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Aziridines in Parallel- and Solid-Phase Synthesis

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Aziridines are versatile and powerful building blocks in organic synthesis due to their high reactivity as well as stereo- and regioselectivity of their ring-opening reactions with nucleophiles. Thus, aziridines possess potential as building blocks in the preparation of combinatorial libraries for biological high-throughput screening. Although the development of strategies for parallel synthesis and solid-phase chemistry utilizing aziridines is still in its infancy, the diverse applications described so far emphasize their utility.

Introduction

The nucleophilic ring-opening of aziridines with a wide range of nucleophiles is an extremely efficient transformation in organic synthesis.[1] Alongside analogous three-membered heterocyclic electrophiles, including epoxides, cyclic sulfates, episulfonium ions, and aziridinium ions, aziridines have been highlighted as important "click" chemistry reactants/tools in the original account on this subject by Sharpless and co-workers.[2] Aziridine chemistry has indeed been extensively exploited by organic synthetic chemists. In the last several decades, more than 200 research papers have been registered in the Chemical Abstracts database every

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Henrik Franzyk was born in Køge, Denmark, in 1966. He received his M.Sc. (chemical engineering) and the Ph.D. (natural products chemistry) degrees at the Danish Technical University (with S. Rosendal Jensen) in 1991 and 1993, respectively. Following employments as a researcher at Fef Chemicals (1993), post-doctoral positions at Carlsberg Laboratory (1994–1996), the Danish Technical University (1996–1997), and Colorado State University (1997, with Frank R. Stermitz), he became a research associate professor at the Danish Technical University (1998–2000) and then associate professor at The Danish University of Pharmaceutical Sciences (2000). Previous work includes structure elucidation of natural products, biosynthetic investigations, synthetic carbohydrate and glycopeptide chemistry, and semi-synthesis of alkaloids and nucleoside analogues from natural products. Current research interests are focused on the medicinal chemistry of polyamine toxins as well as on development of solid-phase methodologies for diversity-oriented synthesis.

Jerzy W. Jaroszewski was born in Lodz, Poland, in 1950. He received his M.Sc. degree and the Ph.D. degree (with Martin G. Ettlinger) from the University of Copenhagen in 1977 and 1980, respectively. Following employments in post-doctoral position at the University of Copenhagen (1980), research assistant- and associate professorships at the Royal Danish School of Pharmacy (1981–1988 and 1991–1996), visiting fellowship at National Cancer Institute, NIH, Bethesda, MD (1988–1990, with Jack S. Cohen), and visiting professorships at the Georgetown University Medical School, Washington DC (1991, 1993, 1994), he became full professor at The Danish University of Pharmaceutical Sciences (then the Royal Danish School of Pharmacy) in 1997. Previous work includes biomimetic synthetic chemistry and aromatic ring cleavage reactions, physical organic chemistry, DNA modifications for anti-sense applications, and structure elucidation of natural products. Current research interests focus on isolation and synthesis of biologically active natural products, structure-activity relationships, and applications of NMR spectroscopy.

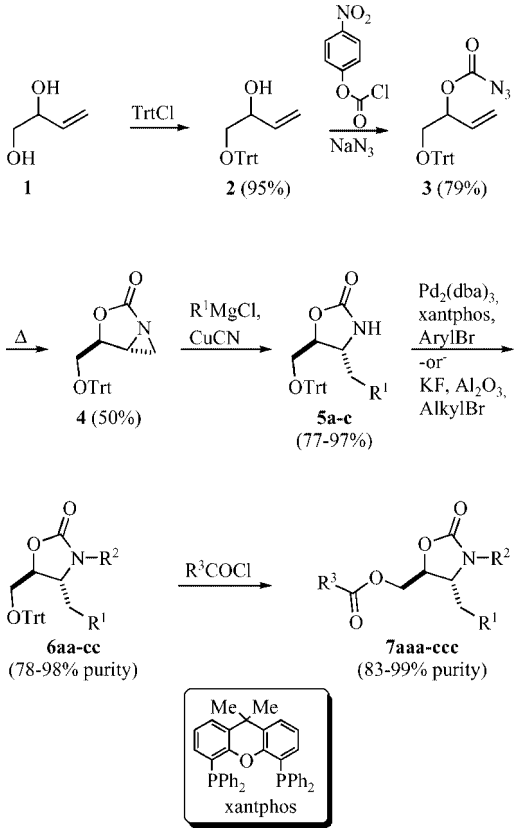
year, and since 2001 the tally has been more than 350 papers a year, which clearly shows a broad interest in the preparation and utilization of aziridines. Moreover, numerous reviews focusing on various aspects of aziridine chemistry have appeared.[1,3] With reference to this massive interest in aziridine chemistry, surprisingly few papers concerning the use of aziridines in the preparation of combinatorial libraries, in parallel synthesis of compound collections, and in solid-phase synthesis (SPS) have appeared.

