2)_4$	CH_2=$CHCH_2SiMe_3$	CH_2=$CHCH_2$	83
5	BnO	n-C_7H_{15}	$MeOC_6H_5$	4-$MeOC_6H_4$	81
6	BnO	Me_2CHCH_2	thiophene	2-thienyl	78
7	BnO	Me_2CHCH_2	CH_2=C(OEt)$OSiMe_3$	CH_2CO_2Et	77

Scheme 52





Scheme 53

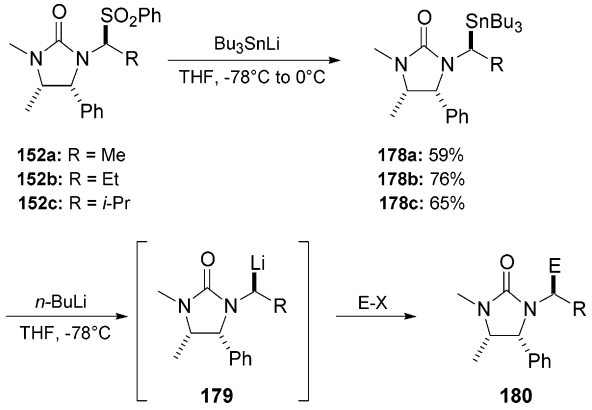


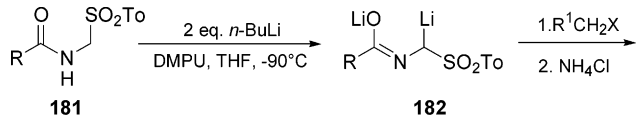
Table 22. Electrophilic Addition to Chiral Organolithium Derivatives 179

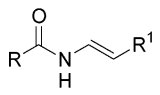
entry	R	E-X	E	imidazolidinone **180** yield (%)
1	Me	DCl/D_2O	D	63
2	Et	DCl/D_2O	D	72
3	Et			78
4	Et	PhCHO	PhCHOH	88
5	Et	*i*-PrCHO	*i*-PrCHOH	91
6	Et	$ClCO_2Et$	CO_2Et	83[a]
7	*i*-Pr	D_2O	D	56
8	*i*-Pr	Bu_3SnCl	Bu_3Sn	67

[a] d.r = 8:92.

The utilization of α-amido sulfones as precursors of reactive C=N bonds other than *N*-acylimino derivatives has received only little attention although some of these reactive compounds are of some interest in synthesis. 1-Tosylalkyl isocyanates **193** can be prepared by reaction of *N*-tosylalkyl thiocarbamates **192** using chlorine in basic conditions (Scheme 57).[115]

Scheme 54

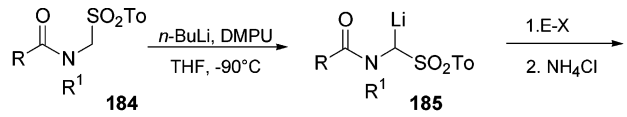


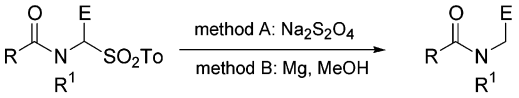


entry	R	R^1	**183** yield (%)
a	*t*-Bu	CH_2=CH	59[a]
b	*t*-Bu	EtO_2C	62[b]
c	Me	EtO_2C	52[b]

[a] *E*:*Z* =1:1 [b] *E* only

Scheme 55





187a R,R^1= $(CH_2)_3$, E = PhCO, A, 70%

187b R = *t*-BuO, R^1= Me, E = EtOCO, B, 75%

Table 23. Electrophilic Addition to Lithiated Sulfones 185

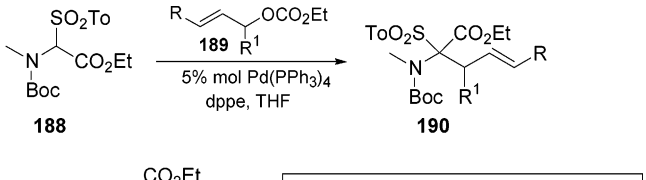
entry	R	R^1	E-X	E	sulfone **186** yield (%)
1		$-(CH_2)_3-$	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	67
2	*t*-BuO	Me	BnBr	Bn	66
3		$-(CH_2)_3-$	*t*-BuO_2CCH_2Br	*t*-BuO_2CCH_2	59
4		$-(CH_2)_3-$	PhCHO	PhCHOH	62
5	*t*-BuO	Me			63
6		$-(CH_2)_3-$	EtOCOCl	EtOCO	72
7		$-(CH_2)_3-$	PhCOCl	PhCO	72

A related procedure can be used for the preparation of tosylmethylisocyanide (tosMIC), a versatile reagent in synthesis.[116] Dehydration of *N*-formyl sulfone **194** using $POCl_3$ leads to tosylmethylisocyanide **195** (Scheme 58).[46,49]

Although this procedure is also suitable for the preparation of tosylalkylisocyanides **196**, these substituted derivatives are better obtained by alkylation of tosMIC **195** under phase transfer conditions using alkyl halides (Scheme 59).[117]

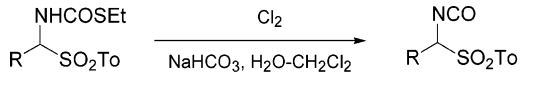
Base-induced cycloaddition of tosylalkylisocyanides **196** to aldimines **197** occurs with concomitant elimi-

Scheme 56

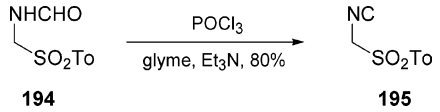


entry	R	R1	190 yield (%)	191 yield (%)
a	H	Me	69	69
b	Ph	H	72	52
c	H	H	40	26

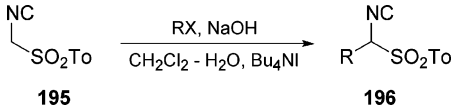
Scheme 57



Scheme 58

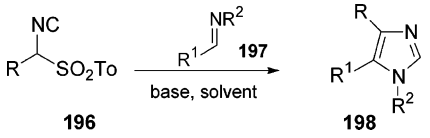


Scheme 59



entry	RX	196 yield (%)
a	MeI	95
b	EtI	90
c	$Me(CH_2)_2I$	85
d	$CH_2{=}CHCH_2Cl$	75
e	BnBr	80

Scheme 60



nation of *p*-toluenesulfinic acid to give trisubstituted imidazoles **198** (Scheme 60 and Table 24).[118]

The imino derivative needed for the imidazole synthesis can also be formed in situ so that the preparation of imidazoles **202** can be realized by a three-component coupling involving isocyanide **199** unsaturated amines **299** and unsaturated aldehydes **201** (Scheme 61).[119] The produced imidazoles are amenable of a further transformation, namely, a RCM, leading to fused byciclic imidazoles **204** that represent useful scaffolds for leads generation.

Similarly, reaction of tosymethylisocyanide **195** with imidoyl chlorides **205** allows the preparation of imidazoles **206** in which the tosyl group is retained in the final molecule (Scheme 62).

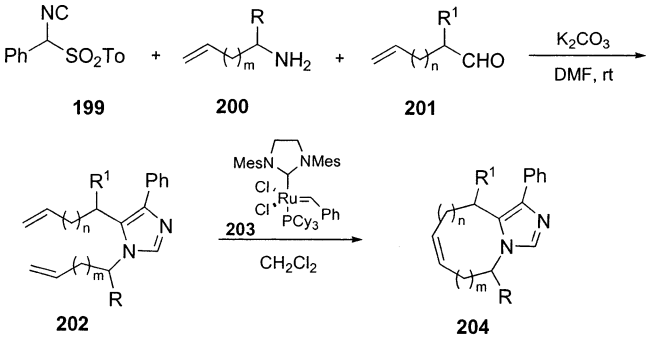
Reaction of sulfones **207** with *i*-amyl nitrite in the presence of TMSCl leads to the formation of *N*-nitroso carbamates **208** that by treatment with basic alu-

Table 24. Synthesis of Substituted Imidazoles 198[a]

entry	R	R^1	R^2	method	imidazole **198** yield (%)
1	H	4-NO_2Ph	Ph	A	82
2	H	Ph	4-NO_2Ph	A	70
3	H	4-NO_2Ph	4-NO_2Ph	A	87
4	H	Me	Et	B	70
5	H	*t*-Bu	Me	B	96
6	H	Me	*t*-Bu	B	94
7	H	Me	*c*-C_6H_{11}	C	96
8	H	*t*-Bu	*t*-Bu	D	75
9	Ph	Me	*t*-Bu	B	89
10	Ph	Ph	Me	A	90
11	Ph	Ph	4-NO_2Ph	E	82
12	Me	Ph	4-NO_2Ph	E	75

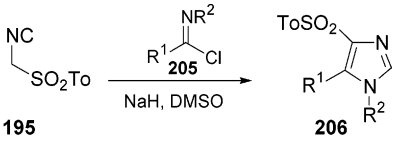
[a] Methods: A, K_2CO_3, MeOH/DME; B, *t*-$BuNH_2$, DME; C, *c*-$C_6H_{11}NH_2$, MeOH; D, *i*-$PrNH_2$, MeOH; and E, NaH, DME.

