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N-ALKYLIDENESULFINAMIDES

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This review covers the preparation and reactions of racemic and chiral *N*-alkylidenesulfinamides or sulfinimines, based on a CA search. Racemic sulfinimines have been prepared by imine formation of sulfinamides with ketones (only ketones containing electron-withdrawing groups react), oxidation of *N*-akylidenesulfenamides, and rearrangement of *N*-chlorosulfoximines. The chiral compounds have been prepared by addition of organomagnesium or organolithium reagents or of diisobutylaluminium hydride to nitriles, followed by *l*-menthyl (*S*)-*p*-toluenesulfinate, displacement reactions of lithium hexamethyldisilazide with *l*-menthyl (*S*)-*p*-toluenesulfinate, followed by CsF and aldehydes, asymmetric oxidation of *N*-alkylidenesulfenamides, and reactions of *l*-menthyl imidic esters with *p*-toluenesulfinyl chloride. Thermal fragmentations, nucleophilic addition reactions (attack at imino carbon) of *N*-alkylidenesulfinamides with various nucleophiles, and 1,3-dipolar cycloadditions illustrate the versatility of this functional group in organic synthesis.

Keywords: *N*-Alkylidenesulfinamides or sulfinimines; α-, β-, and γ-amino acids; β-lactams; β-amino phosphonic acids; imidazolidines; 1,3-dipolar cycloaddition

CONTENTS

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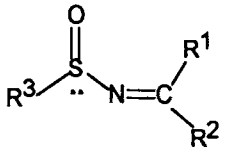
1. INTRODUCTION

The organic chemistry of sulfur has been recognized to be one of the most studied fields in recent years.[1] Particularly, asymmetric induction reactions involving sulfur stereocenters have been investigated extensively due to the availability of many methods for the preparation of enantiopure materials. For example, chiral sulfoxides, *N*-alkylidenesulfinamides (or sulfinimines), and sulfoximines are functional groups that have been used. This review covers preparations and reactions of racemic and optically active *N*-alkylidenesulfinamides.[2]

N-Alkylidenesulfinamides are compounds possessing trivalent nitrogen bonded to tetravalent sulfur where the nitrogen forms a π bond with carbon while the sulfur is bonded to oxygen. This resembles the α-enone functionality. Many useful synthetic organic reactions evolved from this class of molecules and in part are based on the following advantages: (i) The imino functional group is stable at room



***N*-alkylidenesulfinamides 1**

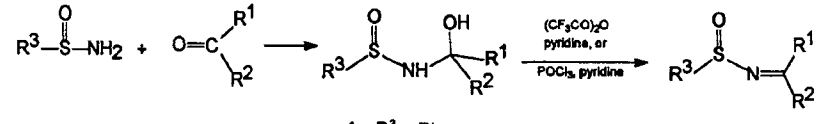
temperature and allows purification by silica gel column chromatography; (ii) the sulfur stereocenter does not racemize at room temperature (in refluxing benzene, decomposition to disulfide, thiosulfonate, and nitrile as the major products has been observed[3]); and (iii) the N–S bond of sulfinamides (derived from addition reactions of *N*-alkylidenesulfinamides with organometallic reagents) can readily be cleaved under mild acidic conditions such as trifluoroacetic acid in an alcoholic solvent at room temperature.

2. PREPARATIONS

2.1. Racemic *N*-Alkylidenesulfinamides

2.1.1. Imine formation by coupling of sulfinamides with ketones

Similar to the condensation of amines and ketones, the coupling of sulfinamides **2** (such as benzenesulfinamide) with ketones **3** yields α-hydroxy sulfinamides **4** which upon treatment with trifluoroacetic anhydride and pyridine or phosphoryl chloride and pyridine give sulfinimines **1** (Scheme 1).[4] It appears that only highly reactive ketones such as hexafluoroacetone and 1,3-dichloro-1,1,3,3-tetrafluoroacetone provide coupling products such as **4**. Hence, attempted coupling of benzenesulfinamide with *n*-butyl glyoxylate and potassium carbonate in refluxing THF failed to provide the adduct or the imine.[5]



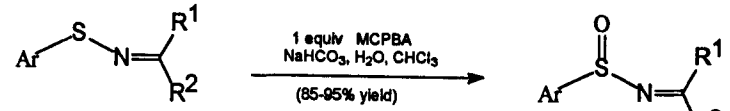
2a: R^3 = Ph
2b: R^3 = *p*-Tol

3a: $R^1 = R^2 = CF_3$
3b: $R^1 = R^2 = CClF_2$

4a: R^3 = Ph
$R^1 = R^2 = CF_3$ (74%)
4b: R^3 = *p*-Tol
$R^1 = R^2 = CClF_2$ (68%)
5a: R^3 = *p*-Tol
$R^1 = R^2 = CF_3$ (70%)
5b: R^3 = *p*-Tol
$R^1 = R^2 = CF_3$ (72%)

1a: R^3 = Ph
$R^1 = R^2 = CF_3$ (42%)
1b: R^3 = *p*-Tol
$R^1 = R^2 = CF_3$ (37%)

SCHEME 1



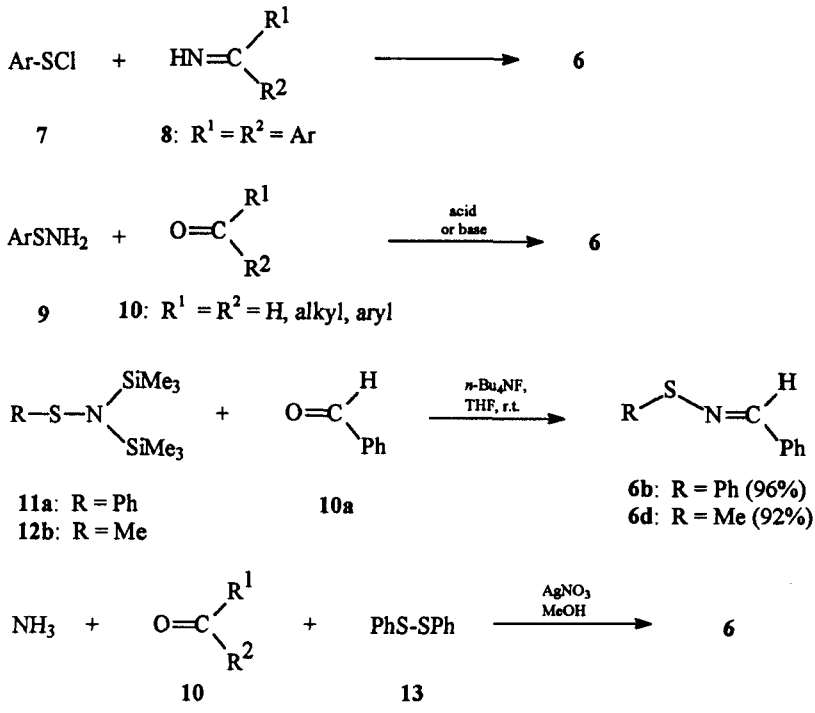
6a: $R^1 = R^2$ = Me
6b: R^1 = H, R^2 = Ph
6c: R^1 = H, R^2 = Me

1

SCHEME 2

2.1.2. *Oxidation of N-alkylidenesulfenamides*

Oxidation of *N*-alkylidenesulfenamides **6** with one equivalent of *m*-chloroperbenzoic acid (MCPBA) and sodium bicarbonate in chloroform and water gave the corresponding *N*-alkylidenesulfinamides **1** in 85–95% yield (Scheme 2).[3] The preparation of *N*-alkylidenesulfenamides **6** has been reviewed[6] and the general methods are summarized in Scheme 3 as: (i) displacement reactions of C,C-diarylimines **8** with arenesulfenyl chlorides (**7**);[7] (ii) condensation of arenesulfenamides **9** with ketones or aldehydes **10** in the presence of acid or base;[8] (iii) condensation of aldehydes or ketones with *N*,*N*-bis(trimethylsilyl)-sulfenamides in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride in THF;[9] and (iv) imine formation from ammonia and a ketone followed by displacement with a disulfide **13** in the presence of silver nitrate in methanol.[10]



