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Synthesis and Use of *N*-(Trimethylsilyl)imines

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Abstract:

The introduction of aminic nitrogen in organic molecules has been achieved in many different ways, one of the most popular being the use of imines. The main disadvantage of these starting materials lies in the difficulty of synthesising and using imines of ammonia, due to their instability, which results in their tendency to trimerize, giving the corresponding triazine. Recently a new class of imines, the *N*-metalloimines, a stable form of the corresponding elusive imines of ammonia, has found very useful applications in the synthesis of nitrogen-containing organic compounds. This review will cover the syntheses and applications of *N*-(trialkylsilyl)imines. It is not intended to be a comprehensive review of the literature; rather it is intended to highlight novel and potentially useful applications. In this context, particular emphasis will be devoted to methodologies which could be easily scaled up to kilogram scale. The synthesis of important small-ring heterocycles such as aziridines, β-lactams, pyrrolines, and piperidines and hetero-Diels−Alder derived compounds will be reviewed. Some aspects of the synthesis of commercially interesting acyclic compounds, such as amines, aminols, nitriles, and amino acids, obtained using *N*-(trialkylsilyl)imines, will be reported.

Introduction

Although many synthetic approaches to nitrogen-containing organic molecules exist, those employing imines as reactive intermediates are certainly the most important. One reason is that both the carbonyl compound and the amine, which are used in the initial condensation step to generate the imine, can be easily varied. Also the stereo- and regioselectivity of the condensation step can be controlled by a number of factors, e.g., internal steric and/or electronic effects with regard to the substitution pattern of the imine, and external factors like Lewis acids or metal catalysts. Very often imines can be prepared in situ, so that isolation of these labile intermediates is avoided. However, two major problems of all reactions involving imines may be identified: first, their decreased reactivity compared to that of the corresponding carbonyl compounds, and second, the necessity of an extra step to remove the nitrogen aryl or alkyl group when it is required.

In order to enhance their reactivity toward nucleophiles, some kind of activation is required.[1] The electrophilicity of imines can be increased by attaching electron-withdrawing substituents to the imino nitrogen (e.g., *N*-tosyl, *N*-acyl),[2,3] or by using Lewis or Brønsted acids, thus forming iminium ions,[4,5] or by attaching electron-withdrawing substituents to the imino carbon atom itself.[3] Whereas the internal activation by substituents increases the reactivity of the imine, external activation by a Lewis acid in principle allows for control of the stereoselectivity by chelation effects. It is reasonable to assume that, as soon as a complete switch from a chelation-controlled mechanism to a non-chelation-controlled reaction by changing the Lewis acid may be realised, high diastereo- and enantioselectivity should ultimately be achieved. Concerning the necessity of an extra step in order to remove the nitrogen aryl or alkyl groups, a relatively new class of compounds, the *N-metalloimines*, has been reported to circumvent, to some extent, this problem. In fact the easy hydrolysis of the N−metal bond at the end of the synthetic process allows the preparation of the N−H derivatives by simple aqueous workup. This review is dedicated to illustrating the syntheses and uses of *N*-(trimethylsilyl)aldimines, paying attention to those methodologies which could be useful for large-scale synthesis.

Synthesis of *N*-(Trialkylsilyl)imines

A simple and high-yielding method for preparing *N*-(trimethylsilyl)imines[6−9] is based on the addition−elimination of alkaline metallo hexamethyldisilylamides[10] to aldehydes and ketones (Scheme 1). The nature of the alkaline metal of the silylamide seems to play an important role in determining the success of the reaction: lithium hexamethyldisilylamide adds and eliminates faster than sodium hexamethyldisilylamide to give the expected silylimine. With potassium hexamethyldisilylamide the elimination step is very slow since the intermediate adduct may be detected by

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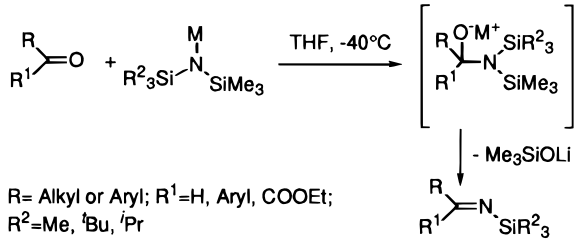
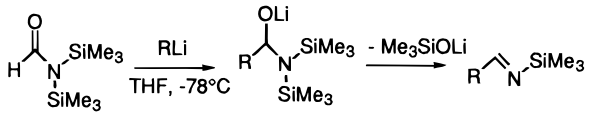
Scheme 1



Scheme 2

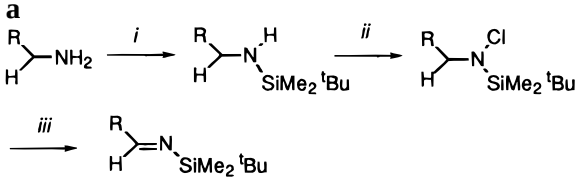


^{1}H NMR after several hours at room temperature.[11] By this method a number of aliphatic and aromatic *N*-(trimethylsilyl)-imines have been prepared starting from aldehydes with linear as well as branched side chains including α- and *β*-hetero-substituted ones. Recently Cainelli[12] reported the preparation of *N*-(*tert*-butyldimethylsilyl)- and *N*-(triisopropylsilyl)imines starting from the corresponding *N*-(trimethylsilyl)-*N*-(trialkylsilyl)amide[13] through the selective elimination of lithium trimethylsilanoate (Scheme 1). It must be pointed out that whereas aldehydes, including enolizable ones, furnish the expected silylimines by this procedure, ketones are less prone to undergo the addition since the strongly basic lithium hexamethyldisilylamide attacks an α-hydrogen quantitatively, thus affording the corresponding lithium enolate. Nevertheless *N*-(trimethylsilyl)ketoimines have been obtained from ketones lacking any α-hydrogens.[14,15] An alternative procedure to obtain *N*-(trimethylsilyl)aldimines takes into account the addition of lithium alkyls or aryls to *N*,*N*-bis(trimethylsilyl)formamide (Scheme 2).[16,17] The direct preparation of *N*-(trialkylsilyl)imines from substrates already containing a nitrogen atom has been achieved starting from the parent amines (Scheme 3). Two procedures have been reported: (1) oxidation of *N*-silylamines by *tert*-butyl hypochlorite followed by base-induced elimination (Scheme 3a)[18] and (2) gas phase dehydrocyanation[19] of α-(*N*-silylamino)nitriles (Scheme 3b).