Scheme 61



entry	200 m	200 R	201 n	201 R^1	202 yield (%)	204 yield (%)
a	0	H	0	H	51	86
b	0	H	1	NHBoc	86	80
c	1	H	1	H	92	39
d	1	H	1	NHBoc	53	89
e	1	CO_2Me	1	H	75	53

Scheme 62



entry	R^1	R^2	**206** yield (%)
a	Ph	4-NO_2Ph	81
b	4-NO_2Ph	Ph	85
c	Ph	*c*-C_6H_{11}	80
d	4-NO_2Ph	*c*-C_6H_{11}	75

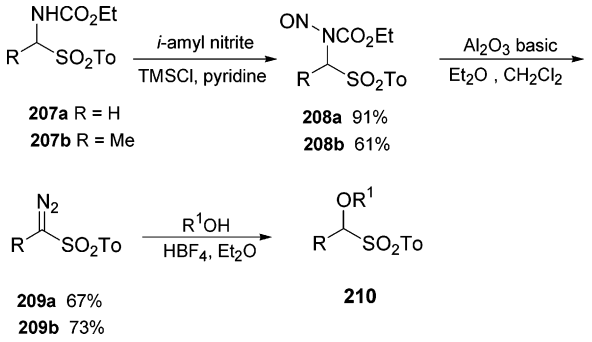
mina affords diazoalkanes **209** (Scheme 63).[120] Tosyldiazoalkanes **209** are useful reagents for the preparation of tosylalkyl ethers **210** by reaction with alcohols in acidic conditions.[121]

3. 4-Sulfonyl Azetidin-2-ones

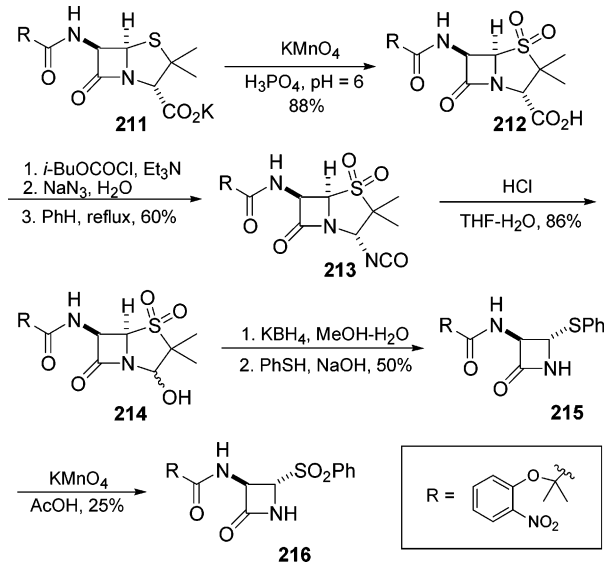
3.1. General Syntheses

4-Sulfonyl azetidin-2-ones are important key intermediates in the preparation of β-lactam antibiot-

Scheme 63



Scheme 64



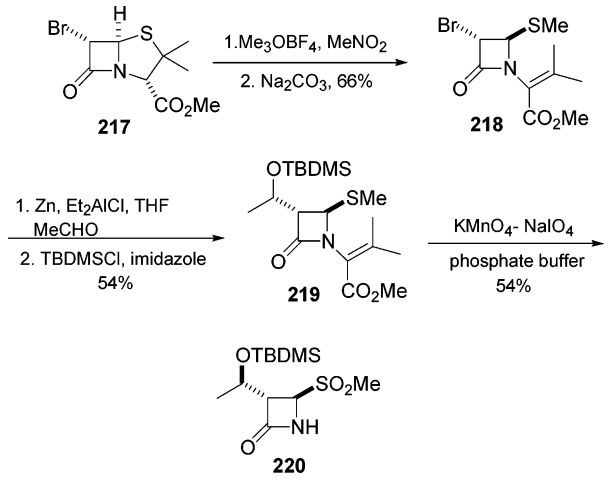
ics, and initially, they represented a synthetic link between penicillin and penem/carbapenem derivatives. Penicillanic acid potassium salt **211** is oxidized to sulfone **212** and then upon transformation into isocyanate **213** is converted to emiaminal **214** (Scheme 64).[122]

Reduction of the hemiaminal group and reaction with sodium benzenethiolate give sulfide **215** that is oxidized to sulfone **216** albeit in low yield. However, it is worth noting that the efficiency of oxidations with $KMnO_4$ is highly substrate-dependent since 3-ethyl-4-tolylthioazetidin-2-one and other unsubstituted thio derivatives are oxidized in high yields (75−89%) in the same conditions.[123,126] In a related approach, cleavage of methyl 6α-bromopenicillanate **217** using Me_3OBF_4 provides a ready access to sulfide **218** that is transformed into compound **219** by a Reformatsky reaction (Scheme 65).[124,125] Oxidation of the sulfide group and the unsaturated ester functions gives sulfone **220** that is a precursor of thienamycin derivatives.

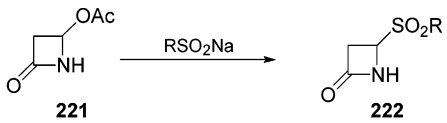
A straightforward procedure for the preparation of 4-sulfonylazetidin-2-ones **222** consists of the direct displacement of the acetoxy group in compound **221** by sodium sulfinate salts in aqueous solution (Scheme 66).[126] The corresponding sulfones **222** precipitate and can be recovered by simple filtration.

4-Acetoxy azetidin-2-one **224** can be prepared by reaction of allenyl acetate **223** with CSI followed by reductive workup (Scheme 67).[127] Reaction of acetate

Scheme 65

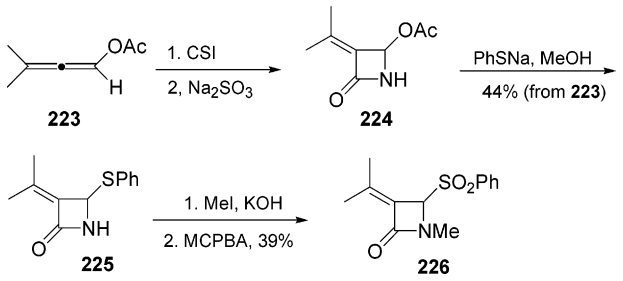


Scheme 66



entry	R	**222** yield (%)	entry	R	**222** yield (%)
a	Et	89	**a**	4-MePh	61
b	$PhCH_2$	84	**b**	4-Cl,2MePh	67
c	Ph	95	**c**	4-NO_2Ph	65

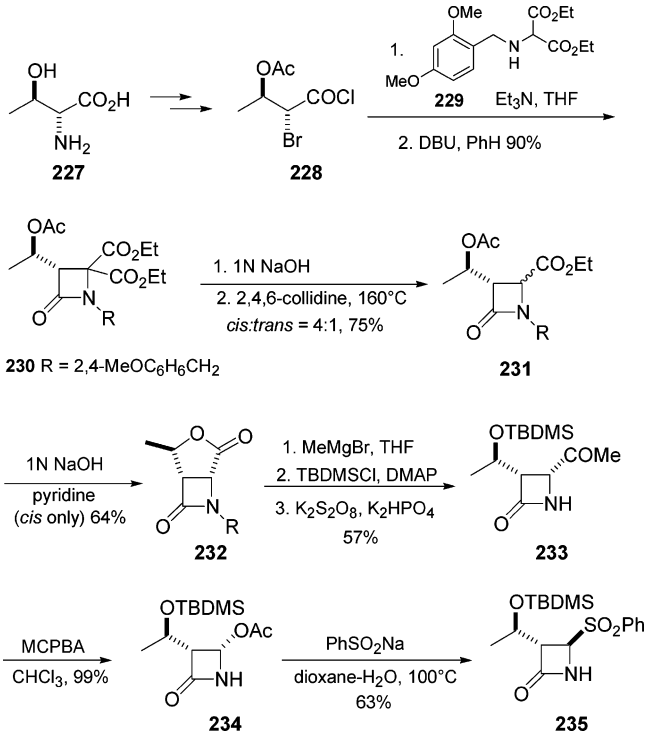
Scheme 67



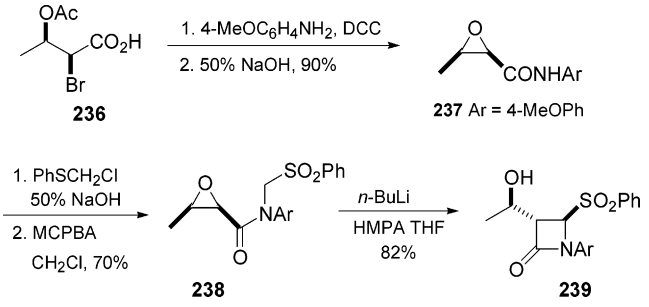
224 with PhSNa affords sulfide **225** that upon methylation and oxidation with MCPBA gives sulfone **226**.[128]

Peracetic acid in the presence of catalytic amounts of $Mn(acac)_3$ is also effective in promoting the oxidation of *N*-TBDMS-4-thiophenylazetidin-2-ones to the corresponding sulfones.[129] α-Amino acids represent a valuable and cheap source of enantiomerically pure compounds suitable for enantioselective syntheses. D-Allo-threonine **227** is converted into acyl chloride **228** in few steps and then by reaction with amine **229** followed by ring closure is transformed into azetidinone **230** (Scheme 68).[130,131] Regioselective saponification−decarboxylation affords monoester **231** as a mixture of cis−trans isomers. The cis isomer is converted into lactone **232** that by reaction with MeMgBr and protecting group manipulations gives ketone **233**. A Baeyer−Villiger oxidation of ketone **233** affords acetate **234**, and finally, reaction with sodium benzenesulfinate leads to the corresponding 4-sulfonyl derivative **235**, a central intermediate for the synthesis of several penam and carbapenam antibiotics.[132]