SCHEME 3

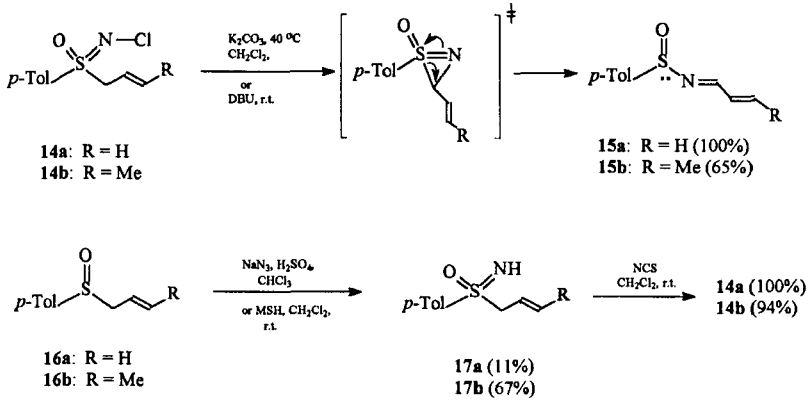
2.1.3. *Rearrangement of N-chlorosulfoximines*

The base induced rearrangement[11] of *N*-chlorosulfoximines **14** with potassium carbonate in CH_2Cl_2 at 40 °C (**14a**) or with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at r.t. (**14b**) affords the conjugated sulfinimines **15a** (100% yield) and **15b** (65% yield), respectively (Scheme 4).[11b] Presumably, the α-sulfoximine anion undergoes intramolecular ring closure to provide a three-membered thiazirine intermediate which then ring opens. *N*-Chlorosulfoximines **14** have also been prepared from allyl sulfoxides **16** with sodium azide and sulfuric acid in $CHCl_3$ (**16a**) or with *O*-mesitylsulfonylhydroxylamine (MSH) in CH_2Cl_2 (**16b**), followed by chlorination with *N*-chlorosuccinimine. It has been found that the reaction of sulfoxide **16b** with MSH gives a higher yield of the sulfoximine (**17b**; 67%) than that with sodium azide.

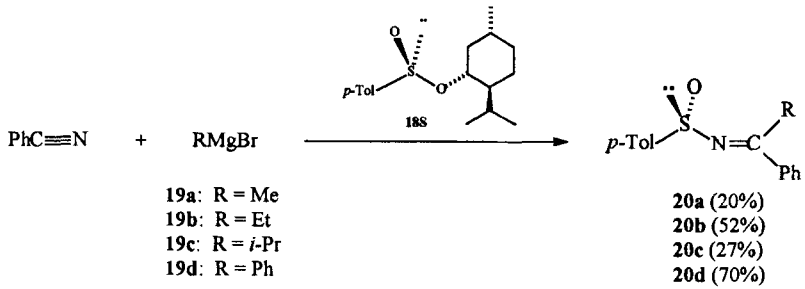
2.2. Optically Active *N*-Alkylidenesulfinamides

2.2.1. *Displacement of N-lithiated imines with l-menthyl (S)-p-toluenesulfinate*

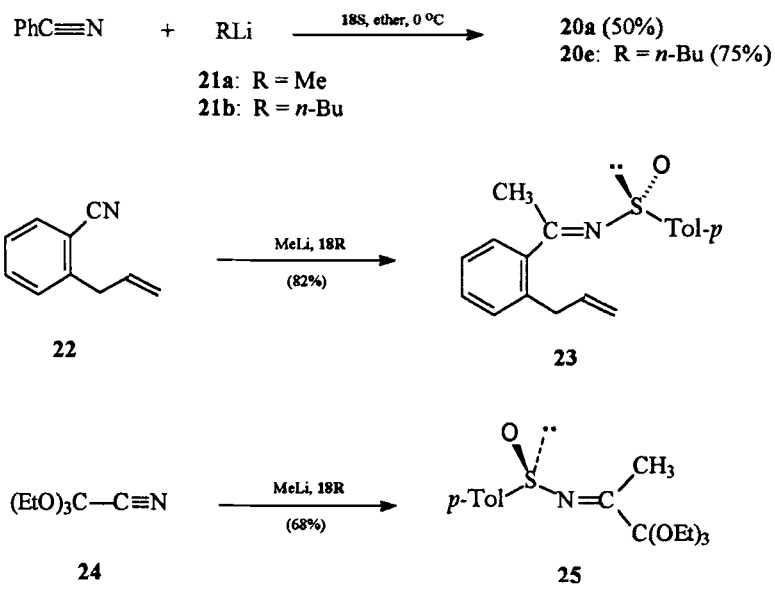
The chiral *N*-benzylidenesulfinamides **20a–d** were first prepared in 20–70% yield by the reaction of Grignard reagents **19** with benzonitrile, followed by *l*-menthyl (*S*)-*p*-toluenesulfinate (**18S**) (Scheme 5).[12] The optical purity of **20a** was determined to be $\geq 95\%$ by ^{1}H NMR with the chiral shift reagent Eu(tfc)$_3$. The partial racemization presumably occurs via attack of the *N*-bromomagnesioimine at the sulfur of (*S*)-**20a** to give the inversion product (*R*)-**20a**. In an improved procedure[13] benzonitrile is treated with alkyllithium **21** in diethyl ether,



SCHEME 4

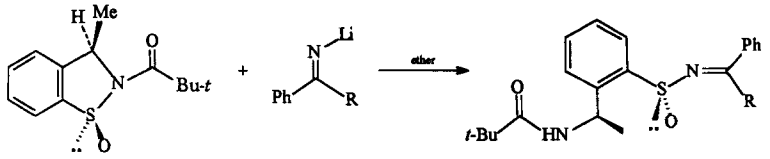


SCHEME 5

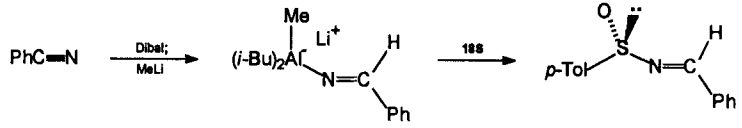


SCHEME 6

followed by **18S** (50–82% yield; Scheme 6).[13] The stereochemistry (including the absolute configuration at sulfur) of the sulfinimine **20a** prepared by this method has been confirmed by X-ray diffraction.[13b] Inversion of configuration at sulfur was found in this displacement reaction. The optical purity of **20a** was determined to be ~100%. Similarly, treatment of *o*-allylbenzonitrile with methyllithium in diethyl ether, followed by *d*-menthyl (*R*)-*p*-toluenesulfinate (**18R**) gave the sulfinimine **23** in 82% yield.[14] The addition reaction of triethoxyacetonitrile (**24**) with MeLi in diethyl ether, followed by sulfinate **18R** gave a 68% yield of the sulfinimine **25**; >98% ee.[15] A drawback of these methods is that when alkanenitriles are used, α-CH deprotonation of the nitrile by the organometallic reagents competes with the nucleophilic addition to the C≡N group. Besides the sulfinates **18**, a different chiral trapping reagent, **26**, was also used in the preparation of the enantiopure sulfinimines **28** by treatment of *N*-lithioimines **27** with the cyclic sulfinamide (+)-**26** in diethyl ether (Scheme 7).[16]



SCHEME 7



SCHEME 8

2.2.2. *Formation of iminoaluminates followed by displacement with l-menthyl (S)-p-toluenesulfinate*

A procedure similar to that described in Section 2.2.1., i.e. reduction of benzonitrile with diisobutylaluminum hydride (Dibal), followed by formation of the "ate" complex with methyllithium, provided the intermediate **29** which underwent a displacement reaction with the sulfinate **18S** to give the *N*-benzylidenesulfinamide **30** in 36% yield (>95% ee) possessing an H at the C=N function (Scheme 8).[17] Again, this method suffers from the basic nature of Dibal, and no sulfinimine was detected when *n*-pentanenitrile was used.

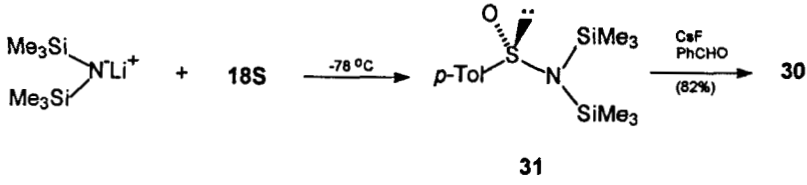
2.2.3. *Condensation of N,N-bis(trimethylsilyl)sulfinamide with aldehydes*

Utilizing the ease of generation of the anion of a sulfinamide from a silylated amide and fluoride ion, *N*,*N*-bis(trimethylsilyl)sulfinamide **31**, prepared from lithium hexamethyldisilazide and the sulfinate **18S** at −78 °C, was treated with cesium fluoride, followed by aldehydes to give the corresponding sulfinimines (Scheme 9).[17] The sulfinimine **30** could be prepared in 82% yield but *n*-pentanal gave only a 30% yield of the corresponding sulfinimine. The optical purities were determined to be >95%. Ketones such as acetophenone gave no detectable amount of the corresponding sulfinimine.