Solid-phase synthesis (SPS), originally developed by R. Bruce Merrifield as a method for efficient sequential synthesis of peptides,[4] has proved to be a powerful tool in the synthesis of the three major types of biopolymers as well as non-oligomeric small-molecules, including complex natural products and their analogues or libraries from diversity-oriented synthesis. Perhaps the most important feature of SPS, however, is the ease by which large compound collections are handled as compared to libraries prepared by solution-phase methods. In the mid-1980s the multi-pin approach[5] and the tea-bag method[6] were developed for parallel synthesis of large numbers (hundreds) of peptides, and in the early 1990s the first reports on the preparation of combinatorial libraries appeared in the literature.[7] Since then the methodologies of combinatorial chemistry and SPS have attracted immense interest.[8]

Another inherent strength of SPS is the possibility of forcing slow reactions towards completion by employing reagents in large excess that are readily removed by filtration upon full conversion of the resin-bound substrate. However, highly efficient, regioselective and stereoselective transformations such as the nucleophilic ring-opening reactions of aziridines are desirable chemical tools in the preparation of libraries of diverse compounds for biological screening. In the present microreview, we focus on the current status of the application of aziridine chemistry in the fields of combinatorial and parallel synthesis in solution as well as in SPS.

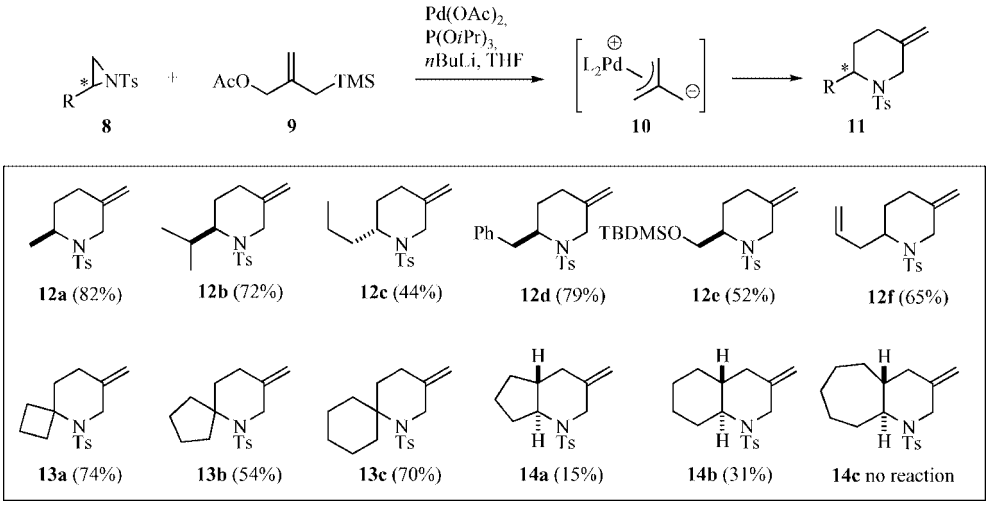
Aziridines and Parallel Synthesis

To the best of our knowledge, aziridines have not yet been employed in combinatorial synthesis of large libraries, but parallel synthesis of compound arrays using aziridine building blocks has been reported. Bergmeier and Katz prepared a bicyclic aziridine building block **4** (Scheme 1), which was applied as a precursor for highly substituted oxazolidinones.[9] The scope of their strategy was demonstrated by the synthesis of a $3 \times 3 \times 3$ collection of substituted oxazolidinones in high yields and excellent purities with minimal purification. The precursor of **4**, i.e., compound **3**, was readily prepared by selective monotritylation of the primary hydroxy group in **1**, followed by conversion of the resulting compound **2** into an activated carbonic ester and treatment with sodium azide. The building block **4** was then obtained as a pure solid by simple filtration after heating of the azidocarbamate **3** in a sealed reaction vessel. In the initial diversification step of compound **4** the aziridine moiety was subjected to ring opening with three different Grignard reagents (i.e., R^1 = Ph, $PhCH_2CH_2$ or cyclohexyl) to give **5a**–**c**, Scheme 1. The carbamate was then either *N*-arylated under Pd-catalysis using the xantphos ligand, or *N*-alkylated using KF and Al_2O_3 as catalyst. Compounds **6aa**–**cc** were obtained in good to excellent purities (78–98%) after work-up and filtration through prepacked silica gel microcolumns. Finally, the compounds **6aa**–**cc** were treated with acyl chlorides (i.e., R^3 = $PhCH_2$, cyclohexyl or *n*-heptyl), which brought about cleavage of the highly acid-labile trityl group with concomitant acylation of the primary hydroxy group to give **7aaa**–**ccc** in good to excellent yields (83–98% by GC analysis) after aqueous work-up.