Scheme 68



Scheme 69

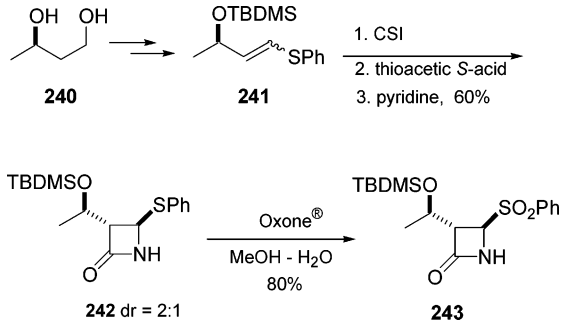


In a complementary approach, (2*S*,3*R*)-bromo acid **236** obtained from L-threonine is used to prepare oxirane **237** that is made to react with phenylthiomethyl chloride and then oxidized to give sulfone **238** (Scheme 69).[133,134] Base-induced ring closure of sulfone **238** gives 4-phenylsulfonylazetidin-2-one **239**, and the whole process occurs with a double inversion (oxirane ring enlargement) thus keeping the same configuration at C-2 of compound **236**.

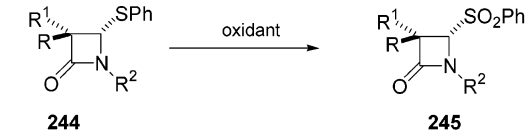
4-Thiophenylazetidin-2-one derivative **242** can be obtained using the same strategy starting from vinyl sulfide **241** that is prepared from chiral diol **249** (Scheme 70).[135] Oxidation of sulfide **242** with Oxone results in the formation of sulfone **243** in high yield.[136]

Beside the synthesis of 4-sulfonylazetidin-2-ones to be used as precursors of *N*-acylimino derivatives, some of these compounds have been prepared and tested for their pharmacological properties. Sulfones **245a**,**b** are potent inhibitors of the human leukocyte elastase, a serine protease involved in chronic inflammatory diseases of the lungs (Scheme 71).[137] Similarly, compound **245c** belongs to a novel class of cysteine protease inhibitors that are promising therapeutic agents for treatment of osteoporosis, rheumatoid arthritis, and some infectious diseases.[138]

Scheme 70

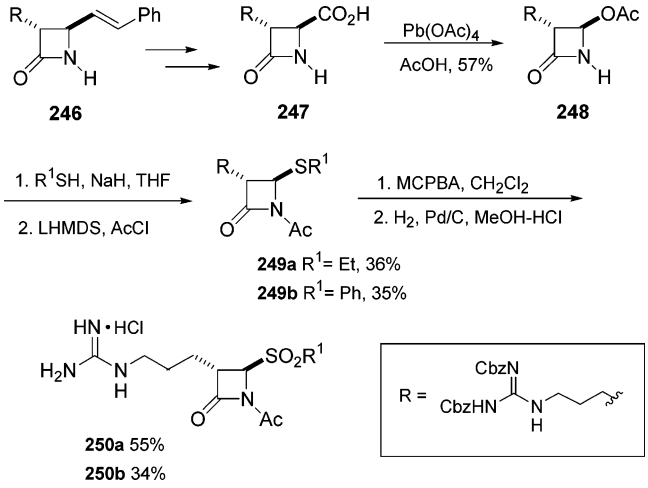


Scheme 71



entry	R	R^1	R^2	oxidant	**245** yield (%)
a	H	H	CH_2OBz	MCPBA	-
b	Et	Et	CH_2OBz	MCPBA	-
c	CbzNH, O, NH, Ph	H	H	$KMnO_4$	70

Scheme 72



Another serine protease, namely, thrombin, can be inhibited by sulfonyl derivatives **250** that can be prepared starting from azetidin-2-one **246**, which upon oxidative cleavage of the double bond gives acid **247** (Scheme 72).[139] Decarboxylation of **247** gives acetate **248** that is made to react with thiolate anions to afford sulfides **249**. Oxidation of sulfides **249** and removal of *N*-carbamoyl groups leads to compounds **250** as hydrochloride salts.

3.2. Synthetic Applications

Reaction of 4-sulfonylazetidin-2-ones **251** with organometallic reagents provides the corresponding adducts **252** in good yield (Scheme 73 and Table 25).[140−149] Grignards are usually the reagents of choice for such additions even though organocuprates give better yields in parallel experiments (Table 25,

Scheme 73

251 **252**

entries 8 and 9). 3-Substituted azetidin-2-ones react with high trans diastereoselectivity with exception of 3-triphenylmethyl derivatives that afford the addition products with modest (3:2 to 2:1) trans stereoselectivity (Table 25, entries 6, 7, and 11). 2-Tetrahydropyranthiol can also be added to sulfones **251** giving the corresponding adduct that can be easily transformed into 2-penems.[147]

A synthetic approach toward the preparation of racemic thienamycin **258** employs azetidin-2-one **253** obtained from the corresponding 4-phenylsulfonyl precursor (Scheme 74).[151]

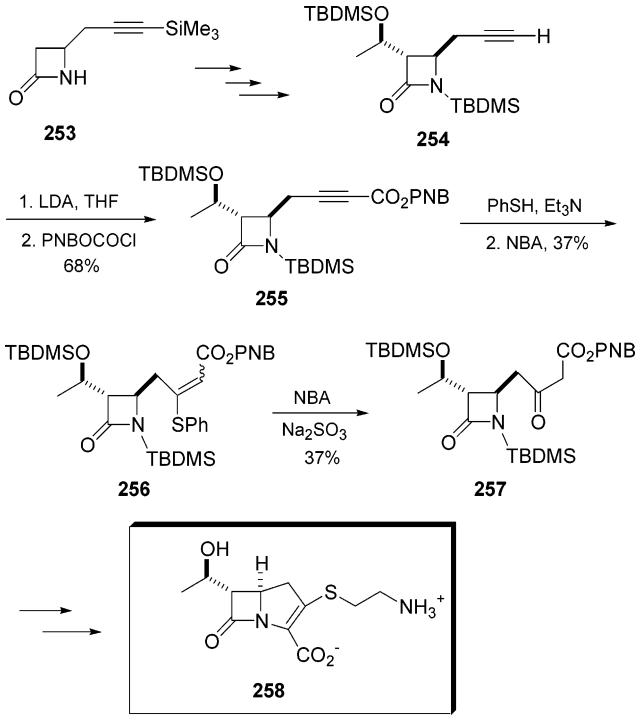
Alkyne **253** is converted into 3-substituted derivative **254** by simple transformations and then to propiolic ester **255**. The key step in this strategy is represented by the conjugate addition of thiophenol to **255** giving adduct **256** that upon reaction with *N*-bromoacetamide (NBA) affords *β*-keto ester **257**, a pivotal intermediate for the preparation of thienamycin **258**. Thienamycin **258** can also be prepared starting from 6-aminopenicillanic acid **259** that by means of some functional group transformations and oxidation is converted into bromosulfone **260** (Scheme 75).[152] Ring cleavage of **260** provides sulfinic acid **261** that is transformed into aryl sulfone **263** by reaction with quinone **262**. After further synthetic manipulations, the obtained sulfone **264** is made to react with Grignard reagent **265** giving the adduct **266** that is converted into thioester **267**, an advanced intermediate for the synthesis of thienamycin **258**.

Tricyclic diazo carbapenems display a broad spectrum antibacterial activity and can be prepared starting from sulfone **235** that upon reaction with alkynylmagnesium reagent **268** gives adduct **269** (Scheme 76).[153] The introduction of the diazine moiety is realized by means of an inverse electron demand Diels−Alder reaction using substituted tetrazine **270** to give compound **271**. Functionalization of the azetidinone ring and oxidation of the sulfide group afford sulfone **272** that by nucleophilic ring closure gives tricyclic carbapenem **273**. The same 4-sulfonylazetidin-2-one **235** can be used for the synthesis of carbapenams. This procedure involves a preliminary reaction of **235** with 3-butenylmagnesium bromide **274** giving adduct **275** that by further synthetic manipulations produces alkyne **276** (Scheme 77).[154] The carbapenam skeleton in compound **277** is subsequently obtained by a palladium-catalyzed C−N bond-forming reaction between the propargyl group and the azetidinone nitrogen.