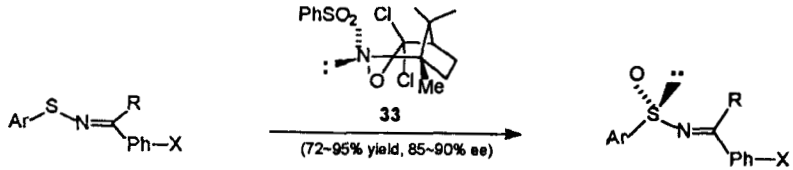
2.2.4. *Asymmetric oxidation of N-alkylidenesulfenamides*

An asymmetric oxidation of the *N*-alkylidenesulfinimides **32** with the chiral oxaziridine **33** in CCl_4 was accomplished in 85–90% ee to provide the sulfinimines **34** (Scheme 10).[18] The stereochemistry of this oxidation is consistent with that of the oxidation of sulfides and selenides where the non-bonded interactions between the R_L and R_S groups of the sulfide (R_L–S–R_S) and the oxidant **33** are minimized (the sulfenimine Ar behaves as an R_L group).

The stereoselective oxidation of the chiral *N*-alkylidenesulfenamide **36** with MCPBA in CH_2Cl_2 at −78 °C furnishes the enantiopure sulfimine **37** (97% yield) (Scheme 11).[19] The camphor-based

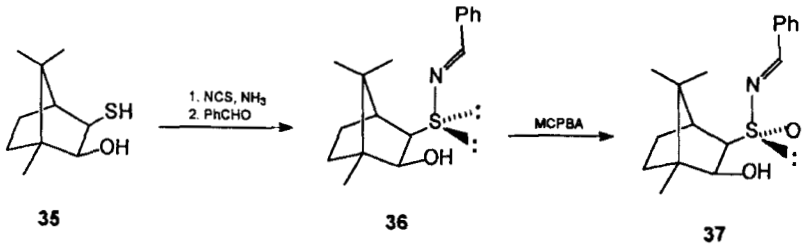


SCHEME 9

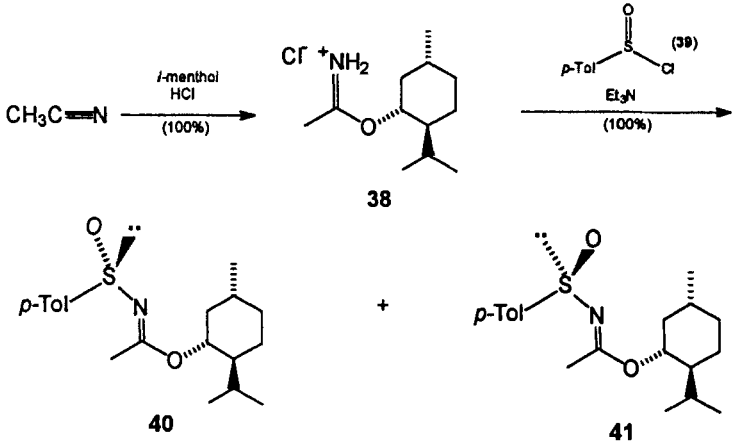


32a: Ar = Ph, R = X = H
32b: Ar = Ph, X = o-MeO, R = H
32c: Ar = *p*-Tol, X = H, R = Me

SCHEME 10



SCHEME 11



(separated by silica gel column chromatography)

SCHEME 12

sulfenimine **36** has been prepared by chlorination of the thiol **35**, followed by displacement with ammonia and coupling with benzaldehyde.

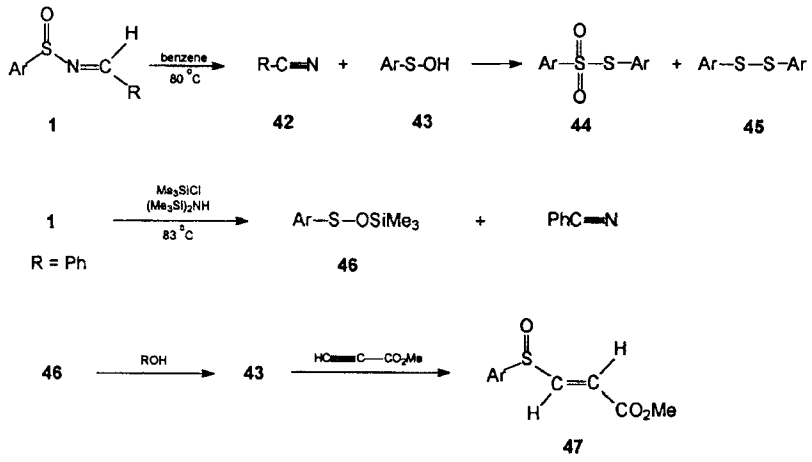
2.2.5. Preparation of l-menthyl N-p-toluenesulfinylimidates

The *N*-sulfinylimidates **40** and **41** are derivatives and precursors of *N*-alkylidenesulfinamides and have been prepared in quantitative yields from the hydrochloride of an imidic ester **38** (derived from acetonitrile, *l*-menthol, and HCl in CH_2Cl_2) with triethylamine and *p*-toluenesulfinyl chloride **39** (Scheme 12).[14a] The imidates **40** and **41** were separated by silica gel column chromatography and the stereochemistry at sulfur has not been determined.

3. REACTIONS

3.1. Thermal Fragmentation

N-Alkylidenesulfinamides undergo thermal elimination to give nitriles **42**, thiosulfonates **44** and disulfides **45** (Scheme 13).[3] A Cope-type elimination has been assumed to provide nitriles and arenesulfenic acids **43**. Compound **43** is unstable and condenses with itself to give water and thiosulfinate which in turn disproportionates to afford the



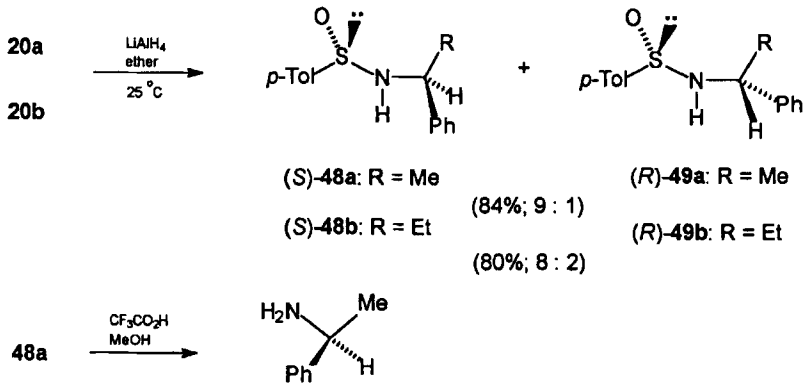
SCHEME 13

compounds **44** and **45**. The intermediate arenesulfenic acids **43** can be independently synthesized from the sulfimines **1** with trimethylsilyl chloride and hexamethyldisilazane at 83 °C to give the trimethylsilyl arenesulfenates **46** which can solvolyse with alcohols to give **43**. The intermediates **43** have been trapped with methyl propiolate to afford the vinyl sulfoxides **47**.[20]