Scheme 1.

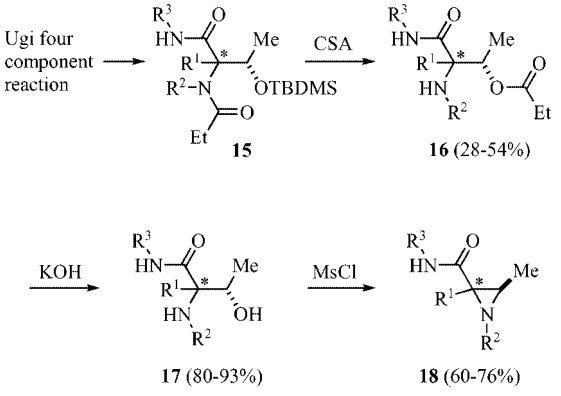
Harrity and co-workers applied enantiomerically pure *N*-(*p*-tolylsulfonyl)-activated aziridines **8** in [3+3] cycloadditions with (trimethylenemethane)palladium (**10**) for the preparation of enantiomerically pure 2-substituted piperidines **11** in good yields.[10] After optimization of the cycloaddition conditions a series of monosubstituted aziridines were converted into the corresponding piperidine adducts **12a**–**f** in high yields (Scheme 2). Furthermore, spirocyclic 2,2-disubstituted aziridines representing various ring sizes were successfully converted into the corresponding spirocyclic piperidines **13a**–**c**. However, the use of 2,3-disubstituted, fused bicyclic aziridines resulted in lower yields of **14a** and **14b**, while only starting material was recovered in an attempt to prepare **14c**.



Scheme 2.

Finally, the authors showed that the bicyclic scaffolds could be further diversified through functionalization of the exocyclic alkene, e.g. by epoxidation, hydroboration, aziridination, or hydrogenation as demonstrated for compound **12d**.[10]

Riva and co-workers have explored multi-component reactions (MCRs) as well as post-condensation transformations. In a recent report, they described the preparation of functionalized aziridine-2-carboxamides from four-component Ugi reaction products.[11] In this approach the condensation adducts **15** were treated with camphorsulfonic acid to cleave the TBDMS groups with a concurrent acyl transfer to give compounds **16** as depicted in Scheme 3. The produced esters were cleaved with KOH/MeOH to give free secondary alcohols **17**, which were activated as mesylates. Under the basic reaction conditions this mesyl group was spontaneously displaced by the vicinal secondary amino group to give diastereomerically pure aziridines **18**. Although only three MCR products were taken all the way through to the aziridine, the MCR conditions and the following work-up were optimized to give **17** in a one-pot procedure, thus making the protocol suited for combinatorial library synthesis.