A series of 2-chiral-substituted penem derivatives **282** has been prepared starting from sulfone **235** that by reaction with the anion of trityl mercaptan affords sulfide **278** (Scheme 78).[155]

Acylation of **278** with allyl oxalyl chloride **279** gives compound **280** that is converted into a number of

Scheme 74

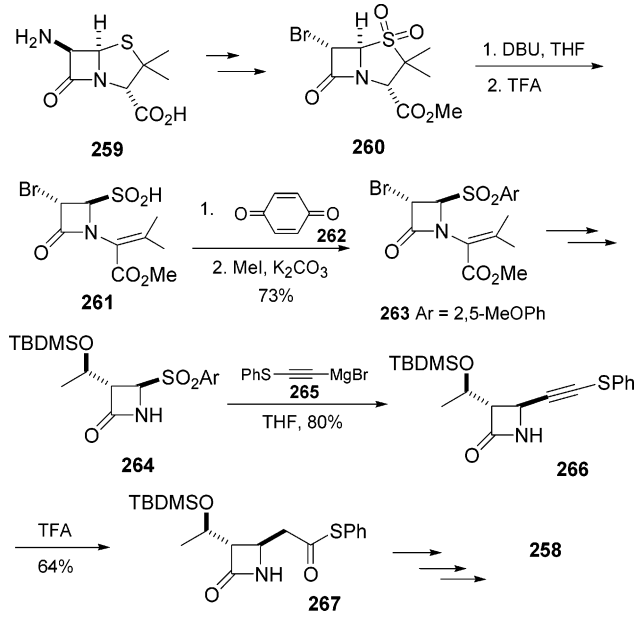


253 **254** **255** **256** **257** **258**

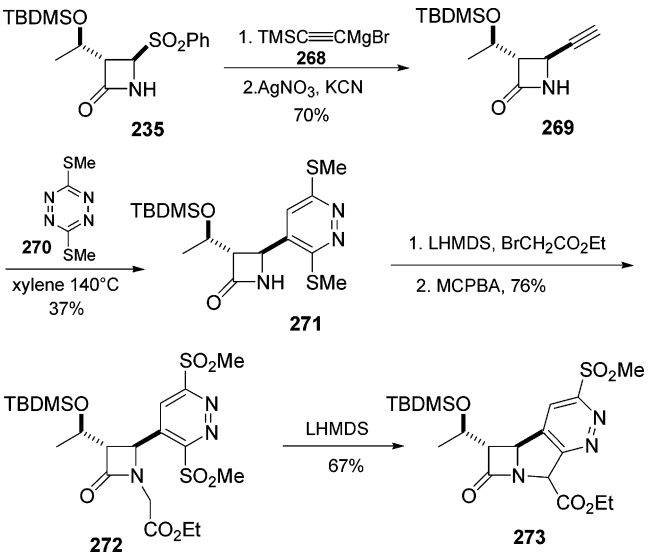
Table 25. Addition of Carbanionic Reagents to Sulfonylazetidin-2-ones 251

entry	R	R^1	R^2M	azetidinone **252** yield (%)	ref
1	H	H	$HC{\equiv}CH_2MgBr$	87	140, 141
2	H	(*R*)-Me(H)COTBDMS	$HC{\equiv}CH_2MgBr$	90	142
3	H	H	$EtOC{\equiv}CMgBr$	95	143
4	H	H	$PhSC{\equiv}CMgBr$	69	143
5	H	Ph_3CNH	$PhC{\equiv}CMgBr$	74	143
6	Ph_3CNH	H	$TMSC{\equiv}CMgBr$	52	144
7	Ph_3CNH	H	$MeC{\equiv}CMgBr$	54	144
8	H	H	$CH_2{=}CHCH_2MgCl$	55	143
9	H	H	$(CH_2{=}CHCH_2)_2CuLi$	100	143
10	H	H	$CH_2{=}CHMgBr$	65	143
11	Ph_3CNH	H	$CH_2{=}CHMgBr$	61	144
12	H	$SiMe_3$	$CH_2{=}CHMgBr$	77	149
17	CbzNH	H	Me_2CuLi	92	145
12	H	H	EtMgBr	74	143
13	H	H	$(n\text{-}Bu)_2CuLi$	94	143
14	H	H	$n\text{-}C_5H_{11}MgBr$	91	146, 147
15	H	H	$n\text{-}C_7H_{15}MgBr$	71	146, 147
16	H	(*R*)-Me(H)COTBDMS	KCN	68	148

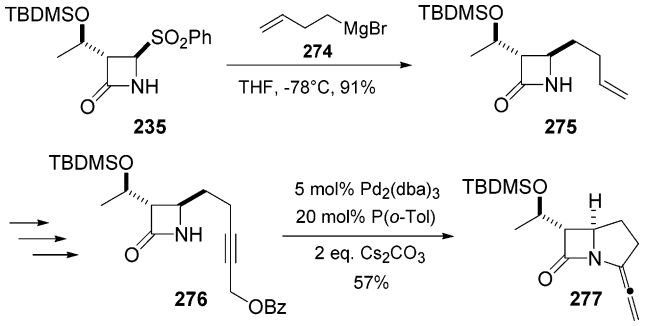
Scheme 75



Scheme 76

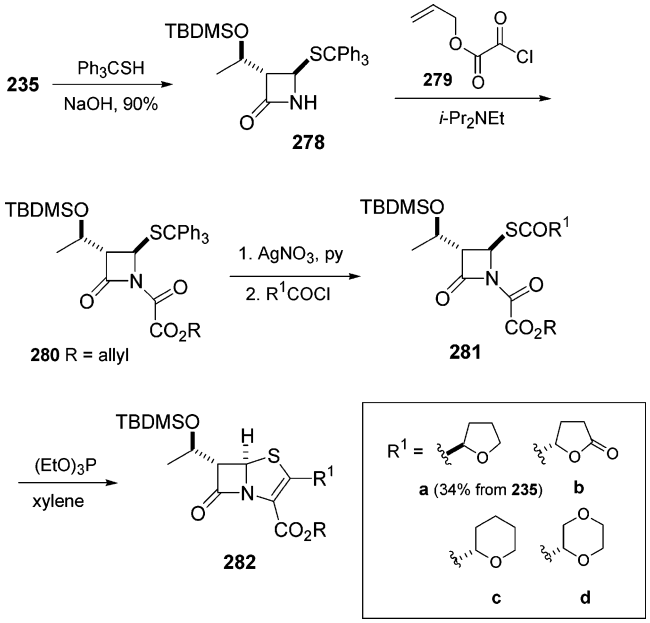


Scheme 77

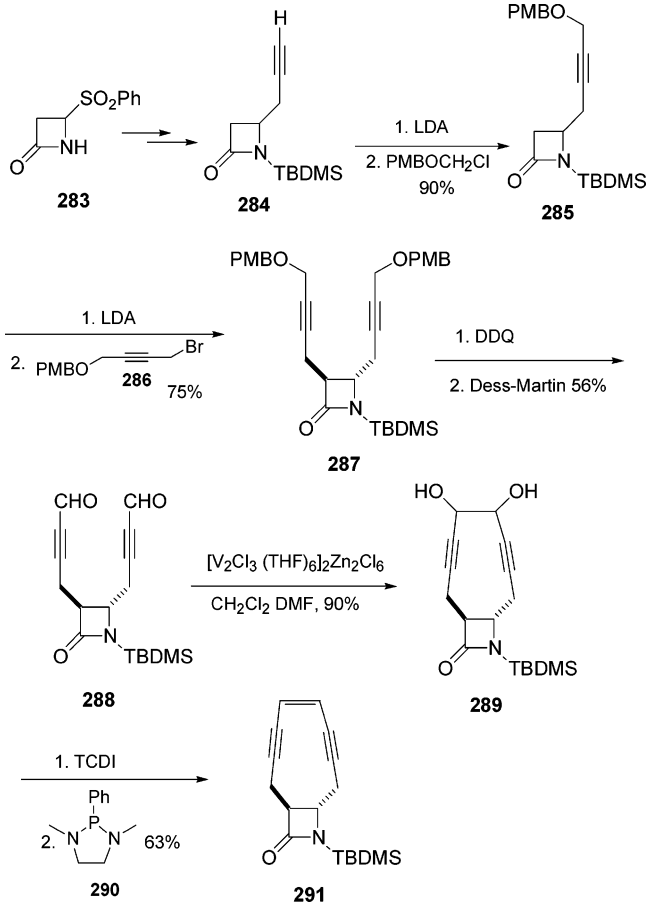


thioacyl derivatives **281** by trityl cleavage and reaction with optically active acyl chlorides. Ring closure to the penem system can be accomplished using triethyl phosphite in boiling xylene to give compounds **282**. Lactenediyne **291** belongs to a novel class of antibacterial compounds featured by a ring fusion between a β-lactam and the enediyne ring. Sulfone **283** can be easily converted into propargyl

Scheme 78



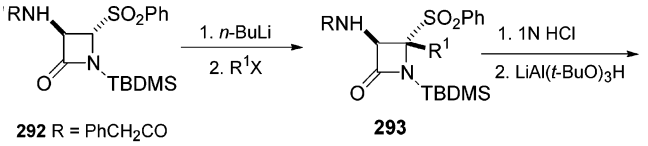
Scheme 79

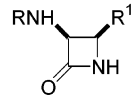


derivative **284** that by chain elongation gives compound **285** (Scheme 79).[156]

A second propargyl unit is then added to the molecule to give derivative **287** that upon deprotection and oxidation afford dialdehyde **288**. Vanadium(II)-mediated pinacol coupling of compound **288** gives the corresponding diol **289** that is converted into a cyclic thionocarbonate and then reduced using phospholidine **290** to afford lactenediyne **291**. A related