3.2. Nucleophilic Attack at Imino Carbon

3.2.1. Hydride nucleophiles

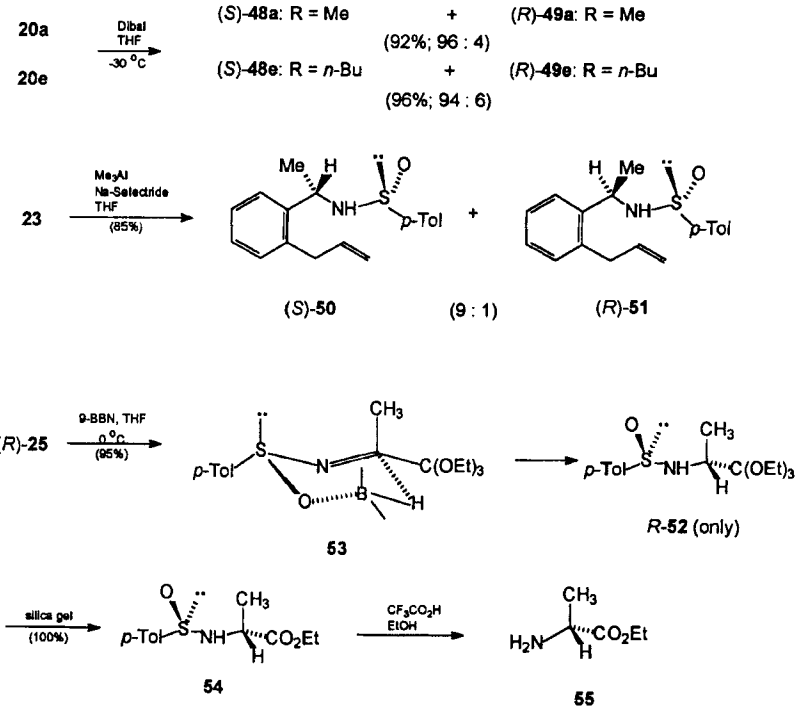
Stereoselective reduction of *N*-alkylidenesulfinamides with sodium borohydride and lithium aluminium hydride (LAH) has been reported, the greater selectivity being observed with LAH.[12] Hence, Scheme 14 illustrates the results of the reduction of **20a** and **20b** separately with LAH in diethyl ether at 25 °C to give **48a** and **49a** (9:1), and **48b** and **49b** (8:2), respectively. The stereochemistry was determined by conversion of the sulfinamide **48a** with trifluoroacetic acid in methanol to provide the known chiral secondary amine, (*S*)-1-phenylethanamine. Presumably, the acid protonates at nitrogen and the methanol attacks at sulfur to displace the amine. Use of *l*-menthol instead of methanol in the alcoholysis reaction provided *l*-menthyl *p*-toluenesulfinate **(18)**. Inversion of configuration at the sulfur center is expected.



SCHEME 14

A greater stereoselectivity was observed[13a] when bulkier hydrides were used and at lower reaction temperature. Hence, reduction of the sulfinimines (*S*)-**20a** and (*S*)-**20b** separately with Dibal in THF at −78 °C gave a 92% yield of (*S*)-**48a** and (*R*)-**49a** (in a ratio of 96:4), and a 96% yield of (*S*)-**48e** and (*R*)-**49e** (94:6), respectively (Scheme 15). The (*S*)- and (*R*)-designations of the products **48** and **49** refer to the stereochemistry of the newly created carbon center. The isomers **48a** and **49a**, and **48e** and **49e** were separated by silica gel column chromatography. Methanolysis of the sulfinamides **48** with CF_3CO_2H–MeOH gave the corresponding optically pure (*S*)-amines. For the hindered *ortho*-substituted *N*-benzylidenesulfinamide **23**,[14b] the stereoselective reduction was obtained only when a combination of trimethylaluminum and Na-Selectride was used; a 9:1 ratio of (*S*)-**50** and (*R*)-**51** was obtained in 85% total yield. It should be noted that the stereochemistry at carbon of the major products in the above Dibal reduction and this Me_3Al–Na-selectride reduction is opposite. It has been predicted[14b] that use of Lewis acids such as Me_3Al to chelate the oxygen of the sulfoxide function in one face facilitates the attack of the bulky hydride Na-selectride from the opposite side of the aluminium complex. Consequently, opposite stereochemistry has been observed.

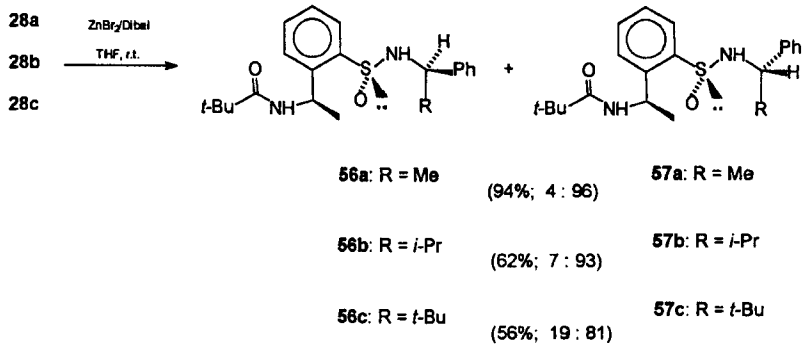
The reduction of the sulfinimine (*R*)-**25** with 9-BBN in THF at 0 °C gave exclusively (*R*)-**52** in 95% yield (Scheme 15).[15] The transition state of the reduction is depicted in structure **53** and presumably a similar transition state is involved in the above Dibal reduction



SCHEME 15

reactions. The absolute configuration at the newly created carbon center was determined to be *R* by hydrolysis of the ortho ester function on a silica gel column overnight, followed by ethanolysis with trifluoroacetic acid in ethanol to give (*R*)-alanine ethyl ester (**55**) which had the same optical rotation as an authentic sample. The optical purity was determined to be >98% ee. Enantiopure (*R*)- or (*S*)-α-amino acids can thus be synthesized by this method.

Results similar to the reduction with Me_3Al–Na-selectride have been reported for the sulfinimines **28a–c** in that when $ZnBr_2$–Dibal is used, the stereochemistry of the newly created carbon center is opposite to that with Dibal as the only reducing agent (Scheme 16).[16] For instance, reduction of **28a** with $ZnBr_2$–Dibal in THF at r.t. gave a 4:96 ratio of **56a** and **57a** while with Dibal in THF at −23 °C a 93:7 ratio of **56a** and **57a** was obtained. The stereoselectivities decrease when the R group in **28** changes from methyl over isopropyl to

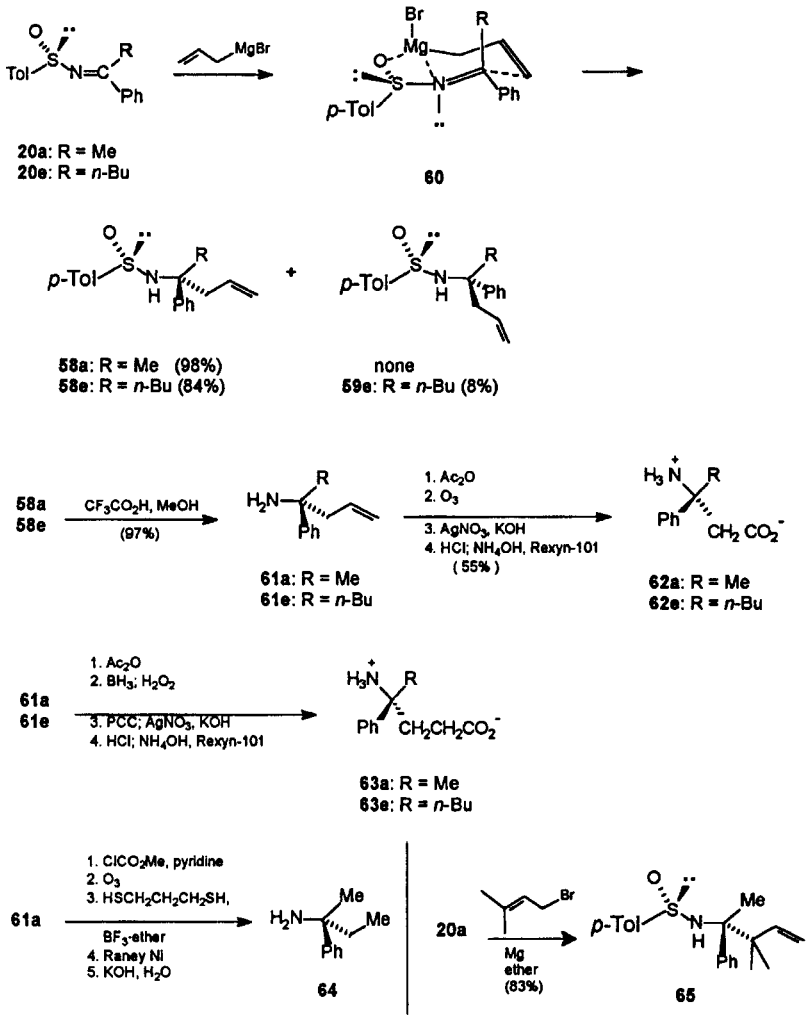


SCHEME 16

tert-butyl. A bulkier R group may change the conformation of the transition state (similar to that of structure **53**; the *t*-Bu group can occupy the equatorial or axial position) of these reduction reactions.[16c]