N-(Trimethylsilyl)imines have also been obtained by transmetalation of the corresponding lithium enaminoaluminates (Scheme 4a), easily prepared from nitriles upon reaction with lithium aluminium triethoxy hydride[20] or lithium aluminium *n*-butyl diisopropyl hydride[20a] and from

Scheme 3

a



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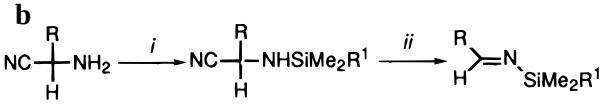
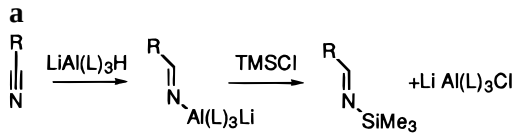


Scheme 4

a



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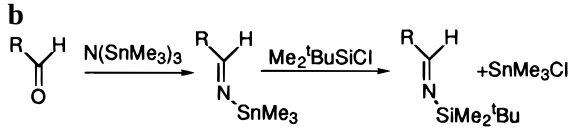

N-(trialkylstannyl)imines obtained in turn from aldehydes and tris(trimethyltin) amide (Scheme 4b).[21]

Properties

The *N*-(trialkylsilyl)imines are, usually, monomeric compounds which are stable under anhydrous conditions. Some of them may be isolated without polymerisation in a pure state by distillation under reduced pressure.[8,22,23] For synthetic purposes, however, it is in general more convenient to prepare them in situ just before their use. In this case it is possible to determine their structure by a combined use of infrared, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic techniques. Since the silicon−nitrogen bond of these compounds is easily hydrolysed, the *N*-(trialkylsilyl)imines may be considered a protected, stabilised form of the corresponding elusive imines of ammonia, which are known to be very unstable, readily trimerizing to the corresponding triazines. Most silylaldimines are oils and are miscible with

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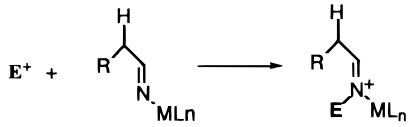
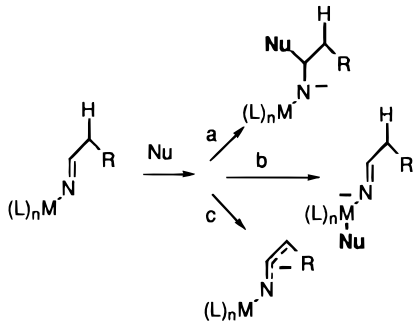
(23) Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605.

Scheme 5



Scheme 6



organic solvents. When allowed to react with water, they are readily hydrolysed to give the parent carbonyl compounds.

Infrared Spectra. The infrared spectra of *N*-silylimines show an intense band near 1650−1670 cm^{-1}, attributed to the C═N stretching vibration.[24] The symmetric deformation band of the trialkylsilyl group appears at 1250 cm^{-1}. A band in the 900 cm^{-1} region may be tentatively assigned to the silicon−nitrogen stretching mode. It is interesting to note that the C═N and Si−N stretching frequencies are rather independent of the nature of substituents on silicon.

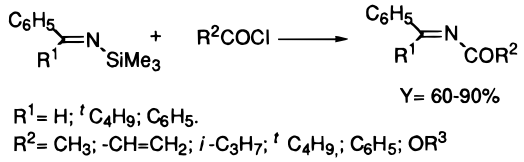
^{1}H and ^{13}C NMR Spectra. The azomethinic proton signals are between 8.00 and 8.20 ppm, whereas the azomethinic carbon signal lies around 167 ppm. This deshielding has been interpreted as an improvement of the electrophilicity of the azomethinic carbon in (trimethylsilyl)-imines compared to that of the azomethinic carbon in alkyl- or arylimines.[25]

N-(Trialkylsilyl)imines can react either as nucleophiles or as electrophiles.[23] The nitrogen atom, in fact, reacts with electrophiles such as alkyl, acyl, or metal halides to generate a new nitrogen−carbon or nitrogen−metal bond (Scheme 5). Nucleophiles may in principle attack three different positions (Scheme 6): (a) the azomethinic carbon; (b) the metal directly linked to the nitrogen atom to give the formation of an *ate* complex; (c) the hydrogen α to the azomethinic carbon to form an enamide species.

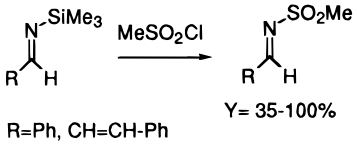
N-(Trialkylsilyl)imines as Nucleophiles

Synthesis of Methylenecarboxamides and Sulfonylimines. *N*-(Trimethylsilyl)imines have been used as nucleophiles in the preparation of *N*-methylenecarboxamides.[26] The method consists of the acylation of *N*-silylimines with acyl halides and the simultaneous removal of the silyl group as the volatile chlorotrimethylsilane. Substitution of acyl halides with alkyl carbonochloridates furnishes the corresponding *N*-methylenecarbamic esters (Scheme 7).

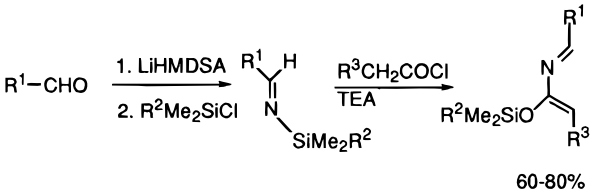
Scheme 7



Scheme 8



Scheme 9



Recently Georg[27] reported on a novel synthesis of *N*-sulfonylimines via a halogen-mediated conversion of *N*-(trimethylsilyl)imines in the presence of an appropriate sulfonyl chloride (Scheme 8). By this method various aldehydes and ketones were converted to their *N*-sulfonylimines in excellent yields and high purity. Unfortunately only stabilised *N*-sulfonylimines (α,β-unsaturated or phenyl substituted) could be prepared by this procedure whereas it is possible to prepare *N*-sulfonylketimines.

Synthesis of Hetero-Diels−Alder Derived Compounds.[28−31] In an elegant series of papers, Ghosez reported on the use of *N*-(trialkylsilyl)imines, as starting materials, in the preparation of 2-azadienes (Scheme 9).[32] The compounds of this class are useful reagents for the synthesis of pyridones, isoquinolones, tetrahydropyridones, piperidones, and pyrimidones with a defined substitution pattern.[33−35]

The reaction of 2-azadienes with electron-poor dienophiles shows an unexpected stereochemical dichotomy (Scheme 10): cyclic dienophiles mainly yielded *endo*-adducts while acyclic dienophiles reacted with a high *exo*-selectivity.[36] Recently the same research group reported on the use of