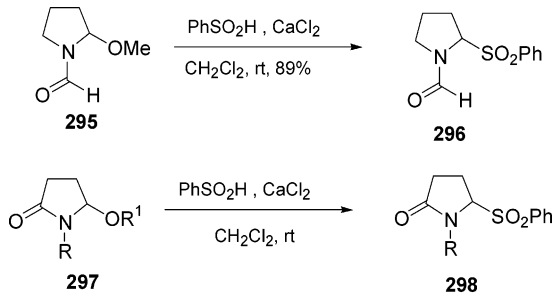
Scheme 80





entry	R^1X	**293** yield (%)	**294** yield (%)	*cis:trans*
a	MeI	69	53	92:8
b	$MeOCH_2CH_2Br$	57	68	93:7
c	$CH_2{=}CH(CH_2)_3Br$	68	57	97:3

Scheme 81



entry	R	R^1	**298** yield (%)
a	H	Et	83
b	Bn	Et	78
c	Bn	H	85

procedure allows the synthesis of other enediynyl monocyclic azetidin-2-ones starting from precursor **283**.[157]

The presence of sterically demanding groups in 3-substituted-4-sulfonylazetidin-2-ones invariably leads, in the reaction with nucleophiles, to the formation of the corresponding 3,4-trans adducts. However, the ability of the phenylsulfonyl group to stabilize carbanions at the α-position can be profitably used to introduce an alkyl framework at the 4-position. Deprotonation on silylated azetidin-2-one **292** followed by alkylation affords products **293** that after *N*-desilylation are stereoselectively reduced to give *cis*-**294** (Scheme 80).[158−160]

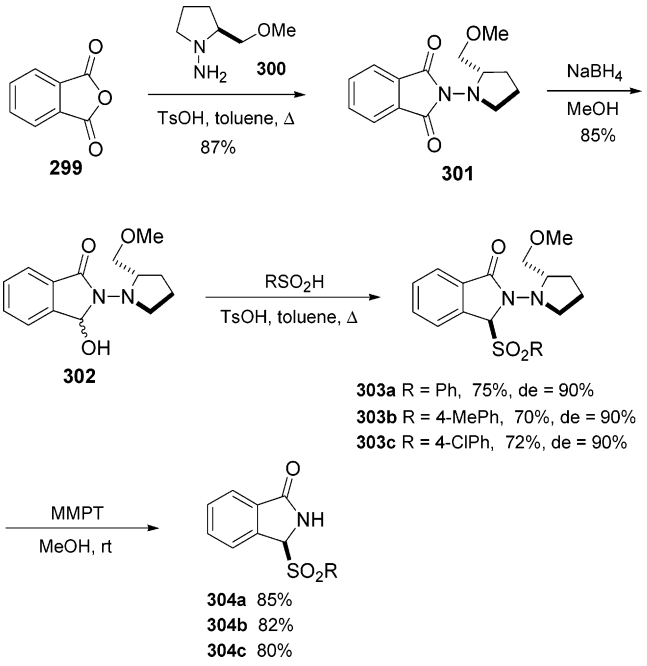
4. 5-Sulfonyl Pyrrolidin-2-ones and N-Acyl-2-sulfonyl Pyrrolidines

4.1. General Syntheses

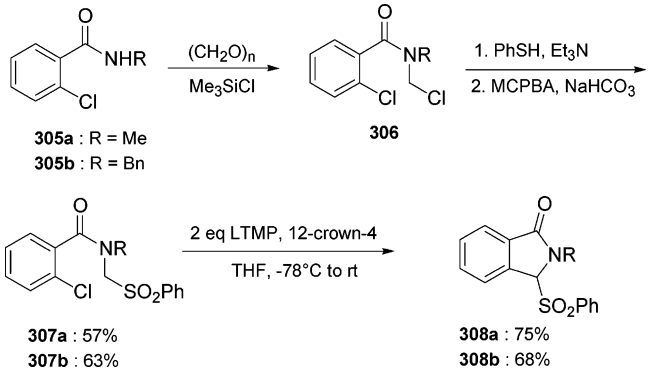
The most effective procedure to prepare α-sulfonylamido derivatives **296** and **298** consists of the reaction of the corresponding aminals or aminal ethers **295** and **297** with benzenesulfinic acid in the presence of dry $CaCl_2$ (Scheme 81).[161] Because compounds **295** and **297** are readily available by partial reduction of pyrrolidinones and cyclic imides,[28] this method has been proved to be of general application in a number of different mono- and polycyclic systems.

Optically active 3-arylsulfonyl isoindolinones **304** can be prepared starting from phthalic anhydride **299** that by reaction with SAMP **300** affords chiral hydrazide **301** (Scheme 82).[162]

Scheme 82



Scheme 83

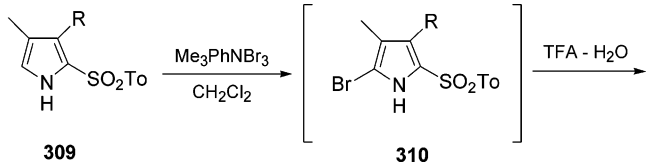


Monoreduction of **301** gives the corresponding hemiaminal **302** that upon reaction with arylsulfinic acids leads to the formation of compounds **303** via the corresponding *N*-acyliminium ion with good diastereomeric excesses that can be further improved by recrystallization. Removal of the chiral auxiliary in oxidative conditions allows the synthesis of isoindolinones **304**.

An alternative procedure can be used for the preparation of racemic *N*-alkyl isoindolinones **308** starting from 2-chloro amides **305** that by chloromethylation give compounds **306** (Scheme 83).[163] Derivatives **306** are made to react with PhSH and then oxidized to sulfones **307** that by base-induced ring closure afford sulfones **308**.

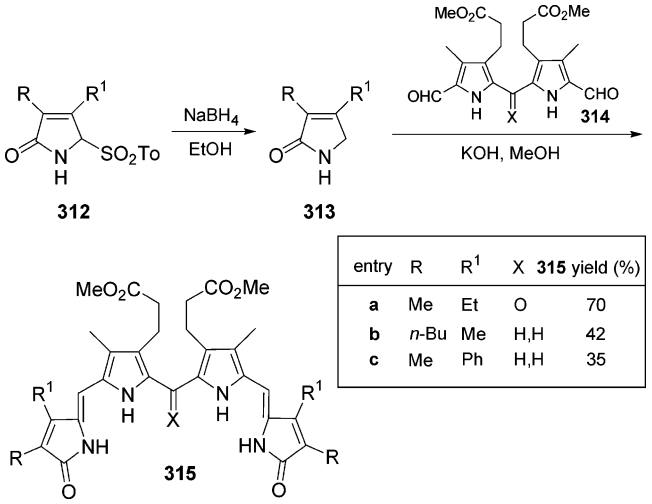
Substituted pyrroles are a convenient source of functionalized pyrrolinone derivatives. Bromination of 2-tosyl-3,4-disubstituted pyrroles **309** gives bromo derivatives **310** that in acidic aqueous conditions (TFA) afford 5-tosyl-3,4-disubstituted 3-pyrrolin-2-ones **311** (Scheme 84).[164] Recently, the acidic hydrolysis has been replaced by a two step procedure (DMSO/TFA and then iodine/Zn) to allow conversion of substituted thiopyrroles.[165]

Scheme 84



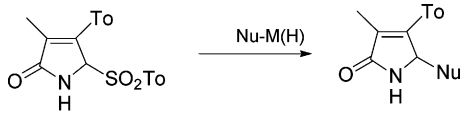
entry	R	311 yield (%)
a	4-MePh	92
b	4-MeOPh	84
c	Et	80
d	$Ph(CH_2)_2$	75

Scheme 85



entry	R	R^1	X	315 yield (%)
a	Me	Et	O	70
b	*n*-Bu	Me	H,H	42
c	Me	Ph	H,H	35

Scheme 86



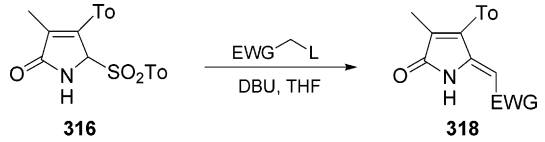
entry	Nu-M(H)	317 yield (%)
a	$MeNH_2$	91
b	MeONa	100
c	MeSNa	85
d	$(MeO_2C)CHNa$	76
e	Me_2CuLi	55

4.2. Nucleophilic Additions to *N*-Acylimino Derivatives and Synthetic Applications

Reduction of compounds **312** using $NaBH_4$ provides a rapid entry to 3,4-disubstituted 3-pyrrolin-2-ones **313** (Scheme 85).[166−170] Derivatives **313** can be coupled with dialdehydes **314** in basic conditions leading to bilirubin analogues **315** that can be used in important metabolic studies.[171] Heteronucleophiles, malonates, and organocopper reagents react with sulfone **316** following the usual pathway that involves an *N*-acylimine as the intermediate. A subsequent nucleophilic addition affords substituted pyrrolones **317** (Scheme 86).[164]

When the active methylene compound bears a good leaving group (L), the addition to the intermediate *N*-acylimine obtained from compound **316** is followed by the elimination of the leaving group, thus giving unsaturated derivatives **318** with enhanced *Z* stereoselectivity (Scheme 87).[164]

Scheme 87



entry	EWG	L	318 yield (%)	*Z*:*E*
a	CN	Ms	75	93:7
b	CN	Ts	74	89:11
c	$PhSO_2$	$PhSO_2$	53	91:9
d	CO_2Et	Ts	63	96:4
e	COPh	Ts	82	72:28