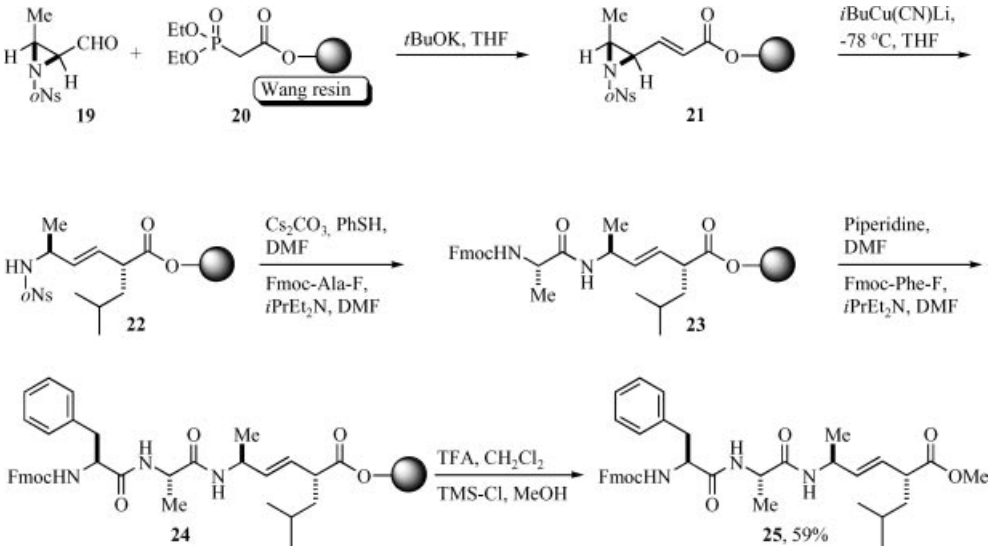


Scheme 3.

Aziridines on Solid Phase

The first synthetic sequence involving a resin-bound aziridine was reported by Wipf and Henninger almost ten years ago.[12] In their efforts to prepare peptide mimics containing an (*E*)-alkene linkage, several reactions were adapted to SPS. The *N*-(*o*-nitrophenylsulfonyl)-activated aziridinecarbaldehyde **19** was freshly prepared in solution prior to use by reduction of the corresponding methyl ester. The first example of a Horner–Wadsworth–Emmons olefination with a Wang resin-bound diethylphosphonacetic acid **20**[13,14] then gave resin **21**, as shown in Scheme 4. This resin was treated with a variety of organocuprates (prepared from Li- Mg- and Zn-organometallic precursors) as exemplified below, to give resin **22** via an S_N2' reaction. At this point, products with Me, Et, *n*Bu, *i*Bu, and $Ph(CH_2)_2$ sidechains were cleaved, and yields were determined to be 55–74%.[12] The high efficiency of this reaction is impressive, since nitrosulfonamide groups are not usually compatible with strongly basic nucleophiles. With these transformations at hand, the *o*Ns group was readily cleaved with thiophenolate, and Fmoc solid-phase peptide synthesis (SPPS) with Fmoc amino acid fluorides afforded the peptide mimics (such as **25**) in high yields and purities.

To the best of our knowledge, the only example of an intramolecular on-resin ring-opening of aziridines reported so far, is the SPS of 4-hydroxy-4,5-dihydroisoxazole 2-oxide derivatives **32**–**34** shown in Scheme 5. These authors have previously developed an analogous solution-phase strategy involving epoxide ring-opening in the cyclative bond formation step,[15] and this strategy was extended to enable the use of enantiomerically pure (hydroxymethyl)aziridines as building blocks in solution as well as on solid phase.[16] The (hydroxymethyl)aziridines **26**–**28** were oxidized to the corresponding aldehydes **29**, after which Merrifield resin-bound nitroacetic acid ester **30** and imidazole were added directly to the reaction mixtures, to form solid-supported heterocycles by tandem intramolecular nitroaldol cyclization (Scheme 5); full conversion of the alcohols was observed

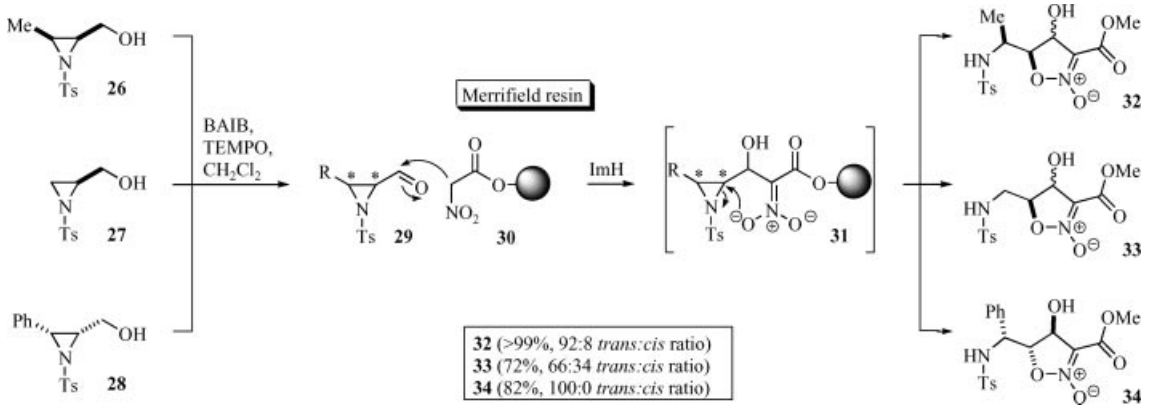


Scheme 4.