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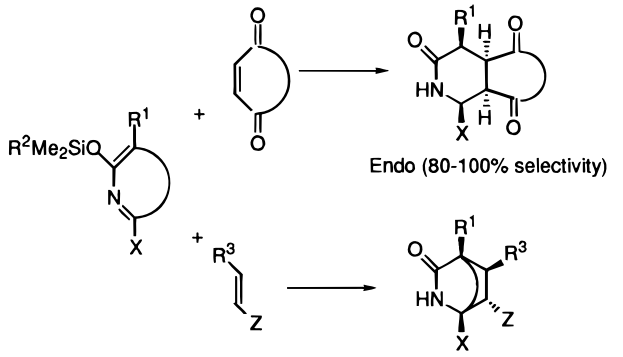
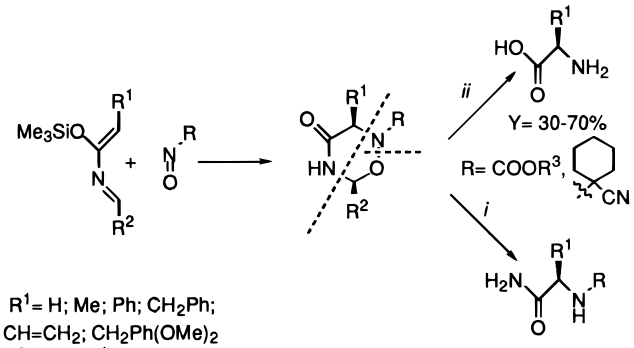
Scheme 10



Z = CN, CO_2Me, $CONR_2$, $COCH_3$
R^3= H, CH_3, Aryl, CO_2Me

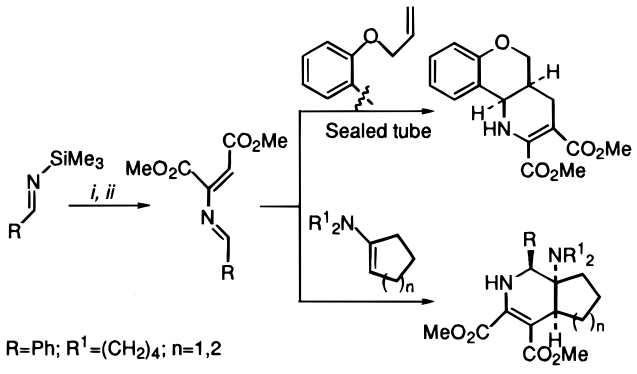
Scheme 11



R^1= H; Me; Ph; CH_2Ph;
$CH=CH_2$; $CH_2Ph(OMe)_2$
R^2= Ph, O-^{i}Pr

i: Na/Hg/MeOH
ii: Na/Hg/HCl 3N, Propylene oxide

Scheme 12



R=Ph; R^1=$(CH_2)_4$; n=1,2

i: MeO_2C—≡—CO_2Me Toluene, rt. *ii*: CsF, MeOH

azadienes in the synthesis of carboxylic acid derivatives (Scheme 11).[37]

While Ghosez's group studied the [4 + 2] cycloaddition process, Barluenga's group[38] has studied the reactivity of 2-aza-1,3-diene, obtained from *N*-(trimethylsilyl)imines, with electron-withdrawing substituents in both inter- and intramolecular [4 + 2] cycloaddition reactions (Scheme 12). In both cases isoquinoline skeletons with different substitution patterns can be prepared. It is also possible to obtain a 2-pyridine skeleton if fluoride-induced desilylation is avoided (Scheme 13).

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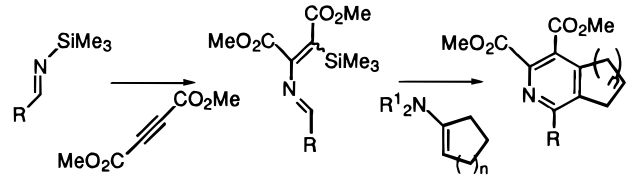
(38) Barluenga, J.; Joglar, J.; Gonzales, F. J.; Fustero, S. *Synlett* **1990**, 129.

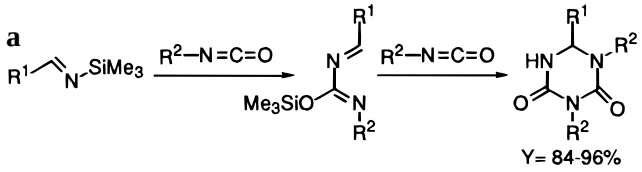
Scheme 13



R=Ph; R^1=$(CH_2)_4$; n=1, 2

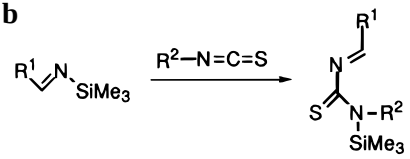
Scheme 14

a



R^1= Ph, 2-Thienyl; R^2= Ph, 3-Cl-C_6H_4, 4-Me-C_6H_4, c-C_6H_{11}.

b



Barluenga's group has also studied the reactivity of *N*-(trimethylsilyl)imines towards isocyanates and isothiocyanates to give different types of 2-aza-1,3-dienes (Scheme 14). Treatment of *N*-(trimethylsilyl)imines with 1 equiv of isocyanate in dichloromethane affords the corresponding substituted 1,3-diazabutadienes, which have been used in the synthesis of triazines (Scheme14a).[39] Using isothiocyanates (Scheme 14b) it is possible to obtain substituted 2-amino-1-thia-3-aza-1,3-dienes, which can react with a number of electron-poor alkenes and alkynes as well as azo dienophiles leading to 1,3-thiazines and 1,2,3,5-thiatriazine derivatives (Scheme 15).[40] Isolation of the azadiene intermediate is unnecessary so that all derivatives can be obtained in one-pot syntheses starting from *N*-(trimethylsilyl)imines. Through coupling with alkynes it is possible to get, regioselectively, 1,3-thiazines. With alkenes, through an *endo*-cycloadduct, regio- and stereoselectivity are observed. Using hetero dienophiles, particularly azo derivatives, cycloadducts with 1,2,3,5-thiatriazine skeletons were obtained through smooth cycloaddition. When the reaction mixture was heated, extrusion of the sulphur occurred. When the diene is a nitrile, 3,4-dihydro-1,3,5-2*H*-thiadiazine derivatives are obtained in high yields.[41] Finally *N*-(trimethylsilyl)imines, derived from aromatic and heteroaromatic aldehydes, react with isothiocyanates to afford 1-thia-3-azabutadienes, which undergo intramolecular cycloaddition to yield heterocyclic compounds (Scheme 16). The process was found to be regioselective and stereospecific.[42,43]