Scheme 88

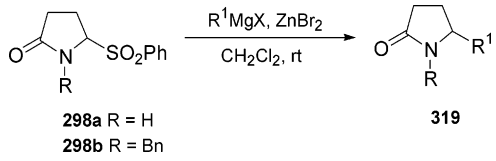


Table 26. Reaction of Grignard Reagents with 2-Sulfonyl Pyrrolidinones 298

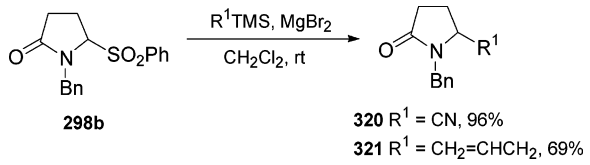
entry	R	R^1MgX	pyrrolidinone **319** yield (%)
1	Bn	MeMgBr	85
2	H	EtMgCl	52
3	Bn	EtMgCl	75
4	Bn	PhMgBr	81
5	Bn	CH_2=$CHMgBr$	82
6	Bn	CH_2=$CHCH_2MgBr$	84
7	Bn	CH_2=$CH(CH_2)_3MgBr$	81
8	Bn	$PhCH_2MgBr$	78

The reaction of sulfonyl derivatives **298** with Grignard reagents in the presence of $ZnBr_2$ leads to the expected substitution products **319** (Scheme 88 and Table 26).[161,172]

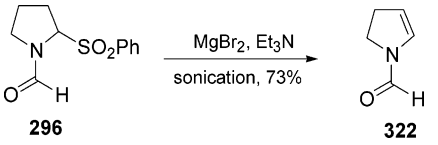
In this context, it is interesting to observe that for this process an intermediate *N*-acylimine is conceivable only with *N*-unsubstituted compound **298a** (Table 26, entry 2). The reaction of compound **298b** clearly involves a different intermediate since the organomagnesium reagent and $ZnBr_2$ are both mandatory for a successful reaction. In principle, the Lewis acidity of $ZnBr_2$ may be responsible for the formation of a *N*-acyliminium ion intermediate that would react with the Grignard reagent giving compounds **319**. On the other hand, a single electron transfer (SET) mechanism that very often occurs when organomagnesium reagents are involved in addition reactions cannot be ruled out. At any event, the *N*-acyliminium ion is certainly involved as an intermediate in the reaction of sulfone **298b** with TMS derivatives promoted by $MgBr_2$, and this observation would also support the formation of this intermediate in the reaction with Grignard reagents (Scheme 89).

The ability of $MgBr_2$ to facilitate the elimination of the benzenesulfinic anion seems to be confirmed by the formation of enecarbamate **322** from sulfone **296** in the absence of any nucleophilic reagent that

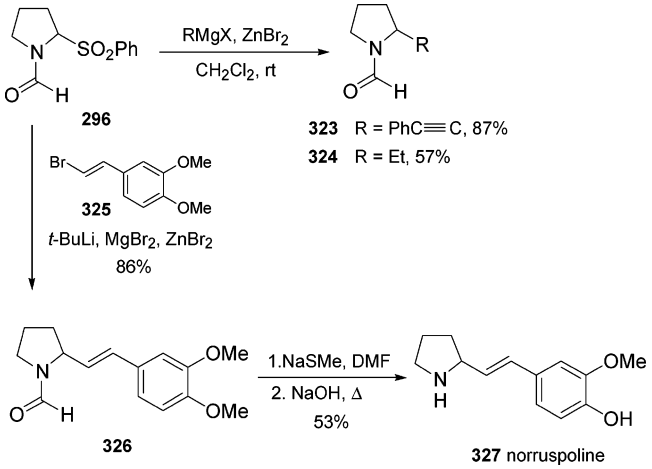
Scheme 89



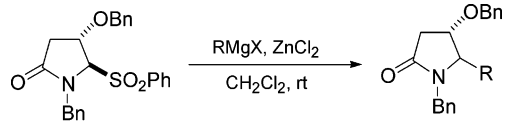
Scheme 90



Scheme 91



Scheme 92



entry	RMgX	**329** yield (%)	*trans:cis*
a	MeMgBr	89	75:25
b	EtMgBr	82	83:17
c	n-$C_7H_{15}MgBr$	71	71:29
d	$PhCH_2MgCl$	62	83:17

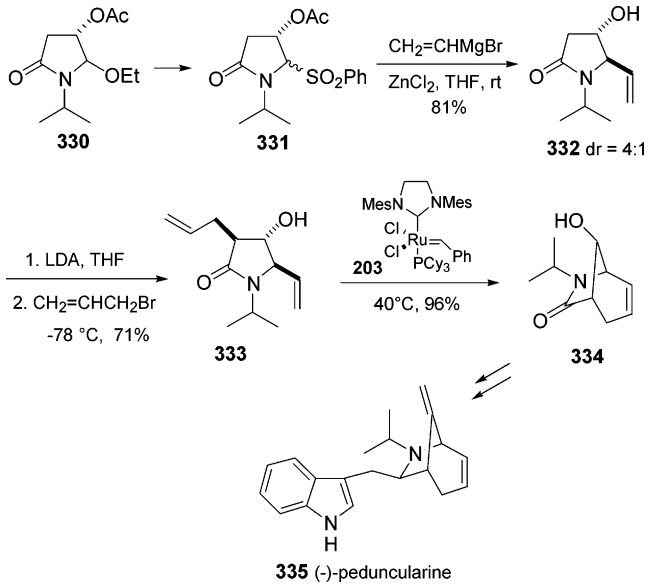
may react with the intermediate *N*-acyliminium ion (Scheme 90).

Grignard reagents also react with *N*-formyl sulfone **296** leading to adducts **323** and **324**, and this strategy represents the key step to the synthesis of the alkaloid norruspoline **327** (Scheme 91). Vinyl bromide **325** is lithiated, converted into the Grignard reagent by transmetalation, and then made to react with **296** to give the adduct **326**. Selective cleavage of the 4-methoxy and *N*-formyl groups completes the preparation of norruspoline **327**.

The presence of a stereogenic center in close proximity to the sulfonyl group is able to exert only a modest degree of trans stereoselectivity in the reaction of **328** with Grignard reagents leading to compounds **329** (Scheme 92).[173,174]

The reactivity of 5-sulfonylpyrrolidinones **331** toward Grignard reagents is far superior than the

Scheme 93



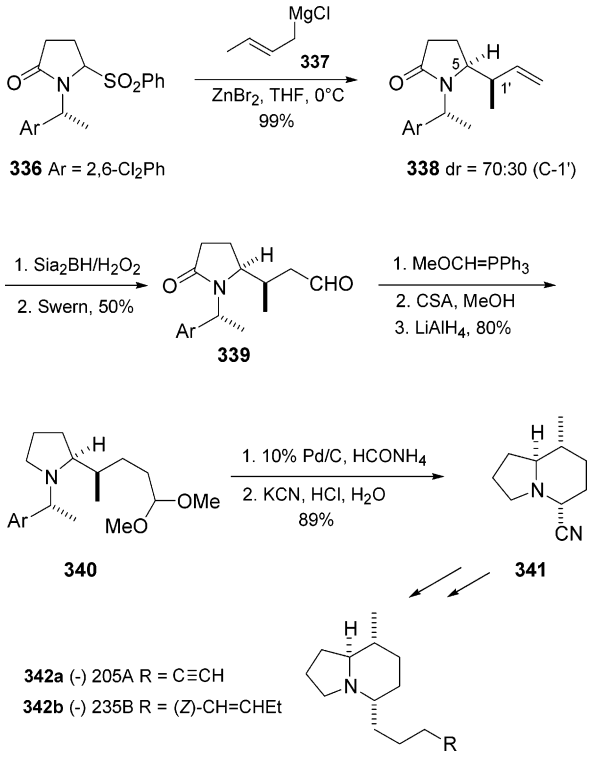
corresponding 5-ethoxylactams **330** as demonstrated by a synthetic approach directed to the preparation of the alkaloid (−)-peduncularine **335** (Scheme 93).[175] Compound **330** gives only poor results in the reaction with Grignard reagents; however, its conversion into sulfone **331** allows a clean and stereoselective reaction with vinylmagnesium bromide leading to adduct **332**. α-Alkylation of the lactam provides diene **333** that by RCM using second generation Grubb's catalyst **203** gives bicyclic derivative **334** an advanced intermediate to the synthesis of (−)-peduncularine **335**.

Chiral substituents on the lactam nitrogen are able to exert better levels of diastereoselectivity than ring substituents in 5-sulfonylpyrrolidin-2-ones. The chiral 2,6-dichloroarylmethyl group in compound **336** represents the optimum choice to completely control the stereochemistry at the 5-position in the reaction with 2-butenylmagnesium reagent **337** leading to adduct **338**, although a lower stereoselectivity is observed at C-1′ (Scheme 94).[176] Hydroboration−oxidation of compound **338** followed by a Swern oxidation affords aldehyde **339** that after chain elongation and acetalization is reduced to the substituted pyrrolidine **340**. Removal of the *N*-protecting group and subsequent reaction with KCN afford α-amino nitrile **341**, a central intermediate for the synthesis of indolizidine alkaloids (−)-205A and (−)-235B **342**.