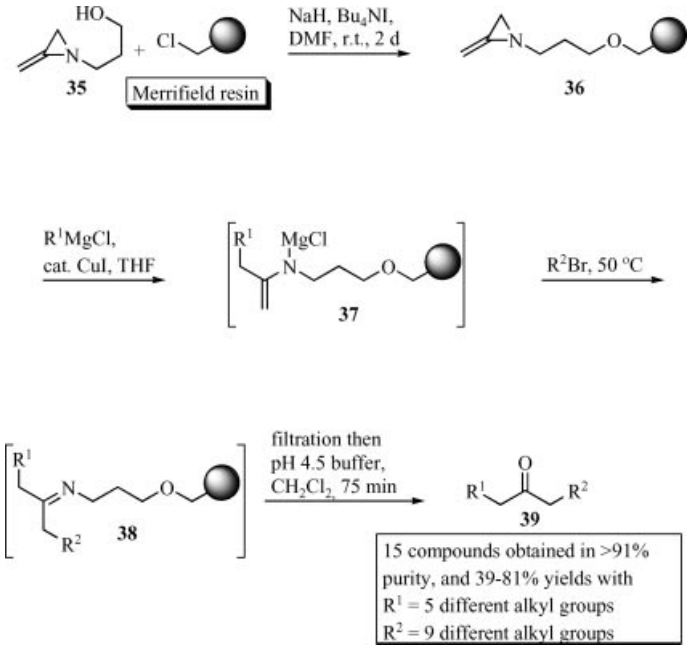
after 4–5 h, and the nitroaldol reactions were completed overnight. The progress of the aldol cyclization was readily followed by IR spectroscopy by the disappearance of the characteristic nitro absorption and the appearance of a typical C=N band of the products. After completion, the final reaction products **32**–**34** were isolated by transesterification of the resins with toluene/MeOH/*i*PrEt$_2$N (Scheme 5). All three compounds were obtained in high yields and purities on an impressive 500–700 mg-scale. Furthermore, the reaction exhibited good diastereoselectivity. While excellent *trans*:*cis* product ratios were observed for aziridine alcohols with C^3 alkyl or aryl substituents (**26** and **28**), the unsubstituted (hydroxymethyl)aziridine building block **27**, derived from (*S*)-serine, resulted in a 66:34 mixture of isomers, that proved inseparable by chromatography. The products **32**–**34** have several handles for further diversification, and thus this strategy might well have a potential for preparation of compound libraries in combinatorial or parallel synthesis.

Shipman and co-workers have applied a Merrifield resin-bound methyleneaziridine in an MCR, or rather a sequential component reaction,[17] to give an array of 1,3-disubstituted propanones.[18] Initially, building block **35** was loaded onto the solid support to give **36**, which subsequently was treated with a series of Grignard reagents in the presence of catalytic amounts of copper(I) iodide (Scheme 6). The resulting intermediates **37** were then heated with a range of alkyl bromides to give resin-bound imines **38**. An array of 15 different ketones **39** was produced in a parallel fashion after hydrolysis of the resin-bound imines **38**. The products were obtained in 39–81% yields and excellent purities without any chromatographic purification steps as determined by ^{1}H NMR, GC analysis, and in some cases also by HPLC analysis. The authors expect that this protocol may be amenable to automation, and furthermore that the use of a reduction step instead of the hydrolytic resin cleavage may give access to amines or nitrogen-containing heterocycles, as described previously for solution-phase versions of this strategy.[19,20]

Until now, the only reported on-resin syntheses of aziridines utilized the Gabriel–Cromwell reaction between amines and α-bromoacrylates or α-bromoacrylamides.[21] Two strategies denoted as the *direct strategy* and the *reverse strategy* were developed for the synthesis of *N*-alkylated aziridine-2-carboxylic acid (Azy) derivatives on a Wang resin, as out-