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(40) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Synthesis* **1995**, 985.
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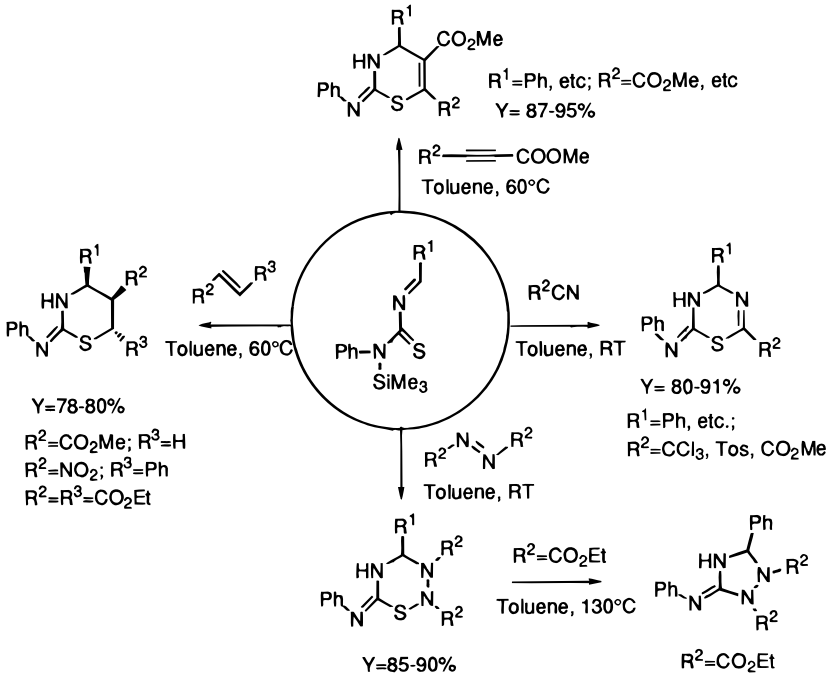
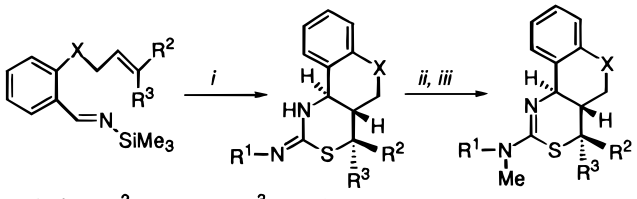
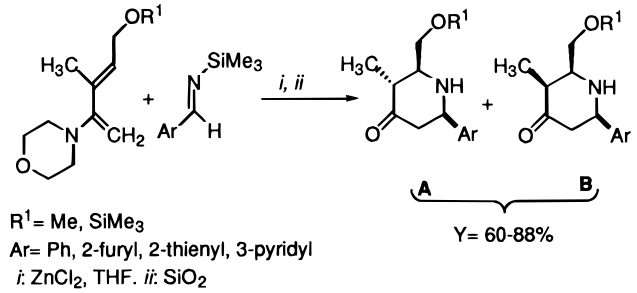
Scheme 15



Scheme 16

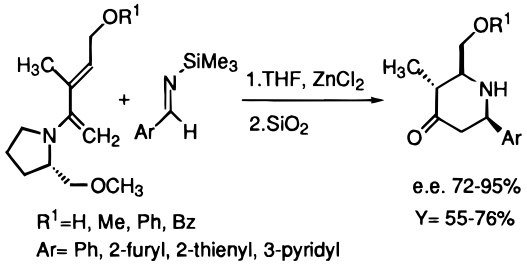


Scheme 17



The same research group has studied also the reactivity of *N*-(trimethylsilyl)imines as dienophiles in [4 + 2] cycloadditions with 2-amino-1,3-dienes to give tetrahydropyridines and 4-piperidinones.[44] The coupling is carried out in the presence of $ZnCl_2$. As depicted in Scheme 17 morpholino-1,3-dienes react with *N*-(trimethylsilyl)imines to furnish diastereomerically pure 4-morpholinotetrahydropyridines. These cycloadducts are usually not isolated but directly hydrolysed to the corresponding 4-piperidinones in moderate to high yields.[44] It is worth noting that *N*-silylimines lead selectively to the 2,6-*cis* diastereoisomers of the 4-morpholinotetrahydropyridines, which, after hydrolysis, afford a mixture of epimers richer in epimer **A**. The mixture can also be converted exclusively to epimer **A** by treatment with LDA (Scheme 17). When *N*-(trimethylsilyl)imines of aromatic aldehydes and homochiral azadiene are used, 2,6-*cis* enantiomerically enriched tetrahydropyridines are obtained (Scheme 18).[31,45,46]

Scheme 18



To summarise, diastereoselective or enantioselective syntheses of highly functionalized six-membered rings have been achieved through [4 + 2] cycloaddition reactions of *N*-(trimethylsilyl)imines with 2-amino-1,3-butadienes. Moreover, through hetero-Diels−Alder reactions, some natural products can be obtained starting from *N*-(trimethylsilyl)-imines. Yamamoto and Uyehara[47] reported the total synthesis of (±)-sedridine, a piperidine alkaloid, on the basis of a diastereoselective intramolecular Diels−Alder reaction of unsaturated *N*-(alkoxycarbonyl)-1-aza-1,3-butadiene, generated in situ from *N*-(trimethylsilyl)-1-azabutadiene and the chloroformate of 4-penten-2-ol (Scheme 19).

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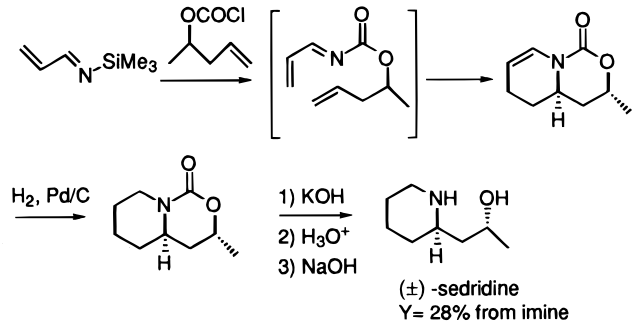
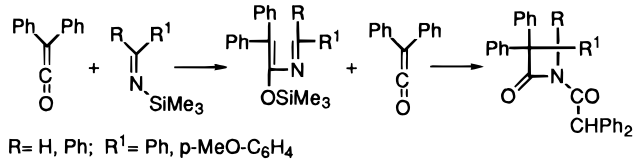
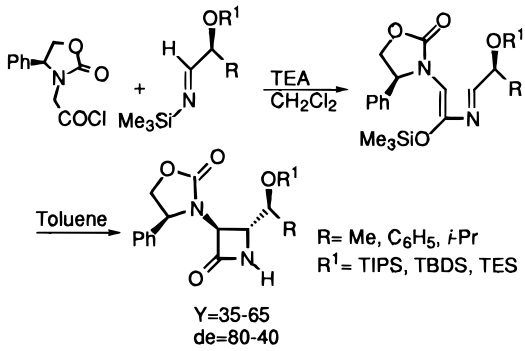
Scheme 19



Scheme 20



Scheme 21



Synthesis of β-Lactams: Staudinger's Reaction. *N*-(Trimethylsilyl)imines have been used by Birkofer in the synthesis of the β-lactam ring[48] through Staudinger's reaction using 2 equiv of ketene.[49,50] Reaction of the *N*-(trimethylsilyl)imine of benzaldehyde with diphenylketene furnished the intermediate 1,1,4-triphenyl-3-[(trimethylsilyl)oxy]-2-aza-1,3-butadiene, which upon reaction with an extra equivalent of ketene furnished the β-lactam ring, *N*-acyl substituted (Scheme 20). Following the Birkofer approach Panunzio has succeeded in the preparation of (3,4-*trans*)-*NH*,3 phthaloyl-4-substituted azetidin-2-ones via a two-step Staudinger reaction without the necessity of adding an extra equivalent of ketene.[51] The main drawback of this approach lies in the almost complete lack of facial diastereoselectivity in the reaction, whereas *complete trans diastereoselectivity* was achieved. A solution of this problem was found[52] by the use of enantiomerically pure (+)-(*S*)-2-oxo-4-phenyl-3-oxazolidineacetyl chloride[53] as chiral reactant in the formation of the azadiene (Scheme 21). The usefulness of this approach to prepare enantiomerically pure 3-aminoazetidin-2-ones was demonstrated by converting the obtained azetidinone, upon removal of the oxazolidine moiety,[54] to a useful derivative for the synthesis of Aztreonam and isocephems.