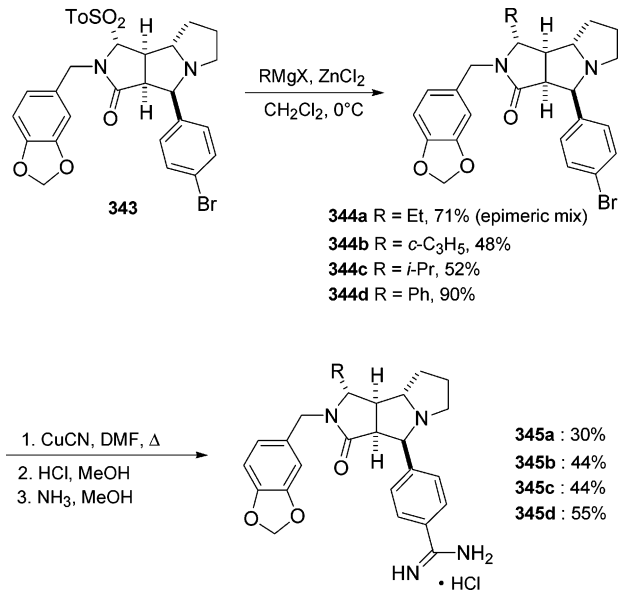
The reaction of Grignard reagents with α-amido sulfones endowed with structurally rigid frameworks usually occurs with high diastereoselectivity. Sulfone **343** is featured by a sterically demanding tricyclic core and by reaction with Grignard reagents gives the corresponding substitution products **344** as single diastereomers with the exception of **344a** that is obtained as an epimeric mixture (Scheme 95).[177−179] Compounds **344** can be converted into amidinium salts **345** that represent a novel class of thrombin inhibithors, **345c** being the more active.

Similarly, tricyclic sulfone **346** reacts with heptylmagnesium bromide with complete *exo* stereoselectivity giving adduct **347** in good yield (Scheme 96).[180,181]

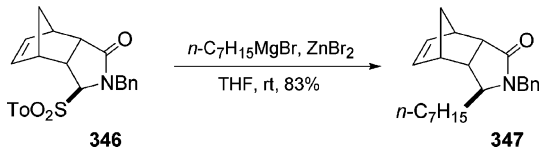
Scheme 94



Scheme 95

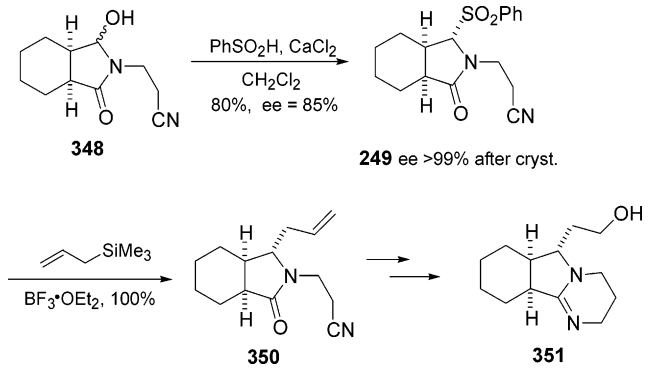


Scheme 96



As previously stated, α-amido sulfones are mostly crystalline compounds and this feature can be of great importance in the preparation of enantiopure intermediates involved in chiral syntheses. The epimeric mixture of hydroxy lactam **348** can be converted into the corresponding sulfone that being a solid compound can be recrystallized to give enantiomerically pure **349** (Scheme 97).[182,183] Sulfone **349**

Scheme 97



Scheme 98

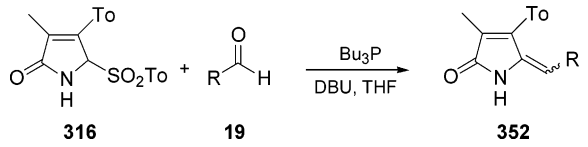


Table 27. Phospine-Mediated Coupling of Sulfones 316 with Aldehydes 19

entry	R	pyrrolidinone **352** yield (%)	*Z*/*E*
1	Ph	64	33/67
2	4-MePh	82	32/68
3	4-NO_2Ph	50	63/37
4	4-BrPh	56	100/0
5	4-BnOPh	54	48/52
6	2-BrPh	52	67/33
7	2-furyl	85	42/58
8	(*E*)-PhCH=CH	87	
9	EtO_2C	98	55/45
10	Me	56	63/37

is allylated via the corresponding *N*-acyliminium ion affording compound **350** that is subsequently transformed into amidine **351**, a potentially useful chiral catalyst in enantioselective conjugate additions.

4.3. Other Applications

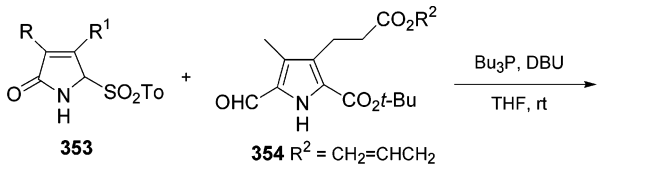
Direct coupling of sulfones **316** with aldehydes **19** in the presence of Bu_3P/DBU affords products **352** in fairly good yields although the stereocontrol of the newly formed unsaturation is not generally notable (Scheme 98 and Table 27).[184]

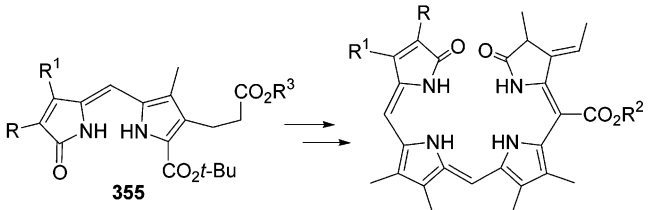
This procedure can be profitably employed for the synthesis of phycocyanobilin derivatives **356**, compounds featured by a linear tetrapyrrole structure involved in higher plants metabolism (Scheme 99).[185−188] Coupling sulfones **353** with pyrrolealdehyde **354** gives adduct **355** that by further coupling with another dimeric pyrrole affords phycocyanobilin derivatives **356**. Other di- and tetrapyrrole derivatives prepared using this procedure are phytochromobilin,[189] phycobilin,[190] biliverdin,[191] and dipyrrinones.[192]

Desulfonylative coupling of amidosulfones **308** with aldehydes and ketones **357** leading to derivatives **358** can be realized using SmI_2 as a promoter (Scheme 100).[193,194] As usual, a large excess (3−5 equivalents) of SmI_2 is required for an efficient process.

Intramolecular conjugate addition of the α-sulfonyl carbanion generated from compound **359** using NaH

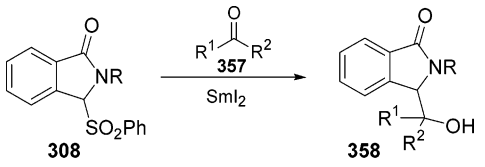
Scheme 99





entry	R	R^1	355 yield (%)
a	Me	Et	88
b	Ar	Et	73
c	Me	Ar	87

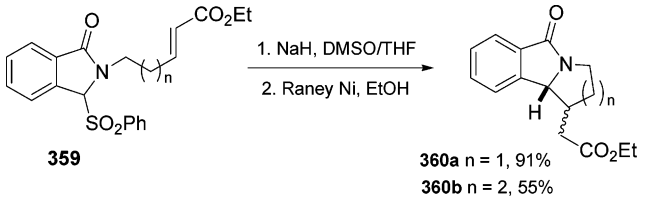
Scheme 100



entry	R	R^1	R^2	358 yield (%)
a	Me	*n*-C_6H_{13}	H	90[a]
b	Bn	*n*-C_6H_{13}	H	80[b]
c	Bn	Me	Me	85
d	Bn	Me	*n*-C_3H_7	73
e	Bn	Me	Ph	85

[a] dr = 98:2; [b] dr = 79:21

Scheme 101



leads to the formation of a tricyclic derivative that by reductive desulfonylation affords compounds **360** as a mixture of diastereomers (Scheme 101).[195]

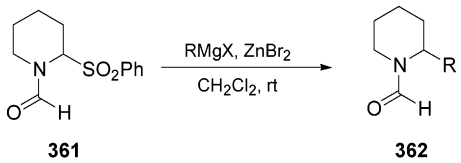
5. 6-Sulfonyl Piperidin-2-ones and N-Acyl-2-sulfonyl Piperidines

5.1. Nucleophilic Additions to *N*-Acylimino Derivatives and Synthetic Applications

The preparation of six-membered ring sulfones **361** parallels that of the corresponding five-membered homologues, and their reaction with Grignard reagents can be realized essentially in the same conditions giving adducts **362** (Scheme 102).[161]