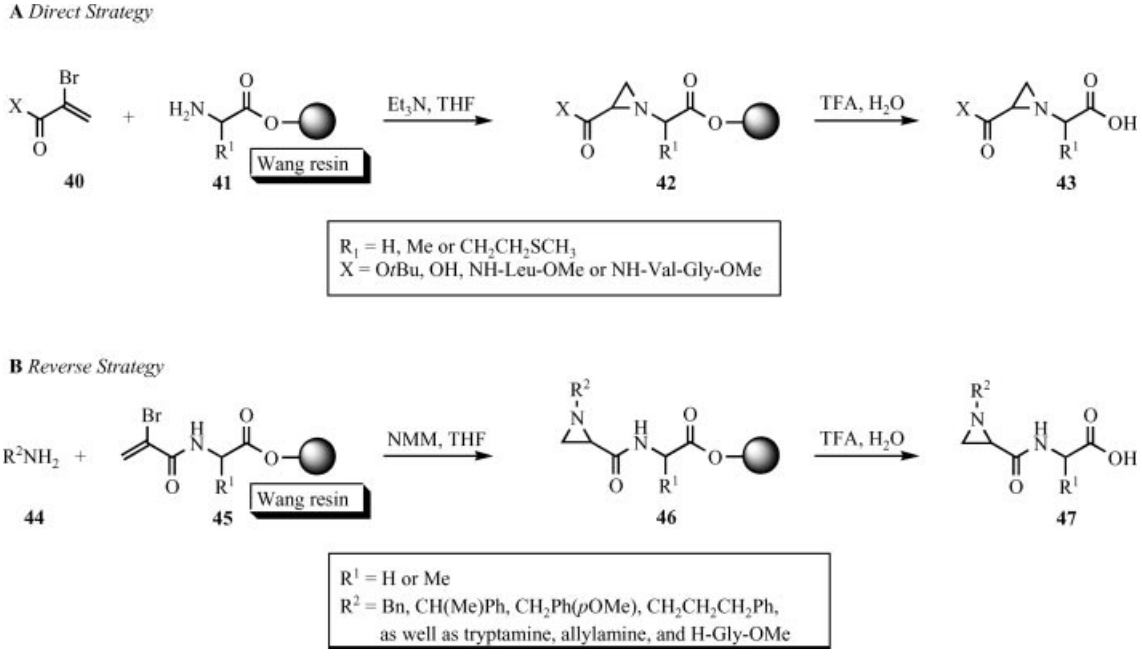
Scheme 5.



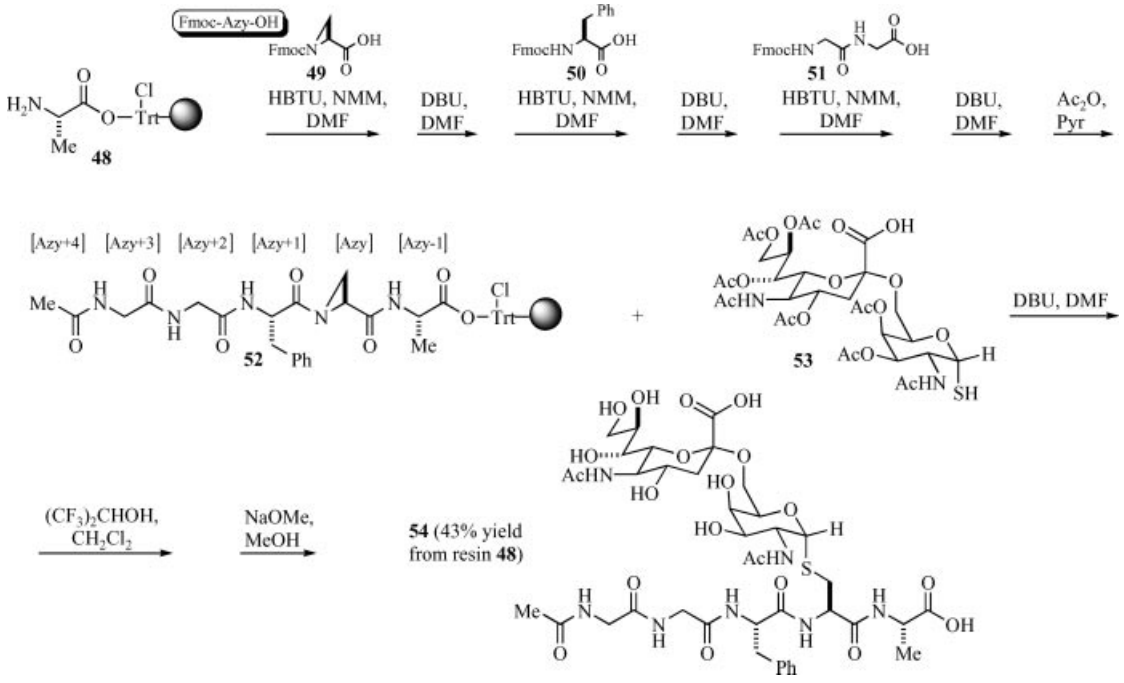
Scheme 6.