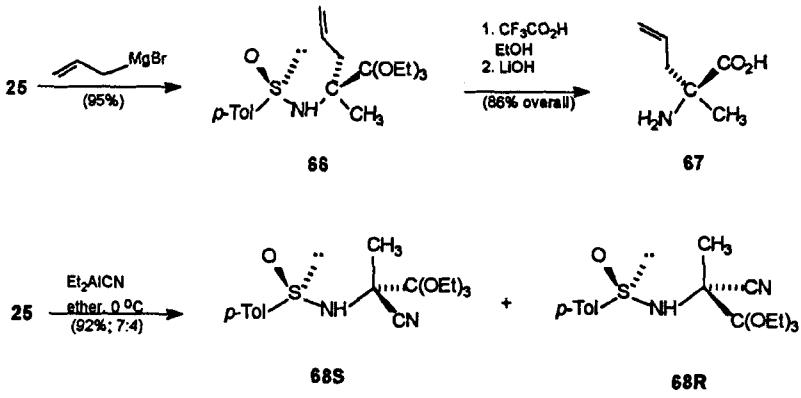
3.2.2. Organometallic nucleophiles

Various organometallic reagents undergo stereoselective nucleophilic addition reactions involving the imine moiety of *N*-alkylidenesulfinamides. The first report[13a] of this class of reactions showed high yield and excellent stereoselectivities (Scheme 17). Thus, the addition reactions of allylmagnesium bromide with the sulfinimines **20a** and **20e** separately gave **58a** (as the sole product; 98% yield) and **58e** and **59e** (84:8), respectively. The transition state **60** was proposed to explain the high stereoselection. The $\sim$100% optical purities of **58** were shown by the NMR spectra of the Mosher derivatives of the amines **61** which were obtained in 97% yield by reaction with trifluoroacetic acid in methanol. The absolute configuration of **61a** was proven by its conversion to the known amine **64** by protection of the primary amine function with methyl chloroformate, followed by ozonolysis of the double bond, deoxygenation of the resulting aldehyde with 1,3-propanedithiol and Raney nickel, and removal of the carbamate protecting group. The γ-attack of the allyl Grignard reagent was apparent in the addition reaction **20a** with (3-methyl-2-butenyl)magnesium bromide to give an 83% yield of **65**. Chiral β-[21] and γ-amino acids[22] are



SCHEME 17

important intermediates in organic synthesis and biological studies. The amines **61** can readily be converted to the β- and γ-amino acids **62** and **63** (Scheme 17). Acetylation of **61** with acetic anhydride, ozonolysis of the resulting amides in CH_2Cl_2 at $-78\,^{\circ}C$, subsequent oxidation with $AgNO_3$–KOH in ethanol, and deacetylation with 1 *N* HCl provided the β-amino acids **62**. Without degradation of the

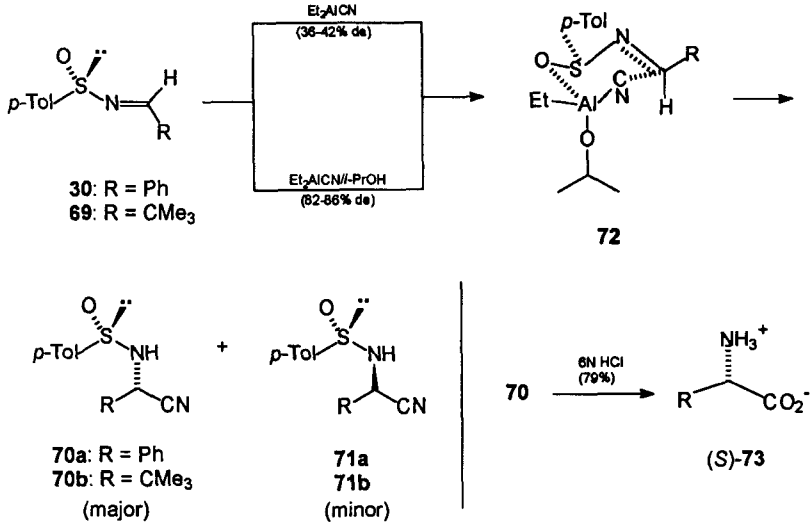


SCHEME 18

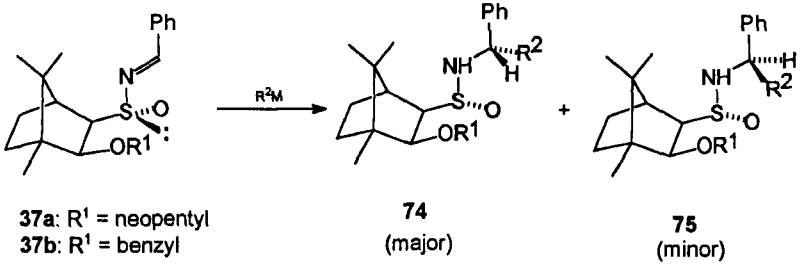
double bond, hydroboration of the olefinic moiety of the amides of **61**, followed by oxidation and removal of the acyl group, afforded the γ-amino acids **63**.

Similarly, the sulfinimine **25** also underwent a completely stereoselective addition reaction[15] with allylmagnesium bromide in ether at 0 °C to give **66** in 95% yield (Scheme 18). The absolute configuration at the newly formed carbon center of **66** was determined by conversion to (*S*)-2-amino-2-methyl-4-butenoic acid (**67**), a known α-amino acid, by ethanolysis with trifluoroacetic acid in ethanol, followed by basic hydrolysis of the resulting ethyl ester with LiOH in THF–H_2O at 80 °C. The addition reaction of **25** with diethylaluminum cyanide in diethyl ether at 0 °C gave a 92% yield of **68S** and **68R** (7:4) which could be separated by silica gel column chromatography. The absolute configuration was deduced based on the reduction reaction of **25** with 9-BBN (see structure **53**). An improved diastereoselectivity was reported[23] using the isopropoxyaluminum complex derived from 1.0 equiv. of isopropanol and 1.0–1.5 equiv. of Et_2AlCN with the sulfinimines **30** and **69**. The six-membered ring transition state **72** was suggested to explain the diastereoselection, and 82–86% de were obtained (Scheme 19). The resulting α-cyano sulfinamides **70** were hydrolyzed with HCl to give the α-amino acids **73**.

Good to excellent diastereoselection has been observed in the addition reactions of the sulfinimines **37a,b** with organometallic reagents.[19] Scheme 20 summarizes the results of the addition reactions



SCHEME 19

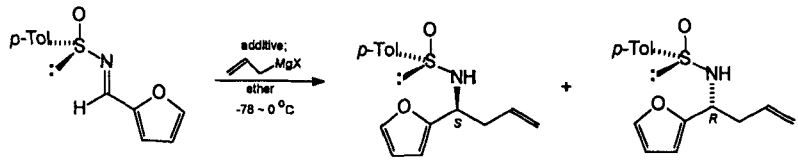


37a: R^2M = allylMgBr: >98% de
R^2M = MeMgI: >97% de
R^2M = EtMgI: 70% de
R^2M = *n*-BuMgBr: 82% de
R^2M = *n*-BuLi: 50% de

37b: R^2M = allylMgBr: >98% de
R^2M = MeMgI: >98% de
R^2M = EtMgI: 30% de
R^2M = *n*-BuMgBr: 70% de
R^2M = *n*-BuLi: 20% de

SCHEME 20

of **37a,b** with various organometallic reagents such as allylmagnesium bromide (in THF), methylmagnesium iodide (in ether–THF), ethylmagnesium iodide (in ether–THF), *n*-butylmagnesium bromide (in THF), and *n*-butyllithium (in hexane–THF). The major products **74** (presumably formed via a transition state similar to that depicted in



76 **77S** **77R**

additive: $BF_3{\cdot}OEt_2$; X = Cl;	99	:	1	(83%)
additive: $BF_3{\cdot}OEt_2$; X = Br;	92	:	8	(31%)
additive: none; X = Cl;	14	:	86	(99%)