N-Silylimines as Electrophiles

Synthesis of β-Lactams. The activity of the β-lactam antibiotics[55] is strictly associated with a *cis* substitution pattern at the 3- and the 4-position of the β-lactam ring, although there are also some biologically active *trans*-β-lactams, e.g., carbapenems, thienamycin, aztreonam, and trinems. Therefore the development of synthetic methods that allow control of the diastereoselectivity and enantioselectivity is an important topic in the synthesis of β-lactams.

Reaction of *N*-(trimethylsilyl)imines with ester enolates produces, in high chemical yields and high enantiomeric−diastereomeric excess, the azetidinone ring. Since, in the ester enolate−imine condensation route to β-lactams, the diastereoselectivity of the products is controlled by the metal counterion,[56−59] a range of metal enolates, usually obtained by transmetalation of the corresponding lithium enolate, have been used. Tin, aluminium, boron, and magnesium enolates have been reacted with enolizable and nonenolizable *N*-(trimethylsilyl)imines to give β-lactams. As far as the geometry of enolate is concerned, it has been demonstrated that (*E*)-enolates afford β-lactam with high diastereoselectivity while (*Z*)-enolates show low diastereoselectivity.[60] In addition to the studies on the enolate countercations and geometry, van Koten's group has recently reported studies on the influence of solvent on the diastereoselectivity of condensation reactions.[61] Through these studies a series of interesting biologically active antibiotics has been obtained.

Hart first reported on the use of *N*-(trimethylsilyl)imines in the synthesis of the β-lactam ring through a condensation reaction between lithium enolates and nonenolizable silylimines[8,62] whereas Cainelli[9] and Yamamoto[17] reported on the use of enolizable and α-substituted silylimines.

The *N*-(trimethylsilyl)imine of cinnamaldehyde and the lithium enolate of (*S*)-ethyl 3-hydroxybutanoate have been used in the total synthesis of the antibiotic thienamycin (Scheme 22).[17,62−65] According to this protocol, a process for the synthesis of carbapenem compounds, including the same thienamycin, starting from *N*-(trimethylsilyl)ethynylaldimine, has been patented by Fujisawa Pharmaceutical Co. (Scheme 23).[66]

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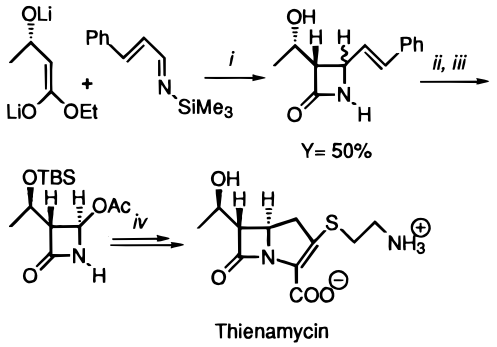
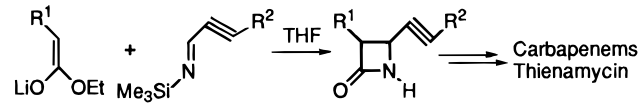
Scheme 22



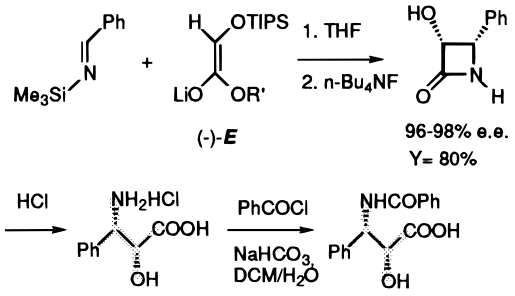
i : THF, -78°C; *ii*: HCOOH, DEAD, TPP, OH^-;
iii: TBDMSCl, DMAP; *iv*: see ref. 64

Scheme 23



R^1=H, organic residue; R^2= H or protecting group

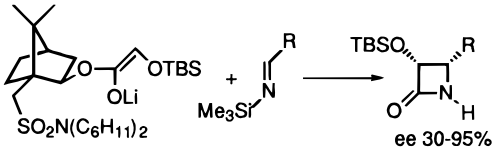
Scheme 24



R* = (-)-*trans*-2-phenyl-1-cyclohexyl

In the last few years the approach of using chiral lithium enolates, bearing the stereogenic centre on the alkoxy group of the ester functionality, has been applied to the preparation of the (3*R*,4*S*)-3-hydroxy-4-phenyl-2-azetidinone precursor of a paclitaxel side chain.[67−72] The chiral alkoxy group of the ester and the *O*-protecting group exert marked effects both on the enantioselectivity and on the chemical yield of the reaction. The use of (−)- or (+)-*trans*-2-phenyl-1-cyclohexyl (Scheme 24)[73] as the chiral auxiliary and triisopropylsilyl (TIPS)[74] as the *O*-protecting group of the acetate moiety gives exclusively the corresponding *cis*-β-lactam in high yields and with extremely high enantiomeric purity. The β-lactam has been further elaborated to *N*-benzoylphenylisoserine by hydrolysis with HCl and benzoylation with

Scheme 25



R=2-pyridyl; 3-pyridyl; 4-pyridyl; 2-furyl; 3-furyl.

PhCOCl (Scheme 24).[69] The same diastereo−enantioselectivity has been obtained by Georg[75] using Oppolzer's chiral auxiliary[76] and different aromatic silylimines as shown in Scheme 25.

In order to achieve the synthesis of β-lactam antibiotics lacking any stereocenter on the nucleophilic component of the cycloaddition, chiral *N*-(trimethylsilyl)imines have been prepared. By using scalemic *N*-(trimethylsilyl)imines derived from α-hydroxy aldehydes, the syntheses of carbapenem antibiotics PS-5,[77] PS-6,[78] and β-methyl-PS-5[79,80] have been achieved (Scheme 26). A further useful application of this approach to optically active azetidinones is illustrated by the enantioselective synthesis of the 3-amido-4-alkylazetidinones, including the commercially available Aztreonam,[81] via addition of the lithium enolate of the STABASE, a cyclic silyl-protected form of the glycine ester,[82] to the *N*-(trimethylsilyl)imine of lactaldehyde.[83] Once again a very high *trans* diastereoselectivity has been observed. In this case, in order to obtain the natural (*R*) configuration on the C-3 stereocenter, the (*R*)-lactaldehyde must be used (Scheme 27). An alternative synthetic route to 3-amido-4-acetoxyazetidinones implied the use of the (*S*)-lactaldehyde protected with TIPS (triisopropylsilyl) coupled with sodium enolate.[22,56] Through this procedure the desired azetidinone with the correct natural stereochemistry at the 3-chiral centre was obtained. Isocephalosporin has been synthesised via this route (Scheme 28).