lined in Scheme 7. The so-called *direct strategy*, where α-bromoacryl esters/amides **40** are in solution while the amines are anchored to the Wang resin **41**, resulted in resin-bound dipeptide analogues **42**, which were cleaved to give nine different products of type **43**.[21] In the *reverse strategy*, the amines **44** in solution were subjected to tandem addition-cyclization with resin-bound α-bromoacrylamides **45** to yield twelve *N*-alkylated aziridine-2-carboxamides **47**. Although the compounds produced by these strategies were racemic mixtures, enantiomerically enriched aziridines have been obtained by the Gabriel–Cromwell reaction using a chiral auxiliary in solution,[22] which may enable future SPS of useful, enantiomerically pure aziridine-2-carboxylic acids.

The versatility of the Fmoc-Azy-OH building block **49**, which is readily available in enantiomerically pure forms from (*R*)- or (*S*)-serine methyl ester, has been exploited by Gin, van der Donk, and co-workers in SPPS protocols allowing introduction of this unnatural amino acid into peptides (e.g., **52**; Scheme 8). In their initial report on this subject, optimized conditions for regioselective conjugation of various thiols with Azy-containing peptides in solution and



Scheme 7.

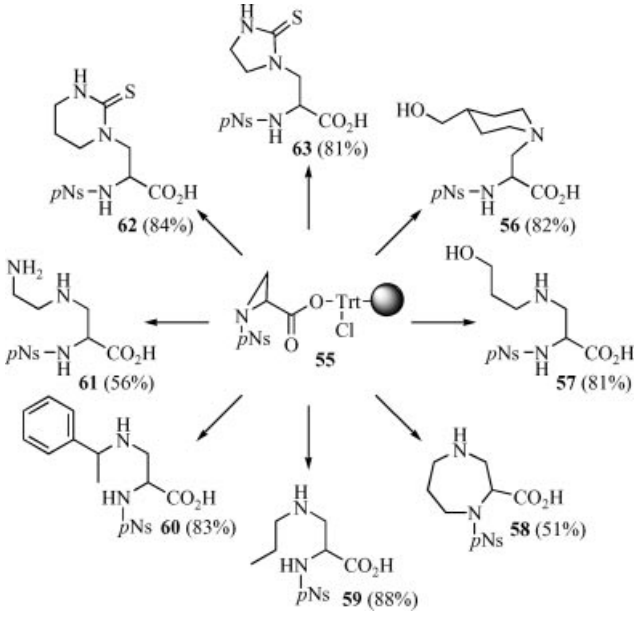


Scheme 8.

on solid phase were described as well,[23] and the relatively complex thioglycopeptide **54**, shown in Scheme 8, was successfully obtained in an impressive 43% isolated yield, thus demonstrating the strength of this strategy. After incorporation of the Azy moiety, it proved necessary to introduce the [Azy+2] and [Azy+3] residues as one dimeric building block **51** due to intramolecular *N*-deacylation observed upon Fmoc-deprotection of the [Azy+2] residue in the resin-bound peptides. Also, a mild Fmoc deprotection protocol (1% DBU in DMF) was necessary to avoid premature aziridine ring-opening.

In a subsequent account, the above strategy has been elaborated to include preparation of peptides containing biochemical tags, lipids, and even unprotected 1-thio-β-D-glucopyranose residue.[24] In addition, the strategy was shown to be compatible with native chemical ligation of unprotected peptide fragments, thus offering convergent access to complex thioglycopeptides. Finally, a third report extended the strategy to encompass selenium nucleophiles.[25]

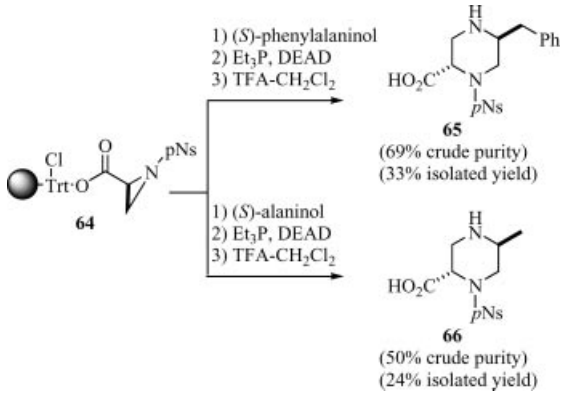
Recently, we have applied another Azy derivative for SPS of a variety of unnatural amino acids and α,β-diamino acids.[26] In this work, the *p*-nitrobenzenesulfonyl (*p*Ns) group was used for activation of the aziridine, and highly efficient and regioselective SPS protocols for aminolysis were established. Initially, a racemic form of *p*Ns-Azy-OH loaded directly onto a 2-chlorotrityl resin (**55**, Scheme 9) was successfully ring-opened with a variety of unprotected amino alcohols (e.g., to give **56** and **57**). Expedient synthesis of rigid scaffolds containing two secondary amino functionalities for further diversification (e.g., **58**) was achieved by subsequent Fukuyama–Mitsunobu cyclization of resin-bound **57**. Primary amine nucleophiles representing different degrees of steric congestion all afforded high product yields (e.g., **59** and **60**). Moreover, intermediary resins obtained from ring-opening with unprotected diamines were cyclized with 1,1′-thiocarbonyldiimidazole to give *N*-protected α-amino acids **62** and **63** possessing heterocyclic side chains.