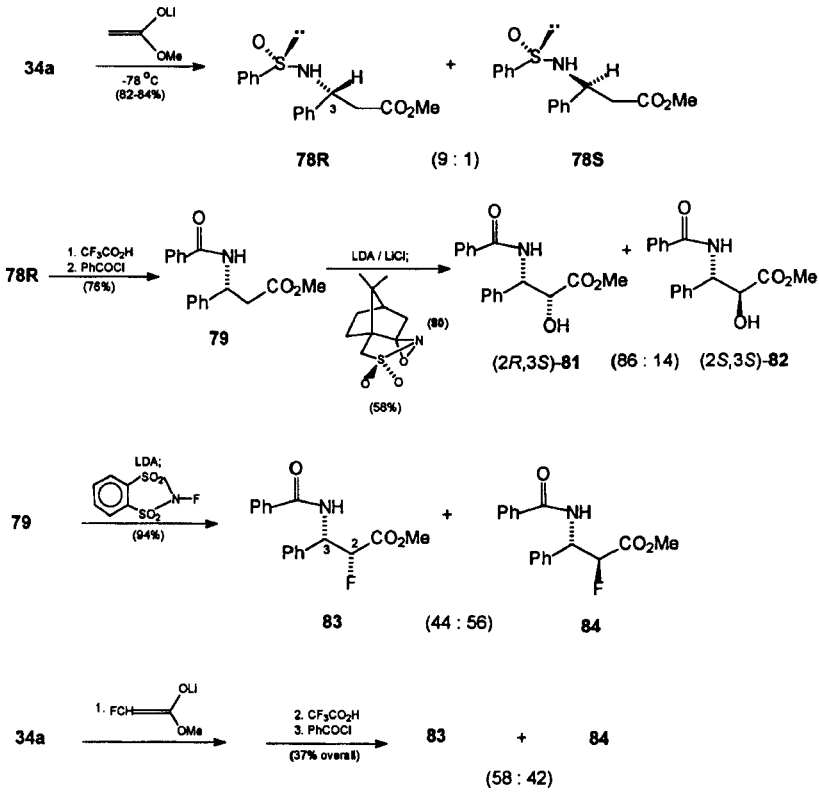
SCHEME 21

structure **60**) were isolated in 50–98% de and then reduced with Zn and $TiCl_4$ in CH_2Cl_2 at r.t. (reduction of sulfoxide to sulfide), followed by methanolysis with HCl–MeOH to give the corresponding primary amines and 3-mercapto-2-alkoxy-1,7,7-trimethylbicyclo-[2.2.1]heptanes. Alkyllithiums provide poorer diastereoselectivities than alkylmagnesium halides.

The addition of a Lewis acid before the Grignard reagent has been shown to provide greater stereoselectivity. Thus, when the sulfinimine **76** was treated with a pre-mixed solution of $BF_3{\cdot}THF$ and allylmagnesium chloride in diethyl ether at −78 °C, a 99:1 ratio of **77S** and **77R** (83% yield) was obtained (Scheme 21).[24] Without the additive, a 14:86 ratio of **77S** and **77R** was observed; a complete reversal of selectivity. Based on the prediction from transition state **60** (see Scheme 17), in the absence of the additive, **77R** would be the major product.

3.2.3. Enolate nucleophiles

Various enolates derived from esters have been used in reactions with *N*-alkylidenesulfinamides and the resulting *N*-sulfinamides can readily be converted into *β*-amino acids, *β*-lactams, and aziridines. The C-13 side chain of the antitumor agent taxol, (−)-*N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**81**), has been synthesized by the addition reaction of the sulfinimine (*S*)-**34a** with lithiated methyl acetate at −78 °C to give the sulfinamides **78R** and **78S** in a ratio of 9:1 (Scheme 22).[18] Removal of the sulfinyl group of **78R** by treatment with trifluoroacetic



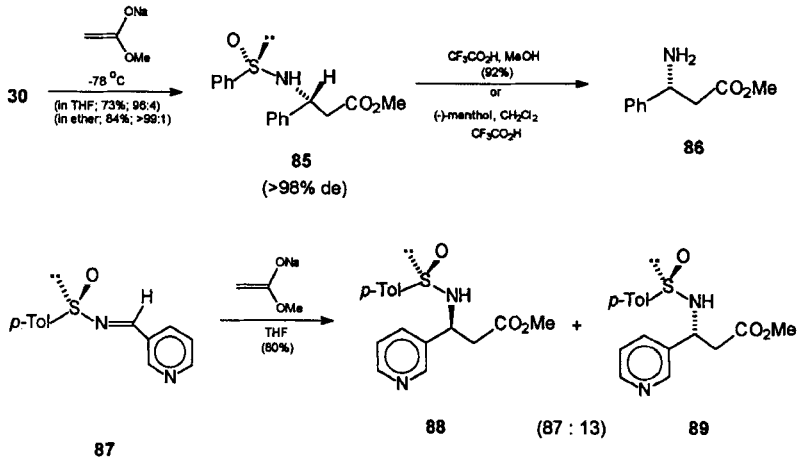
SCHEME 22

acid in MeOH, followed by benzoylation with benzoyl chloride and triethylamine, provided a 76% yield of the amido ester **79**. Hydroxylation of the enolate dianion of **79** (prepared by treatment with 2 equiv. of LDA and 1.6 equiv. of LiCl) with (+)-camphoryl-(sulfonyl)oxaziridine **80** gave an 86:14 *syn–anti* mixture of **81**:**82** in 58% yield. α-Fluorination of the ester **79** has also been reported[25] by treatment with 2.2 equiv. of LDA at $-78\,^{\circ}C$, followed by 1.3 equiv. of *N*-fluoro-*o*-benzenedisulfonimide, to give the fluorinated derivatives **83** and **84** (44:56) in 94% yield (Scheme 22). That the α-fluorination of acyclic enolates containing a stereocenter at the β-position with an achiral fluorinating agent affords a $\sim$1:1 mixture of two stereoisomers is not surprising. A better stereoselection is observed when

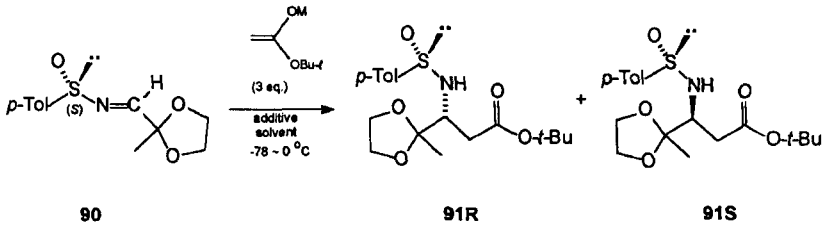
N-fluorobenzenesulfonimide is used (19:81), but in lower yield (65%). The 1,2-addition reaction of *N*-benzylidenesulfinamide **34a** with the enolate ion derived from methyl fluoroacetate and LDA at −78 °C provided a 58:42 ratio of **83** and **84** (stereoisomers at C-2) after methanolysis and benzoylation.[25] It is interesting to note that no stereoisomer at C-3 of **83** and **84** was found in the latter addition reaction.

In a study towards the total syntheses of the antitumor cyclic pentapeptides astin A, B, and C, from the medicinal plant *A. tataricus*, an improved stereoselection of the addition reaction with enolate was reported upon replacement of the sodium enolate with the corresponding lithium enolate.[26] Thus, treatment of the sulfinimine **30** with methyl sodioacetate (derived from methyl acetate and sodium hexamethyldisilazide) in THF or diethyl ether at −78 °C gave 73% yield (96:4) and 84% yield (>99:1) of **85** and its C-3*R* isomer, respectively (Scheme 23). Treatment of **85** with *l*-menthol[26b] and trifluoroacetic acid in CH_2Cl_2 regenerated *l*-menthyl *p*-toluenesulfinate (**18S**). Less stereoselection was reported when the pyridylalkylidenesulfinamide **87** was treated with methyl sodioacetate in THF (the low solubility of **87** in diethyl ether prevented the use of the latter as solvent), i.e. a 87:13 ratio of **88** and **89** (80% yield).[27]

The addition reaction of *t*-butyl lithioacetate with the sulfinimine **90** in THF gave a 14:86 ratio of **91R** and **91S** (65% yield)