Panunzio, in collaboration with GlaxoWellcome-Verona,[84,85] found almost complete stereocontrol in the reaction of the *N*-(trimethylsilyl)imine of *cis*-2-[(*tert*-butyldimethylsilyl)oxy]cyclohexane-1-carboxaldehyde, obtained by reduction of the corresponding keto ester, and the lithium enolate of *tert*-butyl acetate (Scheme 29). The azetidinone thus obtained was elaborated to the new antibiotic Sanfetrinem[86,87]

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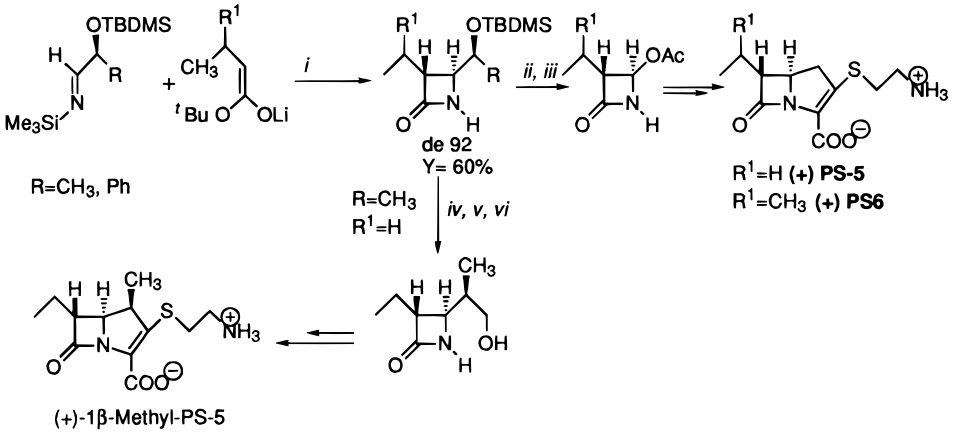
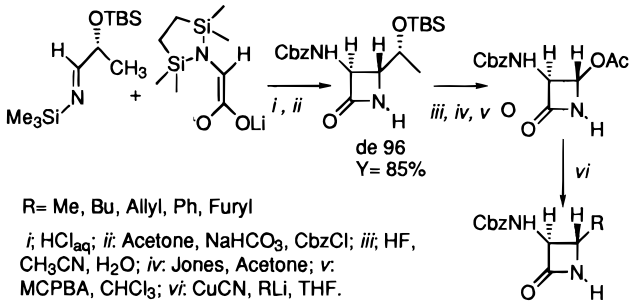
Scheme 26



i: THF, -78°C; *ii:* HF_{aq}, CH_3CN; *iii:* $Pb(OAc)_4$; *iv:* Jones 8N, Acetone; *v*: NaH, DMSO, Methylentriphenylphosphonium bromide; *v*:i DMS-BH_3 Complex, H_2O_2.

Scheme 27



R= Me, Bu, Allyl, Ph, Furyl

i; HCl_{aq}; *ii*: Acetone, $NaHCO_3$, CbzCl; *iii*; HF, CH_3CN, H_2O; *iv*: Jones, Acetone; *v*: MCPBA, $CHCl_3$; *vi*: CuCN, RLi, THF.

and its enantiomeric form through the resolution of the corresponding diastereomeric homochiral enol phosphates.

A more straightforward procedure takes into account the preparation of homochiral (trimethylsilyl)imines via *Pseudomonas* lipase catalysed resolution of the intermediate *cis*-1-(ethoxycarbonyl)-2-hydroxycyclohexane.[88] In addition to the homochiral sanfetrinem, a new tricyclic derivative, namely, enantiomerically enriched 10-ethyltrinem, has been obtained.

β-Lactams have been also obtained in good yields by reaction of *N*-(trimethylsilyl)imine with silylketene acetals in the presence of ZnI_2 and *tert*-butyl alcohol, followed by treatment *in situ* of the intermediate *N*-silyl-β-amino esters with MeMgBr (Scheme 30).[18]

As anticipated above, *N*-(trimethylsilyl)imines have been prepared from nitriles obtained by reduction with triethoxyaluminium hydride[20] or lithium *n*-butyldiisobutylaluminium hydride[20a] followed by transmetalation with trimethylsilyl chloride. Treatment of *N*-(trimethylsilyl)imines so obtained with ester−enolates gave rise to azetidinones (Scheme 31). The stereochemistry of this reaction seems to be strictly dependent on the bulkiness of the substituent on the azomethinic carbon: linear side chains gave rise to *cis*-azetidinones whereas branched substituents produced the *trans* isomer.

Synthesis of Small-Ring Heterocycles. Addition of lithium enolates of 2-halo carboxylic esters to *N*-(trimethylsilyl)imines results in the formation of highly *cis* stereoselective 1*H*-aziridine derivatives (Scheme 32).[89] This approach may be considered analogous to the Darzens reaction for the production of epoxides.[90−92] Using the same strategy, Gennari[93,94] (Scheme 33) reported the synthesis of aziridines with excellent diastereo- and enantiocontrol using boron enolates derived from *tert*-butyl α-halothioacetate, bearing menthone-derived chiral ligands. In this case, however, the intermediate α-halo-β-amino thioesters could be isolated. The so obtained aziridines are key precursors of antibiotic (+)-thiamphenicol and (−)-florfenicol.[91]

Another application of *N*-(trimethylsilyl)imines in the synthesis of small-ring heterocycles has been found by trapping them by treatment with lithium tosylmethyl isocyanate or substituted tosylmethyl isocyanate to form *N*-unsubstituted imidazoles in moderate yields (Scheme 34).[95]

Synthesis of Amines. *N*-(Trimethylsilyl)imines, obtained from aldehydes, have been used in the synthesis of secondary carbinamines using as nucleophiles alkyl- and aryllithium and Grignard reagents (Scheme 35).[8] An enantioselective alkylation of *N*-(trimethylsilyl)benzaldimine with chirally modified organometallic reagents has also been reported (Scheme 36).[96,97]

Allylboration[98] of *N*-(trimethylsilyl)imines has been used to prepare homoallylamines in good enantiomeric excess.[99,100] *N*-(Trimethylsilyl)imines showed higher yields and ee and