Scheme 9.

Finally, the enantiomerically pure (*R*)- and (*S*)-*p*Ns-Azy-OH building blocks were prepared in solution from (*R*)- and (*S*)-serine, respectively, and the resin-bound (*S*)-*p*NsAzy ester **64** enabled SPS of rigid α,β-diamino acid enantiomers **65** and **66** after ring-opening with (*S*)-alaninol

and (*S*)-phenylalaninol, respectively, followed by Fukuyama–Mitsunobu cyclization (Scheme 10).[26] The success of this two-step protocol allows synthesis of a wide selection of six-membered and seven-membered, sterically constrained α,β-diamino acids using commercially available amino alcohols derived from α- and β-amino acids.



Scheme 10.

Summary and Outlook

Aziridines are versatile and powerful chemical tools in organic synthesis due to their efficient ring-opening reactions with a wide variety of nucleophiles. Furthermore, enantiomerically pure aziridines may be prepared by either asymmetric catalytic methods or from enantiomerically pure α,β-amino alcohols, including readily available D- and L-serine. Ring-opening reactions often proceed in a highly stereoselective and regioselective manner, which makes aziridine derivatives highly attractive building blocks in organic synthesis. Thus, aziridines have potential in preparation of combinatorial libraries of structurally diverse chemical entities for biological high-throughput screening. In order to exploit aziridine chemistry in this context, development of combinatorial and SPS protocols utilizing aziridines is required. Although the utilization of aziridines in library synthesis and SPS is relatively unexplored, the examples reviewed here emphasize the versatility and broad scope of aziridine chemistry for library diversification and SPS. Thus, aziridine derivatives have been involved in parallel solution-phase syntheses, multi-component reactions in solution as well as on solid phase, in SPS of biologically relevant 4,5-dihydroisoxazole derivatives and α,β-diamino acids, and in SPS of peptidomimetics and thioglycopeptides. The most recent advances show that aziridines offer efficient means for SPS of nitrogen-containing compounds,[27] and a report using solid-supported bases in the preparation of 2*H*-aziridine phosphonates[28] indicates that aziridine chemistry will benefit from solid-supported reagents.[29] While examples of resin loading with chiral aziridines have been described, further advances are expected from yet unreported direct generation of enantiomerically pure aziridines on a solid support.

Abbreviations

IUPAC three-letter codes are used for the amino acids. Ac = acetyl, ADDP = 1,1′-(azodicarbonyl)dipiperidide, BAIB = bisacetoxyiodobenzene, Boc = *tert*-butyloxycarbonyl, Bu = butyl, CSA = camphorsulfonic acid, d = days, dba = dibenzylidene acetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DMSO = dimethyl sulfoxide, DMF = *N*,*N*-dimethylformamide, Et = ethyl, Fmoc = 9-fluorenylmethoxycarbonyl, HBTU = benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HPLC = high-performance liquid chromatography, HRMS = high-resolution mass spectrometry, Im = imidazolyl, Me = methyl, MCR = multi-component reaction, Ms = methylsulfonyl, NMM = *N*-methylmorpholine, naph = naphthalene, NMR = nuclear magnetic resonance, Ns = nitrophenylsulfonyl, Ph = phenyl, Pr = propyl, Pyr = pyridine, SPPS = solid-phase peptide synthesis, SPS = solid-phase synthesis, TBDMS = *tert*-butyldimethylsilyl, TEMPO = tetramethylpiperidinyloxy radical, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = *p*-tolylsulfonyl, Trt = trityl.

Acknowledgments

C. A. O. thanks The Danish Technical Research Council for financial support (Grant 26-04-248).

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