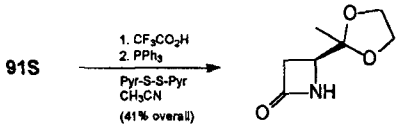


SCHEME 23



90 **91R** **91S**

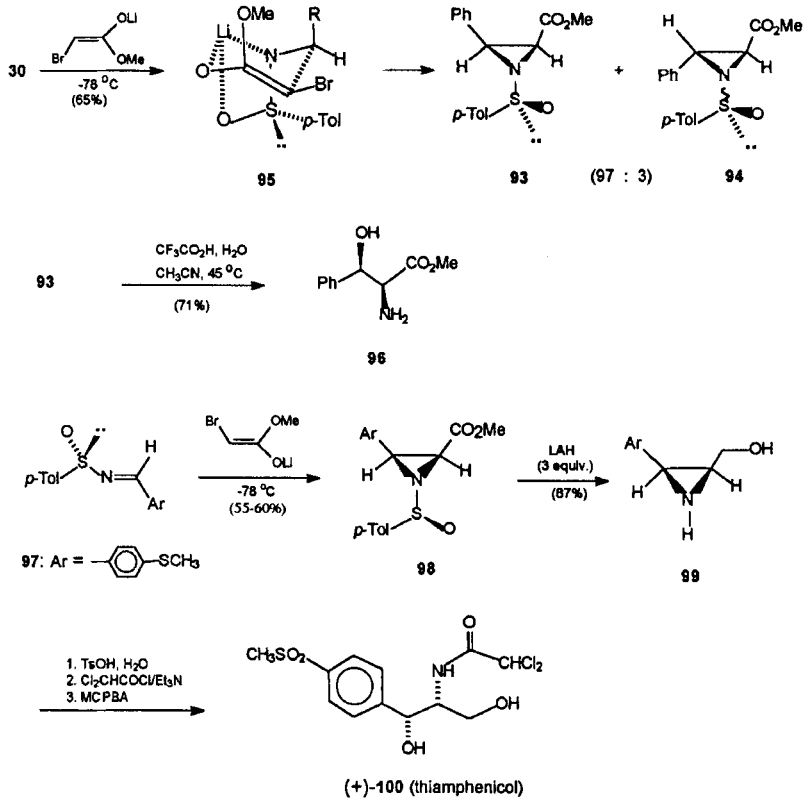
M = Li; additive: none; THF: 14 : 86 (65%)
M = Li; additive: HMPA; THF: 2 : 98 (68%)
M = Ti(OPr-*i*)$_3$; additive: none; THF: 96 : 4 (89%)
M = K; additive: 18-crown-6; THF: 6 : 94 (51%)



92

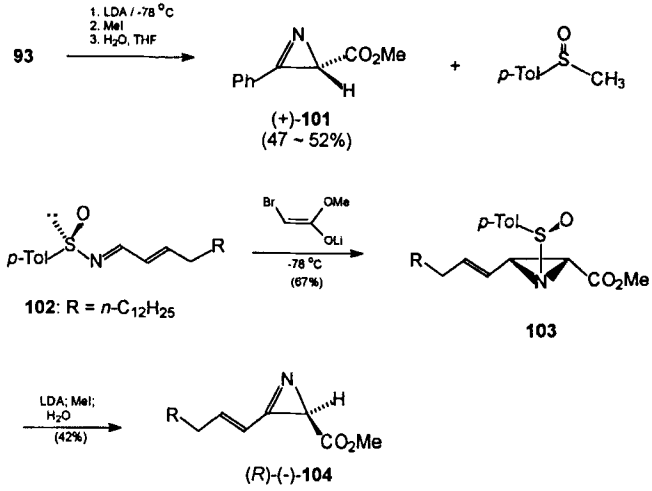
SCHEME 24

(Scheme 24).[28] Remarkably, addition of HMPA (a chelating reagent for lithium) improved the stereoselection to 2:98 in favor of the *S*-product (the same selectivity as that reported by Davis *et al.*[26]). A different explanation of these results (from that described above) was offered to the effect that with the lithium enolate and the potassium enolate with 18-crown-6 in THF, asymmetric addition would favor a non-chelation transition state to give the *S*-adduct **91S**.[28] As a result of the solvation of the lithium cation with HMPA, the stereoselection was improved. In a similar process to that described in the addition with organometallic reagents (see Scheme 21), a complete reversal of selectivity was observed when the titanium enolate prepared by transmetallation of lithioacetate with ClTi(O-*i*-Pr)$_3$ was used. A 96:4 ratio of **91R** and **91S** (89% yield) was isolated. A six-membered chair-like transition state containing a four-membered metallacycle, and/or its seven-membered counterpart has been suggested.[28] Since β-amino acids can be cyclized to β-lactams, **91S** was converted into the β-lactam **92** by treatment with trifluoroacetic acid, followed by PPh$_3$-(PyrS)$_2$ (dipyridyl disulfide) in acetonitrile in 41% overall yield.



SCHEME 25

Enolates derived from methyl bromoacetate[29] have been used to provide chiral aziridines[30] in one-pot addition reactions with sulfinimines, followed by a ring-closure reaction (a Darzens-type reaction). A 97:3 mixture of the aziridines **93** and **94** was formed (65% yield) in the reaction of lithiated methyl bromoacetate with the chiral sulfinimine **30** at −78 °C (Scheme 25). A six-membered transition state **95** was proposed to explain the formation of the major isomer **93**. Ring opening of **93** with 50% trifluoroacetic acid in acetonitrile at 45 °C furnished a 71% yield of the β-hydroxy-α-amino acid **96**. The antibacterial antibiotic thiamphenicol (**100**) has similarly been synthesized by addition reaction of methyl lithiobromoacetate with the sulfinimine **97**, followed by reduction with lithium aluminum hydride (Scheme 25).[29b] The resulting aziridine **99** was ring opened with



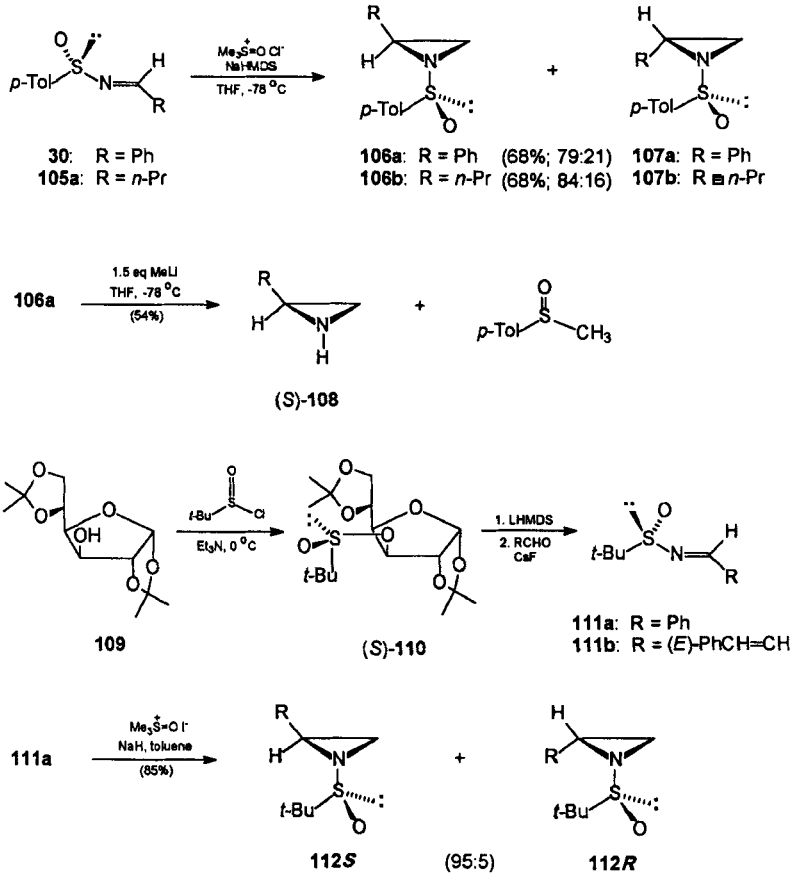
SCHEME 26

p-TsOH, acetylation with dichloroacetyl chloride, and oxidation of the sulfide moiety with MCPBA to furnish the diol **100**.