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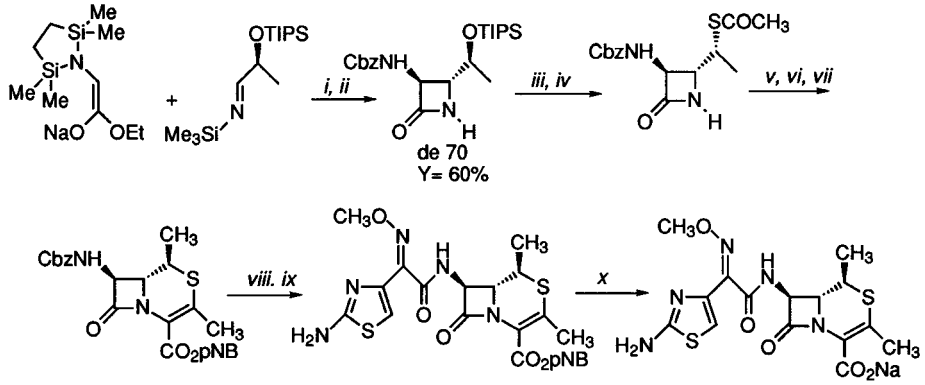
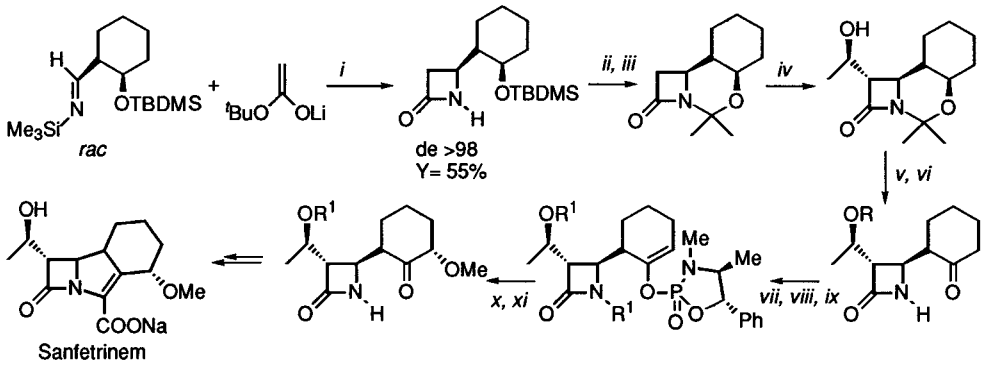
Scheme 28



i: THF, -78°C; *ii:* HCl, CbzCl, pH 8, Acetone; *iii:* HF_{aq}, CH_3CN; *iv*: DIAD, PPh_3, CH_3COSH, THF; *v*; EtO(OH)CHCOOpNB, Molecular sieves, Benzene, Polymeric Hünig base; *vi*; $SOCl_2$, Dioxane; *vii*: Toluene, Refl.; *viii*: $AlCl_3$, anisole; *ix*: TEA, AcOEt; *x*: H_2, Pd/C 10%, $NaHCO_3$.

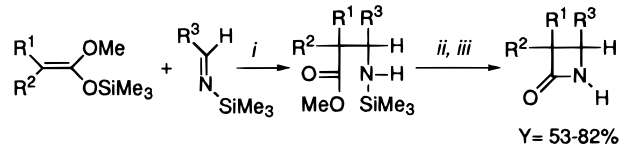
Scheme 29



R=p-NO_2-Cbz; R^1=TBDMS

i: THF, -78°C; *ii:* LiHMDSA, TBAF, THF; *iii*: DMP, BF_3, CH_2Cl_2; *iv* : LDA, CH_3COTMS, ^tBuOK/ ^tBuOH; *v*: p-NO_2-CbzCl, DMAP, CH_2Cl_2; *vi*: Jones, Acetone; *vii*: H_2/Pd; *viii*: Imidazole, TBSCl, DMF; *x*: LDA, THF, -78°C Ephedrine phosphochloridrate;*x*; KF, MeOH; *x*:i : MCPBA, $NaHCO_3$, CH_2Cl_2, then MeOH, 40°C.

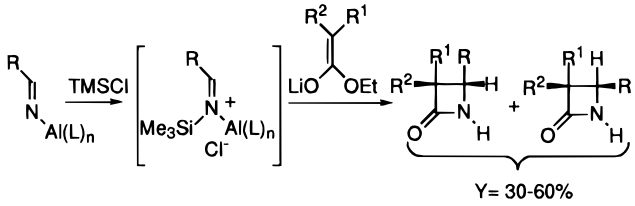
Scheme 30



R^1= H, Me, Et, *i*-Pr, Ph; R^2= H, Me, Ph-O; R^3= Ph, 2-Furyl, etc

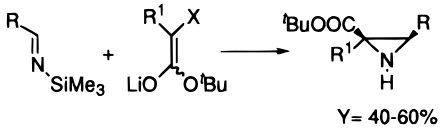
i: ZnI_2. *ii*: ^tBuOH. *iii*: MeMgBr

Scheme 31



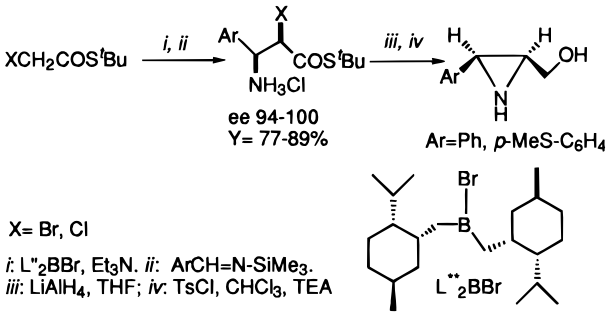
R= 2-Furyl, 2-Thienyl, p-MeO-C_6H_4, *n*-C_3H_8, Ph-CH=CH; R^1= H, Me; R^2= Me, Et, *i*-Propenyl, etc

Scheme 32



R= *n*-Hexyl, *n*-Heptyl, *n*-Octyl, C_6H_{11}; R^1= H, Me

Scheme 33

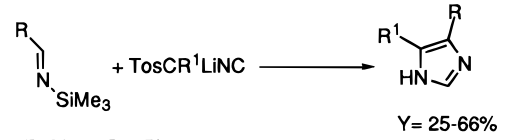


i: L"$_2$BBr, Et_3N. *ii*: ArCH=N-$SiMe_3$. *iii*: $LiAlH_4$, THF; *iv*: TsCl, $CHCl_3$, TEA

proceeded under milder reaction conditions compared with the corresponding *N*-*p*-methoxy-, *N*-sulphenyl-, and *N*-methoxyimines. The enantioselective allylboration was tested with different chirally modified allylboron reagents. The most effective enantioselective reagent was found to be the B-allyloxazaborolidine (Scheme 37).