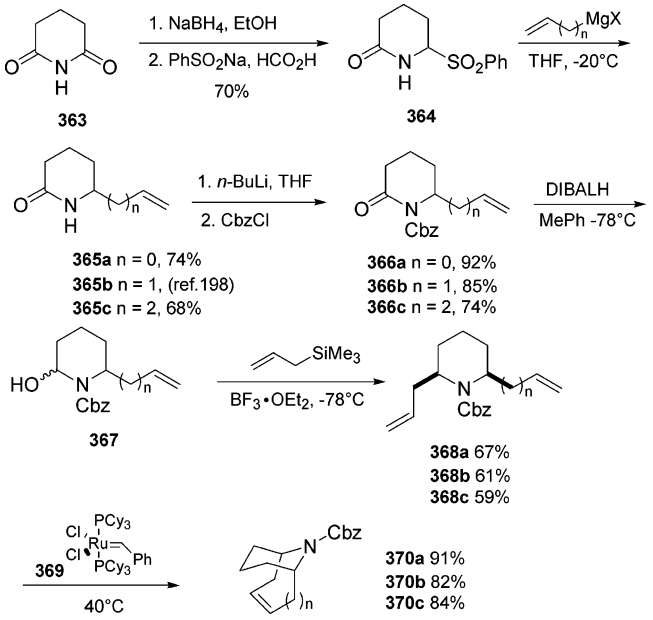
The bridged azabicyclic structure is a common motif in a large number of nitrogen-containing natural and unnatural substances. In a synthetic approach toward this class of derivatives, glutarimide **363** is partially reduced to the corresponding ethoxylactam and then converted into sulfone **364** by the usual procedure (Scheme 103).[196,197] The reaction of sulfone **364** with Grignard reagents occurs via the corresponding *N*-acylimine and affords unsaturated derivatives **365** that are successively carbamoylated at the amide nitrogen to give compounds **366**. Reduction of the amido group in compounds **366** leads to the corresponding aminals **367** that are allylated via the *N*-acyliminium ion leading to dienyl derivatives **368**. Finally, compounds **368** undergo a RCM procedure using catalyst **369** to produce bicyclic derivatives **370**.

Scheme 102



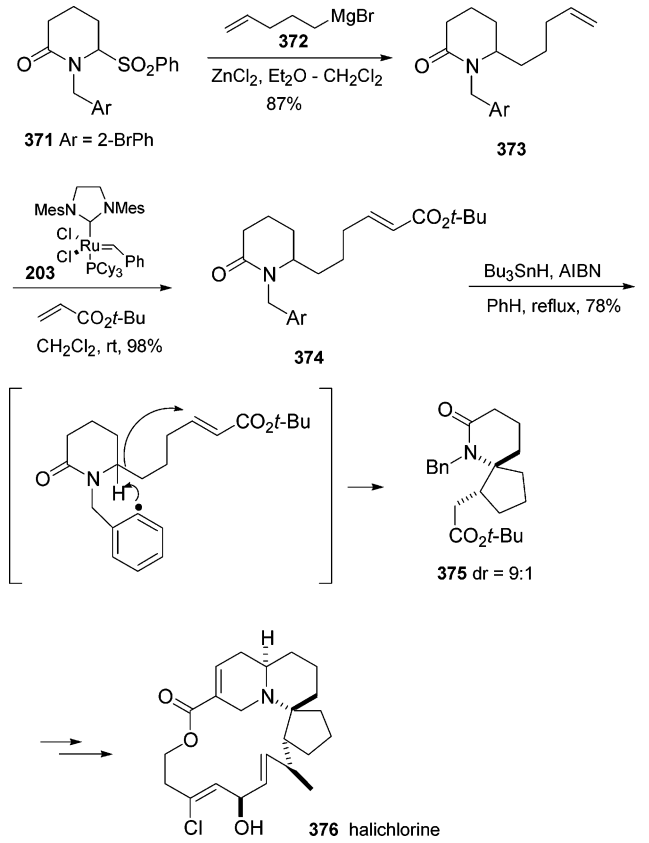
entry	R	362 yield (%)
a	Ph	87
b	2-thienyl	81
c	CH_2=CH	84

Scheme 103

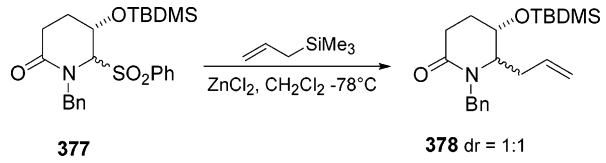


The reaction of 4-pentenylmagnesium bromide **372** to sulfone **371** represents one of the first steps relative to the synthesis of the marine alkaloid halichlorine **376** (Scheme 104).[199] The adduct **373** thus obtained undergoes a chain elongation by means of an intermolecular RCM using catalyst **203** and *tert*-butyl acrylate giving unsaturated ester **374**. The key transformation leading to azaspirocyclic intermediate **375** involves a cascade radical translocation−cyclization process promoted by the slow addition of Bu_3SnH to the reaction mixture. Compound **375** is an advanced intermediate toward the preparation of racemic halichlorine **376**.

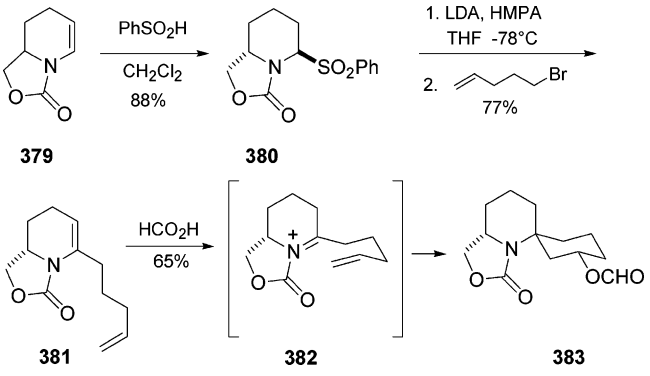
Scheme 104



Scheme 105



Scheme 106



In six-membered ring sulfones such as **377**, the stereocontrol produced by vicinal stereocenters is even worse than that observed in five-membered analogues. As a matter of fact, the reaction of sulfone **377** with allyltrimethylsilane in the presence of $ZnCl_2$ gives an almost equimolar mixture of cis and trans diastereomers of the adduct **378** (Scheme 105).[200]

The ability of the phenylsulfonyl group in promoting the formation of carbanions α to the sulfone moiety can be used to prepare some azaspirocyclic derivatives. Enecarbamate **379** is transformed into sulfone **380** by addition of benzenesulfinic acid and then converted into the corresponding α-sulfonyl carbanion using LDA (Scheme 106).[201] Alkylation of this anion occurs with concomitant elimination of benzenesulfinic acid to afford substituted enecarbamate **381**. This enecarbamate, upon treatment with formic acid, gives the *N*-acyliminium ion **382** that cyclizes by a favored 6-*endo-trig* process to spiro derivative **383**.

6. Conclusion

N-Acylimino derivatives have been introduced in synthesis to overcome the low electrophilic character of *N*-alkyl and *N*-arylimines that is a major drawback in addition reactions with nucleophiles. The enhanced electrophilicity of *N*-acylimino derivatives is usually associated with their instability; this makes advisable the in situ generation of these compounds from suitable precursors. Different α-substituted amido derivatives can be used in order to generate *N*-acylimino compounds by an acid or base-promoted elimination of a good leaving group. The best *N*-acylimino precursors would join ready access from simple reagents, easy handling, and high stability. These features are proper of α-amido sulfones that are easily prepared by a three-components coupling (aldehyde, amide or carbamate, and sulfinic acid or its salt). Furthermore, α-amido sulfones are mostly stable solids easy to purify and store for prolonged times. A wide range of nucleophilic reagents can be used in the reaction with α-amido sulfones including organometallic reagents, stabilized carbanions, heteronucleophiles, and reducing agents. Target molecules prepared using α-amido sulfones include the following: α- and *β*-amino acids, allyl and propargylamines, substituted pyrrolidines, *β*-lactams, alkaloids, and many others. A growing number of asymmetric catalytic processes using chiral catalysts utilize α-amido sulfones as *N*-acylimino equivalents for the preparation of optically active amines. Asymmetric catalysis represents a very important field of application for α-amido sulfones, and other stimulating results are to be expected soon for this class of derivatives.

7. Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*t*-butoxycarbamoyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzylcarbamoyl
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cys	cysteine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-4-benzoquinone
de	diastereomeric excess
DIBALH	diisobutylaluminum hydride
DMAP	4-*N*,*N*-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5.6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
ee	enantiomeric excess

EWG	electron-withdrawing group
Gly	glycine
HMPA	hexamethylphosporic triamide
LDA	lithium diisopropylamide
LHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazide
LTMP	lithium 2,2,5,5-tetramethylpiperidide
MCPBA	*meta*-chloroperoxybenzoic acid
Mes	2,4,6-trimethylphenyl
MMPT	magnesium monoperoxyphthalate
$Mn(acac)_3$	manganese acetylacetonate
MOM	methoxymethyl
Ms	methanesulfonyl
NBA	*N*-bromoacetammide
$Pd_2(dba)_3$	tris(dibenzylideneacetone) dipalladium
PEMP	*N*-methyl-2,2,6,6-tetramethylpiperidine
Piv	2,2-dimethylpropanoyl (pivaloyl)
PMB	4-methoxybenzyl
PNB	4-nitrobenzyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
RCM	ring-closing metathesis
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
Sia_2BH	bis(3-methyl-2-butyl)borane
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulfate
TBDMS	*tert*-butyldimethylsilyl
TCDI	thiocarbonyl diimidazole
Tf	trifluoromethansulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
thexyl	2,3-dimethyl-2-butyl
THF	tetrahydrofuran
TMS	trimethylsilyl
To	4-methylphenyl (tolyl)
Tr	triphenylmethyl (trityl)
Ts	4-toluenesulfonyl (tosyl)

8. Acknowledgments

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