2*H*-azirines have been synthesized by elimination reactions of *N*-sulfinylaziridines with LDA at −78 °C in THF (Scheme 26).[31] Thus, treatment of the *N*-sulfinylaziridine **93** with LDA provided the 2*H*-azirine (+)-**101** and lithium *p*-toluenesulfenate which can be trapped with methyl iodide to give methyl *p*-tolyl sulfoxide. (*R*)-(−)-Dysidazirine (**104**), a marine sponge metabolite possessing inhibitory activities against L1210 cells and the growth of Gram negative bacteria and yeast, has been synthesized from the sulfinimine **102** with methyl lithiobromoacetate, followed by LDA and MeI.[31]

3.2.4. Other stabilized carbanions and azomethine ylides

High to excellent stereoselectivities have been observed in the reactions of chiral sulfinimines with other nucleophiles such as dimethyloxosulfonium methylide.[32,33a] dimethylsulfonium methylide,[33b] and α-phosphonate carbanions.[34] 1,3-Dipolar cycloadditions with azomethine ylides also provide excellent stereoselectivity.[35] *N*-Sulfinylaziridines have been synthesized by addition reactions of sulfinimines with dimethyloxosulfonium methylide or dimethylsulfonium methylide (Scheme 27). The greatest stereoselectivity was found when sodium

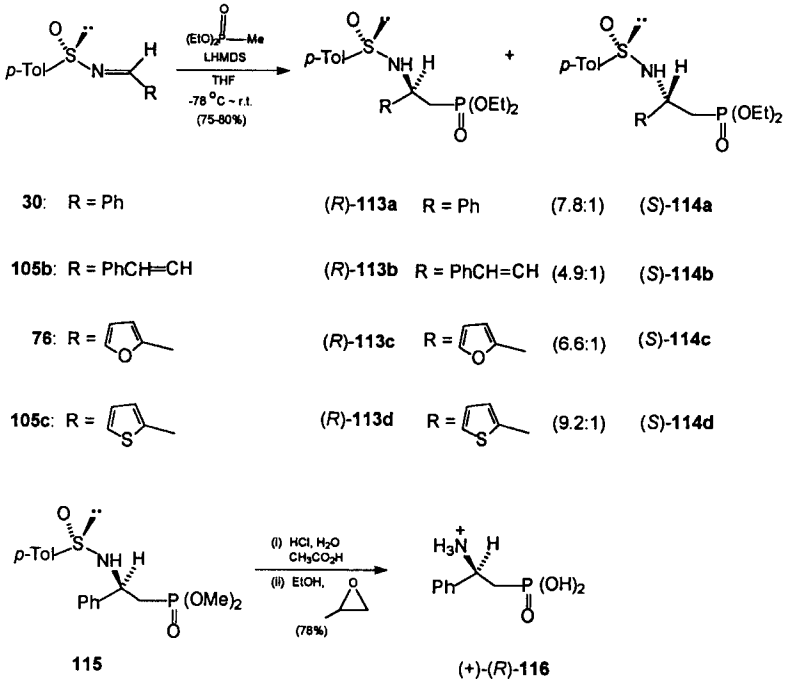


SCHEME 27

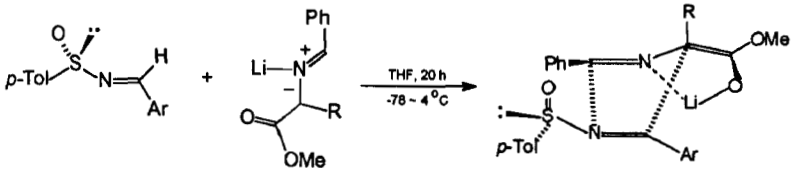
hexamethyldisilazide (NaHMDS) was used to deprotonate trimethylsulfoxonium chloride in THF, followed by addition of the sulfinimines **30** and **105**.[32] A 68% yield of the *N*-sulfinaziridines **106a** and **107a** (79:21) was isolated. The sulfinamide **106a** has been converted to the aziridine (*S*)-**108** by displacement reaction with methyllithium in THF at −78 °C in 54% yield along with methyl *p*-tolyl sulfoxide. Utilizing Davis' method, diacetone-D-glucofuranosyl sulfinate **110** has been transformed into the sulfinimines **111** by reaction with lithium hexamethyldisilazide (LHMDS), followed by aldehydes and cesium fluoride (see Section 2.2.3) (Scheme 27).[33a] The addition reaction

111a with the sulfur ylide derived from trimethylsulfoxonium iodide and sodium hydride in toluene gave an 85% yield of **112S** and **112R** (95:5). A six-membered ring transition state involving Na^+ has been proposed in such addition reactions with sulfinimines.[32,33] Interestingly, when the sulfur ylide was generated from trimethylsulfonium iodide and NaH in DMSO, a 15:85 ratio (reversal of selectivity) of **112S** and **112R** (70% yield) was obtained. This process was suggested to be under kinetic control in which the sulfur ylide attacks the sulfinimine (C=N) from the less hindered face of the C=N moiety (*si* face) of the most populated conformation (the S=O bond orients itself syn-coplanar with C=N; *s-cis*).

Nucleophilic addition reactions of the sulfinamines **30**, **76**, **105b**, and **105c** with the α-carbanion derived from diethyl methanephosphonate and lithium hexamethyldisilazide in THF gave 75–80% yields of the adducts **113** and **114** in good to high stereoselectivities (Scheme 28).[34] A transition state for this addition similar to that for the formation of



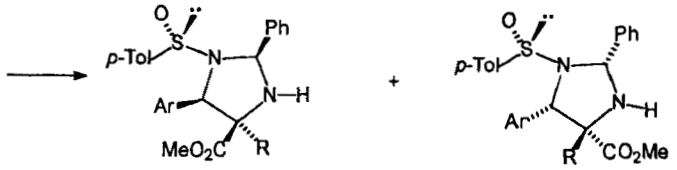
SCHEME 28



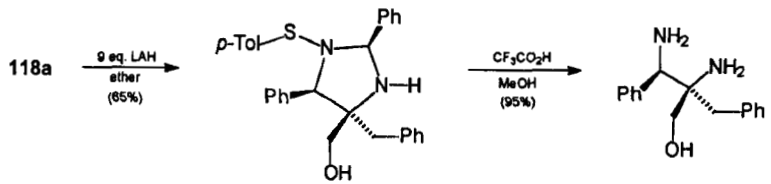
30: R = Ph
105d: R = *p*-O_2N-Ph

117a: R = CH_2Ph
117b: R = Me
117c: R = CH_2CHMe_2

120



118a: Ar = Ph, R = CH_2Ph	(55%; 95:5)	**119a**
118b: Ar = Ph, R = Me	(53%; 95:5)	**119b**
118c: Ar = *p*-O_2NH C_6H_4, R = CH_2Ph	(80%; 97:3)	**119c**
118d: Ar = *p*-O_2NH C_6H_4, R = CH_2CHMe_2	(70%; 98:2)	**119d**



121 **122**

SCHEME 29

112S was proposed. An eight-membered ring transition state involving coordination of the lithium cation to oxygens of the sulfoxide and phosphonate (P=O) moieties and the *s-cis* conformation of the sulfinimine (S=O and C=N are *syn* coplanar) was suggested. It was found that a lithium cation provides greater stereoselectivity than a sodium cation. The stereochemistry of a major adduct, the sulfinamide **115**, was determined by conversion to the α-amino phosphonic acid **116** by hydrolysis with hydrochloric acid and acetic acid in water, followed by

methyloxirane and ethanol, in 78% yield. The absolute configuration of **116** was determined by a single-crystal X-ray analysis as *R*.

Finally, excellent stereoselection has been found in the 1,3-dipolar cycloaddition of the chiral sulfinimines **30** and **105d** to the azomethine ylides **117** (Scheme 29).[35] The ylides **117**, generated from the corresponding imino esters with LDA in THF, undergo stereoselective cycloaddition with **30** and **105d** separately to give predominantly the imidazolidines **118** along with small amounts of the isomers **119** in 53–80% yield. The stereochemistry of **118a** was confirmed by a single-crystal X-ray analysis. An *endo* approach of the ylide (relative to the Ar group) to the less hindered β face of the sulfinimine, structure **120**, was proposed the stereoselectivity being opposite to that found with the enolate nucleophiles.[18,26] This reverse stereochemistry and the high stereoselectivity support a 1,3-dipolar cycloaddition mechanism. The imidazolidines **118** can be converted into enantiopure 2,3-diamino alcohols. Hence, treatment of **118a** with 9 equiv. of lithium aluminum hydride in ether, followed by methanolysis with trifluoroacetic acid in methanol gives the diamino alcohol **122** in 62% overall yield.

4. CONCLUSIONS

The easy preparation of chiral *N*-alkylidenesulfinamides and their stereoselective addition reactions with hydrides, organometallic reagents, enolates, sulfur ylides, and α-carbanions of phosphonates, and their 1,3-dipolar cycloaddition reaction afford enantiopure amines, α-, β-, γ-amino acids, β-lactams, β-amino phosphonic acids, and substituted imidazolidines. Other synthetic methods leading to chiral *N*-alkylidenesulfinamides (such as **1** with $R^1 = H$, $R^2 = \text{alkyl}$; and $R^1 = R^2 = \text{alkyl}$) in high yields and stereoselective reactions such as intermolecular and intramolecular cycloaddition reactions (e.g., Diels–Alder reaction) remain to be explored. The transition states proposed in many of the stereoselective addition reactions need further in-depth studies to provide stronger support. It is hoped that this review will generate creative ideas for the further development of this useful functional group.

Acknowledgments

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