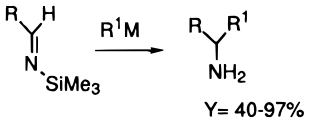
Synthesis of Diamines. Carbon−carbon bond forming routes to diamines are especially rare and are typically limited

Scheme 34



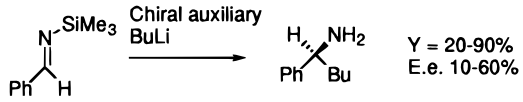
R=Me, n-Bu, Ph
R^1=H,Me,Bz

Scheme 35

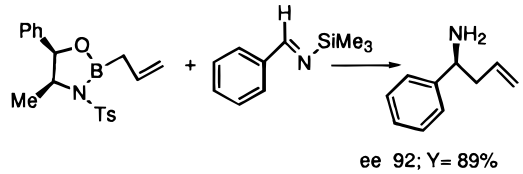


R= Ph, p- MeO-C_6H_4, Ph-CH=CH-, etc;
R^1= Me, Et, *n*-Bu, *t*-Bu, Ph,
CH_2=CH-CH_2-; M= Li, Mg

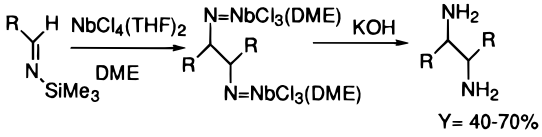
Scheme 36



Scheme 37



Scheme 38



R= Ph, o-Me-Ph, o-Br-Ph, *t*-Bu, C_5H_9. 2-Thienyl, etc

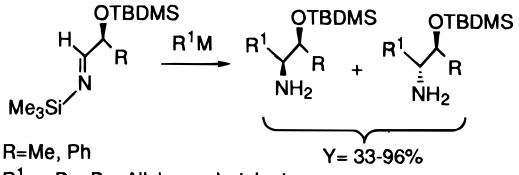
to the synthesis of *N*,*N*-disubstituted amines. *N*-(Trimethylsilyl)imines via *N*-trichloroniobium imines have been used in a convenient synthesis of unsubstituted vicinal diamines (Scheme 38).[101,102]

Synthesis of Aminols. A synthetically useful extension of the use of *N*-(trimethylsilyl)imines in the synthesis of polyfunctionalised amines is represented by the preparation of enantiomerically pure 1,2-aminols. These amines represent interesting starting materials for the synthesis of different amino alcohols of biological interest such as ephedrine, statine, and β-blockers.

When α-(silyloxy)-*N*-(trimethylsilyl)imines are reacted with lithium alkyls or Grignard reagents, a highly stereocontrolled synthesis of *syn*-1,2-aminols takes place (Scheme 39).[103,104] The presence of the α-standing stereocenter bearing a silyloxy functionality addresses the attack of the nucleophile on the strongly electrophilic azomethinic carbon

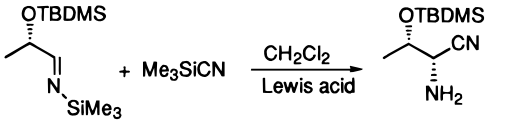
(101) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.
(102) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.
(103) Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967.
(104) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783.

Scheme 39



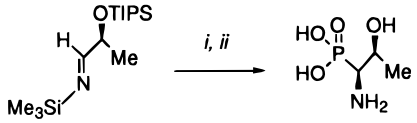
R=Me, Ph
R^1=n-Bu, Bz, Allyl , sec-butyl, etc.
M=Li, MgX

Scheme 40



Lewis Acid: $ZnCl_2$, $ZnMe_2$, $AlMe_3$, TMSOTf, etc

Scheme 41



i: $(EtO)_2POSiMe_3$, THF; *ii*: HCl, 6N

in a stereocontrolled manner so that a preferred diastereoisomer is obtained. Moreover Cainelli has demonstrated a high influence of the solvent and the temperature on the diastereoselectivity of the reaction.[105] Nearly all types of organometallic reagents can be employed. Analysis of the diastereomeric ratio clearly shows a predominance for the *syn* isomer in almost all cases studied. An interesting trend is represented by the increasing amount of the *anti* isomer on going from primary to secondary, tertiary, and allyl metal reagents. A reverse of diastereoselectivity has been achieved using as nucleophiles organo−copper−boron trifluoride reagents.[104] Although the precise mechanism of this reaction is still an open question, the stereoselection might be explained in terms of chelation-controlled and open-chain models.

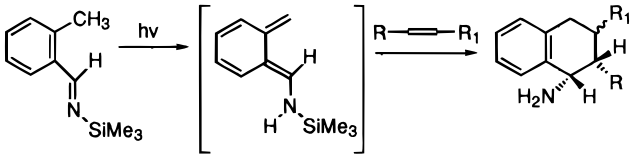
Using as nucleophile trimethylsilyl cyanide in the presence of a Lewis acid, the corresponding α-amino β-silyloxy nitriles, with a preference for *syn* diastereoselectivity, have been synthesised (Scheme 40).[106]

Miscellaneous

Synthesis of Phosphothreonines. *N*-(Trimethylsilyl)-imines derived from (*S*)- and (*R*)-lactic aldehydes have been used by Panunzio[107,108] for the synthesis of α-amino acid phosphothreonines in enantiomerically pure form (Scheme 41).

(105) Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150.
(106) Cainelli, G.; Giacomini, D.; Treré, A.; Galletti, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1593.
(107) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045.
(108) Bongini, A.; Camerini, R.; Panunzio, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1467.

Scheme 42



R=R^1=CO_2Me; R=CO_2Me; R^1=Ph; etc

Photochemistry of Silylimines. *o*-[[*N*-(Trimethylsilyl)-imino]methyl]toluene on irradiation underwent γ-hydrogen transfer to give an *o*-quinodimethane intermediate which could be trapped with dimethyl fumarate, dimethyl maleate, *trans*-methyl cinnamate, methyl acrylate, acrylonitrile, and the imine itself (Scheme 42).[109]

Summary and Conclusions

It is clear that the chemistry of *N*-(trimethylsilyl)imines has been highly developed over the past decade for the synthesis of cyclic as well as acyclic derivatives. The behaviour of a broad spectrum of *N*-silylimines has been delineated, and some aspects of their reactivity have been described. The syntheses of β-lactam antibiotics, amino acids, 1,2-aminols, aziridines, amines, aminophosphonic acids, and a range of heterocyclic compounds have found materialisation using these substrates as starting materials. Applications to the synthesis and the use of these useful reagents in other areas of natural and unnatural product synthesis can be anticipated. Most importantly, the use of *N*-(trialkylsilyl)imines in industrial processes may be, in our opinion, of interest as an alternative to known methods for the preparation of nitrogen-containing compounds due to the easy availability of the starting materials for the preparation of silylimines.

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OP970036K

(109) Kessar, S. V.; Singh, T.; Mankotia, A. K. S. *J. Chem. Soc., Chem. Commun.* **1989**, 1692.

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.